



PH sensitive Drug Delivery system in Cancer Therapy:

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ABSTRACT :

Cancer remains one of the leading causes of mortality globally, suggesting the necessity for novel therapeutic strategies that increase efficacy and the extent of systemic toxicity.

pH- sensitive drug delivery systems (DDS) are a promising technology that take advantage of the acidic microenvironment within tumors to achieve targeted and controlled delivery of effective therapies.

In this review, we will discuss the design, principles, mechanisms of action and recent strategies in utilizing pH-responsive DDS for cancer therapy .(Drug delivery system).

Keywords: cancer therapy; nanomedicine; drug delivery; pH-responsiveness; EPR; intratumoral delivery; intracellular delivery; nanoparticles; metal–organic frameworks.

Introduction:

One of the main causes of death worldwide today is cancer. High efficacy is difficult to achieve with single-drug therapy . Combination drug delivery has therefore been extensively employed in the treatment of cancer. Two medications can be co-loaded and delivered to tumor tissues to achieve synergistic drug delivery, which will increase the therapeutic effect of combination drugs GEM is a difluorinated nucleoside antimetabolite medication that dissolves in water. When used alone it is remarkably effective for a variety of solid tumors however, because of its short half-life and requirement for continuous high doses, it has a relatively high toxicity . PTX is a diterpene alkaloid medication that is highly lipid-soluble. Although it has other issues, like low bioavailability, it is less toxic than some other antitumor treatments.

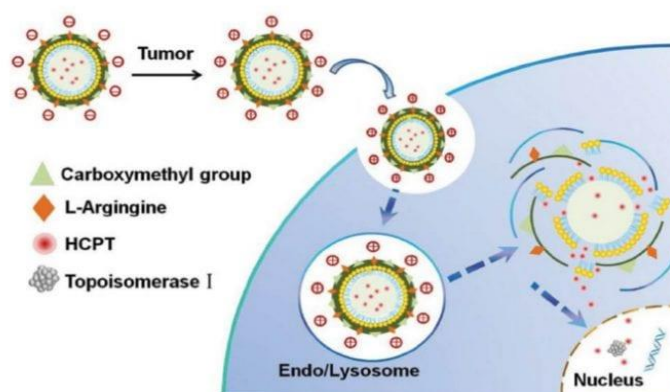
Mechanism Of PH Sensitivity:

pH-sensitive drug delivery systems (DDS) are developed with polymers or other materials. Polymers or other materials are used to develop pH-sensitive drug delivery systems (DDS).capable of being structurally (swelling, degradation, charge reversal, etc.) transformed in the presence of acidity.

A number of release mechanisms might be involved: • Protonation of functional groups (amines, carboxyls) alters solubility.

- Acid-and-reductive-labile linkers (e.g., hydrazone, acetal; imine) are cleaved releasing the drug payload.
- pH-dependent breakdown of by micelles or liposomes that increase diffusion.

Fig .1 Mechanism of ph sensitivity



Types Of PH Sensitive Carriers:

1) Polymeric Nanoparticles :

Polymers such as poly(L-histidine), chitosan, and poly amino esters) are commonly utilized . because of their adjustable pKa values and biocompatibility. For eg: chitosan

2. Liposomes:

pH-sensitive liposomes are composed of phospholipid and synthetic surfactant and will typically destabilize (breakdown) under acidic conditions. These carriers can encapsulate both hydrophilic and hydrophobic formulations and due to their characteristics they offer an additional option for formulators.

3. Micelles:

pH-sensitive micelles are build from amphiphilic block copolymers, which allow for multiple combinations of hydrophilic outer layer and hydrophobic core. Micelles will disassemble at low pH and can be used for release of incorporated drugs. Poly(ethylene glycol)-b-poly(L-histidine) is one example of a micelle.

4. Dendrimers:

Dendrimers are macromolecules that feature a branched tree-like structure with acid-labile linker units. Advantage: This carrier has a very high, controlled, drug loading with a regulated molecular weight.

5. Inorganic Nanoparticles:

The reference to inorganic nanoparticles utilizes mesoporous silica, gold, or calcium phosphate. Their unique size grants them exceptional optical, electronic, and catalytic properties, making them valuable in medicine for drug delivery

6. Hydrogels:

Hydrogels are cross-linked polymer networks that swell or depolymerize in response to pH. Hydrogels as carriers are uniquely useful for locally delivering drugs and for prolonged delivery systems.

Need for Combination Therapy:

Administering two or more drugs together to the tumor can create a synergistic effect while reducing the dosage and toxicity associated with each drug. For instance, Gemcitabine (GEM), a water-soluble nucleoside analog with a brief half-life and a highly toxic profile at elevated doses, can be administered with the fat-soluble drug Paclitaxel (PTX), which is poorly soluble in water but carries a lower toxicity when used in typical doses. Creating a delivery system for the co-administration of both GEM and PTX should improve treatment effectiveness and pharmacokinetics.

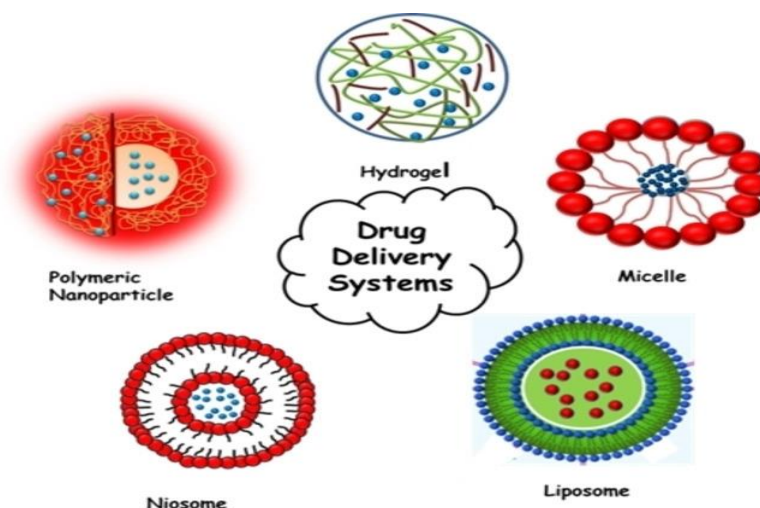


Fig.2. Types Of PH Sensitive Carriers Diagram:

Applications in Cancer Therapy:

DDS that are pH-sensitive have been used for delivering a range of chemotherapeutic drugs. such as doxorubicin, paclitaxel and cisplatin. These systems promote higher accumulation of drugs in the tumor through the enhanced permeability and retention (EPR) effect and respond in releasing drugs in an acidic -microenvironment. for instance, created pH- sensitive nanoparticles that released doxorubicin in acidic tumor tissues, which increased antitumor efficacy . pH responsive nanocarriers can decrease systemic toxicity, while increasing bioavailability in turn.

Advantages of pH-Sensitive Drug Delivery System:

1. Long-term release at the tumor site is called controlled release kinetics.
2. Better cellular uptake: Facilitates endosomal escape.
3. Customizable treatment: Carriers can be carefully designed to the pH profiles of tumor tissue unique to the individual patient.
4. Targeted delivery reduces damage to healthy tissues.
5. Controlled release enhances therapeutic efficacy.
6. Reduced systemic toxicity improves patient compliance.
7. Versatility in drug encapsulation and surface modification.

Future Directions:

1. Multi-stimuli responsive systems: Integrating pH-responsiveness, for example redox, and temperature, or one more enzyme-responsive mechanism.
2. Personalized nanomedicine: Implement AI-generated DDS to create patient-specific designs.
3. Imaging Combination: Employ theranostic nanoparticles which facilitate both imaging and therapy at the same time.
4. Clinical Translation: Extend the scope to include information on biocompatibility, scalability, and regulatory approval.
5. Polymers from nature and biodegradable ones: Lower the toxicity of nanoparticle designs and make the effectiveness the maximum.

Challenges and Limitations :

- 1) Heterogeneity of tumor pH may affect release kinetics.
- 2) Scale-up and reproducibility of nanoparticle synthesis.
- 3) Regulatory hurdles for clinical translation. Future research should focus on multistimuli responsive systems (e.g., pH + redox), real-time imaging capabilities, and personalized nanomedicine approaches.
- 4) Tumor pH is all over the place (pH 5.5-7.0), so drug release can be spotty.
- 5) Nanocarriers may end up in the wrong places, leading to weaker results and more side effects.
- 6) pH-sensitive carriers might break down too soon while circulating in the body.
- 7) It's hard to make a lot of nanoparticles that are the same every time.
Some carriers might be toxic or cause immune reactions.
- 8) The body clears out nanocarriers quickly, so they might not work as well.
- 9) There aren't clear rules for testing these drugs, making clinical approval hard.
- 10) Complex systems are expensive and hard to design.

Conclusion :

Systems for drug delivery that are sensitive to pH are a breakthrough in cancer treatment, providing the ability to control drug release with exact precision and significantly improved therapeutic potential. Advances in the science of material and nanotechnology will continue to address limitations and lead to clinical advances.

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