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# Poly(trimethylene carbonate-co-caprolactone): An emerging drug delivery nanosystem in pharmaceutics

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**Abstract.** As conventional drug delivery system is being improved rapidly by target-based drug delivery system, finding suitable Drug Delivery System (DDS) for new drugs remains a challenge. Although there are many drug delivery vehicles in existence, a significant improvement is required to some DDS such as for local, implant-based treatments used for musculoskeletal infections. Many polymers have been considered for providing the improvement in DDS. Synthetic polymer, for example, has gained popularity for broad-spectrum physicochemical and mechanical properties. This article reviews the biomedical applications of Poly(TriMethylene Carbonate-co-Caprolactone) (PTMCC), which has attracted attention due to its biocompatibility, biodegradability and rubber-like properties. Its synthesis, physical properties, and degradation are also discussed here. Although it is relatively new in biomedical applications, it is readily usable for the fabrication of differing format of DDS of superior mechanical strength and degradation properties. The use of PTMCC is expected to increase in coming years as more is revealed about its potentials.

**Keywords:** biodegradable polymer; biomaterials; poly(trimethylene carbonate-co-caprolactone); DDS; bone disease

## 1. Introduction

Drug delivery refers to various methods of carrying active ingredient of therapeutic agents to the diseased site or cells through systemic administration or local release safely to achieve their desired therapeutic effect (Tiwari *et al*. 2012). However, some of them produce severe side effects due to the lack of adequate delivery of a drug to the pharmacological target; therefore, the benefit does not always outweigh the risk (Liebler and Guengerich 2005). Beside producing severe side effects, some drugs are deemed almost worthless *in vivo* because of the inability to withstand endogenous enzymes, although they showed significant effectiveness *in vitro* (Rostami-Hodjegan and Tucker

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2007). In addition, the effectiveness of drug delivery is affected by the particle size of drugs, its solubility, diffusion, and release process (Aguilar 2012). Since conventional methods of drug delivery have limitations such as low-efficiency rate, poor biodistribution and poor selectivity (Saman and Iqbal 2019), the design and synthesis of efficient Drug Delivery Systems (DDS) to overcome these problems is crucial for medicine and healthcare. Although designing and synthesizing effective drug molecules with their target has taken the DDS to an advanced level, a lot is still needed to improve the DDS and targeting. The use of appropriate biomaterials, for example, may introduce improvement as drug carriers.

Use of biomaterials in biomedical applications has seen a strong and exponentially increasing demand globally. The global market for implantable biomaterials, for instance, was nearly $96.11 billion in 2017. It is expected that implantable biomaterials demand would increase by 8.2% Compounds Annual Growth Rate (CAGR), resulting in its global market value of $195.47 billion in 2026 (R&M 2018). Among the implantable biomaterials, the polymeric implantable biomaterials sector is expected to show the highest growth, at a CAGR of 22.1%, because of its promising potential in a wide range of biomedical applications (Song *et al*. 2018). Polymers are one of the multifarious essential biomaterials that have a vital role in biomedical applications including implant, DDS, scaffold, cell proliferation and others. As they have biocompatible, flexible and biodegradable properties, polymers are being used routinely in surgical sutures, tissue engineering scaffolds, medical implants and drug-eluting devices (Damodaran *et al*. 2016).

An emerging biomaterial that would be suitable for DDS that has biocompatibility, biodegradability and rubber-like properties is Poly(TriMethylene Carbonate-co-Caprolactone) (PTMCC) (Zhu *et al*. 1991). It is readily usable for the fabrication of different drug formats and shaped with desired mechanical strength and degradation properties for the drug (Zurita *et al*. 2006). Since PTMCC has been shown to be processable in a variety of shapes and forms, including porous conduits (Vleggeert-Lankamp *et al*. 2008) and electrospun fibers (Rocha *et al*. 2014), its flexibility presents itself as a valuable tool as a drug carrier in the design of new strategies, such as to form beads for application in the treatment of osteomyelitis. In this review, we focus on the synthesis process, characterization, degradation behavior and possible biomedical applications of PTMCC.

## 2. Mechanical model

A wide range of different polymers is currently marketed. These can be obtained from either natural or synthetic resources. The former includes collagen, silks, alginate and chitosan whereas the latter includes poly(methylmethacrylate), poly(ethylene), poly(propylene), poly-(tetrafluoroethylene) and poly(vinyl chloride) (Fig. 1). Although natural polymers were the first biodegradable scaffold materials and have good interactions with various cell types with negligible toxicity, synthetic polymers have recently attracted great interest for biomedical applications because of their broad-spectrum and reproducible physicochemical and mechanical properties such as tensile strength, elastic modulus, highly controllable and consistent degradation rate (Gentile *et al*. 2014, Maitz 2015, Stratton *et al*. 2016). The functional and desirable shape of synthetic polymers could be based on the monomer units, polymerization reaction and formation of copolymers consisting of different components at adjustable concentrations that have a vital role in DDS in transporting active components of drugs to the target site (Aguilar 2012, Maitz 2015).

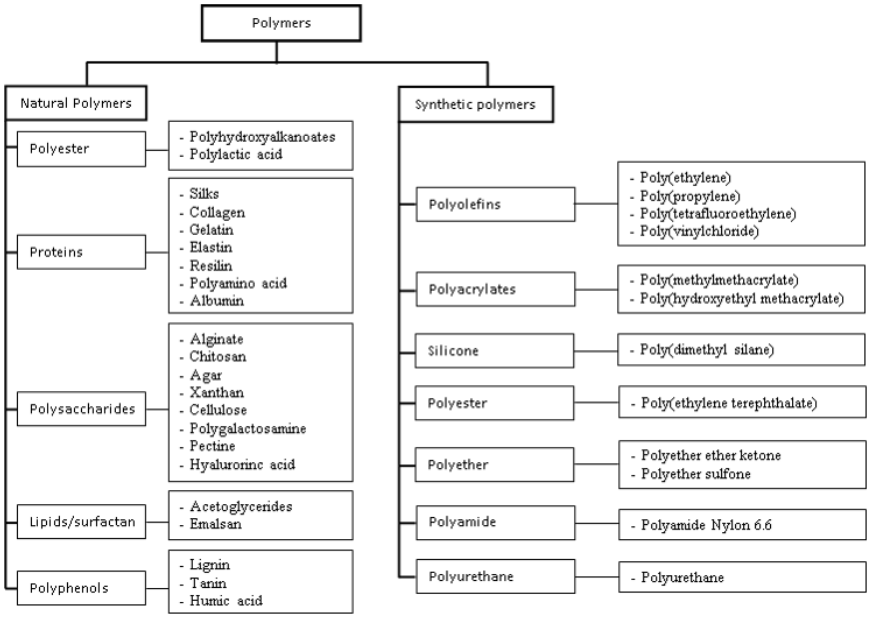



Fig. 1 Classification of polymers. Adapted from (Maitz 2015)

## 3. Use of synthetic biodegradable polymer in biomedical applications

While the use of natural polymer in biomedical applications started thousands of years back, the use of synthetic polymer is relatively new. Synthetic polymers had been used as implants in the form of degradable pins, screws, rods, and small plates since the 1960s (Ulery *et al*. 2011). Then, synthetic polymer started to be used as implant-carriers of antibiotics for local delivery in the 1990s (Garvin *et al*. 1994, Kanellakopoulou *et al*. 1999). The preference of synthetic biodegradable polymer over natural polymer increased rapidly because of the possibility of large-scale production at low cost, reproducibility with longer shelf-life, synthesizing for specific applications and better functionality (Bertrand and Leroux 2012, Dhandayuthapani *et al*. 2011, Ozdil and Aydin 2014).

Synthetic polymers can be biodegradable and non-biodegradable. Biodegradable polymers are more viable as alternatives to natural polymers. The most attractive properties of biodegradable polymers, namely biocompatibility and complete physical clearance from the body, have got considerable interest as DDS design for biomedical applications such as local and controlled delivery of antibiotics and proteins (Burnham 1994), temporary fracture fixation devices (Boontheekul and Mooney 2003, Chen and Mooney 2003, Zisch *et al*. 2003), temporary three-Dimensional (3D) scaffolds in tissue engineering (Griffith 2002, Park *et al*. 2002, Podual *et al*. 1997), nerve guides (Langer and Peppas 2003, Pires *et al*. 2013, Yannas *et al*. 1982) and delivery of genes (Anderson *et al*. 2003, Hwang and Davis 2001, Putnam *et al*. 2001). There are many biodegradable polymers that have already been investigated for sustained release of drugs such as polyparadioxanone, poly(D, L-lactic) acid (PLA) and polyglycolic acid (PGA), polydilactide (PDL) and poly(D, L-lactide-co-glycolide) (PLGA) (Rebelo *et al*. 2017). They have shown better-sustained release modulated by bulk erosion. The degradation products are acidic, causing bone resorption. In zero-order release, the release of drugs is constant for an extended period at optimal conditions, which can be seen when antibiotic is released following surface erosion (Kluin *et al*. 2009, 2013,

2016, Neut *et al*. 2009).

## 4. PTMCC

PTMCC is an intended copolymerized biodegradable polymer to be used in biomedical applications with improved mechanical properties. It is a derivative of poly(trimethylene carbonate) (PTMC). The flexible and rubbery PTMC polymer is copolymerized with a semi-crystalline poly(caprolactone) (PCL) polymer to produce PTMCC. PTMC has been one of the most extensively studied polycarbonate polymers because of its well-documented biocompatibility, biodegradability, and rubber-like properties (Han *et al*. 2010, Yang *et al*. 2014). However, its poor mechanical strength and less predictable degradation rate initiated moves to modulate the physical properties and degradation rate of PTMC. Since copolymerization synthesis process can alter the physical properties and degradation rate of specific biodegradable polymers, PTMCC was produced through the ring-opening polymerization process in order to use for biomedical applications (Pêgo *et al*. 2001, 2002, 2003b, 2003c, Schappacher *et al*. 2001).

### *4.1 Appearance and form*

The appearance of PTMCC ranges from colorless to yellow or white to yellow. These forms could either be solid or chunks (Sigma 2019).

### *4.2 Chemical formula and structure*

The linear formula and chemical structure of PTMCC is shown in Fig. 2.

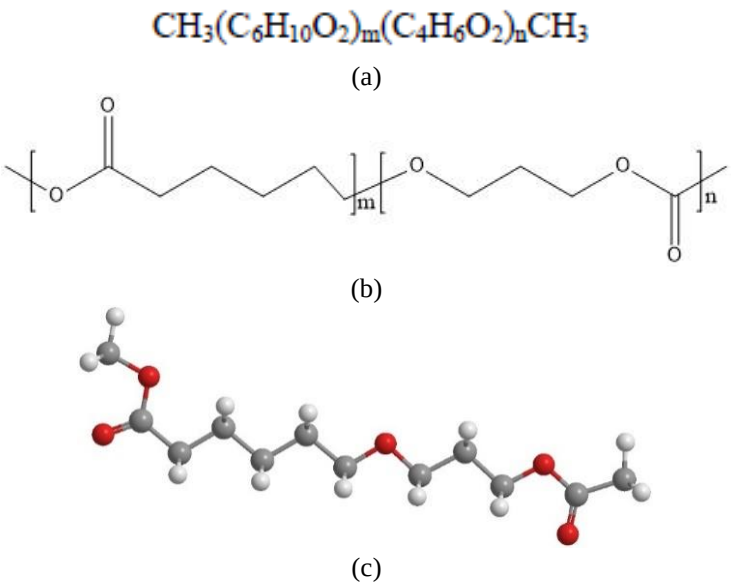



Fig. 2 Linear formula (a) chemical structural (b) (Sigma 2019) and (c) 3D structure of PTMCC. 3D structure was generated from liner formula (Sigma 2019) using ChemDraw Professional 16

### *4.3 Crystallinity*

Based on the ratio of copolymerized compounds, PTMCC can either be amorphous or semi-crystalline. PTMCC becomes amorphous when the homopolymer and the copolymers contain 39-59% PTMC, whereas it becomes semi-crystalline while the homopolymer and the copolymers contain 13-18% PTMC (Bat *et al*. 2013). Hence, flexibility increases with an increased percent of PTMC. The surface erosion behavior is dependent on the nature of copolymerization. Generally, the amorphous compound is more erosive than the crystalline polymer (Grijpma *et al*. 2010). Therefore, the copolymerization of PTMCC is designed based on the desired DDS.

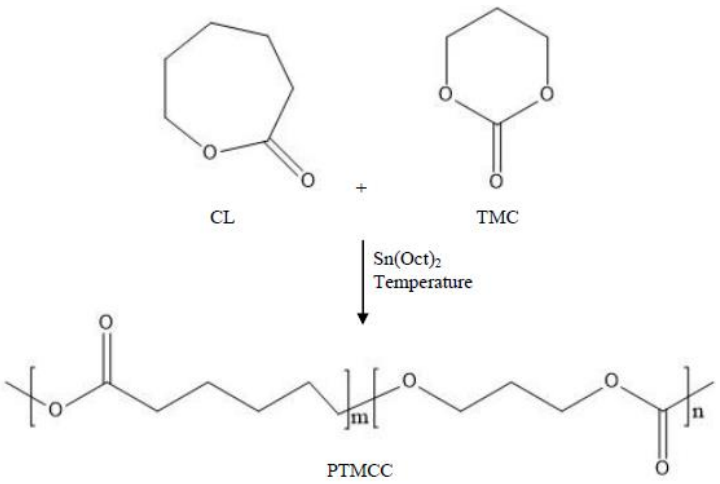
### *4.4 Solubility*

PTMCC is soluble in chloroform, methylene chloride, benzene and tetrahydrofuran, but is insoluble in water, alcohols and ether.

### *4.5 Synthesis*

PTMCC was synthesized by ring-opening polymerization of dried trimethylene carbonate (TMC) with a distilled ε-caprolactone (CL) to glass ampoules under nitrogen atmosphere (Scheme 1) (Bat *et al*. 2008, Yang *et al*. 2012).

A general procedure of PTMCC synthesis is shown in Fig. 3. Initially, both TMC and CL were added to glass ampoules under nitrogen atmosphere. Then a catalyst was added to the mixture to initiate the reaction. The ampoules were then purged three times with dry nitrogen and heat-sealed under vacuum. The mixture was conditioned in an oil bath preheated to the polymerization temperature (most cases 130°C), and vigorous shaking is required to obtain a homogenous mixture of the monomers and the catalyst. The copolymerization time and temperature varied from author to author (Table 1). After the reaction time, the ampoules need to quench to room temperature and discharge the polymer. Finally, the synthesized products must be dissolved in dissolution solvent,




Scheme 1 Schematic ring-opening copolymerization of TMC and CL in the presence of $Sn(Oct)_2$ catalysts to produce PTMCC

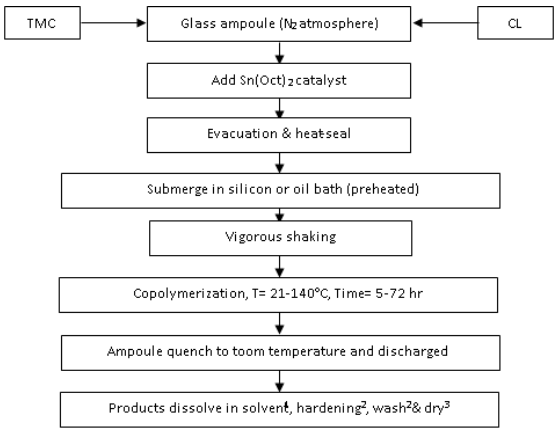



Fig. 3 A general synthesis procedure of PTMCC. [1]Dichloromethane/chloroform, [2]methanol/ethanol/isopropyl alcohol/hexane, [3]room temperature/25°C/60°C for until constant weight

Table 1 Conditions of PTMCC synthesis by ring-opening polymerization of PTMC and CL

| Catalyst | Submerge | CoPT (°C) | Duration (hr) | Dissolution solvent | Hardening solvent | Washing solvent | Drying | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dryer (pressure) | T (°C) | Time |
| [1]$Sn(Oct)_2$/ $ZnAc_2$/ $Bu_2SnO$ | Oil bath | 80-120 | 5-24 | DCM | Methanol | Methanol | 10 mm Hg | RT | UCW |
| [2]$Sn(Oct)_2$ | Oil bath | 120 | 5 | DCM | Methanol | NR | Vacuum | 25 | UCW |
| [3]$Sn(Oct)_2$ | Oil bath | 130±2 | 72 | $CHCl_3$ | 10× methanol | Methanol | Vacuum | RT | UCW |
| [4]Isopropoxide (initiator) | NR | RT | NR | DCM | Cold methanol | NR | NR | NR | NR |
| [5]$Sn(Oct)_2$ | Oil bath | 130±2 | 72 | $CHCl_3$ | 10× IPA | IPA | Vacuum | RT | UCW |
| [6]$Sn(Oct)_2$ | Silicone bath | 140 | 36 | DCM | Methanol | NR | Vacuum | 60 | 48 h |
| [7]$Sm(BH_4)_3(thf)_3$ | NR | 21 | 3-4 | DCM | Cold methanol | NR | Vacuum | 25 | UCW |
| [8]$Sn(Oct)_2$ | NR | 130±2 | 72 | $CHCl_3$ | 10× ethanol | Ethanol | Vacuum | RT | NR |
| [9]$Sn(Oct)_2$, Hexanediol (initiator) | NR | 130 | 72 | $CHCl_3$ | Ethanol/ hexane | Ethanol/ hexane | Vacuum | RT | NR |
| [10]$Sn(Oct)_2$ | Oil bath | 130±2 | 24 | $CHCl_3$ | Excess methanol | Methanol | Vacuum | 37 | UCW |
| [11]$Sn(Oct)_2$ | NR | 130±2 | 72 | $CHCl_3$ | Ethanol | Ethanol | Vacuum | RT | NR |
| [12]$Sn(Oct)_2$ | NR | 130 | 24 | DCM | Methanol/ hexane | NR | NR | NR | NR |

CoPT: Copolymerization temperature, DCM: Dichloromethane, IPA: Isopropyl alcohol, RT: Room temperature, UCW: Until constant weight, NR: Not reported. [1]Albertsson and Eklund 1994, [2]Albertsson and Eklund 1995, [3]Pêgo *et al.* 2001, [4]Schappacher *et al.* 2001, [5]Pêgo *et al*. 2002, [6]Hu and Zhu 2003, [7]Palard *et al.* 2007, [8]Bat *et al.* 2008, [9]Grijpma *et al*. 2010, [10]Yang *et al.* 2012, [11]Bat *et al*. 2013, [12]Hofmann *et al*. 2013

hardened in precipitation medium, and dried until constant weight (Albertsson and Eklund 1995, Bat *et al*. 2008, 2013, Grijpma *et al*. 2010, Hofmann *et al*. 2013, Hu and Zhu 2003, Pêgo *et al*. 2001, 2002, Yang *et al*. 2012).

### *4.6 PTMCC characterization*

The characterization of a polymer is important if it is a newly synthesized material like PTMCC, or if it is a competitive product that is being evaluated, or if the performance of the material needs to be improved (Rancourt 2019). The characterization includes both molecular characterizations and macroscopic property measurement. Molecular characterizations include molecular weight and degree of crystallinity, whereas macroscopic property measurement includes thermal properties, mechanical properties, microstructural information and the time dependence of properties (Marković *et al*. 2016). Characterization of these properties is crucial to ensure the desired functionality as well as the capability of resynthesizing. This is especially important to produce implant that involves encapsulation of active pharmaceutical ingredients. Depending on the desired properties of the final products, different experimental approaches could be applied to determine the properties of a material and selection of appropriate techniques including using a different catalyst, changing of solvent and temperature (Table 2).

The characterization of PTMCC was performed using a variety of experimental approaches. $^{1}$H Nuclear Magnetic Resonance (NMR) and/or $^{13}$C Nuclear Magnetic Resonance ($^{13}$C-NMR), for instance, have been used to check the chemical compositions where $CdCl_3$ was used as a solvent. Pires *et al*. (2013) reported that they had found 11% mol of TMC in synthesized PTMCC, which is in accordance with the monomer ratio charged (10% mol TMC) used in the synthesis process.

Size exclusion chromatography (i.e., Gel Permeation Chromatography, GPC) using chloroform as the mobile phase could be used to determine molecular weight (*Mw*) of the polymer. The average molecular weight was found to be $8.2\times10^4$ g/mol, and the Polydispersity Index (PDI) was 1.61 in PTMCC (Pires *et al*. 2013). The degradation of PTMCC was also determined and quantified using Gas Chromatography-Mass Spectrometry (GC-MS). The degradation rate was reported $3.1\times10^{-3}$ day$^{-1}$ (curve fit $r$=0.98) (Albertsson and Eklund 1995).

The viscosity of the copolymers was measured using viscometer at a concentration of 0.6 g/dl using tetrahydrofuran as solvent at 30°C and intrinsic viscosity was calculated by the one-point method (Eq. (1)) and expressed in dl/g (Hu and Zhu 2003)

$$[\eta] = [2 \times \left(\frac{\eta}{\eta_0} - 1 - \ln\frac{\eta}{\eta_0}\right)]^{1/2} / c \quad (1)$$

where, $\eta$=viscosity of the polymer solution, and $\eta_0$=viscosity of the copolymer the solvent.
There was a relationship of viscosity with temperature and polymerization time. If the temperature increased beyond the optimum polymerization temperature (140-160°C), the viscosity decreased, and thermal degradation should account for this phenomenon (Barrera *et al*. 1995). The polymerization time should be controlled to a certain level. Otherwise, the copolymer composition could have differed from that of the monomer feed. Hu and Shu (2003) reported that in less than 20 h, copolymer composition differed from that of the monomer feed even though the inherent viscosity reach 0.621 and the conversion ratio could be relatively lower (78%). After 36 h, the yield and viscosity could decrease due to thermal degradation and trans-esterification. However, the catalyst concentration had no apparent effect on the yield and viscosity.

The DSC and FTIR were used to assess the physical stability and chemical compatibility of

PTMCC. The FTIR spectrum of PTMCC showed characteristic stretching bands at about 2963 $cm^{-1}$ attributed to $-CH_2-$, 1736 $cm^{-1}$ attributed to ester C=O and the unique ester C=O indicates that there is no block structure in the products and copolymers are random (Fig. 4). According to the DSC test, all the copolymers showed a single glass transition temperature ranging from -65.1°C for PCL to -16.2°C for PTMC, confirming the random nature of the copolymers because block copolymer has two $T_{gs}$. Besides, the general tendency is that the glass transition temperature ($T_g$) decreased while increasing the content of CL unit (Yang *et al*. 2012).

Table 2 Characterization of PTMCC using standard techniques

| Characteristics | Standard techniques for characterization of polymer[†] | Specific feature |
|---|---|---|
| Molecular weight analysis | [1]Colligative property measurements | Freezing point depression, boiling point elevation, vapor pressure lowering, and osmotic pressure |
| | [2]Light scattering techniques | Diffusive processes in soft matter |
| | [3]Size exclusion chromatograph (Gel Permeation Chromatography (GPC) | Polymer's hydrodynamic volume [$\overline{M}n$, $\overline{M}w$, PDI] |
| | [1]Dilute Solution Viscosity Testing (DSV) | Relative, inherent, or intrinsic viscosity |
| | [1]Melt Flow Index testing (MFI) | Flows of a polymer when melted |
| Molecular structure | [4]Fourier Transform Infrared Spectroscopy (FTIR) | Chemical composition |
| | [5]Nuclear Magnetic Resonance Spectroscopy (NMR) | Organic chemical components [$^1$H NMR (using $CdCl_3$); $^1$H NMR, $^{13}$C NMR (using $Cd_2Cl_2$ or $CdCl_3$)] |
| | [1]Electron Paramagnetic Resonance (EPR) or Electron Spin Resonance (ESR) | Unpaired electrons |
| | [1]X-ray crystallography | Atomic and molecular structure of crystal |
| Morphology | [6]Scanning Electron Microscopy (SEM) | Particle sizes and elemental composition |
| | [1]Transmission Electron Microscopy (TEM) | Phase distribution of copolymer, blend |
| | [7]Atomic Force Microscopy (AFM) | Surface roughness, phase separation, surface aging studies, nanoparticle dispersion |
| | [1]Confocal Laser Scanning Microscopy (CLSM) | 3-dimesional images of formulation and particles from optical sections |
| Thermal properties | [8]Differential Scanning Calorimetry (DSC) | Heat capacity [glass-transition temperatures (*Tg*), peak melting temperatures and melting enthalpies] |
| | [1]Rheology Testing | Melt viscosity, creep, stress relaxation responses of polymers as functions of time, temperature, and force |
| | [9]Thermogravimetric Analysis (TGA) | Thermal stability and compositional information such as presence of fillers and carbon black |
| | [1]Dynamic Mechanical testing (DMA) | Mechanical properties of a sample as a function of temperature and frequency simultaneously |

Table 2 Continued

| | | |
|---|---|---|
| Mechanical properties | [10]Tensile testing | The loss in mechanical strength as a function of use, accelerated aging or chemical exposure |
| | [1]Flexural testing | Mechanical property degradation because of product use, accelerated aging or response to chemical exposure |
| | [1]Compression testing | Mechanical property degradation because of product use, accelerated aging or response to chemical exposure |
| | [11]Durometer testing | Hardness |
| | [1]Specific gravity, density determination | Identify a material or follow physical changes, such as the degree of uniformity or variability or the average density of a large item |

†These are the standard techniques used to characterize polymer. Adapted from (Marković *et al*. 2016, Rancourt 2019). NIR: No implementation reported for this technique for the characterization of PTMCC. PTMCC: [1]NIR, [2]Hofmann *et al*. 2013, [3]Albertsson and Eklund 1995, Bat *et al*. 2008, 2010, 2013, Pêgo *et al*. 2001, Rocha *et al*. 2014, Yang *et al*. 2012, 2014, [4]Han *et al*. 2010, Yang *et al*. 2012, [5]Albertsson and Eklund 1995, Bat *et al*. 2008, 2010, 2013, Palard *et al*. 2007, Pêgo *et al*. 2001, Pires *et al*. 2013, Rocha *et al*. 2014, Schappacher *et al*. 2001, Yang *et al*. 2012, 2014, [6]Albertsson and Eklund 1995, Bat *et al*. 2013, Han *et al*. 2010, Pires *et al*. 2013, [7]Rocha *et al*. 2014, [8]Albertsson and Eklund 1995, Bat *et al*. 2008, 2013, Han *et al*. 2010, Schappacher *et al*. 2001, Yang *et al*. 2012, 2014, [9]Yang *et al*. 2014, [10]ASTM-D 882-91 (Bat *et al*. 2008, 2010, 2013, Pêgo *et al*. 2001, Zhang *et al*. 2006) ASTM-D1990-95 (Zhang *et al*. 2006), [11]ASTM-D 882-91 (Bat *et al*. 2008, 2010, 2013)

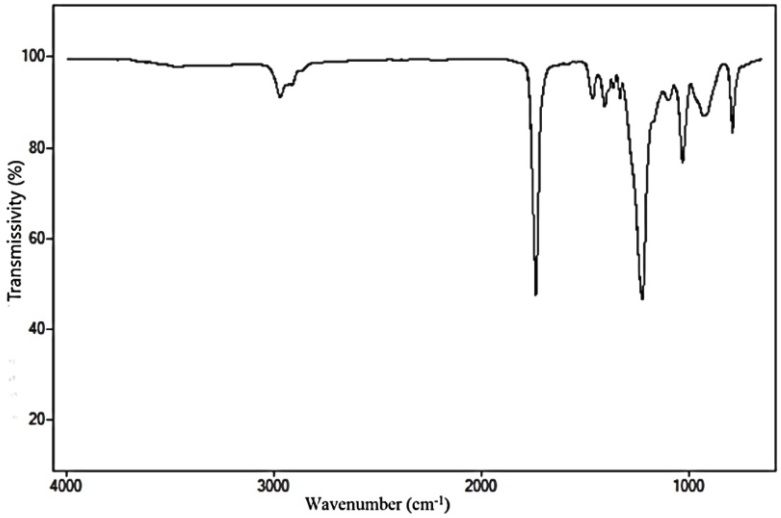



Fig. 4 FTIR spectrum of PTMCC (Authors own results, not published yet)

Water content and static contact angle of distilled water on the polymer surface were determined to evaluate the hydrophilicity. In this case, the polymer film needs to soak in distilled water. The

Table 3 Mechanical properties of PTMCC in comparison to PTMC and CL (Yang *et al*. 2012)

| | | *TMC:CL monomer | $M_n$ | | Young's modulus ($E^b$) | Tensile stress ($\sigma_m{}^c$) | Tensile strain ($\varepsilon_m{}^d$) | Tensile stress at break ($\sigma_b{}^e$) | Tensile strain at break ($\varepsilon_b{}^f$) |
|---|---|---|---|---|---|---|---|---|---|
| No. | Polymer | mol % | $\times 10^5$ | MWD | MPa | MPa | % | MPa | % |
| 1 | PTMC | 100:0 | 2.85 | 1.08 | 9.50 | 18.08 | 941.64 | 10.41 | 915.71 |
| 2 | PTMCC | 90:10 | 2.66 | 1.10 | 9.17 | 2.98 | 1325.80 | 2.14 | 1326.10 |
| 3 | PTMCC | 70:30 | 2.51 | 1.11 | 4.51 | 1.00 | 116.57 | 0.85 | 157.73 |
| 4 | PTMCC | 50:50 | 2.53 | 1.11 | 2.75 | 0.58 | 86.32 | 0.43 | 125.80 |
| 5 | PTMCC | 30:70 | 2.34 | 1.13 | 2.26 | 0.37 | 55.28 | 0.03 | 1267.49 |
| 6 | PTMCC | 10:90 | 2.50 | 1.11 | 143.16 | 23.91 | 1029.10 | 20.22 | 1209.56 |
| 7 | PCL | 0:100 | 2.80 | 1.08 | 261.61 | 27.67 | 825.93 | 25.17 | 826.56 |

*Copolymers were compressed moulded into 2 mm thick films at 130°C. MWD: Molecular weight distribution, PTMC: Poly(trimethylene carbonate), PTMCC: Poly(trimethylene carbonate-co-caprolactone), PCL: Poly(caprolactone)

static angle measured by a contact-angle meter, and it needs to measure at least five different regions of the polymer sample at room temperature (Hu and Zhu 2003). The static contact angle for PTMCC was around 62°-68°, whereas that of PCL was nearly 78° (Schappacher *et al*. 2001). The static contact angle decreased slightly with the increase of TMC content and reached to a plateau at the PTMCC (47/53 mol %). The high values for the static contact angles indicate relatively hydrophobic polymer surfaces, and vice versa (Pego *et al*. 2001). A very low water uptake was observed since the water absorption reached equilibrium after 24 hours and there were no significant changes observed in the water content of the samples after 30 days. It is noted that an increased water uptake (maximum of 1.3%) was reported for PTMCC (31/69 mol %) due to a decrease in crystallinity and water uptake remained constant for higher TMC contents (Pego *et al*. 2001).

#### *4.6.1 Thermal and mechanical properties*

The thermal stabilities of copolymers were detected with TGA. The thermal stabilities of PTMCC was good as discerned from results that showed the temperatures at which the initial weight loss occurred (*Td*) were greater than 280°C and *Td* increased with the increasing number of CL unit. However, with the increasing CL contents in PTMCC, the crystallinity state had changed from amorphous (above 20 mol % TMC) to semicrystal (less than 20 mol % TMC) (Yang *et al*. 2012).

A Reger tester was used to measure the mechanical properties of polymer films. Mechanical properties can influence the effectiveness of biomaterial products since they can affect or regulate the fundamental cellular programs, particularly cell proliferation, migration, and differentiation. The mechanical properties of compression-moulded PTMCC, as well as its comparison to the corresponding homopolymers, are listed in Table 3 (Yang *et al*. 2012). The data indicated that thermal processing had no significant effect on the polymer molecular weights. Moreover, none of the polymers suffered thermal degradation under the applied processing conditions (130°C for 24 hr and feeding dose). In the PTMCC, an increasing amount of cross-linker was determined, which lead to an increase of modulus and decrease in elongation at break (Yang *et al*. 2013). The mechanical properties of PTMCC suggested that the network among the monomers is an elastic and flexible

biomaterial that would be potential for subcutaneous implants.

### *4.7 Degradation of PTMCC*

Polymer degradation refers to the eventual cleavage of the chain into the monomers. On the other hand, erosion denotes the mass loss of the material from the bulk. Biodegradable polymers follow either the mode of bulk erosion process or surface erosion (Nam *et al*. 2004). Some polymers such as PTMCC follows both erosion process based on the number of copolymer compositions and local physicochemical conditions. During surface erosion process, loss of the device occurs only on the surface, resulting in the decrement in the size of the device (Fig. 5a). On the contrary, for bulk erosion process, immediate *Mw* loss is observed because of the proceeding degradation process throughout the polymer matrix, where the mass loss is retarded (Fig. 5b).

#### *4.7.1 In vitro hydrolytic degradation*

Degradation of polymer over time relates to how much drug is releasing to the target site. Yang *et al*. (2014) studied *in vitro* hydrolytic degradation behavior of PTMCC at pH 7.4 PBS and reported that no significant mass loss was observed for PTMCC before ten weeks. The mass loss increased gradually with degradation time. The extremely slow degradation observed while PTMC and CL ratio was 75/25 mol % in the copolymerization, and mass loss was only 5.17±0.28% at 50 weeks. However, when the mol % of CL was increased in the copolymer, the mass loss significantly increased to 18.30±2.00% (50/50 mol %) and 40.73±4.54% (30/70 mol %) after 50 weeks degradation in PBS. Similar results were also observed by other researchers (Albertsson and Eklund 1995, Pêgo *et al*. 2002, Yang *et al*. 2016).

Decreasing *Mw* of PTMCC to 140 KD was faster (20 weeks) in the copolymer that contains the least amount of PTMC. In contrast, the highest mol % of PTMC containing copolymers showed slowest *Mw* declination to 140 KD by 50 weeks (Yang *et al*. 2014). This data supports the slow degradation of PTMC, as reported by other researchers (Pêgo *et al*. 2002, 2003b, Yang *et al*. 2016). Molecular weight distribution (MWD) drastically decreased to 70 KD after 30, and 40 weeks for PTMCC (30/70 mol %) and (50/50 mol %) respectively, indicating that <70 KD PTMCC could be thoroughly dissolved in PBS (Yang *et al*. 2014). Because of the least *Mw* loss and slowest mass loss of PTMCC (70/30 mol %), its MWD change was less than the other compositions. However, a

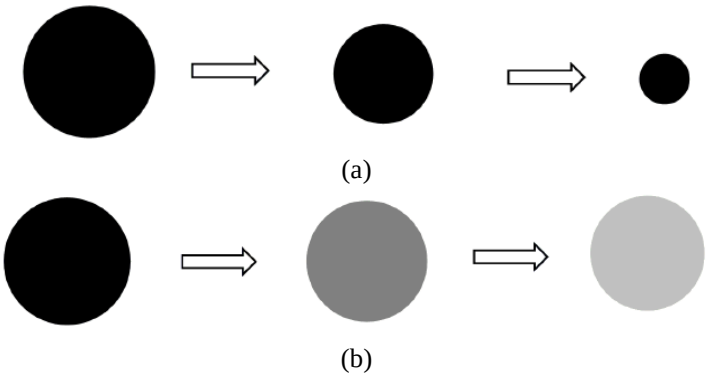



Fig. 5 Schematic illustration of the degradation process of polymer (a) surface erosion and (b) bulk erosion Adapted from Nam *et al*. (2004)

continuous increase of MWD from 1.12 to 1.25 was observed during degradation, which might be attributed due to the higher molecular weight of the residual samples (>138 KD) (Yang *et al*. 2014). Furthermore, remaining mol % of TMC increased significantly during *in vitro* PBS degradation and PTMCC (30/70 mol %) presented the most significant increase in TMC content, indicating CL loss was more compared to TMC, which is supported by a previous study (Pêgo *et al*. 2003b, c).

Degradation of polymers can be observed in two modes: by surface erosion and bulk degradation (Fig. 5). Loss of mass indicates surface erosion, and reducing *Mw* determines bulk degradation. However, in the case of PTMCC, both surface erosion and bulk degradation was observed simultaneously after ten weeks in an *in vitro* study (Yang *et al*. 2014). Mass loss only occurs after exceeding the threshold level of decreasing *Mw* in aliphatic polyesters, which is entirely different when observed in the hydrolysis of PTMCC (Ali *et al*. 1993). This is because the ester linkages in solid polymer specimens are more susceptible to hydrolysis (Fig. 6) than carbonate linkages (Albertsson and Eklund 1995). Moreover, the stability of low mol % of CL containing copolymers was poor, therefore, it is not recommended to long-term use, for example, as a contraceptive (Pitt *et al*. 1981, Yang *et al*. 2014).

### *4.7.2 In vitro enzymatic degradation*

An *in vitro* enzymatic test is recommended test before performing *in vivo* test in order to mimic the biological conditions. Zhang *et al*. (2006) reported *in vitro* enzymatic degradation of PTMCC in lipase solutions in PBS (37°C with gentle shaking and pH 7.4) that mimic the local implantation environment (Fig. 6). A similar study conducted by Yang *et al*. (2014) concluded that the copolymers containing higher CL content had a higher mass loss. They found that even though *Mw* of PTMCC (50/50 mol %) decreased with degradation both with and without lipase, a decrease in *Mw* was faster in enzymolysis than in hydrolysis. In PTMCC (50/50 mol %), enzymolysis took only 12 days to decrease *Mw* to 164 KD while hydrolysis was achieved after 140 days. A similar pattern was observed for mass loss of PTMCC (50/50 mol %), where 18.3% mass loss occurred after 52 weeks in PBS at 37°C (with gentle shaking) in the absence of lipase and after 9 days of degradation in the present of lipase (Yang *et al*. 2014). This result indicates the degradation rate (in terms of mass loss) of the hydrolysis and the enzymolysis processes is 0.057% and 2.07% per day, respectively. It can be concluded that lipase accelerates the degradation of PTMCC, hastening the dispersal of degraded products into surrounding media by acting as a surfactant (Hou *et al*. 2017). This role of lipase can also be confirmed from the outcomes of narrower MWD production through the degradation of PTMCC in lipase medium compared to the hydrolysis medium

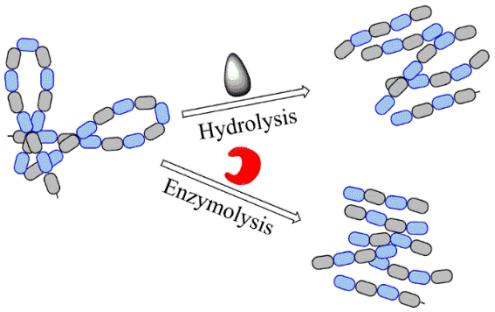



Fig. 6 Schematic illustration of the *in vitro* hydrolysis degradation of PTMCC. Adapted from Zhang *et al*. (2006)

(Yang *et al*. 2014). Therefore, it can be concluded that the degradation of PTMCC relies on the loss of the degradation products that could be accelerated by lipase.

#### *4.7.3 In vivo degradation*

A few *in vivo* degradations of PTMCC have already been reported in recent years. Yang *et al*. (2014) reported that a significant mass loss of PTMCC occurred only after 32 weeks. The mass loss of PTMCC (75/25 % mol) and PTMCC (50/50 % mol) was 37.56% and 50.82%, respectively after 32 weeks. PTMCC (30/70 % mol), a semi-crystalline copolymer, showed extreme slow mass loss (1.84%) at 32 weeks. Similar results were also reported by Pêgo *et al*. (2002), who observed the degradation of PTMCC (11/89 % mol) to 6% mass loss after 52 weeks.

The degradation of PTMCC (30/70 % mol) was faster in *in vitro* degradation process in the presence of lipase, and it is supposed to be the same or even hastened in *in vivo* conditions since there are some other enzymes such as esterases and lipases. However, a slower degradation rate was observed in the *in vivo* conditions compared to the hydrolysis degradation (Pêgo *et al*. 2002, Yang *et al*. 2014). This phenomenon is indicating that cellular-mediated mechanisms did not play a role in the degradation of PTMCC, whereas hydrolysis degradation plays a pivotal role in the degradation of copolymers implanted *in vivo* conditions. Moreover, there is a possibility to form fibrous capsules around the implants that hindered the degradation of PTMCC (Pêgo *et al*. 2003b, c). The change of *Mw* to 180 KD, 160 KD, and 150 KD for PTMCC (75/25 % mol), PTMCC (50/50 % mol), and PTMCC (30/70 % mol), respectively was observed after 32 weeks of implantation in the back of rat animal models. The form-stability of the PTMCC rods implanted in the back of rats was poor. The shape of the retrieved device was no longer cylindrical; instead, the polymers changed to oblate spheres (Fig. 7). Therefore, it has been concluded that the mass loss and *Mw* of PTMCC is prolonged with the degradation of copolymer while CL percentage is less than the PTMC.

## 5. Biomedical applications

As PTMCC is relatively new for biomedical applications, very few information is available presently. Albertsson and Eklund (1994), the pioneers who synthesized PTMCC, had only studied mechanical and thermal properties, and later, *in vitro* degradability reporting comparatively higher degradation than PTMC (Albertsson and Eklund 1995). After this, the cytocompatibility of PTMCC (50:50 % mole) was investigated, and no significant sign of toxicity was observed in direct and indirect cytocompatibility tests (Fabre *et al*. 2001). For tissue engineering, in which the supporting materials usually need to retain a certain level of mechanical properties for more than a few months,

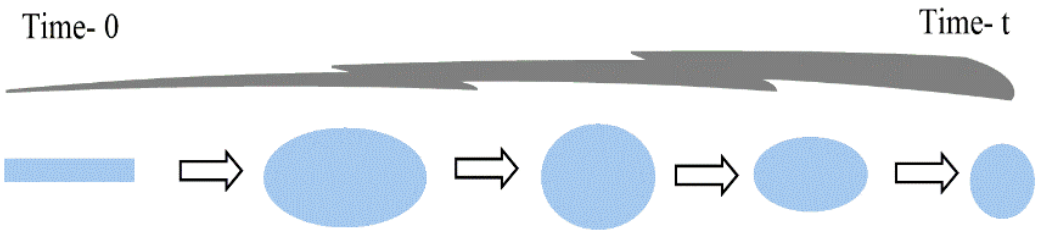



Fig. 7 Schematic illustration of microscopic observation of PTMCC degradation and shape change over time *in vivo* conditions. Adapted from Yang *et al*. (2014)

PTMCC could be appropriate as scaffold biomaterials because of its controlled degradation nature that typically has less effect on the mechanical characteristics of the polymer during the healing process. In view of the degradation behavior of PTMCC, it holds the potential to become a good quality DDS when use with encapsulation of nanoparticles. The general prediction of control drug release of PTMCC is illustrated in Fig. 8. In this case, the PTMCC will lose the mass and *Mw* slowly and release the drugs at the same rate as weight loss. However, when an anti-inflammatory drug, ibuprofen was encapsulated with electrospun PTMCC fibers, it exhibited burst release and 100% release within 24 hr (Pires *et al*. 2013).

### *5.1 Nerve regeneration*

Cell proliferation has been studied using PTMCC as peripheral nerve grafting (Fabre *et al*. 2001). *In vitro* Schwann cells (derived from 3 months old fisher rats) were exposed to pieces of PTMCC to evaluate the cell proliferation to form nerve conduits useful for treating nerve injuries (Feijen *et al*. 2003). It was concluded that it improved the efficiency of peripheral nerve grafting (Fig. 9). In addition, they observed no adverse chronic inflammatory reaction in implanted PTMCC in the rat model even after 60 days of implantation (Fabre *et al*. 2001). Therefore, it has been recommended that this nerve conduit could be potentially use as an alternative for nerve repair. On the other hand, PTMCC (82 % mol PTMC) has been used as an adhesion surface for the growth of Human Schwann Cells (HSCs) that could be utilized in the development of artificial nerve graft (Pêgo *et al*. 2003a). HSCs adhered and proliferated faster and in a higher number on the PTMCC (Pêgo *et al*. 2003b, c). These results demonstrated that PTMCC could be used for the preparation of flexible and slowly degrading nerve guides. In another report, the authors applied PTMCC in the preparation of nerve conduits, which facilitated nerve regeneration. Since PTMCC copolymer is biodegradable and biocompatible, and its degradation rate can be adjusted using different percentages of copolymer composition, it is suitable for the preparation of short- and long-term degradable devices for soft tissue engineering and DDS (Pêgo *et al*. 2003b, c). Thereafter, PTMCC was processed into porous two-ply tubes by means of salt leaching (inner layer) and fiber winding (outer layer) techniques and

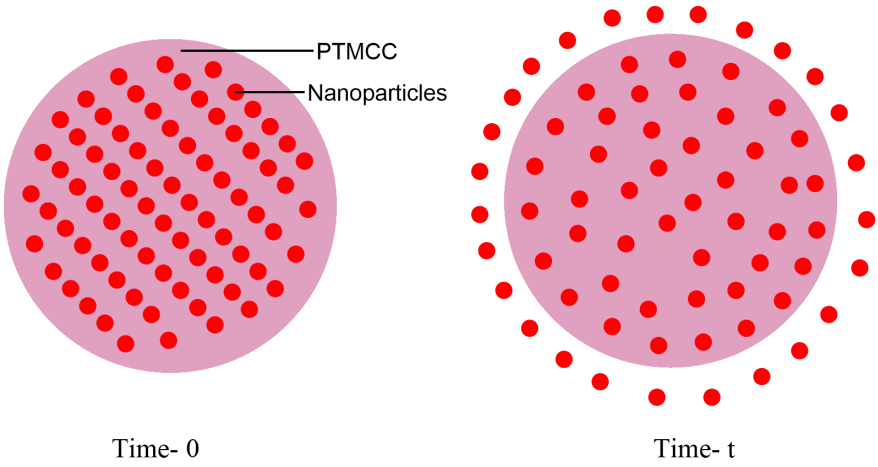



Fig. 8 A predictive schematic representation of control drug release of PTMCC as adapted from Gavasane and Pawar (2014)

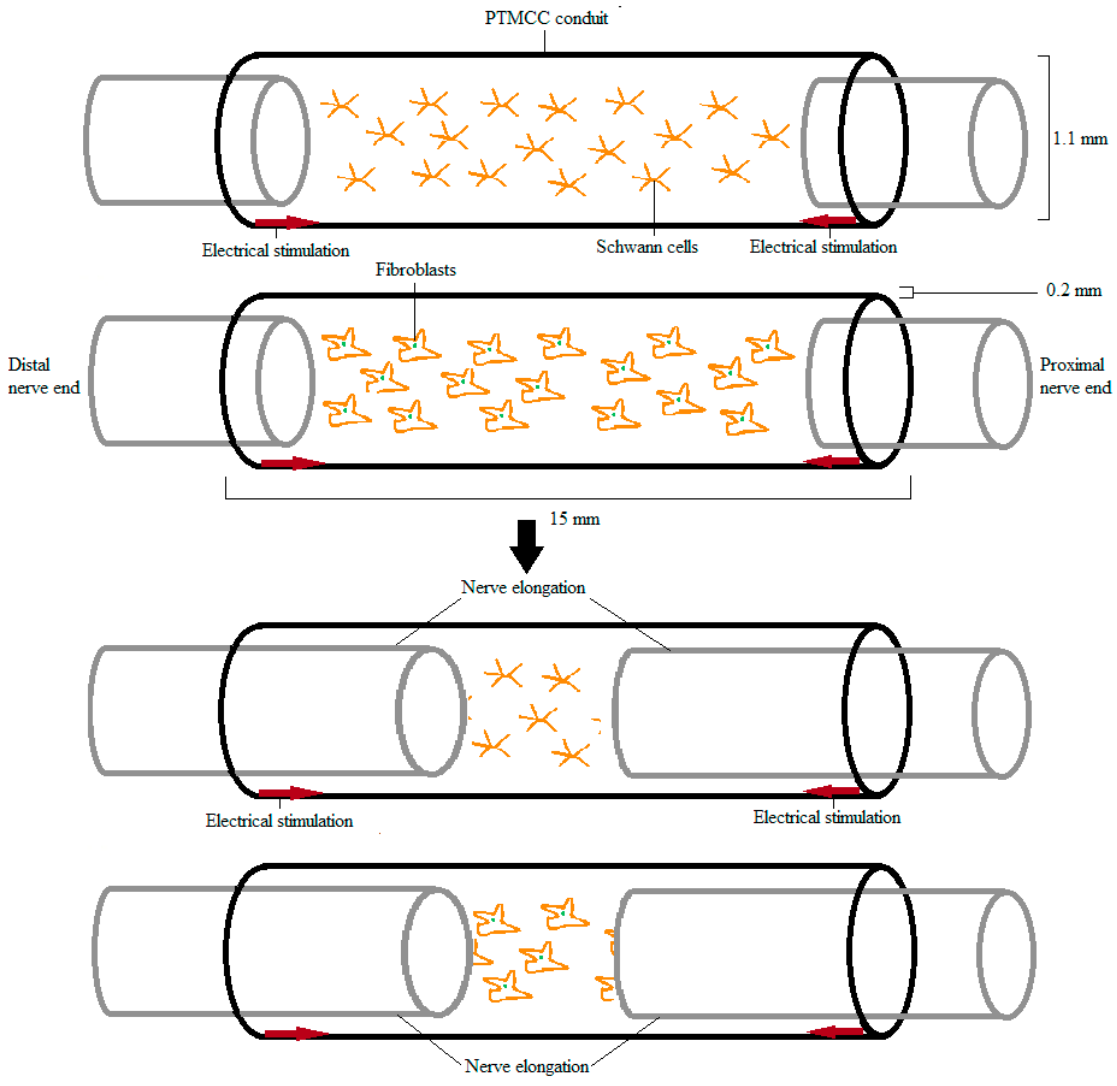



Fig. 9 Schematic illustration of PTMCC nerve conduit to support nerve regeneration. A slowly biodegradable polymer permits axon regrowth through the proximal and distal sutures of the guide. It can deliver small molecules favorable for nerve repair. Adapted from Fabre *et al*. (2001)

used as nerve guides for the bridging of significant peripheral nerve defects (Pêgo *et al*. 2003a). Vleggeert-Lankamp *et al*. (2008) also reported an *in vivo* study that PTMCC can support peripheral nerve regeneration.

The product of copolymerization of PTMC and CL (11:89 % mol) is also a promising material for the Central Nervous System (CNS) regenerative applications. Rocha *et al*. (2014) have used PTMCC as substrates of spinal cord regeneration and successfully demonstrated that PTMCC is capable of significant neuronal polarization and axonal elongation. It can also promote axonal growth if Myelin-Associated Inhibitors (MAIs) are present at a spinal cord lesion. As surface

mechanical properties of PTMCC can mediate Glycogen Synthase Kinase 3β (GSK3β) activity, consequently increasing the level of phosphor-collapse in response mediator protein 4 (phosphor-CRMP4), neurite outgrowth and elongation could be mediated (Rocha *et al*. 2014). In the context of CNS regeneration, Pires *et al*. (2013) also reported that if PTMCC used as a substrate for microglia cells, it has a positive impact on the microglia-mediated phagocytosis of myelin thus promoting the tissue regeneration of injured CNS significantly.

A few studies also reported on PTMCC electrospun fibers, which hold immense potential in the field of nerve regeneration. Ibuprofen was incorporated in PTMCC electrospun fibers to serve as DDS to enhance axonal regeneration of nerve cells as well as limit inflammatory response against spinal cord lesion (Pires *et al.* 2013). The drug-loading efficiency of PTMCC was above 80%, and it was released within 24 hr drug dissolution test. Biological drug released was investigated on the human-derived macrophages and reported that the amount of prostaglandin $E_2$ was reduced in the cell culture medium, indicating the biological significance as DDS of ibuprofen-loaded PTMCC electrospun fibers. Therefore, PTMCC-based nerve conduits with anti-inflammatory properties can be used for nerve regeneration. Pires *et al.* (2017) also developed an easily implantable bi-layer polymeric patch based on PTMCC-loaded with ibuprofen by electrospinning. They demonstrated *in vitro* that fibrous or flat PTMCC films provide cues that may guide microglia, the resident immune cells of the CNS, towards a pro-regenerative profile. Moreover, it showed that these homogenously drug-loaded fibrous structures mediated the release of ibuprofen over 24 h, yielding fibers with anti-inflammatory properties.

### *5.2 Other biomedical applications*

PTMCC is a material that can be processed in a variety of shapes and forms. In a recent preliminary study, Hossain *et al.* (2019) formulated PTMCC beads loaded with Gentamicin sulphate-*Nigella sativa* oil Emulsion (GNE). They reported sustained antibacterial activities against different strains of *Staphylococcus aureus*, including osteomyelitis causing strain. Therefore, they suggested that these beads can potentially be used shortly for the local delivery of drugs as implant beads for osteomyelitis. An interesting feature of the beads is that it is pliable even after manufacturing, while maintaining its overall integrity, which would enable modification as plug to cover bone crevices.

PTMCC can also be processed into porous conduits and electrospun fibers that could be a valuable tool in the design of new strategies for application in the treatment of spinal cord lesions, while supporting axonal growth and taming myelin dependent neurite outgrowth inhibitions without the need of the administration of any therapeutic drug (Rocha *et al.* 2014).

Due to the slow degradation nature of PTMCC, as apparent from *in vivo* studies, it could be a potential DDS for a contraceptive agent for long term or a specific period of birth control. Depending on the overall properties of PTMCC it can be predicted that this polymer can be potentially used for the following applications as well: suture coating, orthopedic implants, tissue repair, hybrid tissue-engineered heart valves, cardiac patches, vascular grafts, adhesion barriers, dural substitutes, stents, ear implants and tissue or cell engineering scaffolds.

The findings from the above discussion suggested that PTMCC has many advantages as biomaterials to be used as DDS or any other biomedical applications. Firstly, it's *in vitro* and *in vivo* degradation rates could readily be tuned by adjusting both the molecular weight and the composition. Secondly, due to having tuneable degradation rates and rubbery properties, this polymer is well suited for clinical applications, for example, long-term contraceptive implants. Thirdly, its thermal

stability and biocompatibility are excellent, therefore, it can be used for control release systems. Last but not least, PTMCC could be processed into porous scaffolds with different shapes, pore sizes and porosities, and these properties make it suitable for culturing in different cell types. Therefore, this polymer would be an excellent candidate for use in soft tissue engineering.

## 6. Conclusions

PTMCC is a biocompatible and biodegradable polymer, and to date, it has limited application in the biomedical arena. Considering its physical, mechanical and chemical properties, it could be a suitable candidate as a drug carrier for local delivery, especially for musculoskeletal-related diseases, for example, osteomyelitis. It would prolong the controlled release of antibiotics locally due to its extremely slow degradation nature *in vivo*.

As PTMCC's physical and chemical properties can be controlled by manipulating the amount of PTMC and CL in the synthesis process, the improvement of PTMCC is still possible depending on the target diseases pathogenicity. Additionally, the modified PTMCC is still easy to use for *in vitro*, *in vivo* and subsequent clinical testing. This polymer materials could be loaded with numerous drugs such as anti-inflammatory drugs (i.e., ibuprofen), antimicrobial drugs (i.e., gentamicin, vancomycin, etc.) for various biomedical applications. Additionally, the release kinetics of PTMCC is morphology dependent (Pires *et al.* 2013). Hence it would be interesting to design DDS based on the disease nature and treatment mechanism.

The use of PTMCC as a regenerative tool and targeted DDS is expected to increase in foreseeable future. Another use includes as drug carrier like an implant to deliver drugs and antibiotics since its biodegradation properties have good utilities as control released DDS. In the near future, based on the regulating capabilities and formulation of PTMCC, nano-formulations of PTMCC could be further developed for many diseases like arthritis, bone infections, diabetes and even cancer. It is necessary to understand and take full advantage of the specific characteristics of the main chain of PTMCC, such as elasticity, hydrolysis resistance, properties of hydration, biocompatibility and non-generation of acidic degradation products. It is only then the PTMCC can be considered as DDS. It is also essential to determine new characteristics observed only in the PTMCC, which is attractive as a biodegradable functional biomaterial over other polymers with the same structural side chain.

## Author contributions

Conceptualization, MSH and MAMS; writing—original draft preparation, MSH; review and editing, MAMS and FM; supervision, MAMS and FM; project administration, MSH; funding acquisition, MAMS.

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## Conflicts of interest

The authors declared no conflict of interest.

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## Abbreviations

| | |
|---|---|
| 3D | Three-dimensional |
| AFM | Atomic force microscopy |
| CL | ε-caprolactone |
| CLSM | Confocal laser scanning microscopy |
| CNS | Central nervous system |
| DDS | Drug delivery system |
| DMA | Dynamic mechanical testing |
| DSC | Differential scanning calorimetry |
| DSV | Dilute solution viscosity testing |
| EPR | Electron paramagnetic resonance |
| ESR | Electron spin resonance |
| FTIR | Fourier transform infrared spectroscopy |
| GC-MS | Gas chromatography-mass spectrometry |
| GNE | Gentamicin sulphate-*Nigella sativa* oil as an emulsion |
| GPC | Gel permeation chromatography |
| GSK3β | Glycogen synthase kinase 3β |
| KD | Kilo Dalton |
| MAIs | Myelin-associated inhibitors |
| MFI | Melt flow index testing |
| *Mw* | Molecular weight |
| MWD | Molecular weight distribution |
| NMR | Nuclear magnetic resonance |
| PBS | Phosphate buffer solution |
| PCL | Poly(caprolactone) |
| PDI | Polydispersity index |
| PTMC | Poly(trimethylene carbonate) |
| PTMCC | Poly(trimethylene carbonate-co-caprolactone) |
| RT | Room temperature |
| SEM | Scanning electron microscopy |
| TEM | Transmission electron microscopy |
| *Tg* | Glass-transition temperatures |
| TGA | Thermogravimetric analysis |
| TMC | Trimethylene carbonate |
| UCW | Until constant weight |