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Organic Pharmaceutical Chemistry IV

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Chemical Drug Delivery Systems

Strategies and Applications

- The development of effective pharmaceutical agents with minimal side effects remains an elusive goal.

- To minimize the undesirable drug properties, the chemical modulation(i.e. drug derivatization) has been utilized.

- This offers high flexibility and has been demonstrated as an important means of improving drug efficacy.

Polymeric Prodrugs

- Improving the therapeutic index (TI) of drugs is a major impetus for innovation in many therapeutic areas.

- Is it feasible to influence the TI?

  - Conventional drug delivery systems:
  - Non-specific
  - High doses
    - Short biological half-life
  - Excessive or insufficient water-solubility
  - Low drug specificity towards the affected organs

- Different drug delivery systems have been developed in the last few years to improve the pharmacokinetic and pharmacodynamic profile of such compounds.

  - liposomal preparations
  - controlled release systems
  - covalent modifications of the drug by:

    - ✓low molecular weight reagent or
    - ✓by polymer conjugation

Polymeric Prodrugs

- A conjugation of a drug with a polymer forms so-called ‘polymeric prodrug’.

- Polymer materials were designed and proposed as matrices or depot systems for injectable or implantable systems or devices.

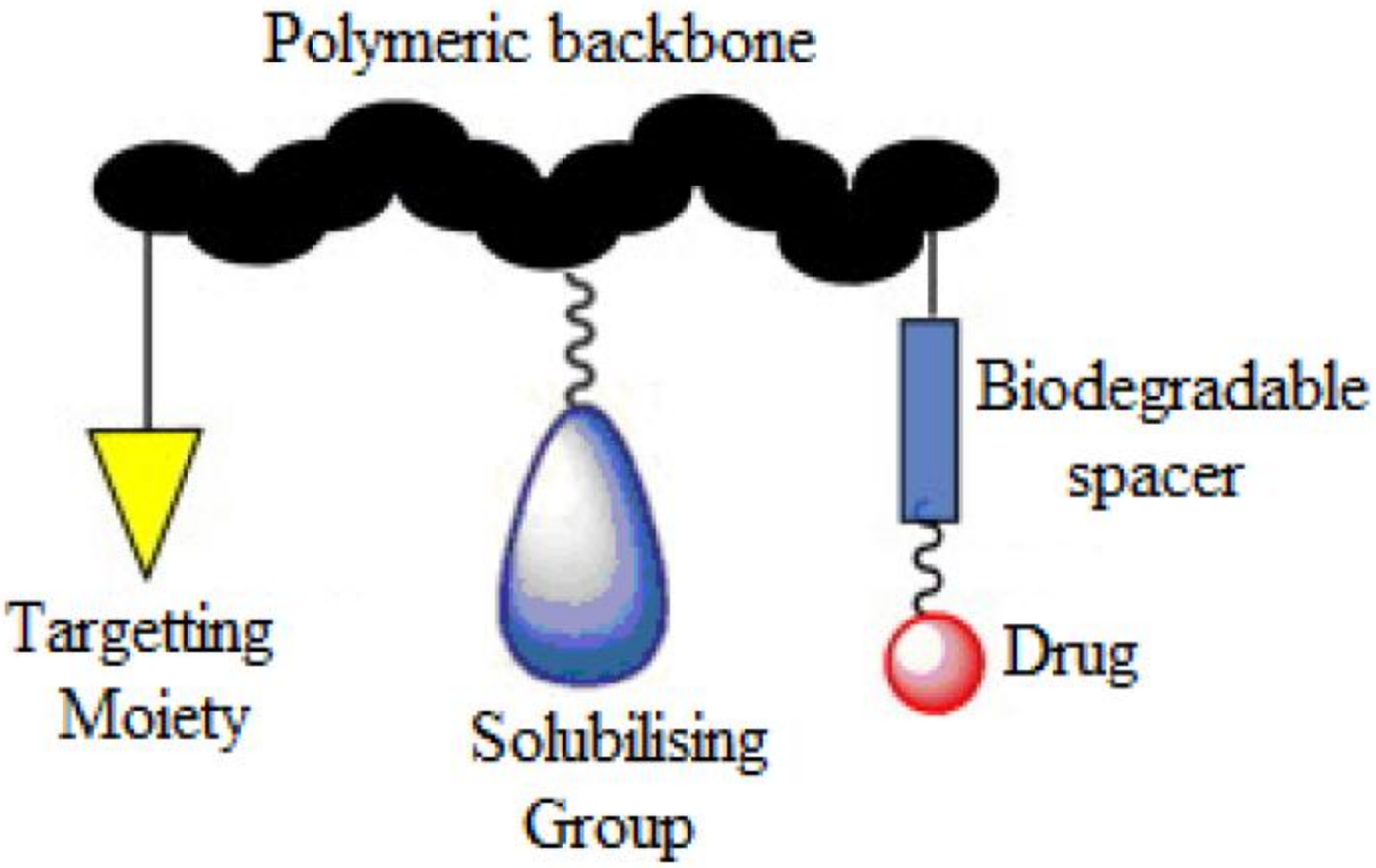
Examples on polymer conjugation

Conjugate	Indication	Marketing year	Company
Branched PEG–interferon a2a (Pegasys)	Hepatitis C	2002	Roche/Nektar
PEG–growth hormone receptor antagonist	Acromegaly	2002	Pfizer (Pharmacia)

Polymeric Prodrugs

- The proposed model of the Polymeric Prodrugs consists mainly of five components:
  1. The polymeric backbone
  2. The drug
  3. The spacer
  4. The targeting group and
  5. The solubilizing agent

Ringsdorf's model of polymeric prodrug



Advantages of Polymeric Prodrugs

1. **Prolongation of drug action**
2. **Controlled drug release**

The controlled drug release can be achieved via:

a) *pH controlled drug release.*

b) *Enzymes for drug release.*

Prolongation of drug action

- The duration of action of the drug is determined by its plasma concentration which is usually measured as area under curve (AUC).
- The duration of action can be prolonged by linking a drug to a polymer in order to obtain a conjugate:
  - slower renal excretion
  - longer blood circulation and
  - an endocytotic cell uptake.

Controlled drug release

- The polymeric prodrug formed by conjugation of drug with polymeric carrier should be:
  1. stable in circulation.
  2. able to release the macromolecular drug intra-cellularly.

pH controlled drug release

- the tumor tissue or lysosomes are slightly acidic in comparison to the healthy tissues.
- This relatively low pH has been exploited to design pH sensitive spacers .
- N-cis-aconityl spacer used to form polymeric prodrug of daunorubicin-linked aminoethyl polyacrylamide beads.

Enzymes for drug release

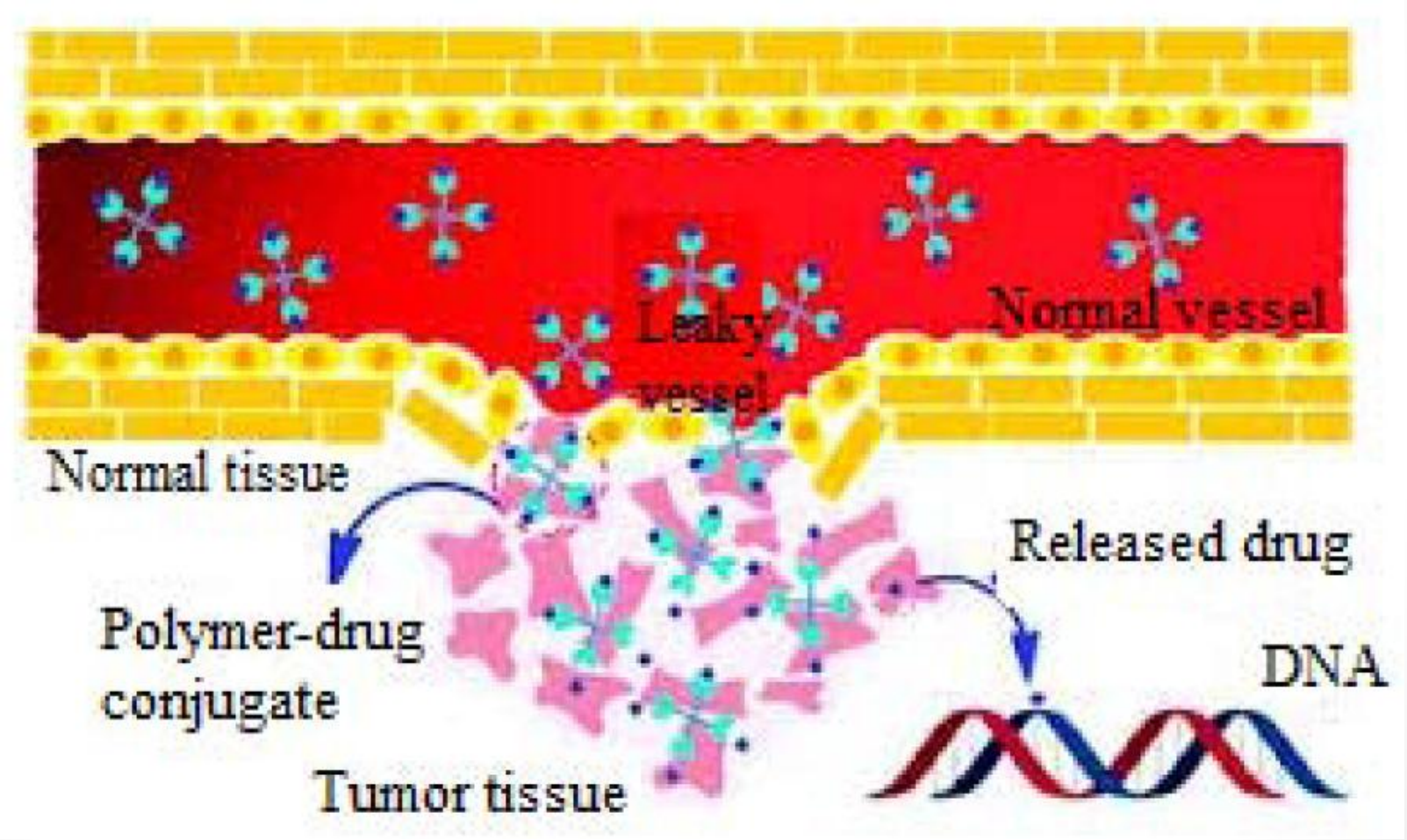
- The polymeric prodrug enters the lysosomes in the tumor cells.
- In the lysosomes the polymeric prodrug releases the drug by the act of cathepsins and metalloproteinases.
- The release of cytotoxic drug with the help of these enzymes destroys the tumor tissue.

- The polymeric prodrugs are taken up by solid tumors by pinocytosis.

- This passive tumor uptake increases the targeting of drug due to their characteristic feature of “enhanced permeability and retention” effect .

- This effect is due to increased tumor vascular permeability and poor tissue drainage from the tumor cells

The Enhanced Permeability and Retention (EPR) effect



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Any question?

Thank you