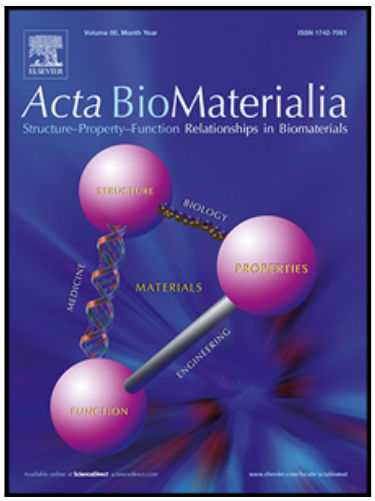

Poloxamer: A versatile tri-block copolymer for biomedical applications

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Poloxamer: A versatile tri-block copolymer for biomedical applications

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Abstract

Poloxamers, also called Pluronic, belong to a unique class of synthetic tri-block copolymers containing central hydrophobic chains of poly(propylene oxide) sandwiched between two hydrophilic chains of poly(ethylene oxide). Some chemical characteristics of poloxamers such as temperature-dependent self-assembly and thermo-reversible behavior along with biocompatibility and physiochemical properties make poloxamer-based biomaterials promising candidates for biomedical application such as tissue engineering and drug delivery. The microstructure, bioactivity, and mechanical properties of poloxamers can be tailored to mimic the behavior of various types of tissues. Moreover, their amphiphilic nature and the potential to self-assemble into the micelles make them promising drug carriers with the ability to improve the drug availability to make cancer cells more vulnerable to drugs. Poloxamers are also used for the modification of hydrophobic tissue-engineered constructs. This article collects the recent advances in design and application of poloxamer-based biomaterials in tissue engineering, drug/gene delivery, theranostic devices, and bioinks for 3D printing.

Statement of Significance

Poloxamers, also called Pluronic, belong to a unique class of synthetic tri-block copolymers containing central hydrophobic chains of poly(propylene oxide) sandwiched between two hydrophilic chains of poly(ethylene oxide). The microstructure, bioactivity, and mechanical properties of poloxamers can be tailored to mimic the behavior of various types of tissues. Moreover, their amphiphilic nature and the potential to self-assemble into the micelles make them promising drug carriers with the ability to improve the drug availability to make cancer cells more vulnerable to drugs. However, no reports have systematically reviewed the critical role of poloxamer for biomedical applications. Research on poloxamers is growing today opening new scenarios that expand the potential of these biomaterials from “traditional” treatments to a new era of tissue engineering. To the best of our knowledge, this is the first review article in which such issue is systematically reviewed and critically discussed in the

light of the existing literature. Undoubtedly, investigations on the use of poloxamer biomaterials needs further advancement and a lot of critical questions have yet to be answered. Herein, we introduce the salient features, the hurdles that must be overcome, the hopes and practical constraints into further developments.

Keywords: Poloxamer; Pluronic; Biomaterials; Biomedical engineering; Tissue engineering; Drug delivery

Abbreviations: poly(propylene oxide) (PPO), poly(ethylene oxide) (PEO), multidrug-resistant (MDR), arginylglycylaspartic acid (RGD), 3,4-dihydroxyphenyl-L-alanine (DOPA), nitric oxide (NO), S-nitrosothiols (RSNOs), β-cyclodextrin (βCD), heparin-poloxamer (HP), ε-polylysine (EPL), acrylic acid (AA), critical micelle concentration (CMC), critical micelle temperature (CMT), tocopherol (TOC), N-acryloyl-6-aminocaproic acid (AACA), extracellular matrix (ECM), glycosaminoglycans (GAGs), human adipose-derived mesenchymal stem cells (hASCs), human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), Hydroxyapatite (HAp), central nervous system (CNS), peripheral nervous system (PNS), poly(lactic-co-glycolic acid) (PLGA), nerve growth factor (NGF), polycaprolactone (PCL), polydioxanone (PDO), P-glycoprotein (P-gp), doxorubicin (DOX), mononuclear phagocytic system (MPS), vincristine sulfate (VCR), polyethyleneimine (PEI)

1. Introduction

Biomedical uses of materials inspire scientists and researchers to investigate and discover advanced materials with adjustable features under various conditions. Synthetic polymers can be designed in different structure to fulfill the biomedical aims. Therefore, the acquisition of thorough knowledge about biomaterials is of great importance [1, 2]. In this regards, the utilized polymers including synthetic and natural ones [3, 4] should be designed based on final usage such as drugs/gene delivery, cancer therapy, 3D-printing and tissue engineering [5-7]. Among synthetic polymers, poloxamers have found a wide variety of applications due to their triblock structure which hydrophilic and hydrophobic segments are present within the poloxamer structure simultaneously which endow the unique properties such as thermosensitivity and micellar formation [8]. Poloxamers were first commercially manufactured in 1950 by BASF Corporation in the US. They are now produced in several countries by various trade names, e.g., Pluronic®, Synperonic®, and Tetronic® [9]. After patenting the poloxamer, Schmolka used Pluronic F127 for treating burn injuries [10]. Poloxamers are non-ionic triblock copolymers composed of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) blocks in the form of (PEO/PPO/PEO) [11]. Changing the length of hydrophilic and hydrophobic blocks will alter the total molecular weights and the final properties of the polymer; therefore, various grades of poloxamer could be obtained. The most universally consumed grades of poloxamers are Poloxamer 188 and 407 [12]. The coexistence of hydrophilic and hydrophobic segments endows poloxamers with a systematic transformation of physical properties with the temperature [13, 14]. The main distinguishing features of poloxamer solutions are their temperature-dependent self-assembling and thermo-reversible

characteristics. Poloxamer solutions with the concentrations above their critical micelle concentration (CMC) form gels at temperatures higher than their sol-gel temperature (critical micelle temperature). Moreover, at high temperatures, the hydrophobic PPO blocks dehydrate and become less soluble in water, leading to the micelles formation with the dehydrated PPO core and hydrated PEO shell. Gelation occurs in sufficiently concentrated solutions due to micelles packing [15]. Poloxamers can form hydrogels [16], injectable hydrogels [17], 3D scaffolds [18], micro/nano-fibers [19], cell carrier constructs [20], and drug micro/nano-carriers [21-23] in blends and nanocomposites. Due to its versatility, poloxamer-based biomaterials have been used in diverse fields of tissue engineering such as chondrogenesis [24], neurogenesis [25], angiogenesis [26], bone regeneration [27], and wound healing [28]. Poloxamers are also regarded as inactive molecules with no cytotoxicity for various pharmaceutical applications such as gene and drug delivery systems (DDS) [29-32]. The main application of the poloxamer is illustrated in figure 1.

Figure 1.

They can also act as biological response modifiers and make multidrug-resistant (MDR) cancer cells more vulnerable to drugs through specific biological mechanisms (poloxamers functions in MDR cells are depicted in figure 2)[33]. The amphiphilic nature of poloxamers has made them a proper surfactant for the synthesis of particles particularly in micro/nano-emulsion systems [34, 35]. Moreover, they are appropriate materials for surface modification of hydrophobic drug carriers to decrease their elimination through systemic circulation and to enhance their targeting efficiency [36, 37]. Engineered constructs should resemble the native tissue structure in terms of morphology, mechanical properties, porosity, and chemistry. Thus,

according to the properties of the targeted tissue, appropriate physical and chemical modifications must be applied to the poloxamers. Incorporation of mineral nanoparticles, blending with stronger biomaterials for improving the mechanical properties, and introduction of a more biocompatible polymer or oligopeptide such as Arginyl-glycyl-aspartic acid (RGD) for enhancing the bioactivity are some of the common modifications for this purpose [38]. Suitable stem cells, growth factors, or drugs may also be accommodated in the hydrogel structures for facilitating the regeneration process [39-41].

Figure 2.

One of the most primary effects of poloxamers in MDR cells is the decrease in cell membrane microviscosity due to the integration of their hydrophobic chains in the cell membrane. They also demonstrate enforcement to dramatically decrease the adenosine triphosphate (ATP) contents of cancerous cells because of the poloxamer penetrating into membranes which inhibit the drug efflux transporters like Pgp [42], multidrug resistance proteins [43], and breast cancer resistance protein [44] consequently accumulation of anticancer drugs in the cancerous cells [45].Poloxamer increases cytochrome C release, reactive oxygen species (ROS) levels in the cytoplasm and pro-apoptotic signaling and decreases anti-apoptotic defense in MDR cells [46]. In addition, poloxamer restrains the glutathione/glutathione S-transferase detoxification system eliminates drug sequestration within cytoplasmic vesicles [47]. Inhibiting the function of detoxifying systems like glutathione/glutathione S-transferase will put an end to the drug importation through endocytosis of vesicles. Glutathione S-transferases (GST) as a

detoxifying system, are a member of family of enzymes that are also functioning as transport proteins, when GST is going to be inhibited so both functions are going to be suppressed, when GST function is suppressed it will help to increase cytosolic drug accumulation and efficacy of drug in MDR cells [45, 47]. Figure 2 summarize the Pluronic effect in cancer cell in which the poloxamer bind to MDR cancerous cells and stimulate the membrane fluidization, disrupt the microdomain of membrane and inhibit drug efflux transporters' activity. Reaching the poloxamer to the mitochondria hampers mitochondria respiratory portion and stimulate depolarization of internal mitochondrial membrane which cause to ATP depletion and enhance the cytochrome c release and ROS generation which damage some vital part of cells such as cytosolic proteins, mitochondrial membrane and nuclear DNA that are important triggers of apoptosis (programmed cell death). Totally, MDR cells react to poloxamer by an enhanced proapoptotic signaling and declined antiapoptotic defense [48] .

This review paper summarizes the recent signs of progress in the utilization of poloxamer-based materials for tissue engineering, drug/gene delivery, theranostic particles, hyperthermia, and 3D bioprinting. It could supply the biomaterialists and biologists with logical selection criteria for the materials to design and fabricate constructs with privileged properties.

2. Poloxamer chemistry and rheological properties

2.1. Chemistry

Poloxamer is an ABA tri-block copolymer consisting of a hydrophilic block PEO (A) and a hydrophobic block PPO (B), which is commercially available as Pluronic®. Nomenclature was introduced by BASF for Pluronic grades which are accessible in three types [liquid (L), paste (P),

and flake (F)] mentioning before the digits, for example, L61 and P181 denotes liquid and paste types, respectively (Figure 3). The first one or two digits multiplied by 300 describes the PO molecular weight approximately, and the last one explains the one-tenth of EO weight percentage in the copolymer [49]. The Poloxamer exhibit a decrement in the zeta potential with molecular weight increment from Pluronic F68 to F127. Moreover, the there is a common trend of a more reduction by concentration increment (particularly for F127). Decrement in zeta potential proves the creation of a sterically stabilizing adsorbed polymer layer. With reducing pH the polyelectrolyte concentration raises, causing to reduce zeta potential. [50]. Moreover, Table 1 describes the physiochemical properties of the various Pluronic.

Figure 3.

Based on segmental weight, poloxamer can be utilized in various applications from surfactants to drug carriers. PEO exhibits high solubility in water whereas PPO has low solubility in such media; hence, their block copolymer acts as an amphiphilic structure with surface-active properties. Sequential anionic ring opening polymerization of ethylene oxide and propylene oxide in the presence of potassium and sodium hydroxide (as an activator) has been utilized for the synthesis of poloxamer. PPO segments are firstly formed and subsequently, PEO is polymerized to the chain (Figure 4) [51]. Moreover, using diacrylate functions, the photo crosslinking Pluronic was synthesized by Choi et al. which showed a sudden volume transition over a temperature rang of 4-40 ^{o}C [52]. Kim et al. used photo-crosslinked chitosan-conjugated Pluronic F68 and F127 to target the tumor. Chitosan conjugation did not alter their dimensions

or temperature responsive feature of the nanoparticles, but considerably enhanced in-vitro cellular internalization [53].

Figure 4.

The amphiphilic structure of poloxamer has attracted significant attention for encapsulation and delivery purposes; hence, various molecules can be conjugated to the poloxamer. On the other hand, amphiphilic nature of the poloxamers can be combined with other intriguing properties of emerging biomaterials in order to make multifunctional materials with more versatile applications. For instance, mussel–inspired chemistry can endow the poloxamers with enhanced water solubility and wet adhesion. In this regard, 3, 4-dihydroxyphenyl-L-alanine (DOPA) which is a mussel-inspired moiety containing a catechol group, has been used for the modification of poloxamers. As shown in figure 5, the hydroxyl group of poloxamer was activated using *N, N*′-disuccinimidyl carbonate and then DOPA was grafted onto the poloxamer. Succinimidyl carbonate-activated poloxamer can dissolve in cold water and undergo micellization transition by temperature elevation [54].

Figure 5.

Figure 6 exhibits the conjugation of poloxamer to aptamer AS1411, Rhodamine B, and Cyclodextrin for targeted drug delivery [55]. The resulting multifunctional composite micelles show improved stability and enhanced loading capacity for doxorubicin anticancer drug.

Figure 6.

Table 1. Physico-chemical features and application of some popular Pluronic copolymers.

Name	Molar mass	Average no. of PO units	Average no. of EO units	HLB	CMC	Cloud point	Application	Ref.
L35	1,900	16.3	21.5	19	5.3	73	Surfactant, using for synthesizing copolymer	[56]
L43	1,850	22.3	12.6	12	2.2	42	Surfactant, drug encapsulation	[57]
L44	2,200	22.7	20	16	3.6	65	Surfactant, cosmetics and pharmaceuticals applications	[58]
L61	2,000	31	4.5	3	1.1	24	Inhibitory effect, assist drug delivery system	[59, 60]
L62	2,500	34.4	11.3	7	4	32	Nonionic surfactant, delivery system	[61]
L64	2,900	30	26.3	15	4.8	58	Surfactant	[62]
L81	2,750	42.6	6.2	2	2.3	20	Inhibition of multidrug resistance-associated protein	[63]
L92	3,650	50.3	16.5	6	8.8	26	Surfactant, additive, gene delivery	[64-66]
L101	3,800	58.9	8.6	1	2.1	15	Drug delivery	[67]
L121	4,400	68.2	10	1	1	14	Nanoparticle engineering (lymphotrophic particles), inhibition of multidrug resistance and adjuvant activities	[68, 69]
P84	4,200	43.4	38.1	14	7.1	74		
P85	4,600	39.6	52.2	16	6.5	85	inhibition of multidrug resistance	[70]
P103	4,950	59.7	33.75	9	6.1	86	Body and hand creams, lotions,	[71]
P104	5,900	61.03	53.6	13	3.4	81	Hair tonics, dressings, delivery system	[72, 73]
P105	6,500	56.03	73.8	15	6.2	91	Mouthwashes and breath fresheners, delivery system	[74, 75]
P123	5,750	69.4	39.2	8	4.4	90	inhibition of multidrug resistance, drug delivery	[76, 77]
F68	8,400	28.9	152.7	29	4.8	>100	Antithrombotic, hemorheological activities, cell membrane sealing, phagocyte activation (stimulations of phagocytosis and superoxide anion production), and neutrophil degranulation. improve expression of	[78, 79]

							osteogenic and chondrogenic genes	
F87	7,700	39.8	122.5	24	9.1	>100	Scaffold, delivery system	[80, 81]
F88	11,400	39.3	207.2	28	2.5	>100	Modulation of red blood cell aggregation	[82]
F98	13,000	44.8	236.3	28	7.7	>100	Modulation of red blood cell aggregation	[82]
F108	14,600	50.3	265.4	27	2.2	>100	Surfactant, coating	[83]
F127	12,600	65.1	200.4	22	2.8	>100	Long circulating particles, slow release gels, macrophage stimulation, stimulating EGFc production, tissue engineering	[84]

Polymers can be architected to achieve a unique structure such as brush-like polymers to be utilized in special applications like soft-robots. Conventional polymerization control is arduous and tailoring polymer structure is impossible. Atom transfer radical polymerization as a one of the living polymerization method using metal complex results in architected structure including polymers with controlled topology and dispersity [85]. Pluronic has been used in ARTP reaction as a macromonomer/macroinitiator which can endow thermosensitivity and micellar form to the architected polymer [86]. Dual thermosensitive polyrotaxane triblock copolymer was synthesized via ATRP of isopropyl acrylamide which it was initiated from 2-bromoisobutyryl end-capped Pluronic 17R4. It was proposed that such smart structure can be used as a DDS and biosensor [87, 88]. Different type of block copolymers can be synthesis using Pluronic as a macromonomer. For instance, Peleshanko et al. utilized Br-terminated Pluronic as macroinitiator to synthesis a pentablock terpolymer poly ((diethylaminoethyl methacrylate)-b-(ethylene oxide)-b-(propylene oxide)-b-(ethylene oxide)-b-(diethylaminoethyl methacrylate)) which was shown the reversible changes at the air-water interface. Wide ranges of morphology diversity were observed at different pH and temperature because of the blocks diversity. Hydrophobicity of the polymer can

be tuned by temperature and pH variation. Terminal blocks hydrophobicity was increased by temperature increment or unprotonated state at high pH value. Such behavior is so useful in interface tissue engineering [89]. Cationic polymers have been known as nonviral gene delivery system. Haung et al. synthesized a series of cationic polymers based on pluronic via ATRP as a gene delivery vector (pluronic F127-poly(dimethylaminoethyl methacrylate) (PF127-pDMAEMA), pluronic F127-poly (dimethylaminoethyl methacrylate-tert-butyl acrylate) (PF127-p(DMAEMA-tBA)), and pluronic F127-poly(dimethylaminoethyl methacrylate-acrylic acid) (PF127-p(DMAEMA-AA)). Block polymers formed nanoparticles with plasmid deoxyribonucleic acid with ranges from 80-180 nm and exhibited the positive zeta potential. PF127-p(DMAEMA-AA) showed the highest capacity for gene delivery which the DMAEMA segments as a cationic site considered plasmid DNA, pluronic segment resulted in self-assembly and decreasing cytotoxicity and acrylic acid groups coupled with fluorescent dye for nanoparticle tracing. Such polymer because of the intramolecular electrostatic interactions of amino and carboxyl groups enhanced the DNA dissociation speed from the endolysosomal compartment which declined the positive charge density causing to cell viability enhancement [90]. In another study, Huang et al. synthesized pentablock terpolymer based on various types of Plurinic (F127, P123 and L121) and poly(N,Ndimethylamino-2-ethyl methacrylate) which formed micelles and enabled to deliver the plasmid DNA and hydrophobic anticancer drug. Pluronic L121 exhibited the highest gene transfection because its highest hydrophobicity resulted in better cellular internalization [91]. Ulah et al. synthesized ATRP macroinitiator based on Pluronic L64 and synthesized pentablock polymer using methyl methacrylate. Critical aggregation concentration of block polymer was decreased with temperature increment which caused to dehydration of polymer blocks and

hydrophobicity was increased [92]. Perveen et al. synthesized the comb-like pentablock polymer based on Pluronic L64 and poly (ethylene glycol) methyl ether methacrylate (PEGMA) via ATRP reaction. Such polymer cannot aggregate because of the steric hindrance and leaded open-shell aggregation mechanism. LCST temperature of block polymer was higher than Pluronic and enhanced with increasing PEGMA concentration. The clouding point affected by inorganic additives like KBr and K_2SO_4 which ions of inorganic compounds affected the LCST based on their position in Hofmeister series [93].

2.2. Rheology

Poloxamer because of its thermosensitive feature have attracted significant attentions in various application. Injectable scaffold and bio-ink are promising and developing applications of the poloxamer. To design a proper platform for such applications the poloxamer behavior under the shear and temperature should be well understood. Hence, the rheological feature of the poloxamer is discussed.

Amphiphilic polymeric solutions such as poloxamers behave in a more complex way than conventional polymeric solutions because their hydrophilicity depends on the test conditions such as temperature and concentration [94]. Depending on the temperature and concentration, flow behavior of the aqueous solution of Pluronic may vary from Newtonian to viscoelastic to unstable rheological behaviors [95]. The aqueous solutions of Pluronic with the moderate concentrations (13- 19 wt%) behave as Newtonian fluids at low temperatures, while at higher temperatures –around gel temperature (T_g) and higher- they behave as thermoplastic gel showing a yield stress [95]. In fact, at low temperatures and moderate concentrations, separate

micelles are present in the solution; while at elevated temperatures, the solubility of PPO segments is decreased, and the micelles are formed at lower concentrations. An increase in the values of concentration or temperature increases the density of micelles such that they may overlap through PEO shells which form gel. At much higher temperatures, relative to T_g, PEO shells shrink due to dehydration resulting in the collapse of gel structure [95]. The gelling temperature can be detected while observing a sudden increase in the viscosity values, or while a yield stress point emerges [95].

For $T<T_g$ and relatively low concentrations, the shear stress versus shear rate at a constant temperature is approximately linear similar to Newtonian fluids. The corresponding viscosity values of the solution decrease with the temperature increment until reaching the T_g, where a significant increase in the viscosity values is observed [95]. As shown in Figure 7, the viscosity variation with temperature and concentration can be estimated using a master curve equivalent to the empirical equation. This relation denotes that the viscosity values at each temperature depend on the viscosity values at 0° C (η_0) and are a function of T/T_g ratio, where η_0 is linearly correlated to the concentration values.

$$\eta\left(\frac{T}{T_g}\right) = \eta_0(c) f\left(\frac{T}{T_g}\right)$$

Figure 7.

In sol state, viscous reaction is constantly higher than the elastic response (G" > G'). After the physical network formation, the structure exhibit Solid like behavior (G' > G"), and the G' and G" crossover is referred as a gelation time. Li et al. evaluated the rheological behavior of the

Pluronic and UV-cure Pluronic (Pluronic was crosslinked after micelle formation using UV-irradiation). Nevertheless, as the micellar transition UV-cured Pluronic displays frequency and temperature related manners, traditional rheological evaluations are not capable to determinate of loss/storage modulus crossover over a critical concentration. Owing to the micelles presence in UV-cured Pluronic, storage modulus is larger than loss modulus at all temperatures at the critical concentration. But the complex viscosity enhanced quickly with temperature increment. T_{gel} can be referred as a intersection of the two linear regression lines which is depicted in Figure 7d [96]. The Poloxamer behavior (Figure 7a) under shear can be described in 4 regions including I) (Linear regime): at low strain amplitudes, the cage shape remains untouched and the exhibited linear viscoelastic solid-like behavior. II) (prior to yield): The behavior is viscoelastic solid-like yet but tend to exhibit the non-linear behavior. G" raises indicating enhanced energy dissipation assigned to shear induced in-cage diffusion or rearrangements because of cage confinement. III) (just after yield): The behavior is viscoelastic liquid-like but is elastic modulated as the strain hardening intracycle nonlinearity sets in. This response is assigned to cage breaking and stress relaxation. IV) (post-yield): The behavior is viscoelastic liquid-like but is viscous modulated as the shear thinning intracycle nonlinearity prevails. This response is related to overall shear melting with continuous breaking and reformation of cages within each cycle [97].

Similar results were previously reported for the aqueous solutions of F127 with the concentrations of 15-30 wt% and in the temperature range of 15-35° C; it was reported that the viscosity is exponentially related to the temperature, where curve's slope is related to the concentration [98]. Poloxamer can be considered as a non-ionic surfactant which create micelles in water where PEO and PPO create shell and core, respectively. Increasing molecular weight of

PEO segments increase its hydrophilic nature and water absorption capability which may resemble that of PEG at limit; accordingly increasing $\frac{MW_{PEO}}{MW_{PPO}}$ results in a hydrogel with rheological properties similar to PEG itself which may show delayed sol-gel transition; i.e., increasing $\frac{MW_{PEO}}{MW_{PPO}}$ leads to improved water retention properties. On the other hand, increasing the molecular weight of PPO segments rapidly decrease it water absorption capability and temperature decrease its capability, as well. Furthermore, increasing the molecular weight of poloxamer can enhance the storage modulus and gel integrity at first, but at high molecular weight it may not dissolve in water. Narrow molecular weight distribution resulted in higher storage modulus and viscosity [99].

One of the promising usages of the rheology is adjusting the 3Dprinting condition to obtain the proper product. Gioffredi et al. used Pluronic F127 to print cellularized scaffolds. Pluronic F127 hydrogel (25%w/v) was chosen as bio-ink because of rapid gelation (5 min @ 37°C), appropriate viscoelastic feature for printing (G'= 16500 Pa at 37°C), pseudoplastic performance and rapidly viscosity recovery after shearing (about 5 s). acellularized and cellularized (with Balb/3T3 fibroblast cells) platform with a 0°/90° paradigm were printed by additive manufacturing method. Cells were well dispersed in scaffold filaments and cells preserved their viability during bioprinting [100].

It was proved that the purification/modification processes could change the rheological properties of Pluronic 407 which can adjust the rheological properties based on desired condition which can be adjusted for injectable scaffold and bioprinting. A purification procedure using different solvent such as ethanol eliminated low molecular weight polymers and impurities

from the poloxamer 407 causing to higher viscosity values with $T_{sol\text{-}gel}$ in a narrow temperature range. $T_{sol\text{-}gel}$ can be regulated by solvent, for instance, it was decreased by adding salt without any effect on maximum storage modulus and viscosity [99].

3. Various structures based on Poloxamer

3.1. Hydrogel

Hydrogels are 3D networks of hydrophilic polymers which can absorb a huge amount of water. They have been widely used in different fields such as industrial, agricultural, and biomedical applications. In biomedicine, hydrogels have attracted much interest for drug delivery, wound dressing, implantable devices, and biosensors. Many diverse natural and synthetic polymers have been utilized for manufacturing hydrogels. However, poloxamer has been of special interest due to its amphiphilic nature [101, 102]. The gelation mechanism of poloxamer is illustrated in Figure 8.

Figure 8.

The Pluronic hydrogel can be loaded by various biomolecules and drugs for tissue engineering applications [103, 104]. Pelegrino et al. synthesized Pluronic F-127 hydrogel containing nitric oxide (NO)-embedded chitosan nanoparticles for topical usages. NO was utilized in S-nitrosothiols (RSNOs) which were decomposed with an increase in temperature. In fact, NO acts as a signaling molecule at the skin wounds which controls blood flow and participates in the

orchestration of wound healing [105]. The utilization of this system prolonged the contact time of NO and the skin, leading to enhancement of the performance (Figure 9) [106].

Figure 9

Dopamine-modified Pluronic F68 exhibited high self-healing and extensibility features due to catechol-Fe^{3+} interaction. Moreover, it responded to the pH variation such that at lower values of pH, the hydrogel exhibited liquid-like behavior. Nevertheless, at higher pH values, it exhibited elastomeric behavior [107]. Self-healing thermosensitive hydrogel based on alginate-graft-β-cyclodextrin (βCD) and Pluronic F108 was synthesized based on host-guest inclusion interaction which acted like pseudoplastic materials. β- βCD is composed of an inner hydrophobic cavity and an outer hydrophilic surface which can interact with non-polar guest molecules. Moreover, it showed appropriate biocompatibility and enough strength in the body temperature; hence, it can be used in biomedical applications [108-110]. Hydrogels are widely used as the supportive platform to hinder the intrauterine adhesion after endometrial injury; so, controlled drug release can ameliorate the healing process [111-114]. Xu et al. synthesized a mucoadhesive hydrogel based on heparin-poloxamer (HP) with ε-polylysine (EPL) as the functional excipient (Figure 10). The EPL content affected the rheological behavior and mucoadhesion of the hydrogel. The hydrogel storage modulus was around 2E+05 Pa with 3.18 N adhesion force. Such a hydrogel resulted in endometrial cell and glands regeneration along with the increment of angiogenesis [115]. Poloxamer also can be utilized as a stimuli-sensitive platform which can be used in various applications like DDSs [116]. Yu et al. synthesized pH and

thermoresponsive hydrogels based on chitosan and Pluronic to be used as the ophthalmic drug carriers. Glutaraldehyde was used as a crosslinking agent. It was found that the hydrogel underwent the sol-gel transition at 32° C and the maximum drug release was at 35° C and pH of 7.4 due to the large porosity of the system [117].

Figure 10.

3.2. Micelle

Amphiphilic poloxamers tend to self-assemble in an aqueous solution to form micelles with various sizes from micro to nano scales [118, 119]. The core of micelle is composed of PPO while the surrounding shell is the hydrophilic PEO. Hydrophobic drugs can be embedded in the hydrophobic part of poloxamer. The molecular weight of the segments determines the micelle properties such as CMC, critical micelle temperature (CMT), shape, and aggregation. Increasing the PPO content decreased the CMC value due to an increase in the hydrophobicity of the system. In addition, PEO content exhibited a direct relation with the CMC values. Higher PEO contents further destabilized the micelle [120, 121].

Poloxamer has a very low CMC and can be hardly considered as a stimuli-responsive biomaterial. Liu et al. synthesized the redox-responsive micelles based on Pluronic F127/tocopherol (TOC). TOC was coupled to Pluronic by disulfide bonds which were sensitive to the redox environment with stable micelles at low CMCs (Figure 11). Micelles were homogeneous with a smooth spherical shape with particle sizes of around 50 nm. Such micelles could maintain the colloidal stability due to negative zeta potential (around -8.5 mV) [117].

Nahain et al. synthesized the crosslinked Pluronic micelles with covalent benzoic-imine and disulfide bonds endowing pH and redox-responsive properties, respectively, for controlled release of Taxol which is a cancer chemotherapy drug [122].

Figure 11.

Various routes were suggested for the synthesis of self-healing hydrogels. One of the striking usages of Pluronic which has attracted significant attention is the crosslinking micelles. A hydrogel based on N-acryloyl-6-aminocaproic acid (AACA) was synthesized in which Pluronic micelles were used as cross-linkers. Poly AACA (PAACA) with self-healing properties revealed highly stretchable and puncture resistance features. Pluronic macro-crosslinker had a high elongation ratio, tensile strength, and toughness due to the presence of micelles (Figure 12) [123]. Bioreducible crosslinked Pluronic micelles (with the size of around 150 nm) were used as the pH-triggered drug release platforms for cancer therapy. To this aim, acrylic acid (AA) was grafted to the aminated Pluronic F127 (AA-Pluronic-NH_2), and then folic acid, hydrazine, and cystamine were conjugated. An accelerated release was observed in the reduced pH (5.2). Moreover, a redox-responsive substrate was obtained due to the presence of disulfide bonds in the core of micelles [124].

Figure 12.

4. Poloxamer Applications

4.1. Poloxamer in Tissue Engineering

Reconstruction of damaged and degenerated tissues requires new feasible strategies. Tissue engineering strategy is a potential alternative and complementary solution for the cases where traditional therapies are not sufficient [125, 126]. Tissue engineering assembles functional constructs through a combination of cells, biomaterials, and biochemical factors in order to provide an artificial extracellular matrix for cells to regenerate the damaged tissues [127].

The scaffolds utilized in tissue engineering must be biocompatible with negligible immune reactions and inflammatory responses [128, 129]. They also should exhibit controllable biodegradability and proper mechanical and architectural characteristics which provide an appropriate microenvironment with interconnected pores for growth, proliferation, and differentiation of the cells [130-132]. Furthermore, in order to better supply the requisites of the tissue regeneration process, tissue engineering provides guaranteed methods for controlled delivery of regenerative factors and drugs [133, 134]. Moreover, non-invasive methods have been attracted significant attentions and the risk of the surgical process is eliminated. In this context, poloxamers as a non-toxic class of polymers with high water solubility and thermosensitivity properties have attracted increasing attention which can be used as an injectable scaffold and non-invasive method [135]. Based on the application, befitting modifications are exerted on poloxamers to endow essential prerequisites. These modifications include attaching oligopeptides to a Pluronic structure, blending or coupling with various natural or synthetic polymers, and incorporation of various minerals and active agents in order to modulate their robustness, durability in the body, critical gelation temperature/concentration,

and biocompatibility [136, 137]. Moreover, their amphiphilic nature and the ability to self-assemble into micelles make them suitable materials for the delivery of hydrophobic drugs as well as hydrophilic ones [21]. They are extensively utilized for delivery of cells [138], proteins [139], growth factors [140], genes [141], and drugs [142, 143].

Table 2 overviews the biomaterials commonly used in tissue engineering and Table 3 overviews the latest applications of poloxamers in tissue engineering.

Table 2. biomaterials commonly used in tissue engineering

Polymers	Advantage	Disadvantage	Ref.
Chitosan	Biocompatible, antibacterial	Need toxic cross-linking agent, non-injectable, need surgery to apply in injured tissue	[4]
Agarose	Biocompatible, non-immunogenic, self-gelling	Poor cell adhesion	[144]
Gelatin	Biocompatible, ECM-like properties	Low mechanical properties, non-injectable	[145]
Poly lactic acid	Biodegradable, biocompatible, low-inflammatory response	low biocompatibility compared to natural polymers (need surface modification), non-injectable	[146]
Poly caprolactone	Biodegradable,	Hydrophobic, non-injectable	[147]
Polyvinyl alcohol	Biocompatible	Need toxic cross-linking agent, non-injectable, need surgery to apply in injured tissue	[148]
Poloxamer	Biocompatible, injectable, amphiphilic feature,	-	[1]

Table 3. Poloxamers' applications in tissue engineering

Scaffold material	Scaffold type	Fabrication method	application	Properties	Findings	Advantages	Ref.
Poloxamer/ oligopeptide	Injectable hydrogel	Gelation	Soft tissue engineering	Elastic/viscous modulus	In vivo differentiation of hASCs, immunohistochemistry analysis	Proper mechanical and biological properties,induced adipose-like tissue regeneration,migration of hASCs into the skin and differentiation to epithelial cell	[33]
RGD-chitosan/ poloxamer	Injectable hydrogel	Gelation	Cell carrier for cartilage tissue engineering	Elastic/viscous modulus, pore size	In vitro cell culture, GAG content evaluation	Higher GAG content and chondrocyte proliferation in comparison to alginate scaffold	[21]
Chitosan/poloxamer/keratin/laponite	Injectable hydrogel	Gelation	Cartilage tissue engineering	Rheological properties, microstructure of the hydrogel, thermosensitive behavior of the gel, swelling and degradation	In vitro cytotoxicity and cell attachment	Superior physico-mechanical properties, cytocompatibility	[68]
Alginate/laponite/poloxamer	Hydrogel	Gelation	Tissue engineering	Rheological properties	-	Enhanced mechanical properties	[69]
Hyaluronic Acid/Pluronic F127	Hydrogel	Photo-crosslinking	Hard tissue engineering	Rheological properties, microstructure of the hydrogel, swelling properties,	In vitro cell viability	High elasticity and mechanical properties	[70]

				degradation			
PCL/poloxamer	NGS	Immersion precipitation	Neural tissue engineering	-	In vitro histological evaluations, Investigating the effect of US and NGFS on nerve regeneration	Sustained release of NGFs	[76]
PLGA/poloxamer	NGS	Immersion precipitation	Neural tissue engineering	Morphology assessment	In vivo immunohistochemical and histological evaluations, investigating the effect of US on nerve regeneration	Selective permeability, hydrophilicity, structural stability	[77]
Heparin/poloxamer	Injectable hydrogel	Gelation	Neural tissue engineering (spinal cord injuries)	Rheological properties, microstructure of the hydrogel, thermosensitive behavior of the gel	In vitro and in vivo histological studies	Sustained release of aFGF, increased neuron and axonal rehabilitation	[46]
Pluronic F127	Injectable hydrogel	Gelation	Neural tissue engineering (spinal cord injuries)	-	In vitro and in vivo evaluation of the effect of Lingo-1 shRNA delivery on nerve regeneration	Potential gene carrier, promoting axonal regeneration	[79]
Tricalcium phosphate/poloxamer	Injectable paste		Bone tissue engineering	Mechanical properties, setting time	-	Tunable rheological properties, increased washout resistance	[99]
n-HA/PCL–Pluronic–PCL	Scaffold	-	Bone tissue engineering	Water absorption, degradation, water contact angle, thermal properties,	In vivo degradation and surface morphology	Tunable degradability, osteoinductive	[101]

				surface morphology			
PCL/Pluronic F127	Membrane	Immersion precipitation	Bone tissue engineering	Surface morphology, mechanical properties, hydrophilicity	In vivo investigation of the US effect on bone regeneration	Asymmetrically porous structure, selective permeability, osteoconductive and osteoinductive	[102]
PDO/Pluronic F128	Scaffold	Melt-molding particulate-leaching	Scaffold and cell carrier for bone tissue engineering	Porosity	In vitro osteogenic phenotypes of periosteal-derived cells, in vivo osteogenic activity of periosteal-derived cells.	Osteoinductive and osteogenic properties	[105]
Pluronic/bioactive glass	Scaffold	3D printing	Bone tissue engineering	Microstructure	In vitro blood vessel formation and histomorphometric analyses	Proper biological properties for bone regeneration	[94]
PVA/Pluronic/PEI/TiO_2	Nanofiber	Electrospinning	Wound dressing	Morphology, mechanical properties, thermal properties	Cytotoxicity, antibacterial activity	Infection treatment	[26]
Chitosan/poloxamer	Injectable hydrogel	Gamma irradiation	Wound dressing	Morphology, thermal properties, water uptake	Antibacterial activity, in vivo histological and immunofluorescence analyses, wound closure properties	Control of exudates, antimicrobial/antifungal properties, hgh wound closure rate	[139]
Heparin-poloxamer	Injectable hydrogel	Gelation	Wound dressing	Rheological properties, morphology	In vivo characterization of wound closure rate, granulation formation, re-epithelization, cell proliferation, collagen and angiogenesis expressions	Controlled delivery of aFGF and bFGF, rapid wound healing	[126]

PLCL/Poloxamer	Nanofiber membrane	Electrospinning	Skin tissue engineering	Morphology, mechanical properties, water contact angle, degradation	Cell viability and cytotoxicity assay	Best imitation of the natural characteristics of the skin	[138]

4.1.1. Poloxamer in Cartilage Regeneration

Cartilage, meniscus, tendon, and ligament defects are among the most challenging and painful morbidities restricting the body mobility, for which tissue engineers are looking for innovative solutions to regenerate the damaged tissue [149, 150]. As the most challenging part, articular cartilage is predominantly comprised of hyaline cartilage which is a weight-bearing and low-friction tissue lying on the articulating surfaces of bones and diarthrodial joints. Cartilage is composed of chondrocytes and extracellular matrix (ECM) containing collagen and elastin fibers, glycosaminoglycans (GAGs), proteoglycans, hyaluronan, aggrecan, and non-collagenous proteins [151, 152]. The mechanical and load bearing properties of cartilage is proportional to ECM properties while chondrocytes are considered as the most significant component of cartilage regarding their responsibility for production and maintenance of ECM components such as collagen and proteoglycans [153, 154]. Cartilage defects may happen through disease, trauma, tumor, joint instability, and perennial mechanical loading. Moreover, the density of chondrocytes and their capacity to produce collagens and proteoglycans diminish with aging, leading to a decline in mechanical properties of the cartilage [155]. On the other hand, due to the limited number of chondrocytes existing in the ECM, their low proliferation potential, and the avascular nature of articular cartilage, natural capacity of articular cartilage for regeneration upon injuries is confined [156, 157].

Current clinical approaches for cartilage treatment such as autologous and allogeneic tissue grafts have some deficiencies which delimit their utilization for cartilage therapy. In this regard, tissue engineering provides biocompatible scaffolds as an alternative approach for cartilage regeneration [149, 158, 159]. Poloxamer-based biomaterials are interesting since they

can be utilized as injectable hydrogels with a minimally invasive procedure [160]. Poloxamers can encapsulate cells and improve cell permanence in the cartilage [161, 162]. They also have the potential to harness the inflammatory responses which makes them proper therapeutic materials for post-traumatic osteoarthritis [163]. An impediment restricting the usage of poloxamers is their low bioactivity; thus, they are usually blended with biocompatible polymers like gelatin [164] or oligopeptides leading to the increase of cell attachment and proliferation in the hydrogel systems [24]. In this context, a hybrid hydrogel comprised of a self-assembling oligopeptide with the amino acid sequences and poloxamer 407 encapsulating human adipose-derived mesenchymal stem cells (hASCs) was synthesized, and the mechanical properties as well as in vivo differentiation of hASCs were investigated [38]. The hASCs formed an adipose-like tissue at the injected area which authenticates the potential of this hydrogel for soft tissue regeneration [38].

In a comparative study, four scaffolds of hyaluronic acid, alginate/Pluronic, hyaluronic acid/alginate/Pluronic, and hyaluronic acid/alginate/Pluronic/chitosan containing human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) were prepared and transplanted into a full-thickness articular cartilage defect imposed into the rat knees [16]. The hyaluronic acid hydrogel represented the first potential in cartilage repair as it showed the most copious amounts of type II collagen staining in immunostaining and safranin-O staining analyses (Figure 13) [16].

Figure 13.

Native articular cartilages have the compressive modulus of 0.08 to 2.1 MPa and the tensile modulus of 4.8-28 MPa according to their locality in the body [165]. Hence, hydrogels utilized for cartilage regeneration must have the capability to bear imposed stresses [166]. However, poloxamer hydrogels usually do not have sufficient mechanical properties. In this regard, poloxamer hydrogels are used in the form of blends or copolymers with other polymers or composites containing mineral nanoparticles [167, 168]. Pluronic F127 was grafted into the chitosan chains, and the obtained thermosensitive hydrogel was crosslinked with keratin using genipin and was reinforced by mineral nanoclay (LAPONITE®) [169]. The physicochemical properties of the nanocomposite, such as swelling ratio, pore size, biodegradation, and viscoelastic modulus were tailorable by manipulating the chemical crosslinking density as well as the nanoparticle content. Furthermore, incorporation of the mineral nanoparticles did not change the bioactivity of the scaffolds and enhanced the cell proliferation [169]. Addition of Pluronic F127 to alginate/LAPONITE® nanocomposites also boosted the elastic modulus about two orders of magnitude [170]. Sohn *et al.* synthesized photo-crosslinked hyaluronic acid/Pluronic F127 hydrogels with enhanced toughness and mechanical properties by acrylation of hydroxyapatite and Pluronic. Hydrogels with 8 w/v% Pluronic represented the highest load-bearing and twisting properties. Moreover, the blade was unable to cut off the hydrogels. These properties were attributed to the reversible folding and unfolding of PPO blocks of Pluronic in the hydrogel matrix which leads to the energy dissipation of mechanical forces and aids the hydrogel to resist mechanical stresses and torsions [171].

Cao et al. performed a comparative study using poly(glycolic acid) (PAG), calcium alginate and poloxamer to study the cartilage regeneration. The regenerated cartilage using PAG and

calcium alginate exhibited presence of the regenerated tissue which the fibrocartilage formed with dense collagen bundles and dispersed within the tissue. While, utilizing poloxamer as a scaffold caused to form a tissue similar to native elastic cartilage with high cell arrangement attributing to functional feature as elastin existence in the engineered cartilage and it was observed no pathologic sign such a inflammation nor foreign body giant cell reaction [172].

Bajaj et al. confirmed that the poloxamer exhibit the promising effect on cell survival in the model of acute trauma to human ankle cartilage. Poloxamer hindered Stat1 and Stat3 phosphorylation indicating a role of IL-6/Stat signaling in an instant cellular reaction stimulated by damage. Besides being one of the key transducers of IL-6 signaling, Stat3 was also connected to p38 route, which regulates cellular activities after mechanical tension and damage. Poloxamer treatment hampered activation of p38 and Stat3, accompanied by ATF-2, a downstream target for p38 activity. A crucial function of p38 kinase has a key role in the post-traumatic responses was confirmed with its inhibitor. Moreover, impact on p38 it also hindered Stat3 and GSK3 phosphorylation indicating that p38 plays upstream of these mediators and regulates inflammatory and apoptotic activities to acute injury. It was confirmed that treatment of cartilage explants with p38i boosted cell survival and decreased apoptosis. Inhibition of p38 by poloxamer was more obvious than other pathways contribute to activation of p38 kinase and that poloxamer sets multiple pathways, for example, ERK and JNK as was confirmed by combined treatments of poloxamer and p38i (Figure 13 D) [163].

4.1.2. Poloxamer in Neuro-regeneration

The nervous system is composed of two major components known as the central nervous system (CNS) and the peripheral nervous system (PNS). CNS which is the control center of the body contains the brain and the spinal cord, while PNS contains nerves and sense organs [173-175]. Neurological dysfunctions may happen through physical injuries or neurodegenerative diseases. CNS has shown limited potential to regenerate itself after injuries due to its low capacity to substitute lost neurons and high inflammatory responses engendered in the damaged site [175, 176]. PNS displays superior capacity to regenerate axons upon injury. However, in case of chronic trauma, a conduit is always required to fill the gap and provide an appropriate microenvironment for axonal regeneration.

While the autograft method is natural method, there is some risk affected its efficiency. Extra surgical time is necessary to achieve the autograft sample from another site in the body which means elongated time elapses with anesthesia and increase risks. Several incision sites are required to achieve an autograft, which enhance the risk of nerve damage. Donor tissues are not always available, and the expense is considerably higher than autograft. Allograft increase the risk of immune response complexity including rejection, or failure to integrate appropriately into the function of the host body. Due to drawbacks associated with allograft and autograft, polymeric conduits have attracted much attention [177-180]. In this regard, poloxamer-based hydrogels with high capacity for loading of growth factors and cells are proper candidates. Furthermore, biological cues (e.g., growth factors and Schwann cells) and/or physical stimuli (e.g., electric pulse, laser illumination, electromagnetic fields, and ultrasound) can be utilized in order to maximize the potential of these conduits for recovery and regeneration of PNS [181-

183]. In a study, poly(lactic-co-glycolic acid) (PLGA)/Pluronic F127 nerve guide conduits with asymmetric porous structure were fabricated in which the inner surface was composed of 50 nm pores. This semipermeable nano-sized porous structure inhibits the fibrous tissue infiltration while allowing the nutrients and wastes to exchange. On the other hand, the outer surface is covered by micro-size pores (approximately 50 µm in diameter) which allows the blood vessels to grow inside and supply nutrient to the growing axons inside the conduit (Figure 14) [184]. Moreover, such scaffold was used with low-intensity pulsed ultrasound. It was reported that asymmetrically porous structures with selective permeability, hydrophilicity, and structural stability of a conduit together with physical stimulation engendered a proper microenvironment for nerve restoration [185]. Kim *et al.* have recently prepared nerve guide conduits from polycaprolactone/Pluronic F127 membranes with selective permeability, and then investigated the effect of nerve growth factor (NGF) and low-intensity pulsed ultrasound as the biological and physical stimuli in a rat model. A positive synergic effect on nerve regeneration was observed in the case of dual stimulation. However, the single stimulation by pulsed ultrasound represented superior nerve regeneration [181, 186]. Furthermore, the delivery of growth factors and micro ribonucleic acids (RNAs) by poloxamers can accelerate nerve regeneration [187, 188]. Some modifications may be applied to the structure of poloxamers in order to improve the loading capacity [25]. In this regard, heparin was grafted into a poloxamer polymer to accelerate the axonal regeneration [189]. In order to use electrical stimulation, an electrically conductive hydrogel was required. Thus, the poloxamer-based nanocomposites containing carbon nanobrushes were fabricated with adjusted conductivity [190-193]. The microstructure and morphology of nerve guide conduits play a prominent role in nerve regeneration [194]. Recently,

PCL/Pluronic F127 nerve guide conduits were prepared that had similar chemical and physical characteristics and various surface pore sizes. It was reported that nerve guide conduits with nano-sized pores at the surface can induce nerve regeneration along with the longitudinal direction. On the other hand, in nerve guide conduits with micro-sized pores, new tissue was grown toward the pores in the direction of cross-section of the conduits [195]. Moreover, in traumatic brain injury (TBI), injection of poloxamer 188 alleviated the brain edema and suppressed the neural cell death imposed by the injury [196, 197].

Figure 14.

Follis et al. used poloxamer 188 for ischemic spinal cord injury. The mechanism of action is associated to the hydrophobicity, adhesion, and friction. At normal conditions, the capillary diameter is the same with erythrocytes, but after ischemic damage, with swelling and injured endothelial cells, it is get considerably narrowed. Moreover, injured cells and biological molecules like fibrin possess hydrophobic segments on their surface that come into contact, generating adhesion and friction. It has been proposed that Poloxamer 188 act by attaching to such segments. Hence, poloxamer stabilizes injured membranes and preserve cellular integrity which is known as cytoprotective effect and hampers adhesion and friction among blood cells and vessel wall based on antithrombotic and rheologic features [198].

Curry et al. used poloxamer to reduce the neuronal loss in rat model. In the rat striatum, poloxamer is shielded versus excitotoxicity. Poloxamer exhibited neuroprotective effects as a result of the surfactant intercalation into the neuronal membrane and poloxamers reduces

excitotoxic cell death using interfering with the membrane rupture of necrosis and by reducing cell death in apoptosis to a lesser amount [199]. Poloxamer enhances cerebral blood flow through improved rheology and the anti-inflammatory effect of poloxamer decrease the lesion size [200]. Poloxamer can save cells from necrosis by intercalating to the cell membrane, sealing the membrane rupture, and reducing the depolarizing, nonchannel-mediated ion flux. This blockade of continual depolarization can save vital ATP in a compromised neuron, possibly saving it from necrosis or even apoptosis [201].

4.1.3. Poloxamer in Bone Regeneration

Bone as a highly vascularized tissue with an organic-inorganic architecture is mainly composed of collagen, carbonated apatite, non-collagenous proteins, and bone cells [202-204]. In large bone defects, scaffolds with osteoconductive, osteoinductive, and osteogenic properties are ideal replacements for allogeneic and autologous bone grafts [205-207]. The scaffolds for bone regeneration should support bone growth on the surface or inside the pores (osteoconduction); hence, they should have interconnected porous structures with micro and macro pores supporting cellular development, vascularization, and bone ingrowth [208]. There is a range of strategies to prepare bioceramic powders as scaffolds with aforethought pores and multi-oriented hollow channels promoting bone formation even in the center of the scaffolds [209-211]. The osteoinductive properties of scaffolds can be improved by utilizing poloxamer-based biomaterials with osteoinductive materials such as ceramics, bioactive glass [212, 213], growth factors [214], and mechanical stimulus [215]. Calcium phosphate ceramics like hydroxyapatite (HAp) and biphasic calcium phosphates are proved to have osteoinductive

properties [216, 217]. However, their low washout resistant and lack of processability impede their usage in some situations. In a recent study, it was demonstrated that incorporation of poloxamer 407 in calcium phosphate ceramics could improve the handling and processing without deteriorating their osteoconductive potential *in vivo* [218]. Maazouz *et al.* fabricated thermoresponsive alpha-tricalcium phosphate/Pluronic cements which showed promising potential for minimally-invasive surgeries for bone regeneration [219]. It has also been shown that injectable crosslinked networks of poloxamers with hyaluronic acid mineralized with HAp could enhance the interaction of hydrogels with osteoblasts [220]. In a comparative study, two injectable/moldable calcium phosphate bioceramics, first one made up of micro-porous biphasic calcium phosphate granules with a polysaccharide-based hydrogel, and the second one made up of pure hydroxyapatite granules containing silicate with a poloxamer-based hydrogel were fabricated and tested in rabbit bone defects. It was observed that the first class of scaffolds could lead to a higher cell colonization and bone tissue ingrowth [221]. Architected polyurethane based on PCL/Pluronic was synthesized with tunable degradation behavior. Addition of HAp enhanced the water contact angle, indicating that the surface became more hydrophobic. An increment in HAp content resulted in a lower contact angle attributed to the aggregation of HAp and the reduction of hydrophobicity. It is noteworthy that increasing the HAp content will accelerate the degradation rate. *In vivo* degradation was faster than *in vitro* degradation due to the enzymatic degradation, cell-mediated degradation, and phagocytosis [222]. It has been recently shown that utilizing ultrasound as physical stimulation can induce bone regeneration in Pluronic-based scaffolds. Asymmetrically porous polycaprolactone (PCL)/Pluronic F127 membranes containing bone morphogenetic protein (BMP-2) as biological cues and ultrasound

as physical stimulation were fabricated and tested in a rat model. The results authenticated the inductive effect of ultrasound and BMP-2 in bone regeneration. Based on the obtained results, the ultrasound could be used as a stimulant for Pluronic scaffold in clinical applications [215, 223]. Adjuvant complementary materials have also been used in Pluronic-based scaffolds to supply scaffold with special properties crucial for an appropriate regeneration. It was reported that polydioxanone (PDO)/Pluronic F127 porous particles were synthesized and BMPs were immobilized onto the surface of the particles using heparin. BMPs accelerated the formation of the new bone tissue. BMP-2 showed greater potential to improve the osteogenesis of bone marrow stem cells (BMSCs) in comparison to BMP-7. PDO/Pluronic F127 scaffolds containing periosteal-derived cells and adipose tissue-derived CD146 positive endothelial-like cells as osteogenic factors were prepared and tested in a miniature pig model. The scaffold provided an appropriate condition for osteogenic differentiation of periosteal-derived cells and restoration of bone defects [224, 225]. *In vivo* studies pave the way for Pluronic-based scaffolds to be used in clinical applications. Toward this aim, thermo-responsive osteogenic composites containing demineralized bone matrix and bone marrow cells were implanted into large defects on the parietal bone of the skull of rats. After thirty days of implantation, a new bone tissue was formed which was well integrated with the native bone tissue. Moreover, the newly formed tissue exhibited a rather analogous shape and properties without any inflammatory responses [226]. In this context, in a clinical study on fourteen patients, the efficacy of osteogenic composites containing demineralized bone matrix and non-demineralized cancellous bone embedded in a poloxamer carrier was investigated. Proper bone formation and enhanced bone remodeling and maturity during 6 months of implantation confirmed the potential of these constructs for bone

regeneration [227]. Kayal et al. used gamma irradiated demineralized bone matrix (DBM)-Pluronic F127 composite for bone regeneration in the femur of Wistar rat. It was observed that gamma irradiation results in a decrease in BMP level sterilized DBM while preserving bone regeneration capability [228] (Figure 15). Pluronic is also used as a surfactant during the fabrication of nanofibers [214] or as a binder solution to form a proper bioink for preparation of bioactive glass scaffolds by a robocasting machine [229, 230] for bone tissue engineering.

Figure 15.

Kim et al. used poloxamer to repair cuff in rat model. It was demonstrated that the poloxamer enhanced the healing compared to collagen. Stiffness of repaired tissue using poloxamer was higher than collagen-repaired one. Poloxamer promote the early stage healing and maintain the initial biomechanical feature of repaired cuff [231]. Among other poloxamers, Pluronic F68 enhanced the multi-potency of stem cells, and effectively differentiated them into osteogenic, chondrogenic, and adipogenic tissue [232]. Moreover F68 inhibits cellular aggregation and preserve cells against mechanical tension by binding to the cellular membrane surface [233]. In comparison with F68, It should be mentioned that Pluronic P85 hinder different transporters like breast cancer-resistant protein, MDR2, and P-glycoprotein, thus increasing the cellular accumulation of drugs that are generally prevented from cells by these transporters [234]. Pluronic F127, simply form micelles and use as an effective transporter for several hydrophobic drugs. F127 interacts with cell surfaces and can be utilized as a scaffold in tissue engineering applications [235]. F68 and F127 drastically improved alkaline phosphatase

intensities through the osteogenic differentiation. F68 exhibited more calcium deposition as a characteristic of osteogenic transformation compared to F127. F68 elevated cellular attachment to the cell-culture dish by associating lipid bi-layers that induces cell growth in vitro. Moreover, F68 increased the unsaturated fatty acid amounts of cell membranes which F68 can integrate to membranes and alter their structural and functional features by changing the lipid composition [236]. An improved unsaturated proportion can enhance membrane fluidity and elevate cellular differentiation [237].

4.1.4. Poloxamer in Wound Healing

Skin is the exterior covering of the body which conserves the body against the outer environment and microorganisms [238, 239]. Skin is composed of three layers including epidermis, dermis, and hypodermis [240, 241]. Skin defects may occur due to traumatic damages to the skin such as injury, surgery, and burn or due to metabolic disorders created by diseases like diabetes, vascular insufficiency, and obesity [242, 243]. Development of appropriate wound dressings facilitates the healing process. An ideal wound dressing should be non-allergenic and non-adherent in order to prevent the dressing from sticking to the wound. However, they must be able to absorb exudates and maintain the humidity of the wound at the right level [244]. Moreover, antibacterial and antimicrobial features, as well as sufficient gaseous permeation, should be incorporated into the dressings [245, 246].

Poloxamers have been demonstrated to encompass the healing characteristics [247, 248]. Their mild inflammatory nature along with the ability to stimulate the expression of VEGF and TGF-β and VEGF could enhance the wound healing process. Pluronic enhanced the

expression of the TGF-β and the enhanced the tissue granulation along with fibroblast proliferation [249]. In order to endow the dressings with antibacterial properties, various antimicrobial drugs such as chloramphenicol [250], chlorhexidine hexametaphosphate [251], melatonin [252], and peptides 57 (AP-57) [253] have been utilized in poloxamer hydrogels. Boron-containing poloxamer-based hydrogels can be applied to the diabetic [254], burn [255], and cutaneous [256] wounds which not only results in a faster wound closure and increases the vital growth factors as well as gene expression levels of dermal cells, but also leads to significant antimicrobial features against bacteria and fungi. It is expected that incorporation of exogenous cells [257], growth factors [258], and active agents [259] into wound dressings may accelerate the wound healing and regeneration process. Embedded adipose-derived stem cells (ADSCs) within a Pluronic F127 hydrogel applied to the chronic diabetic wounds leads to the enhancement of angiogenesis and cell proliferation at wound site [260]. Recent reports have indicated that injection of poloxamer-based gel containing human stromal vascular fraction (SVF) cells into the wound site accelerated the wound closure via increasing the re-epithelialization [261]. Furthermore, thermosensitive heparin-poloxamer hydrogel containing acidic and basic fibroblast growth factors (aFGF and bFGF) revealed improved granulation formation, re-epithelization, and angiogenesis [262]. In fact, inserting growth factors in the heparin modified polymeric hydrogels improve the healing process where heparin binding domains bind to growth factors efficiently. However, different growth factors (e.g., aFGF and bFGF), because of different isoelectric points (IP) and surface charges, attach to heparin binding domains differently such that the release behavior and healing are not the same. It was observed that aFGF (IP=6.5 in saline) is more effective in healing process compared to bFGF (IP=9.6). High-density lipoproteins

(HDL) [263], substance P (SP) [264], and nitric oxide [265] are active agents which exhibit therapeutic effects for healing chronic wounds and may be embedded into the poloxamer hydrogels in order to design more effective wound care products. Poloxamers have also been used for the synthesis of solid lipid nanoparticles (SLNs) loaded with astragaloside IV which stimulated the wound healing and diminished the scar formation [266]. The sustained release of astragaloside IV from SLNs can effectively increase the migration and proliferation of keratinocytes while improving drug uptake for fibroblast cells.

Different sorts of tissue engineering scaffolds with non-woven nanofibrous structures have been fabricated by electrospinning method [267, 268]. These scaffolds displayed proper morphological characteristics resembling natural ECM in the skin tissue which provided an appropriate microenvironment for the seeded cells to proliferate and to produce ECM [269]. Poloxamers can be combined with hydrophobic polymers in order to boost hydrophilicity of the surface and simplify cell adhesion and diffusion to the scaffold. For instance, poloxamers have been used with poly(hydroxybutyrate) [270], poly(L-lactide-co-ε-caprolactone) [271], and silk fibrous [272] scaffolds in order to enhance the surface hydrophilicity. A bilayer scaffold containing poly(ε-caprolactone-co-lactide)/Poloxamer (PLCL/Poloxamer) nanofiber membrane in the outer layer and dextran/gelatin hydrogel in the inner layer was fabricated to mimic the architectural and morphological features of the native skin. The outer layer acted as the mechanical support for the inner layer. The scaffold also showed a high swelling ratio and provided appropriate space for cellular proliferation [273]. Electrospun nanofibers of polyvinyl alcohol/poloxamer/polyethyleneimine containing TiO_2 nanoparticles provided a moisture-controlled microenvironment with antimicrobial properties for wound repair [28]. The initial

concentration of poloxamer affects the diameter and surface morphology of the obtained nanofibers.

Combining thermosensitive behavior of poloxamer with antimicrobial features of chitosan can improve the wound healing process. Chitosan-poloxamer hydrogel obtained by gamma irradiation exhibited low gelation temperature, high exudate absorption, and fast wound closure [274]. Gamma irradiated chitosan enables cross-linking with poloxamer 407 and affect the behavior of chitosan-poloxamer mixtures. The hydrogel increases the level of macrophages, α-SMA, and collagen deposition when applied to wounds.

The emergence of bacterial biofilm in most of the chronic wounds is an obstacle against wound healing since they can endure many antibiotic and antimicrobial treatments. Physical removal of biofilms is not sufficient since it just removes the superficial layer and the bacteria in the deeper layers continue their activity. In a study on an *ex vivo* porcine skin explant model, it was demonstrated that using non-ionic poloxamer surfactant gels, could improve the biofilm removal and increase the sensitivity of biofilm to antimicrobial treatments in comparison to traditional methods of wiping with moistened gauze only [275]. A combination of DispersinB® as an anti-biofilm enzyme and an antimicrobial peptide in Pluronic F-127 wound gel provides synergistic efficacy against wound infections for the gel [276]. DispersinB® enhances the antimicrobial activity of the peptide while Pluronic provides sustained antibacterial activity over time. In an investigation, a series of mussel-inspired thermosensitive polymer based on peptide-Pluronic was synthesized for versatile surgical adhesive and hemostasis. This triblock copolymer exhibited appropriate biocompatibility, thermosensitivity, antibleeding, and adhesion properties (Figure 16) [277]. In vitro studies on porcine skin and porcine bone revealed good wet adhesive

properties while in vivo studies showed superior antibleeding for skin wounds and osteotomy gaps. These properties are related to different interactions between side chains of the copolymer (e.g., catechol, guanidyl, and sulfhydryl) and functional groups (e.g., amine and thiol) that present on the tissue surface.

Figure 16.

Wound healing process includes haemostasis and inflammation, re-epithelialization, and granulation and remodeling. Poloxamer as a non-ionic surfactant which do not ionize in water because of hydrophilic groups that form covalent bonds are commonly used in wound healing. The capability of surfactants to enhance wound healing is suggested because of different factors such as wound cleaning, restraining protein aggregation and denaturization and sealing/repairing tissue/cell membranes [278]. When surfactants are used in wound rinsing media, fewer tension is needed to eradicate bacteria and cellular debris. surfactant support autolytic debridement via degrading collagen debris, by activation of matrix metalloproteinases (MMPs). It was known that poloxamer surfactant-based dressings increased the performance of MMP 2 and 9 gelatinases, whilst at the same time preventing MMP-8 collagenase. It is expected to accelerate autolytic debridement by degrading the damaged collagen and extend protection of untouched collagen [279].

4.2. Poloxamer in Drug Delivery

Poloxamer with hydrophilic ethylene oxide and hydrophobic propylene oxide segments are described by different hydrophilic-lipophilic balance (HLB) causing whether the poloxamer solubilize in water or oil (Figure 17). Owing to amphiphilic feature, poloxamer displays surfactant feature such as capability of interaction with hydrophobic surfaces and biological membranes. In aquatic media above critical micelle concentration (CMC), poloxamer self-assemble into micelles. The size of Pluronic micelles differ from around 10 nm to 100 nm. The micelles core contains of hydrophobic PPO segment that are divided from the aqueous surface by the shell hydrated of hydrophilic PEO blocks. Core of such micelle can be used for carrying different therapeutic or diagnostic agents. PPO due to the hydrophobic nature capable to load water-insoluble drugs. The PEO shell guarantees that the micelles stay in a dispersed state and reduces unwanted drug interactions with cells and proteins. Sahu et al. used Pluronic F127 and F68 to encapsulate the curcumin and study the releasing behavior. The drug encapsulation was dependent on drug-to-copolymer ratio. It was observed that Pluronic F127 exhibited higher encapsulation than Pluronic F68. The efficiency of encapsulation increased with increasing the drug/polymer ratio which the efficiency at ratio 1/5 was about 35% and efficiency increased to 95% at ratio 1/50. Pluronic F127 exhibited the lower release rate compared to F68. Curcumin was encapsulated within the Pluronic core (PPO segment) as a hydrophobic segment which form the micelle in aqueous solution. The main parameters in drug-loading capacity and encapsulation efficiency of Pluronic are the core forming block, core block length, and total copolymer weight. Pluronic F127 possesses more hydrophobic PPO segment compared to Pluronic F68 and the ratio of hydrophobic PPO to hydrophilic PEO segments are also higher in Pluronic F127. The hydrophobic

–CH3– side groups in the PPO segment (as a core) interacted with hydrophobic drug. Hence, Pluronic F127, with lower CMC and higher hydrophobic interaction than Pluronic F68, shows better performance for curcumin loading [280]. Nguyen et al used series of Pluronic (P123, F68, F127 and F108) to modify and conjugate on polyamidoamine. The nanocarrier conjugated with the highly lipophilic Pluronic P123 showed 76% drug loading efficiency which was higher than the other one. Drug release profile indicated that the drug release amount was slow at initial days. After 4 days, quarter of the loaded drug was released which exhibited that the drug was encapsulated in hydrophobic domain. Highly lipophilic Pluronic are useful for encapsulating hydrophobic drugs and sustained release of the drugs canincrease bioavailability in vivo [281].

Croy et al. evaluate the effect of the Pluronic on nystatin aggregation which relates directly with larger hydrophobic block length, higher temperature, and lower CMC [282]. Basak et al. loaded ibuprofen, aspirin, and erythromycin in Pluronic F127. The hydrodynamic radius and polydispersity of the micelles increased with decreasing the temperature and in the presence of drug molecules. pH increment cause to the drugs ionization in the micelle cores. This leads to micelles rupture and drugs release at the highest pH (Figure 17) [283].

Figure 17.

Conveying an adequate amount of drug with a desirable rate to predetermined sites is the major goal of DDSs. This approach which minimizes the side effects of the drug/therapeutic agent on other tissues has attracted growing attention during the last few years [284-287]. Moreover, some grades of poloxamers could act as inhibitors of P-glycoprotein (P-gp) and

sensitize MDR tumors against anticancer drugs [288]. Owing to these properties, poloxamers are considered as potential carriers for controlled/targeted drug delivery purposes primarily for the transportation of hydrophobic drugs [289]. Despite the high therapeutic specifications of hydrophobic drugs, their usage is hindered by challenges related to delivery [290]. Hydrophobic drugs, due to the hydrophobic nature of the core of poloxamer micelles, can be loaded in these micelles that are soluble in aqueous media in order to be delivered to the targeted sites [291]. The solubility and loading efficacy of drugs in poloxamer micelles vary with altering the length of hydrophilic and hydrophobic blocks and the total molecular weight of the chains [292]. Curcumin is a drug with antioxidant, anti-inflammatory, and anti-carcinogenic properties with the potential to suppress the proliferation of a wide range of tumor cells [293, 294]. But the hydrophobic nature of this drug could limit its application in the human body. However, poloxamer micelles (e.g., Pluronic P123 and Pluronic F68) could act as carriers for hydrophobic drugs such as curcumin [295]. Besides, modification of poloxamer with alanine oligomers further enhanced the entrapment efficiency of curcumin [296]. In fact, alanine oligomers decrease the critical micelle concentration and molecular motion of poloxamers resulting in enhanced drug loading. Das *et al.* synthesized chitosan-alginate-Pluronic nanoparticles for the delivery of curcumin. This study demonstrated that poloxamer-based biomaterials could increase the encapsulation efficiency of curcumin in chitosan-alginate nanoparticles [297]. Docetaxel, a poorly soluble antitumor drug, was loaded in a mixed micelle composed of Pluronic P105 and F127 with an encapsulation efficiency of 92.4% and storage stability of 95.7% after six months in the lyophilized form [298]. To improve the efficacy of poloxamer micelles for drug delivery, they could be functionalized or blended [299-301]. Composite micelles comprised of aptamer AS1411-modified Pluronic F127

and beta-cyclodextrin-linked poly(ethylene glycol)-b-polylactide were synthesized for delivery of doxorubicin (DOX) to human breast tumors. According to these observations, such composite micelles displayed an enhanced antitumor activity, reduced cardiotoxicity, and improved accumulation in the tumor site (Figure 18) [55].

Figure 18.

There have been several attempts to propose innovative strategies for the delivery of drugs to the brain [302, 303]. In this regard, poloxamer micelles have been used for drug delivery against the blood-brain barrier (BBB) [293, 304]. Delivery of proteins to brain tissue is hampered due to physiochemical characteristics of proteins and infiltrative nature of BBB. Chitosan-conjugated Pluronic-based carriers have shown great potential for delivering β-galactosidase to the brain [305]. Hydrophobic nanoparticles are quickly eliminated by the mononuclear phagocytic system (MPS) and fetch up in the liver/spleen. Hence, surface modification is indispensable in most situations. Poloxamer-based biomaterials are beneficial for this goal since the PPO blocks stick to the hydrophobic surface and the PEO hydrophilic blocks form the outside surface [36]. Pluronic F127 was used to modify the vincristine sulfate (VCR)-loaded poly(butyl cyanoacrylate) nanoparticles resulting in lower clearance of VCR from the systemic circulation and enhanced the efficiency of targeted release [306]. Pluronic P85 was used to control the release behavior of the Doxil® from liposomes at the tumor sites. In fact, Pluronic P85 is combined into the liposomal membrane, where the drug is encapsulated, and creates transient holes in the membrane which results in enhanced permeability of the membrane [307]. It has

been reported that Pluronic F127 could act as a surfactant for Zein nanoparticles and sustained the release profile of Lutein by improving the physical stability of the nanocarrier [308]. The literature studies demonstrate that poloxamer-based biomaterials are also suitable carriers for cells [38, 260] and growth factors [189].

Sexually transferred infections and unintended pregnancies represent a huge threat to the reproductive women health. Patel et al. loaded curcumin to the thermosensitive poloxamer 407/188 which was used to the pregnancy control and disease prevention [309]. The temperature-sensitive feature of the poloxamer is attractive for designing of vaginal microbicides platform [309, 310]. Poloxamers increase drugs absorption via the mucus membranes. Prolonged toxicity evaluation and clinical trials propose that poloxamer pharmaceutical products are safe for human use. Poloxamer has a significant effect on sperm motility and have sperm immobilization effect and spermiostatic action [311]. Poloxamers as a non-ionic surfactant are proposed to act on the mid piece and tail of sperm, directly affecting the lipid layer, which provides protection to the surface of sperm [312, 313]. And also, as they are non-ionic surfactants, increase the solubility of curcumin and also used to avoid the staining problems of curcumin because of its washability from the site of application [311]. Moreover, Poloxamer based hydrogel has less ability to dilution with vaginal fluid [314].

4.3. Gene Therapy/Delivery

Gene therapy/delivery is a process through which a foreign DNA is introduced to the cell and can be assisted by a mechanical process, a chemical compound like nanoparticle/vesicle, and biological routes. It was observed that DNA injection resulted in gene expression; however,

pristine DNA cannot perform effectively [141, 315]. Pluronic has attracted much attention in gene therapy due to its unique structure which can be self-assembled and modified by a wide range of materials [316]. One of the applicable materials used as a non-viral gene delivery vector is polyethyleneimine (PEI); nevertheless, toxicity is an obstacle for the efficiency and proper targeting of PEI. Overcoming such a problem, Pluronic-modified low molecular weight PEI was developed. Then, it was conjugated with a cell-penetrating synthetic peptide which could bind to the DR5-receptor overexpressing in cancerous cells. The degradable modified Pluronic was observed to exhibit higher gene transfection to cancerous cells and lower to normal cells rather than PEI and Pluronic-PEI [317]. Electrotransfer of DNA has been performed using a short-high voltage and a long-low voltage for cell electropermeabilization and DNA electrophoresis in the cell respectively. However, short-high voltage resulted in histological and functional damages to the tissue. Therefore, Pluronic L64 accompanied by a low-voltage pulse was used as an efficient and safe way to deliver the plasmid gene to the skeletal muscle [318].

4.4. Theranostic Device

Cancer targeting, imaging, and therapy are some challenging issues which nanotechnology endeavors to cover all in one device. Theranostic nanoparticles act as a therapeutic, meanwhile, a diagnostic device which can be used in cancer therapy and bioimaging [319-321]. Naphthalocyanines along with Pluronic F127 has been utilized as a therapeutic agent, lymphatic mapping, and tumor photoacoustic imaging that has been injected intravenously/intradermally to a rodent [322-324]. Meli et al. formulated a lipid-based hexosome nanoparticle containing an insoluble anti-cancer drug called docetaxel which was stabilized using

folate- and rhodamine-grafted Pluronic F108. The nanoparticle exhibited imaging, therapeutic, and targeting features simultaneously with a steady and gentle drug release and the toxicity 20 times higher than free docetaxel. The hexosomes functionalized by folic acid which bind with the cell receptor and internalized within HeLa cells. Hence, the loaded drug within the hexosome can deliver efficiently to the cells rather than unloaded drug. Such a nanoparticle was proposed as a potential theranostic platform in oncology [325]. Pluronic-coated nano-assembled gold nanoparticle with appropriate cellular imaging, therapeutic, and diagnostic features was loaded with methylene blue as a visual mark and photosensitizing drug. Such a plasmonic nanoplatform exhibited photodynamic therapeutic activity against murine colon carcinoma cells in comparison with the pristine photosensitizer [326]. Polymeric bubbles with gas core have been utilized as a new emerging theranostic device for MRI-guided therapy. Pluronic-stabilized nanobubbles based on chitosan with Perfluoropentane core were used for encapsulation of prednisolone phosphate as a therapeutic agent and Gd(III) complex as an MRI diagnostic agent. Ultrasound stimulation was used for on-demand drug release. In vitro assessment declared that the nanobubbles could be easily tracked using MRI or ecography [327]. Choi et al. synthesized a novel MRI contrast agent based on iron oxide nanoparticle encapsulating by Pluronic which showed prolonged blood circulation and appropriate tumor targeting. Nanocarrier with the higher amount of iron oxide nanoparticle exhibited increased MR contrast impact with elevated T2 relaxivity and greater intracellular uptake in vitro [328].

4.5. Bioink/ 3D Printing

3D printing technology in tissue engineering attempts to achieve the biomimetic scaffolds. The ink utilized in 3D bioprinting, often referred to as bioink, should exhibit ECM-like properties [329]. Pluronic exhibits a sol-gel transition near the physiological temperature because the increase in temperature increases the CMC enhancement which leads to micellar crystallization and formation of a self-supporting gel. Based on such behavior, Pluronic can be a qualified candidate as a bioink for 3D printing [330]. However, because of the inferior mechanical properties of Pluronic, it is suggested to fabricate a blend gel of Pluronic with other polymers like alginate. Hybrid bioinks enhanced the printing quality [331]. Armstrong et al. used Pluronic-Alginate gel as a bioink for 3D printing. Due to gelling features of Pluronic, the mixture was prepared at 4 °C, then the temperature was raised to 25 °C to form a homogenous fluid containing human mesenchymal stem cells. Finally, the bioink was printed at 37 °C. Sol-gel transition resulted in a self-supporting geometry which was braced with $CaCl_2$. The prepared bioink exhibited appropriate mechanical and biological properties (Figure 19) [332]. Pectin-Pluronic F127 was used as a bioink in which warm Ca^{2+} was utilized to form a gel due to the temperature-sensitive nature of Pluronic and pectin crosslinking behavior [333]. In order to compensate the Pluronic inferior long-term flaws, acrylate was utilized to stabilize the Pluronic using UV crosslinking [18]. Han et al. synthesized a conductive bioink based on aniline tetramer/PEI/Pluronic. Nanoparticles were around 50 nm diameter with appropriate electroactive properties and superior printability. Conductivity of around $2*10^{-3}$ S/cm was

achieved; denoting that the 3D printed platforms of aniline tetramer/PEI/Pluronic could be used in cardiac, neural, and mussel regenerations applications [334].

Figure 19.

4.6. Hyperthermia

Magnetic hyperthermia treatment is a method through which the magnetic nanoparticles convert the altering magnetic field energy to heat Néel and Brownian relaxation mechanisms. Magnetic nanoparticle injected into the tumorous area and converted heat obliterate the cancerous cells [335-337]. Fe_3O_4 as a hydrophobic particle interacted with the hydrophobic segment of Pluronic and self-assembled in an aqueous solution. Particles were blocked at 300 K and showed Verwey transition at 119 K. 43 °C temperature enhancements in 350 seconds was observed. The specific absorption rate was around 6.4 W/g. Accordingly, the particle could be used in tumor lyse as a magneto hyperthermia nanoparticle [338]. Thermosensitive drug release has been used vastly in DDSs, but most of carriers are removed before the complete release; therefore, the hyperthermia method has been supposed as a stimulator for controlled release. Thermosensitive Pluronic L64 noisome was used as a drug release method controlled by hyperthermia [339]. Fullerene has shown promising potential for cancer treatment using hyperthermia microwave [340]. It was reported that fullerene-embedded Pluronic-chitosan nanoparticle with microwave exhibited appropriate cancerous cell destruction. Those nanoparticles inside the cells caused the cells to implode due to the generated heat [341]. The cytotoxicity of iron oxide nanoparticles was improved using encapsulation with Pluronic F127-

conjugated peptide. Moreover, targetability was enhanced due to the presence of peptide which lead to the optimal cancer treatment [342]. Choi et al. loaded gold-nano rod to chitosan-Pluronic F68 nanocarrier as a hyperthermia system using for photothermal therapy of cancer. Such nanocarrier exhibited prolonged circulation time, proper tumor accumulation, and minimum liver uptake. In addition, an intravenous injection and NIR laser irradiation caused to a efficient thermolysis in rat model and perfect tumor resorption was attained without harm other tissues [343].

5. Conclusion and Future Perspective

Poloxamers are a class of biocompatible polymers with thermo-reversible gelling and self-micelle assembling properties. Moreover, their adjustable mechanical and morphological properties achieved by functionalization or blending with other biomaterials endows them with a wide variety of applications in biomedical applications. The amphiphilic nature and the potential to self-assemble have made poloxamers exquisite carriers for both hydrophobic and hydrophilic drugs. Furthermore, their ability to sensitize MDR tumors against anticancer drugs has improved their application in cancer therapy. They are also used as potential surfactants in microemulsion systems for the synthesis of nano-/micro-particles. It is anticipated that their ability for the surface modification of hydrophobic nanoparticles increases their usage in critical delivery systems when enhanced drug availability is required in the body. It can also revolutionize controlled/targeted DDSs for brain-targeted delivery and cancer therapy. Considering the literature available on poloxamer-based biomaterials, there are advantageous features increasing their versatility in the field of tissue engineering. Future applications in tissue

engineering will be based on ameliorated techniques like 3D printing for producing scaffolds with predetermined porosities and structures which has a determinative effect on cell proliferation, or microfluidic systems in order to investigate cell differentiation in micrometer level. Ingenious incorporation of specific biomaterials or bioactive agents into the poloxamer structures is an indispensable procedure in order to heighten their capabilities for regeneration of targeted tissues. Poloxamer-based biomaterials are expected to play a crucial role in the progression of multifunctional scaffolds in the upcoming years and bring about even more exciting breakthroughs within the field of tissue engineering and regenerative medicine.

Data Availability Statement:

All the data have been presented in the article. For more information, the readers can contact the corresponding authors of the article. It is also to confirm that the relevant data comprise the minimal underlying data that an independent researcher would need in order to replicate all of your results, conclusions, means, tables, figures, graphs, images, standard deviations, standard errors, and other summary statistics.

Disclosure

The authors of the present work have no conflict of interest to declare.

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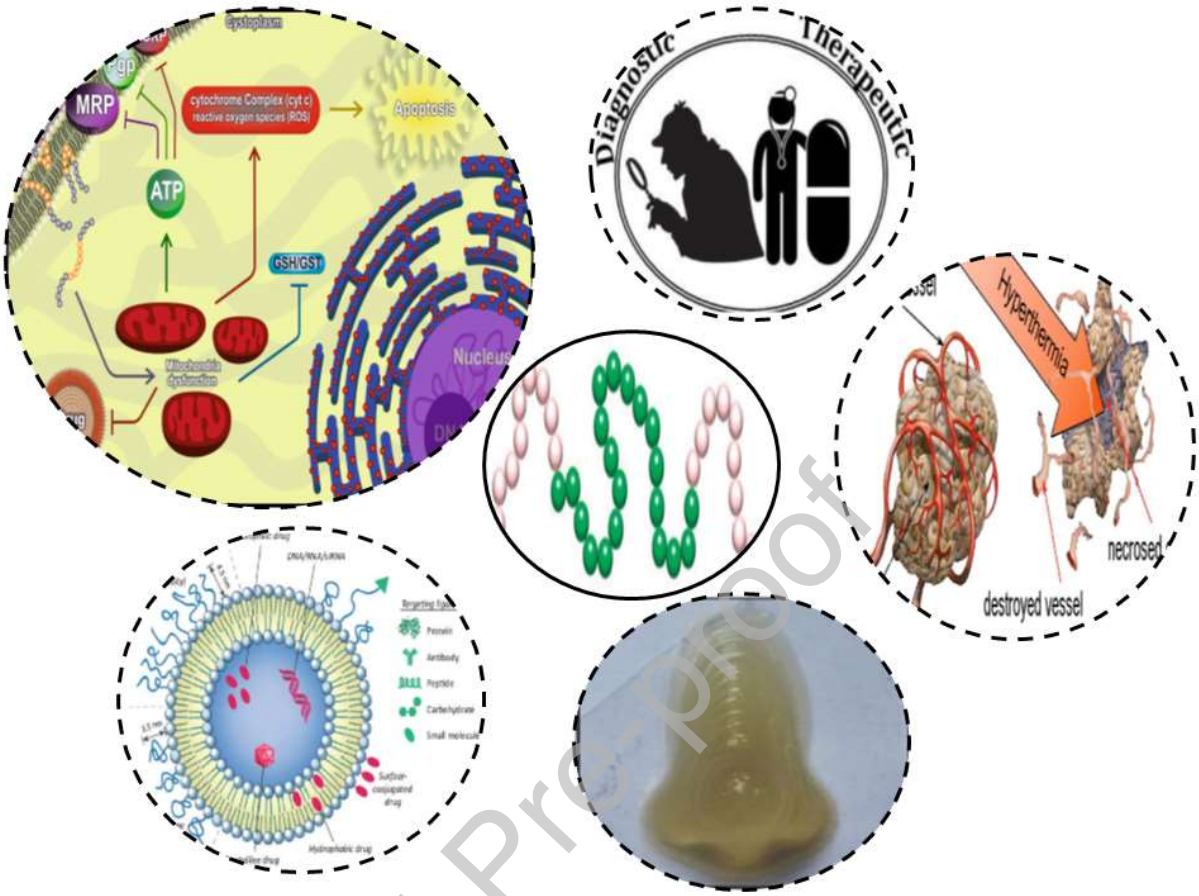


Figure 1. Poloxamer in biomedical application: Delivery systems, Tissue engineering, Cancer therapy, Theranostic platforms, Bio/3d printing

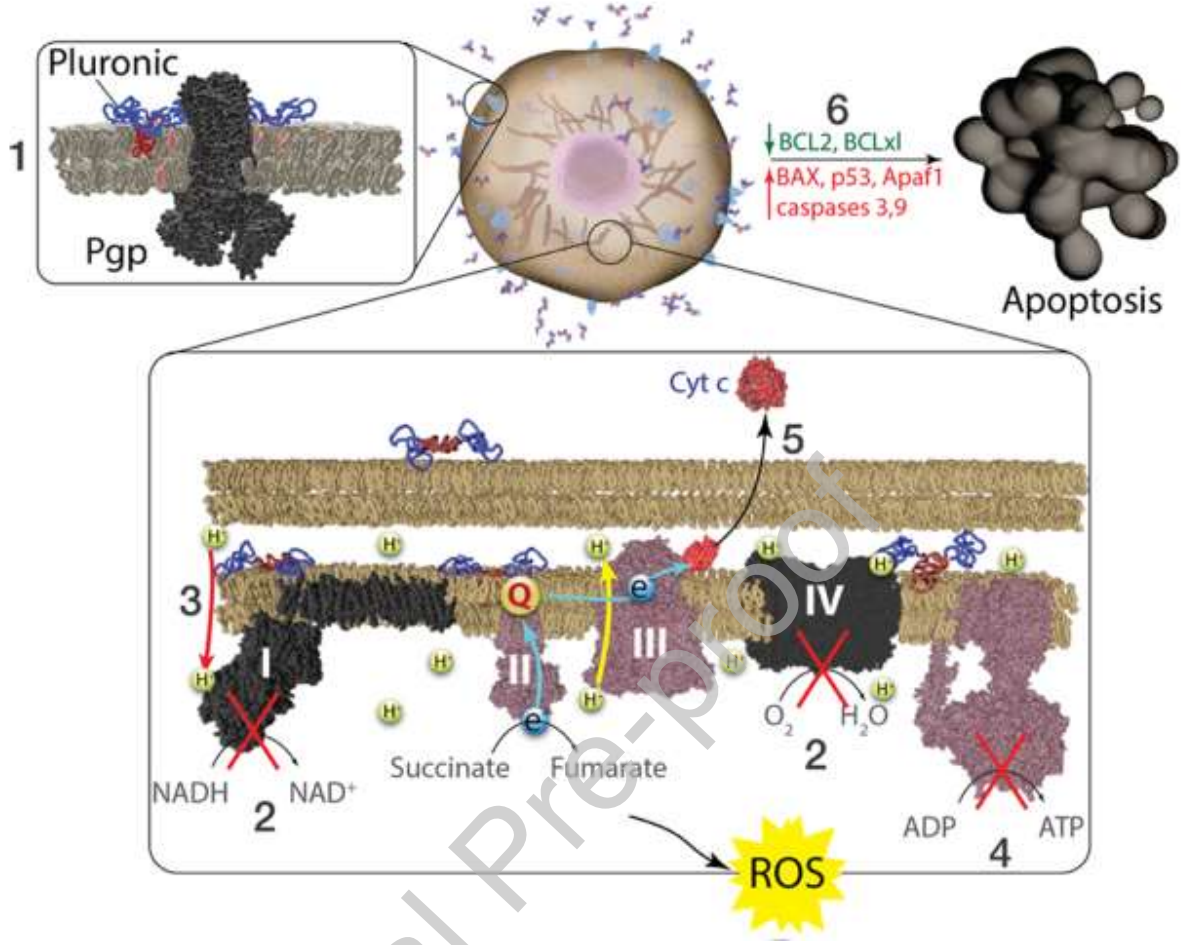


Figure 2. Summary of Pluronic effects in cancer cells. Pluronic binding with plasma membrane of MDR cancer cells (1) induces membrane fluidization, disruption of membrane microdomains, and inhibition of drug efflux transporters' activity (Pgp shown as an example). Pluronic also reaches mitochondria where it (2, 3) inhibits complexes I and IV of mitochondria respiratory chain and (3) induces inner mitochondrial membrane depolarization. This (4) results in ATP depletion and (5) promotes cytochrome c release and ROS generation in MDR cells. Altogether, the MDR cells respond to a Pluronic combination by (6) an increased proapoptotic signaling and decreased antiapoptotic defense Reprinted with permission from [48].

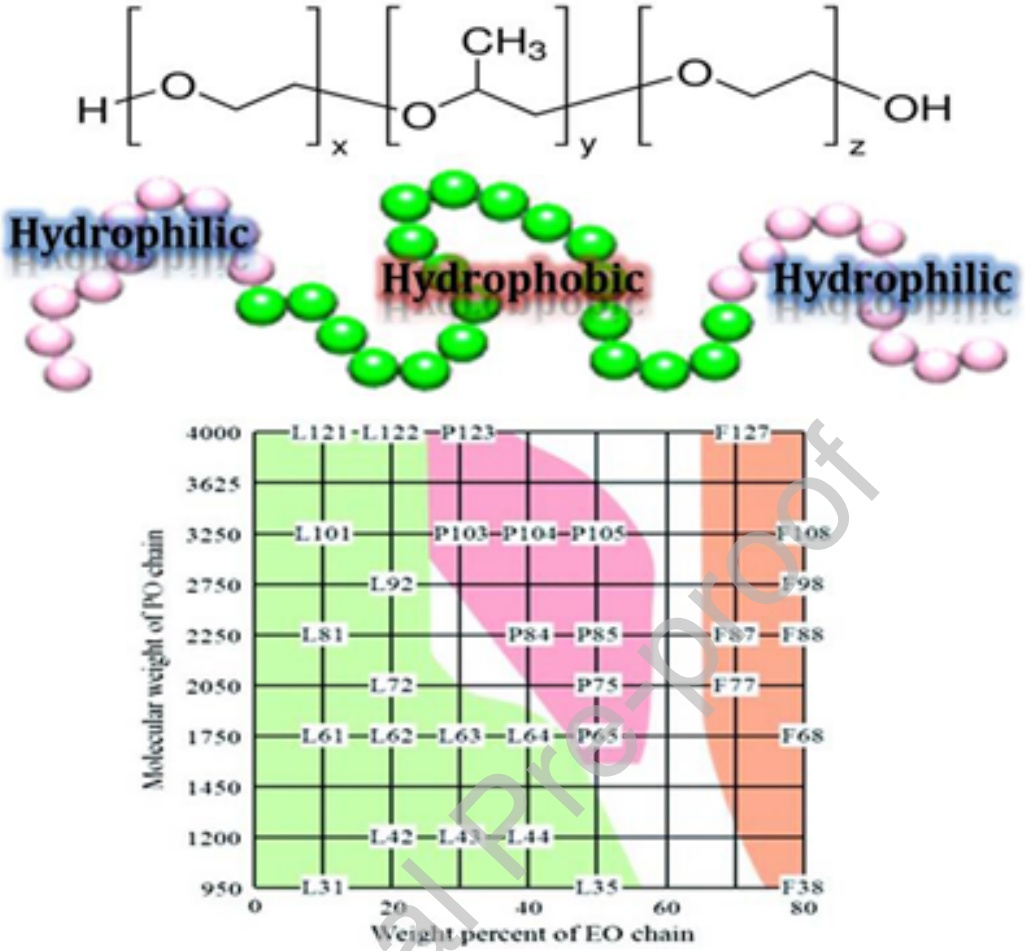


Figure 3. Molecular structure and grades of poloxamer. Reprinted by permission from [33].

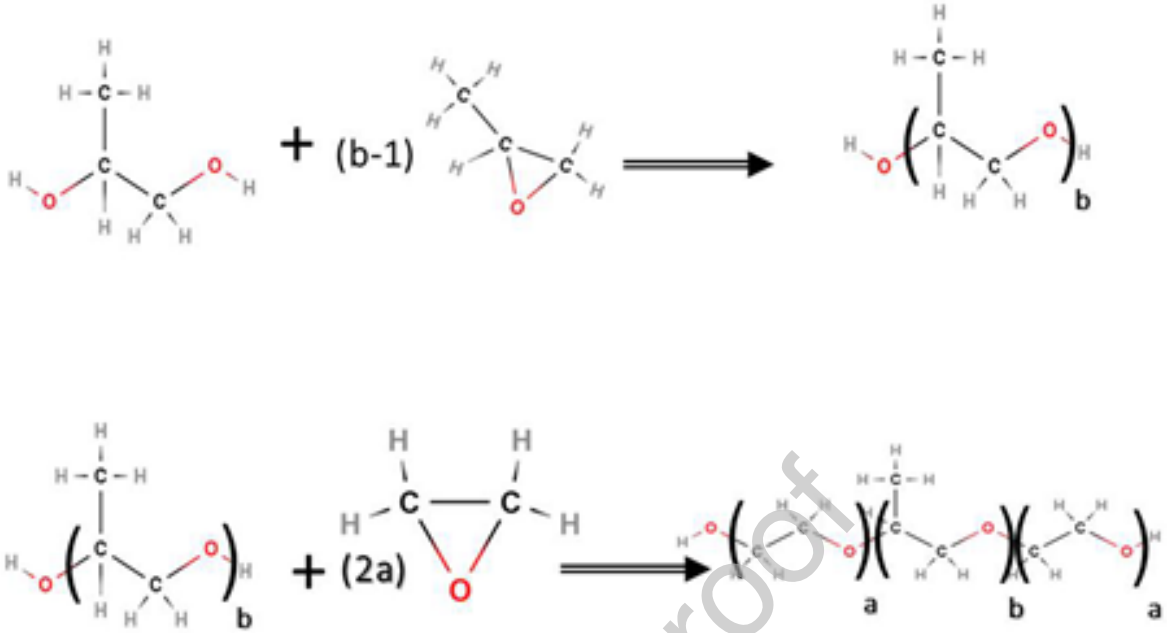


Figure 4. Poloxamer synthesis through anionic ring opening polymerization of EO and PO. Reprinted by permission from [51].

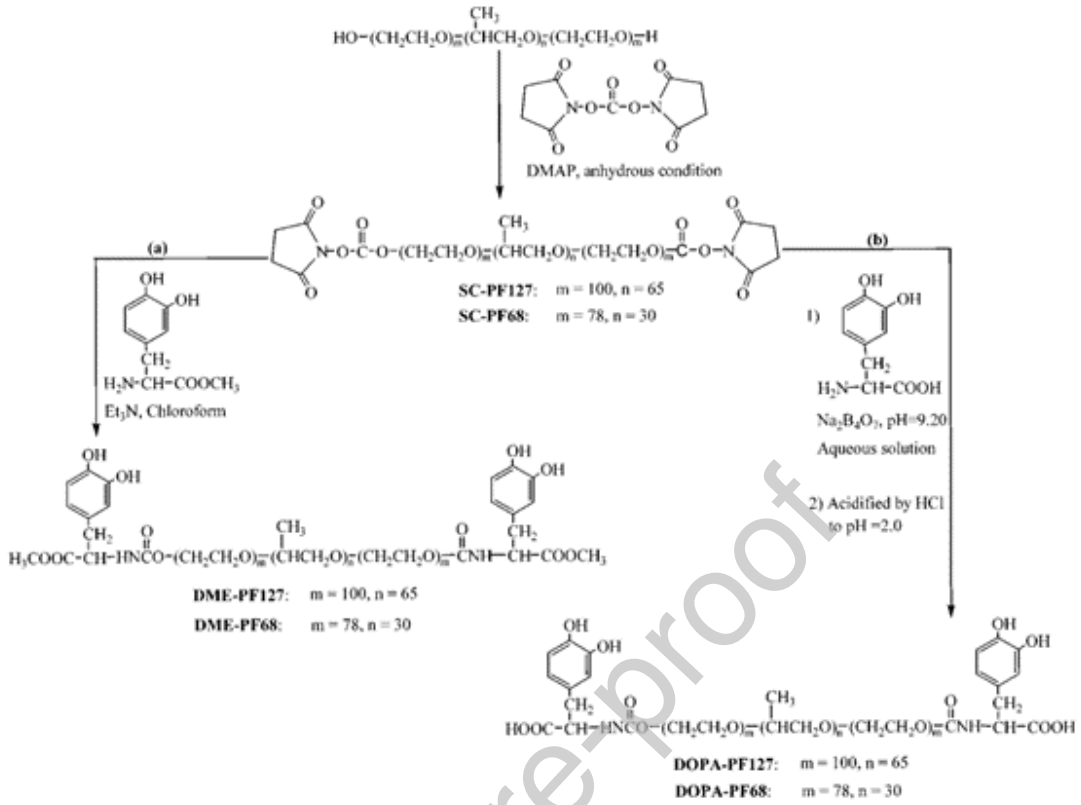


Figure 5. Synthesis of mussel-inspired poloxamer in (a) organic solvent (b) aqueous solvent. Reprinted by permission from [54].

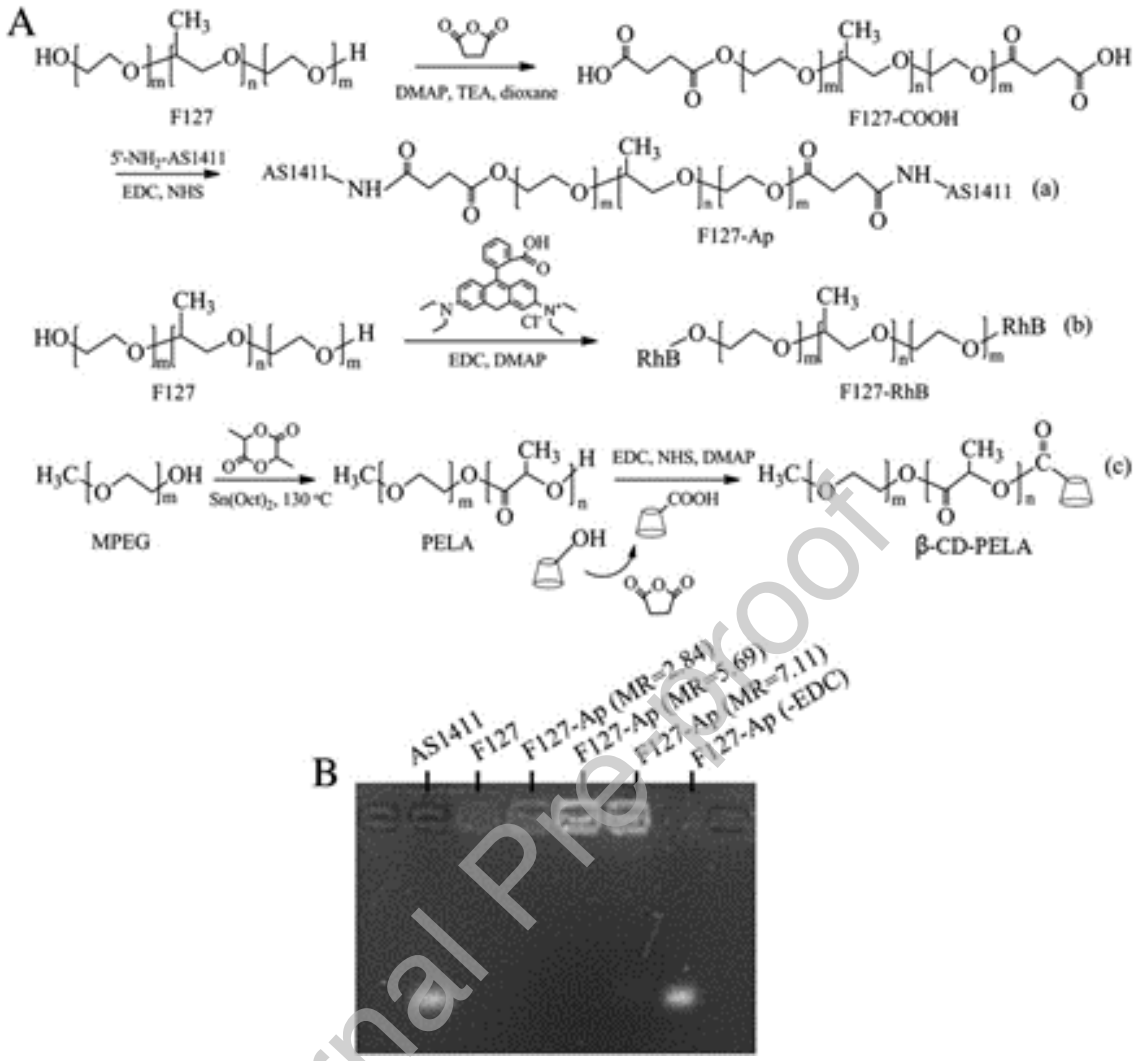


Figure 6. A) Conjugation of Pluronic to Aptamer, Rhodamine B, and Cyclodextrin B) evaluation of Aptamer conjugation to Pluronic. Reprinted by permission from [55].

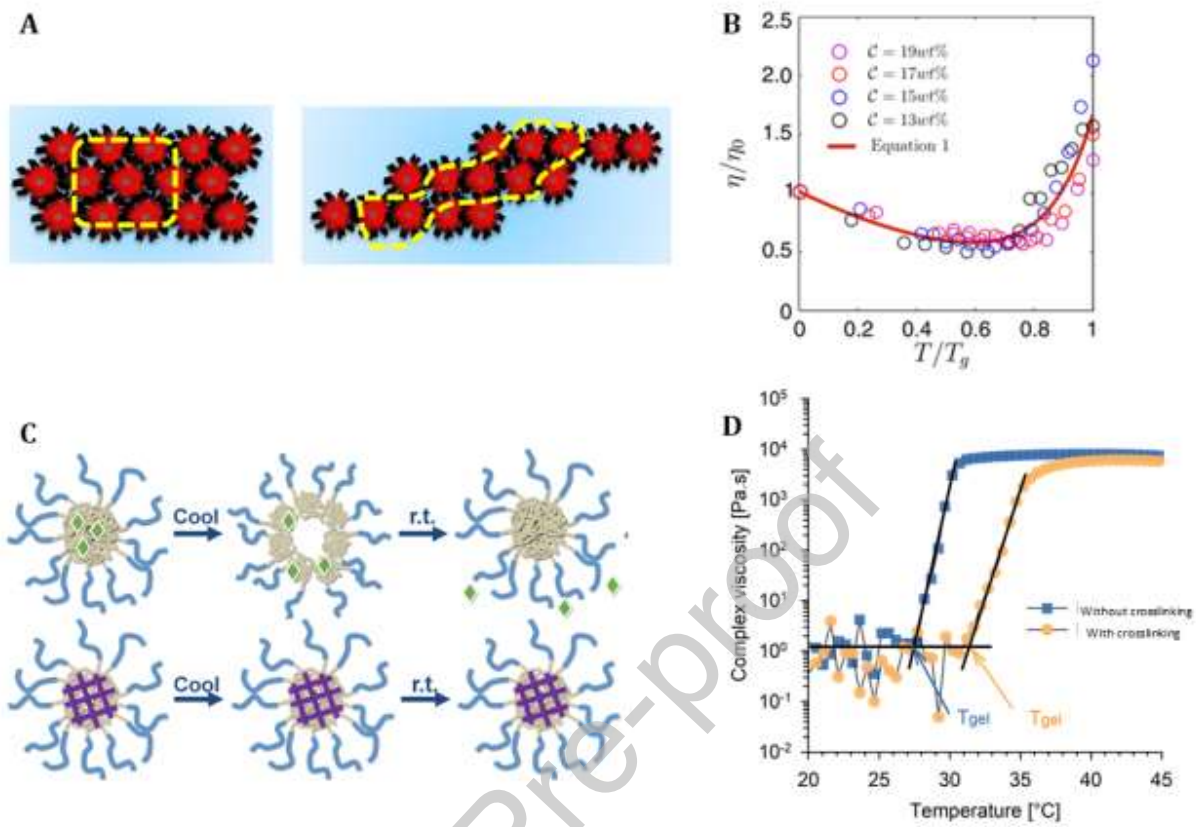


Figure 7. A) Schematic illustration of structural behavior of Pluronic gels under shear [97]. **B)** Viscosity as a function of temperature and concentration [95] **C)** Schematic illustration of Pristine Pluronic and crosslinked Pluronic behavior under the temperature variation. **D)** Complex viscosities of pristine Pluronic and crosslinked Pluronic as a function of temperature [96].

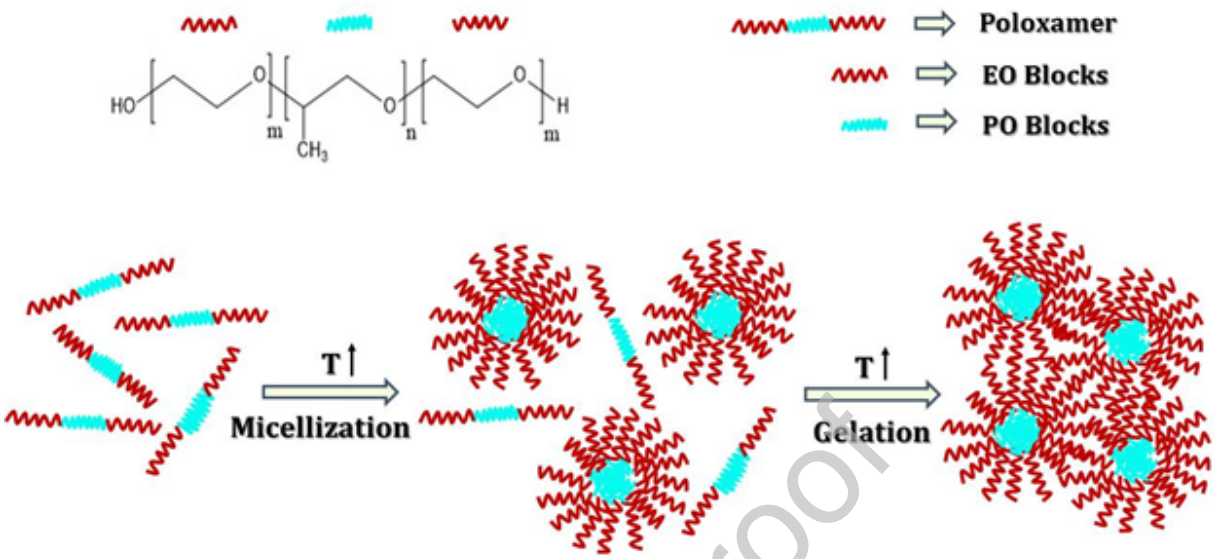


Figure 8. Schematic demonstration of poloxamer gelation mechanism

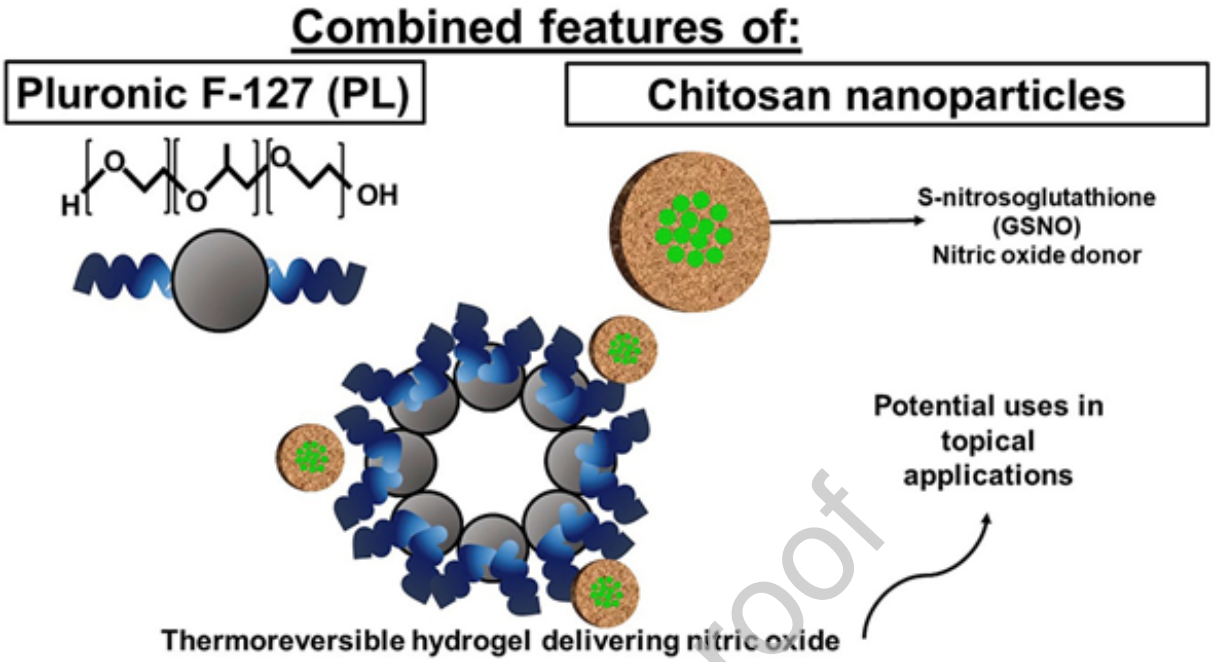


Figure 9. Pluronic hydrogel contains NO-embedded chitosan nanoparticles [106].

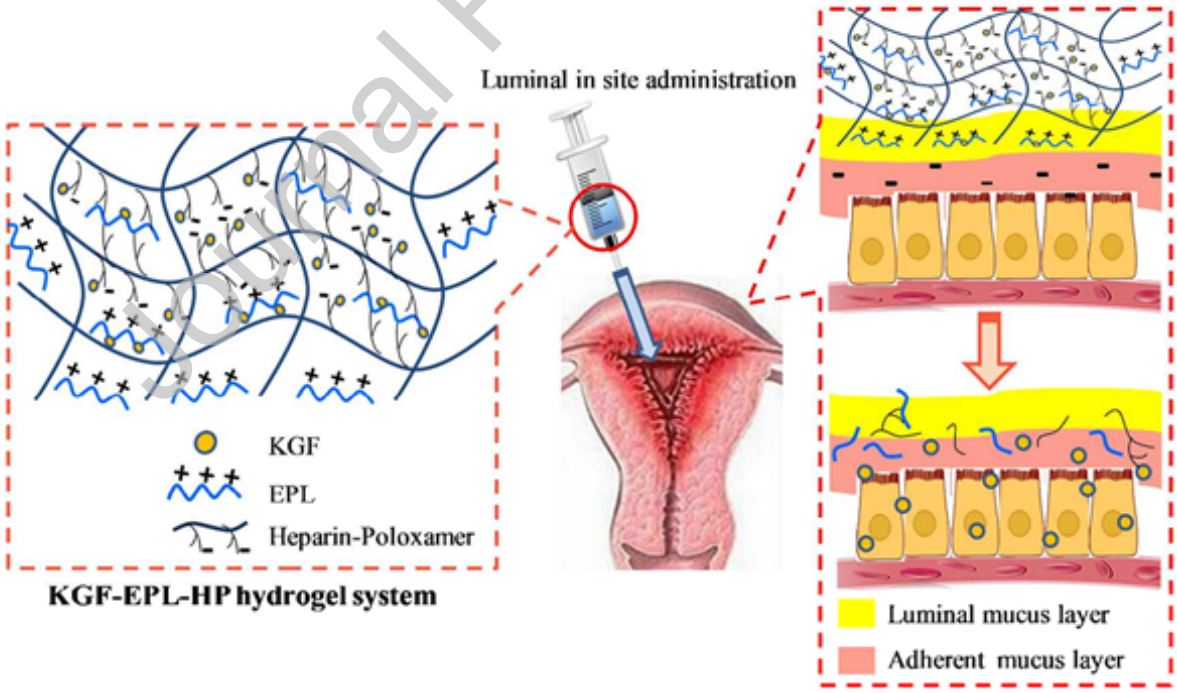


Figure 10. temperature responsive bioadhesive hydrogel for injured uterus [115].

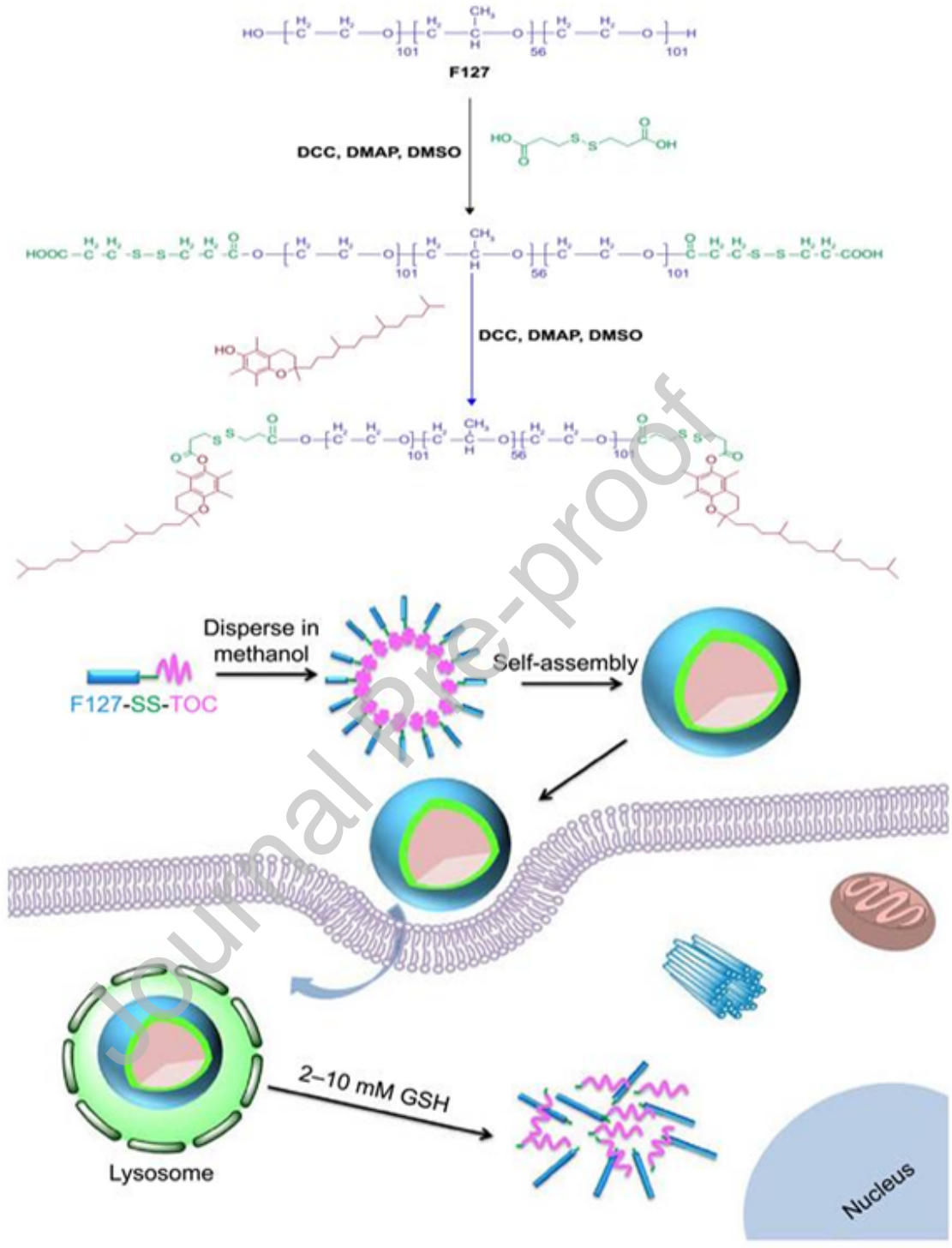


Figure 11. Synthesis route of F127-ss-TOC polymer and schematic illustration of self-assembly of F127ss-TOC micelles [117]

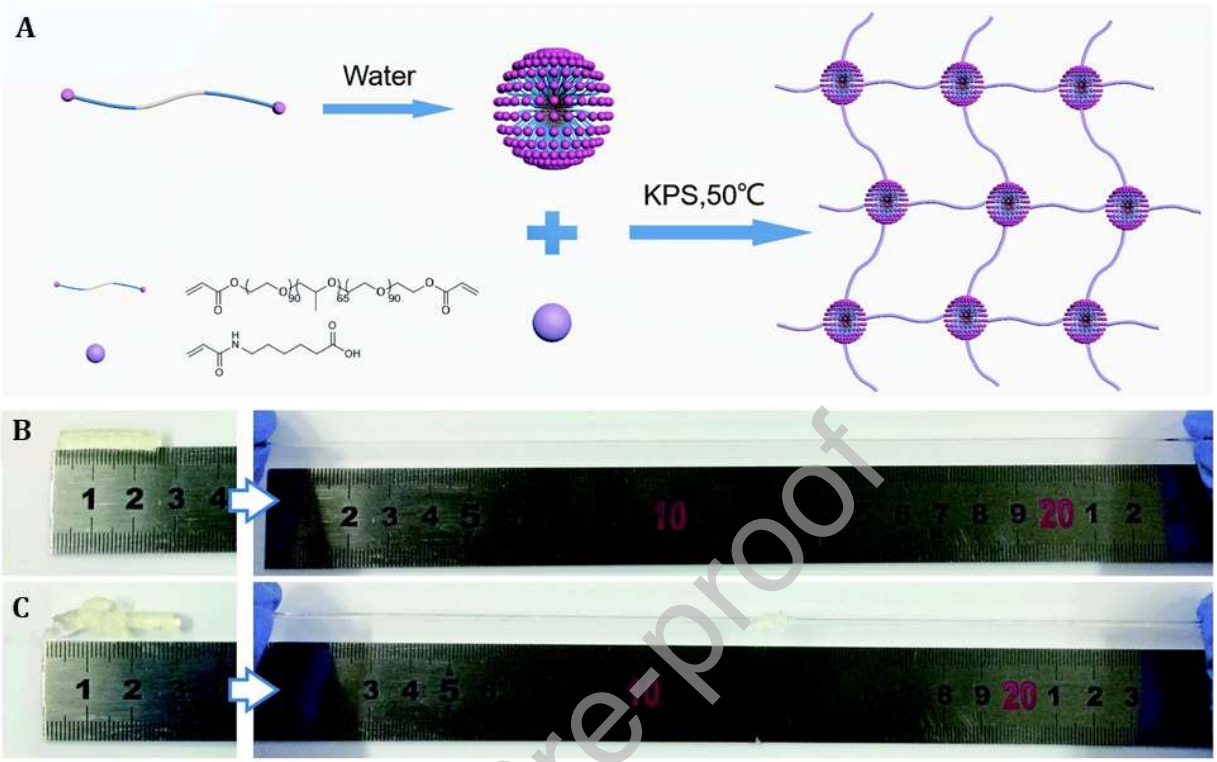


Figure 12. (a) illustration of hydrogels preparation. prepared hydrogels with proper extensibility, and high-level deformations such as elongation (b), and elongation after knotting (c) [123].

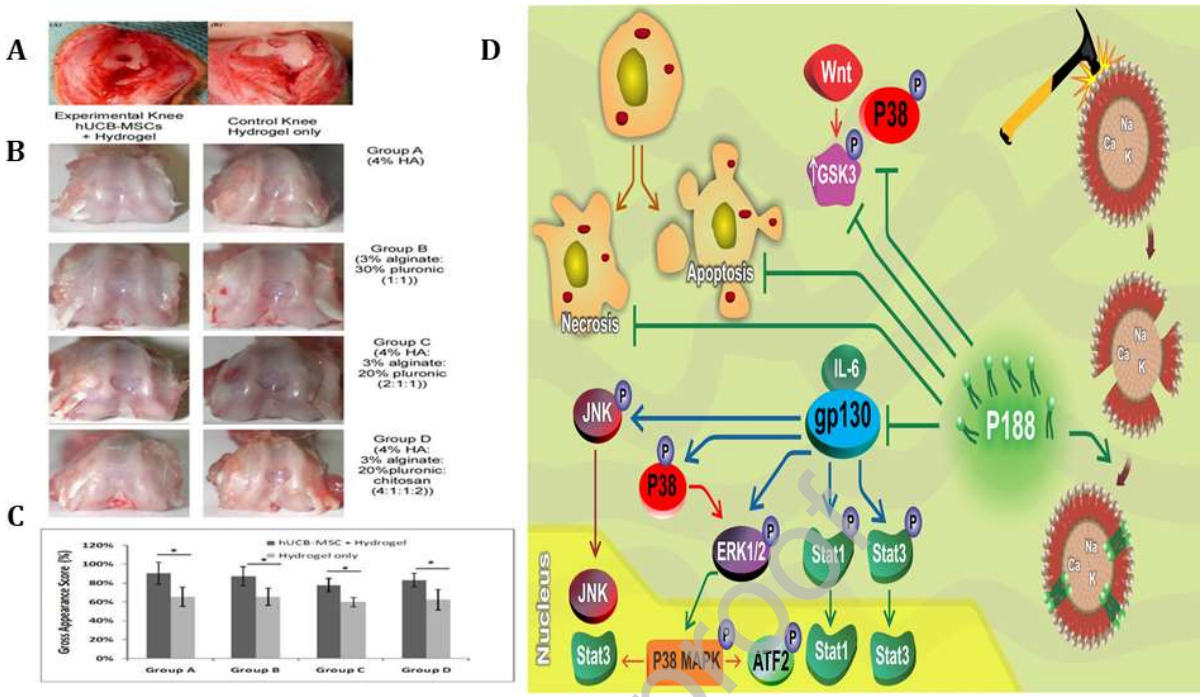


Figure 13. **A)** Articular cartilage defects in a rat model **B)** articular cartilage defects in a rat model with different compositions of the scaffold **(C)** Gross appearance scores of experimental and control knees in hydrogel groups [16]. **D)** Suggested mechanism of P188 impact. Shock to cartilage stimulates matrix disruption and cell death, which translates on the cellular stage to the activation of IL-6, p38, and GSK3 signaling. And also sealing cell membrane, P188 hinders necrosis, apoptosis, IL-6, p38, and GSK3 pathways.

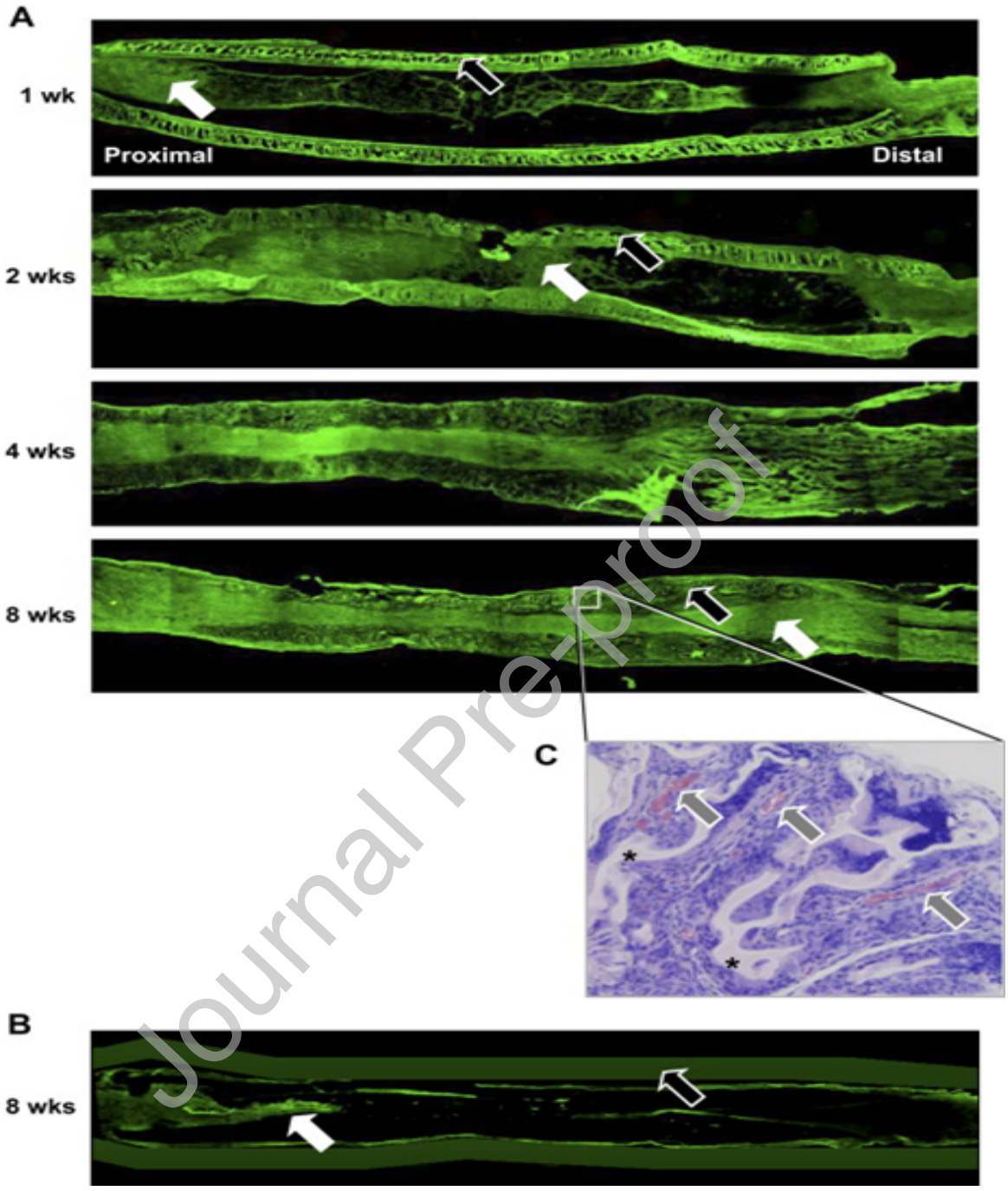


Figure 14. nerve regeneration using **(A)** PLGA/F127 and **(B)** silicone tubes (white arrow shows regenerated nerve; black arrow shows tube wall) and **(C)** cross-sectional perspective of PLGA/F127 tube wall exhibiting the presence of blood vessels infiltrated within the wall [184].

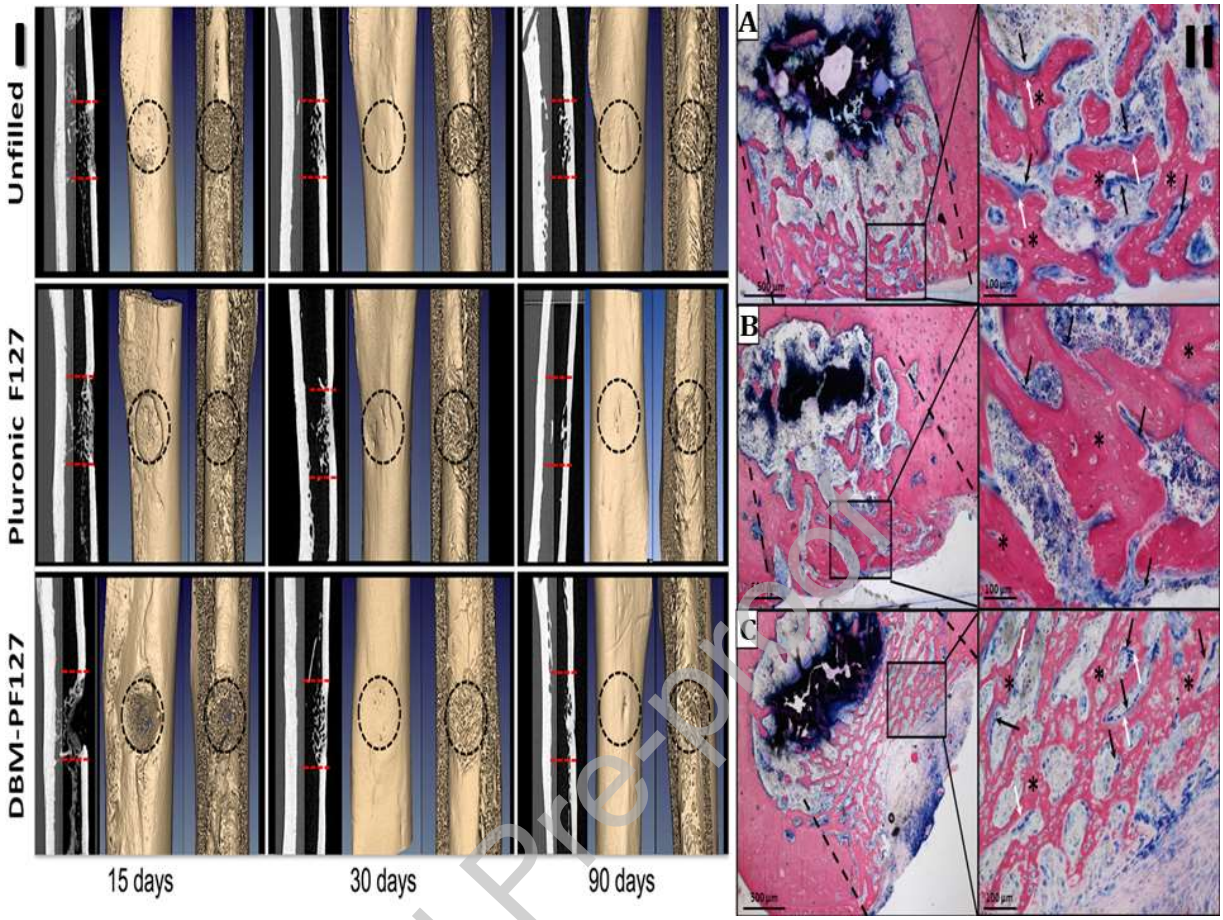


Figure 15. I) Micro-CT ex vivo picture of femurs. Defect edges are marked with dashed line. II) a) Unfilled defect; b) PF127-filled defects; c) DBM-PF127-filled defects. Dashed line indicates the edges of defect, (*) shows the fresh formed bone, the black arrow shows osteoblast cells, and the white arrow shows osteoid [228].

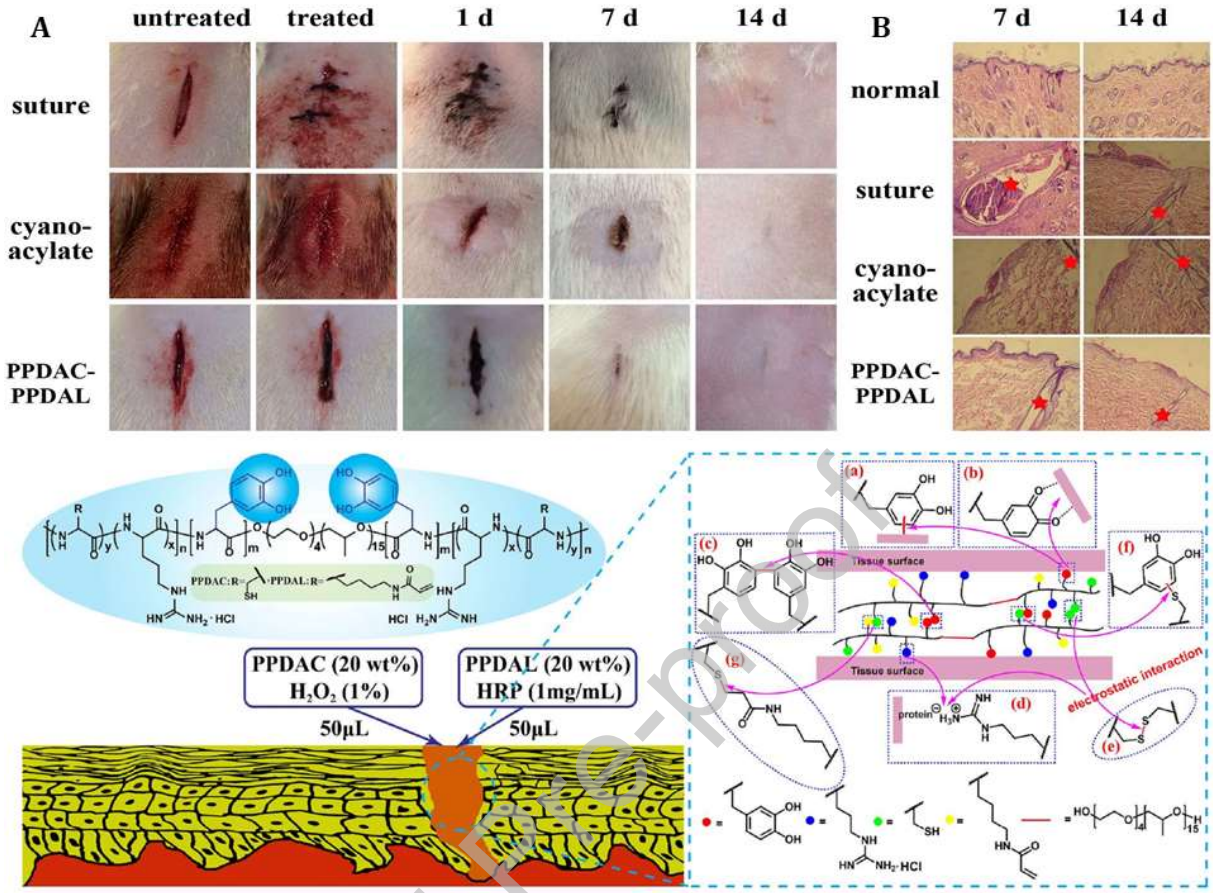


Figure 16. A) Image of wound closures. B) Histological evaluation. The sites of wound are showing by red stars [277]. (C) illustration exhibit a mechanism of tissue adhesion [277].

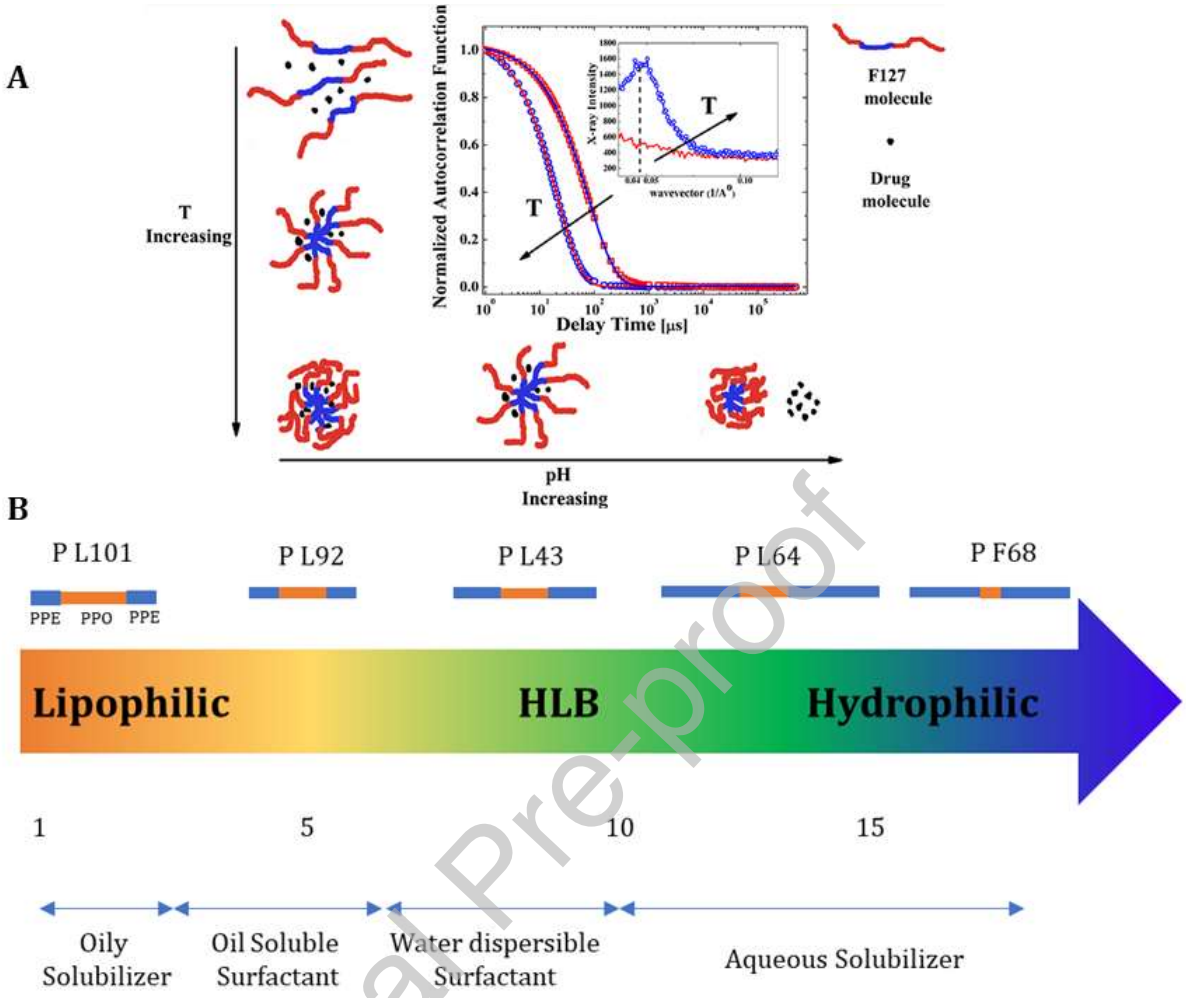


Figure 17. A) pH, temperature effect on Pluronic structure and drug release (reprinted with permission from[283]) . **B)** HLB ranges of the different Pluronic

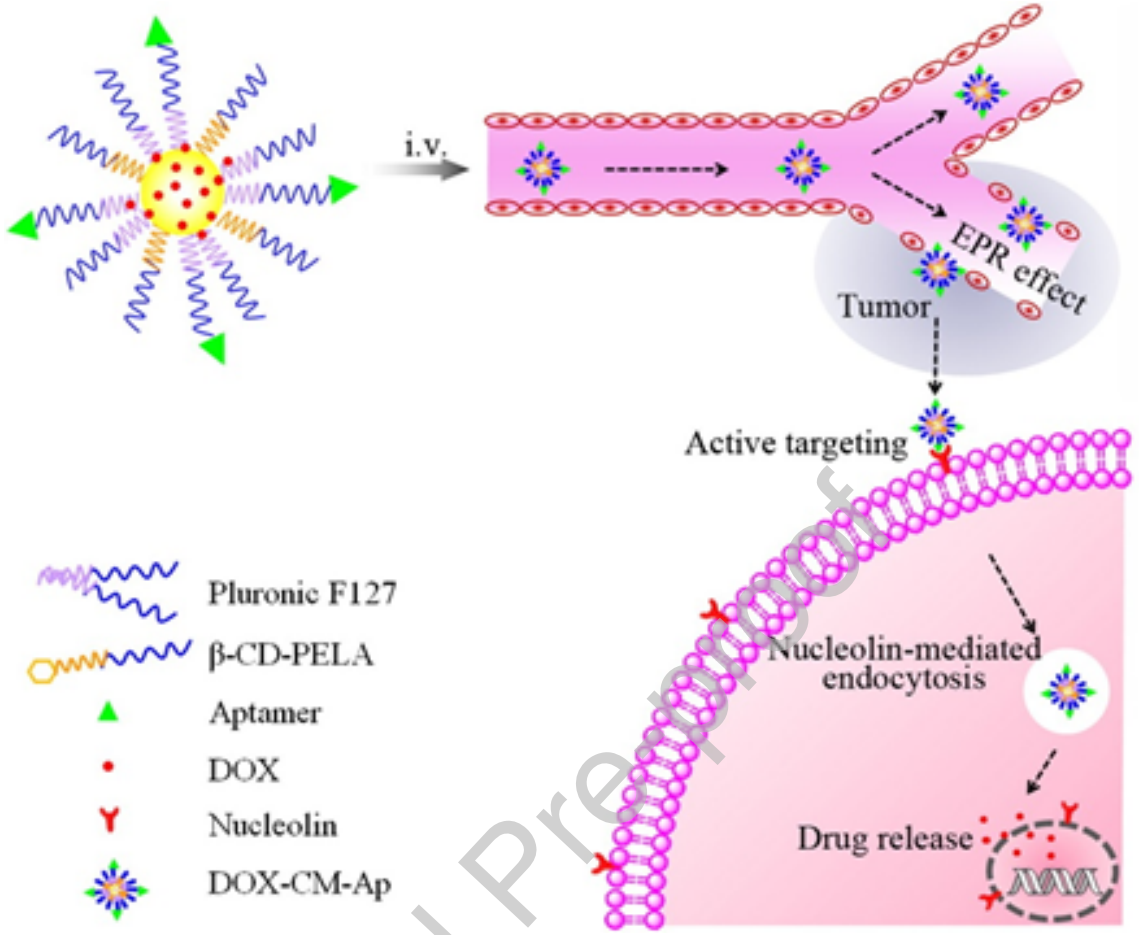


Figure 18. Aptamer-modified Pluronic as an anti-cancer drug carrier [55].

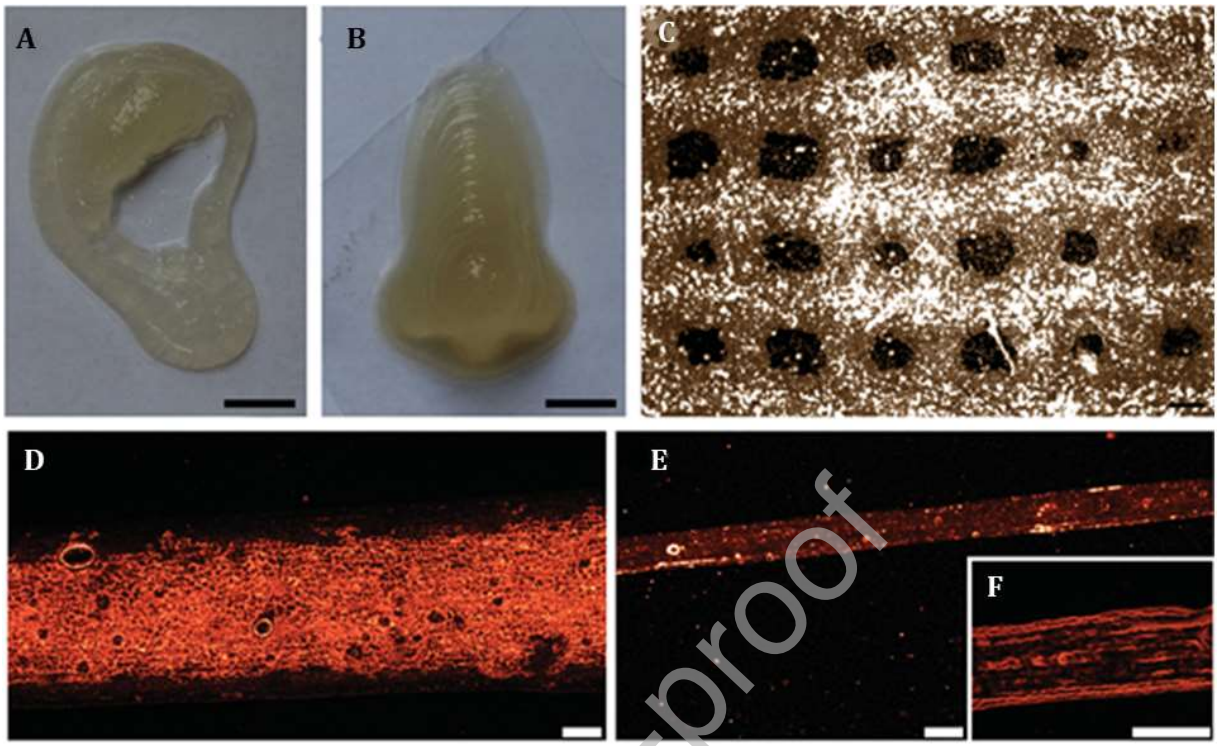
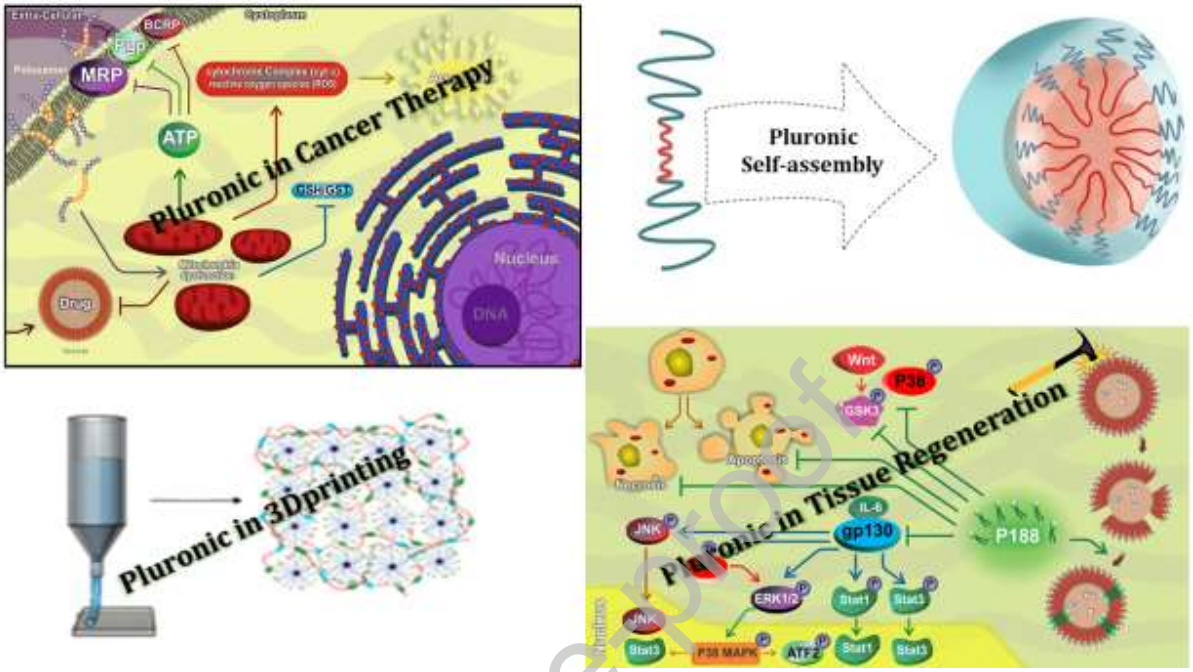


Figure 19. 3D printing using Pluronic F127-alginate gel. a,b) Post-crosslinking image of ear and nose c) a crosshatch motif printed through a 25-gauge syringe needle d) a single printed fiber using a pipette tip, e and f) a printed fiber using a 30-gauge needle. Extruded fiber using large nozzle, such as the pipette tip [332].

Graphical Abstract



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: