The *in vivo* pharmacokinetics of block copolymers containing polyethylene glycol used in nanocarrier drug delivery system

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Abbreviations:

NDDSs, Nano-drug delivery systems; PEG, Polyethylene glycol; PEG-PLA, Polyethylene glycol-Poly lactic acid; PEG-PCL, Polyethylene glycol-Poly caprolactone; PEG-PLGA, Polyethylene glycol-poly lactic-co-glycolic acid; PEG-DSPE, Polyethylene glycol- distearoyl-sn-glycero-3-phosphoethanolamine; *i.v.*, intravenous; PEO, Polyoxyethylene; PPO, Polyoxyethylene; GPC, Gel permeation chromatography;

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Abstract:

Polyethylene glycol is one of the most commonly used synthetic macromolecular polymers for modifying small molecule drugs, peptides, proteins or Nano-drug delivery systems to improve their water solubility, biocompatibility and stability. Block copolymers containing PEG have been widely used in Nano-drug delivery systems such as solid lipid nanoparticles, polymeric nanoparticles, polymeric micelles and liposomes. To date, although numerous PEGylated Nano-drug delivery systems have been developed, only a few have been approved for clinical application. Poor safety and effectivity are important reasons for the high failure of Nano-drug delivery systems clinical trials. These factors are not only related to the loaded drugs and released drugs, but also related to the nanocarriers. Therefore, investigating the *in vivo* spatiotemporal fate of block copolymers containing PEG used in Nano-drug delivery systems is necessary and important for evaluating their safety, efficacy and toxicity. In this article, we will review the information that has been reported about the absorption, distribution, metabolism and excretion of block copolymers containing PEG. We believe this review is helpful to understand the biological fate of block copolymers containing PEG.

Key Words: PEG; ADME; Pharmacokinetic; Nano-drug delivery systems.

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Significance Statement

This review describes pharmacokinetic study of block copolymers containing polyethylene. The main focus of this paper is the *in vivo* fate of these PEG related copolymers after their release from Nanocarriers. This review is helpful for understanding of the *in vivo* fate of block copolymers containing polyethylene glycol used in Nanocarrier drug delivery system.

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Introduction

During these years, great progress has been made in the development of nano-drug delivery systems (NDDSs)(Fan et al., 2021; Rai et al., 2021). NDDSs are specially designed as drug delivery vehicles to deliver active pharmaceutical ingredients to their target locations, which have numerous advantages such as improved targeting, decreased toxicity and prolonged circulation time(Aggarwal et al., 2021). Polyethylene glycol (PEG) is composed of repeating oxyethylene subunits. It is one of the most commonly used synthetic macromolecular polymers for modifying drugs with various molecular weight or NDDSs to improve their water solubility, stability and biocompatibility (Fu et al., 2021). Furthermore, block copolymers containing polyethylene glycol such as Polyethylene glycol-Poly lactic acid (PEG-PLA), Polyethylene glycol-Poly caprolactone (PEG-PCL), Poloxamer, Polyethylene glycol-poly lactic-co-glycolic acid (PEG-PLGA), and Polyethylene glycol -distearoyl-sn-glycero-3-phosphoethanolamine (PEG-DSPE) have been commonly used as pharmaceutical excipients in the preparation of solid lipid nanoparticles, polymeric micelles, polymeric nanoparticles and liposomes(Owens and Peppas, 2006; Markovsky et al., 2012). These macromolecular polymers containing PEG could offer sterical barriers to other NDDSs and blood components such as opsonin proteins, preventing their macrophage phagocytosis and prolonging their circulation time in blood, consequently a ‘invisible features’ *in vivo*. In particular, the end groups of these synthetic macromolecular polymers can be connected to different targeting ligands,

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which could enhance the bioavailability, decrease the side effects, and especially target specific locations. Figure 1 is the overview of PEGylated carrier systems for drug delivery. However, to date, although numerous PEGylated Nano-drug delivery systems (NDDS) have been developed, only a few of them(eg. Genexol, Doxil, Krystexxa and several marketed LNP formulations) are clinically approved(Kim et al., 2001; Gabizon et al., 2003; Li et al., 2020). Moreover, many problems of these approved PEGylated Nano-drug delivery systems have not been fully explained, especially the *in vivo* fate of loaded drugs and polymer excipients, which are very important for the safety and effectivity of these PEGylated Nano-drug delivery systems. Furthermore, numerous reasons contribute to the high failure rate of clinical trials of the NDDS just like potential toxicity and unsatisfactory pharmacokinetic behavior. These defects are associated with both NDDS and the nanocarriers that are released *in vivo*. Therefore, investigating the *in vivo* spatiotemporal fate of block copolymers containing PEG used in NDDS viz. their absorption, distribution, metabolism and excretion is necessary and important for evaluating their safety, effectivity and toxicity.

Figure 1

In this article, we have concentrated on the following PEG related block copolymers: PEG, PEG-PLA, PEG-PCL, Poloxamer, PEG-PLGA, and PEG- DSPE, the chemical structures of these synthetic macromolecular polymers are illustrated in

figure 2. The existing information related to the absorption(A), distribution(D),

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metabolism(M) and excretion (E) of these block copolymers containing polyethylene glycol *in vivo* are summarized in figure3. PEG and PEG copolymers can be absorbed into blood across the gastrointestinal, nasal epithelia, lung epithelial membranes and skin. PEG related block copolymers are relatively easy to be accumulated in liver, spleen, lung and kidney. These polymers can be eliminated in urine, bile and feces. The summary of ADME information for these block copolymers containing PEG is shown in table1. Distribution and excretion of these PEG related copolymers are shown in figure 4. We believe this review is helpful for understanding the pharmacokinetic of block copolymers containing PEG.

Figure 2

Figure 3

Table 1

Figure 4

Pharmacokinetics of PEG

Polyethylene glycol (PEG) polymers are composed of repeating ethylene oxide units and their general formula is $\text{HO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$. This kind of hydrophilic and neutral polymers has been authorized by US Food and Drug Administration for human oral, dermal and intravenous (*i.v.*) applications. PEG related polymers are widely used in pharmaceutical industry as solubilizer, stabilizer, control releasing modifier or

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conjugated with small molecular compounds or proteins (PEGylation) and drug delivery systems, which can increase the hydrophilicity, prolong residence time in circulation, and reduce the immunogenicity and antigenicity of these chemicals. The *in vivo* pharmacokinetics of PEGylated drug delivery systems are usually well characterized during their development phases. However, information about the *in vivo* pharmacokinetics of PEG part is relatively sparse. During these years, it has been reported that PEG can cause vacuolation in animal tissues (Irizarry Rovira et al., 2018; Fletcher et al., 2019). Some studies also indicated that adverse reactions of PEG polymers usually occur through complement (C) activation, resulting in hypersensitivity reactions that can cause an anaphylactic shock (Chanan-Khan et al., 2003; Fruijtier-Polloth, 2005; Szebeni, 2005). Moreover, Wang et al. reported that PEG can act as P-glycoprotein inhibitors, which may influence the absorption and efflux of the medical compounds taken at the same time. The uptake of PEG polymers with small molecular weight (< 2000 Da) occurs through passive diffusion, while the uptake of PEG polymers with large molecular weight (> 5000 Da) occurs through both passive diffusion and caveolae-mediated endocytosis (Wang et al., 2020). Fasinu and his coworkers found that PEG10K and PEG20K were able to act as CYP3A4 inhibitors and inhibit the metabolism of felodipine (Fasinu et al., 2013). Therefore, PEG may not be as non-toxic and bioinert as we usually think. Detailed information about the pharmacokinetic of PEG polymers is necessary and important for evaluating the safety, effectivity and toxicity of PEGylated drug delivery systems in their clinical

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applications. It is helpful for establishing a relationship to the functional effects of the PEGylated drug delivery systems, particularly when administered chronically.

Absorption, distribution, metabolism and excretion of different sized PEG polymers in various species with different administration routes have previously been reported (Soderholm et al., 1993; Soderholm et al., 1996; Soderholm et al., 1997; He et al., 1998; Webster et al., 2007; Pelham et al., 2008; Baumann et al., 2019; Su et al., 2019; Wang et al., 2020). PEG polymers can be absorbed across the gastrointestinal, nasal epithelia, lung epithelial membranes and skin. Absorption of PEG polymers is size dependent, decreasing with increasing molecular mass. For example, Yanling He and his colleagues studied the oral bioavailability of PEG 400 and PEG 900 in rats and dogs after oral and intravenous administrations(He et al., 1998). In their study, the mean oral bioavailability of PEG400 in rats and dogs is 23.8% and 112.2%, respectively. The mean oral bioavailability of PEG900 in rats and dogs is 3.24% and 16.4%, respectively. Oral bioavailability decreased with increasing molecular mass in the same species. Amidon and his colleagues examined the absorption of PEG600, PEG1000 and PEG2000 across the gastrointestinal and nasal epithelia in rats. For PEG600, the extent of absorption is less than 60% after intranasal and gastrointestinal administrations; For PEG1000, the extent of absorption is about 14% and 9% after intranasal and gastrointestinal administrations; For PEG2000, the extent of absorption is about 4% and 2% after intranasal and gastrointestinal administrations. The permeabilities of both the gastrointestinal and the nasal mucosae showed similar

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molecular weight dependencies for PEG polymers. Furthermore, Hema Gursahani and his coworkers studied the absorption behavior of fluorescently labeled PEG polymers with different molecular weight across epithelial membranes in rats lung(Gursahani et al., 2009). Their results indicated that PEG synthetic polymers could be absorbed across epithelial membranes with first-order kinetics after intratracheal administration to rats. They also found that PEG polymers with small molecular weight (<2 kDa) were effectively cleared within 48 hours, while large PEG polymers (>5 kDa) remained in lung cells and tissues for seven days. The size of PEG polymers plays an important role in controlling their absorption rate and absorption mechanism. The same absorption results were found in humans. For example, Shaffer and his coworkers' study showed that the oral absolute bioavailability of PEG500 and PEG1000 in human volunteers is about 57% and 9.8%, respectively. And the oral bioavailability of PEG6000 in human volunteers was basically zero(Shaffer et al., 1950). Moreover, Pelham et al. found that oral absolute bioavailability of PEG3350 in healthy individuals is only 0.17%, most of the PEG3350 was not absorbed into the blood and excreted in the feces(Pelham et al., 2008). As for transdermal administration route, PEG polymers with small molecular weight can only be absorbed minimally through the intact skin, and PEG polymers with large molecular weight (≥ 4 kDa) cannot be absorbed through the intact skin at all(Fruijtier-Polloth, 2005). However, PEG polymers can penetrate through injured skin regardless of their molecular weight(Herold et al., 1982).

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The tissue distribution of PEG polymers depends on many factors just like size and route of administration. Extravascularly, PEG polymers with small molecular weight may permeate tissues faster than PEG polymers with higher molecular weight. In particular, large PEG synthetic polymers have relatively slower renal clearance and greater potential to accumulate within tissues and cells. It was observed by standard histological examination that the intracellular PEG synthetic polymers can be accumulated within the lysosome, eventually leading to vacuolation and distension (Baumann et al., 2014). There are several studies about the tissue distribution of PEG polymers have been reported. For instance, Longley and his coworkers found that PEG40k polymers administered by *i.v.* injection with a dose of 1250 mg/kg to mice could be monitored in most tissues just like liver, lung, kidney, heart, gastrointestinal tract, spleen, fat, bladder, testes, eyes, muscle and brain. The concentrations of PEG40k polymers was relative high in liver, kidney, lung and heart, and the maximum concentration of PEG40k was detected in the kidney (Longley et al., 2013). Rudmann and his colleagues used immunohistochemical assay to study the cellular distribution of PEG10K, PEG20K and PEG40K after *i.v.* injection of 100 mg/kg in rats. In their study, three months after *i.v.* administration, they found that PEG10K, PEG20K and PEG40K were still detected in liver, lung, heart, spleen, kidney and choroid plexus. Moreover, the concentrations of both PEG10K and PEG20K polymers were higher in hepatic Kupffer cells, alveolar macrophages and renal tubule epithelium than the other tissue cells. In contrast, the concentrations of

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PEG40K polymers were higher in choroid plexus epithelial cells, renal interstitial macrophages and splenic subcapsular red pulp macrophages (Rudmann et al., 2013). Yamaoka and his coworkers examined the tissue distribution of PEG polymers after *i.v.* administration to mice (Yamaoka et al., 1994b). Their results indicated that large PEG polymers were retained longer in blood circulation compared with small PEG polymers. With the increasement of the molecular weight of PEG polymers from 6K to 190K, the half-life of the synthetic PEG polymers in blood circulation was extended from 18 min to 24 h. The concentrations of these related PEG polymers in the tissues such as liver, muscle, skin and bone are higher than that in other tissues. Vascular permeability is an important factor for the time dependence of the accumulation of PEG polymers in tissues. Their results also showed that small PEG polymers tended to translocate freely from blood to various tissues and return to blood again via diffusion, while large PEG polymers transferred more slowly from blood circulation to different tissues. Their results indicated that chronic administration of high molecular weight PEG polymers may lead to serious accumulation and cause potential toxicity in related tissues. Generally speaking, PEG polymers are relatively easy to be accumulated in the following tissues: highly perfused tissues; tissues containing mononuclear phagocyte system and neovascular tissues with low lymphatic drainage (Markovsky et al., 2012).

So far, there have been some reports on metabolism of PEG polymers (Hunt et al., 1982; Webster et al., 2007; Su et al., 2019). Schaffer and his coworkers' study with

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PEG400 synthetic polymers showed that the subunit ethylene glycol is not generated as the metabolite of PEG synthetic polymers in humans(Shaffer et al., 1950). The main metabolic pathway of PEG polymers is the oxidation of the terminal alcohol group to carboxylic acid group. For instance, Hunt et al. developed analytical method based on triple-quadrupole mass spectrometry technique and detected both the diacid and hydroxyl acid metabolites of PEG polymers in urine and serum samples of a burn patient who was treated with an antibacterial cream containing PEG(Hunt et al., 1982). Friman et al. detected carboxylic acid metabolites of PEG900 in cat bile after intravenous injection(Friman et al., 1990a; Friman et al., 1993). They also calculated the percentages of both PEG polymers and their carboxylic acid metabolites in cat bile. Their results indicated that 74% of PEG molecules were existed in cat bile as unchanged form, 26% of PEG molecules were oxidized to carboxylic acids. Moreover, PEG polymers can be metabolized by sulfotransferases. Roy and his colleagues observed the sulfated metabolites of PEG400 and PEG1000 in rat and guinea pig *in vitro* liver preparations (Roy et al., 1987; Roy et al., 1988). It was also reported that a small amount of oxalic acid can be released after PEG metabolism(Fruijtjer-Polloth, 2005). In general, the phase I oxidation of PEG polymers is mainly mediated by alcohol dehydrogenase in mammalian systems. It was also reported that the oxidation of PEG synthetic polymers can be mediated by CYP450s(Herold et al., 1989; Veronese and Pasut, 2005). Compared with alcohol dehydrogenase, CYP450s plays a lesser role for the oxidation of PEG polymers. Furthermore, it was reported that the

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acid metabolites of PEG polymers are related to their adverse effects such as acidosis and hypercalcemia(Bruns et al., 1982).

PEG polymers can be eliminated in urine, bile and feces. The excretion of PEG polymers is associated with many factors such as size, shape and administration routes. For *i.v.* administration, urinary excretion is the main excretion pathway for PEG polymers. He et al. studied the excretion of PEG400 and PEG900 in rats and dogs after *i.v.* administration. In their study, PEG400 and PEG900 were mainly excreted unchanged in urine. Mean 24h percent urinary recoveries of total radioactivity of [14C]PEG 400 and [3H]PEG 900 following *i.v.* administration to rats and dogs are 85.1%, 82.5%, 85.1% and 81.9%, respectively(He et al., 1998). Shaffer et al. found that 86% of PEG1000 polymers and 96% of PEG6000 polymers were excreted in urine within 12 h after *i.v.* administration to humans(Shaffer et al., 1950). Friman and Svanvik found that almost 100% of PEG1000 were excreted in urine after *i.v.* administration to rats(Friman and Svanvik, 1997). Urinary excretion of PEG polymers is also size dependent as it occurs by passive glomerular filtration. Yamaoka and his coworkers' study in mice indicated that urinary clearance decreased significantly when the molecular weight of PEG polymers exceeded 20K Da (Yamaoka et al., 1994a). Biliary excretion is another excretion pathway for PEG polymers. It is also molecular weight-dependent. Yamaoka et al. founded that liver clearance decreased with the increase of PEG molecular weight when the PEG molecular weight is less than 50k Da, while liver clearance increased with the increase of PEG molecular

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weight when the PEG molecular weight is larger than 50 kDa(Yamaoka et al., 1994b). PEG polymers with smaller and larger molecular weight have greater hepatobiliary clearance. However, for PEG polymers with very small molecular weight, their bile excretion is not high. Shaffer et al. found that PEG400 is not excreted into bile after *i.v.* administration to dogs(Shaffer et al., 1950). Friman et al. found that the bile excretion of PEG900 is high in patients with T-tube cholecystectomy and the concentrations of PEG900 in bile samples were 31 times higher than those detected in human plasma samples(Friman et al., 1995). They also observed high bile/plasma ratio of PEG 450, PEG 900, PEG 2500 and PEG 4000 in pigs and cats after *i.v.* administration(Friman et al., 1988; Friman et al., 1990b). Carpenter et al. found that 61% of PEG4000 was excreted into urine and 20% of PEG4000 was detected in feces after *i.v.* administration to rats(Carpenter et al., 1971). Their data indicated that biliary excretion plays a less role for elimination of PEG4000 compared with urinary excretion. Generally speaking, both the kidney and liver are important for elimination of PEG *in vivo*. Urinary excretion is the major elimination route of PEG polymers. As for oral administration, fecal excretion is the main excretion pathway of PEG polymers. For example, Pelham et al. studied pharmacokinetics of PEG3350 in humans after oral administration. The oral absolute bioavailability of PEG3350 in healthy individuals is only 0.17%; 93% of the PEG3350 was excreted in the feces and only 0.19% to 0.25% of the PEG3350 was excreted in urine(Pelham et al., 2008).

Pharmacokinetics of PEG-PLA

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Poly (lactic acid) (PLA), also known as poly (lactide), is a kind of polyester polymer derived from the polymerization of lactic acid as the main raw material. PLA is too hydrophobic and has certain defects as an excipient for hydrophilic drugs, but the properties of PLA can be improved by connecting with hydrophilic PEG. The molecular formula of PEG-PLA is $H[OCH(CH_3)CO]_mO(CH_2CH_2O)_nH$. PEG-PLA block copolymers such as diblock polymers(PEG-PLA) and tri-block polymers(PLA-PEG-PLA) have a wide range of effects, which can be used to increase the drug load of hydrophobic drugs, prolong blood circulation time, improve drug bioavailability and efficacy(Xiao et al., 2010; Chen et al., 2014; Ghasemi et al., 2018; Goudarzi et al., 2018; Amani et al., 2019; Girard et al., 2021; Massadeh et al., 2021). Although *in vivo* fate studies of triblock PLA-PEG-PLA polymers have not been reported, pharmacokinetic studies of diblock PEG-PLA polymers in rats after *i.v.* administration have previously been reported (Shi et al., 2019; Meng et al., 2021). Specifically, Meng et al. studied the pharmacokinetic of PEG-PLA copolymers in rats by LC-MS/MS technique(Meng et al., 2021). They found that the concentration of PEG-PLA was high in plasma and extracellular fluid after *i.v.* administration. Most of the PEG-PLA polymers were eliminated from plasma within 48h. Small amounts of PEG-PLA were excreted into bile(<0.8%). PEG-PLA polymers can be metabolized into PEG and lactic acid. 86% of PEG-PLA polymers were metabolized into PEG and then excreted in urine. For tissue distribution study, the concentrations of PEG-PLA synthetic polymers were higher in

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liver, kidney, spleen and fat, lower in muscle and brain. PEG-PLA has a low permeability to the brain, possibly due to the blood-brain barrier. In addition, Meng et al. also studied the inhibitory effects of PEG-PLA synthetic polymers on human CYP450s (Meng et al., 2019). They found that PEG-PLA had a weak inhibitory effect on CYP2C8, CYP2C9, CYP2D6 and CYP3A4 in the range of 0.075-250 μ M, while it had no inhibitory effect on CYP1A2, CYP2B6 and CYP2C19. Shi et al. characterized the pharmacokinetics of mPEG2000-PLA2500 in SD rats after *i.v.* injection of 5mg/kg (Shi et al., 2019). The extrapolated concentration (C_0) of mPEG2000-PLA2500 in rat plasma was $25.3 \pm 2.78 \mu\text{g} \cdot \text{mL}^{-1}$ after *i.v.* administration. The area under the plasma concentration-time curve (AUC_{0-t}) of mPEG2000-PLA2500 was $44.9 \pm 2.95 \mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}$. The *in vivo* elimination of mPEG2000-PLA2500 was found to be fast. Its plasma elimination half-life ($t_{1/2}$) is only 1.31 ± 0.155 h. Moreover, S. tolrik and his coworkers also studied the pharmacokinetic of PEG-PLA polymers in rats (Stolnik et al., 2001). They found that PEG-PLA copolymers with small molecular weight were quickly cleared from the systemic circulation after *i.v.* administration. High molecular weight PEG-PLA copolymers could reduce liver intake by half and increase blood circulation time after *i.v.* administration. PEG-PLA particles were mainly distributed in liver parenchymal cells.

Pharmacokinetics of PEG-PCL

PCL is a biodegradable hydrophobic aliphatic polyester formed by ring-opening

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polymerization of 2-caprolactone monomer (da Silva et al., 2009). The biocompatibility of drug-loaded PCL polymer is poor due to its strong hydrophobicity (Zhang et al., 2006). The introduction of hydrophilic polymer PEG to construct the amphiphilic PEG-PCL copolymer can compensate for this deficiency. PCL(A) modified with PEG(B) in different proportions can be divided into AB diblock, ABA or BAB triblock, star block, multi-block and graft polymer (Liu et al., 2008). The drug delivery systems based on PEG/PCL, PCL-PEG-PCL and PEG-PCL-PEG present good potential benefits (Gou et al., 2009; Feng et al., 2012; Han et al., 2015; Luo et al., 2016; Lee and Jeong, 2020; Singh et al., 2020; Di Trani et al., 2021; Yang et al., 2021). However, recent studies suggested that PEG-PCL micelles may be involved in nanocarrier-drug interaction by influencing the activity of cytochrome P450 (Qiu et al., 2018; Li et al., 2019). In addition, Zhang et al. found that mPEG_{2K}-PCL_X micelles can reduce the plasma concentration of metformin by inhibiting the uptake function of organic cation transporters in rats, indicating that there are potential risk of drug interaction between PEG-PCL carrier system and organic cation drugs (Zhang et al., 2021). Therefore, revealing the *in vivo* fate of PEG-PCL polymers is crucial for its medical application. To date, pharmacokinetic differences *in vivo* between small molecular drugs and PEG-PCL loaded particles have been extensively studied (Feng et al., 2012; Wang et al., 2014; Manjili et al., 2018; Kurd et al., 2019). However, *in vivo* fate studies of triblock polymers such as PCL-PEG-PCL or PEG-PCL-PEG have not been reported, only a few studies have

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focused on the *in vivo* fate of PEG-PCL monomers (Liu et al., 2007; Kao et al., 2013; Sun et al., 2018).

Specifically, Liu et al. studied the pharmacokinetics of mPEG₅₀₀₀-b-PCL₅₀₀₀ micelles and mPEG₅₀₀₀-b-PCL₅₀₀₀ monomer in mice by isotope labeling method (Liu et al., 2007). Their results of the interaction between mPEG₅₀₀₀-b-PCL₅₀₀₀ copolymer monomer and plasma protein showed that the copolymer monomer did not bind to plasma protein. Therefore, the existence of plasma protein would not likely affect the critical micelle concentration (CMC) of mPEG₅₀₀₀-b-PCL₅₀₀₀ significantly. After *i.v.* administration of mPEG₅₀₀₀-b-PCL₅₀₀₀ monomer (lower than CMC concentration), due to its low molecular weight and amphipathicity, the monomer had a faster distribution to tissues compared with micelles. The concentrations of mPEG₅₀₀₀-b-PCL₅₀₀₀ monomer in tissues within 1h from high to low were: liver, kidney and spleen. Compared with monomer, mPEG₅₀₀₀-b-PCL₅₀₀₀ micelles had a longer blood circulation time and a slower elimination rate.

Kao et al. (Kao et al., 2013) studied the *in vivo* pharmacokinetics of ¹³¹I benzyl PEG-PCL micelles and ¹³¹I benzyl PEG-PCL monomer in mice after *i.v.* injection by isotope labeling method. The radiation accumulation of monomer and micelle in tissues reached the highest values after 1h, and significant radiation retention was detected in reticuloendothelial system (RES) tissues. At the same time, the PEG-PCL monomers and micelles had a large radioactive accumulation in urine, indicating that they were excreted mainly through the kidneys. Sun et al. (Sun et al., 2018) explained

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why PEG-PCL monomer has a faster blood clearance compared with PEG-PCL micelles. This is due to the fact that intact PEG-PCL micelles are not easily captured by Kupffer cells. While the exposed hydrophobic fragments of PEG-PCL monomers can be quickly identified and captured by Kupffer cells.

In summary, at present, there is no information about the absorption of PEG-PCL *in vivo*. The administration route used in current pharmacokinetic studies of PEG-PCL polymers is *i.v.* injection. PEG-PCL polymer monomer has a rapid plasma elimination and faster distribution to RES tissues such as liver and spleen compared with micelle. PEG-PCL mainly excretes out of the body in urine. Although there is no study to reveal the metabolism process of PEG-PCL *in vivo* right now, we speculate that the ester bonds between PEG and PCL would break *in vivo*. PEG-PCL can be metabolized into PEG and PCL under the action of esterase.

Pharmacokinetics of Poloxamer

Poloxamers, also called Pluronics or Tetronics, are amphiphilic non-ionic triblock copolymers composed of polyoxyethylene (PEO) and polyoxyethylene (PPO) ($\text{PEO}_m\text{-PPO}_n\text{-PEO}_m$). The triblock copolymers can self-assemble into micelles. The hydrophobic core (PPO) of such micelles can carry different drugs. And the hydrophilic shell (PEO) guarantee the micelles' stability (Kabanov et al., 2002). Poloxamer polymers are widely used in drug delivery (Das et al., 2010; Sahu et al., 2011; Basak and Bandyopadhyay, 2013; Chen et al., 2013; Nguyen et al., 2017). In the past, poloxamers are traditionally considered "inert". However, recent studies

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suggested that poloxamers may have biological effects (Blonder et al., 1999; Ren et al., 2009). Specifically, Blonder et al. demonstrated that poloxamer-407 would result in hyperlipidemia(Blonder et al., 1999). Ren et al. found that poloxamer188 may have an inhibitory effect on Cytochrome P450 3A (Ren et al., 2009). Cytochrome P450 3A family is the main metabolic enzyme which accounts for more than 70% of the cytochrome P450 in the small intestine. Substances that inhibit cytochrome P450 3A activity can increase plasma concentration of the substrate drugs and may result in toxicity. These results indicate that there are potential risk of interaction between poloxamer carrier systems and drugs. Therefore, it is necessary to reveal the *in vivo* fate of poloxamers polymers for their medical application.

There have been some reports on the *in vivo* fate of poloxamer polymers. For example, Feng et al. studied the pharmacokinetics and tissue distribution of poloxamer188 in rats after *i.v.* injection of 5mg/kg (Feng et al., 2021a; Feng et al., 2021b). The pharmacokinetic parameters of poloxamer188 were as follows: AUC_{0-t} was $3.0 \pm 0.6 \mu\text{g/L} \cdot \text{h}$, MRT was $0.6 \pm 0.1 \text{h}$, CL was $1.7 \pm 0.3 \text{ L/h/kg}$, $t_{1/2}$ was $2.0 \pm 1.1 \text{ h}$, V_d was $5.1 \pm 3.2 \text{ L/kg}$. The results of tissue distribution study indicated that poloxamer188 could be rapidly distributed to tissues with a high clearance rate. Poloxamer188 was mainly distributed in kidney ($26.8 \mu\text{g/g}$ at 0.2h and $11.63 \mu\text{g/g}$ at 4h). A small amount of poloxamer188 was detected in the other tissues such as stomach, liver, lung, muscle and spleen. Poloxamer188 couldn't pass through the blood-brain barrier into brain. Moreover, Li et al. studied the pharmacokinetics of

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poloxamer124 in rats after *i.v.* injection of 10mg/kg (Li et al., 2021). The pharmacokinetic parameters of poloxamer124 were as follows: AUC_{0-t} was 9.84 ± 3.02 mg/L*h, V_d was 2.89 ± 1.14 L/kg, MRT was 0.7 ± 0.08 , $t_{1/2}$ was 2.06 ± 1.04 h, CL was 0.98 ± 0.21 L/h/kg. Their results indicated that poloxamer124 could be rapidly eliminated in rat plasma after *i.v.* injection. Willcox et al studied the distribution and excretion of poloxamer 188 in dogs by radioisotope labeling method (Willcox et al., 1978). After *i.v.* injection of 3H labeled poloxamer188, nearly 75% of poloxamer188 circulated in plasma was in free form, and 25% tended to be bound to albumin. Within 24 hours after *i.v.* administration, about 40% of poloxamer188 was excreted through urine, and some remained in extravascular fluid and tissues. The highest concentration of poloxamer188 was found in bile after 24h. These results demonstrated that poloxamer 188 was mainly excreted through kidney and bile. Grindel et al. (Grindel et al., 2002) studied the pharmacokinetics of purified poloxamer 188 in rats, pregnant rats, pregnant rabbits, dogs and humans by Gel permeation chromatography (GPC). They found that the plasma clearance of poloxamer188 in rats and rabbits was faster than that in dogs and humans. Moreover, the plasma clearance of poloxamer188 was not related to dose or gender. Their study indicated that poloxamer188 polymers are mainly distributed in highly vascularized tissues and extracellular fluid after continuous *i.v.* infusion of purified poloxamer 188. They also found a single metabolite HW1 of poloxamer188 in both dog plasma and human plasma. The metabolite was a block copolymer and its molecular weight

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was 16000 Daltons. Compared with the parent compound, the clearance rate of the metabolite was slower. Their study also indicated that renal clearance accounted for 90% of total plasma clearance in man. Urinary excretion is the major route of elimination for poloxamer polymers(Jewell et al., 1997; Grindel et al., 2002). Wang and Stern studied the distribution and excretion of poloxamar 108 in rats by isotope labeling assay(Wang and Stern, 1975). Immediately after *i.v.* administration, P108 polymers were detected highly in kidney and lung. And 20h after *i.v.* administration, only a small part of P108 polymers were remained in kidney, liver, small intestine and carcass. P108 polymers were found in urine as unchanged form. About 94% of the initial dose of P108 polymers was excreted in urine and 6% of the initial dose of P108 was excreted in feces within 72h after *i.v.* administration. Batrakova et al. examined the effects of micelle formation on the distribution kinetics of poloxamer85 in mice by radioisotope labeling method(Batrakova et al., 2004). The results of their study indicated that the aggregation state of poloxamer85 would affect its half-life time *in vivo*, ranging from 60 to 90h. Poloxamer85 could remain in the blood for a long time in both monomer and micellar state. The micellar form of poloxamer85 had a longer circulation time and an increased exposure to the tissues compared with the unimer. But the formation of micelles could reduce the uptake of poloxamer85 in liver. In their study, after *i.v.* administration to mice, poloxamer85 were detectable in several tissues and its concentrations decreased in the following order: liver>spleen>kidney>lungs>brain. Furthermore, they also found that the

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micelle formation reduced the uptake of poloxamer85 in liver but had no effect on the total clearance of poloxamer85, which suggested that the elimination of poloxamer85 depended on the renal elimination of poloxamer85 unimers rather than the rate of micelle disposition or disintegration.

In summary, so far, there is no information about the absorption of poloxamers *in vivo*. The route of administration used in current pharmacokinetic studies of poloxamers polymers is *i.v.* injection. Most of poloxamers would not bind to plasma proteins when release to the blood. Poloxamers are mainly distributed in highly vascularized tissues such as liver, kidney, spleen and lung. The primary elimination of poloxamers is renal excretion.

Pharmacokinetics of PEG-PLGA

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable functional organic compound from the random polymerization of two monomers, lactic acid and glycolic acid. PLGA also has strong hydrophobicity. Due to its poor biocompatibility with hydrophilic drugs, its application is limited. However, it can be combined with PEG to form a coblock polymer, PEG-PLGA. And the connection with hydrophilic PEG can change the properties of PLGA. PEG-PLGA block copolymers are widely used in drug delivery systems for improving the drug bioavailability, prolonging the half-life of drugs *in vivo* and so on (Ahmed and Badr-Eldin, 2020). So far, only a few studies reported the biological fate of PEG-PLGA *in vivo*. For instance, Avgoustakis and his coworkers studied the biological distribution of mPEG-PLGA in

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mice(Avgoustakis et al., 2003). mPEG-PLGA was labeled with radioactive labeling, and 2 mins after *i.v.* administration, significant radioactivity was detected in liver and muscle. The amount of radioactivity in blood is about 75.8%. Over time, the radioactivity of mPEG-PLGA is slowly eliminated from the blood circulation and accumulates in liver and spleen. There was little change in other tissues. The excretion of mPEG-PLGA in intestine and urine increased with time, and the excretion of mPEG-PLGA was 6% ~ 8% of the total at the end of sampling. The effects of different PLGA/mPEG ratios on biological distribution were also studied. When PLGA/mPEG ratio ranged from 256 to 153, mPEG content increased and blood clearance rate decreased. The ratio was further reduced from 153 to 61 and 34, and blood clearance increased. Panagi et al. studied the biological distribution of mPEG-PLGA nanoparticles in mice by radioactive labeling assay(Panagi et al., 2001). A large proportion of mPEG-PLGA was found in liver and spleen after *i.v.* injection. About 70%- 80% of the proportion was detected in blood, liver and spleen, about 20% -30% of the proportion was detected in the other tissues. The half-life of mPEG-PLGA was about 7 hours. The distribution of mPEG-PLGA was not affected by dose.

Generally speaking, PEG-PLGA polymers are mainly distributed in liver and spleen and excreted through the bile and urine after *i.v.* administration. Although there is no detailed study to reveal the metabolism process of PEG-PLGA *in vivo*, we speculate that the ester bonds between PEG and PLGA would break *in vivo*.

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PEG-PLGA can be metabolized into PEG, lactic acid and glycolic acid under the action of esterase.

Pharmacokinetics of DSPE-PEG

DSPE-PEG is a PEGylated phospholipid. It can be used as a carrier material for nano-formulations to extend the circulation time and improve the biocompatibility and stability of the drug *in vivo*. DSPE-PEG is an amphiphilic macromolecule with good water solubility and has received extensive attention in recent years. Although DSPE-PEG is widely used, its safety and bioactivity *in vivo* have not been studied in detail. It has been reported that after injection of pharmaceutical preparations containing DSPE, the human body will have adverse reactions, such as increased blood pressure, difficulty breathing, chest pain, etc(van den Hoven et al., 2013). Su et al. studied pharmacokinetics of DSPE-PEG2000 and DSPE-PEG5000 in rats after *i.v.* injection with a dose of 25mg/kg(Su et al., 2019). The pharmacokinetic parameters of DSPE-PEG5000 in rats after *i.v.* administration were: AUC_{0-t} was $271.8 \pm 14 \mu\text{g/mL} \cdot \text{h}$, MRT_{0-t} was $2.064 \pm 0.069 \text{ h}$, V_d was $0.198 \pm 0.038 \text{ L/kg}$, C_0 was $104.8 \pm 13.6 \mu\text{g/mL}$, $T_{1/2}$ was $1.54 \pm 0.339 \text{ h}$, CL was $0.09 \pm 0.005 \text{ L/h/kg}$. The pharmacokinetic parameters of DSPE-PEG2000 in rats after *i.v.* administration were: AUC_{0-t} was $104.9 \pm 13.4 \mu\text{g/mL} \cdot \text{h}$, MRT_{0-t} was $1.027 \pm 0.034 \text{ h}$, V_d was $0.327 \pm 0.062 \text{ L/kg}$, C_0 was $83.6 \pm 4.2 \mu\text{g/mL}$, $T_{1/2}$ was $0.981 \pm 0.078 \text{ h}$, CL was $0.23 \pm 0.026 \text{ L/h/kg}$. The results of tissue distribution study indicated that DSPE-PEG2000 and DSPE-PEG5000 were mainly distributed in lung, fat, liver and spleen. The highest

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concentration of both DSPE-PEG2000 and DSPE-PEG5000 were detected in lung. Furthermore, both DSPE-PEG2000 and DSPE-PEG5000 could be detected in brain, indicating that they can pass through the blood-brain barrier. Su et al. also studied the inhibitory effects of both DSPE-PEG2000 and DSPE-PEG5000 on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. The IC₅₀ values of both DSPE-PEG2000 and DSPE-PEG5000 were greater than 100µg/mL for these CYP450 enzymes. These results indicated that both DSPE-PEG2000 and DSPE-PEG5000 did not significantly inhibit the activities of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. DSPE-PEG can be metabolized into DSPE and PEG by esterase *in vivo* and excreted as PEG in urine. The cumulative excretion of DSPE-PEG2000 at 0-168h after *i.v.* administration was 24.21% in urine and 3.82% in feces. The cumulative excretion of DSPE-PEG5000 at 0-168h after *i.v.* administration was 40.37% in urine and 8.79% in feces.

In summary, up to present, the route of administration used in current pharmacokinetic studies of DSPE-PEG polymers is *i.v.* injection, there is no information about the absorption of DSPE-PEG *in vivo* right now. DSPE-PEG polymers are mainly distributed in lungs, fat, liver and spleen and excreted through the bile and urine after *i.v.* administration. DSPE-PEG can be metabolized into PEG and DSPE under the action of esterase *in vivo*.

Current Challenges and Future Perspectives

This review describes the absorption, distribution, metabolism and excretion of block

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copolymers containing polyethylene. The main focus of this paper is the *in vivo* fate of these PEG related copolymers after their release from Nanocarriers. Safety and efficacy are two important considerations for the materials of PEGylated nanomedicine, as the PEG related copolymers are present in large quantities in Nanocarriers and may cause serious toxicity and adverse reactions when released *in vivo*. For example, high molecular weight PEG related copolymers can accumulate in liver, spleen, lung, kidney and other tissues and eventually cause toxic reactions. The polymers used in nanomedicine should be biodegradable and easily excreted. Furthermore, some PEG-related copolymers and their metabolites are biologically active and may cause toxic or adverse effects. For instance, the metabolites of poly lactic acid can cause inflammation in relevant tissues; the acid metabolites of PEG can cause hypercalcemia and acidosis. Furthermore, PEG-related polymers and their metabolites may also influence the biological functions of relevant transporters and metabolic enzymes such as P-gp and CYP450s, resulting in drug-Nanocarriers interactions and potential adverse reactions. Therefore, biological inertness is another required feature of pharmaceutical polymers used in Nanomedicine. Therefore, a thorough understanding of the *in vivo* fate of Nano-drug pharmaceutical preparations and their excipients is very important for the safety and effectiveness of their clinical application. However, most of current studies only focus on the *in vivo* pharmacokinetics of the free drug of nanomedicine, and pay little attention to the excipients, especially the polymers. The research and comprehensive understanding of

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in vivo fate of the Nanocarriers is not adequate. This is also the reason why numerous tested Nanomedicines just like Ferrugose and Resovist have been withdrawn from clinical use. Although a large number of studies have been carried out on Nanocarriers, more studies are needed to deeply understand their pharmacokinetic behavior *in vivo*. More advanced and modern biotechnologies such as bioimaging and LC-MS/MS techniques should be used to strengthen the research on the transport mechanism of Nanocarriers *in vivo*, so as to ensure their reasonable design, safety and effectiveness. We believe this review will contribute to the understanding of the pharmacokinetic of block copolymers containing PEG used in Nanocarrier drug delivery system.

Authorship Contributions

Lei Yin wrote and revised the manuscript. Yiling Pang, wrote and revised the manuscript. Lin Shan, wrote and revised the manuscript. Jingkai Gu, wrote and revised the manuscript.

Conflict of Interest

No author has an actual or perceived conflict of interest with the contents of this article.

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Figure legends

Fig.1. Overview of PEGylated carrier systems for drug delivery.

Fig.2. Chemical structures of PEG(A), PEG-PLA(B), PEG-PCL(C), Poloxamer(D), PEG-PLGA(E) and PEG-DSPE(F).

Fig.3. Absorption, distribution, metabolism and excretion of PEG related copolymers.

Fig.4. Distribution and excretion of PEG related copolymers.

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Table 1. Summary of ADME information for block copolymers containing PEG.

	Administration routes	Animal model	Absorption	Distribution	Metabolism	Excretion
PEG	Intratracheal, Intravenous, Intranasal administrations; Gastrointestinal administrations.	Mice, Rats; Dogs; Guinea pigs; Cats; Rabbit; Humans;	PEG can be absorbed across gastrointestinal, nasal epithelia, lung epithelial membranes and skin. Size dependent, decreasing with increasing molecular mass. The mean oral bioavailability of PEG400 in rats and dogs is 23.8% and 112.2%, respectively. The mean oral bioavailability of PEG900 in rats and dogs is 3.24% and 16.4%, respectively. For PEG600, the extent of absorption is less than 60% after intranasal and gastrointestinal administrations to rats; For PEG1000, the extent of absorption is about 14% and 9% after intranasal and gastrointestinal administrations to rats; For PEG2000, the extent of absorption is about 4% and 2% after intranasal and gastrointestinal administrations to rats. The oral absolute bioavailability of PEG500 and PEG1000 in human volunteers is about 57% and 9.8%, respectively. And the oral	Mainly distribute to heart, liver, spleen, lung and kidney (PEG10K, PEG20K, PEG40K and PEG polymers with molecular weight from 6K to 190K).	PEG polymers can be metabolized to carboxylic acids by alcohol dehydrogenase and CYP450s. Alcohol dehydrogenase plays a major role for the metabolism of PEG. PEG polymers can also be metabolized by sulfotransferases to form sulfated metabolites. PEG polymers can inhibit P-glycoprotein and CYP3A4 (PEG400, PEG1K).	PEG polymers can be eliminated in urine, bile and feces. For i.v. administration, urinary excretion is the main excretion pathway. For oral administration, fecal excretion is the main excretion pathway (PEG 450, PEG 900, PEG1000, PEG 2500, PEG3350, PEG 4000, PEG6000 and PEG polymers exceeded 20K Da).

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			bioavailability of PEG6000 in human volunteers was basically zero			
PEG-PLA	Intravenous administration	Rats	N/A	PEG-PLA polymers mainly distribute to spleen, liver and kidney (mPEG2000-PLA2500, mPEG2000-PLA2000).	PEG-PLA can be metabolized into PEG and lactic acid under the action of esterase.	Most PEG-PLA copolymers are metabolized into PEG and excreted through urine and a small amount through bile (mPEG2000-PLA2500, mPEG2000-PLA2000).
PEG-PCL	Intravenous administration	Rats	N/A	Mainly distributes to liver, kidney and spleen(mPEG5000-b-PCL5000).	PEG-PCL may be metabolized into PEG and PCL under the action of esterase.	Excreted mainly through the kidneys
Poloxamer	Intravenous administration	Dogs; Rats; Rabbits; Humans	N/A	Mainly distributes to liver, spleen, kidney, lung, brain and small intestine (poloxamer188, poloxamer124, poloxamer108, poloxamer85).	The metabolites are components of the high molecular weight distribution of poloxamer(poloxamer188).	Poloxamers are primarily eliminated through renal excretion and bile excretion in an unchanged form(poloxamer188, poloxamer124, poloxamer108, poloxamer85).
PEG-PLGA	Intravenous administration	Rats	N/A	Mainly distributes in liver and spleen.	PEG-PLGA may be metabolized into PEG, lactic acid and glycolic acid under the action of esterase	Mainly eliminated through renal excretion and bile excretion
PEG-DSPE	Intravenous administration	Rats	N/A	Mainly distributes in lung, fat, liver and spleen(DSPE-PEG2000 and DSPE-PEG5000).	PEG-DSPE may be metabolized into PEG and DSPE under the action of esterase. DSPE-PEG2000 and DSPE-PEG5000 do not inhibit the activities of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 significantly.	Mainly eliminated through renal excretion and bile excretion

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polymers

Star-shaped
polymers

Dendritic
polymers

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● = phospholipid

~ = PEG

~ = hydrophobic polymer

Figure 1

Figure 2

Figure 3

Figure 4