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Article

Mini-Review of Poloxamer as a Biocompatible Polymer for Advanced Drug Delivery

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Poloxamer is a biocompatible polymer that has already been approved by the US FDA for multiple applications. Poloxamer itself has many grades and functional categories that enable the improvement of both physicochemical and biological properties of drugs. In this minireview, the functional properties of poloxamer for physicochemical modification, such as solubility and stability, and biological response modification, such as neuroprotection, cell apoptosis, efflux pump modification, membrane cell modification, and cellular uptake, are discussed to provide a broader understanding to assist the development of poloxamer-based formulations.

Keywords: Poloxamer. Biocompatible. Physicochemical Modification and Biological Response Modification.

INTRODUCTION

Poloxamer, also known as Pluronic, is a block copolymer that has been used widely in the pharmaceutical industry as a dispersing agent, emulsifying agent, solubilizing agent, tablet lubricant, and wetting agent (Rowe, Sheskey, Quinn, 2009). Poloxamer is known as a biocompatible polymer (Almeida *et al.*, 2018; Jeong, 2011), and several types have been approved by the US FDA. Poloxamer is a nonionic polymer consisting of polyoxyethylene–polyoxypropylene copolymers with hydrophilic polyoxyethylene and hydrophobic polyoxypropylene segments (Rowe, Sheskey, Quinn, 2009). Poloxamer is commercially available in a wide range of grades or types based on the relative amount of propylene and ethylene oxide added during its manufacture. The amphiphilicity of poloxamer gives it a solubilizing capacity and has been intensely studied for improving drug delivery (Bodratti, Alexandridis, 2018) via oral, nasal, ophthalmic, and injection routes (Adnet *et al.*, 2020; Bodratti, Alexandridis, 2018; Jeong, 2011). To improve the targeting or nontargeting efficacy, several methods have been applied with poloxamers such as the use of polymeric micelles (Gong *et al.*, 2012), mixed micelles (Ćirin, Krstonošić, Poša, 2017), thermosensitive gels (Adnet *et al.*, 2020), and liposomes (Zarrintaj *et al.*, 2020). Poloxamer has been shown to be able to improve drug delivery even to the brain across the blood–brain barrier (Bao *et al.*, 2012; Batrakova *et al.*, 2001; Meng *et al.*, 2017; Wang *et al.*, 2014). With these properties, poloxamer can provide an advantage and solve the issue related to low bioavailability in the brain for drugs targeted to the brain or central nervous system, and cancer drugs to treat metastatic cancer are no exception. This review intends to provide further understanding about the mechanism of poloxamer in improving the physicochemical and biological properties of poloxamer-based drug formulations and delivery.

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POLOXAMER FOR PHYSICOCHEMICAL MODIFICATION

Solubility

Poloxamers 188 and 407 were reported to improve solubility, as shown by the dissolution of loratadine prepared by the solid dispersion method. This phenomenon is believed to be a result of the increased wettability and stabilization of the amorphous state with the addition of poloxamer (Rahman *et al*., 2015). A similar finding was observed in a bicalutamide solid dispersion with poloxamers 188 and 407 using solvent evaporation and spray drying. There were several changes in the bicalutamide characteristics with the addition of poloxamer in solid dispersions, including improvements in wettability, solubility, and dissolution (Szafraniec *et al*., 2019). The dissolution of tacrolimus was also reported to be increased using the solid dispersion method with poloxamers 188 and 407. This result was due to the conversion of tacrolimus to the amorphous phase, leading to increased solubility (Ha *et al*., 2012). Another study confirmed the better characteristics of poloxamer 188 than poloxamer 407 in improving dissolution; this performance was related to the higher proportion of oxyethylene segments in poloxamer 407, which retarded dissolution (Medarević *et al*., 2016). Poloxamer has also been reported to improve the solubility and dissolution of lamotrigine through micellar solubilization. The solubilization, however, decreased with increasing polyethylene oxide (PEO) region proportion in corona micelles and was temperature dependent (Singla *et al*., 2019). It was also reported that the solubilization enhancement of nimodipine by poloxamer 407 was higher than that of PEG 6000 due to the surfactant properties of poloxamer, which can form micelles (Kreidel *et al*., 2012). In addition, poloxamer 407 has been shown to increase the solubility of ibuprofen and griseofulvin through a mechanism of micellar solubilization (Dugar, Gajera, Dave, 2016; Dutra *et al*., 2015).

Stability

Poloxamer was reported to increase the chemical and physical stability of drugs or dosage forms. Poloxamer 407/Pluronic F127 has been shown to affect the chemical stability of insulin with increasing poloxamer concentration (Li *et al*., 2017). Poloxamer was also reported to increase the membrane stability of liposomes, believed to be related to PEO chain length (Li *et al*., 2020b). A similar result was shown with curcumin-loaded liposomes, where Pluronic F127 improved membrane stability (Li *et al*., 2020a). In addition, poloxamer 407 has been shown to increase the thermostability of proteins such as interleukin-1 receptor antagonists due to its viscous nature (Akash *et al*., 2014). Moreover, Pluronic F68 has been shown to affect the colloidal stability of poly(D,L-lactic-co-glycolic acid) (PLGA) nanoparticles, which was related to the surface coverage of Pluronic/poloxamer and micellization (Santander-Ortega *et al*., 2006). Hydroxyapatite nanoparticles modified by grafting with Pluronic F127 were shown to exhibit increased mechanical properties, crystallinity percentages, and thermal stability compared to those of unmodified hydroxyapatite nanoparticles (Mirhosseini, Haddadi-Asl, Zargarian, 2016).

TABLE I - List of Poloxamers and Functionalities

Poloxamer Type	Physicochemical Modification		Biological Response Modification				
	Solubility	Stability	Neuroprotection	Cell Apoptotic	Efflux Pump Inhibition	Cell Membrane Integrity Modification	Cellular Uptake
F68	+	+	+	+ in cancer cell line - normal cell	+	+	+
L121					+	+	
P123					+	+	+
F127	+	+		+	+	+	+
L61					+	+	
L81					+		
P84	+						
P85	+	+			+		+
F87		+					
F108	+						
Note	Act as Micellar Solubilization			Act as unimer			

POLOXAMER FOR BIOLOGICAL RESPONSE MODIFICATION

Neuroprotection

Poloxamer 188 has been shown to contribute to neuroprotection of the blood–brain barrier in traumatic brain injury (TBI). This polymer maintained membrane permeability by (1) reducing the levels of cytochrome-C, caspase-9, and caspase-8, resulting in inhibition of apoptosis, and (2) downregulating aquaporin 4 (AQP4), which is responsible for water channeling across the blood–brain barrier (Bao *et al.*, 2012). AQP4 acts as a selective bidirectional water movement regulator that can facilitate the supply or removal of water from astrocytes, thus affecting blood–brain barrier (BBB) permeability (Verkman *et al.*, 2006). In the case of intracerebral hemorrhage (ICH), poloxamer 188 was demonstrated to have a protective effect by preventing BBB disruption via its involvement in maintaining the levels of proteins such as claudin-5, occludin, and zonula occludens-1 and decreasing the expression of nuclear factor kappa B (NF-kB), matrix metalloproteinase (MMP)-2, and MMP-9, leading to the prevention of tight junction (TJ) degradation (Wang *et al.*, 2014). For MMP-2 and MMP-9, poloxamer showed the opposite action in wound healing, where poloxamer increased the activity of these enzymes, resulting in accelerated autolytic debridement of damaged collagen (Zarrintaj *et al.*, 2020). Poloxamer 188 was shown to protect against cerebral ischemia *in vivo* by significantly reducing the number of propidium iodide (PI)-positive labeled cells

following ischemia/reperfusion injury. This polymer further repaired HT22 cell membrane rupture induced by Triton X-100. In addition, P188 was found to inhibit ischemia/reperfusion-induced activation of MMP-9 and leakage of molecules (Gu *et al*., 2013).

Cell Apoptosis

Poloxamer was demonstrated to have contrary action in multidrug-resistant (MDR) cancer cells compared to normal cells, promoting proapoptotic signaling and reducing antiapoptotic defense (Zarrintaj *et al*., 2020). This mechanism was based on an increase in the expression of cytochrome-C, caspase 3, and caspase 9 (Alakhova, Kabanov, 2014; Batrakova, Kabanov, 2008; Pitto-Barry, Barry, 2014; Zarrintaj *et al*., 2020). Six percent Pluronic F68 was shown to cause G_2/M phase arrest, followed by caspase activation and accumulation of apoptotic cells in the K562 cell line (Aoki *et al*., 2010). Moreover, poloxamer 407 hydrogel alone significantly induced apoptosis and promoted the high expression of Annexin-V in the 3T3NIH cell line (Yang *et al*., 2020). On the other hand, in neural tissue following traumatic brain injury, poloxamer 188 was shown to significantly inhibit apoptosis and necrosis, partly through the inhibition of p38 activation (Serbest *et al*., 2006). A similar finding was obtained in the SH-SY5Y cell line when administered poloxamer 188. In this cell line, prevention of apoptosis was indicated to be associated with the prevention of leakage of cathepsins from lysosomes to the cytoplasm (Dong *et al*., 2019).

Efflux Pump Modification

Poloxamer was found to inhibit drug efflux by transporter-like Pgp (Batrakova, Kabanov, 2008). This effect was mediated by the inhibition of ATPase, leading to ATP depletion and membrane fluidization (Alakhova, Kabanov, 2014; Gaikwad, Bhatia, 2013; Zarrintaj *et al*., 2020). Conformational changes in efflux proteins, steric hindrance (Batrakova, Kabanov, 2008), and interactions between the amphiphilic structure of poloxamer and the cell membrane are believed to be the main mechanisms of ATP depletion (Alakhova, Kabanov, 2014). Inhibition of the efflux pump was a concentration-dependent process and was suppressed when the poloxamer concentration increased (Gaikwad, Bhatia, 2013). This effect has been suggested to be related to the formation of poloxamer unimers at a level below the critical micelle concentration (Batrakova, Kabanov, 2008; Furtado *et al*., 2018). The medium chain length of the polypropylene oxide (PPO) block of poloxamer was found to be more effective than the long-chain type and the highly hydrophobic poloxamer in inhibiting drug efflux in MDR cancer cells without impacting Pgp function and ATP levels (Pitto-Barry, Barry, 2014).

Cell Membrane Integrity Modification

Poloxamer has been shown to decrease the microviscosity of the cell membrane by the integration of hydrophobic chains into cell membranes (Batrakova, Kabanov, 2008; Pitto-Barry, Barry, 2014; Zarrintaj *et al*., 2020). The interaction of poloxamer with the cell membrane was found to consist of 2 steps: the adsorption of poloxamer onto the membrane surface and the insertion of poloxamer into the membrane. The ability of poloxamer to disrupt membrane activity was shown to be due to the interaction of the hydrophilic chain with the polar head group of the lipid molecule in the cell membrane (Alakhova, Kabanov, 2014). Poloxamer 188 was suggested to restore the barrier function of the plasma membrane and maintain cell integrity in injured tissues due to the minimization of free diffusion between intracellular and extracellular fluids, facilitated by the binding of the hydrophobic chain of membrane phospholipids with PPO segments and the water phase with PEO segments (Kwiatkowski *et al*., 2020). Administration of poloxamer 188 was shown to restore lysosomal membrane integrity of SH-SY5Y cells and prevent cathepsin leakage (Dong *et al*., 2019).

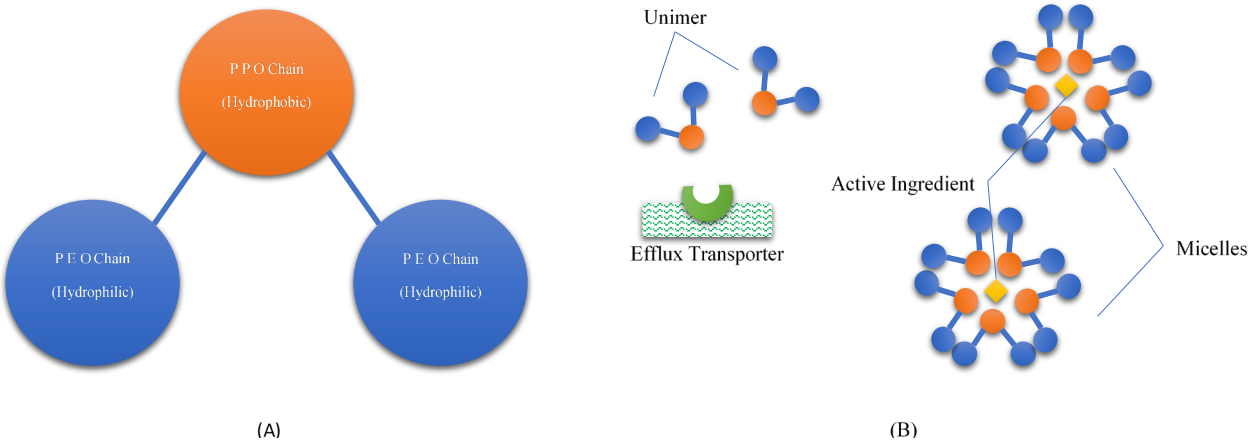

FIGURE 1 - Illustration of the poloxamer structure, which is a triblock copolymer (A); Illustration of contradictory conditions where the poloxamer must be in the form of a unimer to be able to inhibit the efflux pump while it must be in the form of a micelle to be able to dissolve the active ingredient (B).

Cellular Uptake

Surface modification by poloxamer 188 and poloxamer 407 has been shown to increase cellular uptake and transport across the BBB of poly(d,l-lactide-co-glycolide) (PLGA)-based nanoparticles (Kulkarni, Feng, 2011). Moreover, poloxamer 85 was found to increase cellular uptake in multidrug-resistant human carcinoma cell lines (KBv) but not in human carcinoma cells (KB). This cellular uptake increase was associated with overexpression of P-gP in a multidrug-resistant human carcinoma cell line, the substrate probe of poloxamer (Song *et al.*, 2011). Cellular uptake by phagocytosis was shown to be affected by the chain of the EO and PO blocks; the longer the EO and PO blocks were, the lower the phagocytic uptake (Rudt, Müller, 1993). Pluronic P85 has been demonstrated to promote cellular uptake by caveolae-mediated endocytosis at a concentration below the CMC, e.g., 0.001%, under which Pluronic 85 assumes a unimer state. However, at concentrations above the CMC, e.g., 0.1%, Pluronic P85 promoted cellular uptake mainly by clathrin-mediated endocytosis (Sahay, Batrakova, Kabanov, 2008). A polypropyleneimine/pDNA polyplex, which was modified with poloxamer 123, was revealed to exhibit an internalization mechanism by both clathrin-mediated and caveolae-mediated endocytosis (Gu *et al.*, 2016). Another study showed that Pluronic P123 was colocalized to a higher extent by caveolin-1 than by the polyethileneimine/pDNA polyplex (Yang *et al.*, 2008).

DISCUSSION

This review indicates the potential of using poloxamer as a physicochemical and/or biological response modifier. Targeted therapy as the outcome may dictate the grade and concentration of poloxamer that should be used. For example, a poorly soluble drug can be made the target of cellular uptake through caveolae to avoid lysosomal degradation by selecting a type of poloxamer that improves the drug solubility via micellar form or a type that increases caveolae-1 endocytosis via unimer form. An application of formulations derived from targeted drug delivery systems is brain drug delivery, and to that end, multiple factors need to be taken into consideration. These aspects include internalization/cellular uptake, inhibition of Pgp efflux for longer retainment, and neuroprotection ability, contrary to apoptosis.

CONFLICT OF INTEREST

The review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript.

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