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ORIGINAL ARTICLE

Polyethylene Glycol–Based Polymer-Drug Conjugates: Novel Design and Synthesis Strategies for Enhanced Therapeutic Efficacy and Targeted Drug Delivery

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Abstract

Due to their potential to enhance therapeutic results and enable targeted drug administration, polymer-drug conjugates that use polyethylene glycol (PEG) as both the polymer and the linker for drug conjugation have attracted much research. This study seeks to investigate recent developments in the design and synthesis of PEG-based polymer-drug conjugates, emphasizing fresh ideas that fill in existing knowledge gaps and satisfy the increasing need for more potent drug delivery methods. Through an extensive review of the existing literature, this study identifies key challenges and proposes innovative strategies for future investigations. The paper presents a comprehensive framework for designing and synthesizing PEG-based polymer-drug conjugates, including rational molecular design, linker selection, conjugation methods, and characterization techniques. To further emphasize the importance and adaptability of PEG-based polymer-drug conjugates, prospective applications are highlighted, including cancer treatment, infectious disorders, and chronic ailments.

Keywords Polymer-drug conjugates · Conjugation · Linkers · Molecular design · Targeted drug delivery · Enhanced therapeutic efficacy

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Introduction

A potential method for increasing the therapeutic effectiveness of medications and permitting tailored drug administration is the use of polymer-drug conjugates [1–3]. Researchers can get around problems with low drug solubility, short half-life, lack of selectivity, and quick removal from the body by conjugating medicines to polymeric carriers [4]. Polyethylene glycol (PEG), one of the many polymers used for drug conjugation, has drawn a lot of interest because of its advantageous traits, which include great biocompatibility, water solubility, and little immunogenicity [5, 6].

Drug delivery technologies have undergone a revolution thanks to the development and manufacture of PEG-based polymer-drug conjugates [7]. PEG provides stability, increased circulation duration, less immunogenicity, and the ability to control drug release kinetics, making it the perfect polymer backbone for drug conjugation [8, 9]. Additionally, PEG is easily functionalized with various linkers to enable site-specific targeting and promote drug attachment [10].

The capacity of PEG-based polymer-drug conjugates to improve therapeutic results is one of their main benefits [11]. Drugs can be shielded from enzymatic breakdown by using PEG as a carrier, enabling extended circulation in the bloodstream [12]. Through increased exposure to the target region during this prolonged circulation time, the drug's effectiveness is enhanced. Additionally, PEG-based conjugates can minimize off-target effects, as the polymer can shield the drug from interacting with non-target tissues, resulting in reduced toxicity and improved safety profiles [13].

Another critical aspect of PEG-based polymer-drug conjugates is their capacity for targeted drug delivery [14]. By incorporating specific ligands or antibodies onto the PEG backbone, conjugates can be designed to selectively recognize and bind to receptors or antigens expressed on the surface of target cells or tissues [15]. This active targeting strategy improves drug accumulation at the desired site, enhancing therapeutic efficacy while minimizing systemic side effects [16].

Despite the significant progress made in the design and synthesis of PEG-based polymer-drug conjugates, several challenges remain [17]. These include achieving optimal drug loading, maintaining stability during circulation, achieving controlled drug release profiles, and ensuring sufficient conjugation efficiency [18, 19]. Additionally, translating these conjugates from the laboratory to clinical settings requires addressing regulatory considerations and developing scalable manufacturing processes [20].

In light of these challenges and the growing need for more effective drug delivery systems, this research paper aims to explore recent advancements in the design and synthesis of PEG-based polymer-drug conjugates. This study highlights significant research gaps and suggests cutting-edge methodologies for further research through a thorough analysis of the body of existing literature. The article will offer a thorough framework for linker selection and design tactics, conjugation procedures, characterization approaches, and prospective therapeutic applications for rational molecular design of PEG-based conjugates. We want to help promote PEG-based polymer-drug conjugates, which can have a big influence on drug delivery systems, improve therapeutic efficacy, and provide tailored treatment choices for different illnesses, by tackling these important issues.

Rational Molecular Design

The therapeutic effectiveness and targeted drug delivery of polymer-drug conjugates based on polyethylene glycol (PEG) are greatly enhanced by rational molecular design. The choice of PEG as the polymer's backbone, optimisation of PEG's molecular weight and architecture, medication compatibility, and therapeutic goals are only a few of the crucial aspects that must be taken into account.

Due to its advantageous characteristics, PEG, a biocompatible and water-soluble polymer, has been widely employed in drug delivery systems [5]. The molecular weight of PEG is a significant factor that affects the pharmacokinetics and biodistribution of the conjugates. The accumulation and circulation time at the target location can be managed by selecting the ideal molecular weight with attention [9]. Recent studies have shown that PEGylation with longer PEG chains, such as PEG 2000, can increase the duration of systemic circulation and enhance therapeutic outcomes [21].

A further crucial component of rational molecular design is the architecture of PEG. A benefit of the creation of branching or multi-arm PEG designs is that they are more stable, have a higher drug loading capacity, and have better targeting efficiency [22]. Higher drug payloads and regulated release kinetics are possible thanks to the many attachment sites that branched PEG designs, such as dendritic PEG, may afford for drug conjugation [23]. Additionally, the PEG backbone's addition of functional groups makes it easier to conjugate medicines or target ligands, enabling site-specific delivery [24].

The compatibility between the drug and PEG backbone is crucial for ensuring efficient conjugation and maintaining the drug's stability and activity. Considerations such as drug solubility, chemical reactivity, and drug-polymer interaction should guide the selection of appropriate drug candidates for conjugation with PEG. Recent advances have demonstrated successful PEGylation of various classes of drugs, including small molecules, peptides, and proteins, leading to improved pharmacokinetics and therapeutic outcomes [2, 25].

Linker Selection and Design

The effective production of polymer-drug conjugates based on polyethylene glycol (PEG) depends on the choice and design of an acceptable linker. Linkers are essential for assuring the stability of the conjugates, providing regulated drug release, and promoting effective drug conjugation. The stability of the linker under physiological settings, the intended release kinetics, and the unique needs of the medication and target site must all be taken into account when choosing a linker.

For the polymer-drug combination to remain intact during circulation and to guarantee targeted drug release, the linker's stability is crucial. Depending on the intended release mechanism, different linkers, such as cleavable and non-cleavable, can be used. Disulfide bonds, hydrazone bonds, and ester linkages are examples of cleavable linkers that have the benefit of causing drug release in response to particular stimuli, such as the intracellular reducing environment or enzyme activity [26]. For long-lasting therapeutic effects, non-cleavable linkers such as amide bonds or stable coordination bonds offer stability and sustained release patterns [27].

The unique characteristics of the medication and the target site should be taken into account while designing linkers. For instance, linkers having functional groups capable

of conjugating with certain moieties or ligands can be included if the medicine requires a site-specific release or targeting [28]. Selective conjugation with thiol or amino groups present on the medication or targeted ligands is made possible by the insertion of reactive groups, such as maleimide or NHS ester, on the linker [29]. The development of click chemistry–based linkers, made possible by recent developments in linker design, has facilitated the production of very stable and site-specific polymer-drug conjugates. Click chemistry–based linkers enable efficient and selective conjugation operations [30].

Moreover, the linker length and flexibility should be carefully considered to ensure optimal drug loading and release kinetics. The linker should be long enough to prevent steric hindrance between the polymer and the drug, allowing for efficient drug conjugation and preserving drug activity. Additionally, linker flexibility can influence the release rate of the drug, with more flexible linkers generally promoting faster drug release [31]. The rational design of the linker structure and its attachment to the PEG backbone can provide control over drug release kinetics, maximizing therapeutic efficacy. The common structure of the polymer-drug conjugate can be seen in Fig. 1 (where the polymer-drug conjugate is represented with a clear representation of the polymer backbone, drug molecule, and linker). Various linkers are used in design for the design of various polyethylene glycol-linker-dug conjugated drug delivery systems and have been enlisted in Table 1, where their key features have also been reported.

Conjugation Methods

The synthesis of polyethylene glycol (PEG)–based polymer-drug conjugates involves efficient and selective conjugation methods that ensure robust attachment of the drug to the PEG polymer backbone. Various conjugation strategies have been developed, offering versatility in terms of drug compatibility, conjugation efficiency, and control over drug loading (Fig. 2 shows the overview of the preparation of polymer-drug conjugate based on theranostic nanoparticles). The selection of the conjugation method depends on the chemical properties of the drug, the desired linker chemistry, and the specific requirements of the target application.

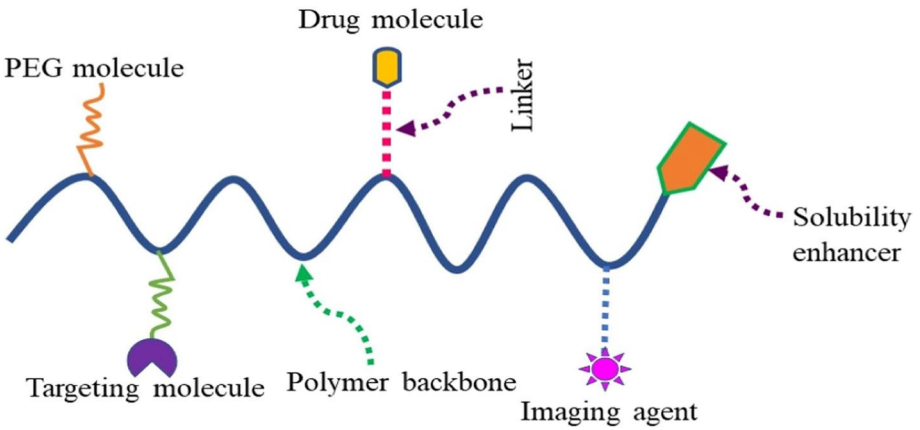

Fig. 1 Representation of polymer-drug conjugate for multipurpose use [32]

Table 1 Different linkers for their pharmacological activity

Sr. no.	Linker name	Functional group(s)	Method of conjugation	Drug name	Polymer name	Clinical condition	Delivery system designed	Mode of administration	Remarks	Reference
1	Maleimide	Thiol and maleimide	Thiol-maleimide coupling	Doxorubicin	PEG	Cancer	Nanoparticles	Intravenous	Controlled release Rapid action Enhanced efficacy	[33, 34]
2	NHS ester	Amine and NHS ester	Amide bond formation	Paclitaxel	PEG	Cancer	Micelles	Intravenous	Dose frequency reduced Controlled release Enhanced pharmacological effect Increased half-life	[35, 36]
3	Azide/alkyne	Azide and alkyne	Click chemistry	Gemcitabine	PEG	Cancer	Nanogels	Intratumoural	Better in vivo performance Improved delivery Improved pharmacological activity	[36–38]
4	Succinimidyl ester	Nucleophilic and succinimidyl ester	Direct chemical conjugation	Methotrexate	PEG	Rheumatoid arthritis	Hydrogels	Intra-articular	Effective and efficient study Increased half-life	[36, 37]

Table 1 (continued)

Sr. no.	Linker name	Functional group(s)	Method of conjugation	Drug name	Polymer name	Clinical condition	Delivery system designed	Mode of administration	Remarks	Reference
5	Enzyme-specific	Enzyme-specific and functional group	Enzymatic conjugation	Insulin	PEG	Diabetes	Microparticles	Subcutaneous	Increased pharmacokinetic activity Targeted drug delivery	[9, 22]
6	Lipid	Hydrophobic and lipid	Liposomal encapsulation	Amphotericin B	PEG	Fungal infections	Liposomes	Intravenous	Enhance the efficacy of therapeutic and diagnostic protocols Targeted drug delivery Improving properties of drug carrier systems	[20, 39]
7	Dendritic	Dendritic and functional group	Dendrimer-based conjugation	Methotrexate	PEG	Cancer	Dendrimers	Intravenous	Targeted drug delivery Multivalency plays an important role	[40, 41]
8	Hydrogel	Crosslinker and functional group	Hydrogel encapsulation	Ibuprofen	PEG	Inflammation	Hydrogels	Topical	Sustained release Controlled degradation properties	[42, 43]

Table 1 (continued)

Sr. no.	Linker name	Functional group(s)	Method of conjugation	Drug name	Polymer name	Clinical condition	Delivery system designed	Mode of administration	Remarks	Reference
9	Protein	Protein and functional group	Protein conjugation	Interferon-alpha	PEG	Viral infections	Protein conjugates	Subcutaneous	Improve therapeutic efficacy Great potential for in vivo and in vitro gene delivery	[44, 45]
10	Thioether	Thiol and thioether	Thiol-disulfide exchange	Trastuzumab	PEG	Breast cancer	Antibody-drug conjugates	Intravenous	Biodegradable polymers Novel therapeutics Stable linkers Better antigen target selection	[46, 47]
11	Peptide	Peptide and functional group	Peptide conjugation	Exenatide	PEG	Type 2 diabetes	Peptide conjugates	Subcutaneous	Enhanced efficacy Enzyme-triggered drug release Good stability	[48, 49]

Table 1 (continued)

Sr. no.	Linker name	Functional group(s)	Method of conjugation	Drug name	Polymer name	Clinical condition	Delivery system designed	Mode of administration	Remarks	Reference
12	Cleavable	Cleavable and functional group	Cleavage-based conjugation	siRNA	PEG	Gene silencing	Polyplexes	Intravenous	Enhanced antitumour effects Reduce adverse effects Enhanced intracellular penetration	[39, 50]
13	Prodrug	Prodrug and functional group	Prodrug conjugation	5-Fluorouracil	PEG	Cancer	Prodrug conjugates	Intravenous	Targeted drug delivery	[51, 52]
14	Amphiphilic	Hydrophobic and amphiphilic	Self-assembly	Curcumin	PEG	Inflammation	Nanomicelles	Oral	Improved activity	[53, 54]

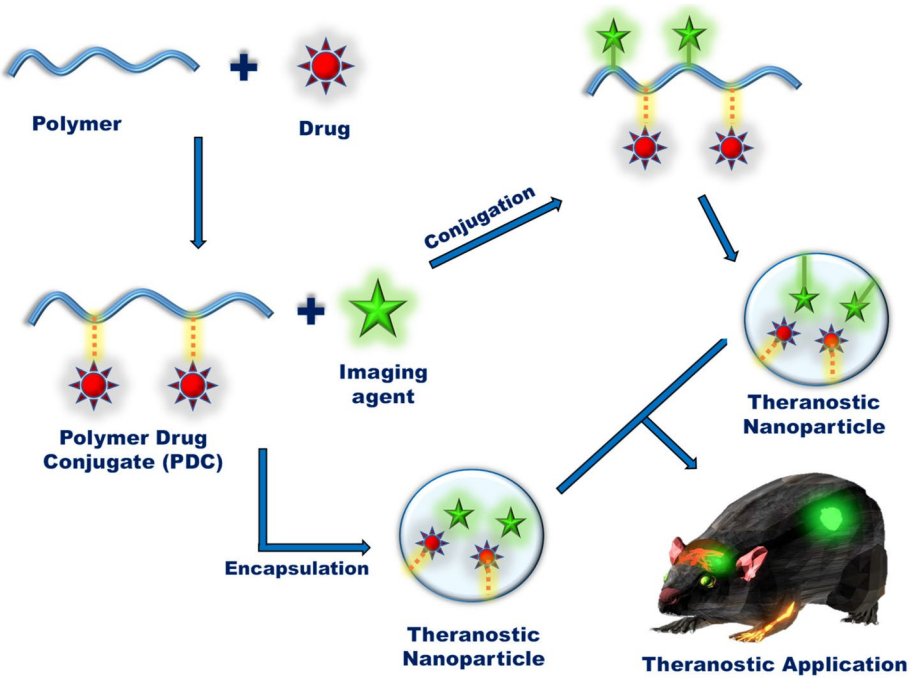

Fig. 2 A general overview of the preparation of polymer-drug conjugate-based theranostic nanoparticles [55]

One commonly employed conjugation method is direct chemical conjugation, where the drug and PEG are functionalized with reactive groups that undergo a specific chemical reaction to form a covalent bond. For example, thiol groups on the drug can react with maleimide groups on the PEG backbone through a thiol-maleimide coupling reaction, resulting in stable drug attachment [9, 56]. Similarly, amine groups on the drug can react with carboxyl or NHS ester groups on the PEG backbone through amide bond formation [29]. Recent advancements have also utilized bioorthogonal reactions (Fig. 3 depicts the bioorthogonal chemistry reactions which is a set of high-yielding chemical reactions that occur in biological contexts quickly, selectively, and without causing negative side effects to endogenous functional groups.), such as click chemistry, to achieve selective and efficient conjugation [57, 58].

Another approach for conjugation is the use of activated PEG derivatives. PEG can be modified with specific reactive groups, such as succinimidyl ester or isocyanate, which react directly with nucleophilic groups on the drug to form stable conjugates. This method allows for efficient and site-specific drug attachment, ensuring high conjugation efficiency and minimal loss of drug activity. Additionally, the insertion of targeted ligands or other capabilities to improve the conjugate's therapeutic qualities is possible when using activated PEG derivatives (see Fig. 4 which shows different linkers to create PEG derivatives) [59].

Enzymatic conjugation methods have also gained attention in recent years. Enzymes, such as transglutaminases, can catalyse the formation of covalent bonds between the drug and PEG through enzymatic reactions, providing a mild and selective approach to

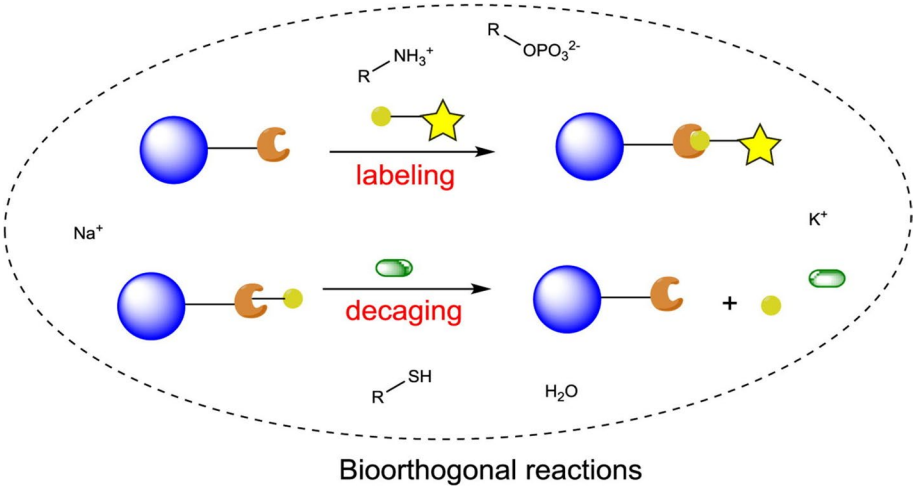

Fig. 3 Bioorthogonal chemical reactions [57]

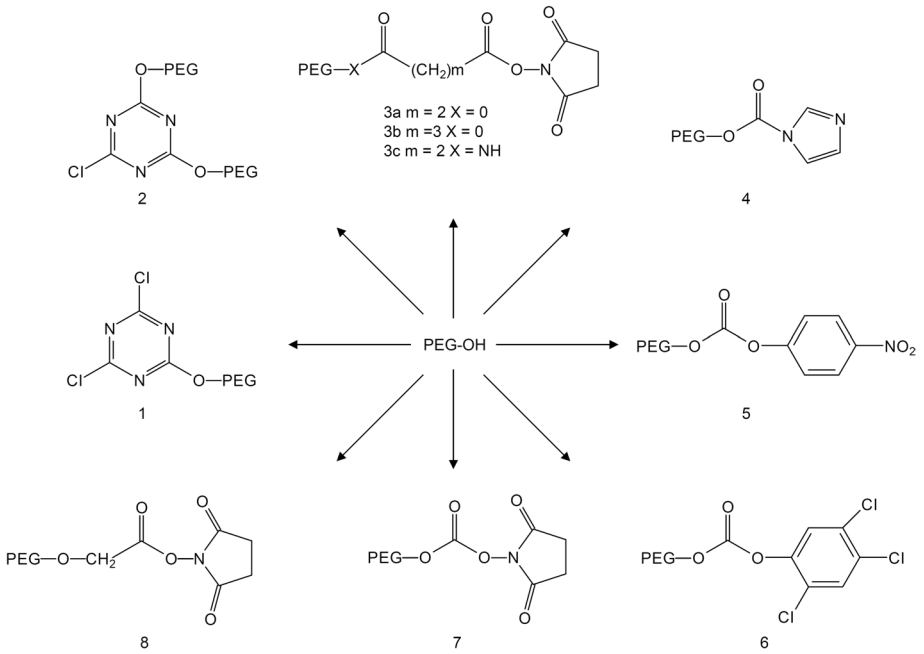

Fig. 4 Different linkers are used to activate polyethylene glycol to create its active PEG derivatives [6]. Where (1) trichloro-s-triazine (cyanuric chloride) method; (2) a variation on the cyanuric chloride method;(3a) method of PEG-succinimidyl succinate; (3b) glutarate substitution by succinate residue; (3c) adding an amide bond to replace the aliphatic ester in 3a; (4) imidazolyl formate method; (5) and (6) are variations using phenyl carbonates of PEG; (7) succinimidyl carbonates of PEG; (8) succinimidyl active esters of PEG

conjugation [59]. Enzymatic conjugation allows for site-specific drug attachment, preserving the drug's activity and minimizing non-specific interactions (see Fig. 5 which shows different groups that are catalysing the conjugation which is very crucial for the activity).

The choice of the conjugation method should consider factors such as the stability of the drug, reaction kinetics, and the desired control over drug loading. Additionally, the scalability and reproducibility of the conjugation process should be taken into account to facilitate translation from the laboratory to clinical settings. A few of the reported methods of conjugation have been tabulated in Table 2 with different drugs conjugated with different linkers with their key features and applications.

Characterization Techniques

Characterization techniques play a crucial role in evaluating the physicochemical properties and performance of polymer-drug conjugates and ensuring their successful development and effective drug delivery. Various techniques are employed which provide valuable insights into the structural characteristics, stability, drug loading, release

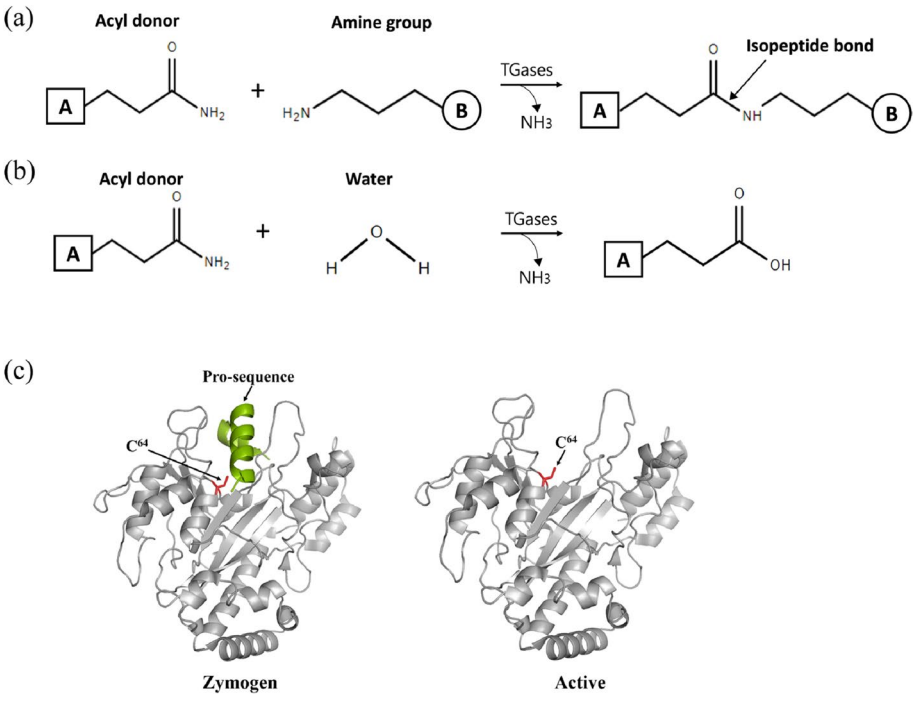

Fig. 5 mTGase is an enzyme that catalyses conjugation. **a** The free amine group and the acyl donor. By releasing an ammonia group, the isopeptide link between these two molecules is created. **b** Water and an acyl donor when there are no free amine groups. **c** The mTGase crystal structure from S. mobaraensis (PDB ID 3IU0). (Left) Due to the pro sequence, the zymogen form of mTGase folds into a helix that covers the active site (C64). (Right) This is essential for activity, the active form of mTGase exposing the active site (C64) of proteases [60]

Table 2 Different drugs conjugated with different linkers with their key features and applications

Conjugate name	Drug conjugated	Linker used	Conjugation method	Clinical condition	Highlight	Reference
PEG-maleimide	Thiol-containing drugs	Maleimide	Thiol-maleimide coupling	Cancer	Enhanced efficacy and better targeting	[61, 62]
PEG-NHS ester	Amine-containing drugs	NHS ester	Amide bond formation	Various	Improved pharmacological activity	[63, 64]
PEG-click chemistry	Various drugs	Azide/alkyne	Click chemistry	Multiple applications	Ensures targeting and controlled drug release	[30, 57]
PEG-succinimidyl ester	Nucleophilic drugs	Succinimidyl ester	Direct chemical conjugation	Various	High target affinity and specificity	[65, 66]
PEG-enzyme catalysis	Various drugs	Enzyme-specific	Enzymatic conjugation	Various	Reduced dosage frequency	[35]
PEG-liposome	Hydrophobic drugs	Lipid linker	Liposomal encapsulation	Drug delivery	Better delivery system for drugs	[67, 68]
PEG-dendrimer	Various drugs	Dendritic linker	Dendrimer-based conjugation	Targeted therapy	Control the load and release of therapeutic agents	[68, 69]
PEG-hydrogel	Water-soluble drugs	Crosslinker	Hydrogel encapsulation	Tissue engineering	Control the load and release of therapeutic agents, significant therapeutic efficacy	[67, 69]
PEG-protein	Protein-based drugs	Protein linker	Protein conjugation	Protein therapeutics	Relieves immunodeficiency	[65, 70]
PEG-antibody	Antibodies	Thioether linker	Antibody conjugation	Immunotherapy	High efficacy, low toxicity, adequate stability, and ability to overcome drug resistance	[71]
PEG-peptide	Peptide-based drugs	Peptide linker	Peptide conjugation	Metabolic disorders	Enhanced permeability and retention, sustained release	[3, 72]

Table 2 (continued)

Conjugate name	Drug conjugated	Linker used	Conjugation method	Clinical condition	Highlight	Reference
PEG-RNA	RNA-based drugs	Cleavable linker	RNA conjugation	Gene therapy	RNA nanoparticles as programmable smart complexes	[73, 74]
PEG-prodrug	Various drugs	Cleavable linker	Prodrug conjugation	Enhanced drug delivery	Improved stability and biocompatibility, enhanced permeability and retention effect, precise targeting	[75, 76]
PEG-micelle	Hydrophobic drugs	Amphiphilic linker	Micelle formation	Drug solubilization	Precise stimuli response, stimuli-responsive drug delivery systems	[77, 78]
PEG-hybrid nanoparticle	Various drugs	Hybrid linker	Nanoparticle conjugation	Combination therapy	Enhanced stability and solubility, better trans-membrane transport, prolonged circulation time, and reduced toxicity	[79, 80]
PEG-glycosaminoglycan	Glycosaminoglycan-based drugs	Spacer molecule	GAG conjugation	Regenerative medicine	More effective and safe ADCs	[81, 82]
PEG-polyphenol	Polyphenol-based drugs	Polyphenol linker	Polyphenol conjugation	Antioxidant therapy	Enhancing the central nervous system's phytochemical efficacy, targeted co-delivery	[83]

Table 2 (continued)

Conjugate name	Drug conjugated	Linker used	Conjugation method	Clinical condition	Highlight	Reference
PEG-exosome	Bioactive molecules	Exosome-derived linker	Exosome conjugation	Cell communication	Enhance delivery of incorporated drugs to target cells, increasing drug therapeutic efficacy, high loading efficacy, sustained release, and catalyse preservation against protease degradation	[84, 85]
PEG-nanobody	Nanobodies	Spacer molecule	Nanobody conjugation	Targeted imaging	Targeted therapy, improving the specificity and efficacy	[76, 86]
PEG-polymer prodrug	Various drugs	Polymer prodrug	Polymer-based prodrug conjugation	Controlled release	Improve their solubility and targeting ability, extended half-lives, high stability	[3, 87]
PEG-cell penetrating peptide	Various drugs	Cell-penetrating peptide	Peptide-based internalization	Intracellular delivery	Good efficacy, potent delivery, low toxicity	[88, 89]
PEG-magnetic nanoparticle	Magnetic drugs	Magnetic linker	Magnetic nanoparticle conjugation	Magnetic targeting	Targeted drug delivery	[90]
PEG-gold nanoparticle	Therapeutic agents	Gold linker	Gold nanoparticle conjugation	Photothermal therapy	Less toxicity and ease of detection, targeted drug delivery	[91, 92]
PEG-hydrophilic polymer	Hydrophobic drugs	Hydrophilic linker	Polymer encapsulation	Controlled drug release	Enhanced bioavailability and biocompatibility, reduced serum protein binding, increased uptake by target cells	[93, 94]
PEG-carbon nanotube	Anti-cancer drugs	Carbon nanotube linker	Carbon nanotube conjugation	Targeted cancer therapy	Improved effect and specificity	[95, 96]

Table 2 (continued)

Conjugate name	Drug conjugated	Linker used	Conjugation method	Clinical condition	Highlight	Reference
PEG-albumin	Albumin-binding drugs	Albumin linker	Albumin conjugation	Enhanced drug stability	Improved efficacy	[97]
PEG-hyaluronic acid	Hyaluronic acid–based drugs	Hyaluronic acid linker	Hyaluronic acid conjugation	Tumour targeting	Good efficacy, potent delivery, low toxicity	[88, 98]
PEG-porphyrin	Photosensitizers	Porphyrin linker	Porphyrin conjugation	Photodynamic therapy	Higher selectivity, minimal invasiveness, localized treatment and spacio-temporal control which minimizes the overall therapeutic side effects	[99, 100]
PEG-drug prodrug	Prodrug	Prodrug linker	Prodrug conjugation	Targeted drug activation	Enhanced efficacy of drug and gene delivery to target cells and tissues, decreased immunogenicity	[101, 102]
PEG-radioisotope	Radioactive drugs	Chelator	Radiolabeling	Molecular imaging	Low safety concern and high therapeutic index, chemically enhanced peptide and protein therapeutics	[103, 104],
PEG-antioxidant	Antioxidants	Antioxidant linker	Antioxidant conjugation	Oxidative stress–related diseases	Target-specific delivery of drugs, avoidance of non-target distribution, alleviated systemic toxicity, and maximized drug internalization into cancer cells	[105]

kinetics, and biocompatibility of the conjugates. Several advanced techniques have been employed to assess the key parameters of polymer-drug conjugates, including the following.

Nuclear Magnetic Resonance (NMR) NMR spectroscopy is widely used to confirm the successful conjugation of drugs to polymer carriers. It enables the identification and quantification of drug-polymer interactions, confirms the successful conjugation of the drug to the polymer backbone, and determines the degree of drug incorporation [106].

Fourier Transform Infrared Spectroscopy (FTIR) FTIR is commonly used to identify the functional group and confirm the chemical bonding between the polymer and drug by analysing the characteristic peaks of functional groups involved in the conjugation process it provides information on the chemical structure and compatibility of the conjugates [107].

Dynamic Light Scattering (DLS) DLS is used to measure the size distribution and stability of polymer-drug conjugates in solution as well as the size distribution of polymer-drug conjugates in solution. It provides insights into their stability, aggregation behaviour, and potential for controlled drug release valuable information on the hydrodynamic diameter, polydispersity, and aggregation behaviour of the conjugates [108].

Transmission Electron Microscopy (TEM) TEM allows for the visualization of polymer-drug conjugates at the nanoscale level. It provides insights into the morphology, shape, and size of the conjugates, confirming the formation of desired nanostructures [109].

In Vitro Release Studies To assess the release kinetics and drug release patterns from polymer-drug conjugates, in vitro release experiments are carried out. To simulate the drug release behaviour in the target region, these experiments are often conducted in physiologically realistic settings. To examine the drug release profiles, several techniques including dialysis, dissolution, or Franz diffusion cells are used [110].

Size Exclusion Chromatography (SEC) The molecular weight distribution and homogeneity of polymer-drug conjugates are assessed using SEC. It aids in determining how conjugation affects the size and stability of the polymer [109].

Mass Spectrometry (MS) The molecular mass and structural integrity of polymer-drug conjugates are determined by MS analysis. It gives details on purity, the ratio of drug to polymer, and if any degradation products are present [111].

Differential Scanning Calorimetry (DSC) Polymer-drug conjugates' thermal behaviour and phase transitions are assessed using DSC. Any modifications in the melting point or thermal stability brought on by drug conjugation can be detected [112].

X-ray Diffraction (XRD) The degree of drug incorporation and crystallinity within the polymer matrix are investigated using XRD analysis. It aids in determining the drug's physicochemical condition and diffusion throughout the circulatory system [111].

Thermal Analysis The thermal behaviour, melting point, and thermal stability of polymer-drug conjugates are evaluated using methods like differential scanning calorimetry (DSC)

and thermogravimetric analysis (TGA). They aid in comprehending medication stability and release patterns in varied environments [113].

Biological Assays The biological activity and biocompatibility of polymer-drug conjugates are evaluated using a variety of biological tests, such as cell viability, cytotoxicity, and cell uptake studies. These tests give information on the conjugates' therapeutic effectiveness and safety [62, 114–116].

It is essential to remember that the choice of characterization methods depends on the unique characteristics and needs of the polymer-drug conjugates under investigation. Combining these methods provides a thorough understanding of the properties and performance of the conjugates, helping their development and improvement for therapeutic uses.

Applications in Therapeutics

Due to their capacity to increase drug delivery, enhance pharmacokinetics, and target certain tissues or cells, polymer-drug conjugates have demonstrated tremendous promise in a variety of medicinal applications. Some significant uses for polymer-drug conjugates include the following.

Cancer Therapy By increasing the selectivity and effectiveness of anti-cancer medications, polymer-drug conjugates have revolutionized cancer therapy. PEGylated liposomal doxorubicin (Doxil®) is one example [15]. Paclitaxel that has been PEGylated (Genexol-PM®) [117] (Fig. 6 displays many polymeric conjugates that are utilised for anti-cancer therapy) demonstrates improved tumour accumulation, extended circulation, and lower systemic toxicity.

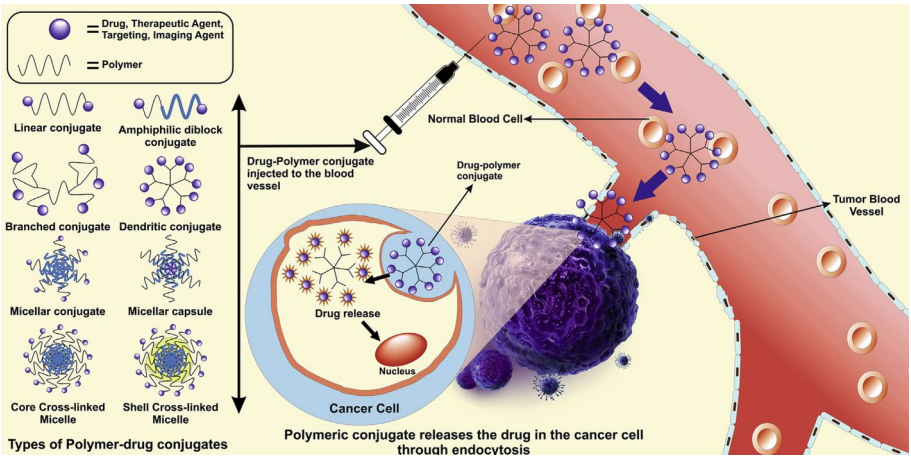

Fig. 6 Conjugate delivers medications into the body's systemic circulation in a certain sequence [118]

Targeted Drug Delivery Targeting certain tissues or cells can be done actively or passively with polymer-drug conjugates. Active targeting involves attaching ligands or antibodies to the polymer backbone, while passive targeting relies on the enhanced permeability and retention (EPR) effect. These strategies improve drug concentration at the desired site and minimize off-target effects [21].

Controlled Drug Release Polymer-drug conjugates offer the advantage of controlled drug release, allowing sustained and localized delivery of therapeutic agents. Stimuli-responsive polymers, such as temperature, pH, or enzyme-sensitive linkers, enable triggered drug release at specific sites (Fig. 7 illustrates the process of transporting and releasing activity of pH-sensitive linkers in the delivery system) [119].

Gene Delivery Polymer-drug conjugates have also been explored for gene delivery applications (see Fig. 8 exhibits the different drug delivery systems, which have been designed using PDCs). PEGylated polymeric nanoparticles can efficiently encapsulate and protect nucleic acids, enabling their delivery to target cells for gene therapy or RNA interference [121].

Anti-inflammatory and Immunomodulatory Therapy Polymer-drug conjugates can be designed to deliver anti-inflammatory or immunomodulatory drugs to treat various inflammatory and autoimmune diseases [122, 123]. Examples include PEGylated glucocorticoids

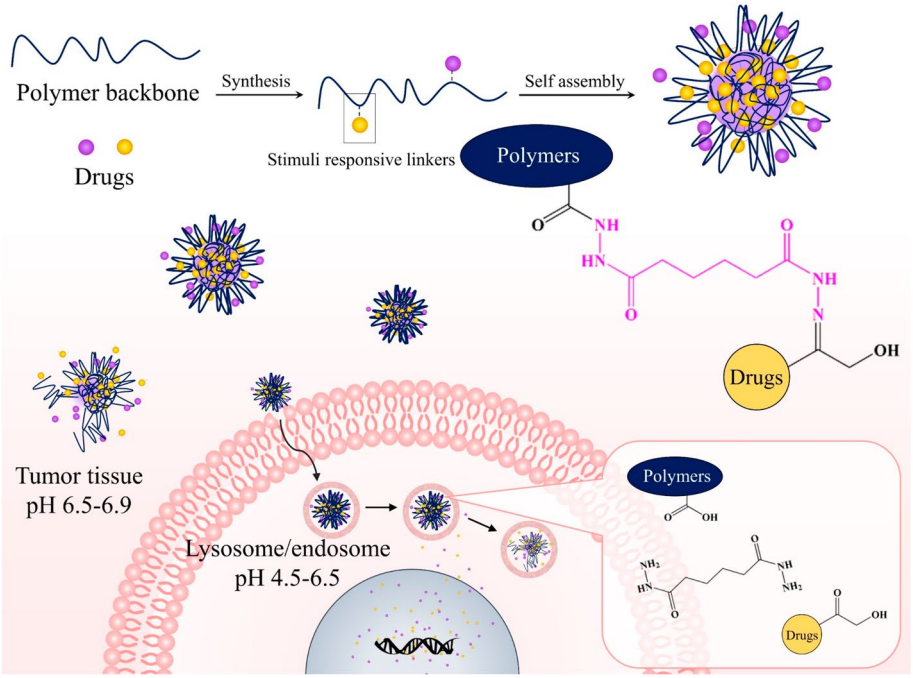

Fig. 7 Using pH-sensitive linkers, PDCs are delivered into cancer cells and released [120]

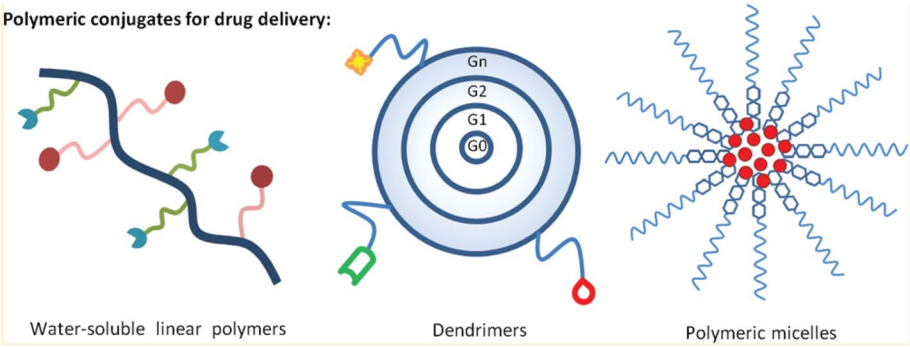

Fig. 8 Polymeric drug conjugates for drug delivery [2]

for the treatment of rheumatoid arthritis [105] and PEGylated cytokines for immunotherapy (see Fig. 9 where methods for managing the inflammatory cascade and inflammation through neutrophils, monocytes, lymphocytes, macrophages, etc. are conveyed) [124].

These applications (Table 3) demonstrate the versatility and potential of polymer-drug conjugates in improving therapeutic outcomes and addressing the limitations associated with conventional drug delivery systems.

Delivery Systems Designed from PEGylated Polymer-Drug Conjugates (PEG-PDCs)

Polymer-drug conjugates (PDCs) have emerged as a revolutionary platform for drug delivery, offering numerous advantages over conventional drug delivery systems [120, 144]. These advantages include improved solubility, enhanced pharmacokinetics, controlled drug release, and targeted delivery [145]. This review critically analyses various delivery systems designed by PEG-PDCs, highlighting their key features, advantages, and limitations.

Types of Delivery Systems from PEG-PDCs

PEG-PDCs can be utilized to design various delivery systems, catering to diverse therapeutic needs. Some of the prominent types include:

1. *Micelles*: Amphiphilic PEG-PDCs can self-assemble into micellar structures, encapsulating drugs within the hydrophobic core. Micelles offer improved drug solubility and controlled release, making them suitable for hydrophobic drugs and sustained drug delivery [146–148].
2. *Liposomes*: PEG-PDCs can be incorporated into the phospholipid bilayer of liposomes, providing them with enhanced stability, prolonged circulation times, and improved drug delivery. Liposomes enable targeted delivery through surface modifications with ligands [36, 149, 150].
3. *Nanoparticles*: Polymeric nanoparticles loaded with drugs offer enhanced bioavailability, controlled release, and targeted delivery. PEG-PDCs can be used to design

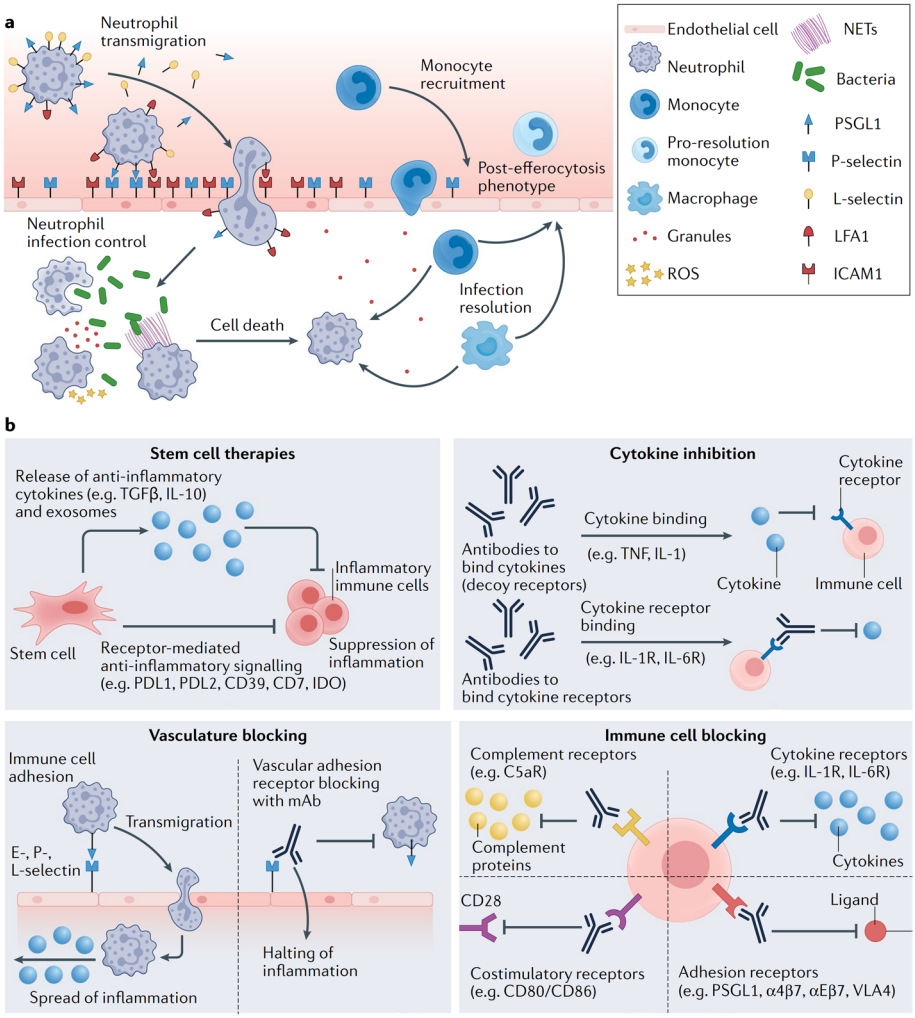

Fig. 9 **a** Recruitment of neutrophils and their roles in inflammation. By expressing P-selectin glycoprotein ligand 1 (PSGL1) and L-selectin, which bind to their respective ligands on the endothelium, neutrophils gently roll along the endothelium. Once at the region of inflammation, intercellular adhesion molecule 1 (ICAM1) on the endothelium and lymphocyte function-associated antigen 1 (LFA1) expressed on the neutrophil lock to start transmigration to the infected or inflammatory tissue area. To stop the spread of infection, neutrophils at the site of infection either phagocytose pathogens or release granules, reactive oxygen species (ROS), or neutrophil extracellular traps (NETs). After that, neutrophils commit to apoptosis, which starts other immune cell types migrating. By using efferocytosis, monocytes and macrophages eliminate dead cellular materials (pathogens and neutrophils), and they eventually go to the liver and lymph nodes to eliminate and deal with pathogenic materials. Furthermore, in order to support tissue repair, post-efferocytosis monocytes change to a pro-resolution phenotype. **b** Therapies not dependent on particles that control inflammation. stem cell therapies: mesenchymal stem cells (MSCs) that have been transplanted have the ability to generate cytokines that suppress the immune system, which can reduce immune cell recruitment and activation, increase the creation of regulatory T (Treg) cells, and block the development of T helper 1 (TH1) and T helper 2 (TH2) cells. Cytokines and antibody-based treatments: inflammatory cytokines attach to blocking antibodies or decoy receptors, which prevents their activation and reduces systemic inflammation. Vascular endothelial cells are the target of biological treatments that block certain leukocyte adhesion molecules, preventing immune cells from transmigrating and so inhibiting the inflammatory response. Targeted blocking of immune cells: by preventing certain receptors on the surface of immune cells, medications can directly revent immune cells from becoming pathologically activated. Monoclonal antibodies, or mAbs [125]

Table 3 Applications of polymer-drug conjugated systems

Application	Polymer-drug conjugate	Drug	Polymer	Clinical condition	Delivery system designed	Mode of administration	Reference
Cancer therapy	PEGylated liposomal doxorubicin	Doxorubicin	Polyethylene glycol (PEG)	Cancer	Liposomes	Intravenous	[126]
	PEGylated paclitaxel	Paclitaxel	Polyethylene glycol (PEG)	Cancer	Nanoparticles	Intravenous	[117]
	PEGylated camptothecin	Camptothecin	Polyethylene glycol (PEG)	Cancer	Micelles	Intravenous	[127]
	Folate-targeted polymer conjugates	Various	Polymer-drug conjugate	Cancer	Folate receptor ligands	Intravenous	[105, 128]
	Antibody-drug conjugates	Various	Polymer-drug conjugate	Cancer	Antibodies	Intravenous	[47]
	Transferrin-targeted polymer conjugates	Various	Polymer-drug conjugate	Cancer	Transferrin receptor ligands	Intravenous	[129]
	Polymer-drug conjugates for combination therapy	Various	Polymer-drug conjugate	Cancer	Combination of multiple drugs	Intravenous	[130]
Targeted drug delivery	Ligand-targeted polymer conjugates	Various	Polymer-drug conjugate	Various	Ligands specific to the target	Intravenous	[131]
	PEGylated nanoparticles with active targeting ligands	Various	Polyethylene glycol (PEG)	Various	Active targeting ligands	Intravenous	[132]
Controlled drug release	Stimuli-responsive polymer conjugates	Various	Polymer-drug conjugate	Various	Temperature, pH, or enzyme-sensitive linkers	Varies	[119]
	Redox-responsive polymer conjugates	Various	Polymer-drug conjugate	Various	Redox-sensitive linkers	Varies	[133]

Table 3 (continued)

Application	Polymer-drug conjugate	Drug	Polymer	Clinical condition	Delivery system designed	Mode of administration	Reference
Gene delivery	PEGylated polymeric nanoparticles	Nucleic acids	Polyethylene glycol (PEG)	Gene therapy, RNA interference	Nanoparticles	Intravenous, intratumoural	[134]
	Cationic polymer–based gene carriers	Nucleic acids	Cationic polymers	Gene therapy	Polyplexes	Intravenous	[135]
Anti-inflammatory and immunomodulatory therapy	PEGylated glucocorticoids	Glucocorticoids	Polyethylene glycol (PEG)	Rheumatoid arthritis	Nanoparticles	Intravenous, intra-articular	[136]
	PEGylated cytokines	Cytokines	Polyethylene glycol (PEG)	Immunotherapy	Nanoparticles	Intravenous	[105]
	Superoxide dismutase (SOD)–polymer conjugates	Superoxide dismutase	Polymer-drug conjugate	Oxidative stress	Polymeric nanoparticles	Intravenous	[137, 138]
	Tumour-targeted immunomodulatory agents	Various	Polymer-drug conjugate	Cancer	Immune system modulation	Intravenous	[139]
Antimicrobial therapy	Polymer-drug conjugates for antibacterial therapy	Various	Polymer-drug conjugate	Bacterial infections	Antibiotics and antimicrobial agents	Varies	[140]
	Antimicrobial peptides conjugated with polymers	Various	Polymer-drug conjugate	Bacterial infections	Antimicrobial peptides	Varies	[141, 142]
Cardiovascular disease	Polymer-drug conjugates for thrombolytic therapy	Thrombolytic agents	Polymer-drug conjugate	Thrombosis	Thrombolytic agents	Intravenous	[143]

nanoparticles with specific sizes, surface properties, and drug release profiles for tailored therapeutic applications [12, 151–153].

4. *Hydrogels*: PEG-PDCs can be incorporated into hydrogels for sustained and localized delivery of drugs. Hydrogels offer excellent biocompatibility and can provide a controlled release environment for sensitive drugs [30, 43, 69, 154, 155].
5. *Conjugates with targeting ligands*: PEG-PDCs can be conjugated with targeting ligands, such as antibodies or peptides, to specifically target diseased tissues. This approach reduces systemic exposure and enhances therapeutic efficacy while minimizing side effects [66].

Research Examples of Delivery Systems Derived from PEG-PDCs

The following table (Table 4) summarizes recent research on delivery systems designed from PEG-PDCs, highlighting key aspects of each study.

Current Challenges and Future Perspectives

PEG-PDC-based delivery systems offer significant advantages over conventional drug delivery methods [55, 163]. They can improve the therapeutic efficacy and safety of various drugs while providing controlled release and targeted delivery [32, 164]. However, further research is needed to address certain challenges, including:

- Development of more efficient and cost-effective synthesis methods [163].
- Improved targeting strategies for specific diseases and tissues [25].
- Overcoming potential immunogenicity concerns of PEGylation [116].
- Developing strategies to control and optimize drug release profiles [110, 165, 166].

Despite these challenges, PEG-PDC-based delivery systems hold immense potential for revolutionizing drug delivery and improving patient outcomes. Future research efforts focused on addressing the existing challenges and exploring new applications will further propel the advancement of this promising technology.

Overcoming Limitations in PEG-Based Polymer-Drug Conjugation

Despite the significant progress in the field of PEG-based polymer-drug conjugates, several challenges still need to be addressed. One of the challenges is the efficient and selective conjugation of drugs to PEG polymers. The development of novel linker chemistries and conjugation strategies that provide controlled and site-specific drug attachment to PEG can enhance the stability and therapeutic efficacy of the conjugates [9, 167]. Additionally, optimizing the ratio of drug to polymer and the polymer size can further improve the drug loading capacity and release kinetics of the conjugates [168, 169]. Overcoming these limitations will contribute to the development of more effective PEG-based polymer-drug conjugates.

Limited In Vitro Validation The study primarily relies on in vitro experiments [165, 170, 171]. While these experiments provide valuable insights into the basic mechanisms of

Table 4 Different delivery systems of PEG-PDCs

Delivery system	Type of PEGylation	Drug	Linker	Important outcome	Reference
Micelles	N-terminus PEGylation	Doxorubicin	Hydrazone	Enhanced tumour accumulation and improved antitumour efficacy	[121]
Liposomes	DSPE-PEG	Paclitaxel	Cleavable dipeptide linker	Enhanced drug delivery to tumours and improved therapeutic efficacy	[156]
Nanoparticles	PEG-PLA	Curcumin	Disulfide bond	Enhanced curcumin solubility, improved bioavailability, and reduced side effects	[157]
Hydrogels	PEG-based hydrogel	Insulin	Click chemistry	Sustained and localized insulin delivery, improved glycemic control	[154]
Conjugates with targeting ligands	PEG-peptide conjugate	Doxorubicin	Acid-cleavable linker	Targeted delivery of doxorubicin to cancer cells, reduced off-target toxicity	[130]
pH-responsive micelles	Methoxy-PEG	Camptothecin	Hydrazone	pH-triggered drug release in the acidic tumour microenvironment	[158]
Redox-responsive nanoparticles	PEG-SS-PLA	Cisplatin	Disulfide bond	Redox-triggered drug release in the reducing environment of tumours	[159]
Stimuli-responsive liposomes	PEG-DSPE	Doxorubicin	Temperature-sensitive linker	Ultrasound-triggered drug release for targeted cancer therapy	[160]
Biodegradable micelles	PEG-PCL	Paclitaxel	Ester bond	Biodegradable micelles for controlled drug release and reduced toxicity	[161]
Antibody-drug conjugates	PEGylation of antibody	Trastuzumab-DM1	Non-cleavable linker	Targeted delivery of cytotoxic drugs to cancer cells expressing HER2 receptors	[162]

action of the PEG-PDC-based delivery systems, they cannot fully predict the complex biological environment in vivo [172]. Further studies involving animal models and clinical trials are crucial to assess the safety and efficacy of these systems in humans.

Potential for Off-Target Toxicity While PEG-PDCs are generally considered biocompatible, there is still a risk of off-target accumulation and potential side effects [173]. This is particularly concerning for nanoparticles that accumulate in organs such as the liver and spleen. Future research should focus on optimizing targeting strategies, such as by incorporating specific ligands or antibodies, to minimize off-target delivery.

Limited Drug Loading Capacity Some PEG-PDC-based delivery systems may have limited drug loading capacity, restricting their effectiveness for certain therapeutic applications [152]. This is especially true for hydrophobic drugs that are difficult to encapsulate efficiently. Developing strategies to enhance drug loading without compromising stability and biocompatibility is crucial for realizing the full potential of these systems.

Scalability and Cost-Effectiveness Scaling up the production of some PEG-PDCs can be challenging and expensive, limiting their widespread clinical use [174]. This is a major hurdle that needs to be overcome before PEG-PDC-based therapies can be made available to patients on a large scale. Future research should focus on developing cost-effective and scalable methods for PEG-PDCs production, such as continuous flow synthesis or microfluidic technologies.

Limited Understanding of Long-Term Effects The long-term effects of PEG-PDC-based delivery systems are not fully understood [172, 175]. This is a significant concern, as nanoparticles can potentially accumulate in the body and cause long-term toxicity. Further studies are needed to investigate the potential for long-term effects and bioaccumulation of PEG-PDC-based systems before they can be widely adopted in clinical practice.

Regulatory Considerations and Clinical Translation of PEG-Based Systems

The clinical translation of PEG-based polymer-drug conjugates requires careful consideration of regulatory aspects. Understanding the regulatory requirements for the development, manufacturing, and clinical evaluation of PEG-based conjugates is crucial for their successful translation into the clinic. Issues related to the safety, toxicity, pharmacokinetics, and immunogenicity of the conjugates need to be thoroughly investigated [39, 176]. Moreover, scalability and reproducibility of the synthesis and manufacturing processes should be addressed to ensure consistent product quality. Collaboration between researchers, clinicians, regulatory authorities, and industry partners is essential to navigate these regulatory challenges and facilitate the clinical translation of PEG-based polymer-drug conjugates [130, 151].

Emerging Trends and Future Directions for PEG-Based Research

The field of PEG-based polymer-drug conjugates is continuously evolving, and several promising trends and future directions can be identified. One such trend is the development of multifunctional conjugates that combine therapeutic agents with imaging probes or targeting ligands to enable personalized medicine and improve treatment outcomes

[177, 178]. Furthermore, the integration of stimuli-responsive properties into PEG-based systems allows for on-demand drug release at specific disease sites, enhancing therapeutic efficacy and minimizing off-target effects [179, 180]. Exploring new polymers, such as dendrimers, hyperbranched polymers, or supramolecular polymers, holds promise for expanding the versatility and functionality of PEG-based conjugates [22]. Additionally, advances in nanotechnology and nanomedicine can offer innovative strategies for the delivery of PEG-based conjugates, including the development of novel nano-carriers or combination therapies [22, 181]. The development and clinical use of PEG-based polymer-drug conjugates will be aided by continued research efforts in these fields.

Future Scopes

Development of Novel PEG-PDC-based Platforms New PEG-PDC-based systems with improved functionalities, such as stimuli-responsive release, multimodality imaging, and combined drug delivery, can be developed to address specific therapeutic needs. These advanced systems can offer greater control over drug delivery and improve therapeutic efficacy.

Integration with Advanced Technologies PEG-PDCs can be integrated with nanotechnologies, biomaterials, and artificial intelligence to create more sophisticated and personalized delivery systems. This integration can lead to the development of smart and responsive systems that can tailor their delivery behaviour to the specific needs of each patient.

Exploration of New Therapeutic Applications PEG-PDCs can be explored for the delivery of various therapeutic agents, including gene editing tools, nucleic acids, and cell-based therapies. This opens up a wide range of potential applications for PEG-PDC-based systems in treating various diseases.

Improved In Vivo Studies More comprehensive preclinical studies using relevant animal models are essential to assess the safety and efficacy of PEG-PDC-based systems in vivo. These studies should involve testing the systems in various disease models and evaluating their long-term effects.

Clinical Translation The successful translation of PEG-PDC-based delivery systems into clinical practice requires robust clinical trials to demonstrate their safety and efficacy in humans. These trials should be well-designed and conducted following ethical guidelines to ensure the safety and well-being of patients.

Discussion and Conclusion

The design and production of PEG-based polymer-drug conjugates and their therapeutic uses, as well as the existing difficulties and promising future directions in this sector, have all been covered in this article. The discussion has highlighted the significance of PEGylation as a tactic to improve drug delivery system effectiveness and get around the drawbacks of traditional formulations.

The benefits of PEG-based polymer-drug conjugates include better solubility, longer circulation times, less immunogenicity, and tailored drug delivery. These conjugates have

proven to improve drug stability, controlled release, and selective targeting of particular tissues or cells through logical molecular design, linker selection, and conjugation techniques [130, 150, 182–184]. The effectiveness and specificity of drug conjugation are greatly influenced by the choice of linker and conjugation technique. The intended release kinetics, stability, and biocompatibility of the conjugates should be taken into account while choosing and designing suitable linkers and conjugation techniques [120, 123, 185]. Characterization methods are essential for evaluating the physicochemical properties, stability, and efficacy of PEG-based polymer-drug conjugates. Numerous techniques, including spectroscopy, chromatography, and microscopy, may be used to analyse the structural characterization of the conjugates, release kinetics, and efficiency of drug loading. These techniques help to guarantee the consistency and quality of the conjugates for use in clinical trials and additional research [153, 180, 184, 186]. The conjugates have enhanced treatment outcomes, decreased systemic toxicity, and patient compliance. They might be designed to specifically target cancer cells or tumour microenvironments, enabling site-specific drug delivery and minimizing adverse effects. PEG-based conjugates can be changed to add other capabilities, such as imaging agents or stimuli-responsive components, expanding their potential for application in diagnostic and therapy monitoring [187–190]. PEG-based polymer-drug conjugates have demonstrated great potential, but there are still several problems that need to be fixed. Overcoming limitations in conjugation efficiency, stability, and scalability is crucial for their successful translation into clinical use. Regulatory considerations play a significant role in the development and approval of PEG-based systems for therapeutic applications, necessitating rigorous preclinical and clinical evaluations. Future research should focus on developing more advanced and multifunctional conjugates, exploring novel polymers, optimizing drug loading and release kinetics, and addressing potential immunogenicity issues.

In conclusion, PEG-based polymer-drug conjugates represent a promising approach for improving drug delivery in various therapeutic areas. Their rational design, selection of appropriate linkers and conjugation methods, and comprehensive characterization enable enhanced therapeutic efficacy and reduced toxicity. The applications of these conjugates in cancer therapy and other diseases highlight their potential impact in the field of therapeutics. However, further research and development efforts are required to overcome existing challenges and realize the full potential of PEG-based polymer.

Abbreviations PEG: Poly ethylene glycol; PDC: Polymer Drug conjugates; DSPE-PEG: 1,2-Distearyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol); SiRNA: Small interfering RNA; PEG-PCL: Poly(ethylene glycol)-Poly(ε-caprolactone)copolymers; RNA: Ribonucleic acid; DNA: Deoxy ribonucleic acid; PEG-PLA: Poly(ethylene glycol)-polyactide-poly(ethylene glycol)

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Data Availability Not applicable.

Declarations

Ethical Approval Not applicable.

Consent to Participation All the authors had their consent for participation in the reported study.

Consent for Publication All the authors had their consent for the publication of the reported study.

Competing Interests The authors declare no competing interests.

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