Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-g-poly(vinyl pyrrolidone): Synthesis and characterization

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Abstract

Pluronic poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO–PPO–PEO) block copolymers are grafted with poly(vinyl pyrrolidone) by free radical polymerization of vinyl pyrrolidone with simultaneous chain transfer to the Pluronic in dioxane. This modified polymer has both thermal responsiveness and remarkable capacity to interact with a wide variety of hydrophilic and hydrophobic pharmaceutical agents which is very attractive for medical applications. The chemical structure of the graft copolymers was characterized by FTIR and $^1$H NMR spectroscopy. Polymerization conditions such as initiators, feed ratio, and reaction times are studied to obtain the ideal graft copolymer.

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1. Introduction

Water-soluble triblock copolymers of the EPE type (P and E represent poly(propylene oxide) and poly(ethylene oxide), respectively), often abbreviated as PEO–PPO–PEO (or (EO)$_m$(PO)$_n$(EO)$_m$ with $m, n$ representing the number of repeated units), are commercially available non-ionic macromolecular surfactants and have many uses [1–3]. These polymers are commercially known as Pluronic or Poloxamer (BASF) or Synperonic (ICI) polyols. They find widespread industrial applications as emulsifying, wetting, thickening, coating, solubilizing, stabilizing, dispersing, lubricating, and foaming agents [4–7]. Polyethylene oxide–polypropylene oxide–polyethylene oxide (PEO–PPO–PEO) triblock copolymers have been extensively studied because of their thermally responsive aggregation behavior, which can be used for a variety of biomedical applications [8,9]. On top of its unique surfactant behavior, its low toxicity and minimal immune response also make this polymer highly attractive for such applications [10,11]. Poly(vinyl pyrrolidone) (PVP) is a well-known water-soluble, biocompatible, and relatively amphiphilic polymer. The highly polar amide confers hydrophilic and polar attracting properties to the polymer while the apolar methylene group in the backbone and the methine group in the ring contribute to its hydrophobic properties [12]. It has been largely used in the pharmaceutical field [13–15].

In the present study, Pluronic grafted with PVP was targeted, which would combine the advantages of Pluronic and PVP to broaden the field of application. The synthesis of such copolymers involves solution polymerization of vinyl pyrrolidone initiated by free radical initiators [16].

2. Experimental

2.1. Materials

Pluronic F127 was purchased from Fluka and was used without further purification. It has a formula of EO$_{99}$PO$_{65}$.
EO\textsubscript{99} and a nominal molecular weight of 12,600. The molecular weight of PPO segment is 3780 and 70 wt% of the chain is made up of EO. The cloud point of F127 is above 100 °C.

N-Vinyl pyrrolidone (VP) was distilled at 100 °C before use. Lauroyl peroxide (LP) (97%, redox initiator) was obtained from Lancaster and 2,2′-azobisobutyronitrile (98%, AIBN) was bought from Teehai and recrystallized from methanol. 1,1′-Azobiscyclohexanecarbonitrile (Vazo 88) was purchased from Dupont Specialty chemicals and was recrystallized from cold acetone and benzyl peroxide (BP). PVP with a molecular weight of 10,000 was obtained from Sigma-Aldrich. Dioxane (HPLC grade) and diethyl ether (HPLC grade) was purchased from Fisher Company and used without further purification.

2.2. Synthesis of graft copolymer Pluronic F127-g-PVP

Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-g-poly(vinyl pyrrolidone) was synthesized by solution polymerization of vinyl pyrrolidone along with simultaneous grafting of poly(vinyl pyrrolidone) onto the Pluronic backbone. A known amount of vinyl pyrrolidone and Pluronic was charged into a 125-ml flask. The polymerization was carried out in the dioxane solution (20 ml under dry nitrogen atmosphere). In the presence of initiator, such as azobisisobutyronitrile (AIBN) or V88 and so on, the resulting solution was deoxygenated by nitrogen flow for 24 h while stirring.

The reactor was equilibrated for 1 h while stirring at 20 °C under nitrogen, after which the heating began and timing commenced. The reactor was heated to a certain temperature at a desired rate (typically 1–2 °C/min) under constant nitrogen flow and it was kept at this temperature for a number of hours under stirring. After that, the reactor was again allowed to equilibrate at 20 °C. After equilibration, the nitrogen flow was discontinued. Excess ethanol and diethyl ether were repeatedly added to the solution and then filtered to precipitate and clean up the product. The resultant white powder was dried under vacuum (10\textsuperscript{−3} Torr) at 40 °C for 24 h. After that, the crude product was washed repeatedly using acetone and THF to get rid of PVP homopolymer and Pluronic, respectively. The resultant product was dried under vacuum at 40 °C for another 24 h.

2.3. Polymer characterization procedures

The chemical structure of the polymer was studied using a Perkin–Elmer System 2000 Fourier transform infrared spectrometer. First, a background spectrum was run with pure KBr pellet (diameter 13 mm). The copolymer sample was then thoroughly mixed with KBr powder upon careful grinding and then the mixture is pressed into pellets. The spectrum of the mixed pellet was collected against the spectrum of pure KBr as the background. A total of 10 scans at a resolution of 4 cm\textsuperscript{−1} (in the mid-IR region of 4000–400 cm\textsuperscript{−1}) were obtained to achieve a good signal-to-noise ratio.

The molecular weight (\(M_\text{W}\)) and molecular weight distribution (\(M_\text{W}D\)) of the polymers were determined using an Agilent series 1100 gel permeation chromatograph. A mixed bed column (PLGel mixed bed C, 5 μm, 300 × 7.5 mm, Polymer Laboratories), along with a guard column (50 × 7.5 mm, Polymer Laboratories), was used. The mobile phase was a mixture of tetrahydrofuran (THF) and dichloromethane (DCM) at a volume ratio of 80:20. The molecular weights of the samples were obtained relative to the polystyrene standards. The flow rate was 1 ml/min and the temperature (both the column compartment and the flow cell of the refractive index detector) was kept at 35 ± 0.1 °C. The samples were dissolved in the mobile phase and filtered through 0.22-μm disposable syringe filters into 2-ml glass vials. These vials were then put into the auto sampler tray. The typical injection volume was 20 μl.

The NMR studies were carried out on a Bruker 400 MHz instrument, operating at 400 MHz (\(\textsuperscript{1}H\)). CDCl\textsubscript{3} was used as the solvent, TMS as the internal zero reference. The \(\textsuperscript{1}H\) NMR spectra were recorded.

3. Results and discussion

3.1. Optimization of synthesis

The proposed scheme of free radical polymerization is as shown below:

\begin{align*}
\text{Initiation} & \\
R^\cdot + nVP & \rightarrow R-VP_n^\cdot \\
R^\cdot + & \rightarrow RH + X \\
RVP_1^\cdot + & \rightarrow RVP_1H + X \\
\text{Propagation} & \\
X & \rightarrow mVP \\
X & \rightarrow VP_n^m \\
X & \rightarrow qVP \\
\text{Termination} & \\
R-VP_n^\cdot + \text{Pluronic}^\cdot & \rightarrow \text{graft copolymer} \\
R-VP_n^\cdot + \text{Pluronic-g-PVP}_n^\cdot & \rightarrow \text{graft copolymer} \\
R-VP_n^\cdot + R-VP_n^\cdot & \rightarrow \text{homopolymer}.
\end{align*}
The macroradicals can be formed by random hydrogen abstraction from methyne and/or methylene groups in the Pluronic chains in the presence of vinyl monomers [17,18]. In the case of reactive propagating radicals, the multiple branches will probably lead to the appearance of a brush structure of the graft copolymer. The recombination of VP and Pluronic radicals also produces the graft copolymer.

Before the discussion of the synthesis conditions can proceed, some terms have to be introduced.

The effective degree of conversion of vinyl pyrrolidone (VP) into the polymer, F, is defined as follows:

\[ F\% = \frac{\text{weight of polymerized VP}}{\text{initial weight of VP in the reaction mixture}} \times 100. \]

The degree of bonding between Pluronic and poly(vinyl pyrrolidone), B, is defined as follows:

\[ B\% = \frac{\text{weight of Pluronic bonded}}{\text{initial weight of Pluronic in reaction mixture}} \times 100. \]

The percentage of grafting, PG, and the grafting efficiency (%), GE, were estimated from the following equations:

\[ PG\% = \frac{\text{weight of grafted PVP}}{\text{weight of graft copolymer}} \times 100. \]

\[ GE\% = \frac{\text{weight of grafted PVP}}{\text{weight of grafted PVP} + \text{weight of homo-PVP}} \times 100. \]

### 3.1.1. Effect of initiators

Parameters chosen for the optimization were the effective degree of VP conversion (F%), the degree of bonding of Pluronic to the resulting copolymer (B%), and the grafting efficiency of VP (GE%). Table 1 shows the F values were high for all initiators except for V88, which possesses a very long half-life. High F value is desirable in our synthesis for the minimization of the residual monomer content. It is also important that the initiator and propagating radicals be spent as fully as possible since radical species remaining in the polymer will result in the formation of hydroperoxides upon contact with air which will lead to chain scission reactions and polymer degradation. Therefore, initiators with a shorter half-life (LP and AIBN) will be more suitable for the synthesis.

Generally, azonitriles has a higher hydrogen abstraction strength compared to peroxy initiators. This results in a much lesser B value because there is a higher chance for the combination reaction between Pluronic macroradicals. While BP resulted in the highest B value, some researchers showed that it also contributed to the appearance of the permanently cross-linked fraction, probably due to multiple branches on one Pluronic chain [12]. Another reason why BP is not selected is that it has a lower grafting efficiency to VP monomer. Hence the initiator used is LP.

The effect of initiator concentration on the grafting efficiency is shown in Fig. 1. The grafting efficiencies was increased up to 2 mM of the initiator but decreased slightly when the concentration increased to greater than 2 mM. The phenomenon is due to the fact that at high initiator concentration, the homopolymer is more favorable to form than the graft copolymer.

### 3.1.2. Effect of feeding ratio

The graft polymerization was carried out in dioxane with 2 g Pluronic F127 and 2 mM lauroyl peroxide at 70 °C for 6 h using several concentrations of VP such as 2, 3, 4, 5, 6, and 7 g. Fig. 2 shows the effect of the feed ratio by weight on the grafting efficiency.

The grafting efficiency reaches a maximum at 5 g VP. The increase in the grafting efficiency at a higher monomer concentration is ascribed to the fact that more VP radicals are present to be grafted onto the Pluronic backbone. At higher VP concentration, there are more VP radicals available to react with a Pluronic chain. Hence, the graft efficiency increased. The grafting efficiency decreased after a critical concentration is reached. A possible reason is that at higher VP concentration the homopolymerization of VP occurs. As the concentration of VP radicals increases, the recombination of VP radicals comes into play. Thus, the tendency for the chain transfer to Pluronic copolymer decreased.

### 3.1.3. Effect of reaction time

The graft polymerizations were conducted with 2 g of Pluronic copolymer and 5 g of VP, and 2 mM LP at 70 °C for several reaction times. The effect of reaction time on the grafting process is shown in Fig. 3.

When the degree of conversion of VP reached the maximum value, the grafting efficiency and the percentage of grafting also reached the highest value. This means that the polymerization of VP monomer to form the homopolymer

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**Table 1**

<table>
<thead>
<tr>
<th>Initiator</th>
<th>Abbreviation</th>
<th>MW</th>
<th>Half-life (h)(^a)</th>
<th>F%</th>
<th>B%</th>
<th>GE%</th>
<th>d</th>
</tr>
</thead>
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<tr>
<td>Lauroyl peroxide</td>
<td>LP</td>
<td>398.63</td>
<td>3.5</td>
<td>92</td>
<td>80</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>2,2′-Azobisobutyronitrile</td>
<td>AIBN</td>
<td>164.21</td>
<td>4.8</td>
<td>87</td>
<td>20</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>BP</td>
<td>242.23</td>
<td>7.3</td>
<td>84</td>
<td>85</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>1,1′-Azobicyclohexane carbonitrile</td>
<td>V88</td>
<td>244.34</td>
<td>143</td>
<td>81</td>
<td>12</td>
<td>33</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) At 70 °C in toluene.

\(^b\) Degree of VP conversion at initiator concentration 2 mM after 10 h in the graft polymerization.

\(^c\) Effective degree of Pluronic bonding.

\(^d\) Grafting efficiency of PVP.
PVP and the grafting of the VP onto the Pluronic backbone occur at the same time. The degree of polymerization of the PVP grafted chains are related to the degree of the homopolymer PVP formation. The homo-PVP is readily formed at the beginning of the reaction, because the grafting efficiency is very low at that time. As the reaction time increased, the concentration of VP monomer in the solution decreased. More and more PVP radicals are present in the system and more chance for PVP radicals to be grafted onto F127. The percentage of VP contributing to homo-PVP decreased. The grafting efficiency reached the maximum.

3.2. Characterization of graft copolymer

3.2.1. Chemical structure

FTIR is used to study the chemical structure of the polymer. Its spectra were recorded in a water-free atmosphere. Fig. 4 shows the spectra for homopolymer PVP, Pluronic F127, and Pluronic F127-g-PVP. The VP carbonyl vibration occurs at around 1650 cm\(^{-1}\). The ether bands of the Pluronic F127 can be obtained near 1100 cm\(^{-1}\) spectral region. Since the graft copolymer, Pluronic-g-PVP, consists of both the carbonyl bond of VP and the ether bond of F127, the vibrations in both areas can be observed in the spectra.

Next we will like to investigate whether the materials obtained were graft copolymer with covalent bond or mere blends where the two polymers are physically mixed. A mixture of PVP and Pluronic F127 is dissolved and cast from chloroform solution at room temperature. The blend was characterized before and after the extraction procedure. The extraction procedure consists of acetone extraction at room temperature. The spectra obtained for the graft copolymer is compared to the spectra obtained for the mixture of PVP and Pluronic F127 before and after the acetone extraction shown in Fig. 5. A strong reduction of the carbonyl peak of PVP after the acetone extraction for the blend was found. These findings strongly indicate that when no covalent bond exists between the PVP and Pluronic copolymer chain, such as in the case of the blend, both components of the system could easily be separated by a selective solubilization procedure.

After the graft copolymer was extracted twice from acetone, the PVP carbonyl peak could clearly be seen, which means that the PVP is chemically bonded to the Pluronic backbone. It can thus be concluded that there is covalent bond between
3.2.2. Molecular weight

The effect of the reaction time on the molecular weight of the samples is shown in Fig. 6. The molecular weights are measured using GPC and the values are estimated using polystyrene as the standard. The value is found to be 26,000, which is similar to those obtained from $^1$H NMR. Simultaneous polymerization of VP and Pluronic/PVP bonding increase the molecular weights of the product. After the molecular weight of the graft copolymer reaches the maximum value, it decreases. From Fig. 6, one can observe that the molecular weight of the graft copolymer decreased slightly after 8 h, the key reason may be that the longer the reaction time, the opportunity for the oxidation and decomposition reactions to happen increases. There may still be some unfavorable chain transfer reactions in the synthesis system after 8 h. Hence, the optimal reaction time is 6 h.

3.2.3. Composition

The major features of NMR spectra of Pluronic F127-g-PVP copolymer in CDCl$_3$ are shown in Table 2 and Fig. 7. The $^1$H NMR is used to determine the composition of the copolymer.

The VP/Pluronic unit ratios can be obtained from the integration ratio of resonances arising from protons due to the methyl group in Pluronic and P$_4$ hydrogen in PVP, shown in Fig. 7. Hence, the mole ratio of PVP in the whole graft copolymer can be obtained. This mole ratio can be converted to a weight fraction for calculation of the percentage of grafting.

The percentage of grafting can be calculated as the equation:

$$W_{\text{vp}} = 1.5 \times \frac{M_{\text{vp}}}{(198_{\text{EO}} + 69_{\text{PO}})} \times \frac{I_{\text{CH}_2\text{CO}}}{I_{\text{CH}_3}} = 1.16,$$

where 198 and 69 are the units of PEO and PPO in F127, respectively. $PG\% = W_{\text{vp}}/(W_{\text{vp}} + W_{\text{F127}}) = 52\%$.

The percentages of grafting calculated using NMR and weight reduction data are similar, which implies that the calculation of percentage of grafting calculation by weight (in Section 3.1) is correct. The value obtained from NMR is cal-
Table 2

<table>
<thead>
<tr>
<th>Assignment</th>
<th>δ, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methine HC–OC in EO, PO</td>
<td>3.4–3.5</td>
</tr>
<tr>
<td>Methylene H₂C–OC in EO, PO</td>
<td>3.5–3.6</td>
</tr>
<tr>
<td>Methyl in PO</td>
<td>1.0–1.1</td>
</tr>
<tr>
<td>P₁, P₅⁺</td>
<td>2.2–1.7</td>
</tr>
<tr>
<td>P₂, P₆⁺</td>
<td>3.9–3.4</td>
</tr>
<tr>
<td>P₄⁺</td>
<td>3.19</td>
</tr>
</tbody>
</table>

*PVP:

Fig. 7. ¹H NMR spectrum (CDCl₃) of the graft copolymer.

4. Conclusions

In this study, the novel graft copolymer, Pluronic-g-PVP, was successfully synthesized by simultaneous polymerization and chain transfer of VP monomer onto the Pluronic copolymer. The copolymers were produced through radical grafting polymerization. The optimal grafting condition was obtained. The reaction products were graft copolymers and not physical mixtures of individual polymers of Pluronic F127 and PVP as demonstrated by selective extraction and FTIR. With ¹H NMR spectroscopy, the chain structure of the copolymer was characterized and the compositions of the copolymers were also obtained.

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References