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# Evaluation of Solubilizing Potential of Functional Poly(jasmine lactone) Micelles for Hydrophobic Drugs: A Comparison with Commercially Available Polymers

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# Evaluation of Solubilizing Potential of Functional Poly(jasmine lactone) Micelles for Hydrophobic Drugs: A Comparison with Commercially Available Polymers

**Abstract**: Achieving the high solubilization capacity with the aid of polymeric micelles (PM) is still one of the major challenges. To address this shortcoming, novel poly(jasmine lactone) (PJL)-based PM were developed and compared with Soluplus® and poly(lactide) copolymer. The presence of "ene" groups on PJL's backbone offers a unique opportunity to insert functionality. We introduced -COOH and phenyl groups onto the PJL copolymer and observed ~334-fold increments in aqueous solubility of clotrimazole with -COOH-terminated PJL copolymer compared to Soluplus. We successfully demonstrate that the presence of appropriate free functional groups on the polymer chain can facilitate the solubilization potential of PM.

**Keywords**: poly(jasmine lactone); functional polymer; polymeric micelles; aqueous solubility; renewable polymer; non-covalent interactions; polymer-drug interaction.

## 1. Introduction

Aqueous solubility of active pharmaceutical ingredients (APIs) has a direct impact on its bioavailability via the oral route. Although it is possible to achieve 100% bioavailability via the intravenous (IV) route, formulating an IV formulation is challenging for many reasons; one of the main ones being that it requires sufficient solubility of drug in aqueous solvent. Consequently, several methods for increasing the aqueous solubility such as spray drying, reduction in API particle size, and nanoparticle formulation have been developed [1]. Lately, nanoparticle-based approaches have gained increased interest in solving the poor aqueous solubility of APIs. Particularly, polymeric micelles (PM) have turned out to be a very promising platform for the delivery of poorly soluble APIs. PM demonstrates improvement in bioavailability and pharmacokinetic profiles of APIs, and thus, quite a few PM formulations are approved for human use, and several others are in clinical trials [2]. PM composed of polymeric surfactants, are thus usually prepared from amphiphilic polymers containing a hydrophobic and hydrophilic block.

Among several polymers, amphiphilic block copolymer of poly(lactic acid) (PLA) with poly(ethylene glycol) (PEG), mPEG-b-PLA, have been extensively explored for micelle formulations. Genexol® PM, the first PM formulation approved for human use, also contain PLA. The polymer used to develop Genexol® PM contain 2.0 kDa of PEG and 1.75 kDa of PLA, which self-assembles into micelles to encapsulate paclitaxel via hydrophobic interaction to generate a safer and more effective version of the free drug [3]. Encapsulation of numerous other drugs within mPEG-b-PLA micelles has been reported in the literature, demonstrating improvement in the safety and efficacy of hydrophobic drugs [4]. However, on several occasions, it was revealed that mPEG-b-PLA micelles exhibited poor drug loading and stability. Thus, modified versions of PLA have been developed to solve these issues [5].

Another commercially available block copolymer that has been developed with the objective of increasing the aqueous solubility of drugs is commonly known as Soluplus® (SP). SP is an amphiphilic copolymer containing PEG, polyvinyl caprolactam, and polyvinyl acetate (13% : 57% : 30%, respectively). The technical document published by BASF in August 2019 reported that SP self-assembled into micelles with a critical micelle concentration (CMC) of 7.6 µg/mL. The same document suggested that SP can increase the aqueous solubility of several hydrophobic drugs such as estradiol, carbamazepine, griseofulvin, etc. by several folds. Numerous research groups also tested the solubilization potential of SP for poorly soluble drugs such as furosemide [6], curcumin [7], silymarin [8], and so forth [9]. Jin et al. encapsulated fenbendazole in PM prepared from SP and reported an enhancement in oral bioavailability of fenbendazole in Male Sprague-Dawley rats with increment in AUC by 1.5 fold compared to free drug [10]. Other studies also reported the enhancement of oral bioavailability of poorly soluble drugs in animal models using SP owing to the increment in aqueous solubility [11].

Generally, the loading efficiency of hydrophobic drugs in PM, or in other words, solubilization capacity of PM, is usually governed by the interaction between the drug and the hydrophobic part of the PM via hydrophobic interactions. Thus, the length of the hydrophobic chain and the type of functionality present greatly influence the solubilization capacity of PM [12]. Nevertheless, hydrophobic interaction does not always result in superior drug loading, and other non-covalent interactions between polymer and drug are being investigated to achieve high drug loading. For instance, positively charged cisplatin was successfully loaded within negatively charged methoxy-polyethylene glycol-block-poly(glutamic acid) (mPEG-b-PGA) via electrostatic complex formation. The mPEG-b-PGA micelles demonstrated high cisplatin loading up to 23.1% w/w [13]. In another study, Shixian et al. utilized phenylboronic acid-functionalized hydrophobic

polymer for the fabrication of PM. This PM exhibited high loading (49% w/w) of doxorubicin via donor-acceptor coordination interaction between polymer (electron acceptor) and drug (doxorubicin – electron donor) [14].

The development of polymers from renewable resources is an emerging and sustainable approach to replace fossil-based materials [15]. Recently, we have reported the synthesis of an amphiphilic novel poly(jasmine lactone) (PJL)-based block copolymer using renewable jasmine lactone as starting material and PEG as the initiator (mPEG-b-PJL) for drug delivery applications [16]. Due to the presence of allyl groups on the PJL side chain, we successfully demonstrated the post-synthesis functionalization of mPEG-b-PJL to insert free functional groups (Figure 1). Functional end groups such as alcohol (OH), acid (COOH), and amine ($NH_2$) were successfully incorporated into the polymer chain via thiol-ene click reaction. As discussed above, we believed that the presence of free functional groups on the polymer chain could affect the drug loading in PM.

In this study, we utilized mPEG-b-PJL, mPEG-b-PJL-COOH, and mPEG-b-PJL-Phy (having benzene ring) to investigate the effect of non-ionic interaction on drug loading within PM. The drug loading results from PJL-based micelles were compared with mPEG-b-PLA and SP micelles as these polymers have been extensively studied for increasing the aqueous solubility of drugs. Six drugs from the technical document published by BASF for SP were chosen for the study, namely estradiol, danazol, fenofibrate, itraconazole, clotrimazole, and cinnarizine. The micelles were prepared via the nanoprecipitation method, and drug content was determined by ultraviolet-visible spectrophotometry (UV-Vis).

## 2. Materials and Methods

### *2.1 Materials*

L-lactide ((3S)-cis-3,6-Dimethyl-1,4-dioxane-2,5-dione) (LA) (98%), poly(ethylene glycol) methyl ether (mPEG, $M_n$ = 5.0 KDa), and tin(II) 2-ethyl hexanoate ($Sn(Oct)_2$) (92.5-100.0%) were purchased from Sigma Aldrich. 2-Phenylethanethiol (99%) was purchased from Fisher Scientific. Estradiol, fenofibrate, itraconazole, clotrimazole, and cinnarizine were purchased from TCI Europe. Danazol (≥99.8%), methanol for HPLC (≥99.9%), acetone for HPLC (≥99.8%), toluene anhydrous (99.8%), dichloromethane (≥99.9%), and diethyl ether (≥99.8%) were purchased from Sigma-Aldrich. Soluplus® was purchased from BASF, Germany. The 0.45 μm polyethersulfone membrane filters were purchased from VWR (Puerto Rico and China). MilliQ® water was used throughout the study. All chemicals were used as received except LA, which was purified by recrystallization in anhydrous toluene before use.

### *2.2 Instruments*

Nuclear Magnetic Resonance (NMR) spectroscopy: The chemical structure of polymers was examined by proton nuclear magnetic resonance ($^1$H-NMR) on Bruker NMR 500 MHz spectrometer (Bruker, Coventry, United Kingdom). Deuterated chloroform ($CDCl_3$) was used as a solvent.

Particle size analysis: Size and polydispersity index of PM were measured by ZetaSizer NanoZS® (Malvern Instruments, UK) based on dynamic light scattering (DLS). The light used by the instrument is sourced from a Helium-Neon laser with a wavelength of 633 nm. Samples were diluted (100 μg/mL) with MilliQ water and transferred into respective cuvettes for analysis. Measurements were performed at 25 °C, and data

analysis was carried out using the Malvern ZetaSizer software version 7.12.

Ultraviolet-visible (UV-Vis) spectroscopy: NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, USA) was used to determine the drug content in the samples. The drug concentrations were calculated using pre-prepared standard calibration curves in methanol. The $\lambda_{max}$ used for fenofibrate, danazol, cinnarizine, clotrimazole, itraconazole, and estradiol was 287, 285, 253, 261, 260, and 281 nm, respectively. The drug-loaded micelles were diluted appropriately in methanol. Absorbances were recorded against blank micelles of similar concentrations to avoid overlapping of the peaks.

### *2.3 Methods*

#### *2.3.1 Synthesis of polymers*

The synthesis and characterization of polymer mPEG-b-PJL and mPEG-b-PJL-COOH was reported in our previous publication (Figure 1) [16]. The same polymers were used in this study.

##### *2.3.1.1 Synthesis of polylactide (PLA) block copolymer (mPEG-b-PLA)*

A di-block (AB type) copolymer of LA was synthesized via ring-opening polymerization (ROP) of the recrystallized LA monomer using mPEG as macroinitiator and Sn(Oct)2 as catalyst. The synthesis was performed according to the reported method with slight modifications [17]. First, recrystallized LA (2.8 g, 19.4 mmol) and mPEG (5.0 kDa, 2.5 g, 0.5 mmol) were mixed in a round bottom double-neck reaction flask and dried in a vacuum oven at 50 °C overnight. Then, the reaction flask containing dried LA and mPEG was placed on an oil bath, and a condenser was set up and connected to a Schlenk line apparatus. Next, the mixture was heated at 100 °C under vacuum conditions to obtain a homogeneous mixture of LA and mPEG, upon degassing of the reaction mixture was

performed. Afterward, nitrogen gas was purged into the system, and anhydrous toluene (25 mL) was added as solvent into the melted solution under agitation. Next, the reaction temperature was raised to 110 °C, and a predetermined amount of $Sn(Oct)_2$ (0.25% w/w of LA) as a solution in anhydrous toluene was added via syringe. The reaction was continued for 26 h at 110 °C under nitrogen. After the reaction, the solvent toluene was evaporated via rotary evaporation. The product was then purified by first dissolving it in dichloromethane and precipitated in excess diethyl ether, and then the precipitate was dissolved in acetone followed by recovery of product in cold water [18]. Finally, the synthesized di-block copolymer, mPEG-b-PLA, was dried under vacuum at 50 °C to a constant weight with 30% yield (1.6 g).

Calculated molecular weight by $^1$HNMR – 9.0 kDa

$^1$HNMR (500 MHz, $CDCl_3$) δ 5.10 – 5.30 (q, 45H), 4.24 – 4.30 (m, 2H), 4.17 – 4.24 (t, 2H), 3.67 (s, 461H), 3.40 δ (s, 3H), and 1.56 – 1.68 (d, 134H).

*2.3.1.2 Synthesis of mPEG-b-PJL-Phy*

The mPEG-b-PJL-Phy polymer was synthesized via thiol-ene click reaction using mPEG-b-PJL as starting material and 2-Phenylethanethiol as a functionalizing agent to introduce benzene ring onto the pendant chain. Briefly, mPEG-b-PJL (1.0 g, 0.11 mmol) and 2-phenylethanethiol (1.10 g, 7.6 mmol) was dissolved in dichloromethane (5 mL). 2,2-Dimethoxy-2-phenyl acetophenone (DMPA, 0.13 g, 0.94 mmol) was then added to the above mixture and stirred for 20 h in a UV cabinet fitted with a stirrer and UV-A bulb. $^1$HNMR analysis of crude reaction mixture suggested 90% of conversion. The reaction mixture was then precipitated in cold diethyl ether followed by removal of residual solvent in vacuum to recover products, which was off-white sticky solid with 88.7 %

yield (1.10 g).

Calculated molecular weight by $^{1}$HNMR – 11.6 kDa

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 50H), 7.21 (m, 59H), 5.49 (m, 2H), 5.31 (m, 3H), 4.87 (m, 20H), 4.22 (t, 2H), 4.05 (m, 2H), 3.66 (s, 561H), 3.39 (s, 3H), 2.85 (d, 39H), 2.72 (d, 40H), 2.53 (m, 20H), 2.29 (s, 40H), 1.98 (m, 7H), 1.57 (m, 228H), 0.96 (m, 65H).

*2.3.2. Micelles preparation and characterization*

PM was prepared by nanoprecipitation according to the reported procedure [19]. Briefly, the drug (3 mg) and polymer (10 mg) were dissolved in methanol or acetone (0.5 mL) with the aid of vortex. For itraconazole, 1 mg of drug and acetone was used for the preparation of the organic phase. This organic mixture was then added dropwise into PBS (pH 7.4, 1 mL) under stirring and left overnight at room temperature to ensure complete removal of the organic solvent. Next, the volume of PM was checked and made up to 1 mL if needed, followed by centrifugation (Microcentrifuge Scanspeed, Labogene, Lynge, Denmark) for 10 min at 13 500 RPM to separate unentrapped drug. The supernatant was then filtered through a 0.45 μm polyethersulfone membrane filter, and the filtrate was used for further analysis [20]. Blank micelles of polymers were prepared via the same method but without the drug. The size and polydispersity of the micelles were analyzed by dynamic light scattering (DLS), and the drug content was estimated by UV-Vis after appropriate dilutions in methanol.

***2.4 Statistical analysis***

Statistical analysis was conducted by ordinary one-way ANOVA with Tukey's multiple comparisons test using $P < 0.05$ (95% confidence interval) as a statistical significance

threshold. GraphPad Prism software (version 6) using n = 3 was used for all statistical analysis. All experiments were performed in triplicate, and the mean with standard deviation is reported.

## 3. Results and Discussion

### *3.1 Synthesis and characterization of polymers*

The mPEG-b-PLA copolymer was synthesized via the well-recognized ROP route and purified by following the reported methods. The synthesis scheme of mPEG-b-PLA is presented in Scheme 1. The purified copolymer was characterized by $^{1}$HNMR to confirm the chemical structure, composition, and molecular weight. The $^{1}$HNMR spectrum of mPEG-b-PLA copolymer is presented in Figure 2, where all the characteristic peaks are assigned. The existence of newly formed proton signals (peak d) confirmed the formation of the ester bond between mPEG and LA through the ROP reaction, and in other words, suggests the successful synthesis of mPEG-b-PLA block copolymer. The molecular weight of the copolymer was determined from the $^{1}$HNMR through the determination of the number of repeating units (i.e., degree of polymerization) of LA with respect to the mPEG (5k). For PLA block, the number of repeating units of LA was calculated by comparing both the peak integrals of (-CO-CH($CH_3$)-O-)x (δ 5.17 ppm) and CH($CH_3$)-O-)x (δ 1.57 ppm) in the PLA block to $CH_3$-O- (δ 3.40) of mPEG block, and was found to be 45 repeating units. Thus, the calculated molecular weight of mPEG-b-PLA copolymer was found to be 9.0 kDa (5k of mPEG + 4 k of PLA).

The PJL derivative, mPEG-b-PJL-Phy containing phenyl groups in its side-chain, was synthesized using mPEG-b-PJL as starting material via thiol-ene click reaction [16]. 2-phenylethanthiol was used to introduce the phenyl group and to avoid steric hindrance.

Attempts were made to make copolymer using benzyl mercaptan, but only 20% conversion was achieved due to steric hindrance owing to the bulky phenyl group. The purified copolymer was analyzed by $^{1}$HNMR to ascertain the successful synthesis and purification. The reduction in the intensity of the characteristic peak of "ene" group at 5.3 and 5.5 ppm (position 14-15) and appearance of -CH group peak adjacent to thiol group at 2.5 ppm (position 11) as presented in Figure 3, suggested the success of the thiol-ene reaction. Due to the 90% conversion, the "ene" group peaks are still visible in the spectrum. Further, the -$CH_2$ group peak and phenyl group proton peaks at 2.7, 2.8, 7.2, and 7.3 ppm confirmed the successful conjugation of 2-phenylethanthiol to the mPEG-b-PJL (Figure 3). The rest of the peaks in the NMR are found to be similar as per our previous publication [16]. The molecular weight was calculated by comparing the proton resonance of the phenyl group (7.2 ppm), the methyl group of mPEG (3.4 ppm), and the methyl group of PJL (0.9 ppm). mPEG-b-PJL-Phy was synthesized to explore the possibility of π-π interaction between polymer and drug to facilitate high drug loading.

### *3.2 Preparation and characterization of drug-loaded micelles*

Poor aqueous solubility of drugs is still a major concern, and researchers are investigating several methods for improving the aqueous solubility of drugs and, consequently, the bioavailability. Polymeric micelles have emerged as one of the finest approaches to achieve this objective; however, they suffer from poor drug loading. Lately, we developed a new polymeric material with free functional groups, which could offer a solution to the above-mentioned problem. Thus, in this study, we compared the drug loading results of PM prepared using different polymers. The drugs were shortlisted from the SP technical document for a better comparison. Micelles were prepared via the reported nanoprecipitation method by keeping 1% (w/v) polymer concentration in the final

formulation instead of 10% as reported in the SP technical document. We chose 1% (10 mg/mL) to keep the amount of polymer low in order to avoid any toxic effects generated by the polymer itself in future studies.

Methanol was used as the solvent in this study to investigate the micelle-forming ability of the polymers. Methanol is an advantageous solvent for micelle preparation considering that certain drugs are only soluble in this volatile solvent, e.g. Amphotericin B, which ruled out the use of common organic solvents (acetone and THF) used for nanoprecipitation [21]. Furthermore, methanol can be easily replaced with ethanol as a less toxic alternative. However, since mPEG-b-PLA is not soluble in methanol, acetone was used instead. During the micelle fabrication, we realized that the drug's solubility in organic solvents plays a key role, and poor solubility may lead to rapid precipitation of the drug in the aqueous phase, hindering interaction with polymer; and consequently, resulting in poor drug loading. Since itraconazole demonstrates poor solubility in methanol, the drug amount was reduced to 1 mg/mL, methanol was replaced with acetone, and a clear drug-polymer solution was obtained.

Only the PJL derivative that yielded highest drug loading for each drug is reported below and compared to SP and mPEG-b-PLA. The drug content results are presented in Table 1 and Figure 4, where the drug concentration after purification of PM was reported as mg/mL concentration. It is apparent from the results that mPEG-b-PJL-COOH demonstrate the capability to dissolve higher amounts of danazol, cinnarizine, clotrimazole, and itraconazole compared to the other polymers. While comparing mPEG-b-PLA with SP, SP demonstrates better solubilizing capability for fenofibrate, danazol, and estradiol. No significant difference was observed between SP and mPEG-b-PLA for itraconazole. SP was found to be superior polymer for solubilizing estradiol. mPEG-b-

PJL was found to be best for estradiol but was still inferior to SP. mPEG-b-PJL-Phy was able to dissolve a high amount of fenofibrate compared to other tested derivatives of PJL and the two polymer comparatives.

From the obtained results, it is evident that no single polymer is suitable for all drugs. However, if we compare the increment in solubility by folds, mPEG-b-PJL-COOH performed remarkably better compared to SP and mPEG-b-PLA for cinnarizine and clotrimazole. The solubility increment for cinnarizine was 39.1 and 15.9-fold, whereas for clotrimazole, 334.2 and 18.4-fold compared to SP and mPEG-b-PLA, respectively. Figure 5 is a picture of clotrimazole in different polymeric micelles prior to purification, this demonstrates the capability of mPEG-b-PJL-COOH to solubilize clotrimazole more efficiently compared to SP and mPEG-b-PLA. These staggering results utilizing mPEG-b-PJL-COOH can be ascribed to the ionic/electrostatic interaction between weakly basic drugs and the acidic functional group (-COOH) on the polymer. The same phenomena was also observed for danazol and itraconazole but were not as astonishing.

Fenofibrate, being a weakly acidic drug demonstrates poor loading with mPEG-b-PJL-COOH, which might be due to the same charge repelling effect. However, mPEG-b-PJL and mPEG-b-PJL-Phy exhibit good potential to solubilize fenofibrate where 1.2-fold higher solubilization power was observed for mPEG-b-PJL-Phy. This slight increment in solubilization power with a polymer containing an aromatic group can be attributed to the π-π interaction between aromatic groups and the drug's benzene rings. Compared to SP and mPEG-b-PLA, 3.8 and 7-fold increment in solubility of fenofibrate was observed, respectively.

On the contrary, we failed to notice similar phenomena when estradiol (neutral drug) was used. The poor performance can be attributed to the weaker π-π interaction

between estradiol and mPEG-b-PJL-Phy. This can be ascribed to the stronger π–π interactions among mPEG-b-PJL-Phy molecules and estradiol molecules rather than between drug and polymer. A similar phenomenon was observed earlier where poor dye loading was observed when the amount of aromatic ring in the copolymer chain increased [22]. Therefore, lowering the number of aromatic rings in copolymer mPEG-b-PJL-Phy might improve the solubilization power of this copolymer for estradiol. SP was found to be the best polymer to solubilize estradiol and demonstrated a 7-fold higher solubilization efficiency than mPEG-b-PJL. We assumed that the SP's hydrophobic region is more compatible with estradiol compared to the other tested polymers. It has been reported that polymer-drug compatibility is directly proportional to the solubilization power of a particular polymer [23].

Later, to determine the hydrodynamic size of the prepared PM, fenofibrate, cinnarizine, and estradiol-loaded micelles were analyzed by DLS technique to cover all types of polymers. As shown in Figure 6, SP produced larger size micelles while mPEG-b-PLA generated the smallest size among all the polymers. The size (by volume) acquired for SP for the major peak ranged from ~ 55-70 (± 2.5) nm and ~ 31-41 (± 2.3) nm for mPEG-b-PLA. The size obtained for PJL derivatives was ~ 41 (± 1.2), ~50 (± 0.5), and 40 (± 1.0) nm for mPEG-b-PJL-COOH, mPEG-b-PJL-Phy, and mPEG-b-PJL, respectively. The larger size obtained for mPEG-b-PJL-Phy could be attributed to the presence of an aromatic ring in the core-forming block. However, we observed a second peak in almost all the tested samples, suggesting the formation of large particles or aggregates. The second peak with the highest diameter is more intense in mPEG-b-PLA compared to other polymers. Since we have prepared PM by manually dropping the volatile solvent with no control on dropping rate, variations in size were expected. As the objective of this study was to analyze the solubilizing potential of different polymers, the

focus was not placed on controlling the size of PM. Nevertheless, manipulation of organic solvents, polymer concentrations, and microfluidics techniques could be utilized in future to generate uniform sized PM [24].

## 4. Conclusions

In this study, we demonstrate that mPEG-b-PJL and its derivatives hold great potential towards increasing the aqueous solubility of drugs. This study reveals that the PJL-based copolymers are superior compared to commercially available SP and mPEG-b-PLA copolymers for several drugs. It is apparent from this study that no single polymer can be suitable for all drugs. Nevertheless, due to the versatility of PJL-based copolymers, it is possible to tune its property to match the need, i.e., the molecular structure of the API. For instance, an amine-terminated polymer can be utilized to improve the aqueous solubility of acidic drugs. Moreover, the crosslinking of PJL-based PM is also possible due to the presence of free functional groups, which could improve the stability of the micelles [25]. In addition, an increment in the chain length of PJL could also be helpful in achieving enhanced drug solubilization capacity of PJL-based copolymers. We have also observed that the solubility of the polymer and the drug in the organic solvent also directly affect the solubilization power of PM. Thus, the selection of an appropriate solvent is also a key parameter to obtain PM with high drug content via the nanoprecipitation method.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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Table 1. The mean values (±SD) of drug content (mg/mL) in different polymeric micelle formulations determined by UV. For poly(jasmine lactone) samples, only the best derivative is included. SD = standard deviation, ND = not detectable. *prepared using acetone as solvent.

| | **Soluplus** | | **mPEG-b-PLA** | | **mPEG-b-PJL-COOH** | | **mPEG-b-PJL** | | **mPEG-b-PJL-Phy** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Drug** | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **Fenofibrate** | 0.054 | 0.009 | 0.029 | 0.001 | - | - | - | - | 0.205 | 0.002 |
| **Danazol** | 0.061 | 0.013 | 0.037 | 0.007 | 0.113 | 0.012 | - | - | - | - |
| **Cinnarizine** | 0.033 | 0.006 | 0.081 | 0.018 | 1.289 | 0.220 | - | - | - | - |
| **Clotrimazole** | 0.008 | 0.006 | 0.145 | 0.050 | 2.674 | 0.204 | - | - | - | - |
| **Itraconazole*** | 0.009 | 0.001 | 0.007 | 0.001 | 0.019 | 0.002 | - | - | - | - |
| **Estradiol** | 0.672 | 0.048 | ND | - | - | - | 0.096 | 0.011 | - | - |

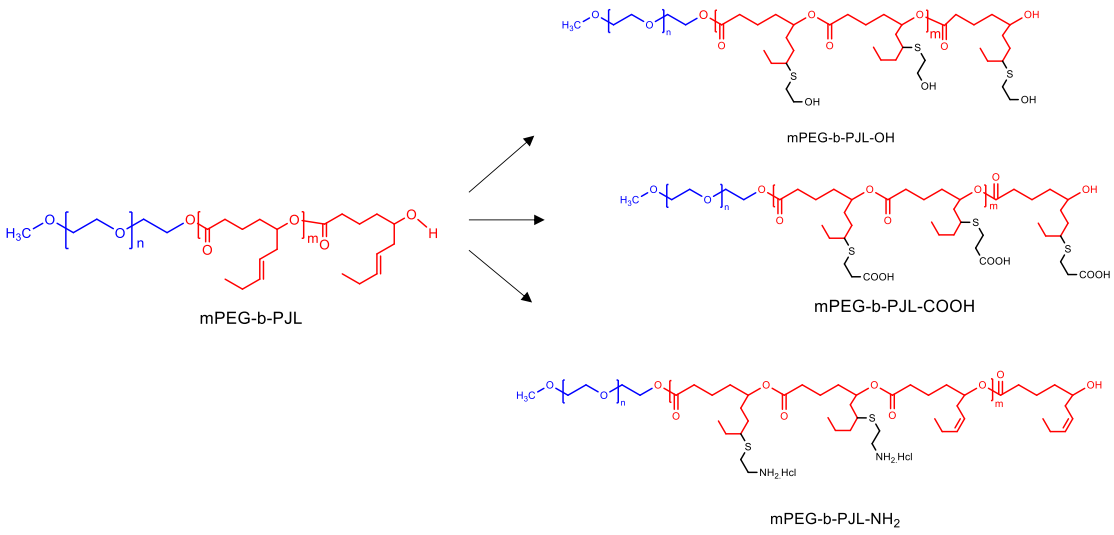



Figure 1. Chemical structure of mPEG-b-PJL and its functional derivatives containing free alcohol, carboxylic acid, and amine groups on its side chain [16].

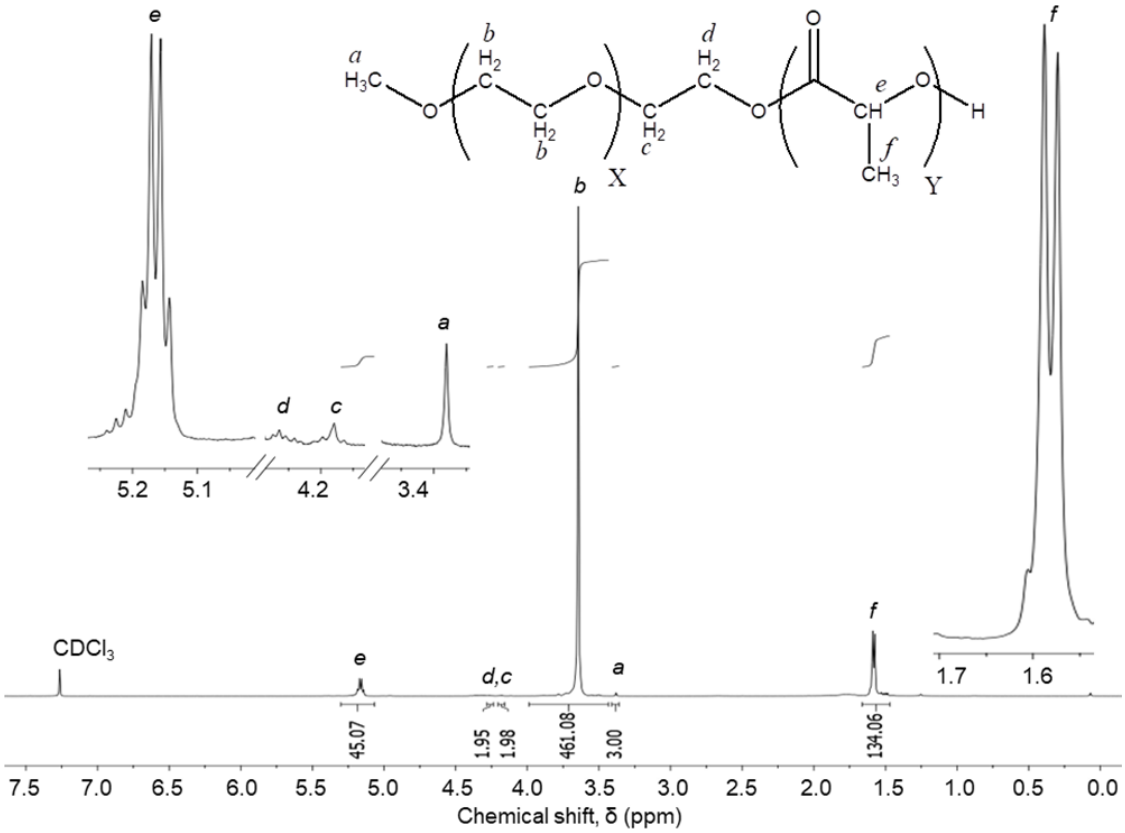



Figure 2. [1]HNMR spectrum of copolymer mPEG-b-PLA.

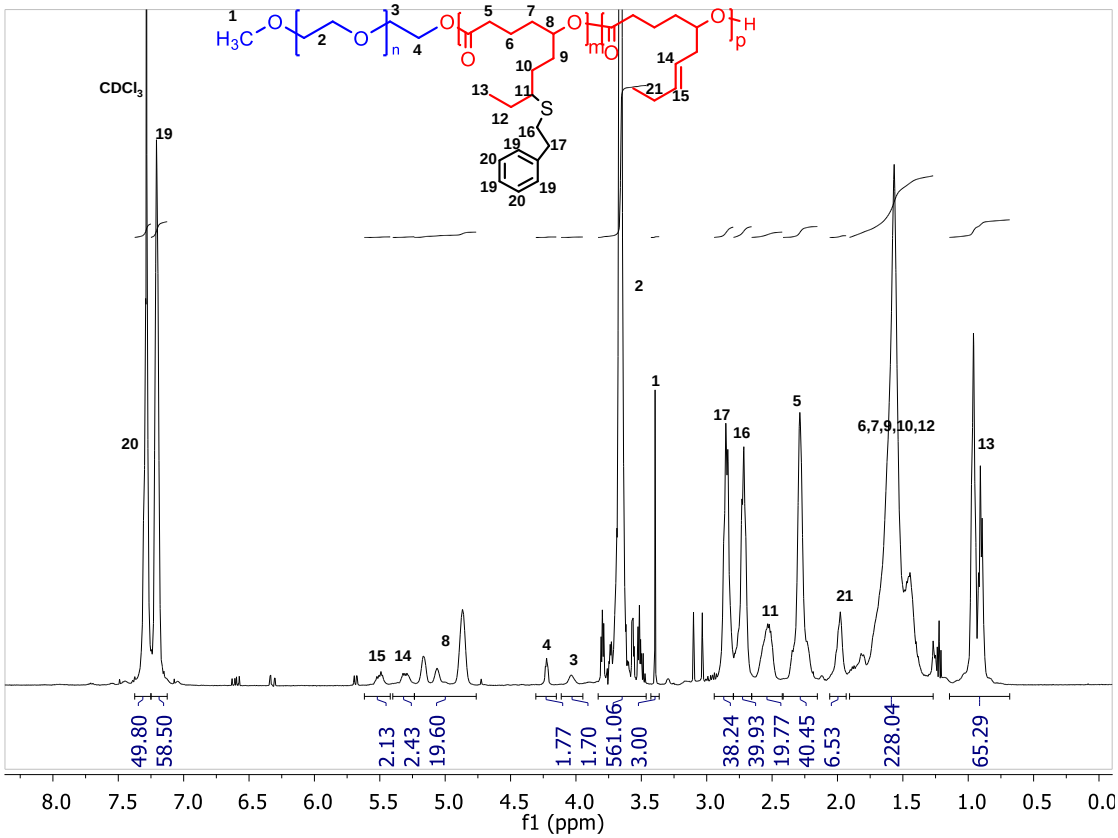



Figure 3. $^{1}$HNMR spectrum of mPEG-b-PJL-Phy in $CDCl_3$.

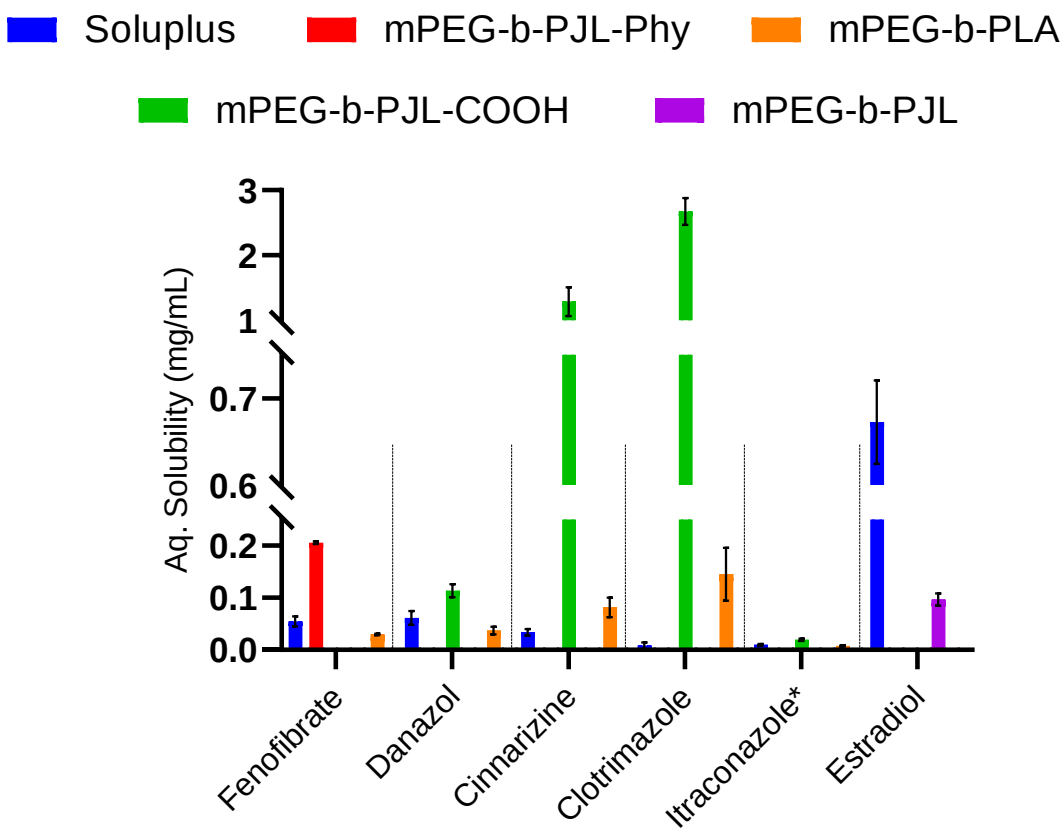



Figure 4. Representation of enhanced aqueous solubility of different drugs by utilizing polymeric micelles. Micelles were prepared via nanoprecipitation method using methanol as solvent except for itraconazole, where acetone was used as solvent.

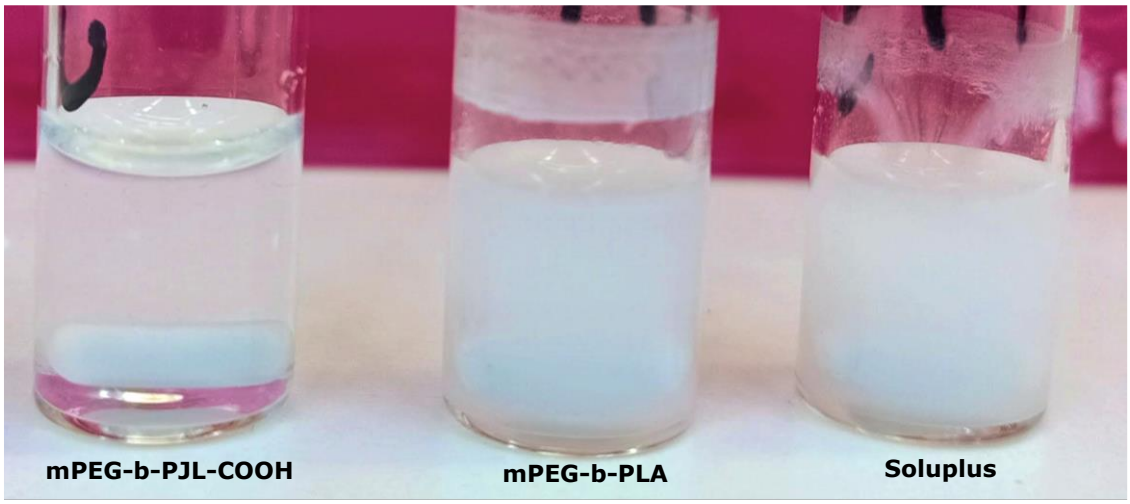



Figure 5. Physical appearance of crude clotrimazole-loaded PM. The picture was taken before centrifugation to demonstrate near to complete solubilization of the drug in the mPEG-b-PJL-COOH sample.

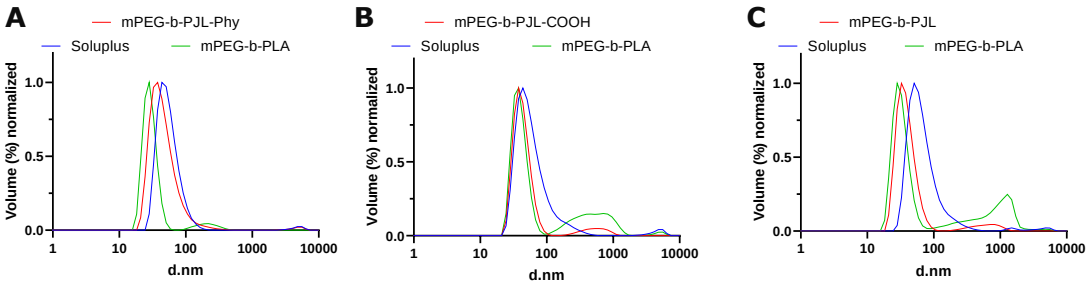
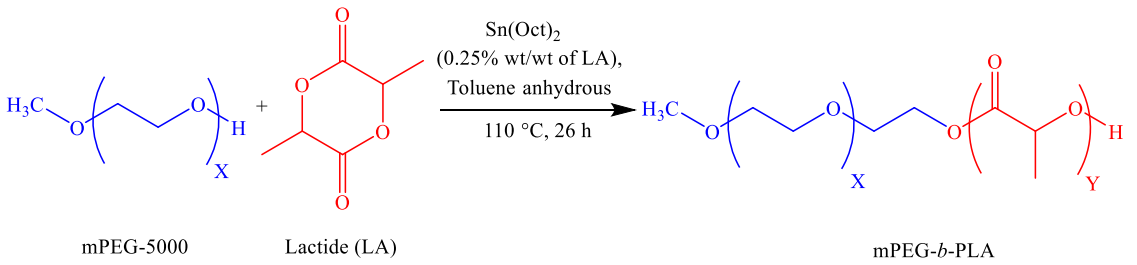
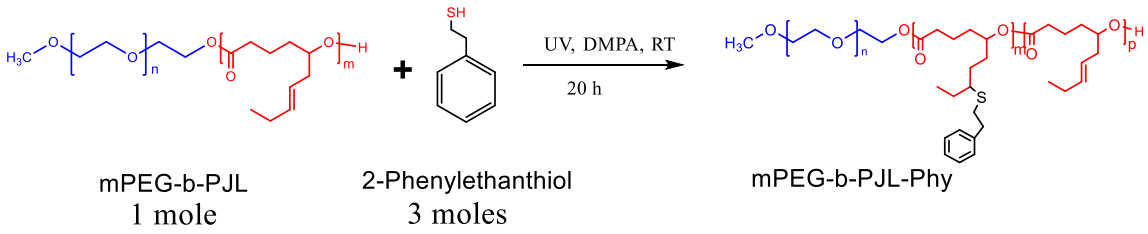



Figure 6. Size distribution by volume of polymeric micelles loaded with (A) fenofibrate, (B) cinnarizine, and (C) estradiol determined by DLS in water at a concentration of 100 µg/mL.




Scheme 1. Synthesis scheme of mPEG-b-PLA via ROP using mPEG5k as initiator and tin(II) 2-ethylhexanoate (Sn(Oct)2) as catalyst.




Scheme 2. Synthesis scheme of mPEG-b-PJL-Phy via UV light-activated thiol-ene click reaction.

**Table 2.** The mean values (±SD) of drug content (mg/mL) in different polymeric micelle formulations determined by UV. For poly(jasmine lactone) samples, only the best derivative is included. SD = standard deviation, ND = not detectable. *Prepared using acetone as solvent.

**Figure 7.** Chemical structure of mPEG-b-PJL and its functional derivatives containing free alcohol, carboxylic acid, and amine groups on its side chain.

**Figure 8.** $^{1}$HNMR spectrum of copolymer mPEG-b-PLA.

**Figure 9.** $^{1}$HNMR spectrum of mPEG-b-PJL-Phy in $CDCl_3$.

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