Kerbala University
College of Pharmacy
Dep. of Pharmaceutical Chemistry

Organic Pharmaceutical Chemistry IV

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Classification of polymers used for bioconjugation

Classification of polymers

- **Synthetic polymers:**
  1. **Polyethylene glycol (PEG)**:
  2. **Vinyl polymers:**
     a) *N-(2-hydroxypropyl)methacrylamide (HPMA)*
     b) *Poly(styrene-co-maleic acid/anhydride) (SMA)*
  3. **Divinylethermaleic anhydride/acid copolymer (DIVEMA)**
  4. **Polyethylenimine (PEI) or polyaziridine**

- **Natural polymers:**
  1. **Dextran.**
  2. **Chitosan.**
  3. **Proteins.**
  4. **Pullulan.**

Synthetic polymers

1. Polyethylene glycol (PEG)

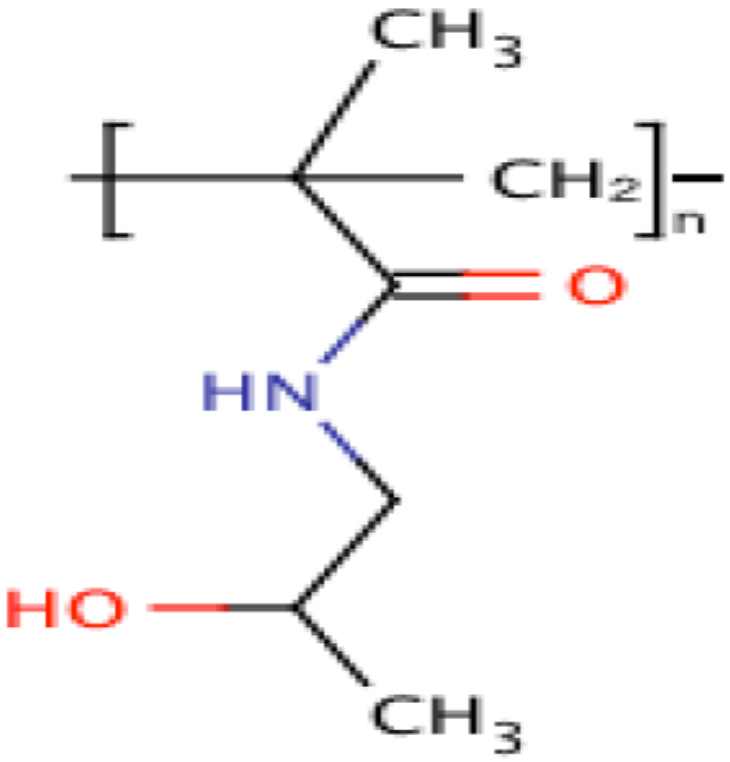
- ***Advantages of PEG***
  - non-toxic and non-immunogenic.
  - flexible, highly water-soluble
  - site-specific conjugation to a drug
  - Available in wide range M.Wt (300-10,000,000 Da)

- ***Disadvantage***
  - PEG molecule has only two reactive groups, therefore at most only two drug molecules can be attached to a bulky PEG molecule.

$$H\text{-}(O\text{-}CH_2\text{-}CH_2)n\text{-}OH$$

2. Vinyl polymers

- *N-(2-hydroxypropyl)methacrylamide (HPMA)*

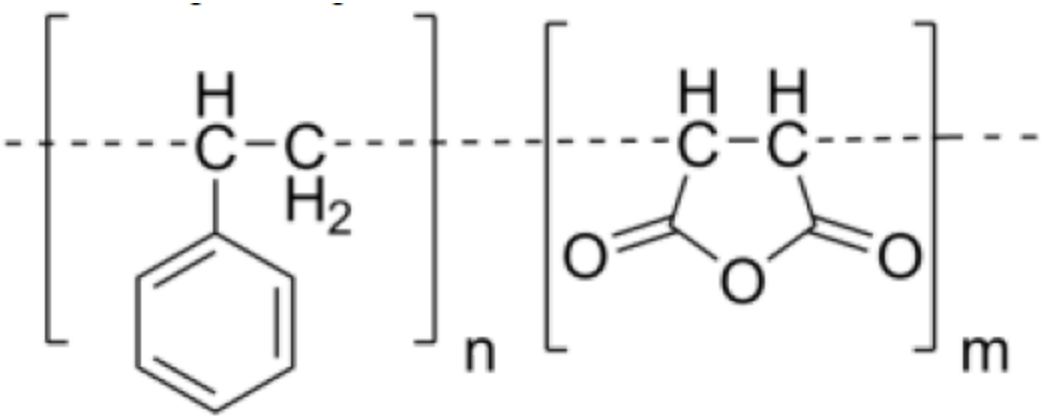


a) N-(2-hydroxypropyl)methacrylamide (HPMA)

- ***Advantages:***
  - Non immunogenic.
  - Nontoxic.
  - Well resides in blood circulation.
  - It is frequently used as macromolecular carriers for low molecular weight drugs (especially anti-cancer chemotherapeutic agents) to enhance therapeutic efficacy and limit side effects.

b) Poly(styrene-co-maleic acid/anhydride) (SMA)

Advantage: Ampiphillic nature of SMA is utilized in stable micelle formation.



3. Divinylethermaleic anhydride/acid copolymer (DIVEMA)

- ***Advantages:***
  1. It has antitumor activity.
  2. It induces the formation of interferon.
  3. It has antiviral, antibacterial, and antifungal activity.
  4. It is an anticoagulant and an anti-inflammatory agent.

- ***Disadvantages:***
  1. Pyrogenicity.
  2. Thromobocytopenia.
  3. Inhibition of microsomal enzymes.
  4. Sensitization to endotoxin.
  5. Liver damage.
  6. Organomegaly, and
  7. Depression of the reticuloendothelial system.

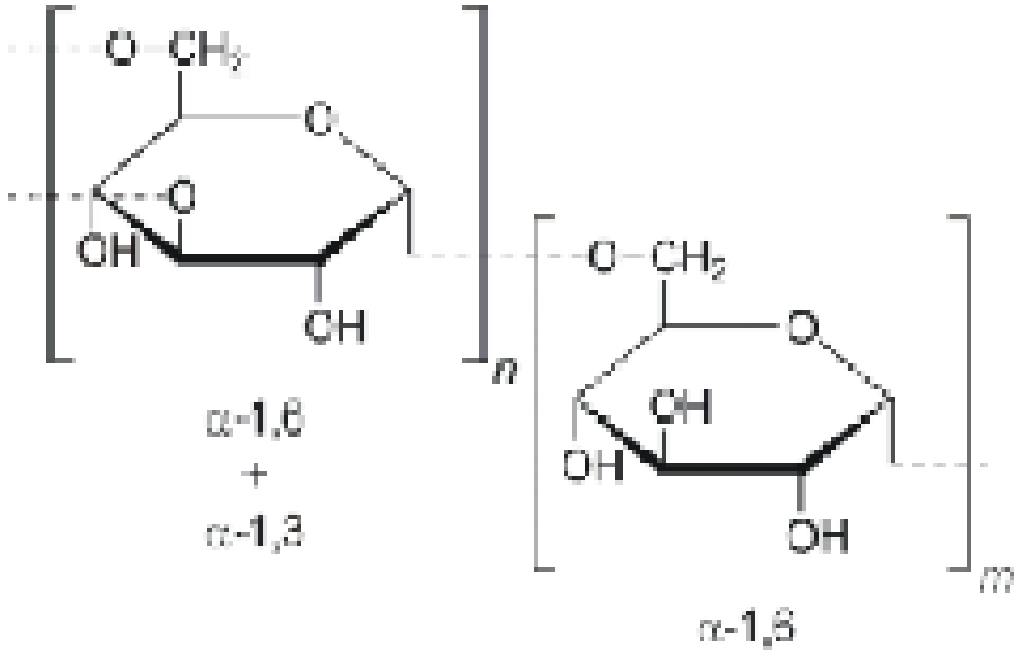
4. Polyethylenimine (PEI) or polyaziridine

- ***Advantage***:
- Linear PEIs of mol. wt. 22,000 are best to overcome nuclear barrier and yields the highest transfection rates.

- ***Disadvantage***:
- It has a limitation of relatively high toxicity and this could prove problematic for repeated systemic use.

Natural polymers

1) Dextran



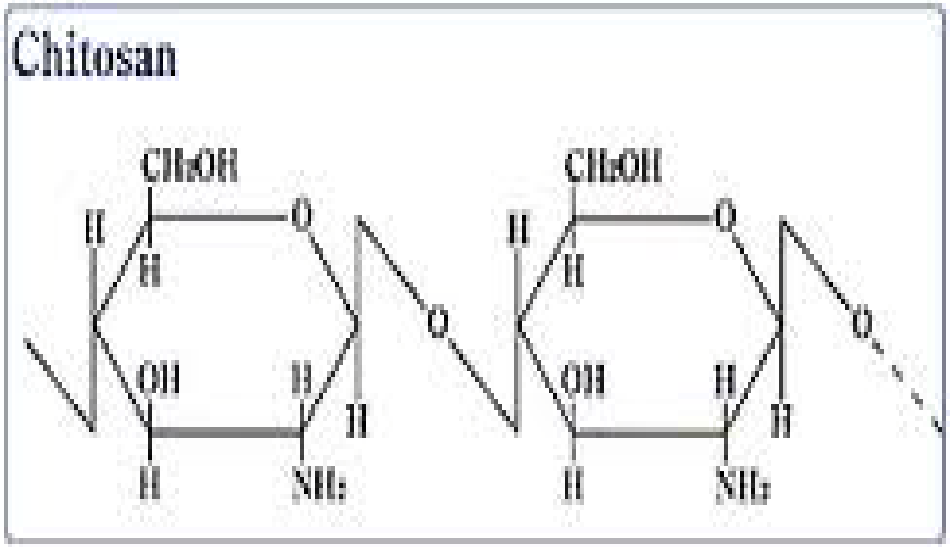
1) Dextran

- **Advantages:**
  - It is biocompatible and biodegradable.
  - It is biologically active
  - possesses thrombolytic activity.
  - It is non-immunogenic and non-toxic.

- **Disadvantages:** These include:
  - Anaphylaxis.
  - volume overload.
  - pulmonary edema.
  - cerebral edema, or
  - platelet dysfunction.

2) Chitosan

Advantages: Chitosan enhances the transport of polar drugs across epithelial surfaces, and is biocompatible and biodegradable.

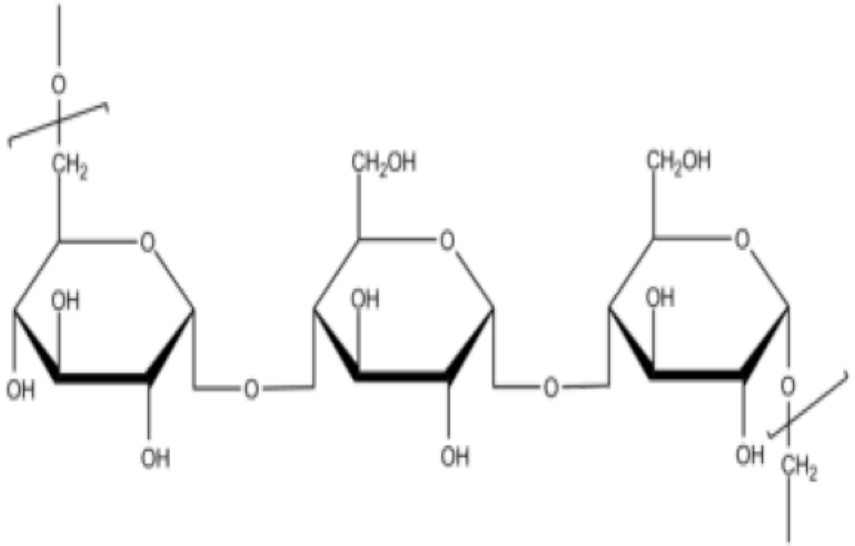


3) Proteins: *Albumin*

- ***Advantages:***
  - Albumin gets accumulated within solid tumors and hence is used for drug delivery and tumor targeting.
  - It also increases the stability of attached therapeutic proteins.

4) Pullulan

- ***Advantages:*** Biodegradability, low immunogenicity and polyfunctionality and fair solubility in aqueous and few organic solvents, blood compatible, non-toxic, non-mutagenic and noncarcinogenic.



Cross-linking Reagents

Polymer-Drug Conjugates

Polymer-Drug Conjugates

- Polymer anticancer-drug conjugates are designed to:
  - enhance the physico-chemical properties of the drug and
  - administer the drug specifically to the tumor site
- They are prepared by conjugating anticancer drug to a polymeric backbone via covalent linkage.

Cross-linking reagents

- Biodegradable spacer is inserted in the conjugate to:
  - insure stability during systemic circulation and
  - facilitate specific enzymatic or hydrolytic release of the drug
  - e.g. Doxorubicin-HPMA (N-(2-hydroxypropyl) methacrylamide) conjugate

Doxorubicin-HPMA conjugate

- The polymer used is N-(2-hydroxypropyl) methacrylamide copolymer.
- The anticancer drug is bound to the polymer backbone using peptidyl spacer (Gly-Phe-Leu-Gly linker).
- This linker designed to be cleaved by Lysosomal thiol dependant proteases.
- The conjugate has a molecular weight of approx. 30,000 Da and a Doxorubicin content of approx. 8.5% (w/w).

“Antibody-Directed Enzyme Prodrug Therapy” (ADEPT)

Approach	Enzyme	Prodrug	Drug
ADEPT	Carboxypeptidase A	Methotrexate alanine	Methotrexate
ADEPT	B - Glucuronidase	Epirubicin glucoronide	Epirubicin

“Gene-Directed Enzyme Prodrug Therapy” (GDEPT)

Approach	Enzyme	Prodrug	Drug
GDEPT	Thymidine kinase	Ganciclovir	Ganciclovir triphosphate
GDEPT	Cytosine deaminase	5-Fluorocytosine	5-Fluorouracil
GDEPT	Nitroreductase	4-nitrobenzyloxy carbonyl derivative	Actinomycin D

References:

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2. http://www.pcb.ub.edu/fama/pdf/Current%20Drug%20Delivery,%202012,%209,%20000-000.pdf
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THANK YOU FOR YOUR LISTENING