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ORIGINAL PAPER

# Two novel methods for synthesizing poly (propylene fumarate): Technical aspects and role of vacuum and $N_2$ purging effects

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## ABSTRACT

Poly (propylene fumarate) (PPF), a linear unsaturated polyester consisting of alternating propylene glycol and fumaric acid units, can be cured in vivo to fill the skeletal defects with minimal surgical intervention. Many different methods have been reported for synthesizing PPF, but none of them gives a clear method. The present paper introduces two new methods in PPF synthesis: Modified reflux system (MRS) and mixed reflux-distillation system (MRDS). Similarly, the effects of applying vacuum (vacuum sequence, time, vacuum applying position, and the distance between vacuum applying position and reactor) as well as nitrogen gas (used continuously or only as an $N_2$ blanket) on the PPF synthesis have been studied. The PPF obtained using optimum reaction condition has been characterized by using NMR, FTIR, and GPC analyses. It is demonstrated that the efficiency of MRDS in synthesizing PPF is higher than that of MRS. Nitrogen gas, vacuum applying position, continuously/stepwise-continuously applying vacuum and other parameters show an important role in the polymerization of PPF in both the MRDS and MRS systems. **Polyolefins J (2017) 4: 27-41**

**Keywords:** Poly (propylene fumarate); modified reflux system; mixed reflux-distillation system.

## INTRODUCTION

These days, biodegradable materials are becoming popular in packaging, agriculture, medicine, and other areas. The biodegradable unsaturated polyesters, due to their ability to be cross-linked in situ and to degrade gradually, are the most promising materials in the tissue engineering field [1]. Due to slow hydrolysis, polyesters are the most common degradable synthetic polymers used in tissue engineering applications. For example, polyesters such as poly (L-lactic acid) and poly (D, L-lactic-co-glycolic acid) are biocompatible and biodegradable materials that can form scaffolds for in-situ tissue engineering applications [2, 3].

Poly(propylene fumarate) (PPF) as one of the most important biodegradable polymers is a linear unsaturated polyester consisting of alternating propylene glycol and fumaric acid units [4]. The main advantage of the unsaturated polymers is their ability to cure in vivo; thereby the possible skeletal defects in any shapes or sizes will be filled with minimal surgical intervention. PPF has the inherent advantage of fumarate units that allow the polymer chains to be covalently cross-linked through its carbon-carbon double bonds with relatively

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low levels of heat release [5, 6].

Thus, PPF can be fabricated in situ to obtain a three-dimensional scaffold. The molecular weight of linear PPF affects the mechanical and degradation properties of cross-linked composites that will be used in the orthopedic applications [2, 5-10]. In order to synthesize PPF with a reproducible molecular weight and to control the polymer synthesis, many different methods have been reported [7-13] that these routes have been associated with significant by-product formation.

As shown in Figure 1, a common method for synthesizing PPF follows a two-step procedure, beginning with diethyl fumarate and propylene glycol reaction, and involving bis(hydroxypropyl fumarate) as an intermediate. More recently, procedure formulations of PPF synthesis were adapted frequently based on Shung et al. studies [13]. In brief, diethyl fumarate is reacted with propylene glycol in a three-necked round bottom flask at a molar ratio of 1:3. Hydroquinone, a crosslinking inhibitor, and zinc chloride as the reaction catalyst are added to the flask containing diethyl fumarate with ratios of 0.003 and 0.01, respectively. Moreover, the other techniques of PPF synthesis have been reported as follows:

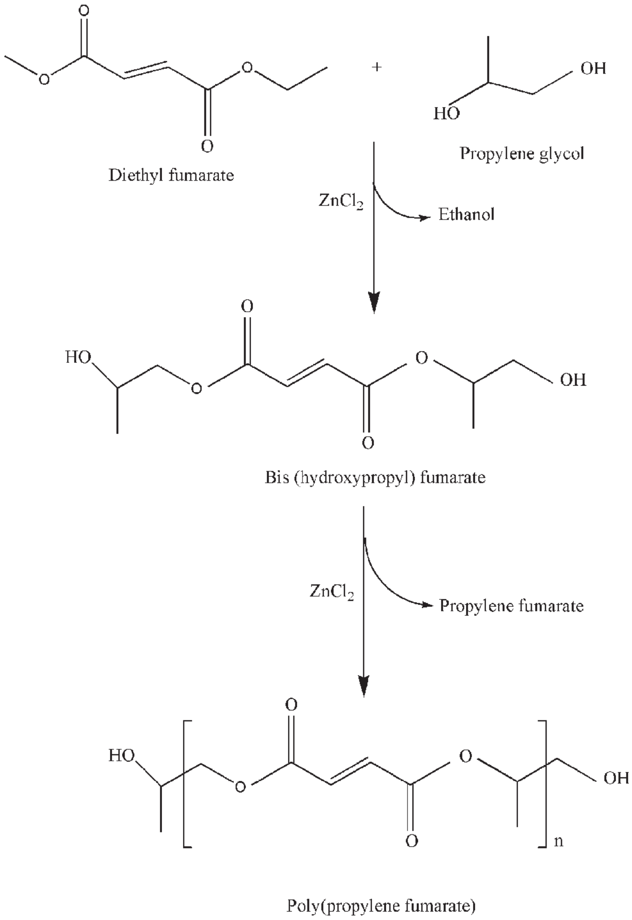


**Figure 1**. Reaction scheme for the step polymerization of poly (propylene fumarate) from propylene glycol and diethyl fumarate.

According to a research conducted by Hakimimehr et al. [14], PPF is synthesized in a Vigreux distilling column attached to the reactor kept under nitrogen while stirring. The reactor is then submerged in an oil bath and the temperature is increased to 140°C over a period of 1h. Upon the removal of 90% of the theoretical ethanol from the system as a distillate, the reactor is cooled down to 100°C and placed under vacuum.Temperature is then slowly increased at a rate of 10°C/15 min to 140°C. At this step, the diester intermediates react through a self-transesterification process and propylene glycol is collected as a distillate. The molecular weight of the polymer is dependent on the period of time (12 h) in which the polymer is kept at the final temperature 140°C.

In the research done by Temenoff et al. [15], the reaction runs for approximately 8h in an inert atmosphere and the temperature gradually increases from 100°C to 160°C. This reaction produces the intermediate bis (hydroxypropyl fumarate) as well as ethanol, and the reactor is heated when 80-100% of the theoretical ethanol has been collected in a receiving flask. In the second step, PPF and the by-product propylene glycol will be produced. This reaction is run for approximately 8 h under vacuum (<1 mmHg) while the temperature is slowly increased from 90 to 150°C.

The synthesis of PPF presented by Beke et al. [16] is also reported elsewhere [8]. Briefly, fumaric acid is heated in an excess of propylene glycol at 145°C. A Barrette trap is connected beneath the condenser and the water is collected as a by-product. After 3-4 h, the reaction temperature is increased to 180°C for 2 h to collect the unreacted propylene glycol.

According to the work carried out by Timmer et al. [17], the mixture of the reactants is heated to 150°C under a nitrogen blanket. Reaction continues until 90% of the theoretically expected amount of ethanol, as a by-product of the reaction, has been distilled. The reaction then undergoes transesterification by heating the vessel to 130°C under vacuum (1 mmHg).

Polypropylene fumarate is also prepared by condensation through refluxing using a condenser at a high temperature (200°C) and vacuum conditions for 2 h [18].

Many different methods have been reported for synthesizing PPF, but none of them gives a clear method. The references 13-18 represent some of PPF synthesizing procedures reported until now. In these papers, PPF synthesis is not reported in detail. In the other word, one or several key points in the synthesis of PPF may be ignored or the procedures are not clearly presented in detail, therefore these shortages can influence on the reproducibility of PPF synthesis. For example, in references 14, 15, and 17 it is said that the reaction will continue to remove 80-90% of amount of theoretically expected by-products (ethanol, water or propylene glycol) from the system as a distillate, but none of them gives a good solution for reaching this situation. Thus, there are some difficulties with the control of polymer molecular structure. In fact, the purpose of this study is to guide and help researchers who want to know how to synthesize this material with high reliability and reproducibility.

After some experiments on PPF synthesis in our studies, the present paper describes two new methods of synthesizing PPF called modified reflux system (MRS) and mixed reflux-distillation system (MRDS). The latter provides a high efficient synthesis procedure which is our final target. MRSD overcomes most problems associated with PPF synthesis that MRS and other reported techniques are encountered. This method which is a mixed reflux system is coupled with a simple distillation system to allow synthesizing PPF efficiently. Likewise, the effects of applied vacuum (vacuum sequence, time and vacuum position, and vacuum applying position-reactor distance) and type of applying nitrogen gas used (continuously or only an $N_2$ blanket) on PPF synthesis in MRS and MRDS have been studied. According to FTIR analysis, the best-synthesis system and conditions for the preparation of PPF have been introduced. Furthermore, the polymer composition of the PPF obtained using the best synthesizing system (MRDS) has been investigated by using NMR and FTIR spectroscopies. Gel permeation chromatography (GPC) has been employed to determine the molecular weight distribution of PPF.

## EXPERIMENTAL

### Materials

Diethyl fumarate (DEF), propylene glycol (PG), zinc chloride ($ZnCl_2$), methylene chloride and hydrochloric acid were the reagent-grade and purchased from Merck and hydroquinone was obtained from Sigma-Aldrich.

### Synthesis of polypropylene fumarate

Diethyl fumarate was reacted with propylene glycol in a three-necked round bottom flask (reactor) at a ratio of 1:3.5. Hydroquinone, a crosslinking inhibitor, and zinc chloride as the reaction catalyst and diethyl fumarate were added to the reactor with a molar ratio of 0.002 and 0.01, respectively. For PPF synthesis, each of modified reflux system (MRS) and mixed reflux-distillation system (MRDS) was used separately. MRS is a simply designed reflux setup that was equipped with an Erlenmeyer trap for the collection of by-products. Also, MRDS which is more complex than MRS consists of both reflux and distillation setups. The type of applied reflux condenser in MDRS is different than the simple condenser used in MRS. MRDS which is equipped with a distillation system is proposed to provide an optimized collection of by-products.

It should be noted that all conditions applied for polymer synthesis were kept constant for both the systems except differences in type of applying nitrogen gas (continuously or only at an $N_2$ blanket) and manner of vacuum applied (time and sequence of the applied vacuum and vacuum-reactor distance) in several batches. The details of these systems and their utilization in the PPF synthesis procedure are completely discussed in the results and discussion.

However, the reactants depending on the type of the applied system, were purged by continuous nitrogen flow (in MRDS) and non-continuous nitrogen flow (in MRS) in a reactor that was submerged in an oil bath, and magnetically mixed using a stirrer. The temperature was increased to 120°C over a period of 1h.

In the first step, bis (hydroxypropyl fumarate) was produced as an intermediate. The reaction performance in this step was different for each system. At the beginning of the second step (after 4 h from the start of reaction), the reactor of diesters was cooled down to 90°C and then placed under vacuum (400 Pa). The applied vacuum in one batch was continues (MRDS) and in another batch was stepwise (MRS) (5 min vacuum every 30 min from starting time of the cycle of applying vacuum). The temperature was then slowly increased to 140°C (10°C/15 min) and then the reaction continued at this temperature. Diester intermediates were run through a self-transesterification process and propylene glycol was collected as a distillate. The molecular weight of the polymer depended on the period that the polymer was kept at the final temperature.

The PPF was prepared by keeping the temperature constant to 140°C for 10 h [14]. Finally, the reactor was cooled up to room temperature under a purge of nitrogen. When the desired PPF molecular weight was achieved, it could be detected by reduction in OH groups signals in FTIR spectrum.

Consequently, the reaction product was dissolved in methylene chloride, and then washed with 5% aqueous HCl to remove the unreacted monomers and $ZnCl_2$. Afterward, it was purified by washing with pure water and brine. Sodium sulfate was used as a drying agent for the organic phase. Concentrated product was then precipitated in ethyl ether twice to remove the inhibitor. Finally, the remained solvents were removed from PPF by vacuum-drying at 60-70°C during 24 h. The purified resin was highly viscose and light brown. The obtained resin was characterized by FTIR and H NMR analyses. The molecular weight of PPF was also determined by GPC.

### Chemical and physical characterization

*Fourier transforms infrared spectrometry (FTIR)*

FTIR spectra were obtained by a BOMEM SPG5800G FTIR spectrometer. The characteristic peaks at 1726 $cm^{-1}$ belongs to the ester linkages, 1646 $cm^{-1}$ due to a vinyl moiety, 1455 and 1375 $cm^{-1}$ correspondence to the methyl stretching and at 1296 $cm^{-1}$ belongs to a secondary alcohol can be observed in the FTIR spectrum of PPF shown in Table 1 [19].

*Nuclear magnetic resonance spectrometry (NMR)*

H NMR spectra were obtained using a Bruker Avance 400 MHz NMR system (Bruker Analytik GmbH, Rheinstetten, Germany) operated with a Silicon Graphics $O_2$ workstation (Silicon Graphics, Mountain View, CA). Proton spectra were obtained using a 30° pulse angle, 4s acquisition time, and 3s delay time. The samples were run in $CDCl_3$ using TMS as a reference.

*Gel permeation chromatography (GPC)*

The molecular weights of the synthesized PPF were determined by a gel permeation chromatography system (model: GPC Agilent 1100) equipped with a chromatography column (Agilent & PL gel, 3 m, 300×7.5 mm column, 50- 100,000 DA range), and a refractometer index detector. THF as a solvent with a flow rate of 1ml/min was used. Molecular weights were determined using a calibration curve generated according to ASTM D6579-11.

**Table1**. Wavenumbers of bands in PPF [19]

| Bands ($cm^{-1}$) | Assignments |
|---|---|
| 3446 | OH groups |
| 2960 | Stretching frequency of $CH_2$ |
| 1730 | Stretching frequency of acid and ester carbonyl group |
| 1643 | Unsaturation C=C in fumarate unit |
| 1000–1300 | C–O stretching vibrations |

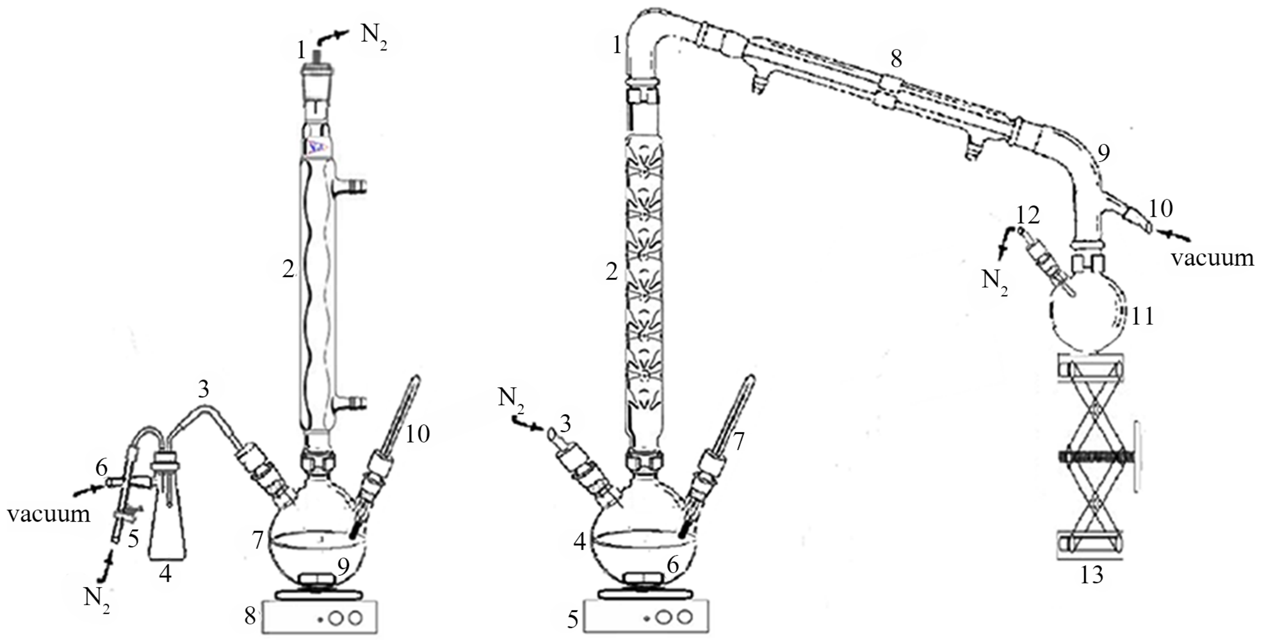
## RESULTS

Both the MRS and MRDS systems were used and compared in some points of view. The product obtained using each system was characterized and the effective parameters of the synthesis reaction were evaluated.

Synthesis of PPF by both the methods required careful implementation of polymerization conditions. The molecular weight of PPF increased during poly-esterification and trans-esterification procedures at the temperatures about 130-140°C. The reaction time was 14 h and 17 h for MRS and MRDS, respectively. In the second step, vacuum was necessary for both the methods. The chemical structures of products were studied using FTIR. Reduction in absorption of terminal hydroxyl groups in the region of 3300 $cm^{-1}$, was used to evaluate polymerization progress. Finally, NMR and GPC were used to characterize the best product.

### Modified reflux system (MRS)

This system was equipped with an Allihn condenser and an Erlenmeyer as a trap (Erlenmeyer-trap) which cooled with an ice-water bath to condense hot vapors. The Erlenmeyer-trap was connected to one of the reactor-openings (see Figure 2 (a)) to collect by-products. By-products consisted of ethanol produced in the first step and excess propylene glycol produced in the second step of the PPF synthesis reaction. At first, reactants including diethyl fumarate (DEF), propylene glycol (PG), zinc chloride and hydroquinone with the molar ratio of 1:3.5:0.01:0.002 were added to a tree-necked reactor. The reactor was placed on a stirrer and equipped with a tube under a continuous $N_2$ flow at a rate of 5 bubbles/second. The temperature was increased to 120°C in 1 h; then, the reaction continued at this constant temperature. After 30 min, the temperature was increased to 140°C at a rate of 5°C/min; 2.5 h after starting the reaction a frothy material was observed in the reactor, resulting from passing ethanol as a by-product through the monomers



(a): MRS (b): MRDS

**Figure 2**. (a): Modified reflux system (MRS). (b): Mixed reflux-distillation system (MRDS).

MRS: 1-Injection needle, 2- Allihn condenser, 3- commun tube, 4- Erlenmeyer-trap, 5- N$_2$-inlet, 6-Vacuum applying tube, 7- Reactor, 8- Stirrer, 9-Lab magnet, 10-Thermometer

MRDS: 1-Glass adaptor, 2-Vigreux condenser, 3- N$_2$-inlet, 4- Reactor, 5-Stirrer, 6- Lab magent, 7- Thermometer, 8-Leibig condenser, 9-Glass vacuum adaptor, 10-Vacuum tube, 11- Received flask, 12-N$_2$-outlet, 13- lab jack

and dimers in the reactor. Then the temperature was decreased to 80-90°C rapidly (10°C/min). Just in this moment, continuous N$_2$ inlet valve was closed and the mixture in the reactor was maintained under N$_2$ blanket at this temperature for 30 min.

The amount of the by-product in the first-step of the reaction remained in the Erlenmeyer-trap was about %75 of theoretical ethanol. Then, N$_2$ gas was entered continuously similar to the initial stage of the reaction. The temperature was risen up to 140°C at a rate of 5°C/min and the reaction continued at this temperature. Again, after 1h, all above steps were repeated for three times one by one (with intervals of 1h). This step was achieved during 6-7 h. Then, the vacuum tube was replaced with the N$_2$ tube. In the second step, the applied vacuum (400 Pa for 5 min at 140°C) caused boiling of PG, removing PG vapors from the reactor and developing the reaction. A 30 min interval was used for applying vacuum, 10°C temperature increase and applying vacuum for 5 min. This step was lasted for 6-7 h (10 times vacuum applying for 5 min, every 30 min).

In this step, increasing temperature to 165°C would cause decomposition of oligomers in the reactor. Afterward, the reactor was cooled to the room temperature under an N$_2$ blanket. Finally, the product was washed and purified. Figure 3 (a) shows the FTIR of distilled ethanol in the first step; and the by-product of the second step (propylene glycol) is seen in Figure 3 (c). In this reaction, the amounts of PG and ethanol collected in the both steps were 22% of the initial amounts of PG and DEF by volume. After collecting by-products, the reaction finished and continuing the reaction led to produce a solid-like material. In general, the product of this system was a high viscous and dark-yellow clear material. Figure 4 (c) shows the FTIR of the PPF obtained using MRS.

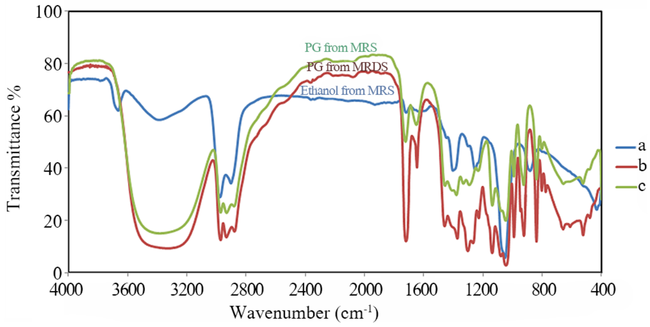


**Figure 3**. (a): FTIR of ethanol (as a by-product): sampling from the vapor phase of the reactor in MRS. (b): FTIR of propylene glycol (as a by-product) from MRDS. (c): FTIR of propylene glycol (as a by-product) from MRS.

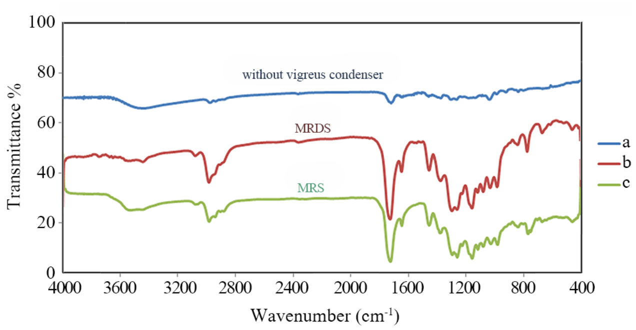


**Figure 4**. (a): FTIR spectrum of the product when Vigreux column is not used. (b): FTIR spectrum of poly (propylene fumarate) in MRDS. (c): FTIR spectrum of poly (propylene fumarate) in MRS.

## Mixed reflux-distillation system (MRDS)

In this method, a simple distillation apparatus was modified by inserting a Vigreux condenser between the reactor and Liebig condenser head. Volatile compounds such as ethanol in the first step and PG in the second step were heated to boil the mixture. Then, the generated vapors were cooled and liquefied by several passing through a Liebig water-cooled condenser and collected in a separate container, called the receiver flask (see Figure 2 (b)). All steps were similar to those in the MRS procedure, but with some differences as follows:

(Note: In the whole of the text, the mixture term refers to all reactants, by-products, intermediate, catalyst and inhibitor that exist in the reactor).

1. The reaction continues under continuous purging of $N_2$ until the first step finishes (about 6h).
2. There is not any ethanol in the first step.
3. The vacuum must be applied stepwise for 8h after starting of the second step.

In this system, the amount of collected propylene glycol in the reactor was 21% of the initial amount of PG and DEF by volume. After 17h, the reaction was finished and continuing the reaction led to the formation of a high-viscous material. In general, the product obtained by using this system was a high-brown and clear material with a higher viscosity than that obtained by the MRS. Figure 3 (b) shows the distilled PG as a by-product which was obtained in the second step. In addition, the FTIR of the PPF obtained by the MRDS is shown in Figure 4 (b).

## Chemical and physical characterization

### *FTIR results of MRDS and MRS*

The infrared spectra of synthesized PPF by MRDS

**Table 2**. Effects of production parameters on properties of the products based on primary studies (MRS and MRDS)

| Number | DEF/PG | (h) Time | Temperature (°C) | Vacuum applying | Properties of obtained product | FTIR |
|---|---|---|---|---|---|---|
| 1 | 1:1.5 | 7.5* | 140 | - | A Light brown substance similar to a hard ball | a |
| | 1:2.5 | 9* | 140 | - | Light brown- high viscosity | b |
| | 1:3.5 | 10 | 140 | - | Light brown-middle viscosity | c |
| | 1:4 | 13 | 140 | - | Light brown- middle viscosity | d |
| 2 | 1:3.5 | 3 | 140 | - | Light yellow liquid | a |
| | 1:3.5 | 8 | 140 | - | Dark yellow liquid | b |
| | 1:3.5 | 2 phase-12 | 140 | Stepwise over phase 2 | Light brown- middle viscosity | c |
| | 1:3.5 | 2 phase-17 | 140 | Stepwise over phase 2 | Light brown- high viscosity | d |
| 3 | 1:3.5 | 20.. 2 phase- | 90 | Stepwise | Light brown- middle viscosity | a |
| | 1:3.5 | 2 phase-14 | 120 | Stepwise | Light brown-relatively- high viscosity | b |
| | 1:3.5 | 2 phase-12* | 160 | - | A dark brown solid - very pungent smell | c |
| | 1:3.5 | 3.5* | 190 | - | A light brown solid foam- very pungent smell | d |
| 4 | 1:3.5 | 2* | 140 | Continuous at the first step | A dark yellow solid | a |
| | 1:3.5 | 2 phase- 10* | 140 | **Stepwise-Continuous | A light brown gel | b |
| | 1:3.5 | 2 phase- 14 | 140 | Stepwise over phase 2 | Bright red- middle viscosity | c |
| | 1:3.5 | 2 phase-14 | 140 | Stepwise over phase 2 | Dark brown- high viscosity | d*** |

*The reaction during stated time will have been spontaneously stopped with producing a solid or highly viscous material.

**Stepwise applying vacuum in the first step of the reaction and applying continuously in the second step.

***d and c in number 4 are related to MRS which was performed by the same procedure, but the obtained products are not similar (Lack of reproducibility).

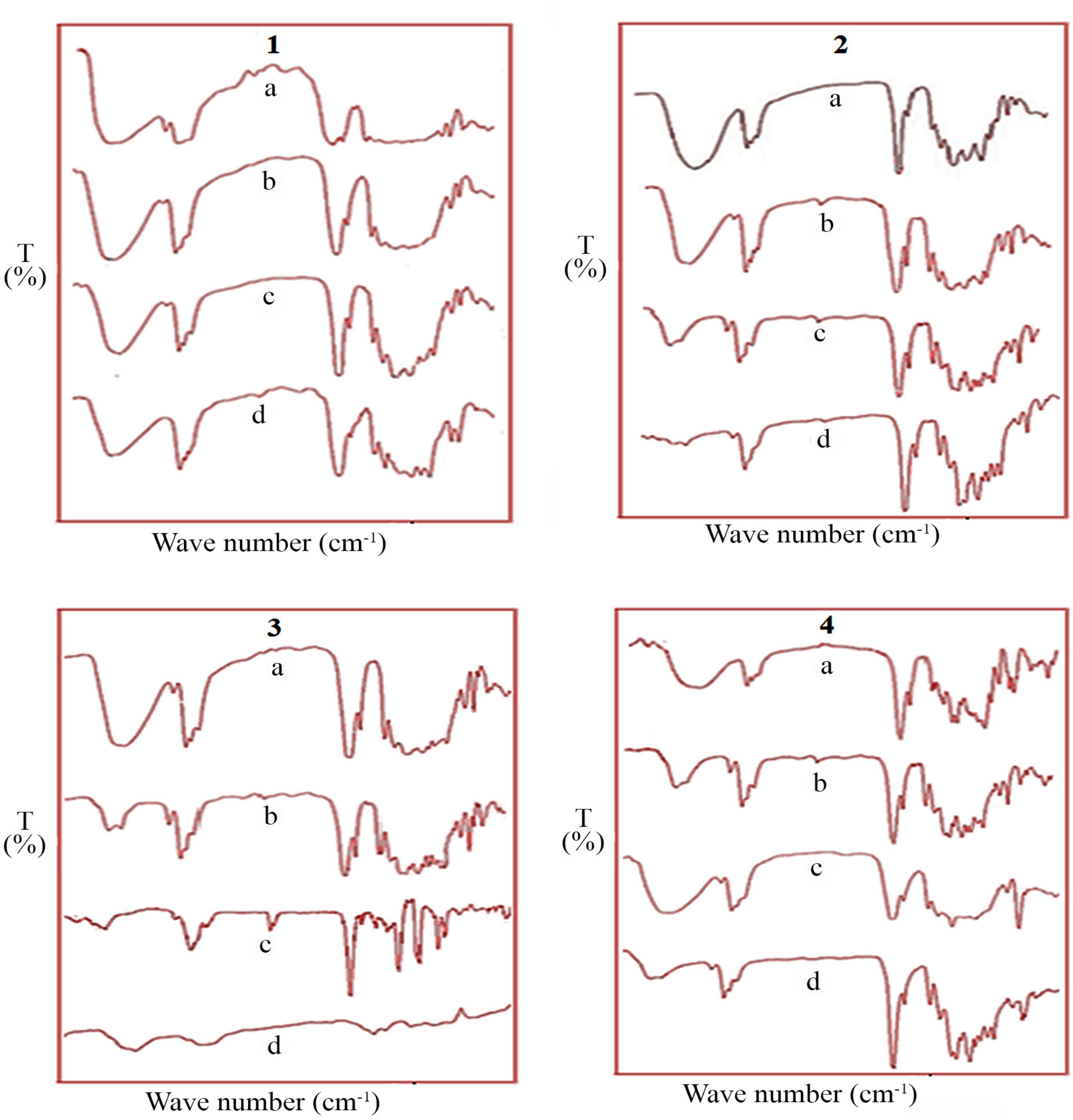


**Figure 5**. FTIR spectra of obtained products from different experiments (by various setups) according to earlier reported methods, MRDS, and MRS (numbers 1-4 each are related to changing a parameter).

and MRS are presented in Figure 4.

### *Comparison of some effective parameters in synthesizing PPF by primary studies*

There are numerous different parameters in the PPF synthesis procedures that can influence the properties of the final products such as molecular weight, the number of conjugated bonds (crosslinking density), the amount of by-product entrapped into the polymer chains, viscosity and etc. We have presented the data in the Table 2 and Figure 5 (corresponding to the Table 2) indicating the results of our experiments (by various setups), according to the reported earlier methods, MRDS and MRS. The table and figure make easier evaluation of some parameters such as time, temperature, vacuum applying and the molar ratio of monomers on the properties of the products.

### *H-NMR result for MRDS*

The H-NMR spectrum of the PPF synthesized by MRDS is represented in Figure 6.

### *GPC for MRDS*

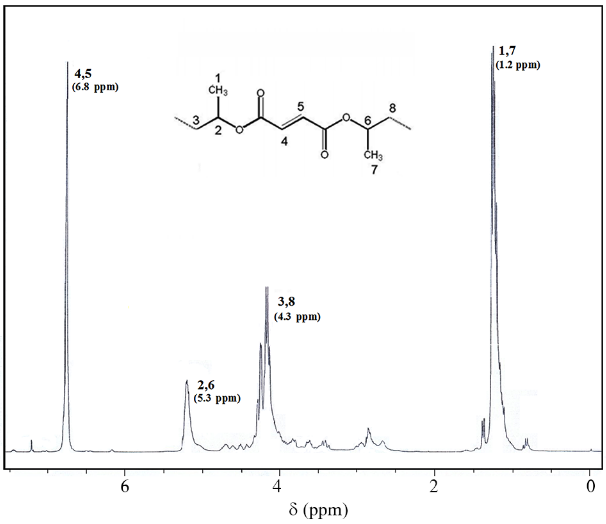


**Figure 6**. $^1$HNMR (400 MHz, CDCl$_3$, ambient temperature) spectrum of PPF

The GPC chromatogram shows that the PPF synthesized by MRDS has an $M_n$ of 1167 gr/mol, $M_w$ of 2195 g/mol and PDI of 2.8 (Figure 7).

## DISCUSSION

### Technical and experimental evaluation of the systems

*Modified reflux system (MRS)*

Reflux was used to save the energy required for continuing the synthesis reactions over an extended period of time. In this method, an Allihn condenser was connected to the reactor to recycle back vapors of PG and DEF to the mixture after cooling, and reflux them to the reaction vessel. The reactor was then heated vigorously during the reaction. Ethanol boils at about 70-80°C. Flowing $N_2$ gas in the reaction exits through the attached needle on top of the Allihn condenser after entering the reactor through a tube which is connected entering nitrogen to Erlenmeyer-trap. The analysis of the composition of collected vapors from upper reactants of the reactor at 90°C (that it condenses to liquid) shows that the majority of the collected vapor is ethanol and the contribution of vapor of PG or DEF (monomer) is minor. In fact, the vapors on the upper phase of the mixture are more volatile components. The upper phase composition is being controlled by Raoult's law as described in the reference [20]:

The vapor was enriched in ethanol (90-95%), however, increasing the temperature had a contrasting effect and caused to change the composition of the condensed liquid, (leading to higher percentages of PG and DEF). Thus, modification of Allihn condenser with Erlenmeyer-trap led to the system being like a simple distillation. Repeated refluxing cycles resulted in the development of polymerization in MRS.

In general, the mentioned method is a complex and low efficient method for producing PPF. In the first step, controlling temperature increase or deacrese is difficult during $N_2$ purging. But, this method is suitable for producing materials such as polyurethanes that their synthesis reactions do not have by-products. MRS is not an efficient method for synthesizing PPF.

*Mixed reflux-distillation system (MRDS)*

Distillation is a widely used technique for separating compounds based on differences in their boiling points. Many organic compounds are relatively volatile, i.e. they have high vapor pressures and low boiling points. Thus, combining a distillation system with a reflux system can be very suitable for refluxing reactants and separating ethanol/excess PG by-products from the reactor mixture in PPF synthesis. After running the first step for 6h, the intermediate diester, bis (hydroxypropyl fumarate), reacted through trans-esterification and produced the final PPF. Propylene glycol was produced in this step as a by-product and collected by the cooling condenser (Liebig).

In addition, PG acted as a solvent in the first step. Therefore, distillation caused to remove the excess solvent in the first step. When the mixture of PG and synthesized oligomers, obtained from the first step, was heated, the temperature raised up to the temperature of substance with lowest boiling point (PG) in the mixture, While, the other components in the mixture, oligomers, remained in the liquid phase. MRDS is based on a numerous performance vaporization-condensation cycles by Vigreux condenser before reaching vapors to Liebig condenser. Each vaporization-condensation cycle is equivalent to a simple distillation, in which vapors reach the top of the Vigreux condenser continuously; it has undergone similarly to several simple distillations (Figure 2 (b)). Hot vapors of PG passed through Liebig condenser and converted to a liquid which was then collected in the receiver flask. These vapors and final distillates contained a high percentage of the PG (liquid with a lower boiling point) that is shown in Figure 3 (b). If the condensation-vaporization cycle repeats sufficiently many times, vapors of PG will be converted to a pure material and the PG obtained from MRDS will be purer than that obtained from MRS.

At the same time, the synthesized oligomers (less volatile compounds) are enriched in the other direction. As the condensed oligomers fall down to the reactor, the reactor mixture will contain a higher percentage of the less volatile compound, gradually. The Vigreux condenser must be positioned vertically because of the condensed oligomers can fall down across rising hot vapors to the reactor. This percolation promotes the equilibrium between liquid and vapor phases, conditions that allow processing to operate at the maximum efficiency and provide the optimum separation of PG and oligomers. Thus, the position of condenser has an effective role in the polymerization.

After above-mentioned steps, recycling oligomers as well as separation of pure PG at 140°C, reaction continued in the reactor in the presence of a catalyst. Therefore, this system is very efficient for purified separation of oligomers and PG. If the received vapors are cooled by Liebig's condenser, PG vapors will be collected in the receiver flask more efficiently. This is proved that it is pure PG and its FTIR spectra is similar to the FTIR spectra of INDEX pure PG as shown in Figure 3 (b). Similarly, the presence of oligomers (less volatiles) in the reactor leads to polymerization of oligomers in the presence of a catalyst.

Oligomers (high-boiling compounds) will vaporize only if heat is increased continuously. If the temperature is not increased, it is impossible that oligomers reflux in Vigreux condenser, because the evaporation cannot be taken place. Thus, increasing the temperature of the reaction up to maximum 140°C is an important parameter to promote the oligomers condensation.

When Vigreux condenser is not used, the mixture of distilled PG will not separate completely as shown in the FTIR spectrum in Figure 4 (a). This problem is referred to increasing temperature continuously during the second step. The collected distilled sample is consists of two components: PG and oligomers of PPF.

## Evaluation of the systems based on the roles of vacuum and $N_2$ purging in details

*Study on effect of thermodynamic parameters on MRDS and MRS:*

*1) Effect of nitrogen gas as an inert atmosphere*

Generally, polymerization reaction takes place under an inert protective atmosphere of nitrogen. The inert atmosphere protects against thermo-oxidative degradation during the reaction. An $N_2$ purging causes to prevent oxidation, therefore, provides a suitable condition for maintaining a protective layer of gas on the top of the mixture constantly. Flowing $N_2$ gas not only helps to remove by-products vapor but also prevents discoloration (which would occur in the presence of oxygen) [10]. Despite this, nitrogen gas has other roles on polymerization in both systems that have been described in the following parts of the text.

*2) Importance of ethanol extraction in the first step*

Esterification reaction, as an elementary step of poly-esterification, is an equilibrium reaction.

Therefore, increasing the molecular weight of PPF is highly depended on the elimination of by-products from the reactor.

*3)Applying vacuum in the first step*

Applying a vacuum for removing ethanol at the beginning of the reaction led to removing DEF and PG out of the reactor and changing stoichiometry of monomers (molar ratio). Thus, the reaction product did not have a correct molar ratio and its structure was incomplete in both the systems. Applying a vacuum in this setup led to producing a high stiff material that was insoluble in methylene chloride and other organic solvents. However, it has been said that if ethanol is initially distilled off very fast under vacuum, it will facilitate synthesis of polymers [21].

*4) Importance of propylene glycol extraction in the second step*

When ethanol removes from the reactor completely, the polymerization becomes very slow and the second step of poly-esterification starts. PG removal from PPF is more difficult, thus the vacuum needs to be applied for PG elimination [22].

The pressure in the second step should be decreased to 400 Pa before starting this step (when a large amount of ethanol is eliminated). The first important point is that the stirrer speed should be increased during the reaction because with increasing the viscosity of material during the time, removing by-product becomes difficult. If this condition fulfills, the reaction will run smoothly.

*5) Importance of applying vacuum in the second step*

Vapor pressure is a pressure that molecules exert against external pressure at the surface of liquid which is usually an atmospheric pressure. The vapor pressure of a substance roughly doubles for each increase of 10°C. When vapor pressure of reactants mixture equals to applied pressure, the mixture boils. Thus, the boiling point of PG is a temperature, in which vapor pressure equals to applied pressure and evaporation continues until the equilibrium is achieved between the molecules entering and leaving reactants mixture. Note that under vacuum, the boiling point of a mixture will be lower than its boiling point at an atmospheric pressure. This can be exemplified by looking at the boiling point of PG at different pressures since liquid boils at lower temperatures under vacuum. Vacuum distillation is used to distil high-boiling mixture of reactants that would decompose oligomers at their normal boiling points. Then, if pressure on the liquid surface is lower than pressure of PG at its boiling point, it causes to prevent oligomers degradation due to the fact that lower pressure doesn't need to a higher temperature to reach the boiling point of PG.

*6) Importance of vacuum applying position*

Distance of vacuum applying position from the reactor is very important in both the systems. The second step of the reaction should be run under lower pressure and if the position of vacuum head is inappropriate (for example the head is very close to the reactor) reactants or low weight oligomers remove from the reactor and the stoichiometry of the reactants will be changed. Therefore, repeatability of the reaction is reduced dramatically and different products with different structures may be produced.

*7) Applying vacuum: continuously and stepwise*

Applying vacuum consistently and stepwise (15 min vacuum-30 min without vacuum) effects on the product quality. If applying vacuum continues in the whole of the reaction, polymerization will be stopped after 2 and 5 h in MRS and MRDS, respectively. In our experiments, it was found that the best condition in applying vacuum was an stepwise manner with the maximum distance of vacuum position from the reactor. A short distance causes the monomers and oligomers remove suddenly. Vacuum is used to reduce the pressure of the system to encourage removing the by-products. Generally, applying vacuum is a very important factor in increasing the polymerization reaction rate. But, continuously applying vacuum not only causes the reaction proceeds in an unrepeatable manner but also gives unreliable results. It was found that the best condition in applying vacuum was stepwise consisting of two steps: 5 min vacuum (400 Pa) and 30 min without vacuum repeated for 6 - 8 h.

### Modified reflux system (MRS)

*Importance of nitrogen gas*

In the MRS, if the $N_2$ inlet and evolved gas streams (ethanol and PG) have a common narrow channel, the reaction will be controlled via this channel. To run the reaction continuously, two important parameters with a critical effect on the operation of the reaction are:

1- Purging $N_2$ gas continuously,

2- Common route between $N_2$ entrance and by-product collector tube (Figure 2 (a)).

Flowing nitrogen in a stepwise manner in the first step led to collection of ethanol as well as the development of the reaction. When, $N_2$ gas was purged continuously, the reactants in the condenser underwent the esterification reaction to produce frothy material. At this time, ethanol was at its highest volume and temperature needed to be reduced to 80-90°C, leading to reducing the volume of vapors (unless ethanol) to their minimum volume. Reduction of temperature before disconnecting of $N_2$ is very important. The vapors in the Erlenmeyer-trap contained ethanol, DEF and PG (50% by volume of ethanol, 50% by volume of DEF and PG).

Condensation at 90°C led to form more ethanol and less PG as well as DEF collection (85-90% ethanol, 10-15% both PG and DEF). The FTIR spectrum seen in Figure 3a shows the spectrum of the vapors. But, Figure 3 (a) shows that some amount of PG and DEF always evaporate with ethanol in the first step that causes changing the stoichiometry ratio and reducing the efficiency of MRS consequently. Ethanol vapors condensed by passing through the tube located between $N_2$ entrance and Erlenmeyer-trap and by repeating the mentioned steps the amount of obtained ethanol reached up to 90-95% of its theoretical amount. $N_2$ purging rate and stepwise applying of $N_2$ are the effective parameters for synthesizing PPF by MRS.

*Importance of vacuum applying position*

The role of vacuum applying position in MRS is to avoid monomer stripping. If the diameter of the reactor-vacuum connection is very small (about 5 mm) the pressure will be decreased slowly (400 Pa/min). Therefore, suddenly evaporating monomers/oligomers can be avoided. Furthermore, the distance between the vacuum pump and the reactor can be extended using a narrow long tube to reduce monomer evaporation.

*Role of vacuum*

Applying stepwise vacuum in MRS is more appropriate than applying it continuously. Applying vacuum dynamically leads to removal of monomers and lower molecular weight oligomers and can reduce the reaction time in the second step from 6-8 h to 2 h (4a, according to Table 2 and Figure 5). Decreasing of the time causes to incomplete progress of the reaction. The FTIR spectra of the samples synthesized by MRS shown in Figure 5 (4c and 4d) demonstrate that most of terminal OH groups are diminished with applying the vacuum in the second step. In fact, development of the reaction strongly depends on the vacuum, and more importantly the method of applying vacuum. The products resulted from applying stepwise vacuum in MRS are not reproducible as shown in Figure 5 ((4c) and (4d)) (with similar synthesis conditions but different spectra). Therefore, it can be concluded that applying stepwise vacuum in MRS will not lead to a reproducible production.

**Mixed reflux-distillation system (MRDS)**

*Importance of nitrogen*

A dry nitrogen gas flow is usually enough to remove ethanol from the reactor. A moderate nitrogen stream flows through the system and a created nitrogen bubble in the water filled beaker indicates the rate of ethanol exiting from the system. However, an excessively nitrogen flowing rate may result in undesired removal of volatile reactants such as the diethyl fumarate. The polymerization efficiency is also corresponded to nitrogen purging rate directly. If distillation is conducted very rapidly, liquid-vapor equilibrium will not be established in the Vigreux condenser, and a poor separation of by-products will result. Synthesis of PPF by polyesterification between DEF and PG is operated under a moderate inert atmosphere. At the beginning of the reaction, nitrogen flow should be 2 bubbles/second. Afterward, when the most of the ethanol distils off, in order to remove excess glycol, the speed of the bubbles production should be fast (5 bubbles/second). Similarly, $N_2$ flowing has an effective role in transferring PG to the upper part of the Vigreux condenser.

*Ethanol extraction in the first step*

It has been said, ethanol as the first step reaction by-product was collected by distillation and the reaction was run until 90% amount of theoretically expected ethanol was obtained [13-15, 17]. But, such phenomenon was not observed in MRDS. Ethanol is more volatile, therefore its vapors pass through micro-pores of adaptors rather than accumulation. While, propylene glycol is driven off and collected as a distillate during self-transesterification of diesters intermediates, bis (2-hydroxypropyl fumarate).

Some amount of ethanol evaporates into the air and the rest condenses on the inner condenser surface. It is found that after running distillations in the first step, much of the ethanol will be lost. Therefore, ethanol will not be condensed at all.

**Chemical and physical characterization**

*FTIR analysis*

The infrared spectrum of the best synthesized product is presented in Figure 4 (b). Each functional group corresponds to a region of absorption wavelengths, thus, it allows to identify the product. The stretching vibrations of typical organic molecules tend to fall within specific regions of the infrared spectrum, as shown in Table 1. Intermediate diesters have higher relative intensity in OH region due to terminal hydroxyl vibration at 3448 $cm^{-1}$ as a result of higher proportion of hydroxyl end groups compared to unsaturated polyester.

In the synthesized polymer, this hydroxyl peak diminished with the reaction time due to decreasing relative amount of present end groups in the polymer. The ester carbonyl bonds and C=C stretching appear at 1726 $cm^{-1}$ and 1646 $cm^{-1}$, respectively. After trans-esterification of intermediate, a noticeable decreasing in OH band at 3448 $cm^{-1}$ was observed due to the obvious removal of propylene glycols.

The FTIR spectra should be emphasized on the absence of the mentioned peaks that confirms the improvement of esterification reaction. According to the literature, free carbonyl groups should appear at 1690 $cm^{-1}$. At lower wavenumbers, significant peaks, which are presented around 1226 $cm^{-1}$, may be attributed to C-O linkages.

Reaching low terminal OH bands means obtaining the fine product. As shown in Figure 4 (b and c), the FTIR spectra indicate that a significant diminishing of the OH groups after 14h in MRS and 17 h in MRDS are achieved.

### *Comparison of some effective parameters in synthesizing PPF by primary studies*

The FTIR analysis data based on increasing the molecular weight with time can be used to characterize the conversion of intermediates to the final product. The presence of terminal OH groups in FTIR spectra plays an important role in distinguishing the different steps of PPF synthesis. The reduction of peak intensity of OH groups demonestrates that the polycondensation reaction is occurred. The more progress is made in the polycondensation reaction, the higher molecular weight is achieved. Furthermore, decreasing the intensity of OH region means that the synthesizing process is going on correctly [23].

The FTIR spectra indicate a significant diminishing of the OH groups after 13- 14 hours ( 2c, 3b and 4d (MRS) in Table 2 and Figure 5). The PPF with $M_n$ of 1167 gr/mol and $M_w$ of 2195 gr/mol which was produced after 17 h in MRDS was identified as the best product (2d in Table 2 and Figure 5).

Generally, the reaction rate is fast and products with higher molecular weight are obtained in higher temperatures. In the lower temperatures of 90-105°C (3a in Table 2 and Figure 5), the reaction is very slow [23, 24]. But, the products decompose at the temperatures higher than 160°C (3c and 3d in Table 2 and Figure 5).

In order to obtain higher degrees of polymerization, the removal of polypropylene glycol as a by-product from the reactor is necessary for the second stage. Removing the propylene glycol is difficult; thus, the vacuum should be applied correctly to facilitate this process [23, 25]. Obviously, decreasing PG by applying vacuum continuously leads to changing the stoichiometry of the reactants and premature end of the reaction. However, it seems that applying vacuum stepwise in some procedures such as MRS leads to a low reproducibility (4c and 4d in Table 2 and Figure 5) and in some procedures such as MRDS (2d in Table 2 and Figure 5) leads to a high reproducibility. Moreover, applying vacuum continuously in the other procedures are not suitable for synthesizing PPF ((4a and 4b in Table 2 and Figure 5)

The reaction time is increased by increasing the molar ratio of PG: DEF from 1.5 to 4 without applying vacuum (1a-1d in Table 2 and Figure 5) and the polymerization is also proceeded. So, more glycol ( in an acceptable range) leads to the increase of the reaction time and makes it controllable (1c and 1d in Table 2 and Figure 5) [23].

The data in the table indicates clearly that few changes in each parameter result in large effects on quality of the final product. In fact, the PPF is very influenced by the parameters of polymer synthesis. MRDS is a new clear designed method which is a combination of several well-known methods in polymer science that not only can facilitate PPF synthesis as a biopolymer for biomedical application, but also provide a certain method in PPF synthesis with very high reproducibility and efficiency. Finally, in MRDS, 1:3.5:0.01:0.002 molar ratio (DEF: PG: $ZnCl_2$: hydroquinone) of the reactants with stepwise

**Table 3**. Technical aspects and results of the synthesized PPF obtained by using MRS and MRDS.

| Methods | (h) Time | Final temperature (°C) | Applying vacuum | $N_2$ purging | Properties of the products | Collected PG and ethanol | FTIR |
|---|---|---|---|---|---|---|---|
| MRS | 2 phases-14 (phase 1: 6-7h /phase 2:6-7 h) | 140 | Stepwise over phase 2<br>10 times for 5 min 30 min, every over phase 2 | continuous-non in the first step (Continuous during 2.5h and then under $N_2$ blanket) | Dark brown- high viscosity / Lack of reproducibility | 22% V of initial PG and DEF<br>(accumulation of ethanol in the first step) | Figure4 (c) |
| MRDS | 2 phases-17 (phase 1: 6-7h /phase 2:10 h) | 140 | Stepwise over phase 2<br>10 times for 5 min 30 min, every over phase 2 | Continuous in the first step (5bubbles/second) | Light brown- high viscosity/ high reproducibility | 21% V of initial PG and DEF<br>(no accumulation of ethanol in the first step) | Figure 4 (b) |

applying vacuum, 17 h reaction time, and 140 °C temperature has been obtained as the best formulation in the PPF synthesis.

The advantages of MRDS compared with current methods are listed in the following:

1. Due to the lack of ability to fully remove of byproducts from the reactor in the reflux current systems and in order to develop the reaction, the other parameters must be changed to compensate changing parameters including:
   - Increasing reaction time that can damage double bonds in PPF structure and also has not suitable industrial scale perspective.
   - Applying higher temperature can damage the double bonds in the PPF structure and may result in decomposition of polymer structure. In addition, increasing the temperature above the desired temperature, not only is not economical, but also creates some undesirable byproducts that affect the efficiency of the reaction.
   - The use of some strong catalysts such as p-toluene sulfonic acid can influence the progress of polymer reaction and may create the different structures of PPF with various molecular weights [26]. Thus, by applying MRDS for synthesizing PPF, producing undesirable byproducts out of the reaction kinetics may be reduced.
2. The MRDS strongly increases the efficiency of the polymerization reaction. This methodology allows to prepare polymers by polycondensation reaction in a high quality, efficient and reproducible manner.
3. The MRDS can be very effective in the polycondensation reactions, because in addition of the main products, byproducts can be used, too. Thus, purity of by-product is important and can be provided with MRDS.

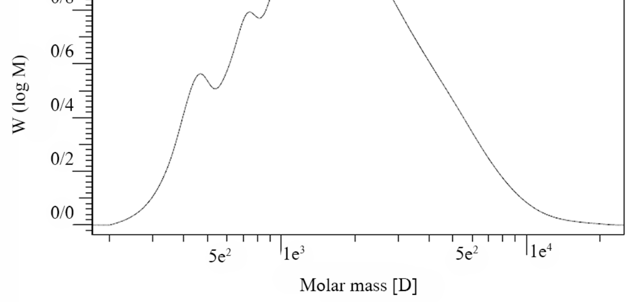


**Figure 7**. GPC chromatogram of final PPF

Furthermore, Table 3 shows technical aspects and results of synthesized PPF by MRS and MRDS.

*H-NMR spectroscopy*

H-NMR spectrum of synthesized PPF by MRDS is presented in Figure 6. The chemical shifts appeared at 6.8 ppm (vinyl protons), 5.3 ppm (-CH), 4.3 ppm (-CH$_2$) and 1.2 ppm (-CH3) confirm the chemical structure of PPF.

*GPC analysis*

The results obtained from the synthesis and characterization of some samples by FTIR show that the best product has a number average molecular weight ($M_n$) of 1167 g/mol, the weight average molecular weight ($M_w$) of 2195 g/mol and PDI of 2.8. The GPC analysis of the PPF obtained by MRDS has been shown in Figure 7.

## CONCLUSION

A new mixed reflux-distillation system (MRDS) was used for synthesizing PPF via esterification reaction. Usefulness of new reaction method results from that all common techniques are inefficient from energy, time, and cost point of views. The reactions could be carried out without employing any special equipment. Vigreux condenser facilitated to retain the monomers in the reactor and to obtain optimum PPF molecular weight. Modified reflux system (MRS) was less efficient than the MRDS. However, in MRDS, refluxing and distillation processes were performed continuously. Pure propylene glycol as a by-product also indicated that the reaction had a higher yield. Thus, this novel system could be considered as a very suitable, efficient and reproducible technique in synthesizing PPF. Nitrogen gas, vacuum applying position, continuously/stepwise-continuously applying vacuum and other parameters showed an important role in the polymerization of PPF in both the systems.

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