Polymeric prodrugs:

- Polymers, including **biopolymers**, are made of repetitive units called monomers.
- **Biopolymers** are polymers produced by living organisms. Cellulose, starch, chitin, proteins, peptides, DNA and RNA are all examples of biopolymers, in which the monomeric units, respectively, are sugars, amino acids, and nucleotides.
- Polymers are used as carriers for the delivery of drugs, proteins, targeting moieties, and imaging agents.
- Several polymers have been successfully utilized in clinical research:
- 1. poly(ethylene glycol) (PEG),
- 2. N-(2-hydroxypropyl)methacrylamide (HPMA),
- 3. poly(lactide-co-glycolide) (PLGA) copolymers

polymeric prodrug

- A conjugation of a drug with a polymer forms so-called 'polymeric prodrug'.
- Based on the site and the mode of action, polymer conjugates possess either 'tuned' degradable or non-degradable bonds.
- Polymeric prodrugs have several advantages over their low molecular weight precursors. The main advantages include:
- 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 passive or active 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.

- Depending on the nature and site of action of a drug, either homopolymers, or graft or block polymers are being extensively used in bioconjugates.
- Due to their higher molecular weight, polymers are known to dominate the physical properties of the bioconjugated moiety.
- Along with the polymer, the physico-chemical properties of the drug or biomolecule to be conjugated are equally important.

- The following properties of the drug molecules make it suitable as an ideal candidate to form the polymeric conjugate:
- 1. Lower aqueous solubility.
- 2. Instability at varied physiological pHs.
- 3.Higher systemic toxicity, and
- 4. Reduced cellular entry

- Numerous polymeric prodrugs are in clinical phases and several others have been approved e.g. liposomal _ Amphotericin B & PEG_Adenosine deaminase.
- Covalent conjugation of biomolecules, e.g. protein drugs to synthetic polymers, particularly poly (ethylene glycol) (PEG) does:
- 1. Increase their plasma stability.
- 2. Reduces protein immunogenicity and
- 3. Can increase therapeutic index.

Successful bioconjugation depends upon:

- The chemical structure.
- Molecular weight.
- Steric hindrance and
- The reactivity of the biomolecule as well as the polymer.

- In order to synthesize a bioconjugate, both chemical entities need to posses a reactive or functional groups such as –COOH, – OH, –SH or – NH2.
- However, the presence of multiple reactive groups makes the task a bit complex. Therefore, the synthetic methodology to form a conjugate involves either protection or deprotection of the groups.

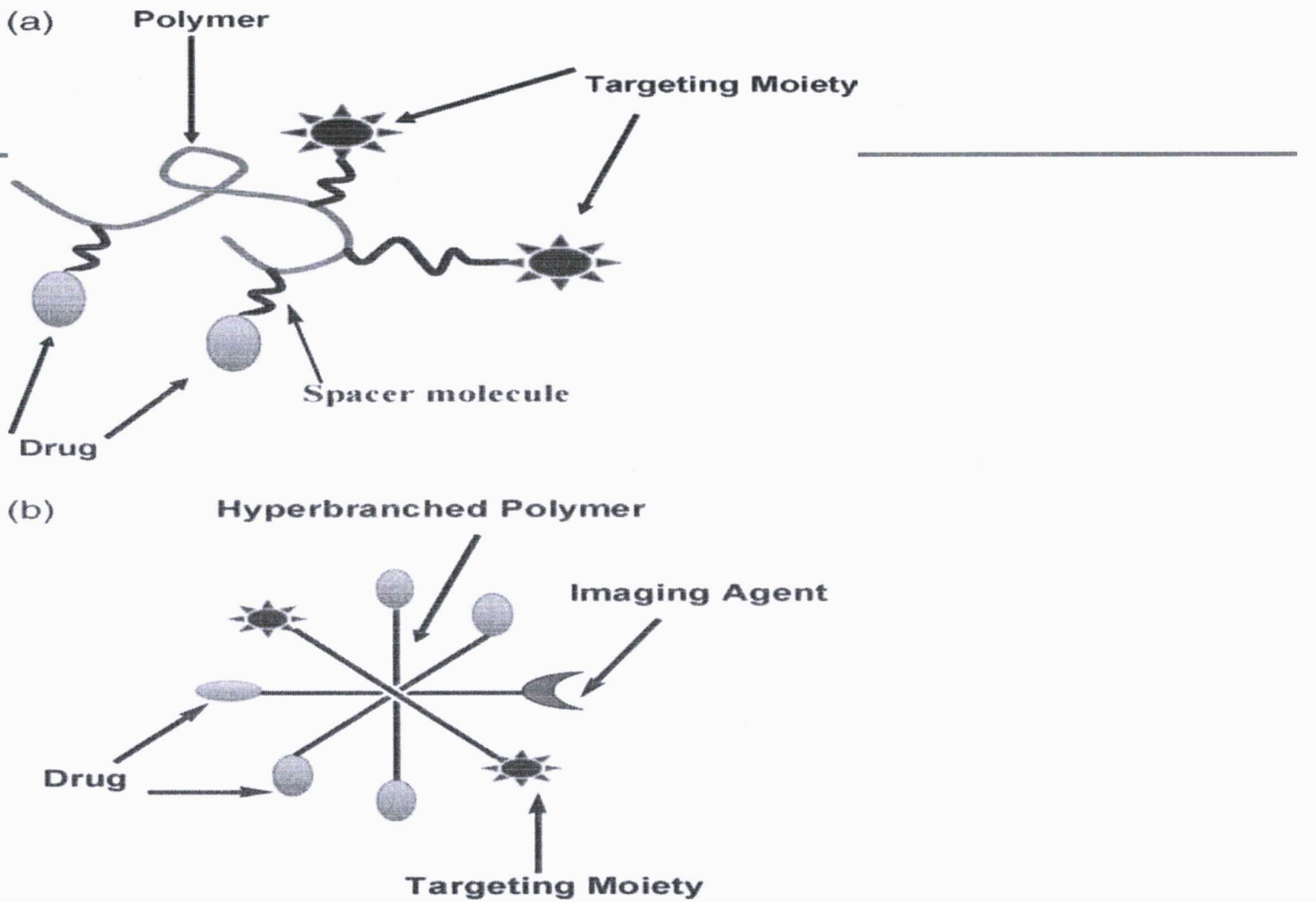
- Many of the most commonly used strategies involve use of coupling agents such as dicyclohexyl carbodiimide (DCC) or use of N-hydroxysuccinimide esters.
- Chemical conjugation of drugs or other biomolecules to polymers and its modifications can form stable bonds such as ester, amide, and disulphide.
- Covalent bonds (e.g. ester or amide) are stable and could deliver the drug at the targeted site, but such bonds may not easily release targeting agents and peptides under the influence of acceptable environmental changes.
- In the past, most of the polymeric prodrugs have been developed for the delivery of anticancer agents. High molecular weight prodrugs containing cytotoxic components have been developed to decrease peripheral side effects and to obtain a more specific administration of the drugs to the cancerous tissues.
- Polymer–drug conjugates can therefore be tailored for activation by extra- or intracellular enzymes releasing the parent drug in situ.

Design and synthesis of polymeric prodrugs:

- The most complete realization of the prodrug approach is possible by the use of an advanced type of prodrug—the drug delivery system (DDS).
- Such a system can be constructed not only to target a desired organ as a whole, its cells or specific organelles inside certain cells but also to release a specified amount of the drug at specific times.

- Three major types of polymeric prodrugs are currently being used:
- 1. Prodrugs that are broken down inside cells to form active substance or substances.
- 2. Prodrugs that are usually the combination of two or more substances. Under specific intracellular conditions, these substances react forming an active drug.
- 3. Prodrugs that are include three components: a targeting moiety, a carrier, and one or more active component(s).

- In general, an ideal polymeric prodrug model consists mainly of a combination of one or more components:
- (a) A polymeric backbone as a vehicle,
- (b) One or more drugs of the biological active components,
- (c) Spacer for hydrolysis of the biomolecule and versatility for conjugation,
- (d) An imaging agent and
- (e) Targeting moiety (Fig. 1a and b).



- Fig. 1. Schematic presentation for (a) polymeric prodrug with targeting agent and (b) hyperbranched polymer conjugate with targeting and imaging agent.

- The drug delivery carrier can be either biocompatible or an inert biodegradable polymer.
- The drug is coupled directly or via a spacer arm onto the polymer backbone.
- Selection of the spacer arm is critical as it opens the possibility of controlling the site and the rate of release of the active drug from the conjugates either by hydrolysis or by enzymatic degradation.
- The most challenging aspect of this protocol is the possibility of altering the body distribution and the cellular uptake by cell-specific or non-specific uptake enhancers.

- The polymers selected for preparing macromolecular prodrugs can be categorized according to:
- 1. Chemical nature (vinylic or acrylic polymers, polysaccharides, poly (a-amino acids), etc.,
- 2. Biodegradability,
- 3. Origin (either natural polymers or synthetic polymers) and
- 4. Molecular weight (oligomers, macromers and polymers).

Polymeric drug delivery system (PDDS)

- Modification of a polymer to form a conjugate with a biomolecule depends upon two interrelated chemical reactions:
- (1) Reactive functional groups present in the polymer and
- (2) Functional groups present on the biological component.
- In general, most of the biomolecules such as ligands, peptides, proteins, carbohydrates, lipids, polymers, nucleic acid and oligonucleotide possess combinations of these functional groups. Selection of a suitable method, process, and reagents are crucial for successful chemical conjugation.

- The following are common strategies adapted to obtain a polymeric drug delivery system as biologically active prodrug conjugates:
- 1. N-hydroxysuccinimide (NHS) ester and coupling methods, due to their higher reactivity at physiological pH makes NHS a choice for amine coupling reactions in bioconjugation synthesis.
- 2. Incorporation of spacers in prodrug conjugates; various spacers have been incorporated along with the polymers and copolymers to decrease the crowding effect and steric hindrance.
- The incorporation of a spacer arm can enhance ligand–protein binding and has application in prodrug conjugates and in biotechnology.

- For example, amino acid spacers such as glycine, alanine, and small peptides are preferred due to their chemical versatility for covalent conjugation and biodegradability.
- 3. Carbodiimide coupling reactions or zero lengths cross-linkers;
- Coupling and condensation reactions are unique to obtain chemical conjugates involving drugs or other biocomponents with polymers. The smallest possible reagents for bioconjugate synthesis are called zero length cross-linkers