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Synthesis of Four-Arms Star-Shaped PCL-b-PEG as a Potential Amphiphilic Hydrogel

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ABSTRACT

Hydrogel formulations have drawbacks in delivering hydrophobic drugs which can aJect its effciency. Introducing amphiphilic system into hydrogel can overcome this limitation and increase hydrogel effectiveness as a drug cargo. In this study, four arms star-shaped block copolymers with polyethylene glycol (PEG) as hydrophilic block and polycaprolactone (PCL) as hydrophobic block were synthesized via a combination of ring- opening polymerisation (ROP) and Steglich esterification. The structures were confirmed by ^{1}H-NMR and FTIR analysis. The polydispersity index (PDI) indices from gas permeation chromatography (GPC) were 1.3 to 1.6, suggesting controlled polymerisation reaction occurred. Average molecular weight analysis, Mn based on ^{1}H-NMR are close to the theoretical value. However, there is a slight difference of Mn between GPC and proton analysis due to the ability of GPC determining Mn for the star-shaped polymer. Both star-shaped polymers possess high thermal stability (>350 °C) based on thermal decomposition study using TGA analysis. The presence of PEG had increased the hydrophilicity and solubility of the PCL in the hydrogel since an opaque homogeneous formulation form when using the amphiphilic star-shaped polymer. The pH (7.25 ± 0.03) and viscosity (9330 cP) of the formulation are set within the compatibility and suitable for human skin and topical application.

Keywords: *PCL-PEG star-shaped polymer; ring-opening polymerisation; hydrogel formulation*

INTRODUCTION

Application of polymers in drug delivery system has gained significant worldwide interest ever since the rapid development of polymer science and modern biochemistry [1-5]. Polymers of different types and architectures have been developed to provide various functions towards the desired applications in drug delivery system. Functional multi-block copolymers, branched macromolecules, dendrimers with a wide variety of characteristics have opened up new possibilities in biomedical applications [6,7]. Star-shaped polymer with the architecture of branched polymer chains around a multifunctional core is one of the best candidates for delivering hydrophobic drug. Its architecture, constituting of hydrophobic and hydrophilic polymers provides useful properties such as protection of drug from premature degradation, elimination of additional surfactants in drug formulations and opportunities for controlled and targeted delivery [8]. The length of hydrophobic block determines the stability, drug encapsulation and also drug release kinetics [9]. Drug encapsulation capability of the synthesized star polymer is expected to increase with relative hydrophobic segment in the polymeric system.

Polyester-polyether type of amphiphilic star-shaped polymers, specifically polycaprolactone-poly(ethylene glycol), (PCL-PEG), has attracted much attention due to its potential to be used in wound treatment and controlled drug release application. This type of amphiphilic polymer gives an advantage in increasing the encapsulation of hydrophobic drug via hydrophobic-hydrophobic interaction or conjugation of drug with PCL [10,11]. The hydrophilic part, PEG, will increase the solubility of the drug cargo for human use [12,13]. Kim et al. [14] prepared three arms star-shaped polymers consisting of hydrophobic PCL core with hydrophilic PEG outer shell. The star-shaped polymer was prepared via arm-first method where the ROP of s-caprolactone was initiated by PEG. Subsequently, the polymeric arm was then attached to 1,3,5-benzenetricarboxylic acid, producing the star-shaped polymer. Wang et al. [15] prepared star-shaped copolymer of PCL-PEG with polyamidoamine dendrimer (PAMAM) that contained 16 arms as the inner core. After ring-opening polymerisation of

s-caprolactone with the PAMAM as co-initiator, the PEG outer shell was attached to the PCL terminus by an ester-forming reaction. In another study, four arms star-shaped PCL-PEO block copolymers were synthesized using diethylzinc catalyst for the ring-opening polymerisation of s-caprolactone with pentaerythritol as multifunctional macroinitiator. The star-shaped PCL polymer was then used for ring-opening polymerisation of ethylene oxide [16]. Choi et al. [17] synthesized star-shaped polymer with PEG in inner shell and PCL within the outer segment. Three and four arms star-shaped polymers of PEG were produced using metallated trimethylolpropane, (TMP) and pentaerythritol as initiator respectively.

Hydrogels are three dimensional, cross-linked structures composed of hydrophilic homopolymers or co-polymers network, with the tendency to imbibe water and swell when placed in an aqueous environment [18,19]. Both synthetic and natural hydrogels or their combinations have huge potential in various applications such as in tissue-engineering scaffolds, drug cargo devices and wound healing [20,21]. In bio-application, a hydrogel is preferable since it resembles natural living tissue more than any other types of synthetic biomaterial due to high water content [22]. Hydrogels also contain a porous network that gives advantages in drug loading and drug release capacity for drug delivery devices. They are mostly studied as drug delivery cargo, particularly in biomedical applications. Protein, peptides, drugs and tissue growth factor can all be delivered via hydrogel drug cargo.

Because a large number of newly develop drugs are hydrophobic in nature, they possess limited applications in hydrogel drug delivery system due to their solubility problems. However, incorporating an amphiphilic polymeric system into hydrogel can immensely improve the hydrogel system, especially in entrapment and drug release profile of hydrophobic drugs [23]. The correlation between the polymer, drugs and the targeted area and solubility play important roles in producing a perfect drug delivery system. The hydrophilic system has limited capacity in carrying hydrophobic drugs due to the limited homogeneity of loaded hydrophobic drugs in the system matrices [24]. However, the hydrophilic polymer part can increase the solubility of the hydrophobic fragment in a hydrogel formulation. On the other hand, the use of hydrophobic polymer to increase lipophilic drug loading poses a problem in producing a water-soluble drug delivery system [24]. In such a way, both hydrophilic and hydrophobic part complement each other to produce high-performance drug delivery system.

In this work, we prepared hydrogel formulation incorporated with an amphiphilic star-shaped block copolymer of polycaprolactone-polyethylene glycol with carbomer as a gelling agent. The star-shaped polymer consists of hydrophobic biodegradable PCL in the inner segment and hydrophilic PEG in the outer segment of the polymer architecture. The amphiphilic polymer architecture is selected for the system to be homogeneously dispersed in the hydrogel formulations. The presence of the star-shaped polymer in the hydrogel is believed to increase the capability of the hydrogel formulation as a drug delivery cargo.

MATERIALS AND METHOD

Material and Reagents

s-caprolactone, succinic anhydride, pentaerythritol, 4-(dimethylamino) pyridine, (DMAP) and 1,3-dicyclohexylcarbodiimide, (DCC) were purchased from Acros Organics and were used without further purification. Stannous octoate, $Sn(Oct)_2$, were purchased from Sigma-Aldrich. Succinylated methoxy-polyethylene glycol, (mPEG-COOH) (Mw=5000) was prepared according to the published report [26]. Methylparaben and ethylparaben were purchased from Merck. Pvt. Ltd., and triethanolamine (TEA) was purchased from Q-rec. All other chemicals and solvents were purchased from Merck, and of analytical reagent (AR) grade.

Synthesis of Four-rms Star-Shaped PCL (4Star PCL) and Star-Shaped Diblock PCL-PEG (4Star PCL-PEG)

The 4Star PCL was synthesized by ring-opening polymerisation method. S-caprolactone (10 g, 0.095 mol), pentaerythritol (32.7 mg, 0.27 mmol) (35:1) were mixed and heated at 110 °C. Subsequently, Sn(Oct)2 (0.005 g, 0.1 mmol) was added to the mixture, and the vial was sealed and maintained at 110 °C for 24 hours. After cooling to room temperature, the polymer was precipitated in cold diethyl ether to give a white powder and dried under vacuum for 48 hours. mPEG-COOH (0.54 g, 0.1 mmol), DMAP (24 mg, 0.2 mmol), DCC (41 mg, 0.2 mmol) and 4Star PCL(1.08 g, 0.025 mmol) were dissolved in 10 mL of methylene chloride. The reaction was carried out at room temperature for 48 hours under nitrogen.

Dicylcohexylcarbodiurea by-product was removed by filtration. Afterwards, the polymer product was precipitated with cold diethyl ether and dried at ambient temperature for 48 hours.

Characterisation of 4Star PCL-PEG Copolymer

Gel permeation chromatograms, GPC were measured on WATERS GPC system calibrated with narrowly distributed polystyrenes. Tetrahydrofuran (THF) standard GPC solvent was used to dilute and run the samples. ^{1}H-NMR spectra were measured using Bruker Avance III 500 MHz in chloroform-d, CDC_{l3}. The chemical shift was calibrated using a standard solution of tetramethylsilane. The FTIR analysis was performed on Perkin-Elmer Spectrum 400 FTIR/FT-NIR instrument. All the FTIR spectra were the product of an average of 50 scans at a resolution of 4 cm^{-1}. Thermogravimetric TGA/DTG analysis of the synthesized polymers was carried out using Mettler Toledo Thermogravimetric Analyzer. A heating rate of 10 ºC and a crucible of aluminum containing 5 mg of sample were used for the TGA analysis.

Preparation of Hydrogel

The hydrogel formulation was selected at desired component ratios. The preparation of hydrogel was performed by adding the weighed components together and stirred until it formed homogenous hydrogel. The carbomer resin was added in 15 mL deionised water and stirred until it was well-dispersed (12 hours). Then, 4Star PCL-PEG copolymer was dissolved in the mixture solvent for 12 hours and subsequently, ciprofloxacin was added and stirred for 12 hours to make sure the mixture was homogenous. The mixture was then neutralised by dropwise addition of trimethylamine, TEA.

Physical Analysis of Hydrogel

The pH of formulation was measured by pH meter (Mettler Toledo). The pH meter was calibrated with the standard buffer solution. The pH meter was dipped into the formulation until the final pH reading was obtained. The measurement of pH was done in triplicate, and the average values were reported. Digital viscometer (Viscometer Brookfield) was used to measure

the viscosity of the gel using spindle level 4 with rotation at 50 rpm. The formulation was allowed to settle over 30 minutes before the measurement was taken. The measurement of viscosity was done in triplicate, and the average values were reported.

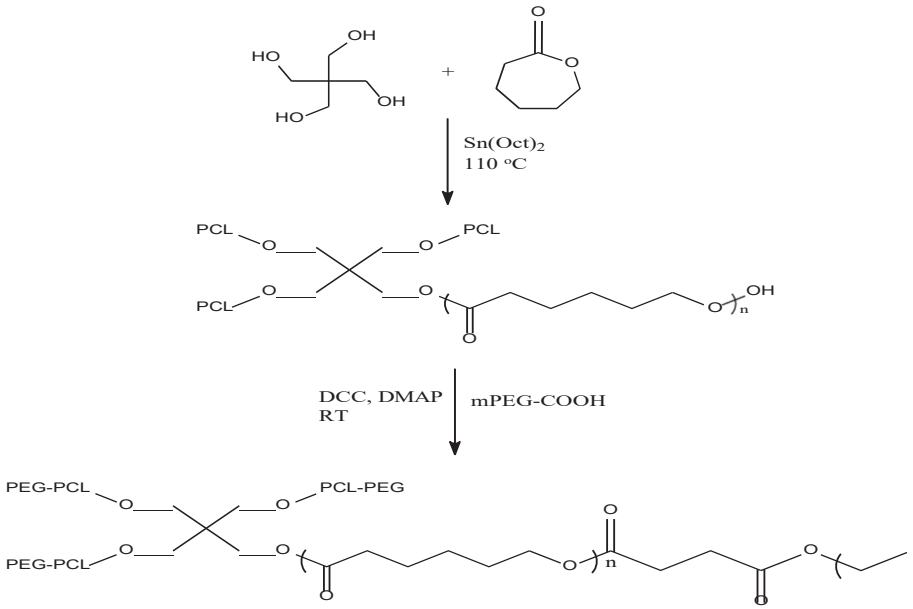
Physical Evaluation of Hydrogel

All developed hydrogel formulations were characterised for homogeneity assessment. This was done by visual inspection of the gel's settlement in suitable containers. The gels were analysed for their appearance and existence of any clog. The formulations were inspected visually for their colour, homogeneity, consistency, and phase separation. In addition, pH values, colour, physical appearance, and texture were also measured after 12 weeks of preparation.

RESULTS AND DISCUSSION

Synthesis and Characterisation of PCL-b-PEG Star-Shaped Polymer

Four arm star-shaped block copolymer was synthesized by a two-step synthetic procedure using the 'core-first approach' as depicted in Scheme 1. The star homopolymer PCL with hydroxyl end-group was first obtained via ring-opening polymerisation (ROP) of s-caprolactone in bulk initiated by pentaerythritol catalysed by $Sn(Oct)_2$. The selection of the reaction temperature (110 °C) is to reduce the formation of side products particularly cyclic polymer by reducing the propagation rate and enhancing the accessibility of hydroxyl group of both initiators in the initiation step [25]. The ratio of s-caprolactone/hydroxyl was varied to obtain star-shaped polymers with different PCL block lengths, assuming an almost quantitative conversion of the monomer. The 4Star PCL-PEG was assumed to have a well-defined four-arm star structure because the functionality of the end hydroxyl groups of the initiator and PCL are the same [26]. Both star-shaped polymers were in white precipitate form with 88% yield. The polymer composition, structure and molecular weight were characterised by FTIR, ^{1}H-NMR and GPC analysis.



Scheme 1: Schematic Route for the Preparation of Four Arms Star-Shaped Polymer

Figure 1 shows the FTIR spectra for both star-shaped homopolymer PCL (a) and block copolymer PCL-PEG (b), respectively. The appearance of C=O stretching around 1720 cm-^{1} and C-O stretch band at around 1172 cm-^{1} indicates the presence of ester group within the polymer backbone, indicating the occurrence of ROP of s-caprolactone cyclic (Figure 1a). The C-H band of methyl group of the PCL polymer chain is around 2943 and 2865 cm-^{1} for 4Star polymer. The intensity of the hydroxyl band was obscured, indicating low content of –OH functional group in the compound [27]. The FTIR of the block copolymer (Figure 1b) shows a band at 1167 cm-^{1} which was due to C-O-C stretching vibrations of the repeated –OCH_2CH_2 units, consistent with the addition of PEG ether unit. The C=O band stretching of 4Star PCL-PEG appeared at 1720 cm-^{1} and bands for C-H stretching appeared at 1294 and 2865 cm-^{1}. C-O-C and –COO- functional groups for the PCL polymer backbone in the block copolymer appeared at 1279 cm-^{1} and 1101 cm-^{1} respectively. Differences in the band for two main functional group, C=O and C-O between homopolymer PCL and block polymer indicating the presence of mPEG in the star-shaped copolymer.

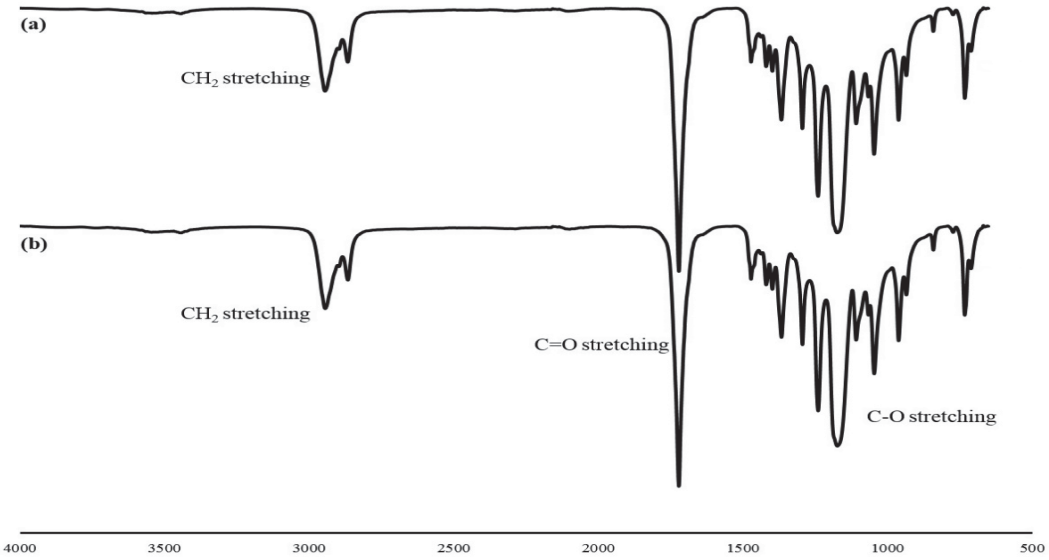


Figure 1: FTIR Spectra of a) 4Star PCL and b) 4Star PCL-PEG

^{1}H-NMR spectra of the homopolymer PCL and block copolymer are shown in Figure 2a and Figure 2b, respectively. The polymer backbone of PCL was represented by the multiplets (Figure 2a) at chemical shifts between 1.3 to 2.4 ppms [(m, -CH_2-),(t, -CH_2-)]. Meanwhile, the chemical shifts at 4.05 ppm and 3.6 ppm are for the ether group (t, -CH_2-O-) and terminal end-group (t, -CH_2-OH), respectively. All pentaerythritol arms have the same hydroxyl functional group that can initiate ROP. Thus, it is assumed that each of the initiator's arms experienced ROP, forming equal 4Star PCL arms. In Figure 2b, a triplet at 2.65 ppm denotes the methylene group linker (t, -$COCH_2CH_2CO$-) between inner segment PCL and outer segment PEG of the polymeric system. A singlet at 3.4 ppm is associated with the methylene group for the end terminal in mPEG while chemical shifts between 3.5 to 3.7 ppm denote poly(ethylene glycol) backbone (m, -$OCH_2CH_2OCH_3$) indicating the successful coupling of PEG and PCL. The disappearance of PCL end-group peak from the spectrum signifies the formation of block star-shaped copolymer.

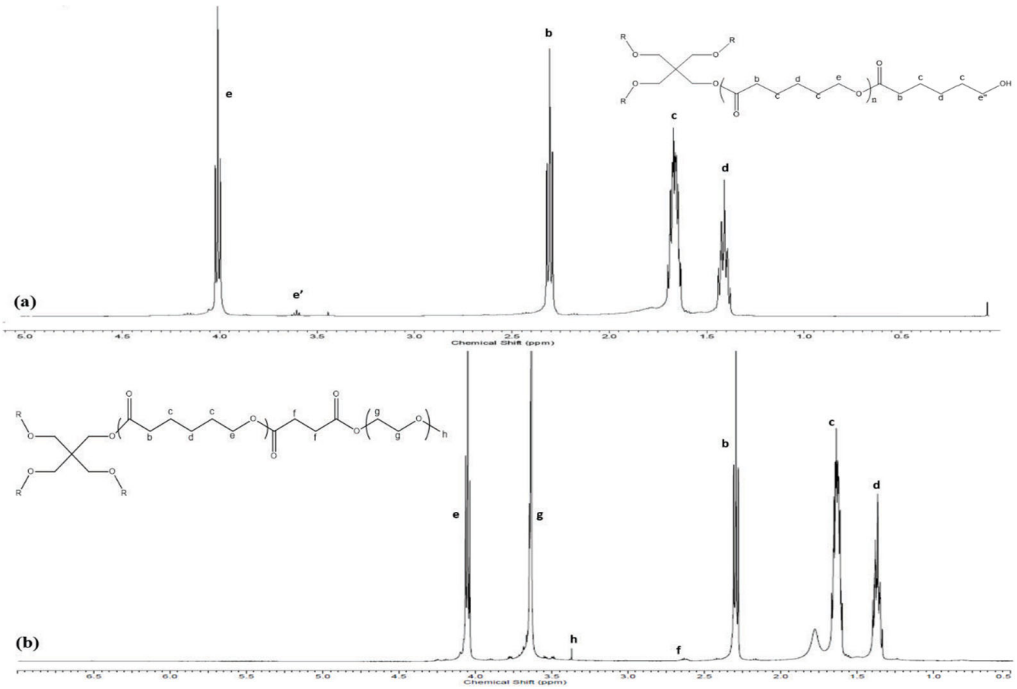


Figure 2: ^{1}H-NMR Spectra of a) 4Star PCL and b) 4Star PCL-PEG

The molecular weight of the star-shaped polymers was determined using ^{1}H-NMR spectroscopy and GPC analysis [28,29]. The ^{1}H-NMR spectroscopy was used to determine the degree of polymerisation, (DP) of caprolactone as well as the determination of molecular weight, (Mn) for the star polymer. The molecular weight of the 4Star PCL homopolymer was calculated from the ratio of the methylene group from the PCL backbone to the peak area of the hydroxyl end group (Figure 2). One mPEG molecule of the star-shaped block copolymer per arm was assumed for each molecule. Therefore, a ratio of the mPEG signal to a signal from the PCL segments was used to calculate Mn for the copolymers. The molecular weight was determined from the ratio peak of the area at 2.31 ppm to the peak area of ethylene group between two ester groups at 2.64 ppm. The results of all samples on polydispersity indexes (PDI) and molecular weights are listed in Table 1.

Since the reported Mn values were close to the theoretical values, and the observed polydispersity indices from GPC were narrow, the polymerisation of s-caprolactone was indeed controlled. From this result, it can be concluded that minimal transesterification or backbiting reaction occurred during copolymerisation and that the polymerisation occurred symmetrically on the different arms [30].

Table 1: Molecular Weight Characteristic of Star-Shaped Polymers

Sample	[a]$M_{n,theoretical}$	[b]DP_{star}	[b]$M_{n,NMR}$	[c]$M_{n,GPC}$	PDI
4Star PCL	40100	95	42100	55100	1.3
4Star PCL-PEG	61000	89	60100	48300	1.5

[a]Theoretical M_n was determined from monomers feed ratio. [b]Calculated from ^{1}H-NMR spectra. [c]Obtained from GPC

The M_n values determined by GPC were higher compared to those calculated theoretical value or calculation via ^{1}H-NMR ratio. These results similarly observed by others in the synthesis of polyester star-shaped polymers [31,32]. This is due to the limitation of GPC in the separation of star-shaped polymers compared to linear polymer and the effect of hydrodynamic volume of star-shaped polymers which is considered independent to the number of arms, on the assumption that all of the arms have the same molecular weight in GPC analysis [33]. Furthermore, the calibration standard used in GPC is a linear polymer standard which may affect the final result. Thermal stability analysis of both polymers using TGA showed decomposition occurred at an initial temperature within the range of 328-353 °C signifying high thermal stability (Table 2).

Table 2: TGA Results of 4Star PCL and 4Star PCL-PEG

Sample	$T_{d\text{-}initial}$ (°C)	$T_{d\text{-}max}$ (°C)
4Star PCL	328.7	356.6
4Star PCL-PEG	353.6	409.2

$T_{d\text{-}initial}$ = temperature at which 2% of weight loss was measured, $T_{d\text{-}max}$ = temperatures of maximum decomposition obtained from DTG thermograms

The presence of mPEG in the amphiphilic polymer system slightly increased the thermal stability of the star-shaped polymer compared to the star-shaped homopolymer PCL due to the more stable end-group which required more energy to decompose (Figure 3). Star copolymers have stable chain terminal groups (-OCH_3), leading to a higher thermal stability compared to star PCL homopolymers which has lower thermal stability due to hydroxyl terminal end group (-OH), that are prone to rapid thermal degradation [15].

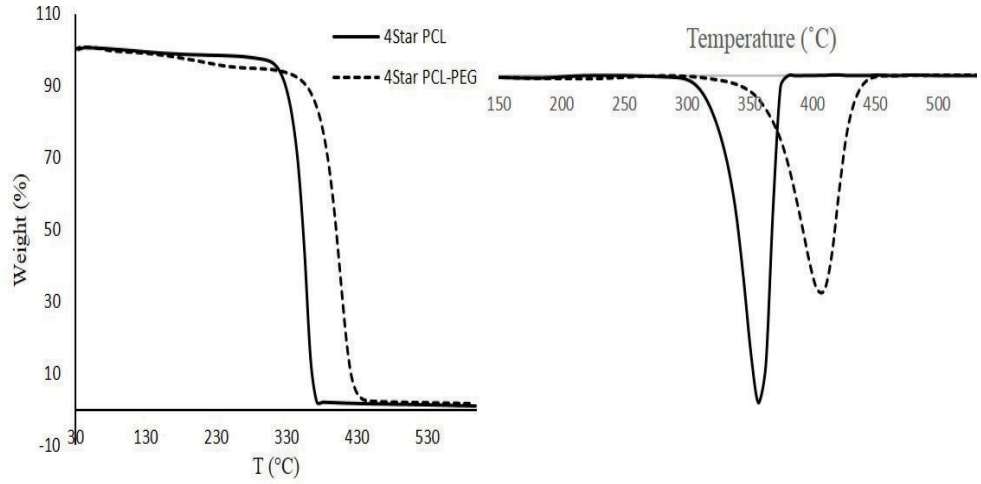


Figure 3: TGA and DTG Thermograms Curve for 4Star PCL and 4Star PCL-PEG

4Star PCL-PEG Formulation

The amphiphilic polymeric system was selected in this study to ensure the homogeneity of the hydrogel. PCL in the inner segment of the polymeric system will act as drug reservoir. Meanwhile hydrophilic PEG will be the interface to increase the star-shaped polymer solubility in the formulation. Table 3 illustrates the basic components in the hydrogel formulation.

Table 3: Hydrogel Composition

Ingredients	Percentage (%)
Carbomer 940	1.5
Methylparaben	0.05
Propylparaben	0.03
Water	97
4Star PCL-PEG	1
TEA	q.s

q.s: quantum satis.

After a homogenous opaque formulation formed without any agglomeration or phase separation after the mixtures of all main component in the hydrogel, triethanolamine, TEA was added to adjust the pH value.

TEA also thickened the hydrogel due to the neutralisation process that ionises the polymer and generates negative charges along the backbone of the carbomer polymer. The repulsion-like charges in the carbomer backbones cause uncoiling of the molecule into an extended structure. This reaction is rapid and gives instantaneous thickening and hydrogel [34]. The TEA was added to the formulation until it reached pH range between 7.2 – 7.4 ± 0.03, which is the normal skin pH range to ensure the formulation would not cause any skin irritation [35].

The pH value will also affect the gel properties. If the formulation becomes alkaline (>pH 8), it will agglomerate and becomes too concentrated and will affect the spreadability when applied on human skin. However, if the formulation is in an acidic form (<5), it will be too dilute. Thus, it is important to ensure the neutralisation is done slowly until it reaches the desired pH. There is no significant change in pH values as a function of time for all formulations, which shows good stability and lifespan of the formulations after three months of the formulation preparation. Viscosity also one of the most important parameters in the evaluation as it governs many properties of the formulation, such as spreadability and pourability of the product from the container [36]. The viscosity of the gel formulations generally reflects its consistency. The viscosity of the formulation is 9330 cP. The formulation maintained its opaque appearance and no changes of colour after 12 weeks. Similarly, the physical appearance, homogeneity, and texture of all formulations also remained the same after the 12-week period.

CONCLUSION

Four arms star-shaped polymer PCL-PEG was synthesized and characterised. The molecular weight determined via ^{1}H-NMR is comparable with the theoretical value suggesting that the polymerisation of the star polymer was controlled. The polymerisation was controlled based on the molar feed ratio of the number of arms and the monomer. The star-shaped block copolymer was incorporated into hydrogel formulation with carbomer as gelling agent producing an opaque homogenous formulation. For future studies, the drug loading and drug release of hydrophobic drug model can be determined to evaluate the capability of the formulation towards drug cargo applications.

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