Synthesis & Characterization of PEG-PCL Di-Block Copolymers

4.1 MATERIALS

Methoxy polyethylene glycol [CH_3O-PEG-OH] (molecular weight 2000 & 5000), monomer ε-caprolactone (CL), HCl (1.0 M) in diethyl ether (HCl-Et_2O) and calcium hydride were purchased from Sigma Aldrich. Toluene, dichloromethane, diethyl ether and triethylamine of dry AR grade were purchased from S.D. Fine-chem Ltd, Mumbai. α-carboxy ω-hydroxyl polyethylene glycol [HOOC-PEG-OH] (molecular weight 2000 & 5000) were purchased from Jenkem Technology Inc. USA. Tetrahydrofuran of HPLC grade was purchased from Merck India. Dichloromethane (DCM) was dried and distilled using calcium hydride before use. CL was dried over calcium hydride for 48 h and distilled under reduced pressure before use.

4.2 SYNTHESIS OF PEG-PCL DI-BLOCK COPOLYMER

PEG-PCL di-block copolymers of different molecular weight were synthesized as reported earlier by living ring opening polymerization with slight modification (Kim et al., 2005; Lee et al., 2007). The typical process for the polymerization to obtain MPEG-PCL of molecular weight 2000-2000 is as follow. A 1 gm of CH_3O-PEG-OH (0.5 mmol, Mn= 2000) was azeodistilled twice with dry toluene (50 ml) to remove water and toluene was distilled off completely. To CH_3O-PEG-OH was added the dried dichloromethane (10 ml), followed by the addition of CL (1.0 gm, 8.75 mmole) using syringe. The polymerization was initiated by the addition of 1.0 M solution of HCl-Et_2O (1.5 ml, 1.5 mmol) and the reaction was maintained at 25 °C for 24 h with vigorous stirring under nitrogen atmosphere. The reaction was terminated with the help of 0.1ml of triethylamine and the precipitated triethylamine-HCl salt was removed by filtration. The copolymer was collected by precipitation of filtered solution in cold diethyl ether (-20 °C) and washed with cold methanol thrice to remove residual monomer. The final product obtained was kept in dessicator for 48 h and used for further studies. Functionalized HOOC-PEG-PCL of molecular weight 2000-3500 and 5000-7000 was synthesized similar procedure using HOOC-PEG-OH of molecular weight 2000 & 5000 as macroinitiator.

The schematic representation and synthetic scheme of polymerization of CH_3O-PEG-PCL copolymer is outlined in Figure 4.1 and Figure 4.2 respectively.

Azeodistill CH_3O-PEG-OH twice with dry toluene

↓

To this add DCM, CL and HCl- Et_2O and keep at 25° for 24 h with vigorous stirring under nitrogen atmosphere

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Terminate reaction using triethylamine and filter to remove precipitate of triethylamine-HCl

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Add cold diethyl ether, collect product and wash with cold methanol thrice to remove monomer.

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Keep the final product in dessicator for 48 h to completely dry.

Figure 4.1 Schematic representation of synthesis of PEG-PCL copolymer

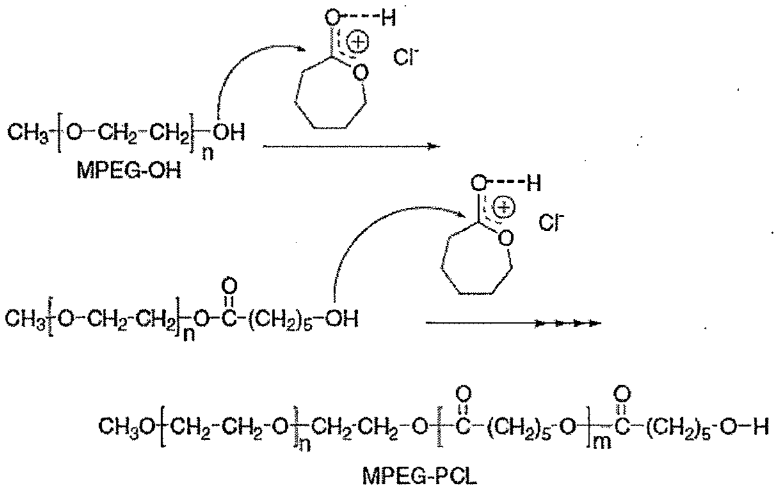

Figure 4.2 Synthetic scheme of synthesis of MPEG-PCL di-block copolymer

Different molecular weight PEG-PCL di-block copolymers were synthesized by varying the feed ratio of PEG and CL as shown in Table 4.1. Two different types of PEG i.e. CH_3O-PEG-OH and HOOC-PEG-OH of molecular weight 2000 and 5000 were used for polymerization along with CL. The amount of initiator HCl-Et_2O used was also varied depending on the mole of PEG used in polymerization.

Polymer Code	**MW of PEG**	**$[CL]/[PEG]^a$**	**Theoretical MW of PEG and PCL block^b**	**Theoretical MW of PEG-PCL**
BCP 2-2	2000	17.50	2000-2000	4000
BCP 2-3.5		30.66	2000-3500	5500
BCP 2-5		43.80	2000-5000	7000
BCP 5-5	5000	43.80	5000-5000	10000
BCP 5-7		61.32	5000-7000	12000
BCP 5-10		87.61	5000-10000	15000
FBCP 2-3.5	2000*	30.66	2000-3500	5500
FBCP 5-7	5000*	61.32	5000-7000	12000

Condition: $[HCl\text{-}Et_2O]/PEG$ (molar) = 3

[a] [CL]/[PEG] is the molar ratio of CL to PEG used in synthesis

[b] calculated from feed amount of CL and MW (molecular weight) of PEG used

* represents HOOC-PEG-OH used to prepare functional PEG-PCL di-block copolymer

Table 4.1 Synthesis of PEG-PCL di-block copolymer of various molecular weights

4.3 CHARACTERIZATION OF PEG-PCL DI-BLOCK COPOLYMER

4.3.1 Nuclear magnetic resonance (^{1}H-NMR)

The structure and molecular weight of synthesized PEG-PCL di-block copolymers were determined by FT-NMR spectrometer (400 MHz, Advance-II Bruker, Germany). The block copolymer was dissolved in $CDCl_3$ and ^{1}H NMR spectrum was recorded using tetramethanesilane as internal standard at room temperature.

The obtained ^{1}H NMR spectrum was used to calculate the number average molecular weight of PEG-PCL di-block copolymer using following equation (Shen et al., 2007)

$$M_{NMR} = (1 + 114R/44) \times M_{PEG},$$

where M_{PEG} was the MW of PEG used and R is the integration ratio of peak at δ 4.05 ppm due to PCL blocks to peak at δ of 3.65 ppm due to the PEG blocks.

4.3.2 Gel permeation chromatography

Molecular weights (Mn) and molecular weight distribution of PEG-PCL di-block copolymers were determined using Perkin Elmer Totalchrom Gel permeation chromatography instrument equipped with PE series 200 RI detector, mixed column PLGel >5 μ, series 200 isocratic pump and rheodyne injector. Tetrahydrofuran (THF) was used as mobile phase at flow rate of 1 ml/min. Samples were dissolved in THF and injected to column and molecular weight and molecular weight distribution was calculated using turbosec size exclusion software. Medium molecular weight polystyrene standards ((Polysciences Inc.), 1mg/ml in THF with molecular weight 1 X 10^3 to 3 X 10^5 were used for calibration of GPC.

4.3.3 Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of PEG-PCL was recorded using Fourier transform infrared spectrometer (Bruker, Alpha-T, Germany). Required quantity of di-block copolymer was mixed with KBr, pelletized under the pressure of 10 tons for 2 min and analyzed at room temperature (25 °C).

4.4 RESULTS AND DISCUSSION

Several methods are reported for the synthesis of PEG-PCL block copolymer using different catalyst like stannous octoate, aluminum alkoxide or HCl-Et_2O (Zhou et al., 2003; Hsu et al., 2004; Kim et al., 2005). Although, it is required that the method used for the synthesis of MPEG–PCL di-block copolymers should generate desired controlled molecular weight polymer. One of the most powerful methods to control ring-opening polymerization is activated monomer cationic polymerization, which can suppress unfavorable reactions such as back-biting and disproportionate (Kubisa & Penczek, 1999). An activated monomer cationic ring-opening polymerization of CL with alcohol in the presence of HCl-Et_2O was reported and found that HCl-Et_2O did not serve as an initiator, but as an activator in this system (Shibasaki et al 2000 & Sanda et al. 2002). Moreover, HCl-Et_2O used for the ring-opening polymerization can be easily removed from the synthesized polymers. On the other hand organometallic tin compounds like stannous octoate is quite difficult to remove and use of such catalyst during synthesis is a subject of controversy for the use of MPEG–PCL di-block copolymers in biological purpose (Kim et al., 2005).

The polymerization of CL by terminal alcohol of PEG as an initiator was performed to synthesize PEG–PCL di-block copolymers via an activated monomer mechanism in the presence of monomer activator (HCl-Et_2O). It is believed that the hydroxyl end group of PEG could attack the carbonyl carbon of the protonated CL in the presence of HCl-Et_2O and starts polymerization (Kim et al., 2005). The polymerization of PEG-PCL was performed varying different feed ratios of CL with respect to PEG of molecular weight 2000 or 5000 in the presence of HCl-Et_2O as shown in Table 4.1. This polymerization gave colorless di-block copolymers with almost quantitative yield (>90%) after isolation by precipitation in diethylether. ^{1}H NMR and GPC were performed to find out the molecular weight of PEG-PCL di-block copolymer. Table 4.2 summarizes the results of the polymerization.

Polymer code	Mw of PEG	Mn cal[a]	Mn NMR[b]	Mn GPC[c]	Mn/Mw (GPC)	Yield[d] %
BCP2-2	2000	4000	3957	4364	1.272	94.45
BCP2-3.5		5500	5349	5870	1.216	94.08
BCP2-5		7000	6843	7291	1.394	97.12
FBCP-2.3.5		5500	5290	5938	1.389	95.34
BCP5-5	5000	10000	9477	10784	1.301	93.98
BCP5-7		12000	11592	12836	1.431	95.65
BCP5-10		15000	14687	16190	1.235	93.09
FBCP5-7		12000	11764	12628	1.370	92.56

[a] Mncalc= MnPEG + MnPCL; MnPCL is the calculated molecular weight of the PCL block based on the feed ratio of caprolactone to MePEG

[b] MnNMR= MnPEG + MnPCL, calculated from ^{1}H NMR spectrum

[c] Mn GPC is the relative molecular weight determined by GPC with respect to poly(styrene) standards.

[d] Yield calculated after precipitation in diethyl ether.

Table 4.2 Characteristics of synthesized PEG-b-PCL di-block copolymers

In order to study the composition and molecular weight determination of synthesized polymer, ^{1}HNMR spectrum was recorded. Figure 4.4 to 4.11 represents the ^{1}HNMR spectrums of various di-block copolymers and it exhibited characteristics peak of PEG and PCL. The signals assignable to terminal methoxy protons (a) and methylene protons (c) of MPEG were observed at $\delta = 3.38$ and 3.65 ppm, respectively (Figure 4.3). The peaks assignable (1-5) to the sequence of α, β, + δ, γ and ε--methylene protons of the ester carbonyl moiety of PCL were also observed at 2.31, 1.63, 1.39

and 4.05 ppm, respectively (Figure 4.3). In addition, polymer chain end proton (8) of PCL was observed at 3.88 ppm and a signal assignable to terminal ω-methylene protons (d) of the MPEG blocked by PCL were observed at around 4.22 ppm. The results obtained are in agreement with earlier reports (Kim et al., 2005; Hu et al., 2004).

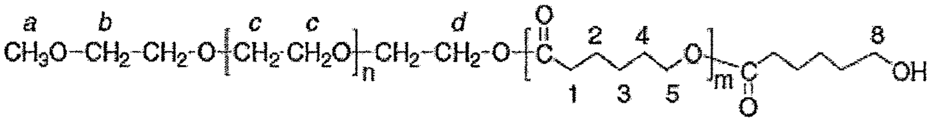

Figure 4.3 Chemical structure of MPEG-PCL block copolymer

The integration ratio of peak at δ 4.05 ppm due to PCL blocks and peak at δ of 3.65 ppm due to the PEG blocks was calculated and placed in the equation to find out the molecular weight. The molecular weight obtained is shown in Table 4.2 and the molecular weight of synthesized copolymer was found relatively closer to those of the theoretical molecular weight.

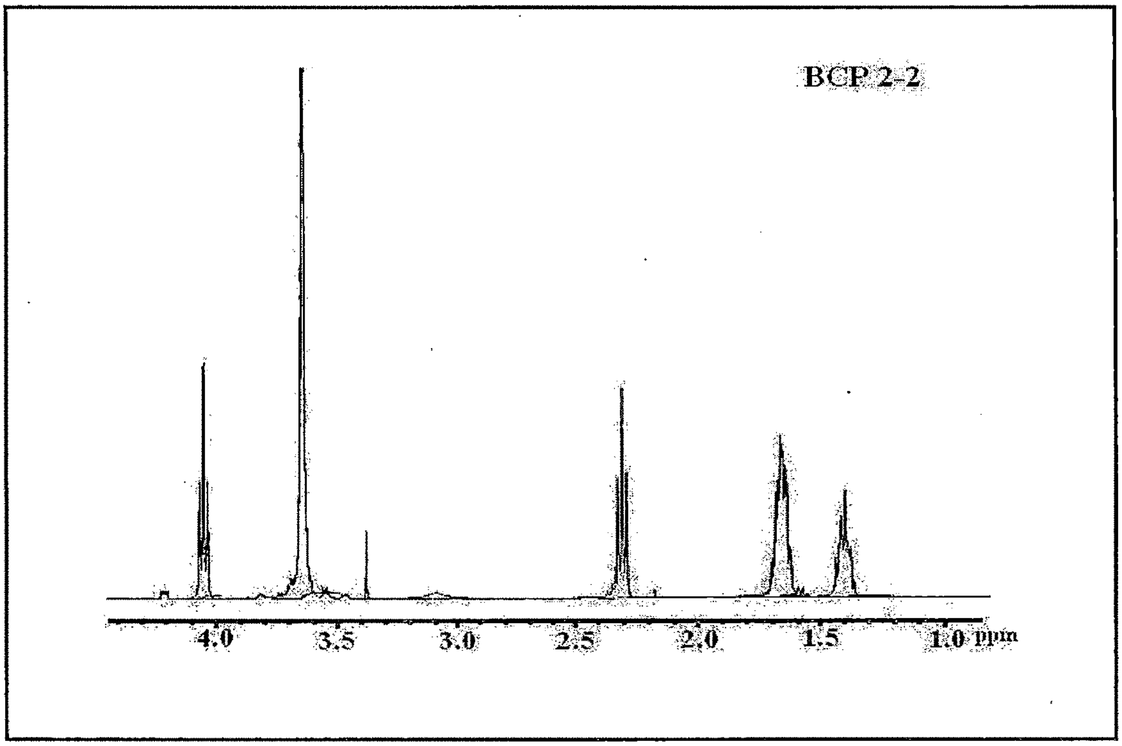

Figure 4.4 ^1H NMR spectrum of BCP 2-2 di-block copolymer

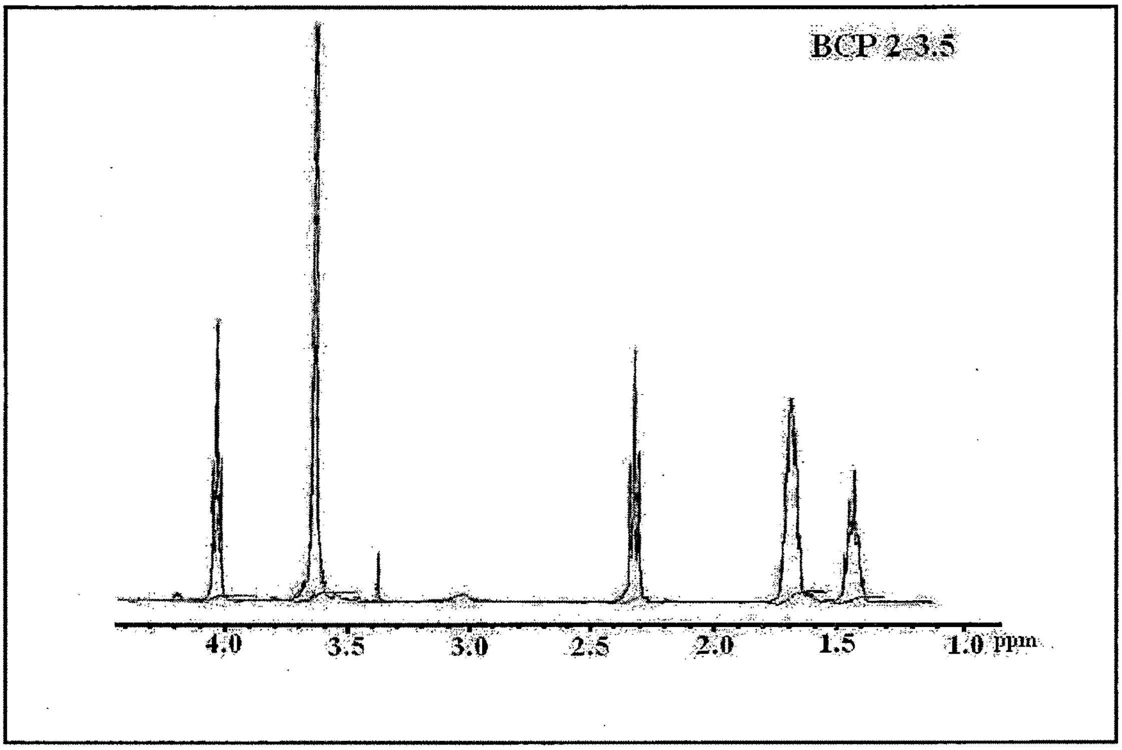

Figure 4.5 ^{1}H NMR spectrum of BCP 2-3.5 di-block copolymer

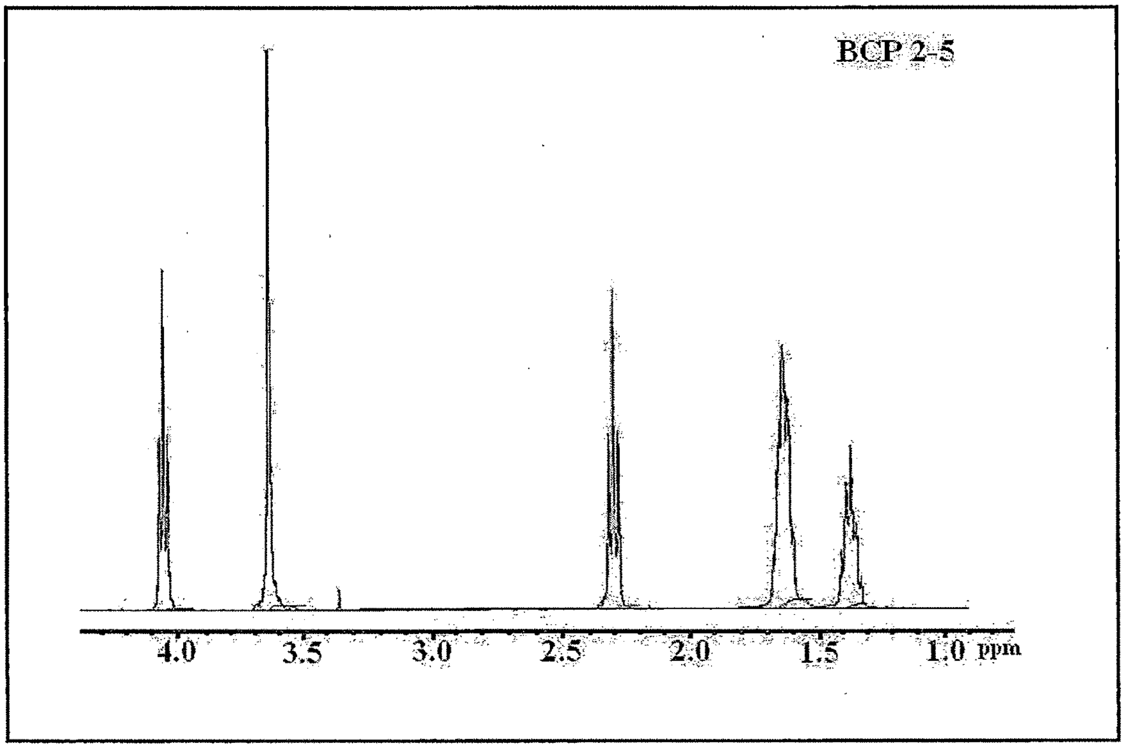

Figure 4.6 ^{1}H NMR spectrum of BCP 2-5 di-block copolymer

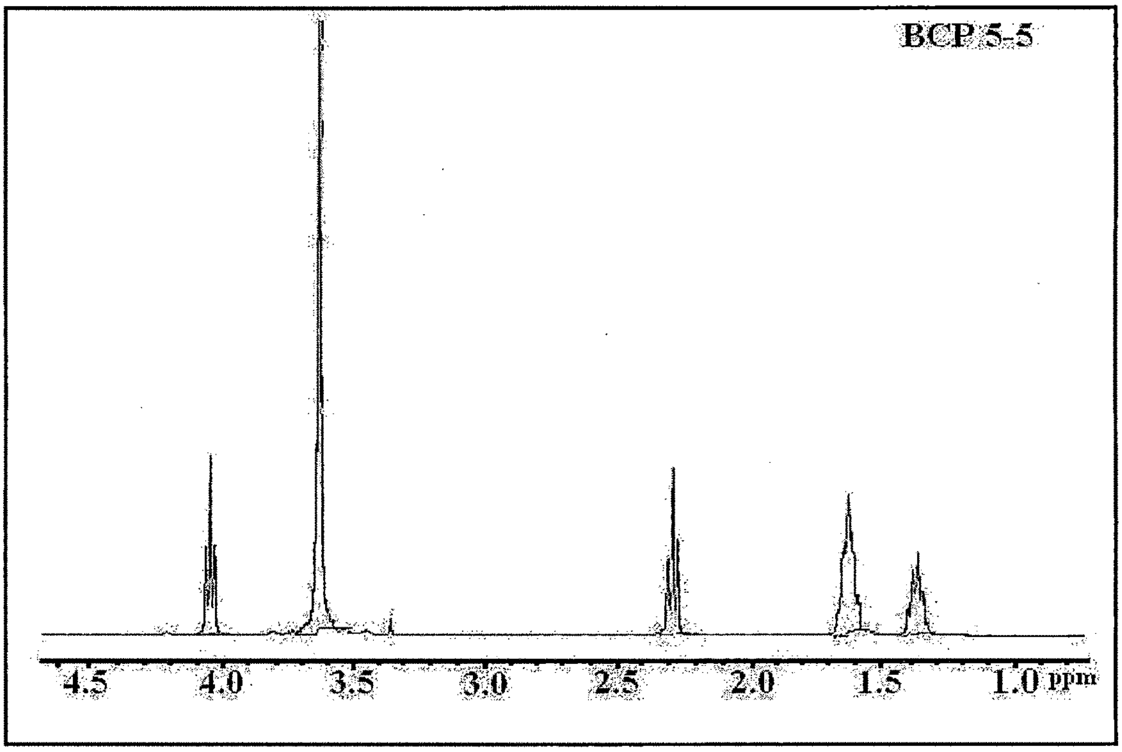

Figure 4.7 ^{1}H NMR spectrum of BCP 5-5 di-block copolymer

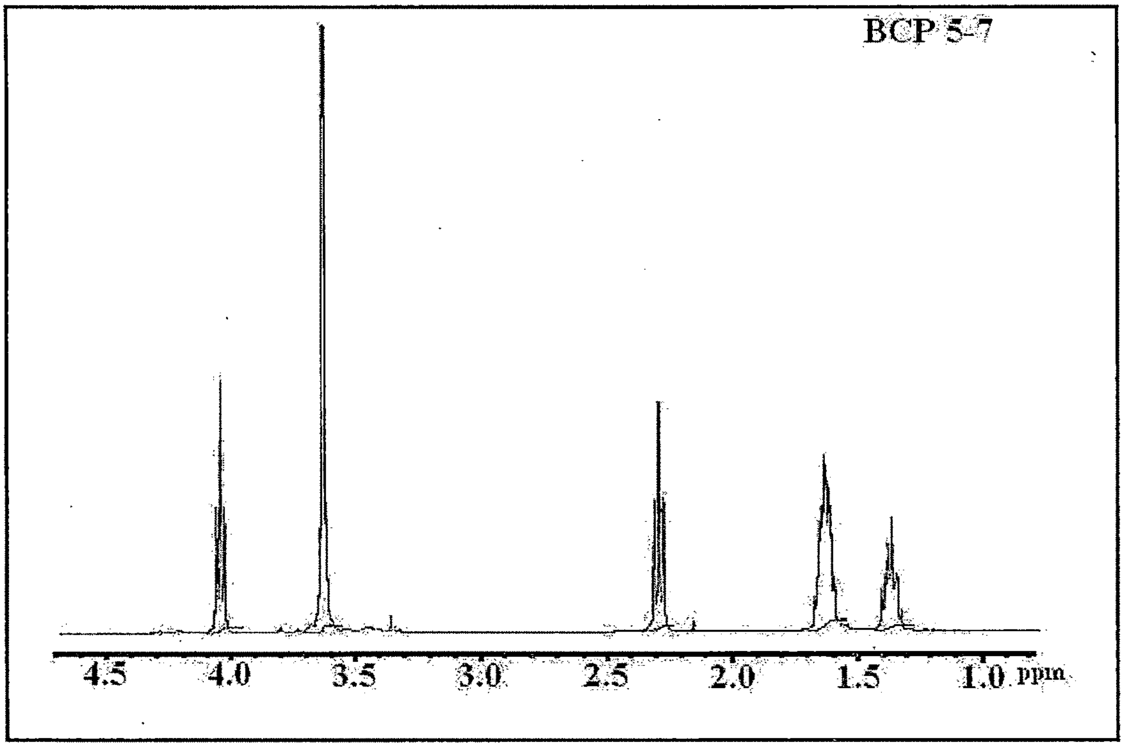

Figure 4.8 ^{1}H NMR spectrum of BCP 5-7 di-block copolymer

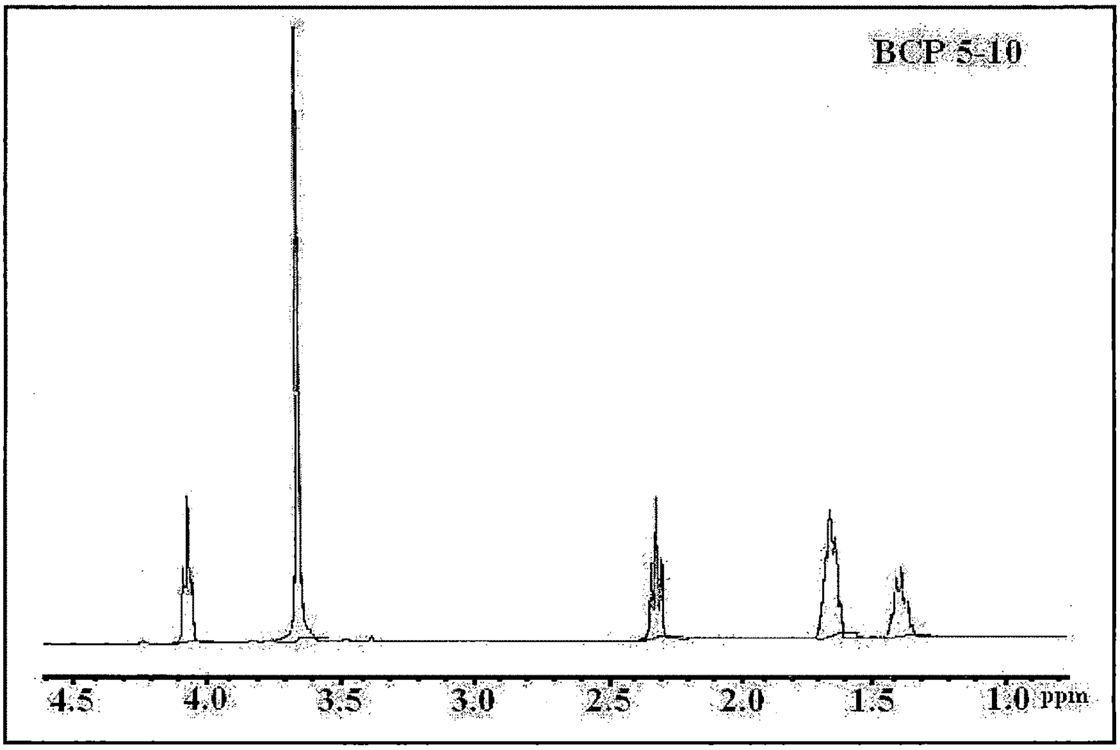

Figure 4.9 ^{1}H NMR spectrum of BCP 5-10 di-block copolymer

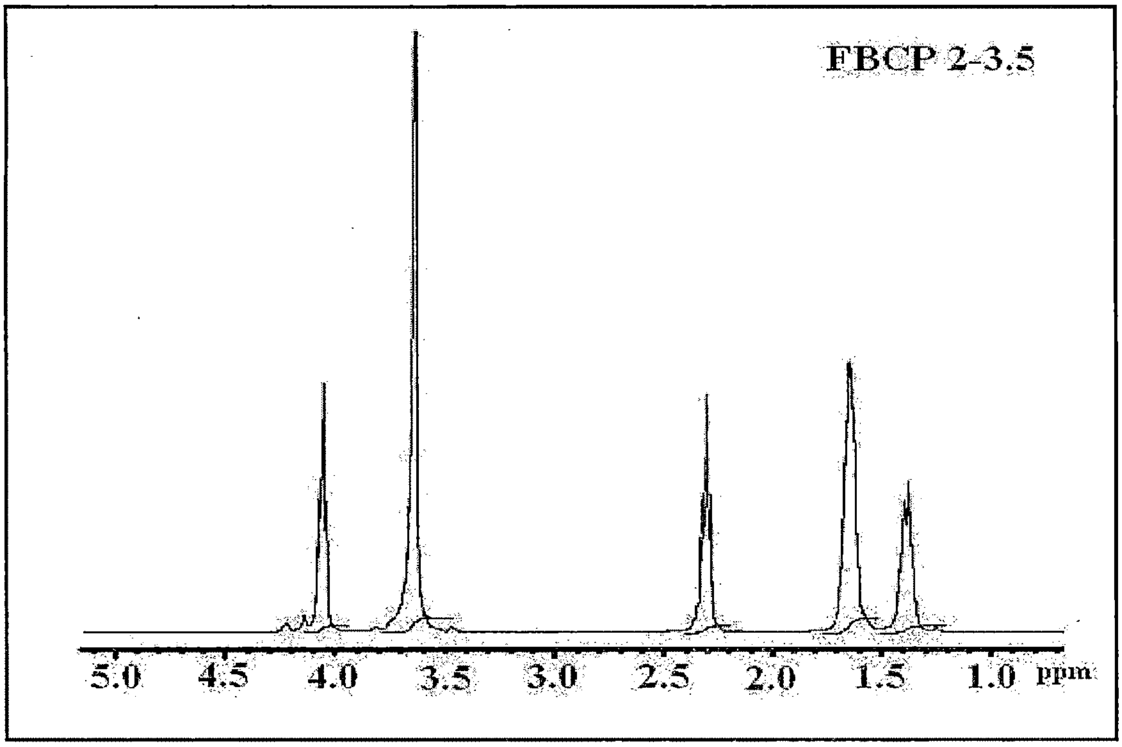

Figure 4.10 ^{1}H NMR spectrum of FBCP 2-3.5 di-block copolymer

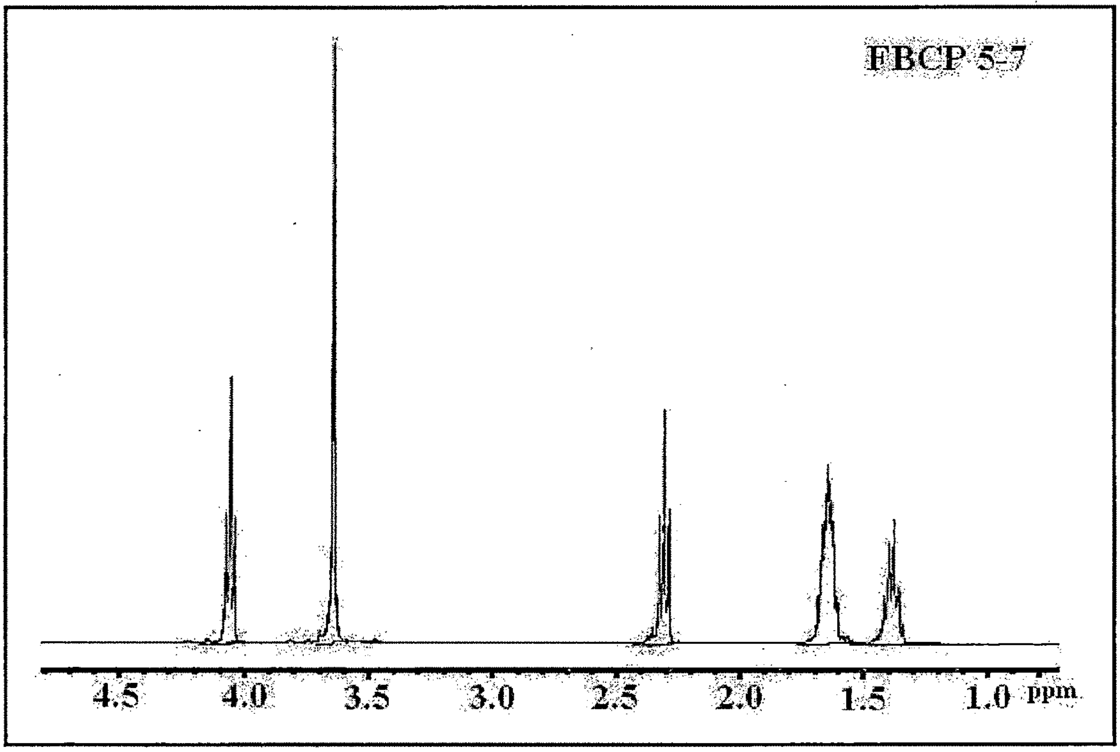

Figure 4.11 ^{1}H NMR spectrum of FBCP 5-7 di-block copolymer

In Gel permeation chromatography analysis, only one peak appeared in GPC chromatograms as shown in Figure 4.12 to 4.14 which indicated that all the impurities were removed after purification. The molecular weight obtained by GPC showed very good correlation between the results obtained to that of theoretical molecular weight of all synthesized PEG-PCL copolymer as shown in Table 4.2. Furthermore, the polydispersity (Mw/Mn) of the copolymer (defined as the ratio of weight average molecular weight to the number average molecular weight) was found in narrow range with less than 1.43 (Table 4.2). In addition, decrease in retention time in GPC chromatograms was observed with increase in molecular weight. The number averaged molecular weight obtained from the GPC chromatogram confirmed the calculated NMR values.

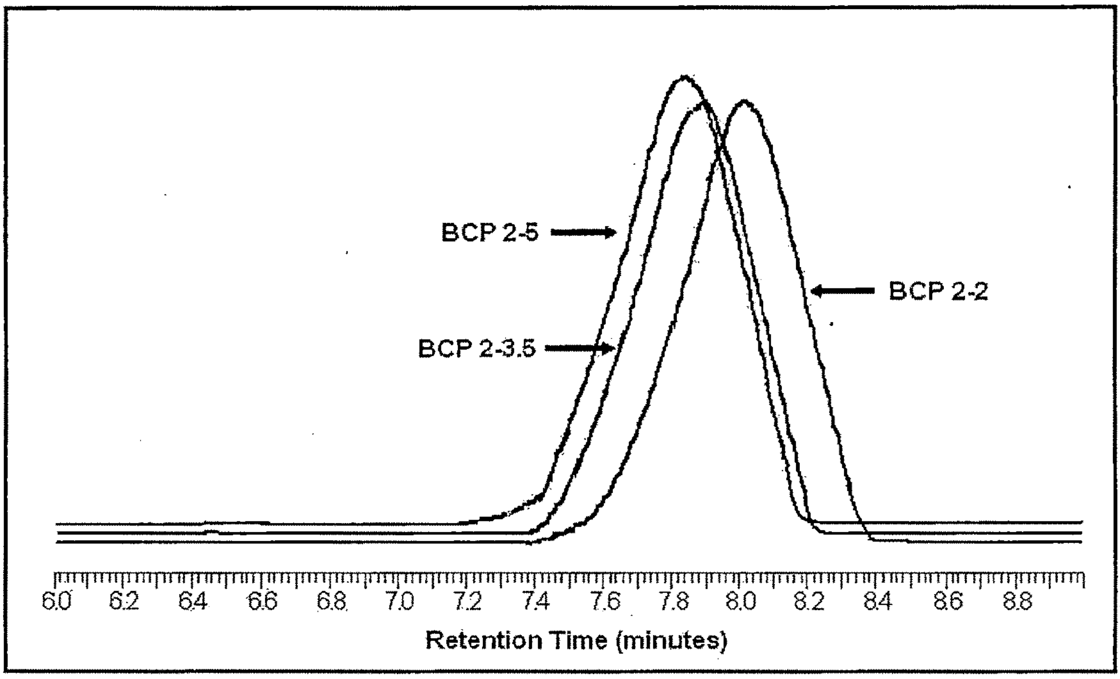

Figure 4.12 GPC chromatogram of BCP 2-2, BCP 2-3.5 and BCP 2-5 di-block copolymer

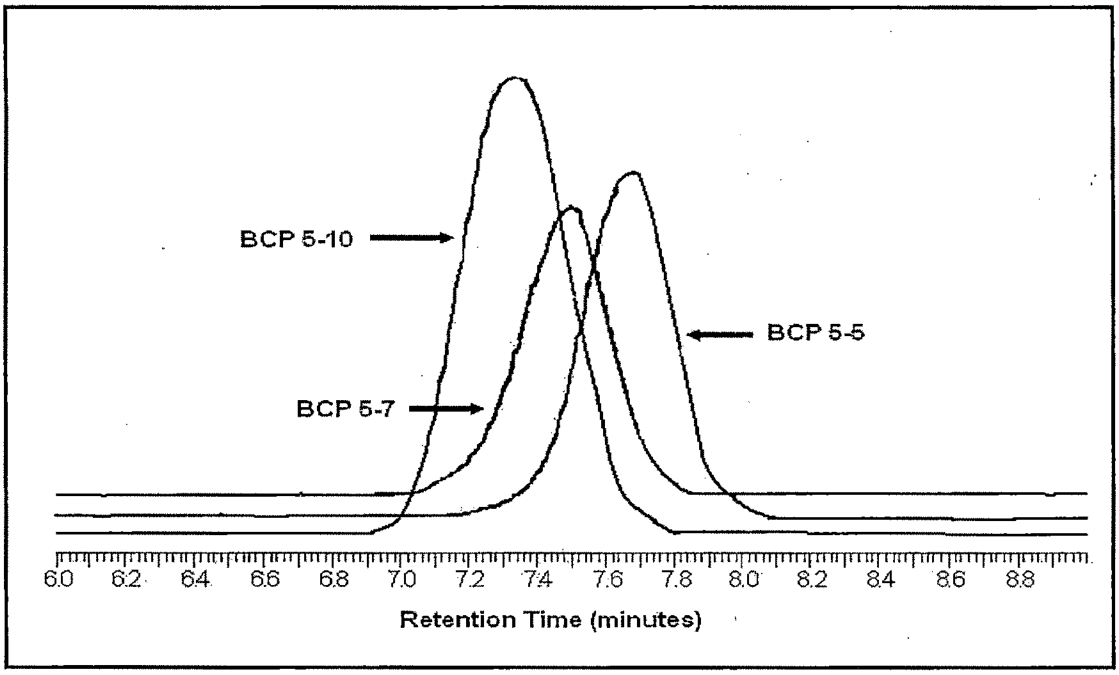

Figure 4.13 GPC chromatogram of BCP 5-5, BCP 5-7 and BCP 5-10 di-block copolymer

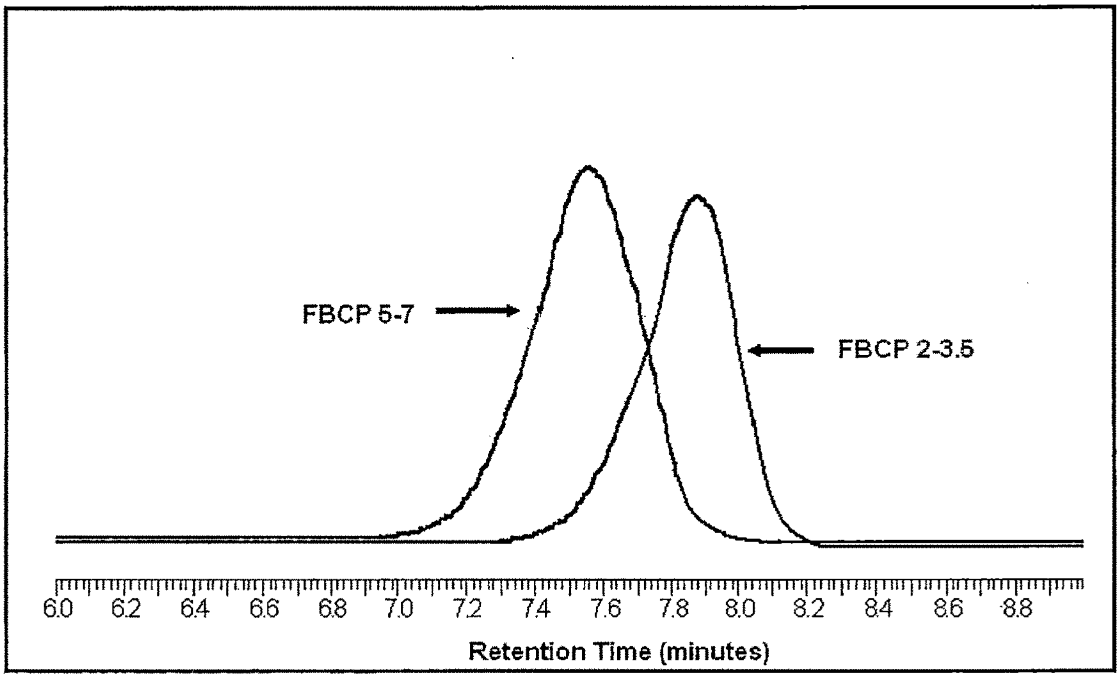

Figure 4.14 GPC chromatogram of FBCP 2-3.5 and FBCP 5-7 di-block copolymer

Figure 4.15 to 4.22 shows the FTIR spectra of different molecular weight PEG-b-PCL di-block copolymer. A strong absorption band appears at 1726 cm^{-1} indicating the presence of the stretching vibration of carbonyl groups attributed to the formation of di-block copolymer of CL and PEG (Shin et al., 1998). Two bands at the 1110 and 1244 cm^{-1} was due to the stretching vibrations of C-O-C and C-O bonds and indicating the existence of ester structural units in the copolymer. The band at 2945 cm^{-1} was assigned to the C-H stretching vibrations of CH_2 in PCL block, whereas the band at 2868 cm^{-1} corresponds to the C-H stretching vibration of PEG. In addition, broad absorption band at 3439 cm^{-1} was attributed to be the terminal hydroxyl groups in the block copolymer and carboxyl group in case of HOOC-PEG-PCL di-block copolymer. The results obtained are in agreement with previously reported studies carried out with PEG-PCL di-block copolymer (Meng et al., 2006).

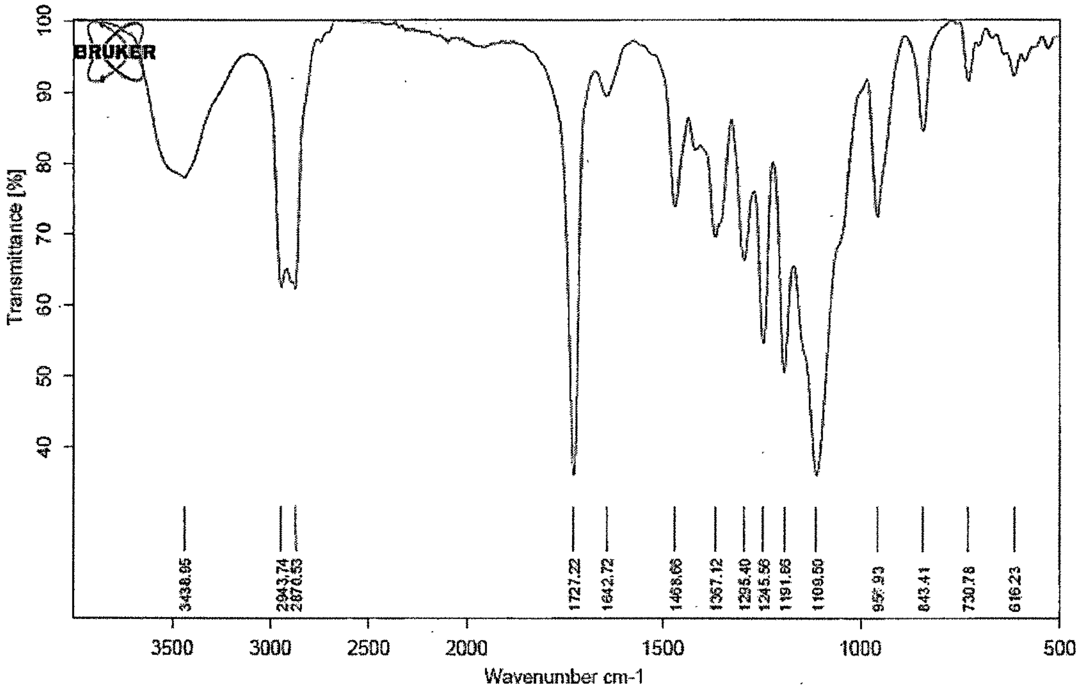

Figure 4.15 FTIR spectrum of BCP 2-2 di-block copolymer

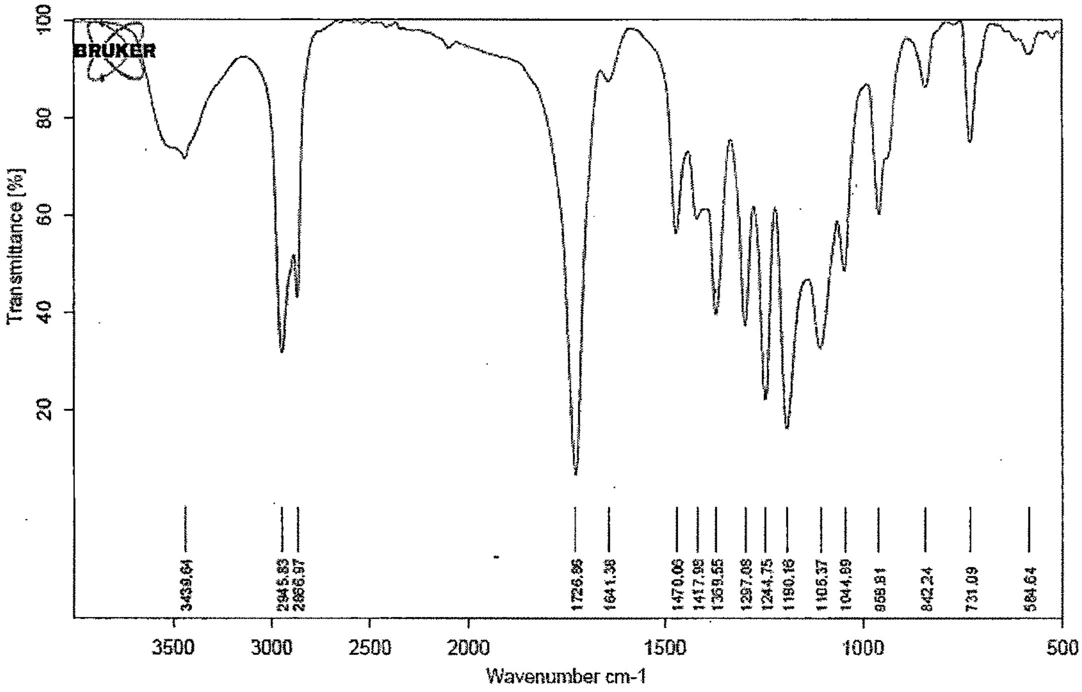

Figure 4.16 FTIR spectrum of BCP 2-3.5 di-block copolymer

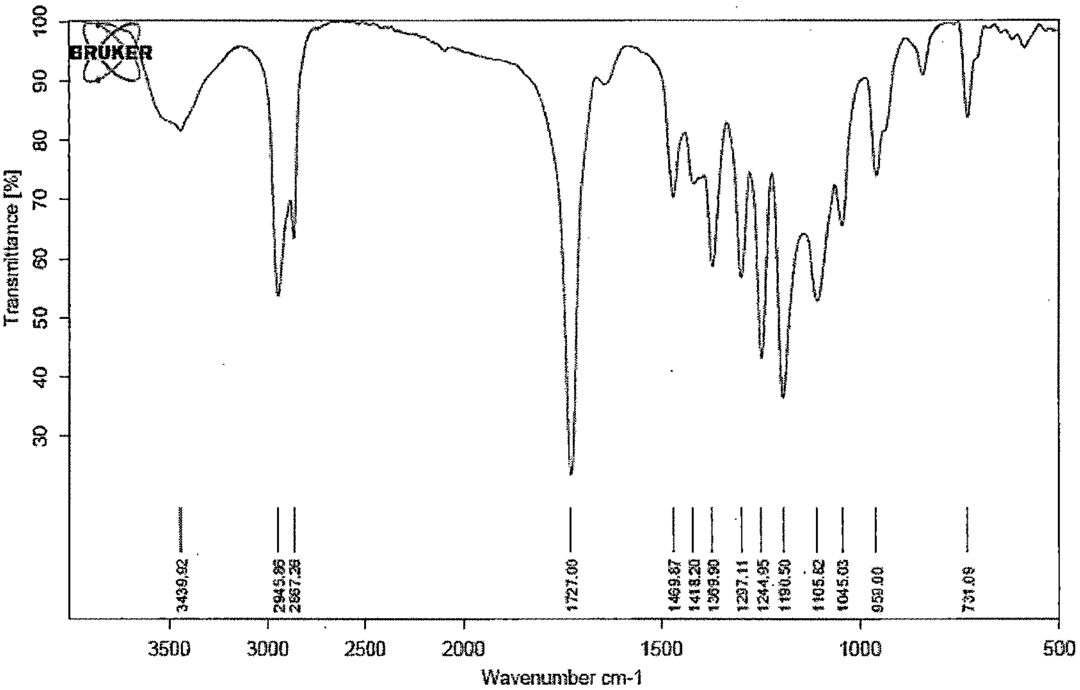

Figure 4.17 FTIR spectrum of BCP 2-5 di-block copolymer

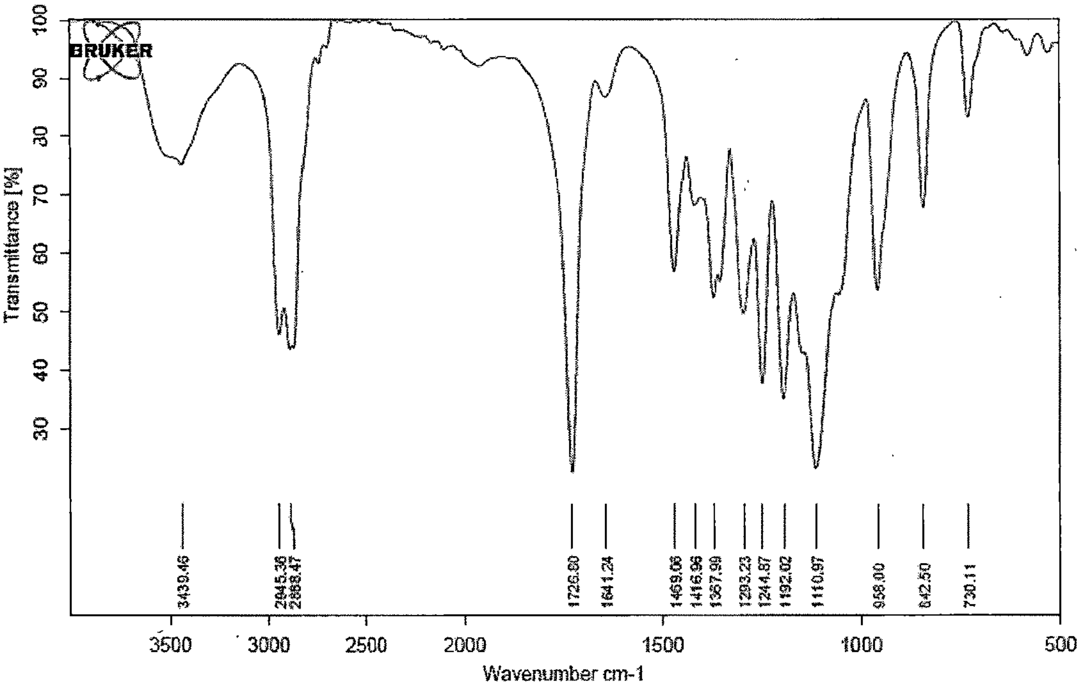

Figure 4.18 FTIR spectrum of BCP 5-5 di-block copolymer

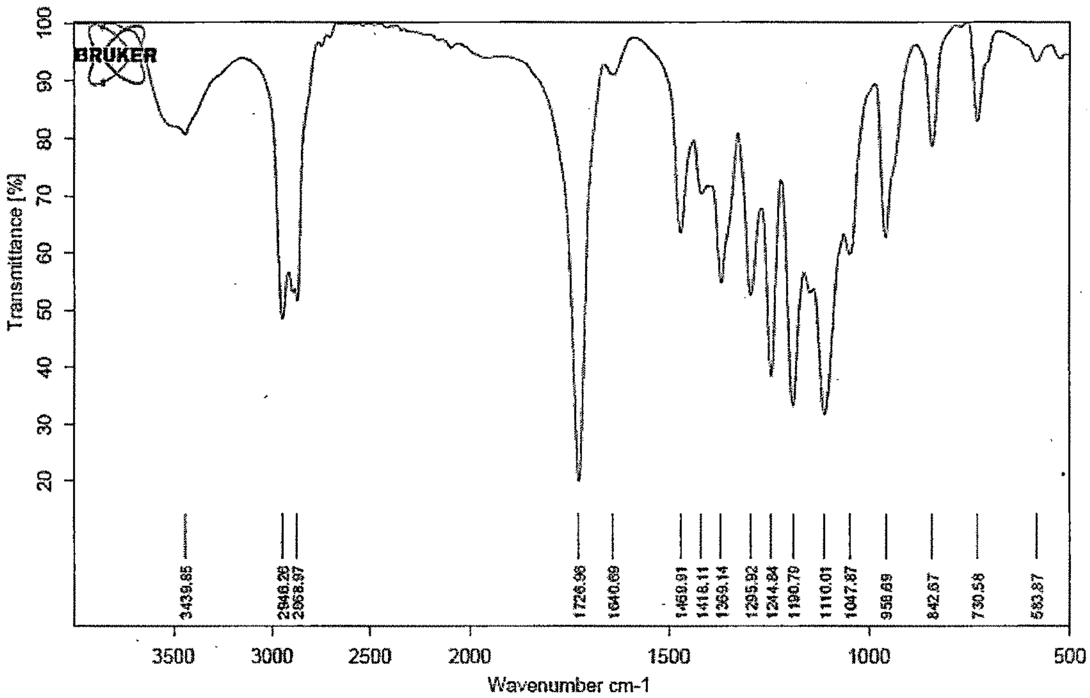

Figure 4.19 FTIR spectrum of BCP 5-7 di-block copolymer

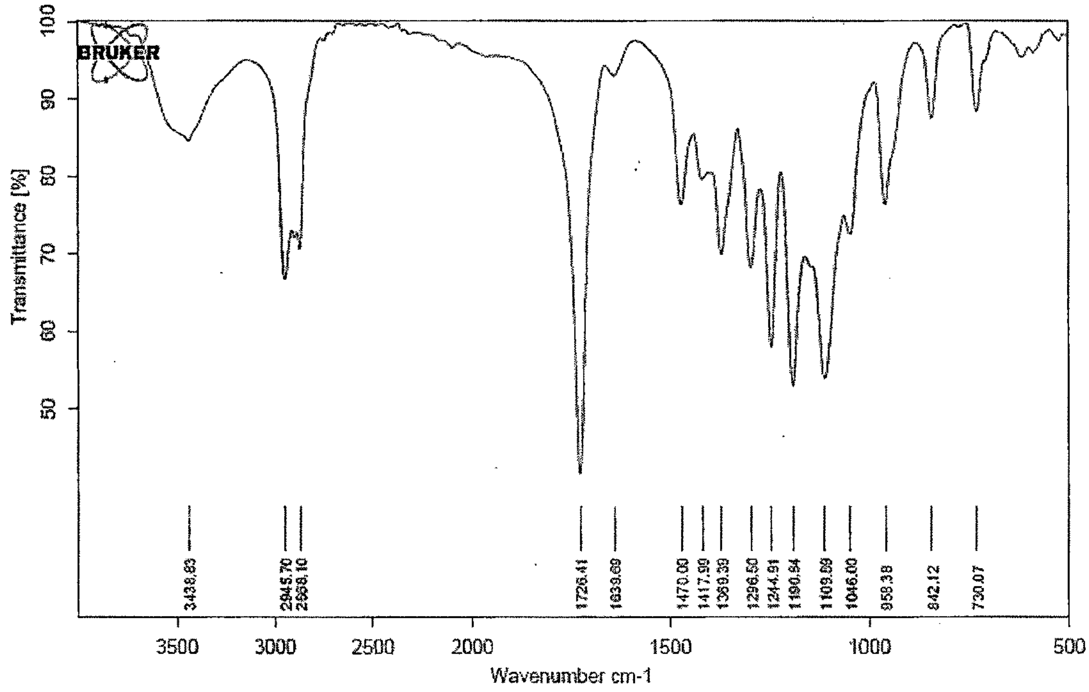

Figure 4.20 FTIR spectrum of BCP 5-10 di-block copolymer

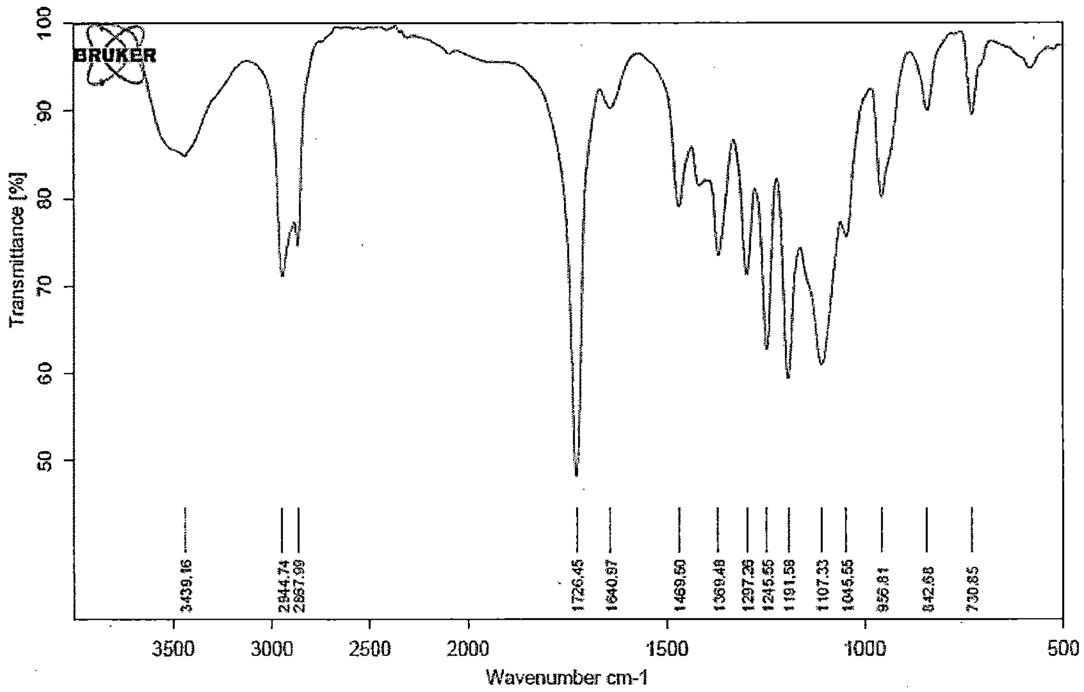

Figure 4.21 FTIR spectrum of FBCP 2-3.5 di-block copolymer

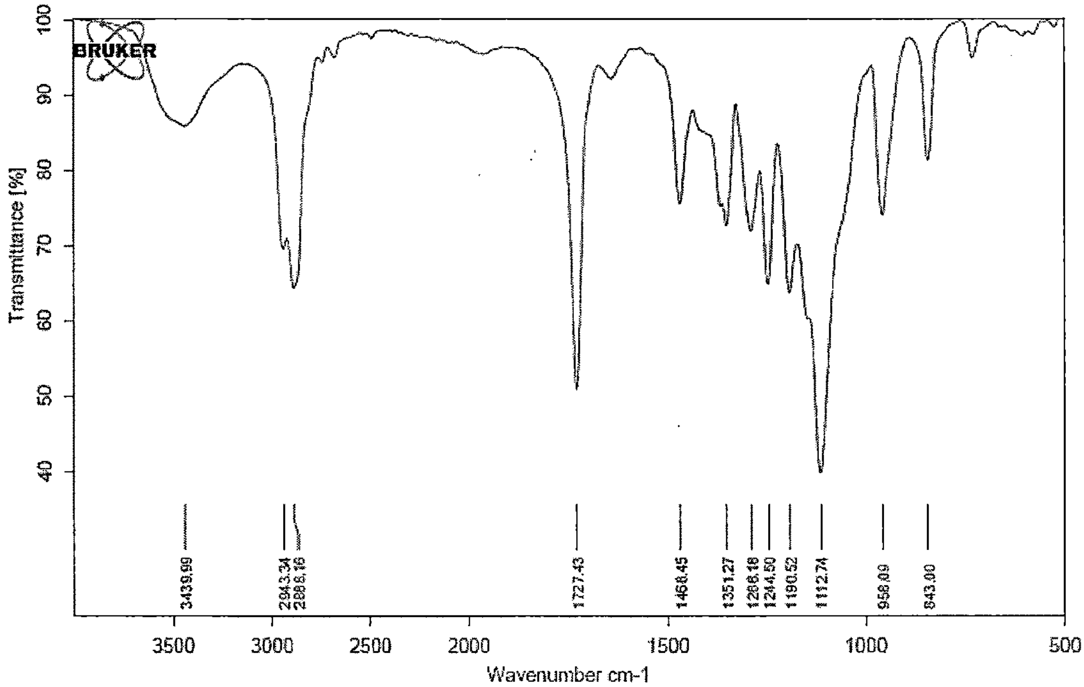

Figure 4.22 FTIR spectrum of FBCP 5-7 di-block copolymer

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