Polymeric prodrug

Lec. 6

Requirements for Selecting Polymers as Candidate Drug Carriers:

a) Availability of suitable functional groups -COOH, -OH, -SH, or -NH_2 for covalent coupling with drugs

b) Biocompatibility: preferably nontoxic, nonimmunogenic

c) Biodegradability or a molecular weight below the renal excretion limit

d) Availability: reproducibly manufactured and conveniently administered to patients

e) Water solubility: hydrophilic to ensure water solubility

f) Low polydispersity, to ensure an acceptable homogeneity of the final conjugates.

Classification of Polymers used for Bioconjugation

- Based on their origin, polymers used for bioconjugation are classified as either synthetic or natural.
- Synthetic polymers can be widely used because the properties of these molecules can be modified by varying their structures.

Classification of Polymers Used for Bioconjugation

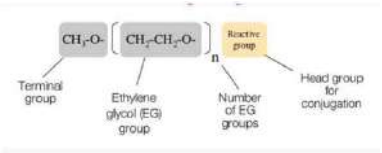
A. Synthetic Polymers

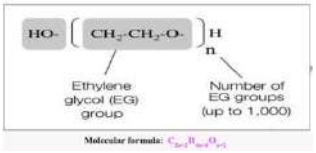
1. Polyethylene glycol (PEG)
   - is a polyether compound with many applications from industrial manufacturing to medicine.
   - The structure of PEG is H-(O-CH_2-CH_2)$_n$-OH.
   - It is available over a wide range of molecular weights from 300 g/mol to 10,000,000 g/mol.
   - PEG is known to be nontoxic and nonimmunogenic.
   - Its high degree of hydration means the polymer chain effectively has a "water shell," and this helps to mask the drug to which it is bound.

Classification of Polymers Used for Bioconjugation

1. Polyethylene glycol (PEG)

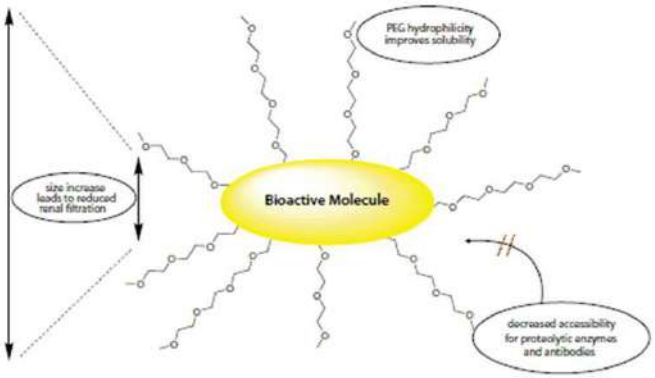
➢PEG can be prepared with a single reactive group at one terminal end, and this aids site-specific conjugation to a drug and avoids cross linking during conjugation.





➢In the macromolecular PEG- drug conjugate, the overall drug content is poor since one PEG molecule has only two reactive groups, therefore at most only two drug molecules can be attached to a bulky PEG molecule. This results in low polymer-drug loading.

Polyethylene glycol (PEG)



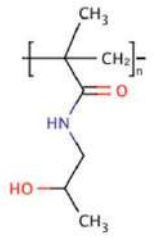
Classification of Polymers Used for Bioconjugation

2. Vinyl polymers:

- are prepared by copolymerization which results in the formation of varied polymers with different polymer properties.

- Examples of this copolymerization are molecules like N-(2-hydroxypropyl) methacrylamide (HPMA), poly (styrene-co-maleic acid/ anhydride) (SMA).

- Vinyl polymers are:
  i. nonimmunogenic and nontoxic,
  ii. they reside well in the blood circulation.

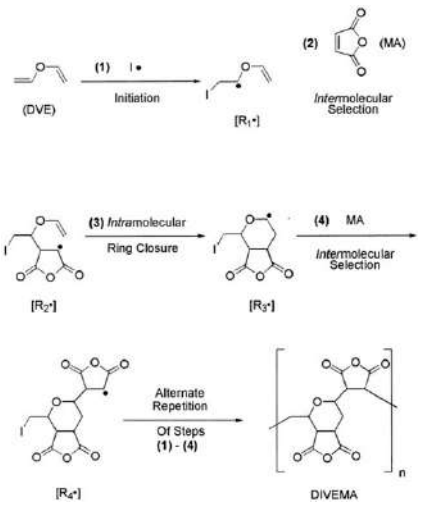


Classification of Polymers Used for Bioconjugation

3. Divinyl ether (DVE) and maleic anhydride (MA) copolymerize with radical and show a wide variety of biological activities.

- They have antitumor activity;
- they induce the formation of interferon;

  they have antiviral, antibacterial, and antifungal activity; they also have an anticoagulant and an anti-inflammatory agent.



Classification of Polymers Used for Bioconjugation

3. Divinyl ether (DVE) and maleic anhydride (MA) copolymerize with radical and show a wide variety of biological activities.

DIVEMA is an immunopotentiator;

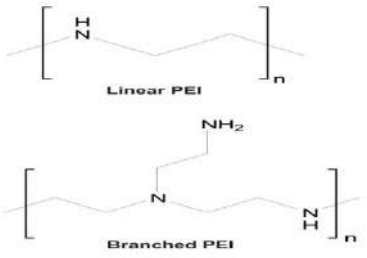
1. it increases the rate of phagocytosis,
2. it activates macrophages selectively, and
3. it inhibits RNA-dependent DNA polymerase.

Disadvantages: pyrogenicity, thromobocytopenia, liver damage.

Classification of Polymers Used for Bioconjugation

4. Polyethylenimine (PEI)

- PEI or polyaziridine is a polymer with repeating unit composed of the amine group and two carbon aliphatic CH_2CH_2 spacer.
- Linear polyethyleneimines contain all secondary amines, in contrast to branched PEIs which contain primary, secondary and tertiary amino groups.
- 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.

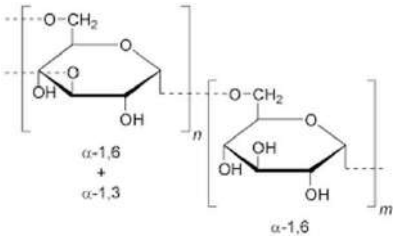


Classification of Polymers Used for Bioconjugation

B. NATURAL POLYMERS:

1. Dextran

- is a complex, branched glucan (polysaccharide made of many glucose molecules) composed of chains of varying lengths ranging from 3 to 2000 kDa.
- It is biocompatible and biodegradable.
- biologically active and possesses thrombolytic activity and is nonimmunogenic and nontoxic.

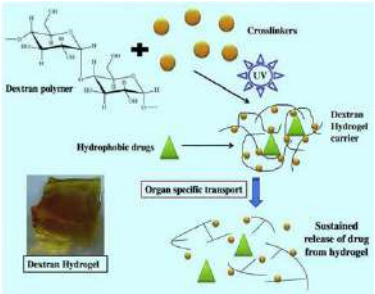


Classification of Polymers Used for Bioconjugation

B. NATURAL POLYMERS:

1. Dextran

- Disadvantages: anaphylaxis, volume overload, pulmonary edema, cerebral edema, or platelet dysfunction.
- It is non immunogenic but modification of the chain with drug attachment may lead to immunogenicity and it may also create non biodegradable polymer.

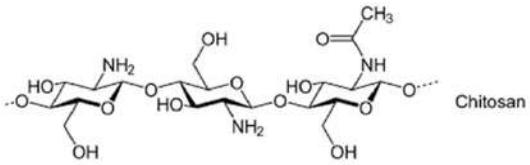


Classification of Polymers Used for Bioconjugation

B. NATURAL POLYMERS:

2. Chitosan

- is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl- D-glucosamine (acetylated unit).
- It enhances the transport of polar drugs across epithelial surfaces, and is biocompatible and biodegradable.
- It helps in natural blood clotting and blocks nerve endings and hence reduces pain.



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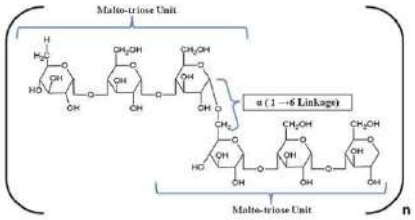
B. NATURAL POLYMERS:

3. Pullulan

- is a polysaccharide polymer consisting of maltotriose units, also known as α-1, 4-α-1, 6-glucan.
- It is biodegradable, with low immunogenicity and poly-functionality,
- having fair solubility in aqueous and a few organic solvents,
- is blood-compatible, nontoxic, nonmutagenic, and noncarcinogenic.



Polymeric prodrugs of several drugs have been synthesized and evaluated

Sr. No.	Polymer Used as Promoieties	Conjugation with Drug	Advantage
1	PEG	Theophylline	Improved biopharmaceutical properties
2	PEG	Ketoprofen	Extended pharmacological effect due to delayed release
3	2-Hydroxyl methyl acrylate	Naproxen	Enhanced potency and longer duration of action
4	PEG 2000	Warfarin	Improved biopharmaceutical properties
5	PEG 5000, 10000	Metronidazole	Improved pharmacokinetic properties
6	PEG esters	Methotrexate	Improved stability and drug delivery
7	PEG	Ibuprofen	Extended duration of action
8	PEG	Theophylline	Improved release of parent drug
9	PEG	Mesalazine	Colon-specific drug delivery
10	Acrylates	Ibuprofen	Increased anti-inflammatory activity

Polymeric prodrugs and targeting

Two approaches are mainly used for targeting polymeric prodrugs:

A. Passive targeting

Enhanced permeability and retention effect is the main approach in passive targeting.

Passive targeting is not very efficient as the polymeric drug enter the cells by means of the concentration gradient between the intracellular and extracellular spaces.

B. Active targeting

The active targeting approach is based on the interactions between a ligand and a receptor or between a specific biological pair (e.g. avidin-biotin, antibody-antigen, lectin-carbohydrate, etc.).

Active targeting: