- UNIVERSITY OF BASRA
- COLLEGE OF PHARMACY
- GRADUATION PROJECT

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"DESIGN POLYMERIC PRODRUG AS " DRUG TARGETING MODEL"

- أشراف : أ.د. رحيم جميل محسن

- أعداد وتقديم :

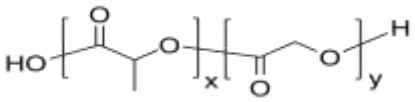
علي ثامر سعيد

علي كاظم يعقوب

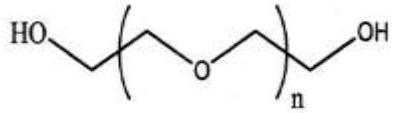
مريم خلف عبد علي

❖INTRODUCTION

Polymeric prodrugs are a class of drug delivery systems that are designed to improve the pharmacokinetic properties and therapeutic efficacy of drugs. These systems consist of a drug molecule that is covalently conjugated to a biocompatible polymer, such as **polyethylene glycol (PEG)**, **poly(lactic-co-glycolic acid) (PLGA)**. The polymer serves as a **carrier** for the drug, protecting it from degradation and clearance, and controlling its release at the target site.



PLGA

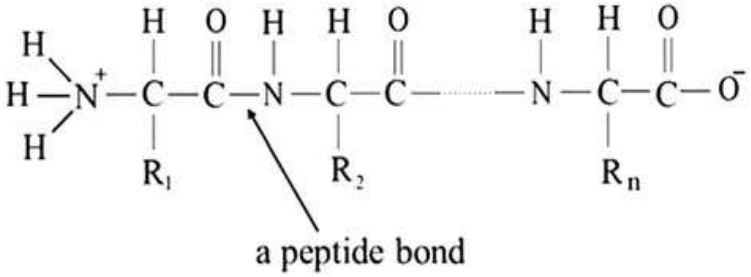


PEG

Drug targeting is a technique used to deliver drugs specifically to the site of action, while minimizing their distribution to non-target tissues. This can be achieved by exploiting the unique properties of the target tissue, such as its **vascular permeability**, **receptor expression**, or **pH**. Polymeric prodrugs can be designed to target specific tissues or cells by incorporating targeting moieties, such as **antibodies**, **peptides**, or small molecules, into the polymer backbone or drug conjugate.

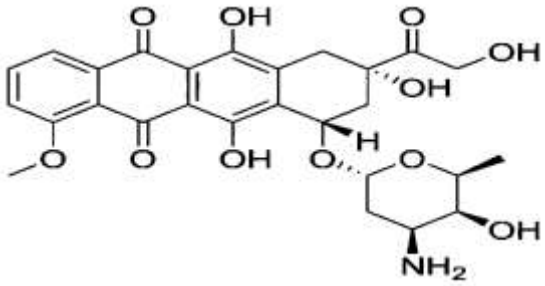
GENERAL

PEPTIDE STRUCTURE.



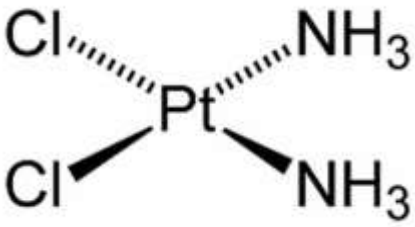
Several studies have demonstrated the potential of polymeric prodrugs for targeted drug delivery. For example, in a study published in Biomaterials in 2017, researchers developed a PEGylated prodrug of **doxorubicin** that was conjugated to a tumor-targeting peptide. The prodrug showed improved **anticancer activity** and reduced toxicity compared to free doxorubicin in a mouse model of **breast cancer.**

DOXORUBICIN



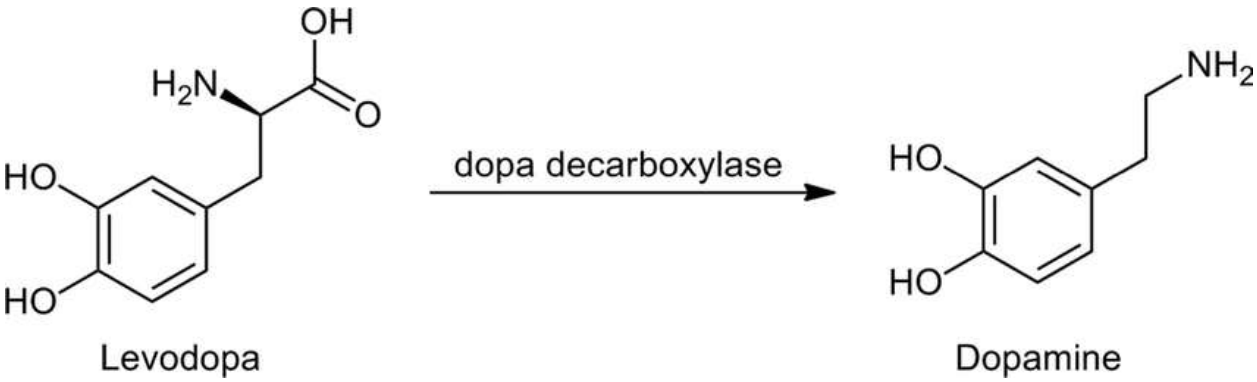
Another study, published in the Journal of **Controlled Release** in 2018, reported the development of a pH-responsive polymeric prodrug of **cisplatin** that was targeted to tumor cells by conjugation to a folate receptor-targeting peptide. The prodrug exhibited increased cellular uptake and cytotoxicity against folate receptor-expressing cancer cells, and reduced toxicity in normal cells compared to free cisplatin.

CISPLATIN



In addition to targeting cancer cells, polymeric prodrugs have also been explored for targeted drug delivery to other tissues, such as the brain. A study published in Biomaterials Science in 2020

reported the development of a **PEGylated prodrug of levodopa** that was targeted to the brain by incorporation of a peptide that selectively binds to the transferrin Load failed barrier. The prodrug showed improved pharmacokinetic properties and therapeutic efficacy in a mouse model of **Parkinson's disease**.



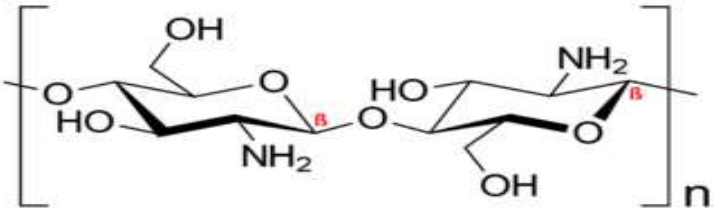
Overall, polymeric prodrugs have shown promising results for targeted drug delivery, and are a subject of active research in the field of drug delivery. However, there are still challenges to be addressed, such as improving the specificity and efficiency of targeting, and optimizing the release kinetics of the drug at the target site. Further research and development of these systems could lead to more effective and safer drug therapies for a range of diseases.

❖ TYPE OF POLYMERIC DRUG

A natural polymeric prodrug is a type of drug delivery system where a biocompatible and biodegradable polymer is used to deliver a drug to its target site. The drug is attached to the polymer through a biodegradable linkage, which allows for controlled release of the drug over time.

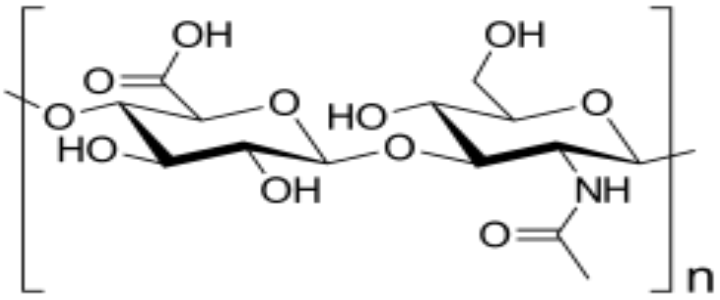
One example of a natural polymeric prodrug is **chitosan**, a natural polymer derived from chitin, which is found in the shells of crustaceans such as shrimp and crabs. Chitosan has been used to deliver a variety of drugs, including anticancer drugs, anti-inflammatory agents, and antibiotics.

Chitosan Structure



Another example is **hyaluronic acid**, a natural polymer found in the extracellular matrix of many tissues. Hyaluronic acid has been used to deliver drugs to treat cancer, inflammation, and other diseases.

Hyaluronic acid structure

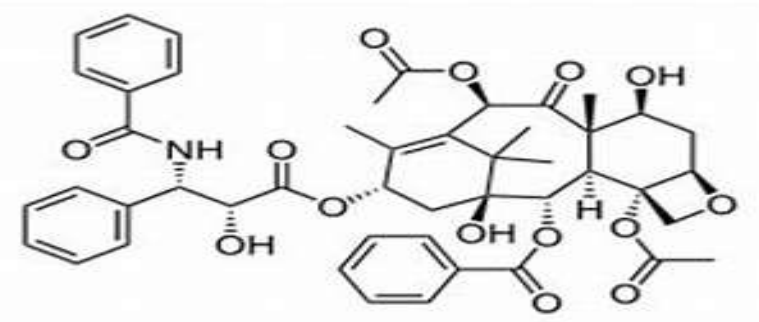


Natural polymeric prodrugs have **several advantages** over other drug delivery systems. They are **biocompatible, biodegradable, and non-toxic, which makes them suitable for use in humans.** They also allow for **controlled release of drugs** over a prolonged period, which can improve therapeutic efficacy and reduce side effects.

A semisynthetic polymeric prodrug is a type of drug delivery system where a polymer is chemically modified to attach a drug molecule to it. The resulting molecule is designed to release the drug in a controlled manner at the target site.

One example of a semisynthetic polymeric prodrug is **paclitaxel poliglumex** (trade name: **Onivyde**), which is used to treat pancreatic cancer. Paclitaxel, a chemotherapy drug, is attached to a biodegradable polymer called polyglutamate to form a prodrug. The prodrug is administered intravenously and is designed to release the paclitaxel slowly, resulting in sustained drug levels at the tumor site and increased efficacy.

Paclitaxel poliglumex



Semisynthetic polymeric prodrugs have **several advantages** over other drug delivery systems. They can improve **drug solubility,**

stability, and bioavailability. They can also **protect the drug from degradation and elimination, allowing for increased drug efficacy**. Additionally, they can be designed to target specific tissues or cells, reducing the risk of side effects.

synthetic polymeric prodrug one example is **PEGylated liposomal doxorubicin** (Doxil® or Caelyx®), which is used to treat various types of cancer. Doxorubicin is a potent chemotherapy drug that can cause severe side effects, such as cardiotoxicity and myelosuppression. However, when it is encapsulated in liposomes and conjugated with polyethylene glycol (PEG), it **becomes a polymeric prodrug that has several advantages**:

1-Increased circulation time

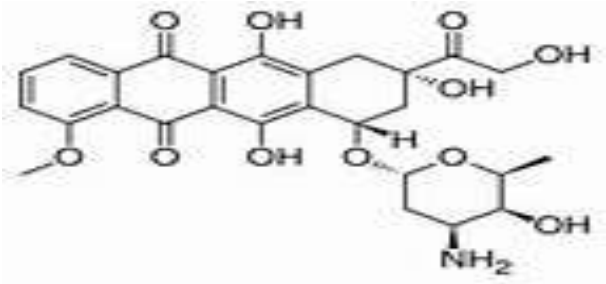
2-Targeted delivery: The liposomes can accumulate in tumor tissues, which have leaky blood vessels and poor lymphatic drainage, allowing the drug to be released selectively in the tumor microenvironment.

3-Reduced toxicity: The liposomes can shield the drug from healthy tissues, reducing the risk of side effects.

Overall, PEGylated liposomal **doxorubicin** is an example of a **synthetic polymeric** prodrug that has been successfully translated

to the clinic and is now used as a standard of care in the treatment of ovarian and breast cancer, among other indications.

Doxorubdin



❖ METHODOLOGY

We will now apply this process to one of the very important drugs that succeeded within the polymer processes.

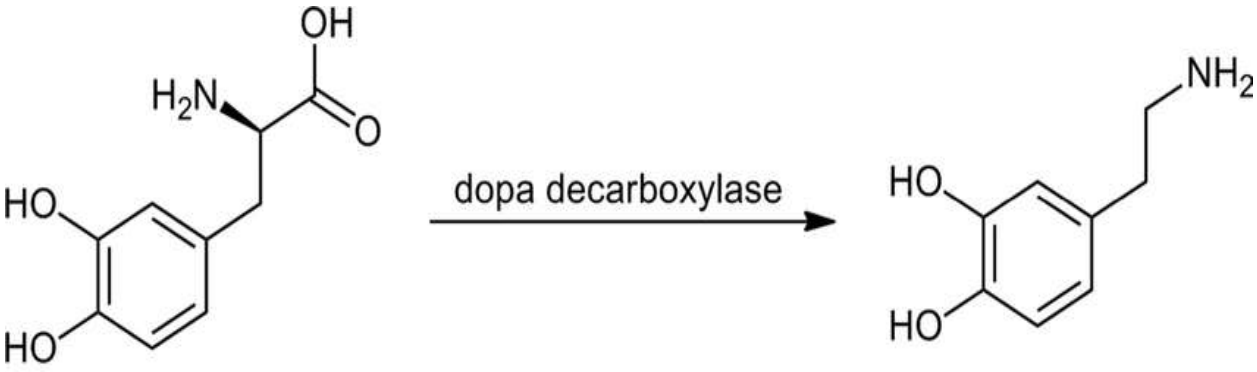
From dopamine, prepare other drugs that are derived from this neurotransmitter and have the same action, but by improving the efficiency of treatment by improving the effectiveness of treatment in the body and avoiding the problems of lack of effectiveness, improving the delivery of the drug to the site of the affected organ more precisely and contributes to reducing side effects and improving the drug and effectiveness.

❖ RESULT OF METHOD

Dopa is an amino acid that acts as a precursor to the neurotransmitter dopamine. Prodrugs of dopa are molecules that are designed to be converted into dopa within the body, in order to increase the bioavailability and effectiveness of the drug.

There are several prodrugs of dopa and its derivatives that have been developed for use in the treatment of Parkinson's disease, a condition in which dopamine levels in the brain are depleted.

The most commonly and important one of this section is levodopa , amino acid precursor of dopamine with antiparkinsonian properties. Levodopa is a prodrug that is converted to dopamine by DOPA decarboxylase and can cross the blood-brain barrier

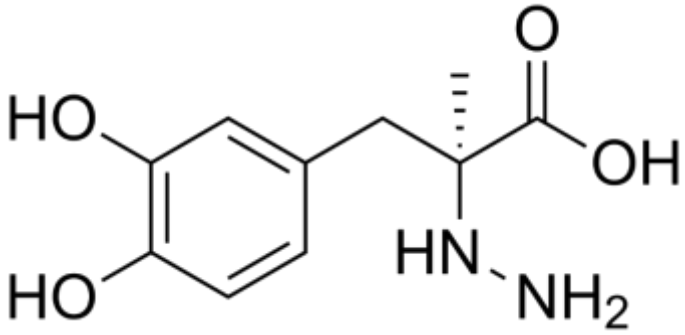


Levodopa Dopamine

Other important and commonly derivative includes ;

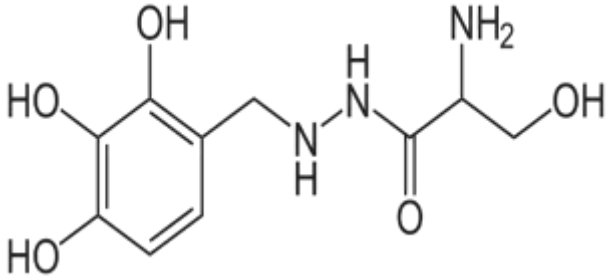
1- **Carbidopa** - **This is a prodrug of dopa that is often used in combination with levodopa (L-dopa), another prodrug of dopa. Carbidopa works by inhibiting the enzyme dopa decarboxylase, which is responsible for breaking down L-dopa before it can cross the blood-brain barrier and be converted into dopamine.**

CARBIDOPA STRUCTURE



2- **Benserazide** - **This is another prodrug of dopa that is used in combination with L-dopa. Benserazide works in a similar way to carbidopa, by inhibiting the enzyme dopa decarboxylase.**

BENSERAZIDE STRUCTURE



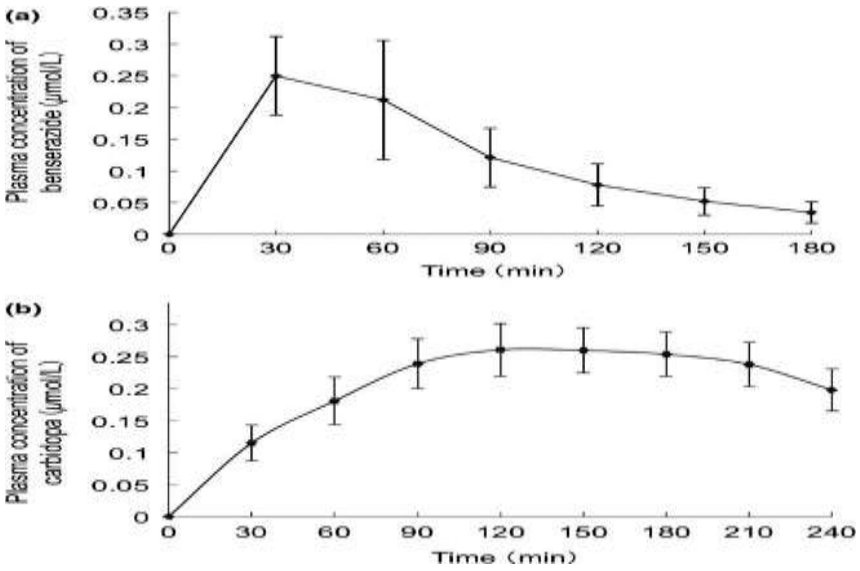


Figure1 : Plasma concentrations of (a) benserazide and (b) carbidopa in healthy subjects after administration of levodopa/benserazide 100/25 mg or levodopa/carbidopa 100/10 mg, respectively.

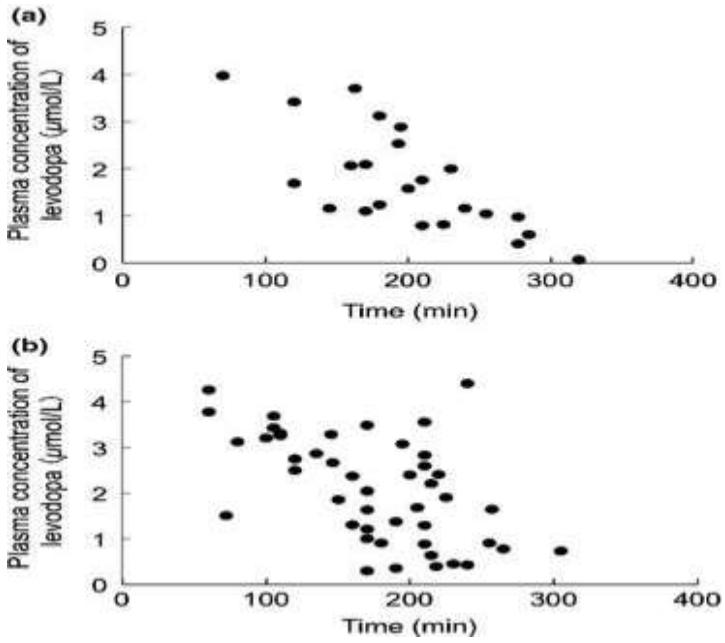
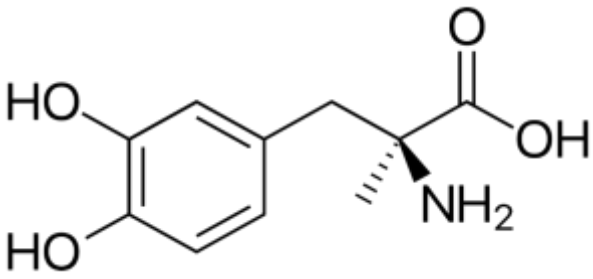


Figure2 : Plasma levodopa concentrations for individual patients with Parkinson's disease after administration of (a) levodopa/benserazide or (b) levodopa/carbidopa. Plasma levodopa concentration equivalent to a 100 mg dose plotted versus the time from dosing to sampling.

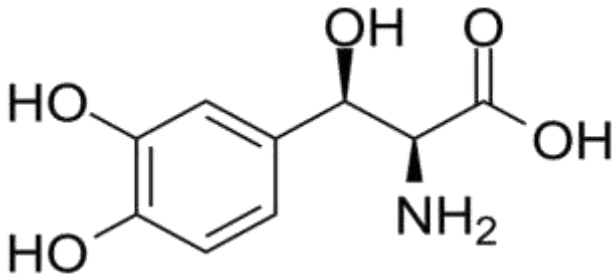
3- **Methyldopa** - This is a prodrug of alpha-methyldopamine, which is a derivative of dopa. Methyldopa is used as an antihypertensive agent, and works by reducing the activity of the sympathetic nervous system.

METHYLDOPA STRUCTURE



4- **L-DOPS** - This is a prodrug of L-dopa that is currently being investigated for use in the treatment of orthostatic hypotension, a condition in which blood pressure drops significantly upon standing up.

DROXIDOPA (L.DOPS) STRUCTURE



Overall, prodrugs of dopa and its derivatives have proven to be effective in the treatment of a variety of neurological and cardiovascular conditions, and continue to be an area of active research and development.

❖ AIMS OF PROJECT

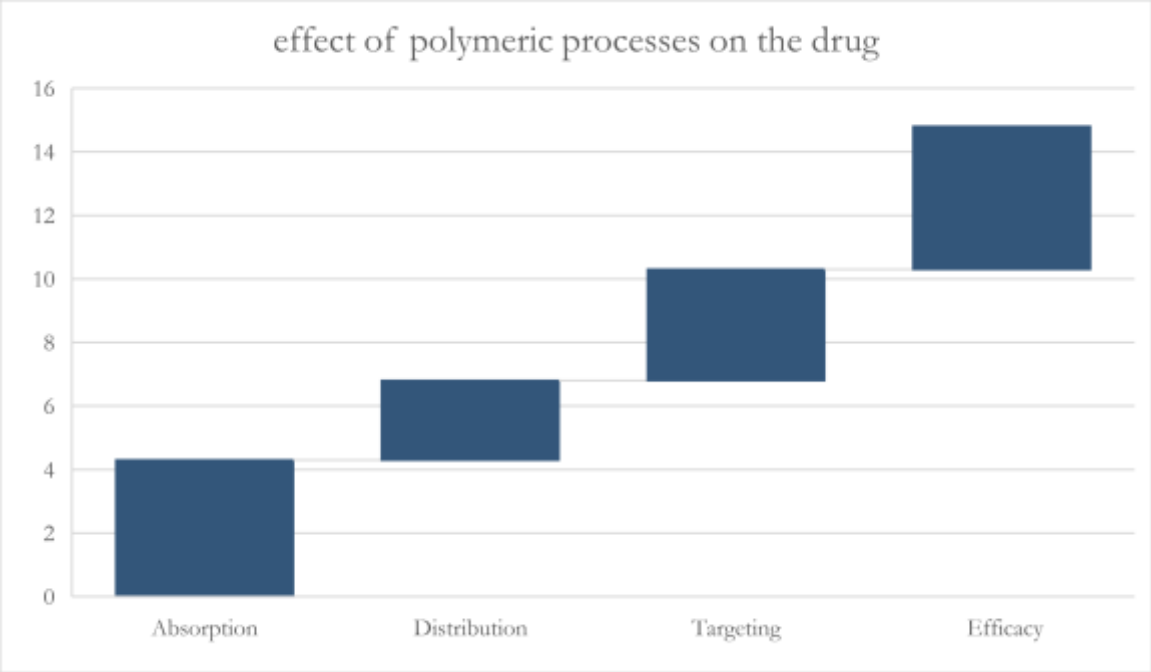
1-Enhanced Drug Targeting: The primary goal of designing polymeric prodrugs is to improve the targeted delivery of drugs to specific sites in the body. By attaching drugs to polymer carriers, it is possible to achieve selective accumulation at the target site, minimizing off-target effects and increasing therapeutic efficacy.

2-Increased Therapeutic Efficacy: Polymeric prodrugs offer the potential to enhance the therapeutic efficacy of drugs. By improving drug solubility, stability, and pharmacokinetics, as well as facilitating cellular uptake and intracellular drug release, polymeric prodrugs can increase drug bioavailability and maximize their therapeutic effects.

3-Reduction of Systemic Toxicity: Another important goal is to minimize the systemic toxicity associated with drugs. Polymeric prodrugs can provide localized drug delivery, reducing drug exposure in non-target tissues and organs. This selective delivery helps to mitigate adverse side effects and improve the overall safety profile of the drug.

4-Combination Therapy: Polymeric prodrugs can be designed to deliver multiple drugs simultaneously or in a

sequential manner. This allows for combination therapy, where different drugs with complementary mechanisms of action can be co-delivered to enhance therapeutic outcomes and overcome drug resistance.



❖ REFERENCE

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- **Xiao, L., Guo, J., Wen, L., & Xu, H. (2015). Design strategies of polymeric prodrugs for enhanced tumor targeting and cancer therapy. ACS Applied Materials & Interfaces, 7(16), 9078-9094.**

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Thank you for reading