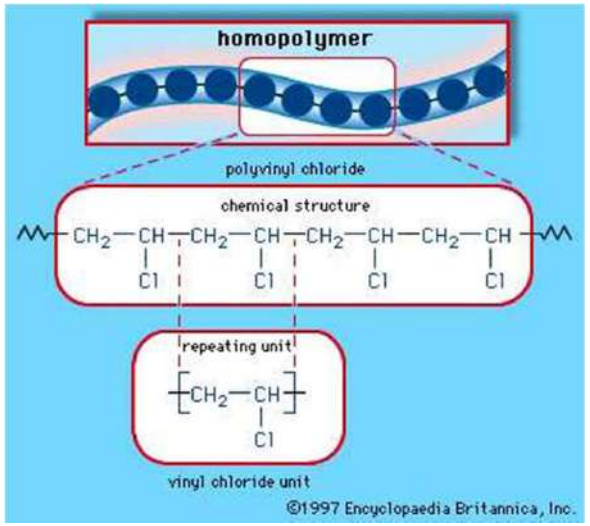
Polymeric prodrug

Lec. 5

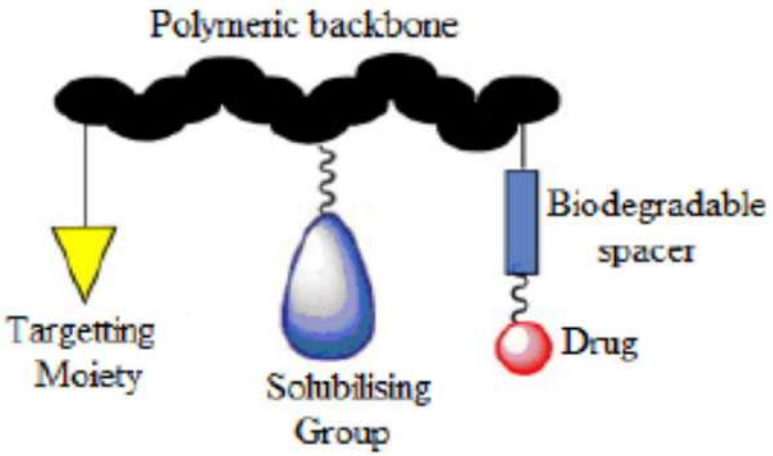
Polymeric prodrug

- Polymeric prodrug: A conjugation of a drug with a polymer
- Polymer: a large molecule consisting of a number of *repeating units*, with molecular weight typically several thousand or higher
- repeat unit - the fundamental *recurring* unit of a polymer
- monomer - the *smaller molecule*(s) that are used to prepare a polymer (may or may not be equivalent to the repeat unit)

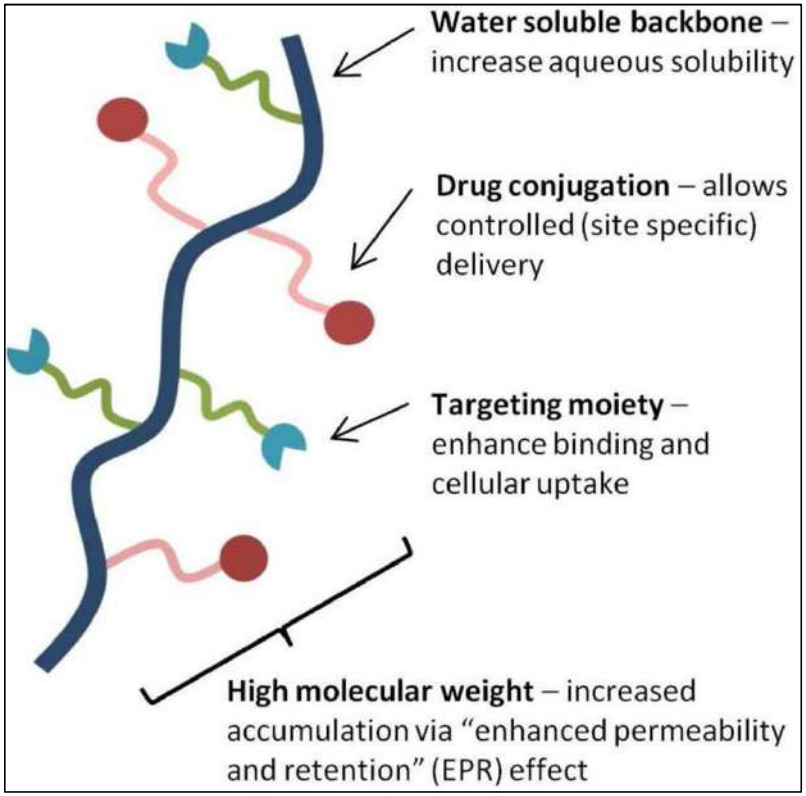


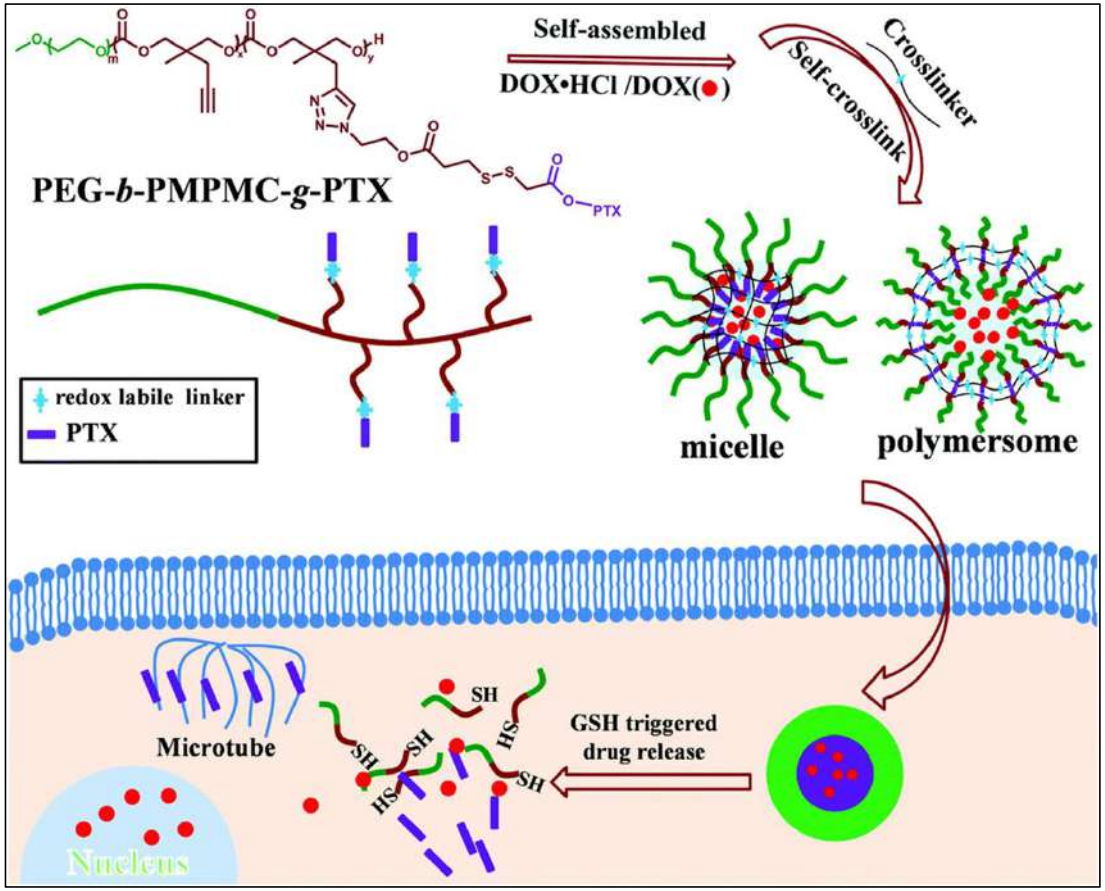
Polymeric prodrug

- Altering and controlling the pharmacokinetics, biodistribution, and often the toxicity of various drugs.
- The proposed model consists mainly of five components: the polymeric backbone, the drug, the spacer, the targeting group and the solubilizing agent.



Polymeric prodrug



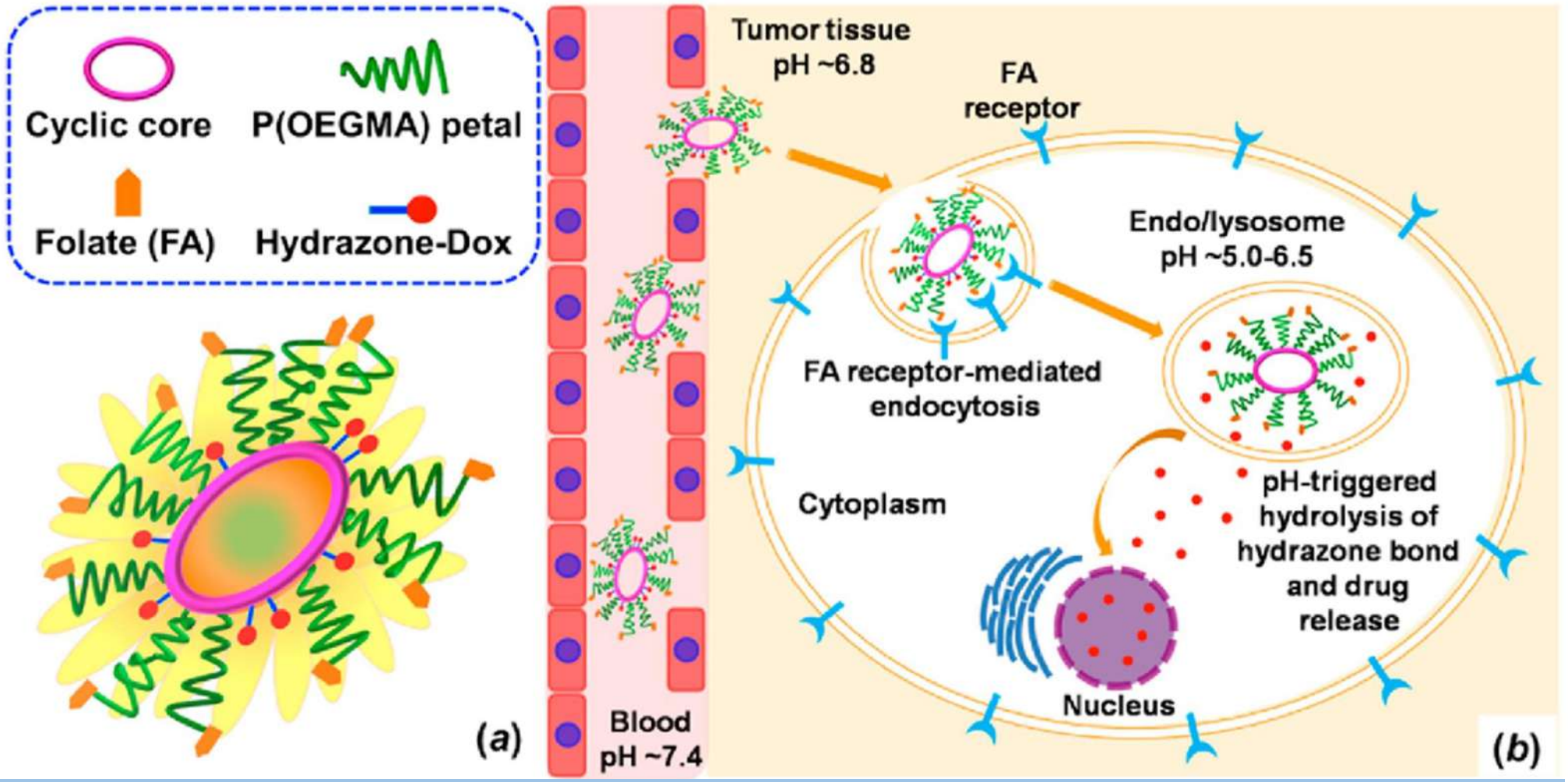


Polymeric prodrug

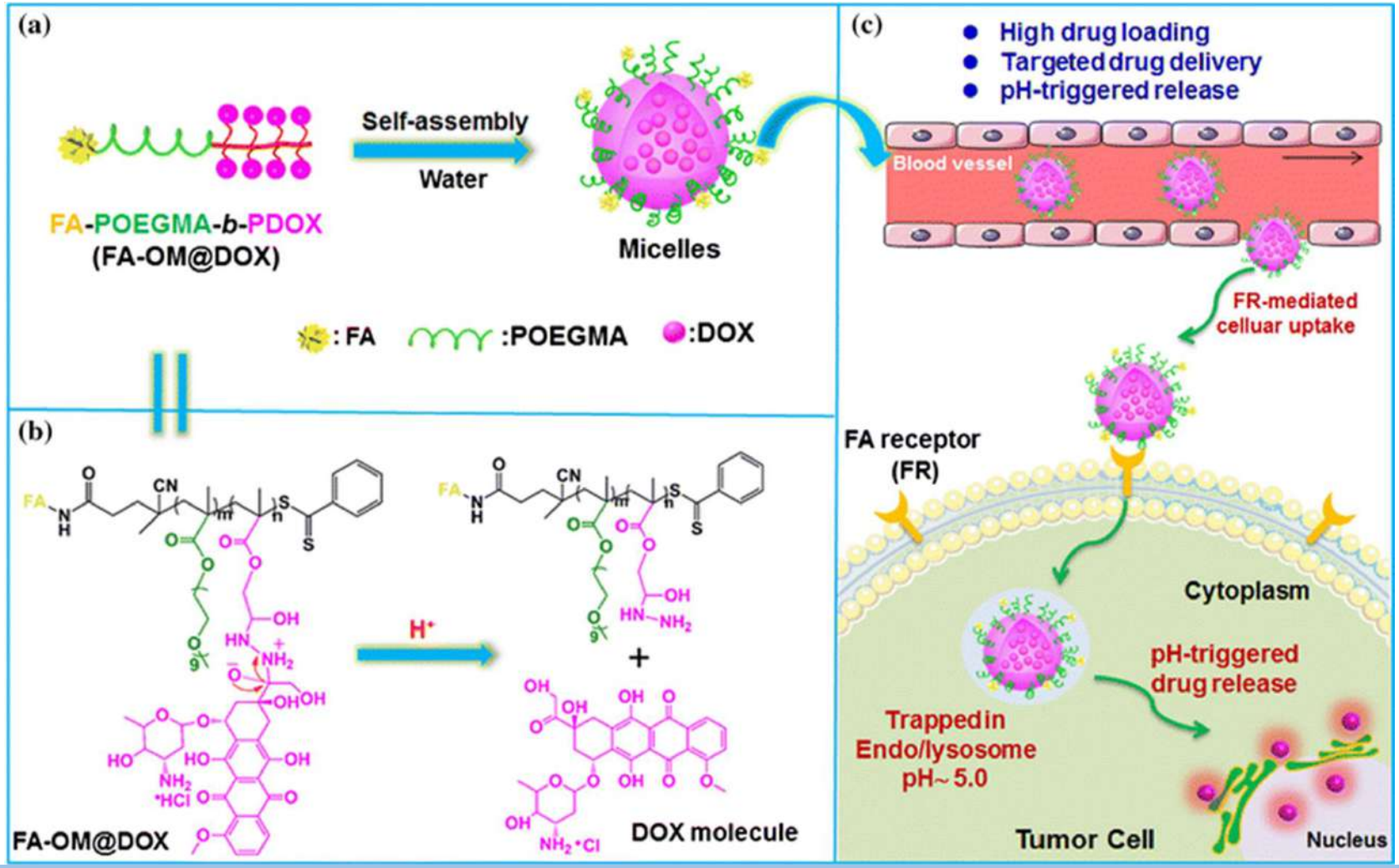
- The polymeric carrier can be either an inert or a biodegradable polymer.
- The role of spacer is to control the site and the rate of release of the active drug from the conjugate by hydrolytic or enzymatic cleavage.
- The drug must be covalently bonded to the polymer and must remain attached to it until the macromolecule reaches the desired site of action.
- The choice of drug for use in this system is based on three criteria.
  - First, only potent drug can be used because there is restriction on the amount of drug that can be administered.
  - Second, the drug should have a functional group by which it can bind with the polymer backbone directly or by means of spacer molecule.
  - Third, the drug must be sufficiently stable and should not be excreted in this conjugate form until it is released at the desired site.

Polymeric prodrug

- The targeting moiety or homing device guide the entire drug-polymer conjugate to the targeted tissue.
- The targeting ability of the delivery system depends on the several variables including:
  - receptor expression;
  - ligands internalization;
  - choice of antibody, antibody fragments or non-antibody ligands;
  - and binding affinity of the ligand.



Polymeric prodrug



Polymeric prodrug

Advantages of Polymeric Prodrugs

1. Prolongation of drug action

   conjugation results in a slower renal excretion, longer blood circulation and an endocytotic cell uptake.

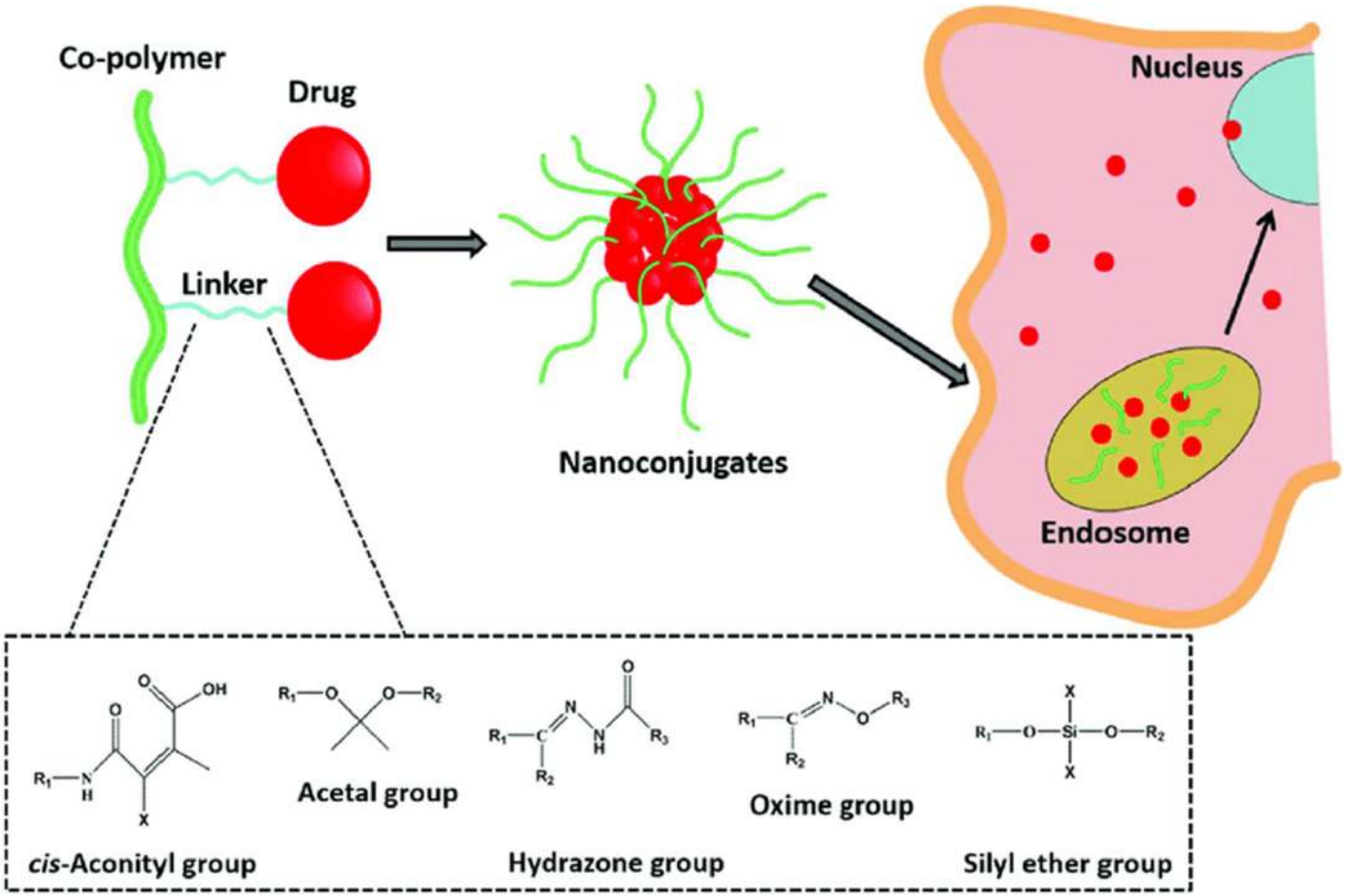
2. Controlled drug release

   achieved by proper selection of linkage between drug and polymeric carrier.

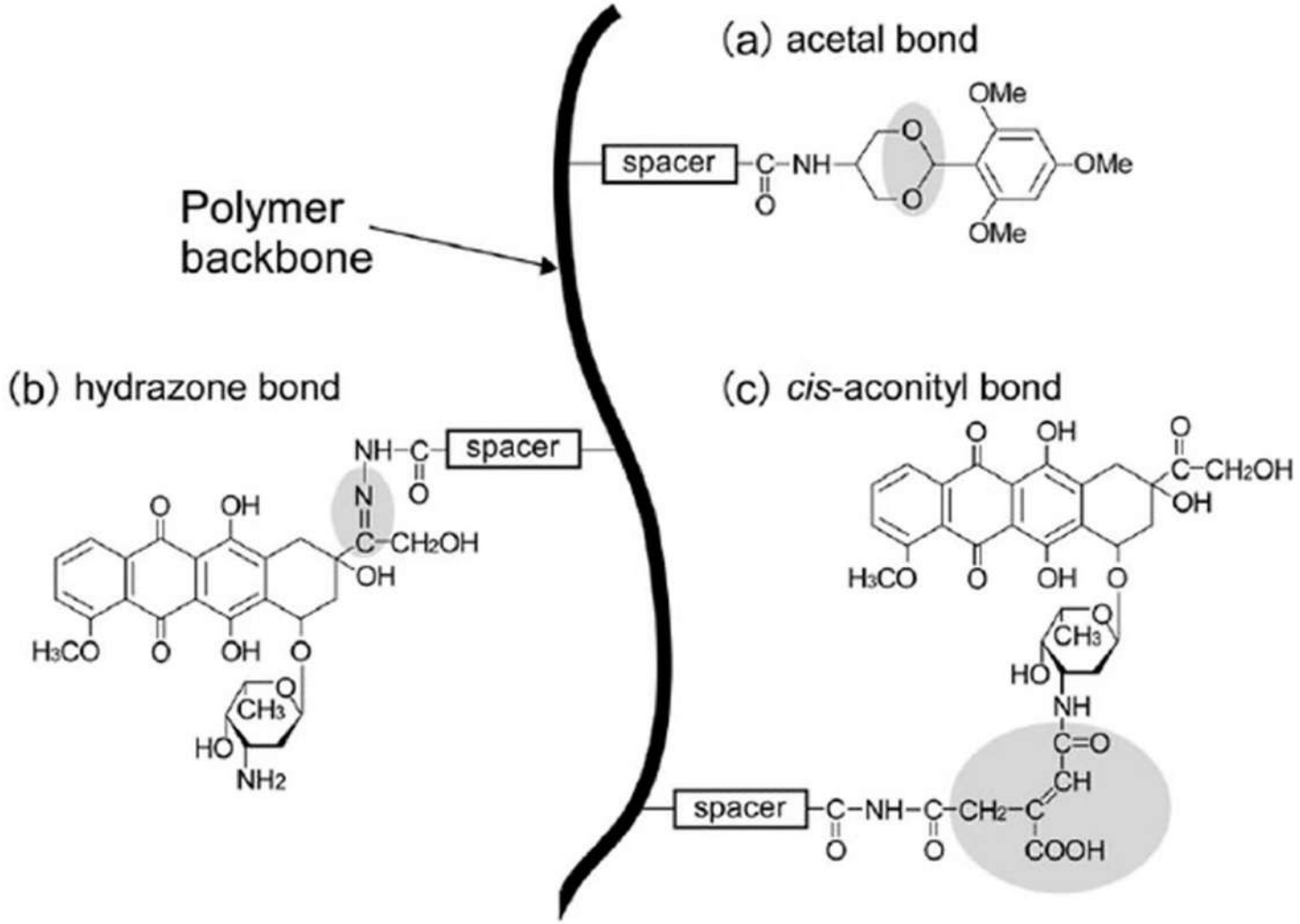
   a. pH controlled drug release: drug is released intracellularly in the lysosomes or tumour tissue which are slightly acidic in comparison to the healthy tissues.

      - pH-sensitive linkers (acid-labile linkers), are a class of chemically cleavable linkers that were first used in early ADC developments.
      - Hydrazonesand cis-Aconityl is among the most widely used pH-sensitive linkers.

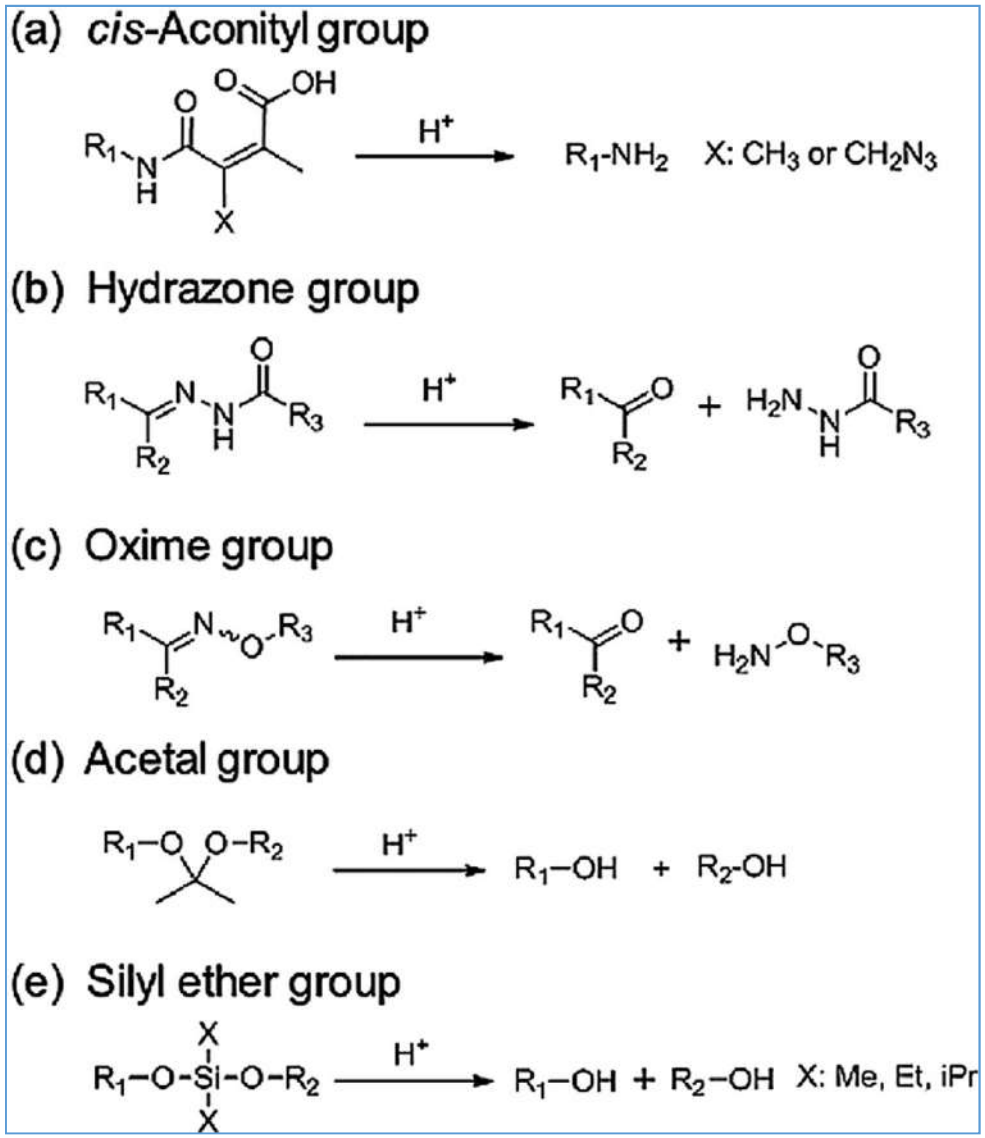
pH controlled drug release:

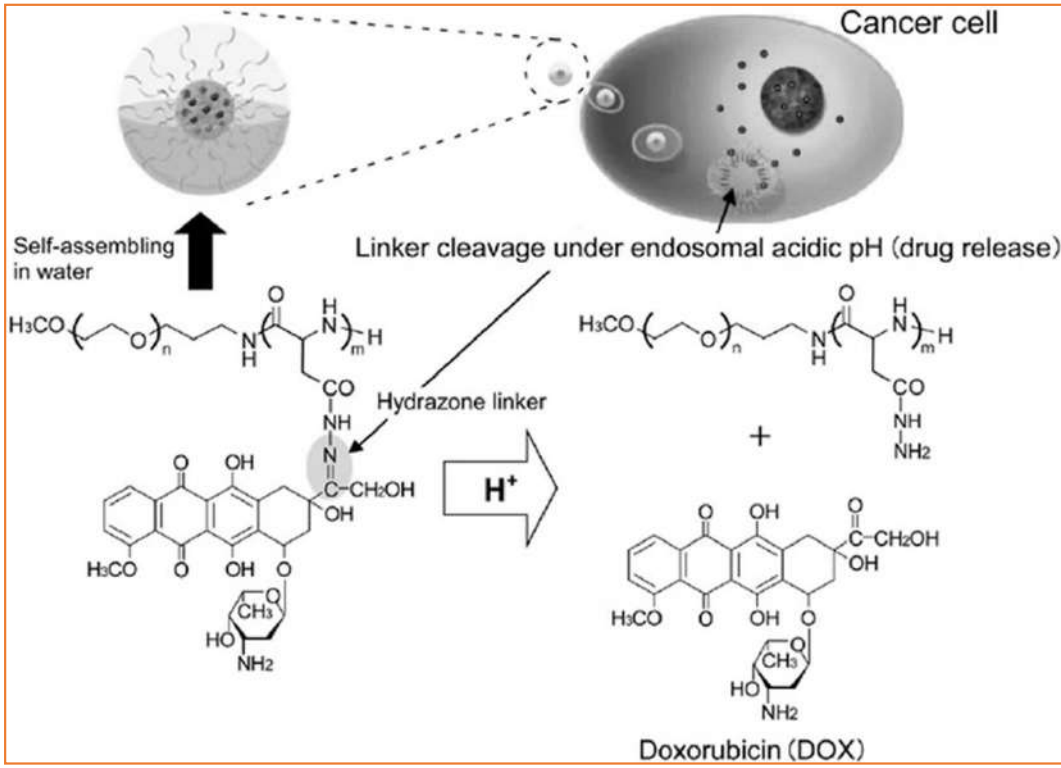


pH controlled drug release:



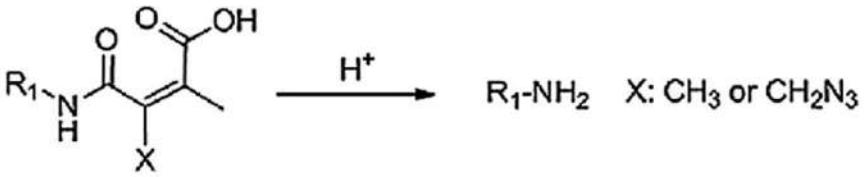
pH controlled drug release:



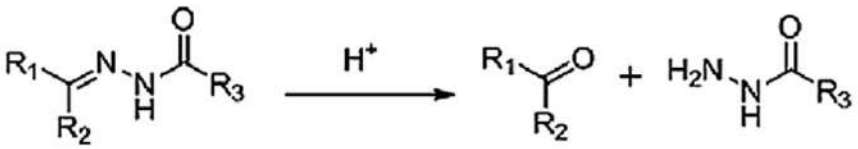


pH controlled drug release:

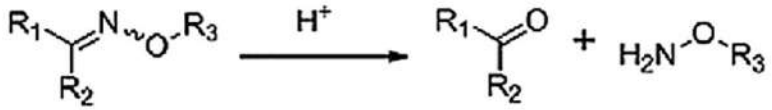
(a) *cis*-Aconityl group



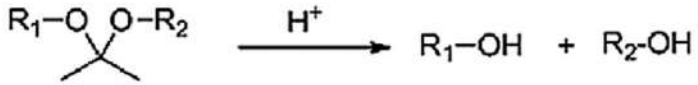
(b) Hydrazone group



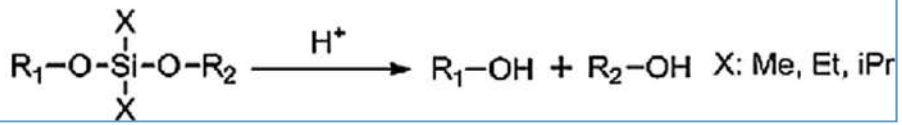
(c) Oxime group

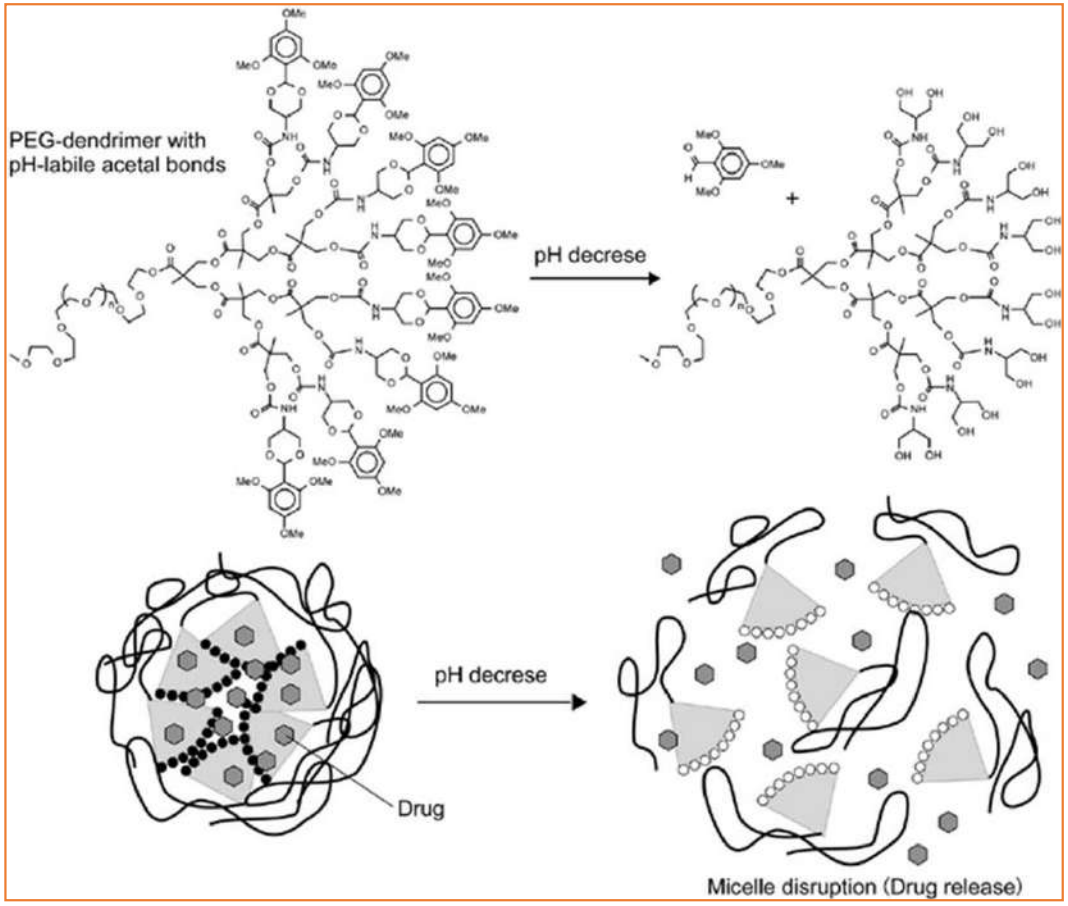


(d) Acetal group



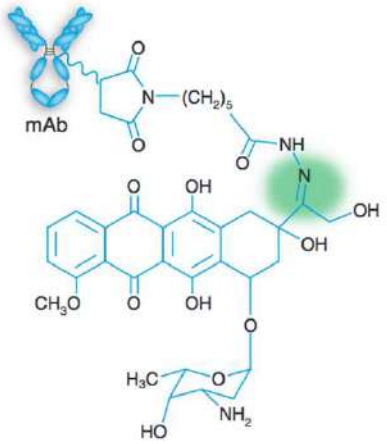
(e) Silyl ether group



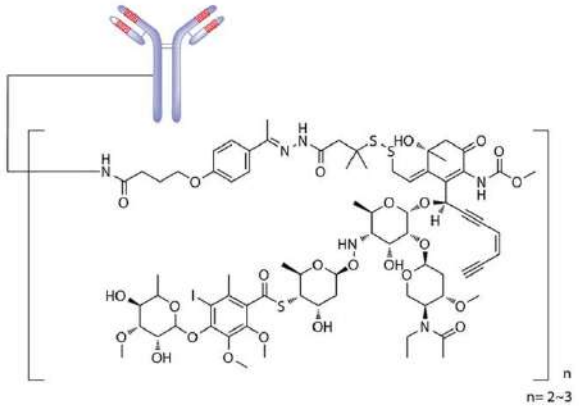


pH controlled drug release:

- pH-sensitive linkers exert a straight-forward mechanism for payload release.
- By design, they retain intact and stable during systemic circulation in the blood's neutral pH environment (pH 7.3-7.5).
- Once internalized, upon sensing of the mildly acidic pH of the endosomal (pH 5.0-6.5) or lysosomal (pH 4.5-5.0) compartments of the cell, the pH-sensitive linkers undergo rapid hydrolysis and thus release the payload drug.



mAb-Doxorubicin



mAb-Calicheamycin

Advantages of Polymeric Prodrugs

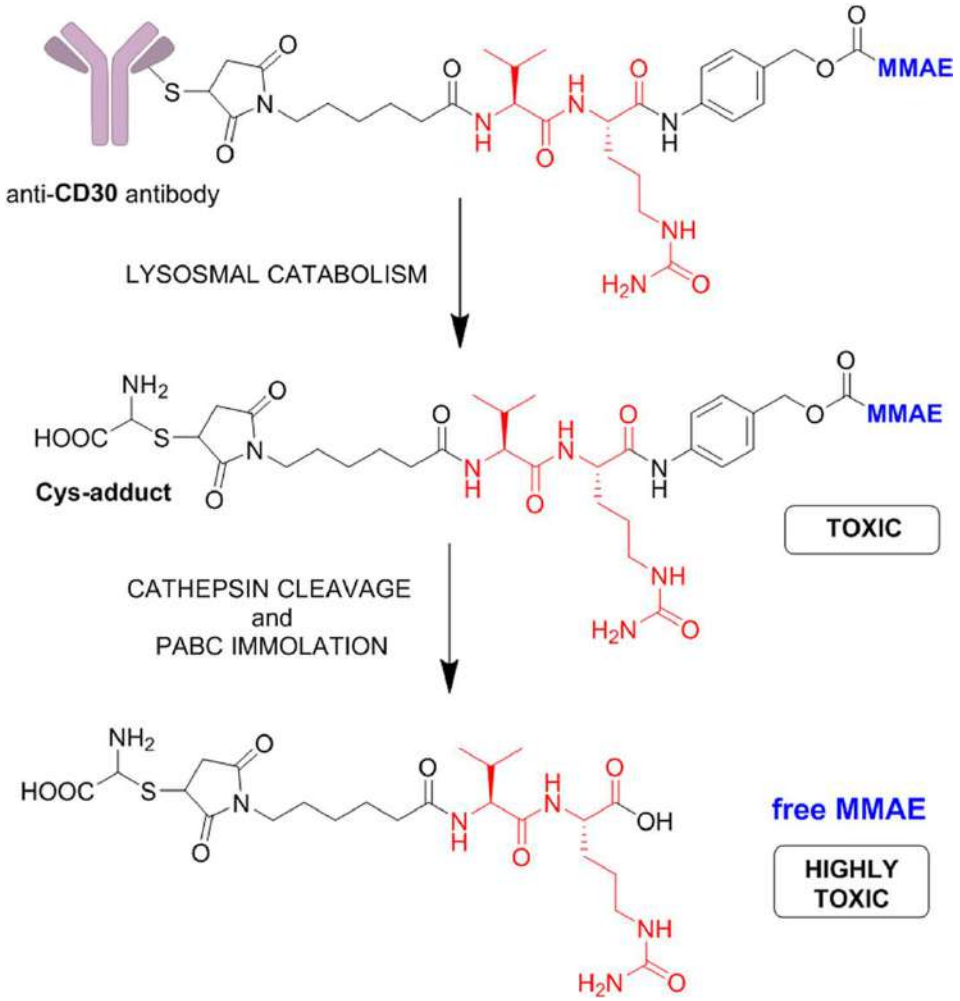
2. Controlled drug release

achieved by proper selection of linkage between drug and polymeric carrier.

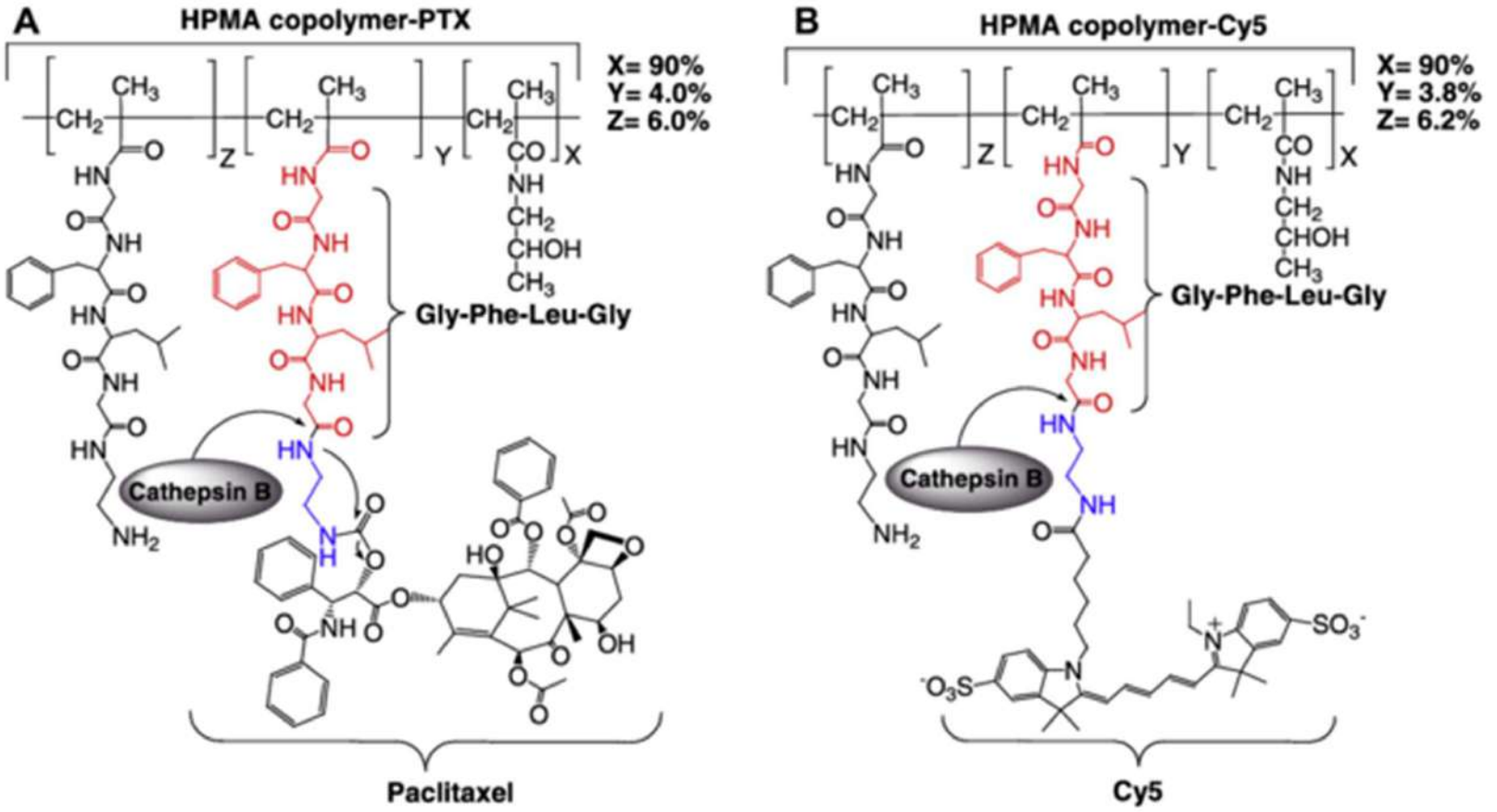
a. pH controlled drug release: drug is released intracellularly in the lysosomes or tumour tissue which are slightly acidic in comparison to the healthy tissues.

b. Enzymes for drug release: When the polymeric prodrug is up taken intracellularly, it enters the lysosomes which are present in normal as well as tumor tissues. lysosomal enzymes such as cathepsins and metalloproteinases release the macromolecular drug.

Cathepsin B controlled drug release:



Cathepsin B controlled drug release:



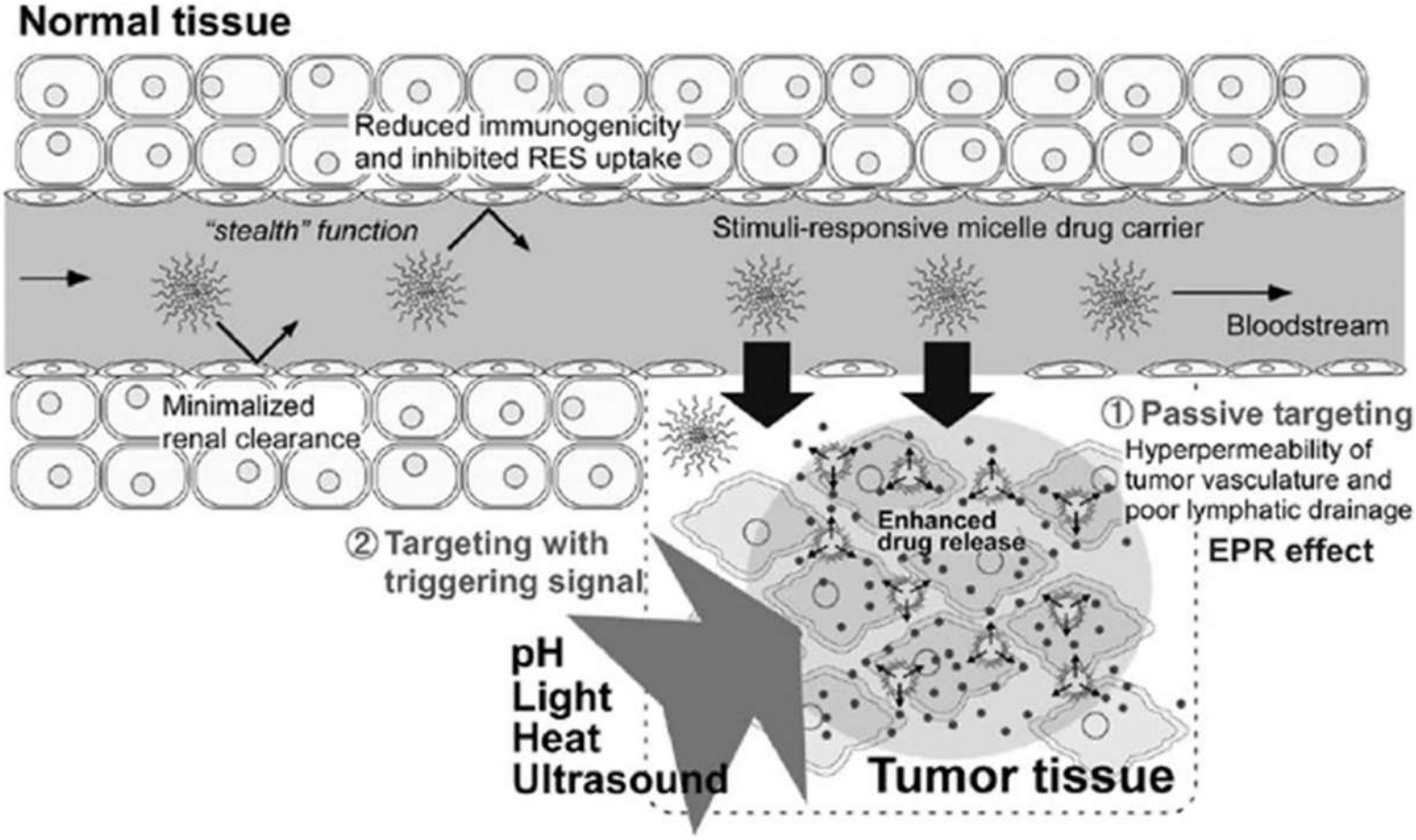
Advantages of Polymeric Prodrugs

3. Enhanced permeability and retention effect

- The polymeric prodrugs are taken up by solid tumors by pinocytosis and this passive tumor uptake increases the targeting of drug due to their characteristic feature of enhanced permeability and retention effect.

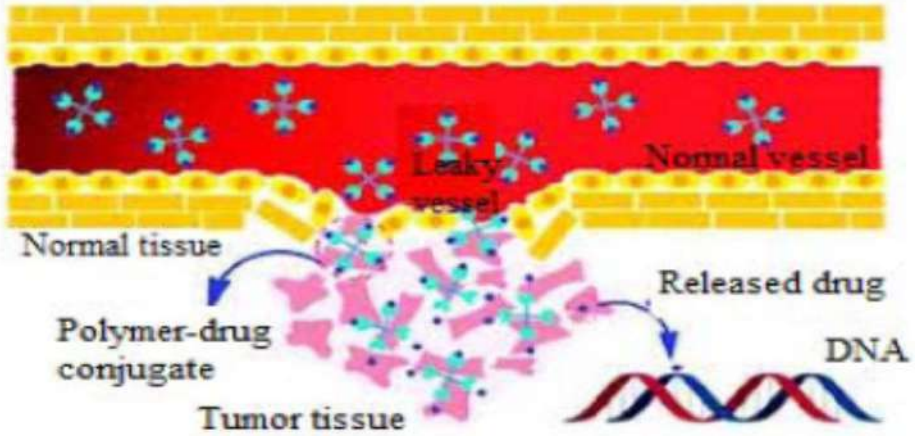
- This effect is due to increased tumor vascular permeability and poor tissue drainage from the tumor cells which increase the duration of action and targeting of the macromolecular drug.

Advantages of Polymeric Prodrugs



Advantages of Polymeric Prodrugs

- The tumor cells contain permeability enhancing factors such as vascular endothelial growth factor (VEGF), bradykinin etc., which increase the permeability of polymeric prodrugs towards tumor tissue and also, lack of effective lymphatic drainage from the tumor tissue increases its retention.



Advantages of Polymeric Prodrugs

4. Active targeting by Polymeric prodrug

   i. Monoclonal antibodies

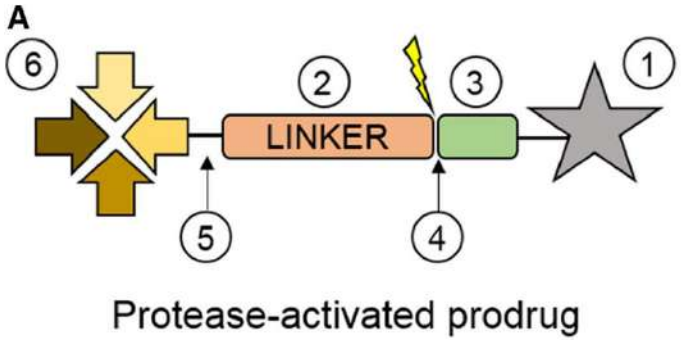
The monoclonal antibodies can be used as targeting group for coupling with the drug to increase the specific targeting of the prodrug on the tumor cells.

These antibodies bind very specifically to tumor cells and this approach has been successfully used in cancer therapy. For example

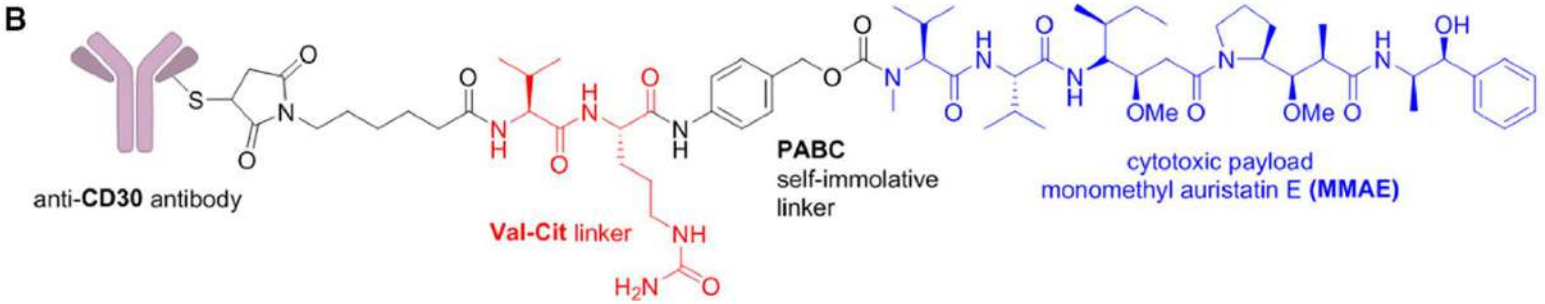
a) Conjugate of plant toxins and antibodies, referred as immunotoxin is a very potent antitumor therapy.

b) Tumor selective monoclonal antibody is covalently attached to an enzyme which converts non toxic prodrug into potent cytotoxic drug after specific targeting at the tumor site. This approach minimizes non specific toxicity.

Monoclonal antibodies Active targeting



1. Drug (payload, cargo) - a cytotoxic agent that kills (cancer) cells
2. Linker - a peptide which is specifically hydrolyzed by target protease
3. Self-immolative linker - allows to release free drug from a conjuagte
4. Protease cleavage site
5. Linker-targeting moiety attachment site
6. Targeting moiety (antibody, tumor-homing peptide)

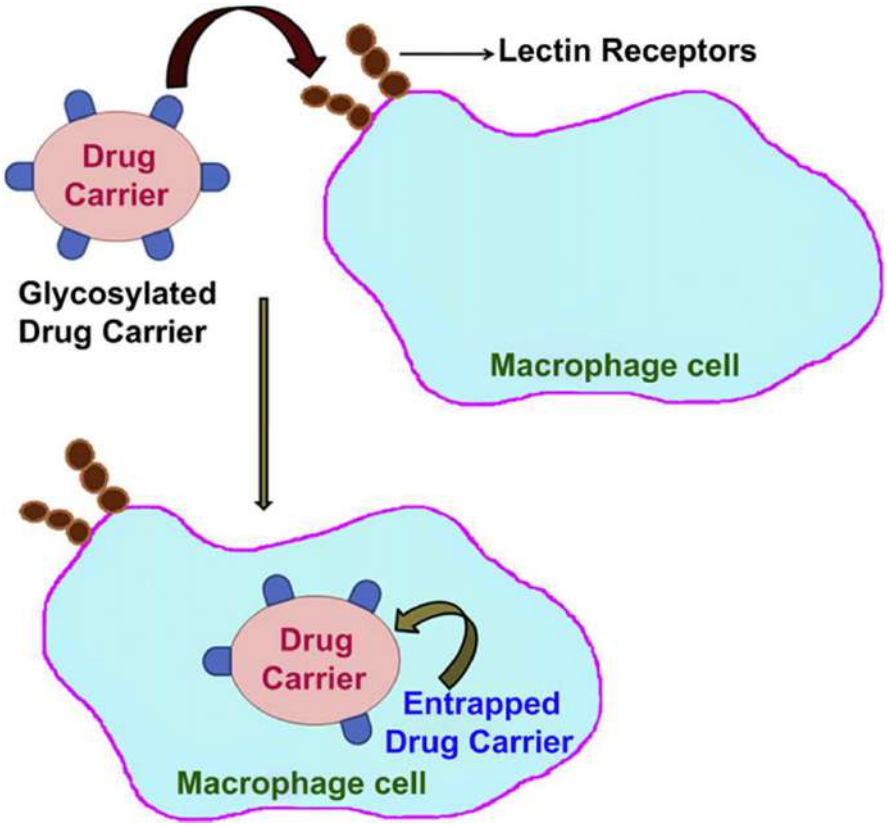


Advantages of Polymeric Prodrugs

ii. Lectins

- The sugar specific receptors present on the plasma membrane are called lectins and they have been characterized mainly on hepatocytes.
- Galactose specifically targets these lectins and this targeting seems to be an attractive approach for target specific drug delivery especially for treatment of liver diseases such as hepatitis, parasitic infections and liver metastasis.
- Drug delivery to macrophages (e.g. Kupffer cells) can be employed for targeted treatment of various malfunctions such as leishmaniasis, Gaucher's syndrome etc.

Lectins Active targeting



Advantages of Polymeric Prodrugs

iii. Angiogenic vessels of tumor cells

- The endothelial cells in angiogenic vessels of tumors show increased expression of cell surface proteins.
- These proteins include receptors for vascular endothelial growth factor (VEGF) and integrin receptors.
- The peptides which specifically bind to these receptors can be used as targeting moiety for drug delivery such as RGD (arginine-glycine-aspartic acid) containing peptides that specifically bind with integrin receptors.
- The conjugation of RGD peptides and poly(ethylene glycol) (PEG) showed increased efficacy of drug against breast cancer.

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

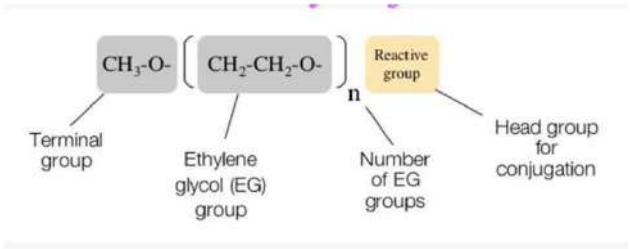
1. Polyethylene glycol (PEG)

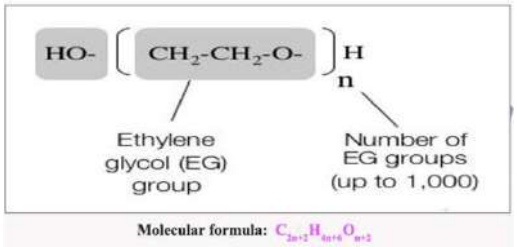
- is a polyether compound with many applications from industrial manufacturing to medicine.
- The structure of PEG is $H\text{-}(O\text{-}CH_2\text{-}CH_2)_n\text{-}OH$.
- It is available over a wide range of molecular weights from 300 g/mol to 10,000,000 g/mol.
- PEG is known to be nontoxic and nonimmunogenic.
- 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)

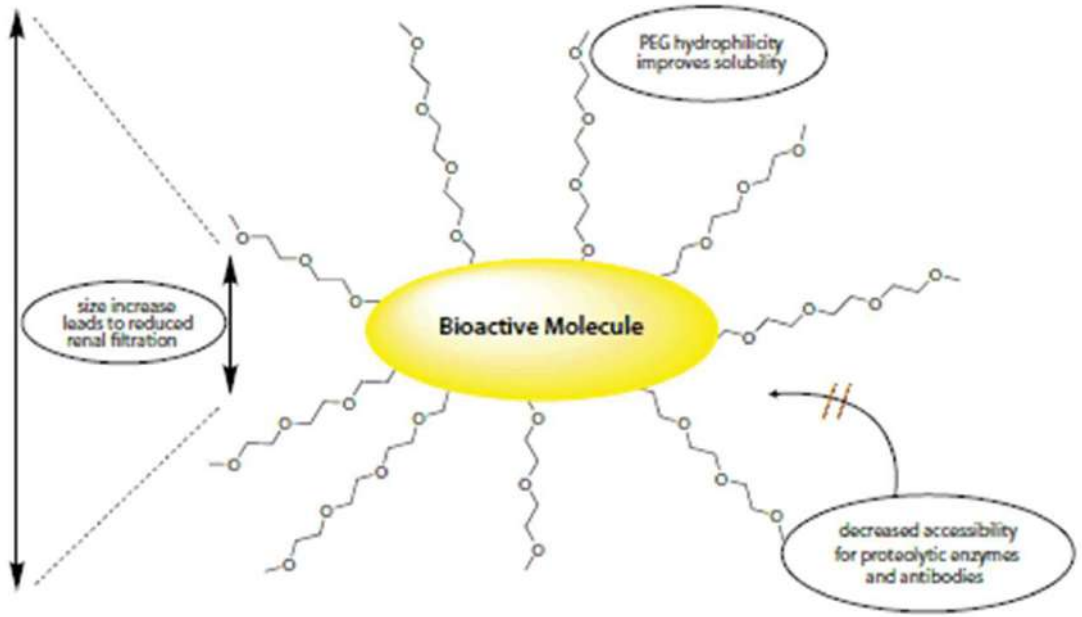
- PEG can be prepared with a single reactive group at one terminal end, and this aids site-specific conjugation to a drug and avoids cross linking during conjugation.





- 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)

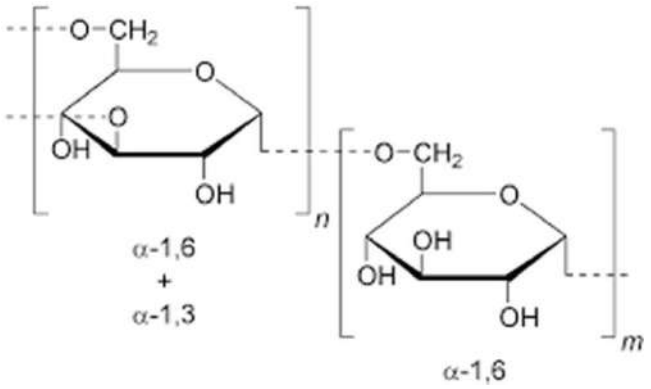


Classification of Polymers Used for Bioconjugation

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.

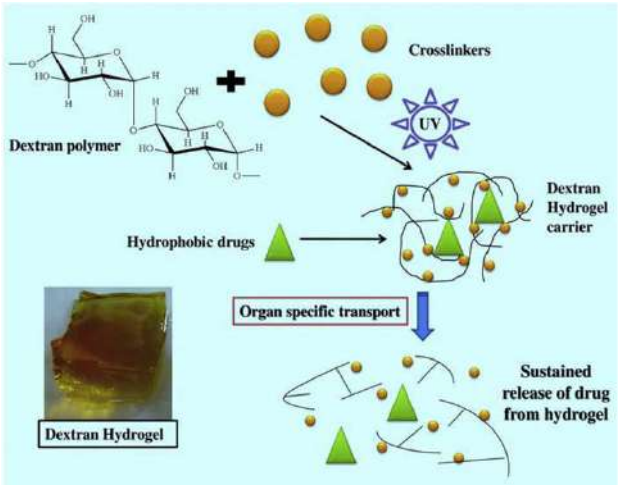


Classification of Polymers Used for Bioconjugation

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.



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: