Organic Pharmaceutical Chemistry IV
1st Semester, Year 5 (2016-2017)
Lecture 4

Chemical Delivery Systems (Polymeric Prodrugs)

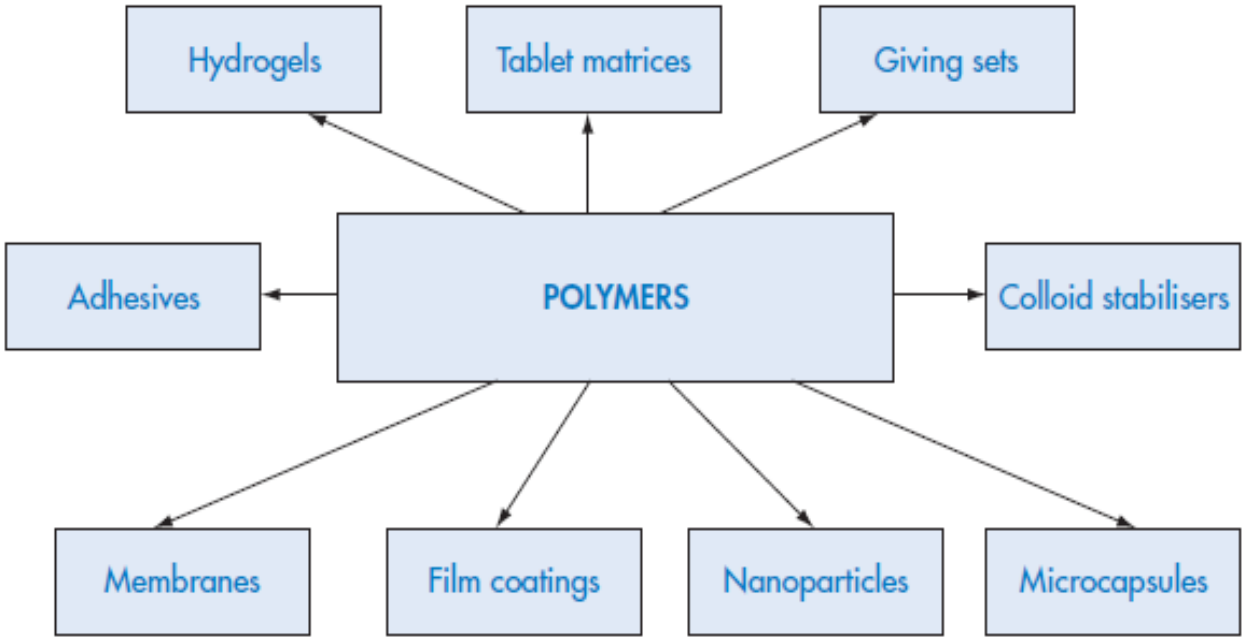
Types and structure of polymers; cross-linking agents and polymeric chemical delivery systems.

Dr Asim A. Balakit
Pharmaceutical Chemistry Dept.,
College of Pharmacy,
Babylon University

Pharmaceutical Polymers:

Polymers are used widely in pharmaceutical systems as:

- Suspending and emulsifying agents
- Flocculating agents
- Adhesives
- Packaging and coating materials
- Controlled and site-specific drug delivery systems



Definitions

Polymers are substances of high molecular weight made up of repeating *monomer* units.

Substances with short chains containing relatively few monomers are called ***oligomers***.

Polymers owe their unique properties to **their size, their three-dimensional shape and sometimes to their asymmetry**.

The **chemical reactivity** of polymers depends on the **chemistry of their monomer units**, but **their properties** depend to a large extent on **the way the monomers are put together**; it is this fact that leads to the versatility of synthetic polymers.

Polymer Architectures

a. Linear Polymers

homopolymer

random copolymer

alternating copolymer

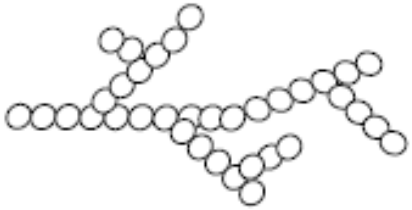
AB-type diblock copolymer

ABA-type triblock copolymer

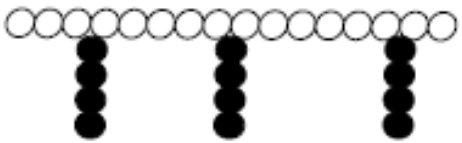
BAB-type triblock copolymer

ABC-type triblock copolymer

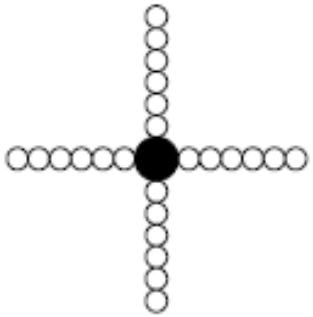
b. Branched polymers



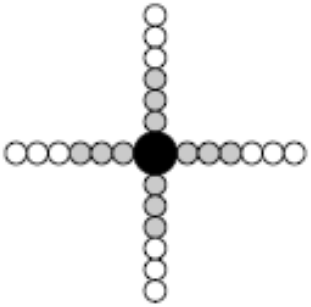
hyperbranched polymer



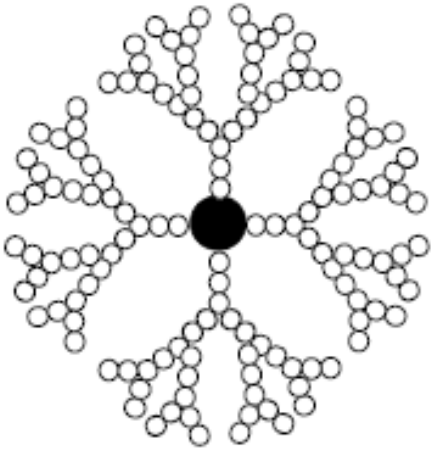
graft copolymer



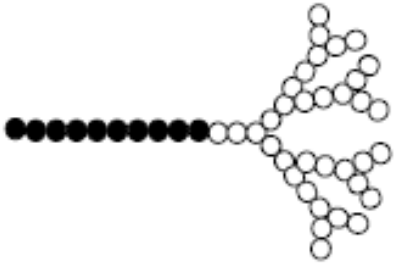
star-shaped polymer



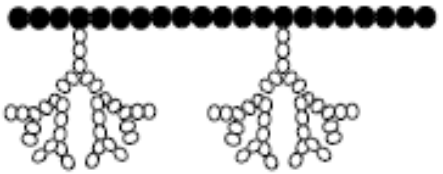
star-shaped block copolymer



dendrimer

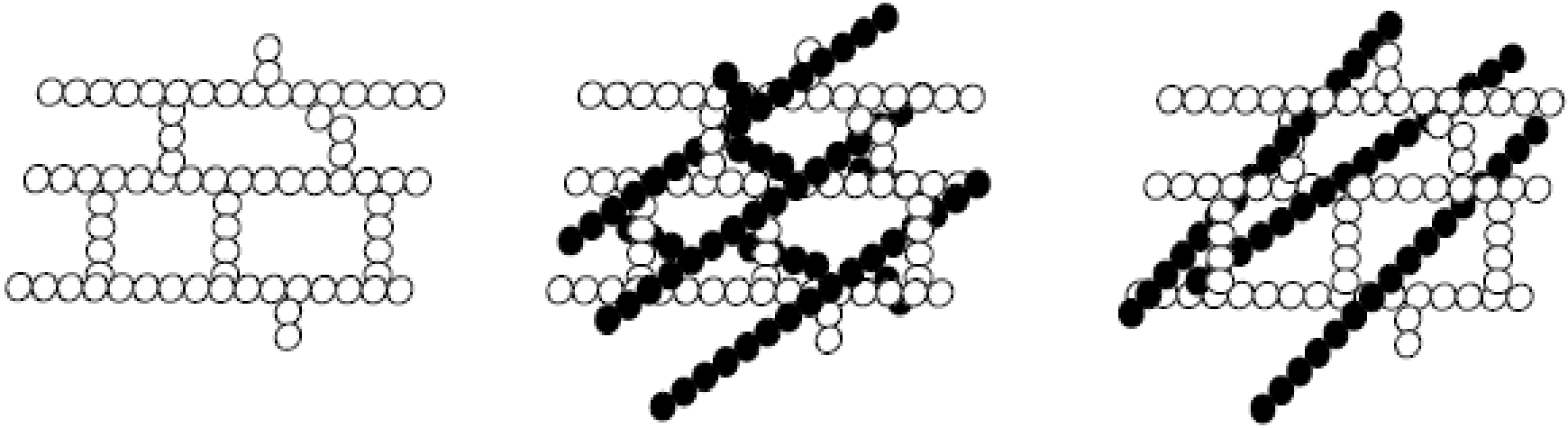


block dendrimer



dendri-graft copolymer

c. Crosslinked polymers

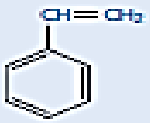
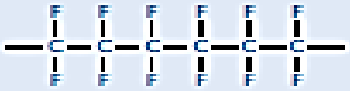
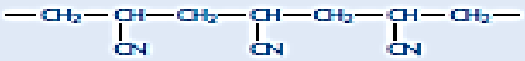
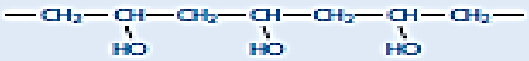
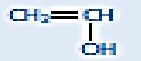
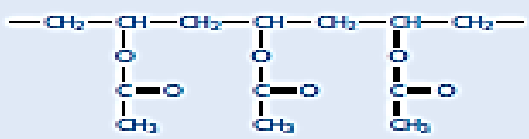
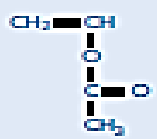
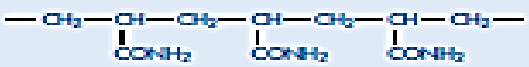
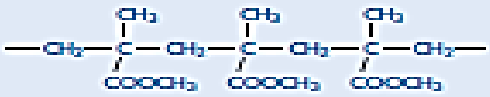
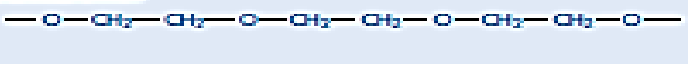
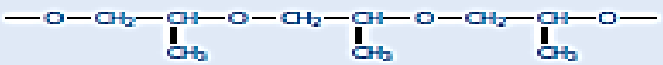
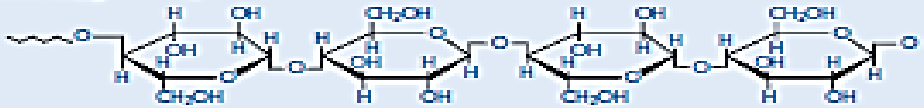
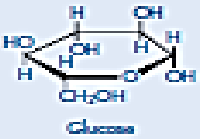


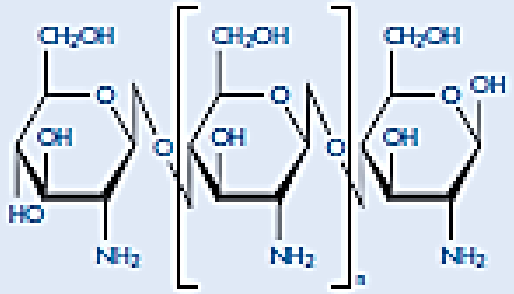
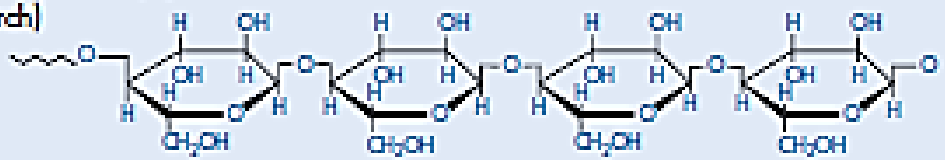
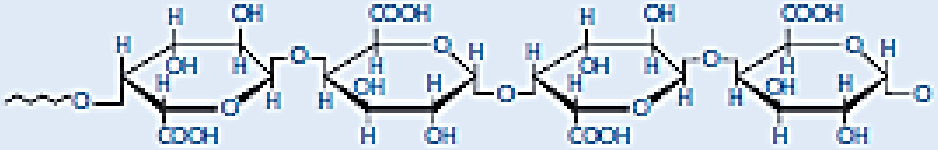
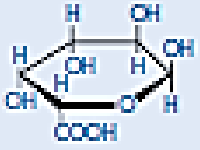
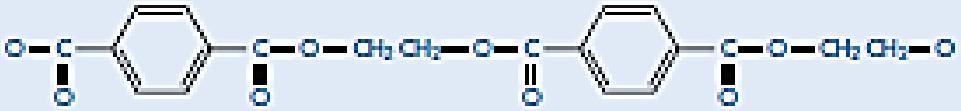
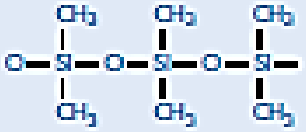
polymer networks

interpenetrating polymer networks (IPN)

semi-IPN

Structural formulae of some macromolecular compounds

Name	Chain structure	Monomer
Polymers with a carbon chain backbone:		
Polyethylene		
Polypropylene		
Polystyrene		
Poly(vinyl chloride)		
Polytetrafluoroethylene		
Polyacrylonitrile		
Poly(vinyl alcohol)		
Poly(vinyl acetate)		
Polyacrylamide		
Poly(methyl methacrylate)		
Polyvinylpyrrolidone		
Polymers with a heterochain backbone:		
Poly(ethylene oxide)		
Poly(propylene oxide)		
Cellulose (polyglucoside, $\beta \rightarrow 1\text{-}4$)		

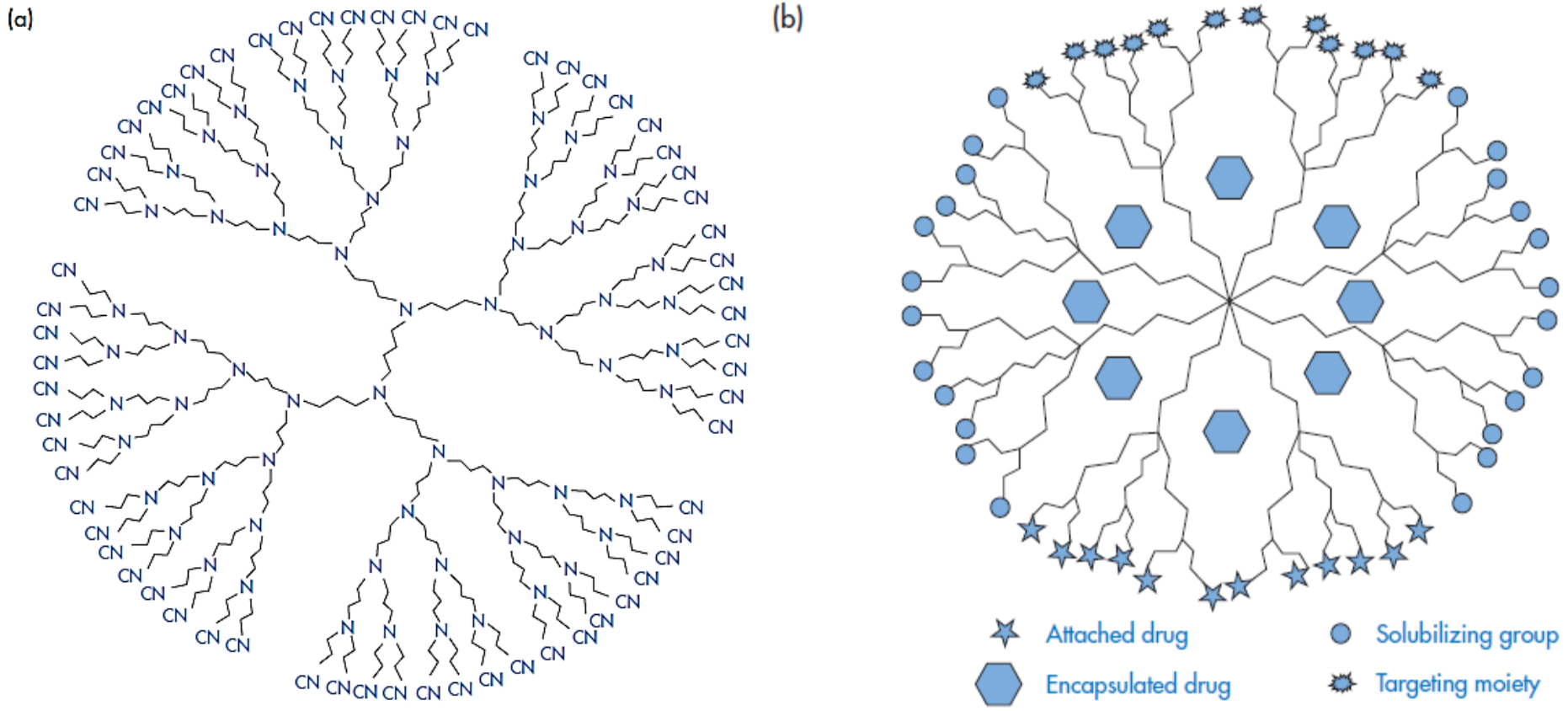
Name	Chain structure	Monomer
Chitosan		
Amylose (polyglucoside, α → 1,4) (component of starch)		Glucose
Pectinic acid (polygalacturonoside, α → 1,4) (jelly-forming component of fruits)		 Galacturonic acid
Polyethylene glycol terephthalate		
Polydimethylsiloxane		

Dendrimers

- Dendrimers are highly branched polymer constructs formed from a central core which defines their initial geometry.

- Their branchlike structure leads to spheres which in higher generations appear to be the size of micelles and ultimately nanospheres of small dimensions.

- They can be functionalised and in this way ‘layered’ systems can be formed by using different monomers for succeeding reactions (generations); such chemical architecture has virtually no bounds. Dendrons are partial dendrimers.



a) A two dimensional view of a dendrimer with 64 cyano functional groups. It is possible to trap small to medium-size molecules in dendrimers which have pores of appropriate dimensions between the branches of the structure.

b) A diagrammatic representation of possible sites for covalent attachment of drugs, solubilising groups and targeting moieties, and encapsulation of drugs.

Some Water-soluble Polymers Used in Pharmacy and Medicine

A- Carboxypolymethylene (Carbomer,Carbopol)

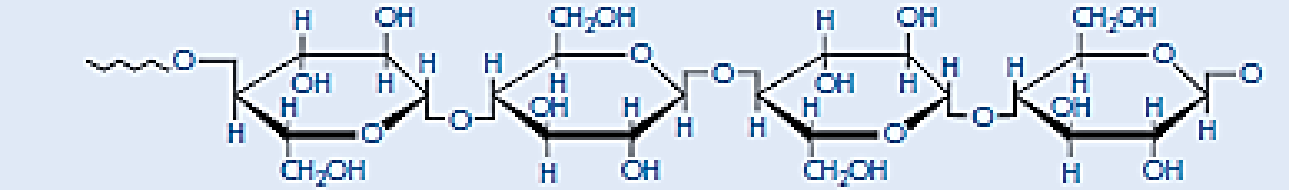
This is used as a suspending agent in pharmaceutical preparations and as a binding agent in tablets, and it is used in the formulation of prolonged-action tablets.

It is a high molecular weight polymer of acrylic acid, containing a high proportion of carboxyl groups.

Its aqueous solutions are acidic; when neutralised the solutions become very viscous with a maximum viscosity between pH 6 and 11. Electrolytes reduce the viscosity of the system and thus high concentrations of the polymer have to be employed in vehicles where ionisable drugs are present.

B- Cellulose Derivatives

Cellulose itself is virtually insoluble in water, but aqueous solubility can be conferred by partial methylation or carboxymethylation.



Ethylcellulose is an ethyl ether of cellulose containing 44–51% of ethoxyl groups.
It is insoluble in water but soluble in chloroform and in alcohol. It is possible to form water-soluble grades with a lower degree of substitution.

Ethylhydroxyethylcellulose is an ether of cellulose with both ethyl and hydroxyethyl substituents attached via ether linkages to the anhydroglucose rings. It swells in water to form a clear viscous colloidal solution. Preparation of solutions of cellulose derivatives requires hydration of the macromolecules, the rate of which is a function of both temperature and pH.

Other cellulose derivatives: *Ethylmethylcellulose, Methylcellulose and Sodium carboxymethylcellulose*

C- Natural Gums and Mucilages

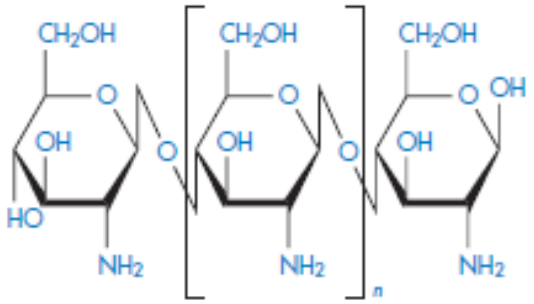
- *Gum arabic* (acacia)
- *Gum tragacanth*
- *Alginates*
- *Pectin*

D- Chitosan

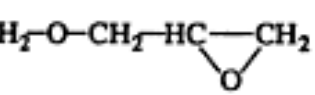
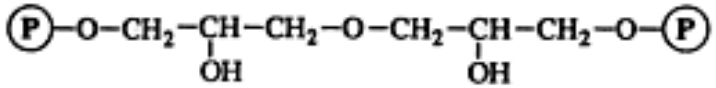
Chitosan is a polymer obtained by the deacetylation of chitin, one of the most abundant polysaccharides.

Chitosan also has film forming abilities and its gel- and matrix forming abilities make it useful for solid dosage forms, such as granules or micro particles.

The molecular weight, crystallinity and degree of deacetylation are all factors that can be varied to control the release rates from chitosan-based granules.



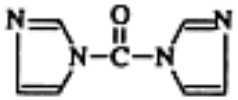
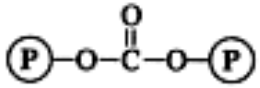
Cross-linking Reagents

1. 2 P–OH +  → 

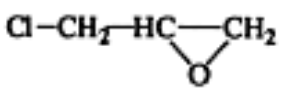
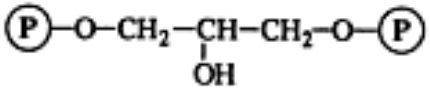
Bis(2,3-epoxy propyl) ether

2. 2 P–OH + $CH_2=CH-SO_2-CH=CH_2$ → P–O–CH_2–CH_2–SO_2–CH_2–CH_2–O–P

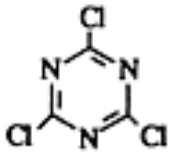
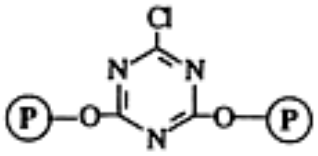
Divinylsulfone

3. 2 P–OH +  → 

Carbonyldiimidazole

4. 2 P–OH +  → 

Epichlorohydrin

5. 2 P–OH +  → 

Cyanuric chloride

6. 

Terephthaloyl chloride

7. 

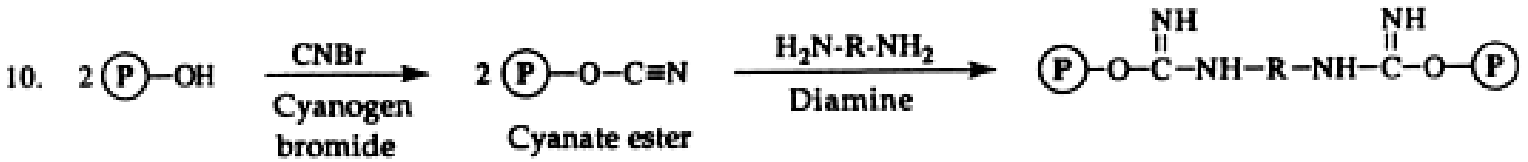
Carbon disulfide

8. 

Formaldehyde

9. 

Glutaraldehyde

10. 

11. 

Dimethylolurea

Prodrugs:

What is the prodrug?!

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.

Prodrug reconversion (i.e. its conversion into its active form) occurs in the body inside a specific organ, tissue or cell. In most cases, normal metabolic processes such as the cleavage of a bond between a polymer and a drug by specific cellular enzymes are utilized to achieve prodrug reconversion.

Polymeric Prodrugs:

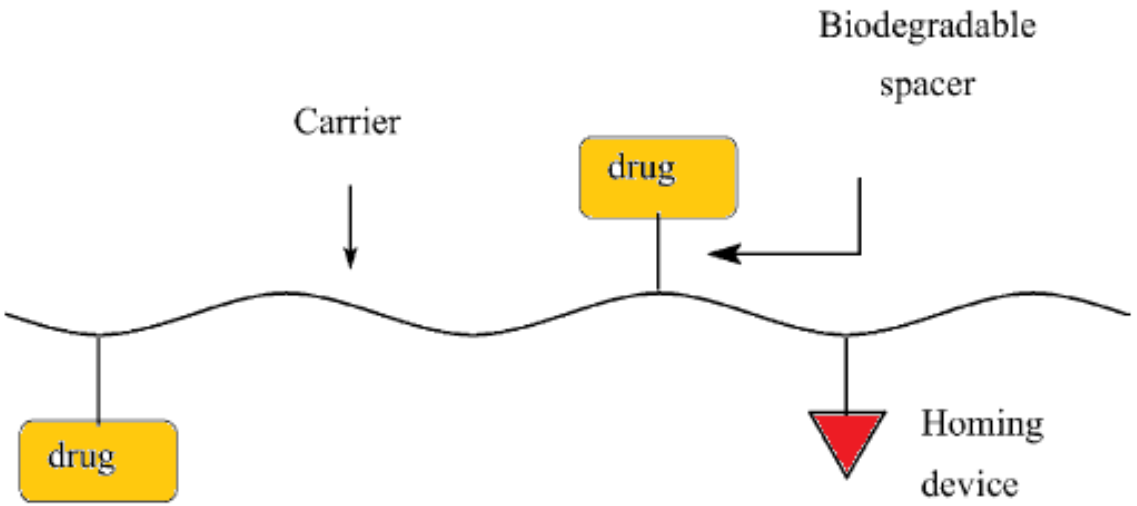
Polymeric prodrug is a kind of prodrugs which is produced by the conjugation of the drug with a polymer, so they are also called **polymeric conjugates** of conventional drugs.

It was already early in the 1950s and 1960s that polymer chemists started to link drugs onto polymers to improve their efficiency.

At that time however, they were mainly concentrating on the chemistry itself and almost any class of polymers was covalently combined with any class of drugs. The biological aspects for the design of polymeric prodrugs were hardly taken into account.

It was for the first time in 1975 that a rational model for pharmacologically active polymers was proposed.
Prof. H. Ringsdorf was the first to recognise the immense potential of polymeric prodrugs, if only polymer chemists and biologists would work together in the field. The proposed model consists mainly of five components: the polymeric **backbone, the drug, the spacer, the targeting group and the solubilising agent**.

The polymeric carrier can be either an inert or a biodegradable polymer. The drug can be fixed directly or via a spacer group onto the polymer backbone. The proper selection of this spacer opens the possibility of controlling the site and the rate of release of the active drug from the conjugate by hydrolytic or enzymatic cleavage.



Ringsdorf Model

The most challenging aspect of this model is the possibility of altering the body distribution and cell uptake by attaching cell-specific or nonspecific uptake enhancers (**homing devices**).

Ringsdorf model, although still oversimplified, has been an important mark in the history of polymeric prodrug design.

It made clear that a more rational design was needed based on information arising from biological work. This remarkable acheivment has also catalysed the interest of biologists and pharmacists in synthetic polymers.

As more information becomes available from cell biology and molecular biology, polymer chemists are trying to design tailor-made polymeric carriers that better fulfil the specified requirements.

In time it has been shown that there is a clear relationship between the structural elements of the Ringsdorf model and the properties of the synthesized polymeric prodrugs based on it.

In fact, the properties that polymer chemists want to reach with the design of their polymer–drug conjugates, are translated in the components of the model.

Why the polymeric prodrugs? What are the advantages of them over their their low molecular weight precursors ?!

The advantages are:

1. An increase in water solubility of low soluble or insoluble drugs, and therefore, enhancement of drug bioavailability.
2. Protection of drug from deactivation and preservation of its activity during circulation, transport to targeted organ or tissue and intracellular trafficking.
3. An improvement in pharmacokinetics.
4. A reduction in antigenic activity of the drug leading to a less pronounced immunological body response.
5. The ability to provide targeting of the drug specifically to the site of its action.
6. The possibility to form an advanced complex drug delivery system, which, in addition to drug and polymer carrier, may include several other active components that enhance the specific activity of the main drug.

References:

The material of this lecture is collected the following references:

1. K. Hoste, K. De Winne, E. Schacht, Polymeric prodrugs, International Journal of Pharmaceutics 277 (2004) 119–131.

2. Jayant Khandare, Tamara Minko, Polymer–drug conjugates: Progress in polymeric prodrugs, Prog. Polym. Sci. 31 (2006) 359–397.

3. Alexander T Florence, David Attwood, Physicochemical Principles of Pharmacy FOURTH EDITION, Pharmaceutical Press 2006 (USA).

4. Haesun Park, Kinam Park, Waleed S.W. Shalaby, Biodegradable Hydrogels for Drug Delivery, Technomic Publications, 1993 (USA).

5. Rohini, Neeraj Agrawal, Anupam Joseph and Alok Mukerji, Polymeric Prodrugs: Recent Achievements and General Strategies, J Antivir Antiretrovir 2013, S15