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A REVIEW ON POLYMER DRUG CONJUGATE - WHAT, WHY AND HOW?

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ABSTRACT: It is well known that polymeric prodrug or polymer-drug conjugate is an effective and fast growing technique for improved use of drugs for therapeutic applications. Polymer conjugated drugs generally exhibit prolonged half-life, higher stability, water solubility, lower immunogenicity and antigenicity and specific targeting to tissues or cells. Polymers are used as carriers in polymeric prodrugs/macromolecular prodrugs for the delivery of drugs, proteins, targeting moieties, and imaging agents. The potential of the polymer-drug conjugates have already been proved by success of many products in the market for the treatment of different diseases. The polymeric pro-drug can be regarded as drug delivery systems that exhibit their therapeutic activities by means of releasing smaller therapeutic drug molecules from a polymer chain molecule for a prolonged period of time which results in enhanced pharmacokinetic behaviour by increasing the t 1/2 , bioavailability, and hence prolonged pharmacological action. This review deals with the Rational for design of polymer-drug conjugates (PDC), requirements for selection of drug candidate for polymeric prodrug, requirements for selecting polymers as candidate drug carriers, classification of polymers, design and synthesis of polymeric prodrugs and strategies to enhance the reactivity of polymer and the drug by incorporation of spacers.

INTRODUCTION: What is PDC? Polymer therapeutics is a general term used to define a family of nanoscale entities, whose main common feature is that the bioactive agent is not encapsulated, but linked to a polymeric water-soluble biocompatible carrier [1, 2] . The term covers a wide variety of different molecular structures, but in the present article we focus our attention on polymer–drug conjugates [3–5].

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A model for macromolecular pro-drugs was first proposed by Ringsdorf in the mid 1970s. The pro-drug shows particular properties determined by the macromolecule presence and manifested in the pharmacokinetic behaviour of the drug-polymer conjugate. This review deals with the Rational for design of polymer-drug conjugates (PDC), requirements for selection of drug candidate for polymeric prodrug, requirements for selecting polymers as candidate drug carriers, classification of polymers, design and synthesis of polymeric prodrugs and strategies to enhance the reactivity of polymer and the drug by incorporation of spacers.

Following the Ringsdorf model [6], polymer–drug conjugates are characterized by a biocompatible

polymeric carrier and low-molecular weight biologically active molecule(s), which are covalently bound to the polymer through a bioresponsive linker. In most cases, the presence of the polymer enhances the solubility of the hydrophobic drug[7] and improves its pharmaco kinetic profile[8]. On one hand, it increases plasma half-life and volume of distribution and on the other, it reduces clearance by the kidneys or liver. The polymer also protects the drug against degradation [9].

The aim of the linker goes further than merely binding the polymer to the drug: it can also become active by triggering drug release under certain conditions, such as a change in pH or in the presence of enzymes such as esterases, lipases or proteases [10, 11]. In addition, a targeting moiety or a solubilizer may also be introduced into the conjugate to boost its therapeutic index (**Fig. 1**) [12–14]. After the discovery of the enhanced permeability and retention (EPR) effect, described by Maeda [15, 16], polymer conjugates have become a powerful tool in the treatment of several types of cancer [3, 4, 17] .

Due to the molecular complexity of human pathologies, development of new combination therapies will maximize synergy in the therapeutic effects between more than one drug [18, 19]. Finally, the hunt for new targets, not only in cancer but also in other diseases, including the exciting field of tissue regeneration and repair, can be considered as one of the biggest challenges that will open up this area to a broader range of clinical applications. Although at very early stages of development, this particular topic has been selected to be reviewed in this article due to its expected impact on the development of advanced polymer–drug conjugates.

Why PDC?

Polymer Drug Conjugates or polymeric Prodrugs shows

i) 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. The duration of action can be prolonged by linking a drug to a polymer in order to obtain a conjugate. This conjugation results in a slower renal excretion, longer blood circulation and an endocytotic cell uptake [20-22].

ii) Controlled drug release:

The polymeric prodrug formed by conjugation of drug with polymeric carrier should be stable in circulation but should also be able to release the macromolecular drug intra-cellularly or intra-abnormalally for therapeutic effect. This controlled release from polymeric prodrug can only be achieved by proper selection of linkage between drug and polymeric carrier.

a) 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 tumour tissue which are slightly acidic in comparison to the healthy tissues [23]. This relatively low pH has been exploited to design pH sensitive spacers such as N-cis-aconityl spacer [24] used to form polymeric prodrug of daunorubicin-linked aminoethyl polyacrylamide beads and poly(d-lysine) and Hydrazon linkage used to form cytotoxic adriamycin immunoconjugates [25] which showed highest *in vitro* and *in vivo* anti-abnormal activity.

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 abnormal tissues. In the lysosomes, the polymeric prodrug is acted upon by lysosomal enzymes such as cathepsins and metalloproteinases to release the macromolecular drug [26]. The release of cytotoxic drug with the help of these enzymes destroys the abnormal tissue. Examples of such conjugation include coupling of mescaline with poly(vinylpyrrolidone-coacrylic acid) [27] in order to increase the biological half life of mescaline which enhanced permeability and retention effect.

The polymeric prodrugs are taken up by solid abnormals by pinocytosis and this passive abnormal uptake increases the targeting of drug due

to their characteristic feature of enhanced permeability and retention effect [28]. This effect is due to increased abnormal vascular permeability and poor tissue drainage from the abnormal cells which increase the duration of action and targeting of the macromolecular drug [29].

The abnormal cells contain permeability enhancing factors such as vascular endothelial growth factor (VEGF), bradykinin etc., which increase the permeability of polymeric prodrugs towards abnormal tissue and also, lack of effective lymphatic drainage from the abnormal tissue increases its retention [30].

iii) Active targeting by polymeric prodrug:

a) 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 abnormal cells[31, 32]. These antibodies bind very specifically to abnormal 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 anti-abnormal therapy b) abnormal selective monoclonal antibody is covalently attached to an enzyme which converts non toxic prodrug into potent cytotoxic drug after specific targeting at the abnormal site [33]. This approach minimizes non specific toxicity.

b) Lectins: The sugar specific receptors present on the plasma membrane are called lectins and they have been characterized mainly on hepatocytes[34]. 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., [35].

iii) Angiogenic vessels of tumor cells: The endothelial cells in angiogenic vessels of tomors show increased expression of cell surface proteins. These proteins include receptors for vascular endothelial growth factor (VEGF) and integrin receptors [36]. 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) [37] showed increased efficacy of drug against breast cancer. Immunoprotection by polymeric prodrugs Treatment of cancer by polymeric prodrug can remarkably protect the patient's immunity owing to a mechanism known as Fas-Fas ligand interaction [38]. Fas and Fas ligand (Fas L) are present on cancer as well as immune cells. Interaction between Fas and Fas ligand (Fas L) triggers a cascade of signals, that eventually results in apoptosis i.e. programmed cell death [39].

It has been reported that treatment with free anti-tumor drugs promotes induction of Fas ligands on cancer cells whereas their macromolecular derivatives did not increase Fas L[40]. This is an important outcome that might indicate that polymeric prodrugs are able to protect the patient's immune system.

How to synthesize PDC?

General Strategies Involved for Design and Synthesis of Polymeric Prodrugs:

The delivery of biomolecules using polymeric materials has attracted considerable attention from polymer chemists, chemical engineers and pharmaceutical scientists. While designing the polymeric conjugates considerable attention has to be given on selection of proper drug and polymer candidate. The properties of a drug candidate have already been mentioned while explaining the Ringsdorf's model in the introduction section.

Requirements for selecting polymers as candidate drug Carriers: [41]

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

Biocompatibility: preferably nontoxic, non immunogenic;

Biodegradability or a molecular weight below the renal excretion limit;

Availability: reproducibly manufactured and conveniently administered to patients;

Water solubility: hydrophilic to ensure water solubility;

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

Classification of Polymers for PDC:

Polymers have been used as a main tool to control the drug release rate from the formulations. They are also increasingly used as taste-masking agent, stabilizer, and protective agent in oral drug delivery. Polymers can bind the particles of a solid dosage form and also change the flow properties of a liquid dosage form. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials.

Polymers are macromolecules having very large chains, contain a variety of functional groups, can be blended with other low- and high–molecular-weight materials, and can be tailored for any applications. Polymers are becoming increasingly important in the field of drug delivery.

Advances in polymer science have led to the development of several novel drug-delivery systems. A proper consideration of surface and bulk properties can aid in the designing of polymers for various drug-delivery applications[42]. These newer technological development include drug modification by chemical means, career based drug delivery and drug entrapment in polymeric matrices or within pumps that are placed in desired bodily compartments.

These technical development in drug delivery/targeting approaches improve the efficacy of drug therapy thereby improve human health. Use of polymeric materials in novel drug delivery approaches has attracted the scientists. Polymer chemists and chemical engineers, pharmaceutical scientists are engaged in bringing out design predictable, controlled delivery of bio active agents [43].

Polymers in Pharmaceutical and Biomedical Applications: [44, 45]

Water-Soluble Synthetic Polymers:

- Poly(acrylic acid) in cosmetic, pharmaceuticals, immobilization of cationic drugs, base for Carbopol polymers
- Poly (ethylene oxide) as coagulant, flocculent, very high molecular-weight up to a few millions, swelling agent
- Poly (ethylene glycol) MW <10,000; liquid (MW <1000) and wax (MW >1000) as plasticizer, base for suppositories
- Poly (vinyl pyrrolidone) used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation
- Poly (vinyl alcohol) Water-soluble packaging, tablet binder, tablet coating
- Polyacrylamide Gel electrophoresis to separate proteins based on their molecular weights, coagulant, absorbent
- Poly (isopropyl acrylamide) and poly (cyclopropyl methacrylamide
- Thermogelling acrylamide derivatives, its balance of hydrogen bonding, and hydrophobic association changes with temperature

Cellulose-Based Polymers:

- Ethyl cellulose insoluble but dispersible in water, aqueous coating system for sustained release applications
- Carboxymethyl cellulose as super disintegrant, emulsion stabilizer
- Hydroxyethyl and hydroxypropyl celluloses soluble in water and in alcohol for tablet coating

- Hydroxypropyl methyl cellulose as binder for tablet matrix and tablet coating, gelatin alternative as capsule material
- Cellulose acetate phthalate for enteric coating

Hydrocolloids:

- Alginic acid in oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions; binder and disintegrant
- Carrageenan for modified release, viscosifier
- Chitosan in cosmetics and controlled drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms
- Hyaluronic acid in reduction of scar tissue, cosmetics
- Pectinic acid for Drug delivery

Water-Insoluble Biodegradable Polymers:

- (Lactide-co-glycolide) Microparticle–nanoparticle delivery for polymers protein

Starch-Based Polymers:

- Starch as glidant, a diluent in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder
- Sodium starch glycolate as super disintegrant for tablets and capsules in oral delivery

Plastics and Rubbers:

- Polyurethane in transdermal patch backing (soft, comfortable, moderate moisture transmission), blood pump, artificial heart, and vascular grafts, foam in biomedical and industrial products
- Silicones Pacifier, therapeutic devices, implants, medical grade adhesive for transdermal delivery
- Polyisobutylene in Pressure sensitive adhesives for transdermal delivery
- Polycyanoacrylate in biodegradable tissue adhesives in surgery, a drug carrier in nano- and microparticles
- Polyethylene in transdermal patch backing for drug in adhesive design, wrap, packaging, containers
- Poly (methyl methacrylate) Hard contact lenses
- Poly (hydroxyethyl methacrylate) Soft contact lenses
- Vinyl acetate and methyl acrylate copolymer
- Ethylene vinyl acetate and polyethylene in Transdermal patch backing (heat sealable, occlusive, translucent)
- Polyethylene and polyethylene terephthalate Transdermal patch backing (when ethylene vinyl acetate copolymer is incompatible with the drug)

Design and Synthesis of Polymeric Prodrugs (Coupling methods):

Coupling reactions involves conjugation of drugs or other biocomponents with polymers. In coupling reactions, the reactive functional groups on the different cross-linking or derivatizing reagents and the functional groups present on the target biomolecule are to be modified. Coupling agents mediate the conjugation of the two molecules by forming a bond with no additional spacer atom [46, 47]. In case, the drug or the polymer contains more than one functional group, then the synthetic methodology to form a conjugate involves either protection or deprotection of the groups.

The most commonly used strategies for coupling the components of polymeric prodrug involve use of coupling agents such as dicyclohexyl

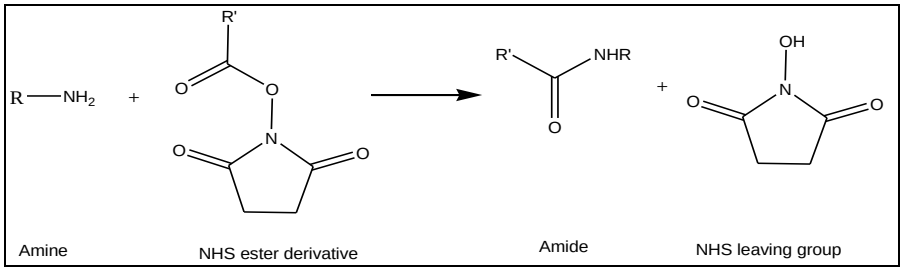
carbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC, EDCI) or use of N-hydroxysuccinimide esters which will be discussed in a more detail as a separate heading. Drugs or other biomolecules are chemically conjugated to polymers through ester, amide or disulphide bonds. The resulting bond linkage should be relatively stable to prevent drug release during its transport before the cellular localization of the drug [48-50]. Most of the bioconjugation strategies involve coupling reactive nucleophiles with the following order of reactivity: thiol, α-amino groups, epsilone amino group, carboxyl and hydroxyl [51-52].

The pH in the reaction and presence of steric hindrance on the coupling moiety controls this order of reactivity. Recent advancements in coupling methods involve use of homobifunctional amine or heterobifunctional coupling reagents. A number of electrophilic groups e.g. epoxides, vinylsulphones, and aziridines are capable of reacting with amines and other nucleophiles. Homobifunctional compounds such as N,N'-ethyleneiminoyl- 1-6-diaminohexane, bis-aziridin, divinyl sulphone (DVS), nitrogen mustard and bis-sulphonyl chloride can form protein-protein linkages while heterobifunctional reagents are useful to couple amines with other functional groups. Reactive groups in protein- carboxyl functions offer alternating thiol reactions as a site for hetero bifunctional coupling with amines[53].

1. Coupling reactions involving N-hydroxysuccinimide (NHS) ester derivative:

NHS shows higher reactivity at physiological pH, therefore it is used for amine coupling reactions in bioconjugation synthesis. As shown in Scheme 1, the NHS ester compounds react with nucleophiles to form an acylated product with NHS as a leaving group [54]. Carboxyl groups activated with NHS esters are highly reactive with amine nucleophiles. Carboxyl groups are easily reacted with amine nucleophiles after their activation by NHS esters [55, 56].

Scheme 1:

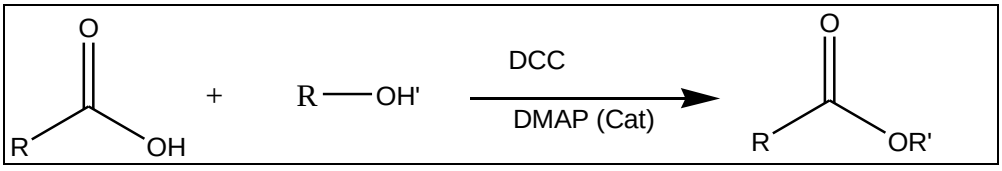


2. Coupling reactions involving coupling reagents:

i) Dicyclohexylcarbodiimide (DCC):

It is mainly used to couple amino acids during artificial peptide synthesis. It is highly soluble in dichloromethane, tetrahydrofuran, acetonitrile and dimethylformamide. It is insoluble in water.R'OH A range of alcohols, including even some tertiary alcohols, can be esterified using a carboxylic acid in the presence of DCC and a catalytic amount of DMAP (Dimethyl amino pyridine) (Scheme 2) [57].

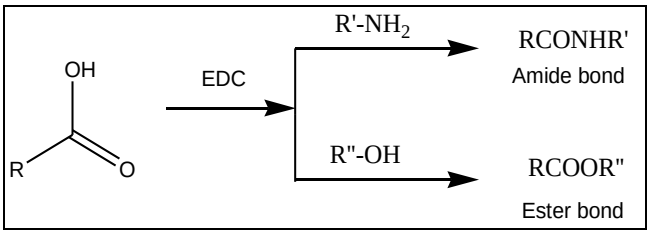
Scheme 2



ii) 1 - Ethyl - 3 - (3-dimethylaminopropyl) carbodiimide (EDC, EDCI): It is mainly used as a carboxyl activating agent for the coupling of primary amines to yield amide bonds. EDC is often used in combination with N-hydroxysuccinimide (NHS) or sulfo-NHS to increase coupling

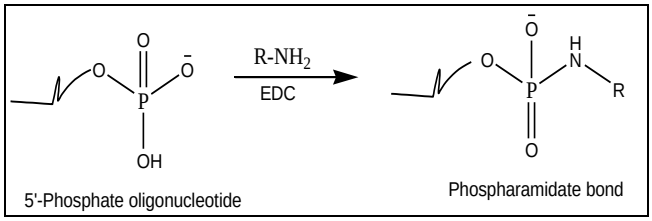
efficiency or create a stable amine-reactive product. EDC is also used to couple a carboxylic acid to alcohol using DMAP as a catalyst (Scheme 3).

Scheme 3



EDC can also be used to activate phosphate groups. Biomacromolecules containing phosphate groups such as the 5' phosphate of oligonucleotide can be conjugated to amine containing molecules by using EDC. EDC activates the phosphate to an intermediate phosphate ester. Further, in the presence of an amine carbodiimide can be conjugated to form a stable phosphoramidate bond (Scheme 4) [58].

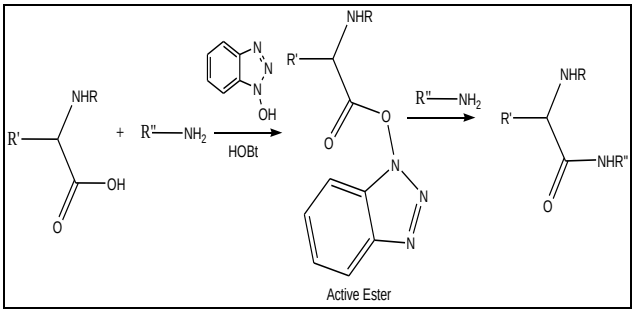
Scheme 4



iii) 1-Hydroxybenzotriazole (HOBT):

HOBt is used for the synthesis of amides from carboxylic acids aside from amino acids (Scheme 5) [59-60].

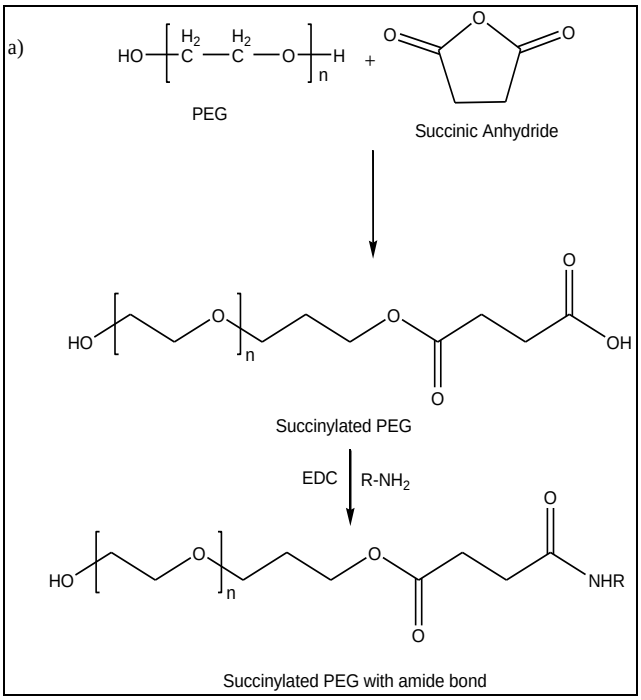
Scheme 5

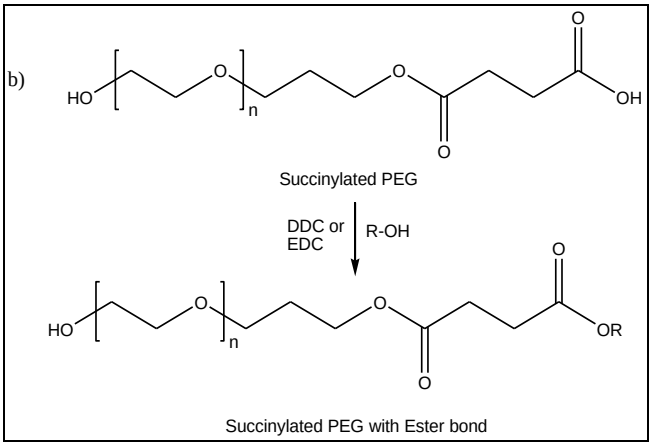


3. Coupling of hydroxyl group containing polymers to alcohols and amines:

Polymers containing -OH groups (e.g. PEG) can be modified to Carboxylic acid derivative by treating with acid anhydrides. PEG or mPEG can be acetylated with anhydrides (e.g. succinic anhydride) to form an ester terminating to free carboxylate groups. The resulting succinylated derivative containing free -COOH group can be further used for conjugation with drugs or proteins (Scheme 6). The succinyl group incorporated in the polymer may act as spacer between the polymer and the drug which may control the site and the rate of release of the active drug from the conjugate by hydrolytic or enzymatic cleavage [61-62].

Scheme 6





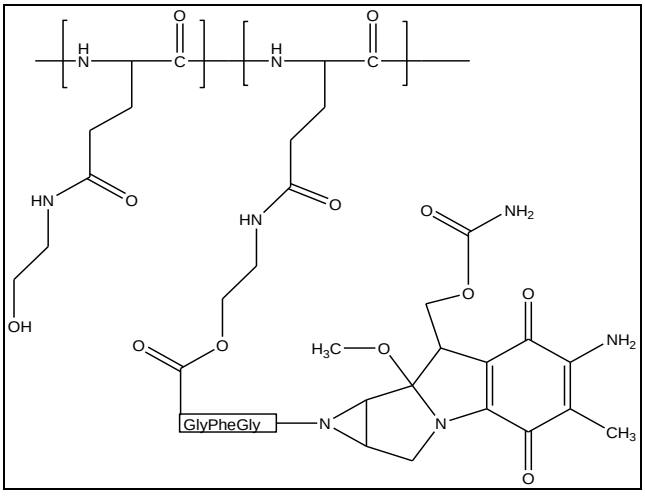
4. Coupling of drug and polymer through spacer:

Spacers may be incorporated during bioconjugation to decrease the crowding effect and steric hindrance and control the site and the rate of release of the active drug from the conjugate. Spacers can enhance ligand- protein binding and has application in prodrug conjugates and in biotechnology. Amino acid such as glycine, alanine, and small peptides are widely used as spacers due to their chemical versatility for covalent conjugation and biodegradability [63]. The α-amino acids in peptides and proteins (excluding proline) consist of a carboxylic acid (-COOH) and an amino (-NH_2) functional group attached to the same tetrahedral carbon atom which extends diversity for conjugation with hydroxyl, carboxyl or amino groups of polymer or biomolecule.

Moreover, amino acid based spacers are short-chained, reactive, and biocompatible and may release the active agent from the conjugate. Di-functional amino acids such as 6-amino caproic acid (6-ACA) or 4 amino butyric acids (4 ABA) have been used as spacer arms between the polymers and the ligands for applications in biotechnology [64].

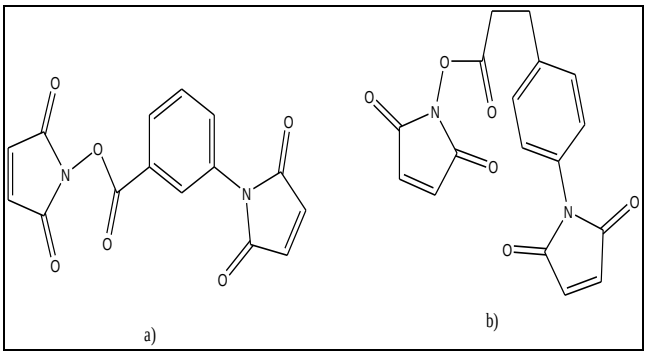
A polymeric prodrug of alkylating agent mitomycin C (MMC) with poly[N5-(2-hydroxyethyl)-L-glutamine] (PHEG) using oligopeptide spacers was designed predominantly for enzymatic degradation which released MMC with a rate dependant manner structure1) [65-66].

Structure 1



Hetero bi functional coupling agents containing succinimidyl group have also been used extensively as spacers [67] (Structure 2).

Structure 2



Future Directions in Polymer Drug Delivery:

The most exciting opportunities in polymer drug delivery lie in the arena of responsive delivery systems, with which it will be possible to deliver drugs through implantable devices in response to a measured blood level or to deliver a drug precisely to a targeted site. Much of the development of novel materials in controlled drug delivery is focusing on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features. Such systems include:

- Copolymers with desirable hydrophilic/hydrophobic interactions.
- Block or graft copolymers.
- Complexation networks responding viahydrogen or ionic bonding.
- Dendrimers or star polymers as nanoparticles for immobilization of enzymes, drugs, peptides, or other biological agents.
- New biodegradable polymers.
- New blends of hydrocolloids and carbohydrate-based polymers.

These new biomaterials—tailor-made copolymers with desirable functional groups—are being created by researchers who envision their use not only for

innovative drug delivery systems but also as potential linings for artificial organs, as substrates for cell growth or chemical reactors, as agents in drug targeting and immunology testing, as biomedical adhesives and bioseparation membranes, and as substances able to mimic biological systems. Successfully developing these novel formulations will obviously require assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials. Sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of the medicines they need to fight a variety of human ailments, including cancer.

Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing [21, 22]. Polymer drug delivery: What is next?

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