OPEN ACCESS Freely available online

Drug Designing: Open access

Commentary

Designing pH-Responsive Prodrugs: A Strategy for Tumor-Specific Drug Activation

Mariana Lopes Ferreira*

Department of Pharmaceutical Chemistry, Institute for Molecular Therapeutics, University of Lisbon, Lisbon, Portugal

ABOUT THE STUDY

The design of pH-responsive prodrugs represents a compelling strategy to overcome one of the most critical challenges in cancer therapy, selective drug delivery to tumor tissues while sparing healthy cells. Tumors often exhibit a distinct extracellular microenvironment characterized by mild acidity (pH 6.5-6.9), primarily due to anaerobic glycolysis and poor vascular perfusion. This pathological hallmark can be exploited as a biochemical trigger for the activation of specially designed prodrugs pharmacologically inactive compounds that are converted into active drugs under acidic conditions. Unlike conventional chemotherapeutics that often distribute indiscriminately throughout the body, pH-sensitive prodrugs enable localized activation at tumor sites, minimizing systemic toxicity and enhancing therapeutic efficacy.

Prodrug design involves the covalent modification of an active drug with a pH-labile moiety or linker that remains stable at physiological pH (around 7.4) but undergoes rapid hydrolysis or rearrangement in acidic environments. Common acid-sensitive linkers include hydrazones, cis-aconityl, acetal/ketal groups, and imine bonds. These linkers are strategically placed between the drug and a carrier or masking group that suppresses its activity or prevents its release. Upon reaching the tumor's acidic microenvironment, the linker undergoes cleavage, releasing the active agent in its functional form. This mechanism ensures that the pharmacologically active compound is only liberated where it is most needed, offering a sophisticated level of spatial control in drug delivery.

A classic example of a pH-responsive prodrug system is doxorubicin conjugated with hydrazone-linked polymers or liposomes. These systems remain stable in circulation but release the cytotoxic agent once they accumulate in the acidic tumor milieu or within endosomes and lysosomes following cellular uptake. Other drugs such as paclitaxel, camptothecin, and methotrexate have also been modified using pH-sensitive linkers to create intelligent delivery systems. In many cases, these prodrugs are further incorporated into nanoparticles, micelles, or hydrogels, providing additional advantages such as extended circulation times, Enhanced Permeability and Retention (EPR) effect, and multi-stimuli responsiveness.

Designing efficient pH-responsive prodrugs requires a detailed understanding of tumor biology, chemical stability, and pharmacokinetics. The pKa of the prodrug's linker must match the pH range of the target tissue to ensure timely activation. Furthermore, the kinetics of drug release must be optimized to maintain therapeutic levels over an extended period. Computational modeling and molecular dynamics simulations are increasingly employed to predict the behavior of prodrugs under various pH conditions and to fine-tune their chemical architecture before synthesis. In vitro studies using tumor spheroids and acidic culture conditions, followed by in vivo validation in murine xenograft models, help bridge the gap between design and clinical application.

In addition to their use in solid tumors, pH-responsive prodrugs show promise in targeting intracellular compartments like endosomes and lysosomes, which also exhibit lower pH levels. This opens up opportunities in treating metastases, hematological malignancies, and even certain infections. Moreover, dual- or multi-responsive systems that respond to both pH and other stimuli, such as redox potential or enzyme activity, are under development to further refine selectivity and control. These advanced platforms can release drugs in response to multiple tumor-specific cues, enhancing their precision and potency.

However, several challenges remain. One of the primary limitations is inter- and intra-tumoral heterogeneity in pH, which can lead to inconsistent prodrug activation. Additionally, premature drug release in mildly acidic non-tumor environments (e.g., inflamed tissues) could reduce specificity and introduce side effects. There is also the need to ensure that the degradation products of the linker are biocompatible and do not interfere with therapeutic outcomes. Regulatory approval processes for prodrugs are often more complex than for traditional drugs, requiring extensive safety, stability, and efficacy data.

Despite these hurdles, the clinical outlook for pH-responsive prodrugs is promising. Several formulations are in various stages

Correspondence to: Mariana Lopes Ferreira, Department of Pharmaceutical Chemistry, Institute for Molecular Therapeutics, University of Lisbon, Lisbon, Portugal, E-mail: m.ferreira@imtlis.pt

Received: 03-Feb-2025, Manuscript No. DDO-25-37589; **Editor assigned:** 05-Feb-2025, PreQC No. DDO-25-37589 (PQ); **Reviewed:** 19-Feb-2025, QC No. DDO-25-37589; **Revised:** 26-Feb-2025, Manuscript No. DDO-25-37589 (R); **Published:** 04-Mar-2025. DOI: 10.35248/2169-0138.25.14.295

Citation: Ferreira ML (2025). Designing pH-Responsive Prodrugs: A Strategy for Tumor-Specific Drug Activation. Drug Des.14:295.

of clinical trials, and the number of publications and patents in this area continues to grow rapidly. As formulation technologies advance and our understanding of tumor pathophysiology deepens, the integration of pH-sensitive mechanisms into broader drug delivery strategies is expected to become increasingly routine. Furthermore, these systems can be readily adapted for combination therapies, where a pH-responsive carrier delivers multiple agents simultaneously, improving treatment outcomes and reducing resistance.

In conclusion, pH-responsive prodrugs exemplify a rational and innovative approach to achieving tumor-selective therapy. By harnessing the acidic microenvironment of cancer tissues, researchers can design smart therapeutics that offer improved safety profiles, enhanced efficacy, and reduced systemic burden. Continued interdisciplinary efforts in chemistry, pharmacology, nanotechnology, and oncology will be critical in translating these advanced drug delivery systems from bench to bedside, marking a significant leap toward more personalized and precise cancer treatments.