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Review article

Poly(ethylene oxide)–poly(propylene oxide) block copolymer micelles as drug delivery agents: Improved hydrosolubility, stability and bioavailability of drugs

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Abstract

The low solubility in biological fluids displayed by about 50% of the drugs still remains the main limitation in oral, parenteral, and transdermal administration. Among the existing strategies to overcome these drawbacks, inclusion of hydrophobic drugs into polymeric micelles is one of the most attractive alternatives. Amphiphilic poly(ethylene oxide)–poly(propylene oxide) block copolymers are thermoresponsive materials that display unique aggregation properties in aqueous medium. Due to their ability to form stable micellar systems in water, these materials are broadly studied as hydrosolubilizers for poorly water-soluble drugs. The present review provides a concise description of the most important applications of PEO–PPO-based copolymers in the Pharmaceutical Technology field as means for attaining improved solubility, stability, release, and bioavailability of drugs.

Keywords: Poly(ethylene oxide)–poly(propylene oxide) block copolymers; Poloxamer; Poloxamine; Drug solubilization; Drug stability; Bioavailability; Drug delivery

1. Introduction and scope

Advances in medicine and related sciences during the last century led to a dramatic increase in lifespan. One of the pillars of this revolution has been the development of novel therapeutic agents for the treatment of incurable pathologies. A critical step forward in this process was the ability to scale up the production of pharmaceuticals, making drugs available for broad portions of the population. At the same time a constant and pronounced development in related disciplines took place. Pharmaceutical Technology (PT) is among the areas that are noteworthy.

A main goal of PT is the design of technologically optimal vehicles for the administration of drugs. Innovative processes allowed an enhancement in the organoleptic properties of the preparations and the maximization of the stability and bioavailability. However, a still existing drawback is the low solubility in the physiological aqueous environment of about 50% of the approved active molecules, resulting in limited gastrointestinal absorption and poor bioavailability. Paradoxically, oral administration of therapeutic agents is the preferred way to achieve the highest patient compliance [1]. Limited solubility also constitutes a hurdle in the development of parenteral and even topical formulations. Since improved solubility usually correlates well with higher bioavailability [2,3], several nanotechnological strategies are being pursued in order to guarantee the appropriate drug solubilization [4]. Among them, it is worth mentioning nanoparticle engineering [5–8]. Another important strategy is the design of nanocarriers such as liposomes [9,10]. Inclusion of hydrophobic

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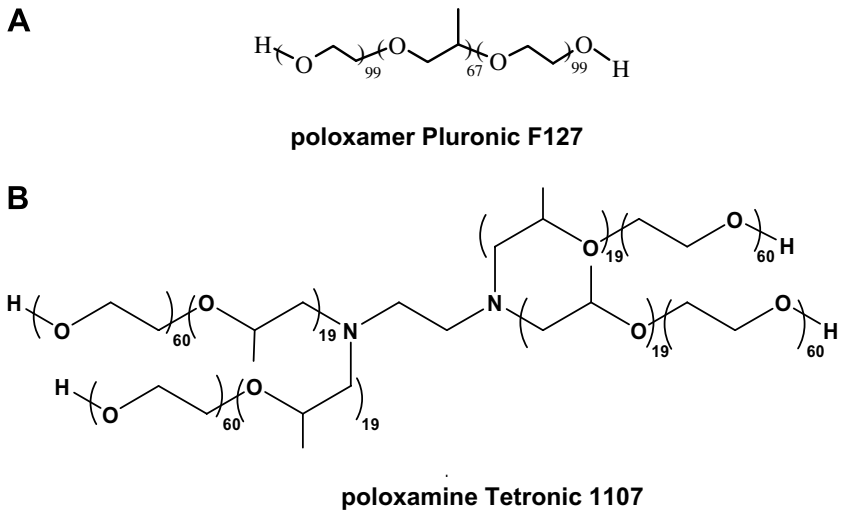
molecules within polymeric micelles is also between the nano-oriented approaches pursued to enhance drug solubilization, stability and bioavailability. Polymeric micelles are nanoscopic (>100 nm) structures formed by amphiphilic block copolymers composed of hydrophilic and hydrophobic chains that self-assemble in water, above a certain concentration named the critical micelle concentration (CMC) [11]. Micelles comprise an inner and outer domain denomined *core* and *shell*, respectively. Due to the hydrophobic nature of the core, these entities particularly suit for the solubilization of water insoluble molecules, protection of unstable agents from chemical degradation and metabolism by biological agents and sustained release in different formulations [12]. Depending on the specificity and the properties of functional groups present in both components, the interactions core–drug will have a chemical, physical or electrostatic character. Polymeric micelles are safer for parenteral administration than solubilizing agents currently in use like polyethoxylated castor oil (Cremophor EL) or polysorbate 80 (Tween® 80) [13–16]. Polymeric micelles are kinetically stable so they dissociate slowly, even at concentrations below the CMC, extending circulation times in blood [16]. In addition, they display larger cores than surfactant micelles, leading to higher solubilization capacity than the regular micelles [16]. Micelles with blocks made of poly(ethylene oxide) are sterically stabilized (Stealth®) and undergo less opsonization and uptake by the macrophages of the reticuloendothelial system (RES), allowing the micelles to circulate longer in blood [17,18]. The importance of drug efflux transporters (i.e. P-glycoprotein or PGP) in disease processes and treatment has led to the development of inhibitors to these transporters as adjuncts to therapy [19,20]. PGP modulators are the most well-known mechanism. Some polymeric micelles inhibit the PGP at different levels and tissues: drug-resistant tumors, GI tract and blood/brain barrier, providing routes to overcome drug resistance or lack of drug absorption [21]. For example, Bogman et al. investigated the effect of several Pluronic derivatives on the activity of PGP and MDRP2 (a transporter involved in multidrug resistance mechanisms) in two cell lines over-expressing these membrane transporters [22]. Data suggested that the materials display a transporter-specific interaction, rather than unspecific membrane permeabilization. Based on this unique combination of advantageous features, the use of polymer-based micelles has become one of the most promising pharmaceutical nanotechnologies [16,23].

Among the polymers displaying micelle-formation ability, it is worth mentioning conjugates of hydrophilic poly(ethylene glycol) segments with hydrophobic blocks of phospholipids [21,24], poly(L-amino acids) [25–28] and poly(esters) [21,29,30]. Other derivatives were developed by the group of Attwood and Booth. They synthesized PEO block with other polyethers such as poly(butylene oxide) (PBO) [31–33], poly(styrene oxide) (PS) [31–34] and phenylglycidyl ether [35,36]. However, the most broadly investigated amphiphilic materials are derivatives of poly(ethylene oxide)–poly(propylene oxide) (PEO–PPO–PEO) block copolymers [37,38]. These polymers belong to the family of the so-called *smart materials*. Aqueous solutions display a sol–gel transition upon heating (sometimes around 37 °C) that makes them attractive for the design of injectable matrices for minimally invasive biomedical applications [39,40]. They can be implanted as low viscosity liquids and they form a solid implant upon heating. These materials are non-irritating when applied topically or subcutaneously, produce little irritation following intramuscular or intraperitoneal administration [41] and show good cytocompatibility when used in contact with different cell types [42,43]. Even though PEO–PPO–PEO materials are non-degradable, molecules with a molecular weight in the 10–15 kDa range are usually filtered by the kidney and cleared in urine [44,45]. Kabanov and collaborator studied the distribution kinetics of Pluronic P85 [21]. Findings showed that renal clearance of unimers (isolated molecules) was the main route. In addition, a significant portion of P85 was reabsorbed back into the blood. Several PEO–PPO block copolymers were approved by FDA and EPA as thermo-viscosifying materials and find application as direct and indirect food additives, pharmaceutical ingredients and agricultural products [46–48]. More recently, Kwon et al. evaluated crosslinked PEO–PPO–PEO matrices as an injectable intraocular lens (IOL) material [49]. Two families are commercially available: (1) the linear and bifunctional PEO–PPO–PEO triblocks or poloxamers (Pluronic®) and (2) the branched 4-arm counterparts named poloxamine (Tetronic®). The molecular structure of both groups of derivatives is exemplified in Schemes 1A and B for Pluronic F127 and Tetronic 1107, respectively. These materials are available in a wide range of molecular weights and EO/PO ratios (Table 1). The most extensive work was performed on the first group. In order to attain relatively stable gels, these applications demand polymer concentrations, usually around 15 wt% [42,50–52]. Pluronic F127 formulations led to enhanced solubilization of poorly water-soluble drugs and prolonged release profile for many galenic applications (e.g. oral, rectal, topical, ophthalmic, nasal and injectable preparations), though the high permeability of the gels has limited the clinical application due to short residence times in the biological environment [53]. Cohn et al. reported a number of modifications that allowed the production of gels using concentrations around 5%: (1) the chain extension of Pluronic with hexamethylenediisocyanate [54,55] and (2) the coupling of different PEG and PPG blocks using bifunctional agents such as phosgene and diacyl chlorides [56,57]. Matrices showed better stability and integrity in aqueous environment along the time. Also, more stable networks were obtained by the covalent crosslinking of PEO–PPO–PEO triblocks modified with methacryloyl [58,59] and silane moieties [59,60]. In contrast, the potential of poloxamines was less explored. Their main drawback probably stems from the even higher concentrations required to produce gels (20–30%). Due to the higher functionality compared to their linear derivatives, poloxamines were mainly applied in the



Scheme 1. Molecular structure of PEO–PPO block copolymers. (A) Lineal bifunctional poloxamer Pluronic F127 (MW = 12.6 kDa) and (B) branched 4-arm poloxamine Tetronic 1107 (MW = 15 kDa), both polymers containing 70 wt% of PEO.

design of crosslinked hydrogels for Tissue Engineering [61], using concentrations under the minimal concentration required for gelation [62–64]. PEO–PPO molecules self-assemble into multi-molecular aggregates having spherical, rod-like or lamellar morphologies. This phenomenon is observed at much lower concentrations than those required for gel formation (<1 wt%) [65]. Fig. 1 presents cryo-TEM micrographs of spherical micelles formed by Pluronic F127 and P64 [66]. The brighter core and darker shell are apparent. An extensive work applying PEO–PPO micellar systems for drug solubilization has been published. These investigations mainly focused on poloxamers. However, in the last years the interest for the application of poloxamine has gradually risen. A remarkable advantage of poloxamine arises from the presence of two tertiary amine groups in the center of the molecule. This structure contributes to the thermal stability and more importantly confers the molecule a dual behavior: temperature and pH sensitiveness [67]. In addition, these functional groups potentially enable further modifications of the molecule by the introduction of additional useful moieties, such as quaternary ammonium groups for improved cell adhesion [64]. The quaternization of poloxamine renders chains that are positively charged, independently of the pH of the medium, and may contribute to increase or to decrease the core affinity of certain drugs. In these derivatives, a different aggregation pattern is expected. The micellization process of methylated Tetronic 1107 is presently being subject of study in our laboratory.

The goal of the present review is to provide a concise and up-to-date summary of the past and recent applications of PEO–PPO-based copolymers in the Pharmaceutical Technology field as means for attaining improved solubility, stability and bioavailability of drugs. Since micellization is the critical stage for these materials to modify the behavior of hydrophobic molecules in aqueous medium and it is directly involved in solubilization and stabilization phenomena, the first part will summarize the main works that investigated the aggregation of PEO–PPO molecules in aqueous media. Afterwards, a thorough and comprehensive summary of relevant research works is disclosed. Finally, the limitations of these materials, as seen by the authors, and the perspectives for the future will be discussed.

2. Aggregation properties of Pluronic.TM and Tetronic.TM

Micellization of PEO–PPO block copolymers in water depends on (1) compositional parameters and (2) environmental features. Due to the relevance of this phenomenon a concise description of the parameters affecting the process is herein included. The works cited are those which even if focused on a limited number of derivatives arrived at conclusions extensive to other materials of the same family.

2.1. The composition: EO/PO ratio and molecular weight

Alexandridis et al. have shown that micellization is strongly driven by an entropy gain and the free energy of micellization is mainly a function of the PPO block [68]. This entropy gain is related to the release upon heating of hydration water molecules ordered around the hydrophobic segment (PPO). The higher the content of PEO (and lower EO/PO ratio) and the lower the molecular weight of the polymer, the higher the critical micellar temperature (CMT) observed [69]. An increase in the content of PPO results in lower CMC and CMT values [70]. Both CMC and CMT values decrease with increasing molecular weight for copolymers displaying similar EO/PO ratios.

2.2. The temperature

A thorough work on the effect of the temperature on the micellization of PEO–PPO–PEO has been reported by several researchers [68–77]. Less hydrophobic copolymers (higher EO/PO ratio) or lower molecular weight do not aggregate at room temperature but start to form micelles

Table 1
Description of PEO–PPO block copolymers commercially available

Copolymer	MW (Da)	Total average number of EO units	Total average number of PO units	Total weight of EO units (Da)	Total weight of PO units	pH (2.5% aqueous)
Pluronic						
L10	3200	7.3	49.7	320	2880	
L35	1900	21.6	16.4	950	950	
F38	4600	83.6	15.9	3680	920	
L42	1630	7.4	22.5	325	1305	5.0–7.5
L43	1850	12.6	22.4	555	1295	
L44	2200	20.0	22.8	880	1320	
L61	2000	4.55	31.0	200	1800	
L62	2500	11.4	34.5	500	2000	
L64	2900	26.4	30.0	1160	1740	
L65	3400	38.6	29.3	1700	1700	6.0–7.4
F68	8400	152.7	29.0	6720	1680	5.0–7.5
F77	6600	105.0	34.1	4620	1980	6.0–7.0
L81	2750	6.3	42.7	275	2475	5.0–7.5
P84	4200	38.2	43.5	1680	2520	
P85	4600	52.3	39.7	2300	2300	6.0–7.4
F87	7700	122.5	39.8	5390	2310	
F88	11,400	207.3	39.3	9120	2280	6.0–7.0
L92	3650	16.6	50.3	730	2920	5.0–7.5
F98	13,000	236.4	44.8	10,400	2600	6.0–7.4
L101	3800	8.6	59.0	380	3420	5.0–7.5
P103	4950	33.8	59.7	1485	3465	
P104	5900	53.6	61.0	2360	3540	
P105	6500	73.9	56.0	3250	3250	
F108	14,600	265.5	50.3	11,680	2920	6.0–7.4
L121	4400	10.0	68.3	440	3960	
L122	5000	22.2	69.0	1000	4000	
P123	5750	39.2	69.4	1725	4025	
F127	12,600	200.5	65.2	8820	3780	
Tetronic						
304	1650	15.0	17.1	660	990	
701	3600	8.2	55.9	360	3240	
704	5500	50.0	56.9	2200	3300	
803	5500	37.5	66.4	1650	3850	
901	4700	10.7	72.9	470	4230	8.0–10.0
904	6700	60.9	69.3	2680	4020	
908	25,000	454.5	86.2	20,000	5000	
1107	15,000	238.6	77.6	10,500	4500	
1301	6800	15.5	105.5	680	6120	
1304	10,500	85.5	108.6	4200	6300	
1307	18,000	286.4	93.1	12,600	5400	

at higher temperatures. A slight increase of temperature leads to a sharp CMC decrease and the increase in the average aggregation number, the micellar size, and the fraction of polymer molecules in micellar form [73,78]. A similar trend was observed with the CMT.

2.3. The ionic strength and salt nature

Since many drugs have an ionic character and media used for the formulations usually comprise salts for pH buffering and ionic strength balance, these parameters may critically influence the behavior of PEO–PPO-based molecules in aqueous medium. Addition of electrolytes having anions and cations of different sizes and polarizabilities may lead to: (1) 'salting out' and stabilizing effect or (2) 'salting in' and destabilizing effect [74]. In general, a gradual decrease in the CMC and the CMT was observed with the increase of neutral salts' concentration [79–83]. It should be stressed that studies with the same cation showed that the properties of the counter-anion are also relevant. For potassium halides, the effect of on micellization follows the sequence $KCl > KBr > KI$ [78,79]. In another work it was shown that while NaCl had a stabilizing effect, NaSCN displayed the opposite influence [84]. Pandit and Kisaka reported that salts with multivalent anions, at characteristic concentrations, prevent Pluronic® F127 solutions from forming gels, being an indication of a destabilizing effect [85]. For example, phosphate anions increased the transition to higher temperatures. In contrast, with carbonate the CMT of Pluronic F88 moved down to lower temperatures [86]. The authors proposed a critical micelle salt concentration (CMSC) as the salt concentration at which the micelles begin to form [86].

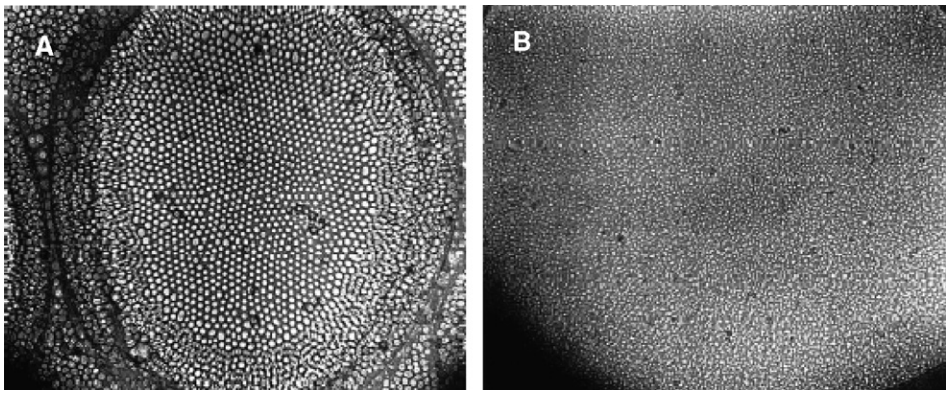


Fig. 1. Electron micrograph of a vitrified sample of (A) 10% Pluronic F127 and (B) 10% Pluronic L64 solutions. Scale bar = 100 nm. (Reprinted with permission from Ref. [66]; © Royal Society of Chemistry, 1999.)

2.4. Small organic molecules

Solubilized drugs are expected to modify the aggregation pattern and the stability of the micelles. Regardless of the relevance of this parameter on the micellization capability, most of the works focused more on the aspects related to drug solubility and less on the reciprocal effect of small organic molecules on the structure of the aggregates. Tontosakis and co-workers showed that small amounts of *o*-xylene increased the tendency of the amphiphile to aggregate on the micellar structure of PEO–PPO–PEO triblocks [87]. Alexandridis et al. reported that urea increased both CMC and CMT [88]. Contrarily, phenol appeared to decrease the CMC due to interactions with PEO chains [89]. When another surfactant, sodium dodecyl sulfate (SDS), was added to Pluronic F127, the surfactant associated to F127 unimers and suppressed micellization completely [90,91]. Naproxen and indomethacin did not affect the CMC, though they caused a slight decrease in the size of the micelles and a large decrease in the aggregation numbers [92]. The same group of investigators evaluated the influence of mammalian-cell media on the gelation properties of the same polymer [93]. Also pilocarpine hydrochloride decreased the CMC from 0.5% to 0.25% [94]. Short-chain alcohols (i.e. ethanol) prevented micellization in water [95], while medium-chain and more hydrophobic aliphatic alcohols (i.e. butanol) favored aggregation [95–97].

2.5. The concentration

The concentration of the polymer is another aspect of consideration [98]. In general, the higher the concentration of the polymer, the lower the temperature required to attain micellization [74,78].

2.6. The pH

Pluronic molecules do not display pH-sensitive moieties in their structure. Thus, the study of the pH influence on the aggregation behavior of Pluronic was very limited. Yang et al. investigated the micellization of Pluronic P123 at different HCl solutions [99]. Findings indicated that the CMT of Pluronic P123 increased when acid was added. This phenomenon could occur due to the enhancement of the interaction between the alkyl group and the protonated water molecules. In the case of poloxamine, the presence of a central diamine group in the molecular structure renders both thermo- and pH-responsiveness. Only a very limited number of works reporting the micellization of poloxamine at different pH were previously published. Accordingly, basic/acid equilibrium appears to have an important impact upon aggregation [100]. A low pH protonated amines lead to coulombic repulsion and curtails aggregation [101]. Poloxamine pK_a values are usually in the 3.8–4.0 to 8.0 range and varying sized chains of blocks of PPO and PEO bounded to the ethylenediamine molecule do not substantially change these values [67]. The shift in the pK_a of the second amine is caused by the effect of charge repulsion. At pH 2.5, poloxamine exists in a diprotonated form and aggregation is shifted to a higher temperature range. An increase in pH leads to a decrease in the temperature range over which aggregation occurs. At pH 6.8, the percentage of aggregation increases and it is even higher at pH > 8 [102]. At physiological pH, there is one positive charge per poloxamine molecule [100]. Alvarez-Lorenzo et al. investigated the influence of pH on the aggregation of poloxamine T904 [103]. Findings showed that the aggregation number is altered by a change in pH or ionic strength. As appreciated in TEM micrographs of T904 30% systems, a great number of significantly small entities (2 nm) were formed at pH 1 (Fig. 2) [103]. Authors assigned them to the presence of small micelles, though the described sizes could also correspond to dehydrated unimers (one single polymer molecule) [55]. In contrast, in a more basic medium, the micelles were larger (10–20 nm) and the size distribution more homogeneous. Another aspect of interest is the potential modification of poloxamine. Sosnik and Sefton reported on the methylation of Tetronic 1107 with iodomethane for enhanced cell attachment in a modular Tissue Engineering construct [64]. Due to the permanent cationic character of the modified molecule, one could expect a behavior similar to the

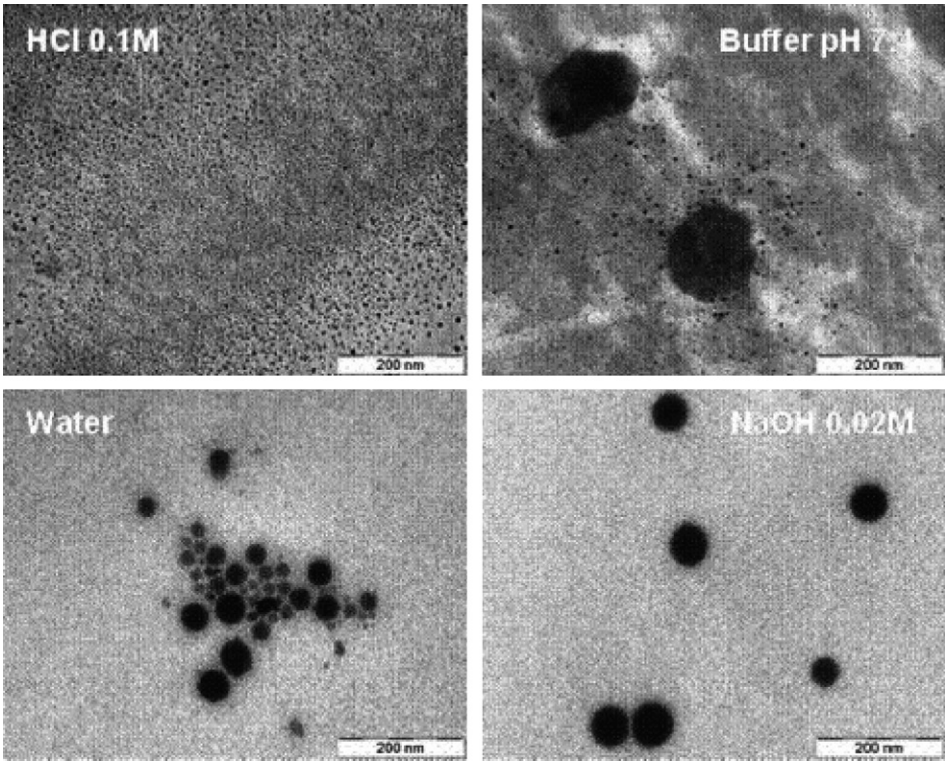


Fig. 2. TEM micrographs of 30% T904 solutions prepared in different media and negatively stained with phosphotungstic acid (110,000×). (Reprinted with permission from Ref. [103]; © Elsevier, 2007.)

pristine poloxamine at low pH (where one or amine groups are protonated) that displays higher CMC and CMT values than the non-protonated molecule. Studies on micellization of this derivative are being pursued these days in our laboratories. Applications where PEO–PPO block copolymers are used for the stabilization of particles exceed the scope of the present review. However, a noteworthy example where the pH-dependency of poloxamine was exploited is the stabilization of negatively charged DNA particles with protonated poloxamine molecules [104].

3. Micellar solubilization of poorly water-soluble molecules

Solubilization properties of the polymeric micelles are usually expressed in terms of micelle–water partition coefficients defined as the ratio between the concentration of the solubilizate inside the micelle and the concentration of the solubilizate that is molecularly dispersed in the aqueous phase, being the concentration in molarity [105,106]. The solubilization capacity can be expressed either in the form of the volume or mass fraction of the solubilizate in the micellar core, as the number of moles solubilized per gram of hydrophobic block or as the molar solubilization ratio (MSR) that is the molar ratio of the moles of guest molecule to the moles of polymer molecules in the aggregate. The maximal solubilization capability of amphiphilic materials relies on the formation of micelles [101]. Nevertheless, Paterson et al. showed improved solubilization of naphthalene even below the CMC [107]. Once the concentration rises above the CMC, a sharp increase in the apparent solubility is observed as molecules accommodate within the hydrophobic micellar core. They proposed a simple solubilization model demonstrating that a turning point (sharp increase in the gradient) will take place at the CMC. The equations describing this phenomenon are the following [107]:

If $C_s < \mathrm{CMC}$

$$\frac{S_{\mathrm{apparent}}}{S} = 1 + K_{\mathrm{unimer}} \cdot C_S$$

If $C_s > \mathrm{CMC}$

$$\frac{S_{\mathrm{apparent}}}{S} = 1 + K_{\mathrm{unimer}} \cdot \mathrm{CMC} + K_{\mathrm{micelle}} \cdot (C_S - \mathrm{CMC})$$

where S_{apparent} is the aqueous solubility measured in the surfactant solution and S is the solubility in pure water, expressed in mol/L. C_S is the concentration of surfactant in the aqueous phase, K_{unimer} and K_{micelle} are equilibrium constants describing the solute–unimers (<CMC) and solute–micelles (>CMC) interaction, respectively. In general, solubilization is found to increase the micelle core radius and to decrease the CMC [105]. The radius increases due to both incorporation of solute molecules and increase in aggregation number. More hydrophobic derivatives (lower EO/PO ratio) display higher solubilization capacity and higher changes in the dimensions. In contrast, the shell thickness (PEO) is less affected. The effect of the concentration of the polymer on solubilization is exemplified in Fig. 3 for

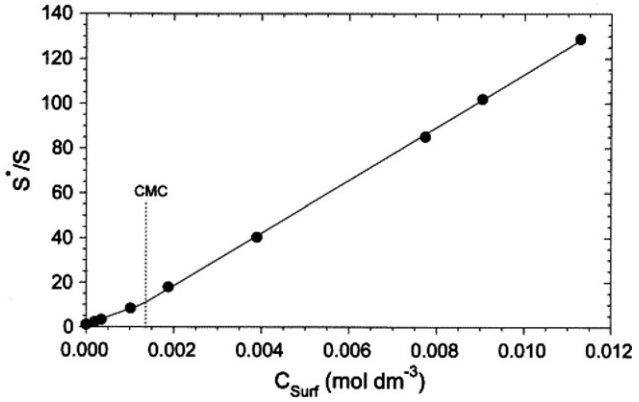


Fig. 3. Naphthalene solubility enhancement ratio (S_w/S) as a function of P103 surfactant concentration. ● represents the experimental data. (Reprinted with permission from Ref. [107]; © American Chemical Society, 1999.)

naphthalene solubilized in poloxamine 803 at 25 °C and pH of 10.3 [107]. It is worth stressing the low C_S initial values at $C_S < \text{CMC}$. In contrast, a dramatic increase in the C_S was apparent when micelles were formed. Then, a gradual increase in the polymer led to higher micellar concentrations and consequently, to higher solubilized solute. Therefore, solubilization will be intimately related to the micellization process and the parameters governing both phenomena are the same. This can be exemplified for the temperature: the apparent aqueous solubility of a hydrophobic solute dramatically rises at higher temperature [101]. This effect is more pronounced at concentration levels close to the CMC. This is exemplified in Fig. 4 for two-model hydrophobes: phenanthrene and pyrene [101]. A similar trend is observed with poloxamine at different pH. Since micellization is favored at pH > 8, hence solubility is. Another important parameter is the hydrophobicity of the surfactant molecule. In general, the micelle–water partition coefficient increases with increasing polypropylene oxide content of the polymer and with molecular weight [108]. Table 2 summarizes the most important studies on solubilization, stabilization and delivery of hydrophobic drugs using PEO–PPO-based polymeric micelles. Concheiro et al. explored the effect of Pluronic F127 grafted with poly(acrylic acid) blocks. These dual materials enhanced the solubility (3- to 4-fold increase) of the lactone form of camptothecin, an antitumoral drug [109]. Also, the stability of the active form of the drug was improved. The amount of drug solubilized per PPO was considerably greater in the Pluronic-PAA solutions than in the parent Pluronic® solution, which suggests that the drug is not only solubilized by the hydrophobic cores but also by the hydrophilic PEO–PAA shells of the micelles. An interesting approach combining micelle encapsulation with additional means to target the drug release is the comprehensive research by Rapoport and colleagues on the design of nanocarriers for the targeted release of doxorrubicin (Dox) to tumors [110–116]. This methodology reduced unwanted drug interactions and nocive effects on healthy tissues and relies on the encapsulation of the chemotherapeutic agent within polymeric micelles and the application of local ultrasonic irradiation on the tumor. Main mechanisms of the biological action of ultrasound are related to the generation of thermal energy, perturbation of cell membranes under the action of microconvection or inertia cavitation and enhanced permeability of blood capillaries [110]. As described by the authors of that work, the encapsulated drug primarily accumulated in the tumoral cells' interstitium and later on, irradiation of the affected area resulted in a more effective cellular uptake. The mechanism recently proposed by the group of Pitt in order to explain the more efficient release of the drug from the micelles relies on the destruction of the micelles during the application of ultrasound [116]. Micelles are destroyed because of cavitation events produced by collapsing nuclei or bubbles in the irradiated area. Once the ultrasonic radiation halts two independent mechanisms take place: (1) reassembly of micelles and (2) the re-encapsulation of Dox. These two mechanisms are responsible for maintaining the drug release at a partial level and for the recovery observed after insonation ceases. Witt et al. studied the opioid analgesia enhancement of an opioid peptide and morphine using Pluronic P85 below and above the CMC [117]. Data showed a clear increase in the peak effect and a prolonged effect. As previously indicated, the CMC and the partition coefficient are the major thermodynamic constants determining the stability of the micellar carrier and the drug release in equilibrium conditions [118].

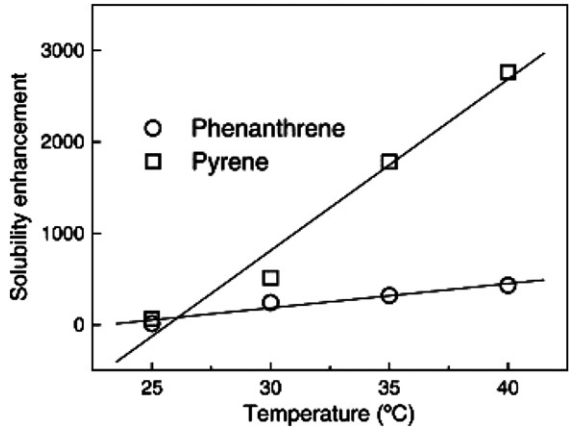


Fig. 4. Solubility enhancement of phenanthrene and pyrene as a function of temperature at a pH of 5.6 and T803 concentration of 5 mM. (Reprinted with permission from Ref. [101]; ©Elsevier, 2004.)

One main concern following the use of polymeric micelles for drug solubilization is the severe dilution they undergo in the biological environment (sometimes below the CMC) that results in a decrease in the portion of the micelle-incorporated drug. The CMC values observed for these block copolymers are generally in the range from 5×10^{-3} to 1 wt%. The rate of dissociation is related to composition, physical state and cohesion of the micelle core [119]. It has been demonstrated that the micellar

Table 2
Summary of the most important studies on solubilization, stabilization and delivery of hydrophobic drugs using PEO–PPO-based polymeric micelles

Drug	Pharmacological activity	Copolymer	Administration[a]	Observations	Reference
Tropicamide	Mydriatic/cycloplegic	L-64, P65, F68, P75, F77, P84, P85, F87, F88, F127	Ocular	Solubility increased linearly with increasing surfactant concentration. Higher solubility for higher EO content.	[128]
Haloperidol	Neuroleptic	P85	i.p.	5-fold increase in solubility.	[129]
Morphine	Central analgesia (CNS)	F127	Ocular	Drug was soluble. Prolonged delivery	[130]
		P85	i.v.	Increased analgesia due to both an increase in peak effect, as well as a prolongation of effect	[117]
Estriol	HRT	L64	–	The solubility of estriol increased with Pluronic concentration and temperature.	[131]
		L64	–	Higher solubilization with higher polymer and salt concentration	[132]
		F127 modified with PAA segments	–	Increased solubility above CMT. Better solubilization in modified polymers than in native Pluronic.	[133]
Dichloroplatinum (II) complexes	Anticancer	F68	Parenteral	Stable colloidal suspension. Effective against hormone sensitive MXT-M-3.2 breast cancer.	[134]
Cyclosporin A	Immune-depressant	F68	–	Thermal analysis of solubilization process.	[135]
Epirubicin	Anticancer	L61, P85, F108	s.c.	Lifespan of animals and inhibition of tumor growth considerably increased with drug/copolymer compositions.	[136]
Naproxen	NSAID	F127	Topical, i.v.	Increased solubility. Longer half-life by i.v.	[137,138]
Doxorubicin (DOX)	Anticancer	P105	i.p.	Local ultrasonic irradiation of the tumor increased drug accumulation in the tumor cells. Substantial decrease of the tumor growth rates.	[110–116,120–122,165]
		P105	–	Lower rat prostate carcinoma cells' (MatLu) proliferation in vitro with micellar system.	[139]
Doxorubicin (DOX)	Anticancer	P85	–	A formulation containing the block copolymer Pluronic P85 and antineoplastic drug doxorubicin (Dox) prevents the development of multidrug resistance in the human breast carcinoma cell line, MCF7.	[140]
		F87 modified with PAA segments	–	Improved inclusion due to interactions between PAA and drug.	[141]
Pilocarpine	Miotic	F127	Ocular	Polymer combined with additives displayed higher solubility.	[142,143]
		F127	Ocular	Base and hydrochloride form. Prolonged activity and higher bioavailability.	[94]
Clonazepam	Psychotropic	F68	–	3.5-fold solubility increase.	[144]
Propranolol	Hypertension	F127	–	Improved release profile.	[145]
Propranolol · HCl		F68, F127	Rectal	Drug is soluble. Located outside micelles. Improved bioavailability when combined with mucoadhesives.	[146]
Insulin	Hormone, glucose transport	F127	Rectal	Formulations containing unsaturated fatty acids. Rectal insulin absorption enhanced. Marked hypoglycemia.	[147]
			Subcutaneous	Formulations containing unsaturated fatty acids. Slower and more prolonged hypoglycemic effect attained in inverse proportion to the polymer concentration.	[50]
			Buccal	Formulations containing unsaturated fatty acids. Buccal insulin absorption enhanced. Marked hypoglycemia.	[148]
Vancomycin	Antibiotic	F127	Subcutaneous	Controlled release and good preservation of the drug.	[149]
Diclofenac	NSAID	F127	–	Study on diethylamine derivative and sodium salt.	[150]
		F127	Rectal	Drug is soluble. Faster absorption.	[151]

Ketoprofen	NSAID	F127	Topical	Enhanced permeability with enhancers.	[152]
Piroxicam	Antiinflammatory	F68, F127	Percutaneous	Better release profile.	[153]
Indomethacin	Antiinflammatory	F68, F127	Ocular	Higher solubility and chemical stability. Prolonged in vitro drug diffusion and showed high physiological tolerance on rabbit eyes.	[154]
Lidocaine/Prilocaine	Local anesthetics	F68, F127	Topical (mouth)	Eutectic mixture. Amount of the active ingredients in the micelle phase depends on the pH: higher at higher pH (non-ionic drug).	[52]
Triamcinolone	Glucocorticoid	F127 combined with carbopol	Topical (mouth)	Enhanced delivery profile.	[155]
Digoxin	Heart muscle stimulant	P85	i.v.	Pluronic P85 can enhance the delivery of digoxin to the brain through the inhibition of the P-glycoprotein-mediated efflux mechanism.	[156]
Griseofulvin	Antifungal	Synperonic P94[b]	–	Lower solubilization ability than polymers with poly(oxybutylene) and poly(oxyphenylethylene) as hydrophobic block.	[33]
		Tetronic 904	–	Higher solubility at higher pH due to improved micellization	[103]
Deslorelin	GnHR agonist	F127	i.m.	Broader peak of luteinizing hormone (LH). Lower peak and delayed activity with the gel.	[157]
Biphalin	CNS analgesia	P85	i.v.	Study to improve BBB transfer. Higher peak effect and longer activity.	[117]
Timolol maleate	Glaucoma	F127	Ocular	Drug is soluble. About 2.4-fold improved bioavailability	[158]
Tropicamide	mydriatic/cycloplegic	P85	Ocular	Solubility increased 1.9 times, faster peak and longer activity.	[159]
Benzoporphyrin	Anticancer	P123	–	No evaluation in vitro or in vivo up-to-date.	[160,161]
Estradiol	HTR	F127	–	Effect on release by carbopol matrix. Increased solubility above CMC.	[162]
Propofol	Anesthetic	F68, F127	–	Higher solubility.	[163]
		F68, F127 and mixed micelles		Higher solubility in mixed systems	[164]
Fluorescent molecule model	Anticancer	P105	i.p., i.v.	Local ultrasonic irradiation of the tumor increased drug accumulation in cancerous ovarian tissue.	[165]
Camptothecin (CPT)	Anticancer	F127, L92 and modified with PAA blocks	–	CPT solubility 3- to 4-fold higher. CPT solubilized per PPO greater in the Pluronic-PAA than parent, suggesting solubilization by the hydrophobic cores and hydrophilic shells. Enhanced stability.	[109]
		F127, F68, P85	–	Improved oral absorption estimated in vitro.	[27]
Megestrol	Hormone replacement therapy	Mixture F127/L61	Oral	Enhanced bioavailability	[166]
Nystatin	Antimycotic	F68, F98, P105, F127		Solubility increased from 20 to >350 μM. The higher the polarity of the molecule the lower the solubility.	[167]
Ibuprofen	NSAID	F68	Oral	Ibuprofen in eutectic mixture with menthol.	[168]
Paclitaxel (PTX)	Anticancer	P123	i.v.	Pluronic P123 solubilize PTX, prolonged blood circulation time and modify the biodistribution of PTX. t1/2 was 2.3-fold higher injection. Increased the uptake of PTX in the plasma, ovary and uterus, lung, and kidney, but decreased uptake in the liver and brain.	[169]
Octaethylporphine		F127, F68, P85	–	Improved oral absorption estimated in vitro.	[170]
Meso-tetraphenyl porphine	Photosensitizer for cancer treatment	F127	–	Improved oral absorption estimated in vitro.	[170]
Rofecoxib	NSAID	F68, F127	–	Improved solubility	[171]

Abbreviations: CNS, central nervous system; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drugs; BBB, blood–brain barrier.

[a] For studies in vivo.

[b] Synperonic® is another PEO–PPO–PEO triblock trademark (ICI C&P). Synperonic P94 (PEO_{21}–PPO_{47}–PEO_{21}) has a molecular weight of 4600 and 60 wt% PEO.

stability increases with the length of the hydrophobic segment and the overall hydrophobicity of the amphiphile. Due to the relevance of this phenomenon, the next section will introduce a number of strategies pursued in order to enhance the stability of PEO–PPO polymeric micelles.

4. Stabilization of micelles

As previously explained, one of the problems related to the use of micelles for drug solubilization is that the aggregates disassociate at low concentration (upon dilution in biological environment) and are no longer able to maintain hydrophobic drugs in the core. The stability of more hydrophilic derivatives is more critically affected. This phenomenon could be explained by the fact that more hydrophobic polymers display lower CMC and CMT and concentrations remain above those values even after high dilution. In order to overcome these disadvantages physically and chemically stabilized micelles were developed. Nevertheless, it is worth mentioning that a prolonged circulation not always leads to an improvement in the therapeutic index of the drug. Kabanov and colleagues well stated that there must be an equilibrated affinity between the components so that the effective inclusion of the drug in the micellar core increases stability and circulation time of the drug on one hand, and gives place to an effective release from the carrier within the critical site of action on the other [47]. Thus, a very strong interaction core–drug will curtail the gradual release of free drug in a manner that allows therapeutic levels' attainment. In an early work, Rapoport explored three alternatives to stabilize Pluronic micellar systems [120]: (1) direct radical crosslinking of a reactive monomer (e.g. styrene) in the micellar cores, (2) inclusion of a small concentration of vegetable oil into diluted Pluronic solutions and (3) polymerization of a temperature-responsive LCST hydrogel in the core of Pluronic micelles and the generation of a core-located semi-interpenetrating network. The first route compromised the drug loading capacity of the micelles due to the high crosslinking density. The second resulted in decreased micelle degradation upon dilution due to the expected decrease of the CMC, while not compromising the drug loading capacity of oil-stabilized micelles. The last one appeared to be the most beneficial. The crosslinkable system was based on poly(*N*-isopropylacrylamide) [120]. Later on, Pitt and coworkers polymerized *N*,*N*-diethylacrylamide in the presence of Pluronic P-105 micelles [121,122]. The interpenetrating network formed stabilized the micelles at concentrations below the critical micellar concentration of free polymer, though the increased micellar stability was not permanent and disappeared over a time period of days to weeks. Petrov et al. applied a similar procedure and stabilized Pluronic F68 aggregates by UV-induced free-radical polymerization of pentaerythritol tetraacrylate in the micellar core [123]. In order to overcome lack of stability Kabanov et al. introduced the concept of binary mixing of hydrophobic (e.g. L121, L101, L81, and L61) and hydrophilic (e.g. F127, P105, F87, P85, and F68) Pluronic block copolymers [65]. Even though, large aggregates were primarily formed and phase separation apparent during the first 24–48 h, sonication (1–2 min) or heating (70 °C, 30 min) stabilized the dispersions. A combination L121/F127 (1:1% weight ratio) formed stable dispersions with a small particle size and displayed about 10 times higher solubilization capacity of a hydrophobic dye compared to that of pure F127 micelles. However, results indicated that mixtures are kinetically stabilized and since they are thermodynamically unstable they will finally separate.

A novel strategy introduced in the last years is the crosslinking of the micellar shell. Terminal hydroxyl groups undergo modification to improve reactivity and are further reacted with coupling agents or by free radical polymerization reactions. Two different effects can be observed: (1) micellar stabilization and (2) tunable shell permeability, being the latter critical for drug inclusion and release rates [124]. Only a few works pursuing this approach were reported. Bae et al. modified two-terminal hydroxyl groups of Pluronic F127 with thiol moieties and were exposed after micellization to gold nanoparticles generated in situ [125]. The resultant shell crosslinked gold–Pluronic micelles exhibited a temperature-dependent volume transition: their hydrodynamic diameter decreased from about 160 nm at 15 °C to about 60 nm at 37 °C as determined by dynamic light scattering. Yang and co-workers stabilized Pluronic P121 micelles by converting the alcohol groups into aldehydes and bridging them with diamines through the formation of Schiff bases [126]. The morphology of the aggregates remained spherical in shape and the mean particle sizes of the micelles before and after crosslinking were comparable (100 nm). This modification significantly reduced the CMC and greatly enhanced the stability of the micelles. A similar chemistry was employed to shell-crosslink Pluronic F127 micelles with a 6-arm amine-terminated PEG [127]. The nanocapsules were used for encapsulation of paclitaxel in an oily core. Regardless of the intended modifications, stabilization of PEO–PPO-based micelles without affecting the sequestration capacity and release profile still remains a challenge.

5. Limitations and perspectives

Hydrosolubilization of pharmacologically active molecules is the critical stage in order to attain bioabsorption and biodistribution. The paradox is that about 50% of the drugs display from a very limited to negligible water solubility values. In this context, different nanotechnological methodologies are being intended. Inclusion into polymeric micelles is one of the most attractive. Among them, PEO–PPO based aggregates are the most broadly investigated. PEO–PPO block copolymers have gained popularity over the decades due to a number of critical reasons: (1) very broad range of compositions (MW, EO/PO ratio), (2) commercial availability (very important in pharmaceutical sciences in order to obviate synthetic procedures), (3)

proven biocompatibility for many of the derivatives and minor side effects in vivo and (4) approval by regulatory institutions (i.e. FDA) to be used in pharmaceutical formulations. Despite all these advantages, it is worth mentioning that PEO–PPO block copolymers still present a number of limitations that depending on the specific case could curtail the application. The most important has to do with the low stability of the self-assembled nanostructures upon dilution in the bloodstream. This phenomenon is more crucial in derivatives with higher EO/PO ratios. Core and shell-stabilized micelles were produced by a number of scientists though agreement exists that the intended modifications affected the release profile of the drugs. The limited stability of the gels in aqueous environment was described above. Cohn et al. design several synthetic alternatives to overcome the high permeability of the matrices that resulted in short residence times [54–60]. Finally, the more hydrophilic representatives of this family of compounds display lower micellization ability at 25 °C and lower solubilization capacity. In this context, a series of more hydrophobic counterparts with similar architecture but where the PPO segment was conveniently replaced by a more hydrophobic one (i.e. poly(butylene oxide) and poly(styrene oxide)) has been developed by the group of Attwood and Booth [31–36]. Due to the higher hydrophobicity, these micellar aggregates showed improved solubilization ability and stability.

Considering pros and contras, PEO–PPO materials represent a very versatile alternative to enhance formulations of poorly water-soluble drugs. They have gone a long route that includes approval of some of the materials by the Food and Drug Administration. Since several drawbacks were overcome at least partially by introducing chemical modifications to their structure, future perspectives will probably need to face the low stability of the aggregates in a more extended and comprehensive way. Our group is dedicating efforts to modify poloxamine molecules in order to allow further stabilization procedures.

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