Organic Pharmaceutical Chemistry IV

Lec4: Chemical Drug Delivery Systems: Strategies and Applications

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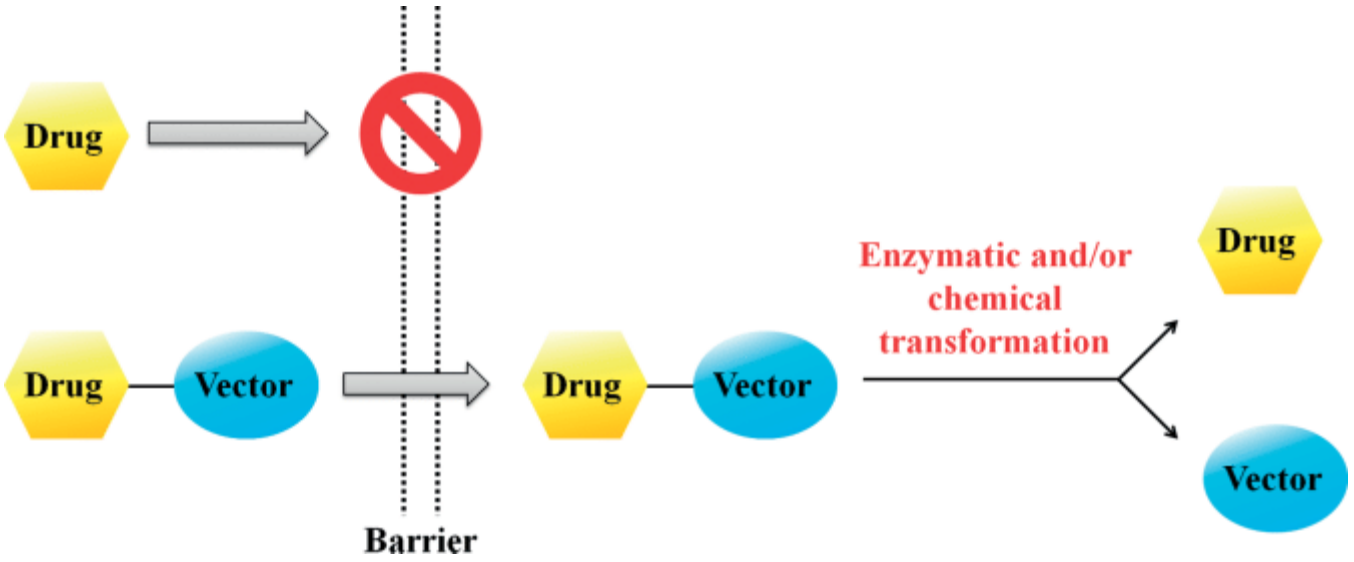


Chemical Drug Delivery Systems: ***Strategies and Applications***

- Despite the considerable progress of the last century, rational drug design that allows the development of effective pharmaceutical agents with minimal side effects remains an elusive goal.

Chemical Drug Delivery Systems: ***Strategies and Applications***

- Many therapeutic drugs have undesirable properties that may become pharmacological, pharmaceutical or pharmacokinetic barriers in clinical drug applications.

Chemical Drug Delivery Systems: ***Strategies and Applications***

- Among the various approaches to minimize the undesirable drug properties, the chemical modulation using drug derivatization offers high flexibility and has been demonstrated as an important means of improving drug efficacy.

Polymeric Prodrugs

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

Polymeric Prodrugs

- Conventional drug delivery systems used frequently are:
  - Tablets.
  - Capsules. Pills.
  - Suppositories.
  - Creams.
  - Ointments.
  - Liquids.
  - Aerosols.
  - Injectables.
  -

Polymeric Prodrugs

- The mentioned drug delivery systems, as drug carriers, have a number of non-specific administrations of a drug and thus may have contraindications such as variable drug concentrations and excessive drug presence also in healthy tissues, with toxic and side effects.

Polymeric Prodrugs

- Frequent high doses are often needed because of the drug's unfavorable physical and chemical properties, such as short biological half-life, excessive or insufficient water-solubility, which restricts drug bioavailability, and also because of low drug specificity towards the affected organs.

Polymeric Prodrugs

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

Polymeric Prodrugs

- These approaches are based on the preparation of more favorable genetic variants or on tailor-made formulations of the drug, as liposomal preparations, controlled release systems, covalent modifications of the drug by low molecular weight reagent or by polymer conjugation.

Polymeric Prodrugs

- The last one is a fast growing technique that already produced several molecules which are available in the market (shown in the next slide).

S. No.	Conjugate	Indication	Marketing year	Company
1	PEG–adenosine deaminase (Adagen)	SCID syndrome	1990	Enzon
2	PEG–asparaginase (Oncaspar)	Acute lymphoblastic leukaemia	1994	Enzon
3	SMANCS (Zinostatin, Stimalamer)	Hepatocellular carcinoma	1993	Yamanouchi Pharmaceutical
4	Linear PEG–interferon α2b (PEG–Intron)	Hepatitis C, clinical evaluation on cancer, multiple sclerosis and HIV/AIDS	2000	Schering Plough/Enzon
5	Branched PEG–interferon a2a (Pegasys)	Hepatitis C	2002	Roche/Nektar
6	PEG–growth hormone receptor antagonist	Acromegaly	2002	Pfizer (Phamacia)
7	PEG–G-CSF (Pegfilgrastim, Neulasta)	Prevention of neutropenia associated with cancer chemotherapy	2002	Amgen
8	Branched PEG–anti-VEGF aptamer	Age-related macular degeneration	2004	EyeTech Pharmaceuticals (now OSI Pharmaceutical)/Pfizer
9	PEG–anti-TNF Fab	Rheumatoid arthritis and Crohn's disease	2008	UCB (formerly Celltech)

Polymeric Prodrugs

- During the past two decades, scientists have focused their attention on developing site specific drug delivery systems and various polymers have shown promising results in this area.
- A conjugation of a drug with a polymer forms so-called ‘polymeric prodrug’.

Polymeric Prodrugs

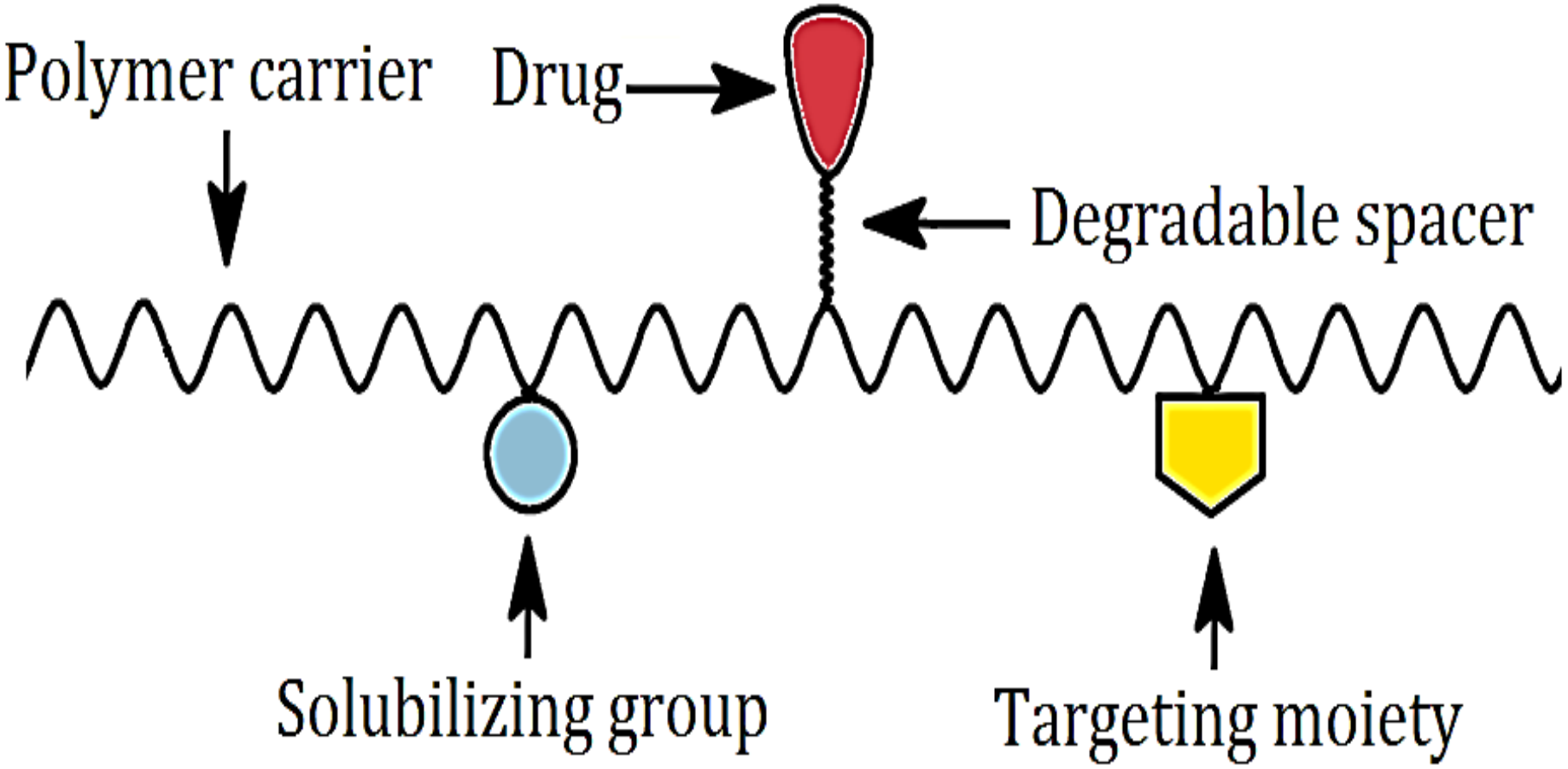
- A prodrug is a form of a drug that remains inactive during its delivery to the site of action and is activated by the specific conditions in the targeted site.
- In other words, a prodrug is an inactive precursor of a drug.

Polymeric Prodrugs

- Polymer materials were designed and proposed as matrices or depot systems for injectable or implantable systems or devices.
- The proposed model consists mainly of five components:

1. ***The polymeric backbone.***
2. ***The drug.***
3. ***The spacer.***
4. ***The targeting group.***
5. ***The solubilizing agent.***

Ringsdorf's model of polymeric prodrug



Ringsdorf's model of 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.

Ringsdorf's model of polymeric prodrug.

- The drug must be covalently bonded to the polymer and must remain attached to it until the macromolecule reaches the desired site of action.

Ringsdorf's model of polymeric prodrug.

- The choice of drug for use in this system is based on three criteria:

1. *First, only potent drug can be used because there is restriction on the amount of drug that can be administered.*
2. *Second, the drug should have a functional group by which it can bind with the polymer backbone directly or by means of spacer molecule.*
3. *Third, the prodrug must be sufficiently stable and should not be excreted in this conjugate form until it is released at the desired site.*

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 drugs which have slow renal elimination and are metabolically inactive have prolonged duration of action.

Prolongation of drug action

- The duration of action can be prolonged by linking a drug to a polymer in order to obtain a conjugate.
- <u>This conjugation results in a/an:</u>
  - *i. Slower renal excretion*
  - *ii. Longer blood circulation and*
  - *iii. Endocytotic cell uptake.*

Controlled drug release

- The polymeric prodrug formed by conjugation of drug with polymeric carrier should be:
  - *Stable in circulation.*
  - *Able to release the macromolecular drug intracellularly or intratumorally for therapeutic effect.*

Controlled drug release

- This controlled release from polymeric prodrug can only be achieved by proper selection of linkage between drug and polymeric carrier.

pH controlled drug release

- The therapeutic effect is achieved only when the macromolecular drug from the polymeric prodrug is released intracellularly in the lysosomes or tumor tissue which are slightly acidic in comparison to the healthy tissues.

pH controlled drug release

- This relatively low pH has been exploited to design pH sensitive spacers such as N-cis-aconityl spacer used to form polymeric prodrug of daunorubicin-linked aminoethyl polyacrylamide beads and poly (d-lysine) and Hydrazon linkage used to form cytotoxic Adriamycin immunoconjugates.

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.
- In the lysosomes, the polymeric prodrug is acted upon by lysosomal enzymes such as cathepsins and metalloproteinases to release the macromolecular drug.

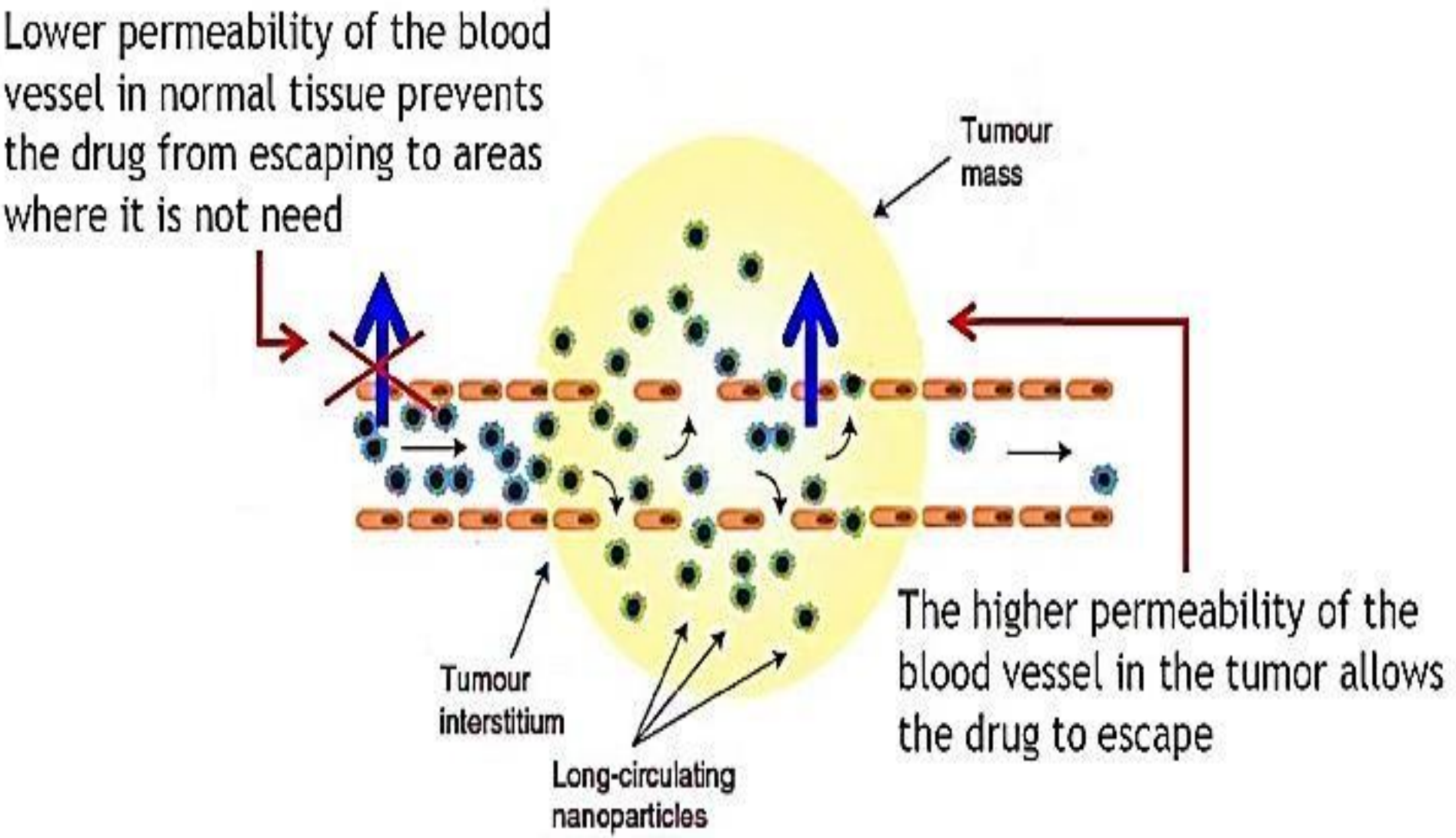
Enzymes for drug release

- The release of cytotoxic drug with the help of these enzymes destroys the tumor tissue.
- Examples of such conjugation include coupling of mescaline with poly (vinylpyrrolidone-coacrylic acid) in order to increase the biological half-life of mescaline and also to achieve the “enhanced permeability and retention” effect.

Enzymes for drug release

- 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 (next slide).

The Enhanced Permeability and Retention (EPR) effect



Pathophysiological factors involved in enhancement of extravasation of macromolecules in solid tumor tissues enhanced EPR effect.