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Polymer–Drug Conjugates for Oral Delivery: Design Strategies, Barriers, and Translational Progress

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ABSTRACT

Oral drug delivery is preferred but frequently limited by physiological obstacles, including enzymatic degradation and poor permeability. Polymer-Drug Conjugates (PDCs) offer a promising strategy by improving stability and absorption; however their practical application for oral delivery significantly trails behind that of parenteral administration. This review examines current progress in oral PDCs, emphasizing strategic design approaches to address gastrointestinal challenges, including polymer backbone selection, linkers, and active targeting mechanisms. We summarize reported improvements on bioavailability and toxicity, while critically examining ongoing translational challenges such as manufacturing scalability and regulatory complexities, offering insights to bridge the gap between academic innovation and clinical application.

Keywords:
Oral drug delivery; Polymer-drug conjugates; Polymeric carriers; Cleavable linkers; Intestinal uptake; gastrointestinal barriers

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1. Introduction

For decades, researchers have focused on developing methods to improve drug delivery through the oral route as the most preferred method due to its convenience, non-invasiveness, and high patient compliance [1]. This method allows for easy ingestion and is familiar to patients, which typically results in better adherence to medication regimens [2]. However, oral administration often has considerable drawbacks that need to be addressed to ensure effective treatment. Poor bioavailability because of the physicochemical properties of drugs, enzymatic degradation, harsh conditions in the GI tract environment, and some drugs could undergo significant first-pass metabolism in the liver are some of the challenges of oral drug delivery [3], [4], [5]. Hence, rational oral administration of biologics or small molecules is essential to achieve optimal bioavailability and therapeutic efficacy.

The concept of polymer-drug conjugates (PDCs) was proposed by Helmut Ringsdorf in the 1970s, with significant advancements occurring in the 1990s [6], [7]. In the field of polymer-based nanomedicine, polymer-drug conjugates (PDCs)—also referred to as polymeric prodrugs—represent a distinct category of macromolecules. In this review, PDCs are defined as therapeutic platforms where a drug molecule is

covalently bonded to a polymeric backbone. PDCs were different from physical entrapment systems, such as nanoparticles or micelles, where the drug is encapsulated through hydrophobic interactions rather than chemical conjugation. This conjugation can be direct or through a linker, which can be designed to release the drug under specific conditions or ensure controlled release by preventing premature drug detachment. As a result, PDCs have emerged as an innovative drug delivery system and offer several advantages over conventional drug formulations [8], [9], [10].

PDCs has undergone significant progress, with most of commercialized products utilizing PDC systems are parenteral formulations that leverage water-soluble polymers, such as polyethylene glycol (PEG) to improve the pharmacokinetics and stability of drugs. While PDCs are predominantly recognized for cancer therapy, their application has broadened to various non-cancer areas, including the treatment of pain, and diabetes. A summary of the marketed and clinical polymer-based therapeutic formulations is presented in **Table 1**.

Despite various successes, nearly all clinically and commercially successful conjugates are prepared for the parenteral route. This is exemplified by the fact that the commercial success for oral delivery remains extremely limited. Movantik is currently the sole PDCs for oral delivery that has received FDA approval in 2014 [11]. Additionally, the number of oral PDCs currently undergoing clinical studies remains extremely low. This situation highlights that the delivery of PDCs via the oral route remains a significant, unresolved challenge.

Nevertheless, the potential of PDCs extends beyond parenteral applications. PDCs offer a unique platform to overcome the main barriers to conventional oral drug delivery. By conjugating the drug to a polymeric carrier, stability can be significantly enhanced, protecting the drug from enzymatic degradation and the extreme pH of the stomach. Furthermore, appropriate PDCs design strategies can improve drug solubility, and modulate mucoadhesion or absorption transport (uptake) across the intestinal epithelium, ultimately aiming to enhance oral bioavailability [9]. Therefore, this review summarizes the key developments and advantages of PDCs for oral delivery, offering insights to support future innovation in targeted and efficient drug administration over the last decade.

2. Methods

This narrative review was conducted using a structured search of electronic databases (Google Scholar, PubMed, Scopus, and ScienceDirect) to identify experimental studies on orally administered polymer–drug conjugates (PDCs). The search covered publications from January 2015 to December 2025, with the last update performed in January 2026. Search strings combined terms related to PDCs and oral delivery, for example: ("polymer–drug conjugate" OR "PDC" OR "polymeric prodrug") AND ("oral delivery" OR "oral administration" OR "intestinal uptake") AND ("bioavailability" OR "pharmacokinetic" OR "efficacy" OR "toxicity"). Original research articles were prioritized as the primary evidence base; however, books and regulatory documents were also consulted for contextual background (mechanistic rationale and translational/regulatory considerations), not as primary efficacy evidence. Review papers, patent and conference proceedings are excluded. Records were compiled, duplicates removed, and studies were selected through sequential screening. The article selection process illustrated in **Figure 1**.

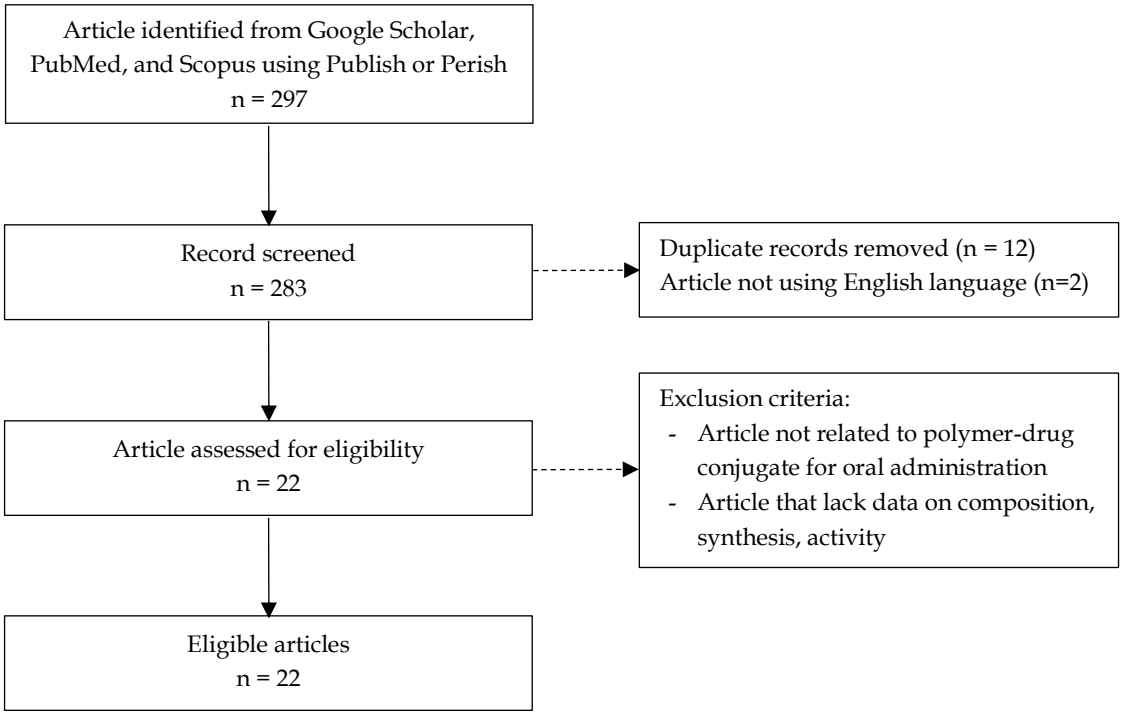

Figure 1. PRISMA flow diagram of article research

3. Results and Discussion

The results of the literature search regarding the development of polymer-drug conjugate (PDC) products, including those currently marketed and those in clinical trials, categorized by their respective administration routes, are summarized in Table 1. These data highlight that while PDCs have seen significant success in parenteral administration, their commercial application for the oral route remains extremely limited.

Table 1. Marketed and clinical polymer-drug conjugate based therapeutic formulations

Name	Polymer carrier	Drug	Indication	Administration Route	Year of approval	Marketed / clinical trial	Refs
Adagen	PEG	Pegademase bovine	Severe combined immunodeficiency disease (SCID)	IM injection	1990	Discontinued	[12]
Neulasta	PEG	Filgrastim	Decrease infection manifested by febrile neutropenia	SC injection	2002	Marketed	[13]
Oncaspar	PEG	L-asparaginase	Acute lymphoblastic leukemia	IV injection	2006	Marketed	[14]
Plegridy	PEG	Interferon b1a	Relapsing multiple sclerosis	SC injection	2014	Marketed	[15]
Movantik	PEG	Naloxegol Oxalate	Opioid-induced constipation	Oral	2014	Marketed	[11]
Adynovate	PEG	Factor VIII	Hemophilia A	IV injection	2015	Marketed	[16]
Revcovi	PEG	Elapegademase	Treatment of ADA-SCCID	IM injection	2018	Marketed	[17]
Enhertu	Deruxtecan	Trastuzumab	HER2-positive breast cancer	IV infusion	2019	Marketed	[18]
NKTR-105	PEG	Docetaxel	Refractory solid tumors	IV infusion	-	Phase III	[19]
ONCOFID-P-B	HA	Paclitaxel	Refractory bladder cancer and peritoneal carcinosis	Intravesical instillation	-	Phase III	[21]
Pegamotecan	PEG	Camptothecin	Gastric cancer	IV infusion	-	Phase II	[22]
Prolindac	HPMA	Platinate	Solid tumors	IV infusion	-	Phase II	[23]
CT-2106	PGA	Camptothecin	Solid tumor malignancies	IV infusion	-	Phase II	[24]
Prothecan	PEG	Camptothecin	Gastric tumors	IV infusion	-	Phase II	[25]
NKTR-102	PEG	Irinotecan	Colorectal and metastatic breast tumors	IV infusion	-	Phase II	[26]
PK1 (FCE28068)	HPMA	Doxorubicin	Breast and lung cancer	IV infusion	-	Phase II	[27]

Name	Polymer carrier	Drug	Indication	Administration Route	Year of approval	Marketed / clinical trial	Refs
PK2 (FCE28068)	HPMA	Doxorubicin	Hepatocellular carcinoma	IV infusion	-	Phase II	[27]
PEX168	PEG	Loxenatide	Type 2 diabetes mellitus	Subcutaneous	-	Phase I	[28]

Polymer-Drug Conjugates

In the area of polymer-based nanomedicines, specifically PDCs which are also known as polymeric prodrugs or polymer therapeutics are currently being developed. PDCs is a drug which covalently bound to a polymer backbone. PDCs represent a distinct category of macromolecules generated through several chemical processes depending on the chemistry of the drugs and polymers involved. PDCs typically consist of four components: the drug, the polymer, a targeting moiety and a linker that connects them. Most PDCs are structurally based on the concept provided by Ringsdorf, wherein therapeutic chemicals are conjugated to a polymer backbone that may additionally have solubilizing units or targeting moieties. Various types of polymers are utilized in drug conjugation, each with unique properties and applications, including natural polymers and synthetic polymers [31]. This polymer plays a multifaceted role in improving drug solubility, stability, and pharmacokinetics. Additionally, it facilitates controlled and targeted drug release, reduces immunogenicity, and supports versatile, customizable drug delivery systems. These features collectively enhance the therapeutic efficacy and safety of drugs [32].

This chemical conjugation via a cleavable linker is what uniquely distinguishes PDCs from other polymer-based drug delivery systems. In contrast, systems such as polymeric nanoparticles, micelles, or solid dispersions operate on the principle of physical entrapment. In these systems, the drug is not chemically bonded but is instead physically encapsulated within the polymer matrix, solubilized in a hydrophobic core (in micelles), or molecularly dispersed [33], [34], [35]. Consequently, these physically entrapped systems are often governed by diffusion or polymer erosion and can be more susceptible to premature drug "burst release" compared to the chemically controlled release of PDCs.

Importantly, the covalent bonding in PDCs minimizes this risk of premature "burst release" and ensures that the drug remains inactive as a prodrug until it reaches the desired site. To achieve this, the linker is a critical component that influences the characteristics of the PDCs. It is a molecule that chemically binds the drug to the polymer backbone via a stable covalent linkage, effectively creating a new macromolecular entity [36]. This linker must strike a crucial balance, it needs to be stable enough to withstand the synthesis and purification process yet remain sufficiently labile to cleave and release the active drug under specific physiological conditions, such as low pH or in the presence of target enzymes [37], [38].

Design Strategies for Oral Pdcs Delivery

When administered orally, PDCs encounter numerous challenges within the GI tract before entering systemic circulation and reaching the target site. The maximum size of molecules that can be absorbed is largely determined by the absorption pathway and physicochemical properties of the molecule. In general, small and lipophilic molecules (MW < 500-700 Da) pass through the membrane by passive diffusion [39], whereas hydrophilic molecules (MW 100-200 Da) utilize more restricted paracellular pathways [40]. For larger molecules, such as peptides and amino acids, absorption is possible through carrier-mediated transport, even up to a size of about 4 kDa [41]. Therefore, the rational design of the polymeric carrier and linker chemistry is essential to navigate these barriers.

Polymeric Carrier Design: Backbone Selection

The transition of PDCs from parenteral to oral delivery necessitates critical polymer selection although the basic principle remains the same, which is utilizing

polymer functional groups to covalently bind therapeutic agents. Selection of the polymer carrier is guided by the need for biocompatibility and biodegradability, alongside the requirement to shield the payload from enzymatic activity and the low pH of the stomach while facilitating absorption [42]. Polymers, both synthetic (such as PEG, MBA, PAMAM, β-cyclodextrin) and natural (such as hyaluronic acid, chitosan, gum arabic, dextran, and other polysaccharide derivatives), are being explored for their ability to protect PDCs from the extreme acidic environment of the stomach and extensive enzymatic degradation. Additionally, natural polymers such as chitosan or functional synthetic polymers are often investigated for their properties to increase bioavailability or their ability to enhance epithelial permeability, which are key factors in improving the generally poor intestinal absorption of macromolecular systems [43], [44].

Ideally, the hydrophilicity profile of a polymer dictates its function in oral delivery. Hydrophilic polymers (e.g., PEG, chitosan), characterized by the presence of polar functional groups (e.g., –OH, –COOH, $–NH_2$) have a strong affinity for water and are optimal for enhancing drug solubility and mucoadhesion. PEG is especially valued for increasing circulation time and solubility of drugs, while chitosan offers mucoadhesive properties ideal for targeting mucosal surfaces [45], [46].

Conversely, hydrophobic polymers are typically used to protect drugs from acidic environments and provide controlled release through slow erosion or diffusion. Their limited water solubility enables them to maintain drug integrity during GI transit and release the drug gradually over time, which is beneficial for drugs with narrow absorption windows or requiring sustained plasma concentrations [47], [48].

Amphiphilic polymers, which possess both hydrophilic and hydrophobic segments (e.g., PEG-PLA and polyphosphazenes), represent a versatile class capable of self-assembling into micelles or nanoparticles that encapsulate a wide variety of drugs. These structures can encapsulate hydrophobic drugs in their core while presenting a hydrophilic shell, offering tuneable properties and stimuli-responsive behavior, making them suitable for both protecting drugs in the stomach and enabling targeted release in the intestine [49], [50]. Their ability to self-assemble and respond to environmental cues (e.g., pH, redox) makes them powerful tools in advanced oral drug delivery systems.

Improving Solubility

A primary challenge for many oral drugs (BCS Class II/IV) is poor aqueous solubility, which limits absorption. Conjugating a hydrophobic drug to a hydrophilic or amphiphilic polymer creates a new, more soluble entity [51]. For instance, Lu [52] designed a cholic acid-functionalized PEGylated paclitaxel (PTX) prodrug that self-assembled into nanoparticles, increasing PTX's aqueous solubility by a remarkable 30,000-fold. Similarly, natural polymers like gum arabic have been utilized to improve the solubility of lipophilic drugs such as curcumin dramatically and achieved a 900-fold increase in solubility [53]. Tian [54] and Zeng [55] both utilized chitosan derivatives (carboxymethyl chitosan and chitosan oligosaccharide, respectively) to dramatically improve the solubility of celastrol, increasing it from <1 μg/mL to over 18 mg/mL.

Enhancing Mucoadhesion and Permeability

Beyond solubility, polymers can facilitate absorption by extending residence time (mucoadhesion) or opening transport pathways (permeability) [44]. Mucoadhesive polymers could prevent rapid GI transit, for example Cesar [56] demonstrated that conjugating mesalamine (5-ASA) to chondroitin sulfate (CS) allowed the conjugate to bypass upper GI absorption and accumulate preferentially in the colon for up to 8 hours.

Chitosan-catechol conjugates have also been confirmed to enhance mucoadhesion properties, confirming their safety for oral use [57].

Furthermore, PDCs can enhance transport across the intestinal epithelium via paracellular or transcellular pathways. Miao [58] showed that conjugating ellagic acid (BCS Class IV) to arabinogalactan has been shown to enhance paracellular transport, leading to a 3.6-fold increased permeability. Another strategy involves increasing the hydrophobicity of hydrophilic drugs; for instance, Liu [43] conjugated LMW heparin with cytarabine, which enhanced its hydrophobicity and resulted in a 5.5-fold increase in oral bioavailability (AUC) after oral administration.

In summary, the hydrophilicity profile of a polymer—whether hydrophilic, hydrophobic, or amphiphilic—greatly influences its suitability for oral drug delivery. Hydrophilic polymers are optimal for enhancing solubility and mucoadhesion; hydrophobic polymers provide sustained, protective release; and amphiphilic polymers combine these strengths to enable targeted, environment-responsive delivery. Selecting the appropriate polymer type is therefore critical in designing effective and stable oral PDC formulations.

Linker Chemistry: The Key to Release

The linker's design is the primary obstacle in the development of oral PDCs, as it must be adaptable to pass through two drastically different biochemical conditions. To ensure the conjugate remains intact during gastric transit, the linker must exhibit high stability against acid-catalyzed hydrolysis (pH 1–3) and pepsin degradation. Premature release in the stomach leads to drug degradation and a significant loss of the dose available for absorption. Conversely, the linker must become labile and cleave to release the active drug once it reaches the lower GI tract or the systemic target site [59].

pH-Responsive Linkers

This strategy exploits the pH gradient of the GI tract or the tumor microenvironment. Ideally, linkers should remain stable in the acidic stomach (pH 1–3) but hydrolyze in the neutral to slightly alkaline environment of the intestine (pH 6.8–7.4) [60]. For example, Nkazi [61] developed PDCs with hydrazone linkers that were stable at neutral pH but rapidly degraded at acidic pH (5.5), designed to release the drug specifically in the slightly acidic tumor microenvironment after the PDC has been absorbed systematically.

Enzyme-Responsive Linkers

Enzymatic triggering is a highly specific strategy, particularly for targeting the colon or responding to metabolic enzymes in the liver/plasma.

- **Intestinal targeting**: Ester-based linkers are commonly used to be cleaved by esterases abundant in the intestine [59].
- **Colon targeting**: Azo bonds and polysaccharide-based linkers are designed to resist digestion in the stomach and small intestine, only to be degraded by specific enzymes (e.g., azoreductase, dextranase) produced by colonic microbiota [59]. Kumar [62] demonstrated this by linking erlotinib to a polyphosphazene backbone via an azo bond, ensuring stability in the upper GI tract and specific release in the colon. Similarly, Lee [63] used a glutamic acid linker for a dextran-celecoxib conjugate, which was cleaved by microbial enzymes, achieving high colonic drug concentration without systemic absorption. In another study, El-Kamel [64] conjugated flurbiprofen to β-cyclodextrin. The conjugate was stable in the upper GI tract but released over 60% of the drug in rat colon homogenates by the action of enzymes produced by microflora in rat colon.

Redox-Responsive Linkers

For PDCs designed to be absorbed intact and release their payload inside target cells (e.g., cancer cells), redox-responsive linkers are effective. Disulfide bonds are stable in the oxidative environment of the GI tract and bloodstream but are rapidly cleaved by high intracellular glutathione (GSH) levels. Hong [65] utilized a disulfide linker for an L-carnitine-modified camptothecin prodrug, which remained stable in simulated GI fluids but triggered tumor-specific release upon exposure to high GSH. Ren [66] applied a similar strategy with a curcumin-PEG conjugate, confirming that significant drug release (>60%) over 72 hours occurred only in high-GSH environments.

Advanced Targeting and Transport

In the field of oral PDCs, selecting polymers based on their drug delivery mechanisms is essential to overcoming physiological barriers in the GI tract. Beyond passive protection, modern PDC designs utilize advanced mechanisms to facilitate uptake and ensure active site-specific delivery.

Stimuli-Responsive Systems

One of the most common strategies is the use of stimuli-responsive or "smart" polymers, which offer sophisticated control by releasing the drug only when exposed to specific physiological conditions such as pH, redox gradients, or enzymes. These systems enable targeted delivery to specific regions like the small intestine or tumor tissue. For instance, Shi [49] developed mPEG–PLA micelles that remained stable in the acidic stomach but disassembled to release docetaxel in the more neutral environment of the intestine. Similarly, dextran conjugated with platinum (IV) compounds was designed to release its cargo specifically in reductive tumor environments, thereby enhancing site-specific delivery and reducing systemic side effects [67].

Receptor-Mediated Targeting

To improve intestinal absorption, polymers can be conjugated with ligands that bind selectively to receptors on the intestinal epithelium or target tissues. This mechanism allows for highly specific uptake through endocytosis, minimizing off-target effects and improving bioavailability.

- **Bile Acid Transporters**: Lu [52] functionalized a PEG-PTX conjugate with cholic acid to target the Apical Sodium-dependent Bile Acid Transporter (ASBT). This modification resulted in a 4-fold greater intestinal permeability compared to the commercial formulation Taxol®.
- **Folate Receptors**: Ren [66] modified a curcumin conjugate with folic acid (FA). Since folate receptors are overexpressed on many cancer cells, this modification led to significantly higher cellular uptake in FR-positive MCF-7 cells. In another study, Mohanty [68] developed galactosamine-HPMA conjugates that selectively deliver drugs to cancer liver tissues with abundant folate receptors.
- **Asialoglycoprotein Receptors (ASGPR)**: Sarika [53] utilized gum arabic, which naturally contains galactose residues. These residues targeted the ASGPR on HepG2 liver cancer cells, leading to selective cytotoxicity.

Carrier-Mediated Transport

Lastly, some PDCs exploit endogenous cellular transporters like SGLT or PEPT1 to cross the intestinal barrier by modifying polymers with nutrient analogs like glucose or peptides. This method is particularly useful for delivering hydrophilic or macromolecular drugs that typically have poor permeability, although it requires balancing transporter saturation and competitive inhibition by endogenous substrates

[45]. A notable example is the study by Hong [65], which utilized an L-carnitine moiety to target the OCTN2 transporter. This facilitated transcytosis, leading to a 188.5-fold higher apparent permeability than free camptothecin (CPT) and achieving a final oral bioavailability of 49.6%, compared to only 6.3% for free CPT.

Together, the stimuli-responsive release, receptor-mediated targeting, and transporter-facilitated uptake mechanisms represent the diverse strategies by which PDCs can improve the safety, efficacy, and specificity of oral drug delivery systems. By tailoring the polymer design to the intended mechanism, researchers can optimize therapeutic outcomes while minimizing side effects and improving patient compliance.

Therapeutic Improvements

It becomes evident that the design strategies discussed previously—from the rational selection of the polymer backbone and linker chemistry to the inclusion of advanced transport mechanisms—are not just isolated technical solutions. They work in concert to directly address the core challenges of oral delivery. Ultimately, the success of the PDC platform is validated by the tangible and often synergistic therapeutic outcomes that emerge from such an integrated design approach.

Enhanced Bioavailability & Efficacy

The primary goal of oral PDCs engineering is to translate improved solubility and stability into superior systemic exposure and therapeutic effect. A study by He [69] provides compelling evidence for this using trimethyl chitosan-paclitaxel conjugates (TMC-PTX and FA-TMC-PTX) for oral delivery.

- **Pharmacokinetic Advantage**: The orally administered conjugates achieved high oral bioavailability (>180%) in rats. Furthermore, they exhibited substantially prolonged circulation compared to intravenous free PTX, with terminal half-lives ($t_{1/2}$) and mean residence times (MRT) increasing approximately 15–17 times and 33–35 times, respectively.
- **Therapeutic Outcome**: This extended circulation translated directly into superior anti-tumor activity. In H22 tumor-bearing mice, the oral conjugates resulted in tumor inhibition rates (TIR) of 60.0% (TMC-PTX) and 69.4% (FA-TMC-PTX), significantly outperforming the 39.5% TIR observed with conventional intravenous free PTX. Crucially, tissue distribution analysis showed lower accumulation in the kidneys compared to the IV group, suggesting that the oral route not only improved efficacy but also mitigated systemic toxicity risks.

These findings collectively demonstrate that the oral administration of these TMC-based conjugates is not only viable but also offers significant therapeutic advantages over standard intravenous PTX therapy.

Reduced Toxicity & Adverse Effects

One of the distinct advantages of PDCs is their ability to alter biodistribution, directing drugs away from healthy tissues. Chi [70] demonstrated this by linking the anti-cancer drug norcantharidin (NCTD) to carboxymethyl chitosan (CMCS) to inhibit the proliferation and migration in BEL-7402 liver cancer cells.

- **Toxicity Reduction**: The conjugate exhibited a 3.2-fold higher AUC and a longer mean residence time in blood compared to the free drug. Importantly, this altered profile significantly decreased drug accumulation in the heart and kidneys. Histological analysis confirmed a reduction in cardiac and renal damage, which are common severe side effects of free NCTD.

- **Efficacy Retention**: Despite the reduced toxicity, the conjugate maintained superior in vivo anti-tumor efficacy, achieving a tumor inhibition rate of 56.20% in H22 tumor-bearing mice compared to 30.27% for the free drug at an equivalent dose, while also preventing the drug-induced body weight loss.

Beyond the toxicity of the drug payload, the safety of the polymeric carrier itself is critical. Kaur [57] conducted a comprehensive acute oral toxicity study of chitosan-catechol conjugates. They established a high safety margin with an LD_{50} greater than 2,000 mg/kg in mice. Over a 14-day observation period, no significant changes in behavioral patterns, hematological markers or organ histopathology (stomach, intestine, kidney, liver, pancreas, spleen, lungs, heart, and brain) were observed, confirming that these modified biopolymers are non-toxic and safe for use as oral drug delivery systems.

Targeted Delivery

For diseases localized in the GI tract, such as Inflammatory Bowel Disease (IBD), PDCs can minimize systemic absorption while maximizing local drug concentration. Hou [71] developed a novel inflammation-retentive PDC by linking mesalamine (MES) to high-molecular-weight hyaluronic acid (HA).

This HA-MES conjugate demonstrated exceptional stability in the upper GI tract, releasing less than 10% of its payload in simulated gastric fluids, which correlated with significantly reduced systemic plasma concentrations (C_{max} and AUC) in vivo compared to free MES or a physical mixture (HA+MES). In vivo fluorescence imaging revealed a 7.3-fold higher accumulation of the conjugate at inflamed colonic sites compared to free drug, persisting for up to 24 hours. This targeted retention allowed for a significant dose-sparing effect, where the conjugate was as therapeutically effective at a low dose (10 mg/kg) as the free drug was at a 3-fold higher dose (30 mg/kg). The therapeutic mechanism was linked to superior mucosal healing, evidenced by the restoration of tight junction proteins zonula occludens-1 (ZO-1), the modulation of inflammatory cytokines (TNF-α, IL-1β), and an increase in anti-inflammatory IL-10.

Synthesis and Conjugation Chemistries of Polymer-Drug Conjugates

The synthesis of PDCs relies on robust and specific conjugation chemistries to covalently link the drug to the polymer backbone, often via a cleavable linker. The choice of reaction is critical to ensure high conjugation efficiency and stability during synthesis and storage, while allowing for predictable drug release at the target site. Among the various techniques, several methods are commonly employed:

- **Amidation and Esterification**: These are classic methods frequently used to attach drugs with free amine ($-NH_2$) or hydroxyl (-OH) groups to polymers possessing carboxylic acid (-COOH) groups. Activation by coupling agents like EDC/NHS is typically required to facilitate these reactions [56], [71].
- **Disulfide Bond Formation**: This method is paramount for stimuli-responsive systems, particularly those targeting intracellular release. Disulfide bonds remain stable in circulation but are rapidly cleaved in the reductive intracellular environment [65], [66], [72].
- **'Click' Chemistry**: More recently, reactions such as the Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC) have gained prominence. Due to their high efficiency, specificity, and mild reaction conditions, 'click' reactions are ideal for conjugating complex biologic drugs without compromising their therapeutic activity [73].

A comprehensive summary of PDCs formulations and their respective synthesis strategies is provided in **Table 2**.

Table 2. Composition and Chemical Linkages of Diverse Polymer-Drug Conjugates

Payload	Polymer	Linker	Conjugation agent	Conjugation bond	Ref.
Celastrol	Chitosan - oligosaccharide	None	EDC/HOBt	Amide bond	[55]
Celastrol	Carboxymethyl chitosan	None	EDC HCl/NHS	Amide bond	[54]
Mesalamine	Hyaluronic acid	None	EDC/HOBt	Amide bond	[71]
Atorvastatin	Chitosan	None	EDC	Amide bond	[44]
Memantine, Tacrine and cinnamic acid	N'N-methylenebisacrylamide (MBA)	None	DCC	Amide bond	[74]
Paclitaxel	Trimethyl chitosan	Succinic anhydride	EDC HCl/NHS	Amide bond	[69]
Ellagic acid	Arabinogalactan	None	EDC HCl	Amide bond	[58]
Norcantharidin	Carboxymethyl chitosan	None	Pyridine	Amide bond	[70]
Cytarabine	Oleic acid	None	Ethyl chloroformate/TEA	Amide bond	[43]
All trans-retinoic acid	mPEG	None	EDC/DMAP	Ester bond	[75]
Simvastatin & citicoline	Chitosan	Succinic anhydride	EDC HCl/DMAP	Ester bond	[76]
Mesalamine	Chondroitin sulfate	None	EDC HCl/DMAP	Ester bond	[56]
Celecoxib	Dextran	Glutamic acid	CDI/TEA	Ester bond	[63]
Camptothecin	L-carnitine	1,4-dithiothreitol	2,2′-dithiobis-ethanol/DMAP	Ester bond	[65]
Paclitaxel	PEG	None	EDC HCl	Ester bond	[52]
Curcumin	Gum arabic	None	DCC/DMAP	Ester bond	[53]
Quercetin	Xylan	Succinic anhydride	EDC HCl, DMAP	Ester bond	[77]
Curcumin	PEG	3,3'-dithiodipropionic acid	NHS/DCC/DMAP	Ester bond	[66]
Docetaxel	mPEG-PLA	Succinic anhydride	DCC/DMAP	Ester bond	[49]
Celecoxib	Dextran	Glutamic acid	CDI/TEA	Ester bond	[63]
Doxorubicin and curcumin	Chitosan and stearic acid	None	None	Disulfide bond	[72]
Aspirin	Dextran	None	Azide-alkyne click reaction	Triazole bond	[73]

Abbreviations:
EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt: Hydroxybenzotriazole; EDC HCl: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; NHS: N-Hydroxysuccinimide; DCC: N,N'-Dicyclohexylcarbodiimide; CDI: 1,1'-Carbonyldiimidazole; TEA: Triethylamine DMAP: 4-Dimethylaminopyridine;

Challenges, and Future Prospects

Clinical Translation Challenges and Future Prospects

Despite promising therapeutic potential, the clinical translation of PDCs for oral administration remains fraught with significant technical and regulatory barriers. From a manufacturing scalability perspective, the major challenge lies in the complexity of synthesizing these conjugates at an industrial scale. The production process typically involves multi-step chemical reactions with stringent conditions, which can limit scalability and batch-to-batch reproducibility [78], [79].

Moreover, the GI tract poses harsh physiological environments, including varying pH levels, extensive enzymatic activity, and mucosal barriers. These factors threaten the structural integrity and efficacy of oral PDCs. Many therapeutic payloads, especially macromolecules like peptides and proteins, remain vulnerable to degradation or exhibit poor membrane permeability despite conjugation, resulting in low bioavailability [80], [81].

Another critical concern involves regulatory complexity. PDCs are classified as hybrid materials that chemically combine drugs and polymers. Consequently, regulatory bodies require developers to provide detailed safety and pharmacokinetic data not only for the final conjugate but also for its individual components (polymer, linker, drug) and their degradation byproducts. These extensive requirements significantly increase development costs and prolong timelines, delaying clinical application [45], [47], [50].

Future Prospects

To address these limitations and bridge the gap between academic innovation and market-ready products, several strategic directions have emerged. Researchers are continuously refining advanced material designs and formulation techniques using stimuli-responsive polymers (e.g., pH- or redox-sensitive), amphiphilic block copolymers (e.g., PEG–PLA micelles), ligand-modified PDCs for receptor-mediated uptake, and lipid–polymer hybrid nanoparticles, all to navigate biological barriers better [48], [49], [67], [68].

The pharmaceutical industry is increasingly interested in the potential of PDC-based oral therapies, owing to their capacity for targeted delivery, improved safety profiles, and enhanced patient compliance. A particularly exciting frontier lies in the development of multifunctional PDCs—systems capable of integrating therapeutic delivery, diagnostic imaging, and real-time monitoring into a single platform. These "theranostic" conjugates are especially valuable for the management of complex diseases such as cancer and inflammatory conditions. While oral administration offers significant economic advantages by reducing the need for clinical supervision and increasing accessibility for chronic disease management, commercial adoption is currently limited by high production costs and shelf-stability issues. Overcoming these hurdles will likely require strategic partnerships between academia and the pharmaceutical industry to foster investment in translational research [47], [50].

4. Conclusion

A collective consideration of the reviewed studies underscores the potential of polymer–drug conjugates as an advanced strategy for overcoming the primary limitations of conventional oral drug delivery. Through the rational design of biocompatible polymer backbones, environment-specific cleavable linkers, and active targeting moieties, these systems provide a versatile platform to address key

physiological barriers. PDCs has been shown in multiple studies to enhanced drug solubility, improved stability against degradation, reduced systemic toxicity, and provided controlled release mechanisms. By transforming poorly soluble or highly toxic compounds into effective oral therapeutics, polymer-drug conjugates emerge as a highly promising avenue for developing safer, more efficient, and patient-compliant drug delivery systems.

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