Study of the Effect of Poly(ethylene glycol) on the Nifedipine Microencapsulation and Release

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ABSTRACT: *Nifedipine is a dihydropyridine derivate calcium channel blocker, suitable as first-line therapy for patients with hypertension. When blood pressure is high, nifedipine will prevent calcium to pass into cardiac and vascular smooth muscle cells. Nonetheless, nifedipine has a low elimination half-life that makes nifedipine needs to be consumed repeatedly to enhance its bioavailability, and thus, gives rise to nifedipine concentration in blood. Hence, a controlled drug delivery system is needed wherein the drug could be delivered at the desired time. One of the options in drug delivery is drug microencapsulation using a polymer as a coating material. In this study, nifedipine was coated with poly(D-L lactic acid) (PDLLA)/poly(ethylene glycol) (PEG) polyblend also polycaprolactone (PCL)/PEG polyblend using solvent evaporation technique. The effect of the mass composition of the polyblend and molecular weight of PEG on the encapsulation efficiency and drug release was investigated. Microcapsules with the variation of PDLLA/PEG and PCL/PEG composition and PEG molecular weight had an encapsulation efficiency of about 90%-92%. Microcapsules with PDLLA/PEG_{600} (9/1) exhibited the highest drug release of 43.2% with an encapsulation efficiency of 91.96% whereas microcapsules with PCL/PEG_{400} (7/3) had the highest drug release of 44% with an encapsulation efficiency of 90.64%.*

KEYWORDS: *Drug release; Encapsulation efficiency; Nifedipine; Poly(caprolactone); Poly(D,L-lactic acid); Poly(ethylene glycol).*

INTRODUCTION

Diseases like cardiovascular diseases, cancer, diabetes, and chronic lung diseases have become the main causes of death. Cardiovascular diseases are greatly associated with hypertension since more than 50% of these ailments have been attributed to hypertension [1]. Hypertension can lead to stroke and heart attack, so it is often referred to as a 'silent killer'. Dihydropyridine Calcium Channel Blockers (CCB) are suitable as first-line therapy for patients with hypertension [2]. One of the CCB that can be used as an antihypertension drug is nifedipine. Nifedipine will block the calcium flow through an ion-specific channel that leads to the relaxation of smooth muscle cells of cardiac and vascular. As a consequence, blood pressure will be lower [3]. However, nifedipine has an elimination half-life of around 1.7 hours which makes nifedipine must be consumed with a dosage of 10 to 20 mg thrice a day in order to enhance its bioavailability [4].

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Conventional drugs are absorbed rapidly and must be consumed repeatedly which results in the fluctuation of drug levels in the blood. [5]. Therefore, a drug delivery system is needed to maintain the therapeutic drug level, reduce the administration frequency of drugs, decrease drug fluctuation in blood, and increase the compliance of the patients. Biodegradable polymers are often used as drug carriers in a controlled drug delivery system. Poly(D,L-lactic acid) (PDLLA) is a polyester that belongs to the α-hydroxy acid family and is widely used in biomedical applications because of its biodegradability and biocompatibility. Polycaprolactone (PCL) is a semi-crystalline aliphatic polyester that has great drug permeability and biocompatibility. However, their hydrophobicity and low degradation rate are the main drawbacks. To overcome this limitation, PDLLA and PCL are often blended with other polymers with higher hydrophilicity [6]. Poly(ethylene glycol) (PEG) is a semi-crystalline polyether that has great biocompatibility and low toxicity, so it is suitable to be used in the drug delivery system. PEG is soluble in water and some organic solvents. Due to its high solubility in the aqueous medium, PEG in the polyblend is expected to be dissolved and forms a pore inside or on the surface of microcapsules. These pores will facilitate drug diffusion into the surrounding medium [7]. Therefore, blending PDLLA and PCL with PEG may enhance the hydrophilicity of the polymers in the blend and increase drug release [8].

Budianto and *Astuti* (2020) used PLA/PCL polyblend to encapsulate nifedipine by using the solvent evaporation method with various mass compositions of the polyblend. The range of encapsulation efficiency of all nifedipine microcapsules was around 78.82%-89.84%. The drug release percentage was determined by soaking the microcapsules in pH 1.2 solution for 3 hours followed by pH 7.4 solution for 52 hours. The drug release of nifedipine from the microcapsules was around 6.80%-39.07%. The best composition was PLA:PCL (9:1) with encapsulation efficiency and drug release of 78.82% and 39.07%, respectively.

In this study, nifedipine was encapsulated with a PDLLA/PEG polyblend and PCL/PEG polyblend as a coating material using a solvent evaporation method with oil-in-water (o/w) emulsion. The effect of the mass composition of the polyblend and molecular weight of PEG on the encapsulation efficiency and drug release was investigated. Span 80 and Tween 80 were used as emulsifiers to help stabilize the emulsion formed, resulting in the uniform size of the microcapsules. To our knowledge, such studies using these polymers are still limited.

EXPERIMENTAL SECTION

Materials

Nifedipine was obtained from PT. Ferron Par Pharmaceutical. PDLLA (MW = 30,000 Da) and PCL (MW= 50,000 Da) (CAS-No: 24980-41-4) were purchased from Sigma Chemical China. PEG (MW = 400, 600, and 4,000 Da) (CAS-No: 25322-68-3), Tween 80 (CAS-No: 9005-65-6), KH_2PO_4 (CAS-No: 7778-77-0), $K_2HPO_4.3H_2O$ (CAS-No: 16788-57-1), HCl (CAS-No: 7647-01-0), and NaCl (CAS-No: 7647-14-5) were obtained from Merck Germany. Moreover, PEG (Mw = 35.000 Da) (CAS-No: 25322-68-3) was purchased from Sigma Aldrich. Dichloromethane (CAS-No: 75-09-2) was purchased from PT. Smart Lab Indonesia, whereas Span 80 was purchased from PT. Evonik Indonesia.

Preparation of Nifedipine Microcapsules

PDLLA/PEG and PCL/PEG polyblend solutions were prepared with the variation of mass composition of the polyblend and molecular weight of PEG according to Table 1 and Table 2. Microcapsules with PCL/PEG_{4000} (7/3) polyblend were optimized by some variations of Span 80 surfactant concentration as shown in Table 3. The optimum surfactant concentration was used in all variations of the polyblend solutions. About 0.5 g of polyblend was dissolved in 10 mL of dichloromethane and stirred for 10 minutes at a speed of 400 rpm with a magnetic stirrer. After that, 60 mg of nifedipine was added and the emulsion was stirred for an hour at a speed of 700 rpm. The emulsion was dispersed into the aqueous solution containing 0.05% (v/v) Tween 80 and was stirred for another hour at a speed of 900 rpm to form microcapsules at room temperature (25 ºC). Finally, microcapsules were filtered, washed with 2 mL of ethanol, and dried in the oven overnight at a temperature of 38-40 ºC.

Characterization of the Nifedipine Microcapsules

Fourier transform-infrared (FT-IR) IR Prestige-21 Shimadzu was used to determine the functional groups.

Particle Size Analyzer (PSA) Horiba Scientific was used

Table 1: Variation of PDLLA/PEG polyblend composition (%w/w) and PEG molecular weight.

PEG Molecular Weight (Da)	PDLLA (%)	PEG (%)
-	100	0
600	90	10
600	80	20
600	70	30
4,000	90	10
4,000	80	20
4,000	70	30
35,000	90	10
35,000	80	20
35,000	70	30

Table 2: Variation of PCL/PEG polyblend composition (%w/w) and PEG molecular weight.

PEG Molecular Weight (Da)	PCL (%)	PEG (%)
-	100	0
400	70	30
400	30	70
4,000	70	30
4,000	30	70
35,000	70	30
35,000	30	70

Table 3: Variation of Span 80 surfactant concentration (%v/v).

Sample	Span 80 Concentration (%)
PCL/PEG_{4000} 7/3	3.0
	3.5
	4.0
	4.5
	5.0

to determine the mean of the particle size distributions. Morphology of the microcapsules was observed using an optical microscope DM-15 Binocular Digital and Scanning Electron Microscope (SEM) Carl Zeiss EVO MA 10.

Encapsulation Efficiency Test

The filtrate obtained from the preparation of microcapsules was used to measure the encapsulation efficiency. The absorbance of the filtrate at nifedipine maximum wavelength (λ_{max} = 237 nm) was measured using a UV-Vis spectrophotometer. After that, the absorbance was converted to the mass of nifedipine in the filtrate. The encapsulation efficiency can be determined with Equation (1):

$$\text{Encapsulation Efficiency} = \frac{\text{NIFL-NIFF}}{\text{NIFL}} \times 100\% \qquad (1)$$

where NIFL is the initial weight of nifedipine loaded, and NIFF is the weight of nifedipine in the filtrate.

Dissolution Test

The nifedipine microcapsules were dispersed in 900 mL HCl solutions of pH 1.2 for 3 hours and in 900 mL PBS of pH 7.4 for the next 52 hours. The suspension was incubated at 37 ºC under mild agitation at a speed of 100 rpm. The release media was removed and replaced with a fresh one at the pre-selected intervals. The absorbance of the release media was determined using a UV-Vis spectrophotometer at the maximum wavelength of nifedipine. At the end of the test, microcapsules were collected, dried, and their morphology was observed using SEM.

RESULTS AND DISCUSSION

Characteristics of Nifedipine Microcapsules

The solvent evaporation method of o/w was used in this study because this method suits best for water-insoluble drugs such as nifedipine [9]. PDLLA/PEG and PCL/PEG polyblends were used as coating materials. These polymers were dissolved in a volatile organic solvent because droplet solidification happens with the evaporation of the solvent. In this study, dichloromethane was used as the solvent because it has a boiling point of 39.8 °C. After the polyblend became homogeneous with the help of stirring, Span 80 was added. After that, nifedipine was added to the solution. Span 80 has the role to stabilize the emulsion when the organic phase is being dispersed in the continuous phase. The hydrophobic tail

of the surfactant in the organic phase will help to hold the drugs. Hence, the drugs will be well incorporated into the polyblend [10].

The next step was the formation of emulsion droplets. The organic phase was dispersed to the continuous phase containing distilled water and Tween 80. In the continuous phase, the surfactant is used to lower the surface tension and stabilize the emulsion droplets. The dispersion was accompanied by stirring in the continuous phase to help the evaporation of dichloromethane in the droplets. Evaporation of dichloromethane could change the droplets of the dispersed phase to solid particles [11].

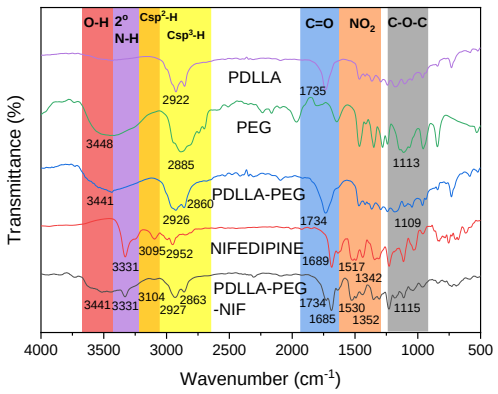
FT-IR Analysis

The resulting microcapsules were analyzed using FT-IR spectrophotometer to determine the functional groups of the PDLLA, PCL, PEG, and nifedipine and studied their interactions in the microcapsules. The interactions that were found in the polyblend and microcapsules were physical interactions, such as hydrogen bonding, dipole-dipole, and van der Waals interactions [12].

Spectra of the PDLLA, PEG, nifedipine, and PDLLA/PEG microcapsules were shown in Fig. 1 (a). In the PDLLA/PEG spectrum, peaks were shown at a wavenumber of 1735 cm^{-1} for C=O ester bonds. Moreover, peaks of the functional groups of -OH stretching and C-O-C ether were found at a wavenumber of 3448 cm^{-1}, and 1113 cm^{-1}, respectively [13]. Nifedipine spectrum shows that there was a peak at a wavenumber of 3331 cm^{-1} for the secondary amine groups. Peaks of the C=O ester bonds were found at 3095 cm^{-1} [13, 14]. There were no new peaks in the nifedipine microcapsules spectrum and only peaks found in PDLLA/PEG polyblend and nifedipine appeared. Therefore, the interactions between nifedipine and PDLLA/PEG polyblend were physical interactions.

Fig. 1 (b) shows spectra of the PCL, PEG, nifedipine, and PCL/PEG microcapsules. Characterization with FT-IR has shown that the peaks in the nifedipine microcapsules with PCL/PEG only consist of the characteristic absorptions of each compound used in the microcapsules, as shown in Fig. 1 (b). The peak of O-H stretching and C-O-C ether absorptions could be seen in 3441 cm^{-1} and 1115 cm^{-1}, respectively, which corresponds to the absorptions found in the PEG spectrum. In 3331 cm^{-1}, there was an absorption for secondary N-H that could also be seen in the nifedipine spectrum. In the wavenumber

(a)



(b)

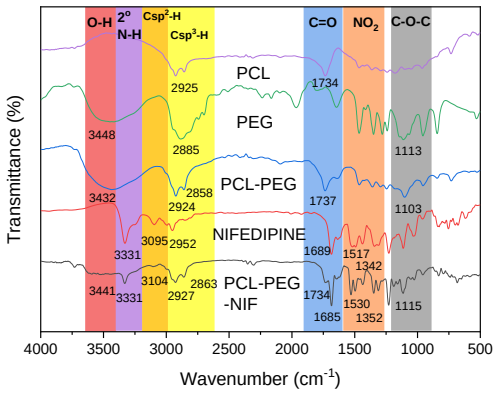


Fig. 1: FT-IR spectra of (a) PDLLA, PEG, nifedipine and PDLLA/PEG microcapsules and (b) PCL, PEG, nifedipine and PCL/PEG microcapsules.

of 1685 cm^{-1} and 1734 cm^{-1}, the absorptions are from the C=O ester in nifedipine and PCL respectively. The absorptions in 1362 cm^{-1} and 1530 cm^{-1} correspond to the $-NO_2$ group in nifedipine. The appearance of the nifedipine peaks indicated that nifedipine was incorporated inside or on the surface of microcapsules.

The microcapsules were agglomerated; thus, the variation of Span 80 concentration was used to optimize the resulting microcapsules. Optimization of Span 80 concentration was used only in the PCL/PEG microcapsules with the composition of PCL/PEG 7/3 and PEG molecular weight of 4,000 Da.

Optimization of Span 80 Concentration of PCL/PEG Microcapsules

The variation of Span 80 with the concentration of 3%; 3.5% and 4% almost have the same yield as shown in Fig. 2.

It is because the surfactant concentration was sufficient to decrease the surface tension and stabilize emulsion droplets [15]. Thus, microcapsules could be formed. The highest yield is obtained by Span 80 concentration of 4.5%, which means in this concentration the smaller droplets could be stabilized.

In Fig. 3 (a), the smallest microcapsules were obtained in a Span 80 concentration of 4.5%. The increase in surfactant concentration led to a decrease in particle size because surfactant could lower the interface tension between droplets and the continuous phase. Thus, droplets were protected from coalescence. The size increased in the 5% Span 80 concentration because in this concentration many droplets were formed which led to the collision between droplets. Thus, the coalescence of droplets might happen [16]. In Fig. 3 (b), the lowest polydispersity index is obtained by a Span 80 concentration of 4%. That means Span 80 concentration used in the microcapsules was the optimum concentration so that the surfactant layer around the microcapsules could be uniform.

Fig. 4 shows that the shape of the microcapsules is semi-spherical. Microcapsules with Span 80 concentration of 4% have uniform size and shape in 4x magnification which corresponds to their polydispersity index in characterization with PSA.

Encapsulation efficiency in the variation of Span 80 concentration does not differ much but tends to decrease with the increase of Span 80 concentration as shown in Fig. 5. The decreasing of encapsulation efficiency could be caused by the formation of a thick layer of surfactant around the microcapsules as the surfactant concentration increased. Therefore, the evaporation rate of the solvent would be slower and give chance for the drugs in microcapsules to diffuse from the microcapsules to the continuous phase [17].

Based on the particle size, polydispersity index, morphology, and encapsulation efficiency of the microcapsules, Span 80 with a concentration of 4% was chosen as the optimum concentration due to its low polydispersity index with a small standard deviation. Uniform particle size has a great impact on drug release profiles. Size uniformity leads to greater control of the drug release rate with the possibility to release a drug in a constant manner [18]. This concentration of Span 80 was used for all samples.

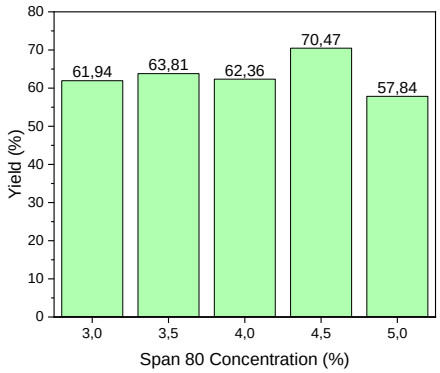
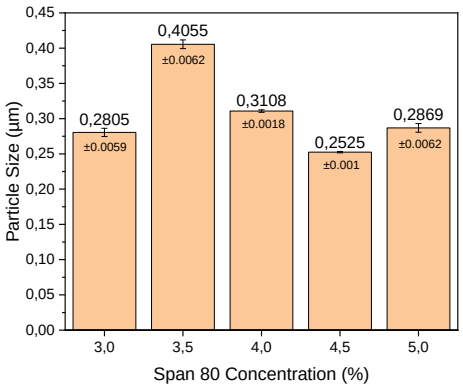


Fig. 2: The effect of Span 80 concentration on the yields of PCL/PEG microcapsules.

(a)



(b)

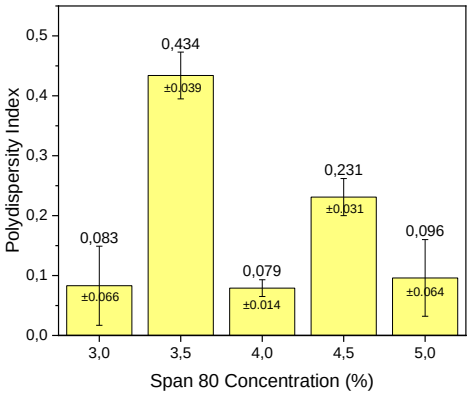


Fig. 3: The effect of Span 80 concentration on microcapsules (a) particle size and (b) polydispersity index of PCL/PEG microcapsules.

Particle Size Distribution of Nifedipine Microcapsules

The mean of the particle sizes and the uniformity of the microcapsules were measured using PSA by varying the molecular weight of the PEG. Fig. 6 shows the mean

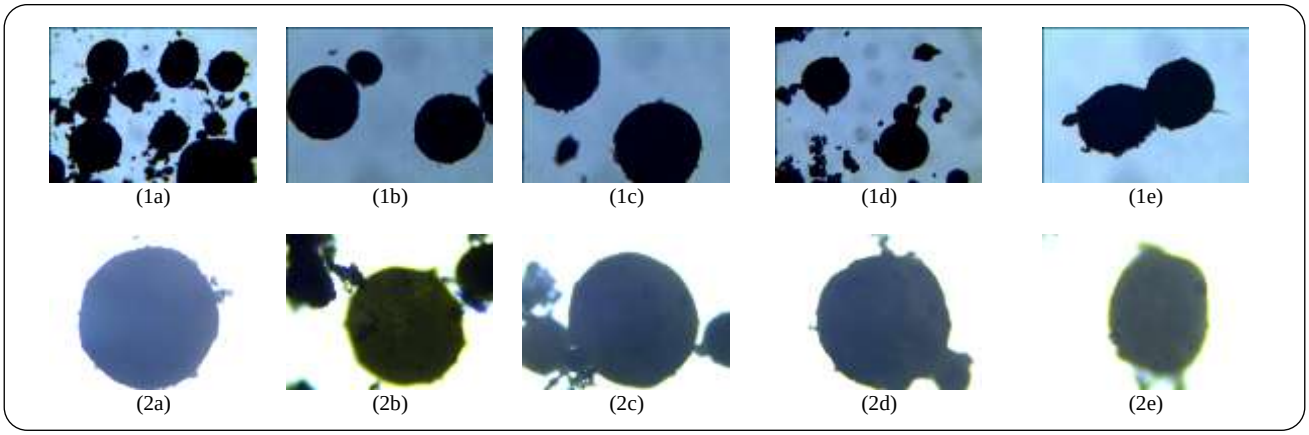


Fig. 4: Optical microscope characterization for (1) 4× and (2) 10× magnification of Span 80 concentration of (a) 3.0%; (b) 3.5%; (c) 4.0%; (d) 4.5% and (d) 5.0% on PCL/PEG microcapsules.

of the particle sizes of the nifedipine microcapsules with PDLLA/PEG and PCL/PEG polyblends. Microcapsules with PDLLA/PEG polyblend had a range of the mean sizes of 0.2-0.3 µm whereas microcapsules with PCL/PEG polyblend had a range of 0.2-2.5 µm. Microcapsules with PCL/PEG polyblend had larger particle sizes compared to microcapsules with PDLLA/PEG due to the molecular weight of PCL and PDLLA used in this study. The molecular weight of PCL used was 50,000 Da whereas the molecular weight of PDLLA was 30,000 Da. The size of the microcapsules was not affected by the molecular weight of PEG in the PDLLA/PEG polyblend. Meanwhile, in the PCL/PEG polyblend, the size of the microcapsules increased with increasing molecular weight of PEG from 400 Da to 4,000 Da, but then decreased.

Morphology of Nifedipine Microcapsules

As seen in Fig. 7, microcapsules with PDLLA/PEG polyblend are semi-spherical and remain intact as observed with the optical microscope. Meanwhile, microcapsules with polyblend composition of PCL/PEG (7/3) have a good semi-spherical shape as shown in Fig. 8. As a comparison, in the composition of PCL/PEG (3/7), the semi-spherical shape of the microcapsules cannot be seen properly. This could correspond to their small particle size.

To observe the surface of the microcapsules, characterization using SEM was conducted for nifedipine microcapsules with PDLLA/PEG_{600} (9/1) and PCL/PEG_{35000} (7/3) polyblends. SEM images of the microcapsules are shown in Fig. 9, which suggested that the structure of microcapsules was semi-spherical without visible pore, which might be caused by the low PEG

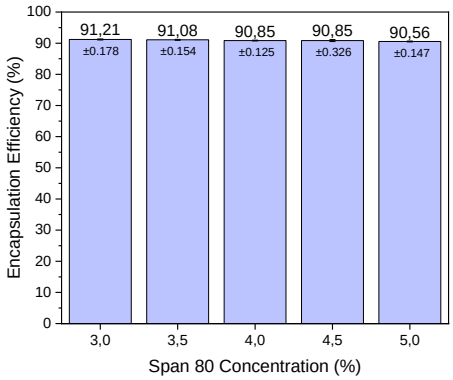


Fig. 5: The effect of Span 80 concentration on encapsulation efficiency of PCL/PEG microcapsules.

composition. The surface of the microcapsules with PDLLA/PEG and PCL/PEG polyblend lacked a smooth texture. Surface smoothness could be affected by the boiling point of the organic solvent, which is dichloromethane which has a low boiling point (39.8 ºC) resulting in rapid evaporation and polymer precipitation [19].

Encapsulation Efficiency of Nifedipine Microcapsules

Encapsulation efficiency was determined for all samples. According to Fig. 10, the higher composition of PEG was, the lower the encapsulation efficiency was obtained. These phenomena might be associated with PEG hydrophilicity which might facilitate drug diffusion into the aqueous phase by forming pores during the formation of microcapsules [19]. In addition, the encapsulation efficiency of nifedipine microcapsules was prone to increase with the increasing molecular weight of PEG.

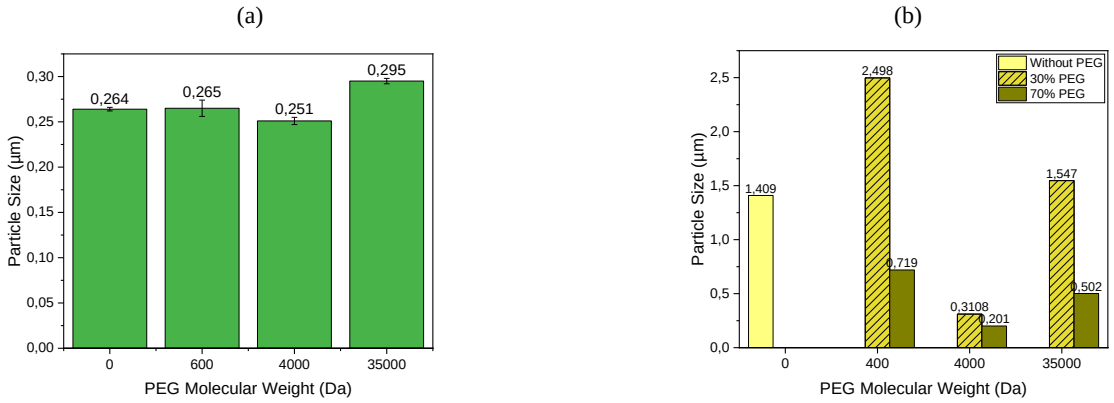


Fig. 6: The effect of (a) PEG molecular weight with PDLLA/PEG (9/1) polyblend and (b) PCL/PEG mass composition and PEG molecular weight on the particle size of microcapsules.

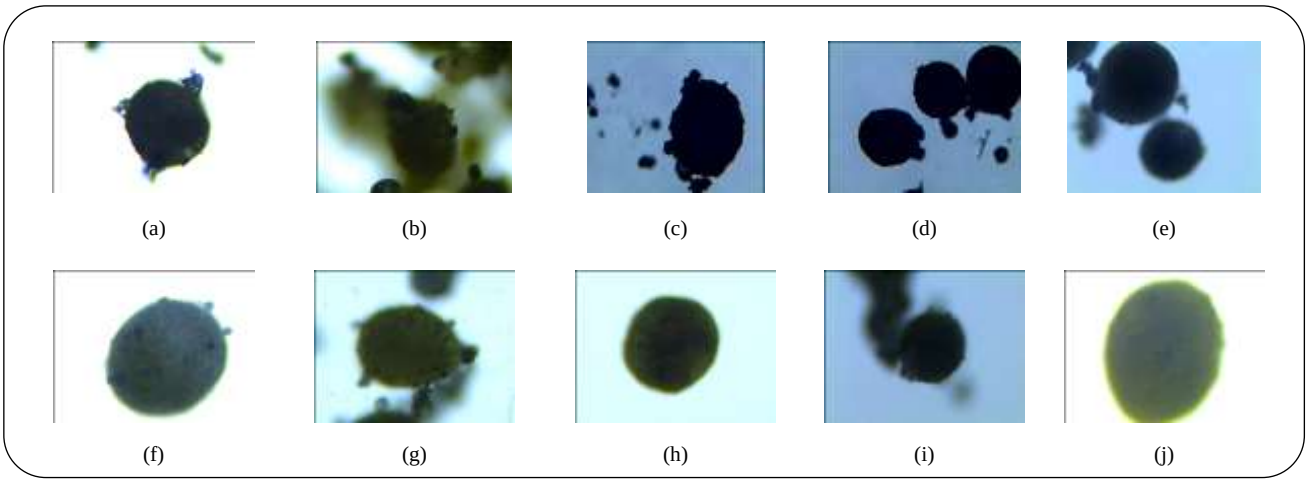


Fig. 7: Optical microscope images of PDLLA/PEG (a) 10/0, (b) 9/1 (PEG_{600}), (c) 8/1 (PEG_{600}), (d) 7/3 (PEG_{600}), (e) 9/1 (PEG_{4000}), (f) 8/2 (PEG_{4000}), (g) 7/3 (PEG_{4000}), (h) 9/1 (PEG_{35000}), (i) 8/2 (PEG_{35000}), and (j) 7/3 (PEG_{35000}) microcapsules with 10x magnification.

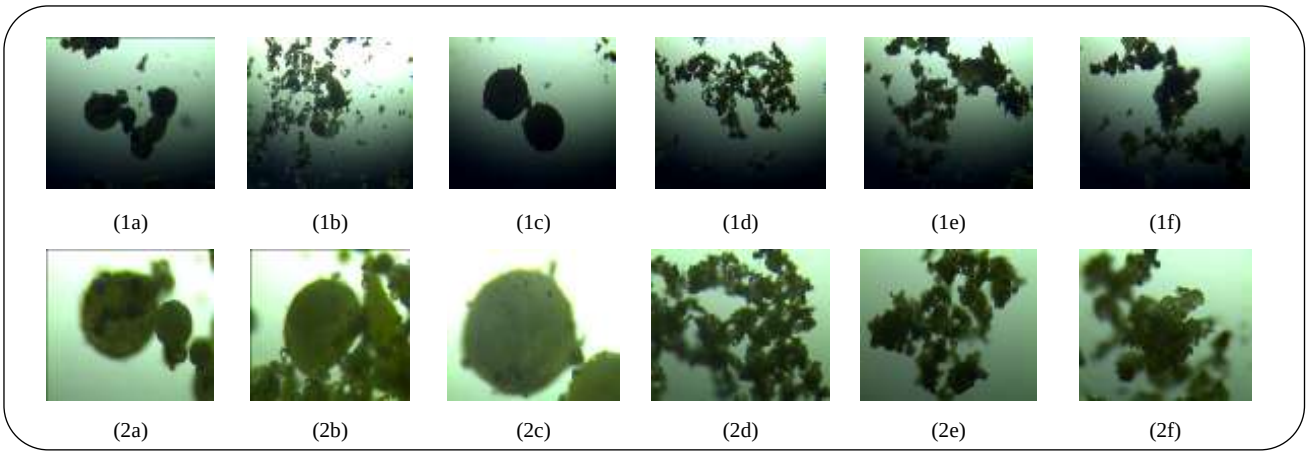


Fig. 8: Optical microscope characterization for (1) 4× dan (2) 10× magnification of sample (a) PCL(10)/PEG(0), (b) PCL(7)/PEG_{400}(3), (c) PCL(7)/PEG_{35000}(3), (d) PCL(3)/PEG_{400}(7), (e) PCL(3)/PEG_{4000}(7) and (f) PCL(3)/PEG_{35000}(7).

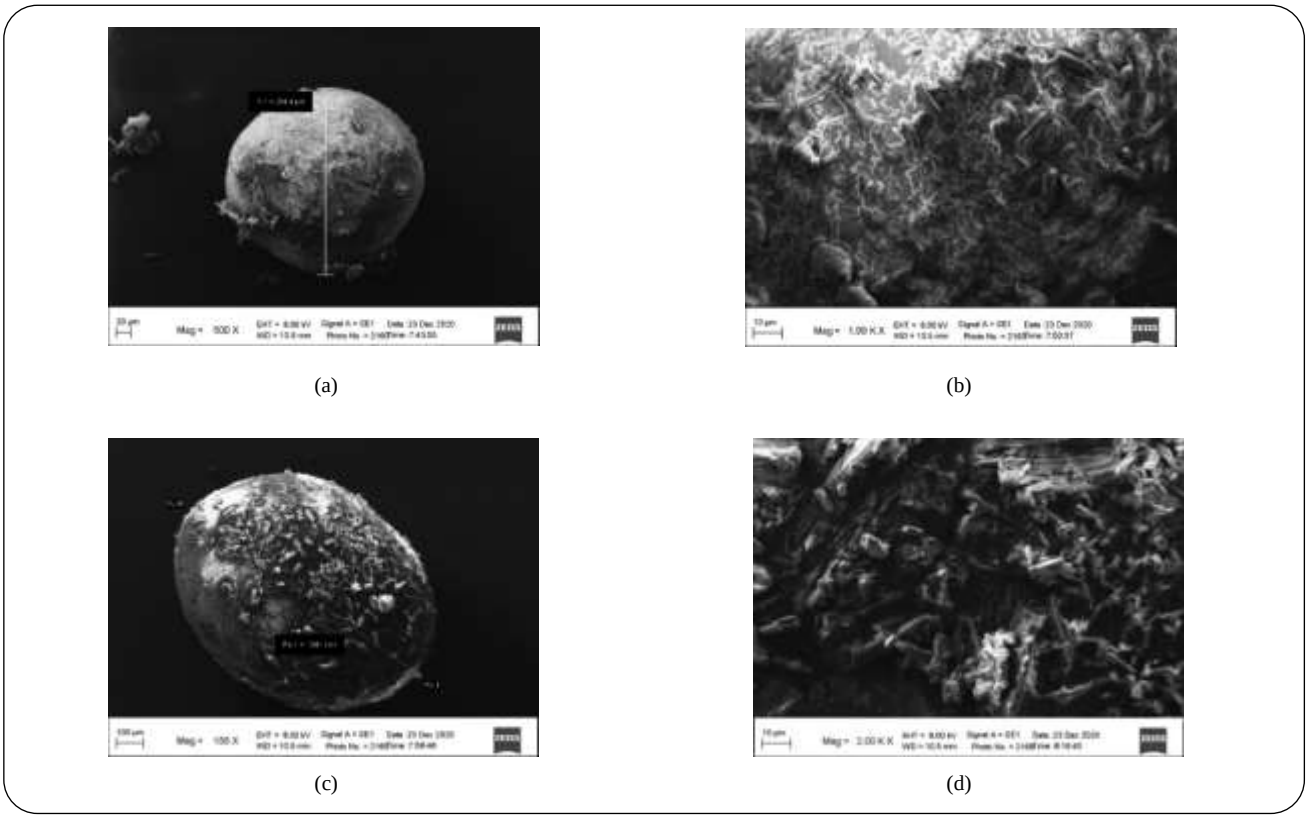


Fig. 9: SEM images of PDLLA/PEG$_{600}$ (9/1) microcapsule with (a) 500x and (b) 2,000x magnification and PCL/PEG$_{35000}$ (7/3) with (c) 188x and (d) 2000x magnification.

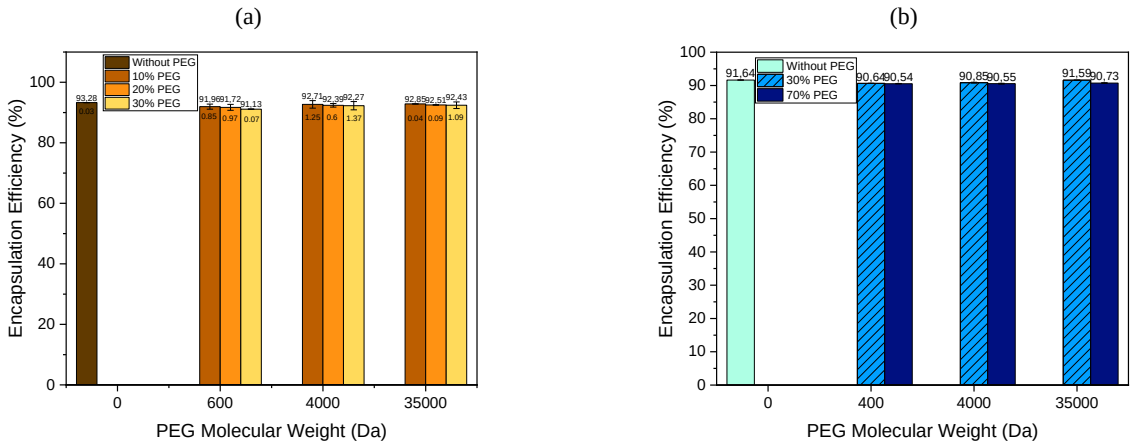


Fig. 10: Effect of the mass composition of (a) PDLLA/PEG polyblend and (b) PCL/PEG polyblend with variations of molecular weight of PEG on the encapsulation efficiency.

PEG with higher molecular weight produced an organic phase with higher viscosity, resulting in rapid polymer precipitation on the surface and preventing drug diffusion to the aqueous phase during the formation of microcapsules [20]. Microcapsules consisting of PDLLA had a higher encapsulation efficiency than that with PCL within the same polyblend mass composition and molecular weight of PEG. The permeability of PCL allows the drug to diffuse to the aqueous phase during the formation of microcapsules and lowers the encapsulation efficiency.

Dissolution Test of Nifedipine Microcapsules

In vitro dissolution test was carried out for 55 hours, in which microcapsules were dispersed into HCl solution with pH 1.2 for 3 hours and PBS pH 7.4 for the next 52 hours. The dissolution test was conducted for microcapsules with various molecular weights of PEG with a constant composition of PDLLA/PEG 9/1 (%w/w) polyblend also various mass compositions and molecular weights of PEG in the PCL/PEG polyblend. A dissolution test was performed at pH 1.2 and pH 7.4 to represent gastric liquid and intestine liquid, respectively.

When microcapsules are in the release medium, the release of drugs starts with the drugs on the surface of the microcapsules. The release of nifedipine from the microcapsules might occur with diffusion.

The dissolution medium could penetrate through the channels in the polymer matrix, reach the drugs inside of the material and then release the drugs to the dissolution medium [21]. Erosion could also happen and might decrease microcapsule diameter, and thus, the diffusion path would be shorter [22]. Degradation is the main process of erosion.

PDLLA and PCL characteristics such as slow degradation rate and hydrophobicity may prevent the drug to release. In order to overcome these limitations, PEG was used to enhance the drug release of the microcapsules. Moreover, the hydrophilicity of PEG can enhance the permeability of PDLLA in the polyblend [23]. PEG may be dissolved into the release medium, resulting in pores and water channels. This might enhance drug diffusion to the release medium and result in a sustained release of the drug [7].

The release profiles from microcapsules coated with PDLLA/PEG and PCL/PEG polyblends and the effect of the molecular weight of PEG can be seen in Fig. 11. The drug release was investigated by varying the molecular weights of PEG with a constant mass composition of PDLLA/PEG (9/1) and PCL/PEG (7/3) polyblends. The highest drug release from microcapsules with PDLLA/PEG (9/1) polyblend was obtained by microcapsules with a molecular weight of PEG of 600 Da, i.e., 43.2%. Furthermore, drug release increased as the molecular weight of PEG decreased. The hydrophobicity of PEG is dependent on size. Therefore, increasing molecular weight might lead to increasing hydrophobicity of the polymer. An increase in hydrophobicity gives rise to the viscous organic phase. Rapid solidification occurred, which might be preventing drug release [20]. Therefore, microcapsules with a lower molecular weight of PEG, which was 600 Da, had the highest drug release because of its hydrophilicity, permeability, and ability to form pores and water channels.

On the other hand, the highest drug release from microcapsules with PCL/PEG (7/3) polyblend was achieved by a sample with a molecular weight of PEG of 400 Da of 44% while the lowest drug release with 23% was achieved by a sample without PEG. In the sample without PEG, drug release was low, which corresponds to the hydrophobicity of PCL which makes microcapsules hydration slower [24]. These results also indicated that the release of nifedipine from both PDLLA/PEG and PCL/PEG microcapsules was higher in moderate basic media. Hence, it can be concluded that pH 7.4 was the optimum pH of the release of nifedipine.

The addition of hydrophilic polymer could facilitate water uptake and improve drug release. In acid conditions, PCL might swell and PCL might degrade which indicated that hydration takes place in the polymer matrix [25]. Degradation happened via ester hydrolysis of PCL in acid conditions. The degradation could open some paths for drugs to be released to the dissolution medium. Nifedipine could diffuse from microcapsules because of the erosion of PCL. Drug release decreased as the molecular weight of PEG increased because the increase of PEG molecular weight caused the increasing viscosity. Thick polymer matrices could make the diffusion path of drugs longer and decrease drug release [22]. The drug release was also affected by the formation of aqueous pores by PEG. The dissolution of PEG to the release medium occurred because of the hydrogen bond interaction that happened between PEG and water molecules in the release medium [7].

According to Fig. 11, microcapsules with PCL/PEG polyblend had a slightly higher drug release compared to microcapsules with PDLLA/PEG polyblend. This might be caused by the greater permeability of PCL compared to PDLLA [26]. Microcapsules consisting of PCL might allow the drugs to easily penetrate through the polymer matrix towards the release medium. The release profiles of microcapsules with PDLLA/PEG polyblend and PCL/PEG polyblend were similar because the degradation of PDLLA and PCL is slow. Therefore, they did not affect the release profile of microcapsules.

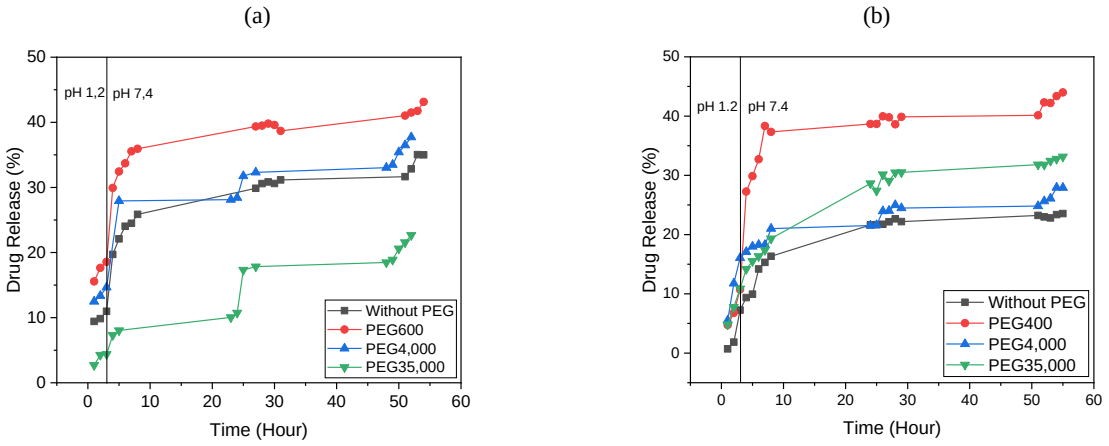


Fig. 11: The effect of PEG molecular weight of (a) PDLLA/PEG (9/1) and (b) PCL/PEG (7/3) on drug release.

The drug release was also investigated by varying the mass composition of the PCL/PEG_{35000} polyblend. After 55 h, the drug release for the composition without PEG was 23%, for the composition of 7/3 was 33.14% and for the composition of 3/7 was 30% as shown in Fig. 12. The composition of 3/7 did not show a significant release because PEG could not be well-incorporated in the microcapsules. The high amount of PEG composition could make PEG leach out of the droplets while the preparation of microcapsules [27]. Thus, the amount of PEG to help the diffusion of nifedipine was not sufficient.

The surface of the microcapsules with the composition of PDLLA/PEG_{600} (9/1) and PCL/PEG_{35000} (7/3) was observed with SEM, as seen in Fig. 13. Fig. 13 (a) shows that the shape of the microcapsule is still semi-spherical and intact. This can be explained by low PEG composition so that fewer pores are formed. In addition, microcapsule exposure to the acidic medium was only for 3 hours.

According to the previous research, PDLLA degradation is faster in an acidic medium, whereas the microcapsules were incubated longer in a moderate basic medium. Judging by the SEM image, the erosion of PDLLA in the microcapsules was not significant. The erosion might be linked to the incubation time of microcapsules; the microcapsules were incubated longer in a moderate basic medium than in an acidic medium [28]. The surface was smoother and there were few visible pores compared to the SEM images before dissolution as seen in Fig. 13 (b). Erosion. of the polymer caused the surface of the microcapsule to be smoother. The smooth surface of microcapsules might also correlate with the release of the drug that was incorporated on their surface into the

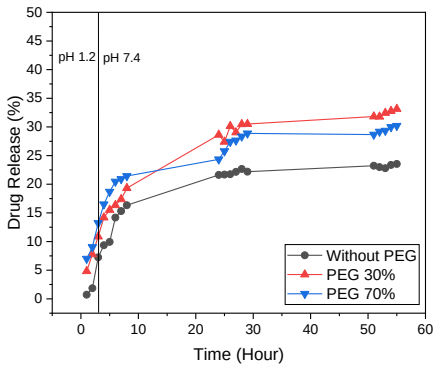


Fig. 12: The effect of PCL/PEG polyblend composition with PEG molecular weight of 35,000 Da on drug release.

surrounding medium. Moreover, visible pores might be formed by the dissolution of PEG in the release medium by forming hydrogen bonds with water or the degradation and erosion of PDLLA [29]. Furthermore, according to Fig. 13 (c), the microcapsule has a hole in its surface which could correspond to the PEG leaching in the dissolution medium. It also could happen because of the degradation and erosion of PCL. In Fig. 13 (d), the microcapsule has a smooth surface, which differs from the rough surface in the microcapsule surface before dissolution. This smooth surface is caused by hydration and erosion of microcapsules.

CONCLUSIONS

Nifedipine microcapsules were successfully prepared using the solvent evaporation method with o/w emulsion and PDLLA/PEG and PCL/PEG polyblends as a coating material. Microcapsules with a mass composition of PDLLA/PEG_{600} (9/1) and PCL/PEG_{35000} (7/3) lacked a smooth surface and no visible pores. An increase

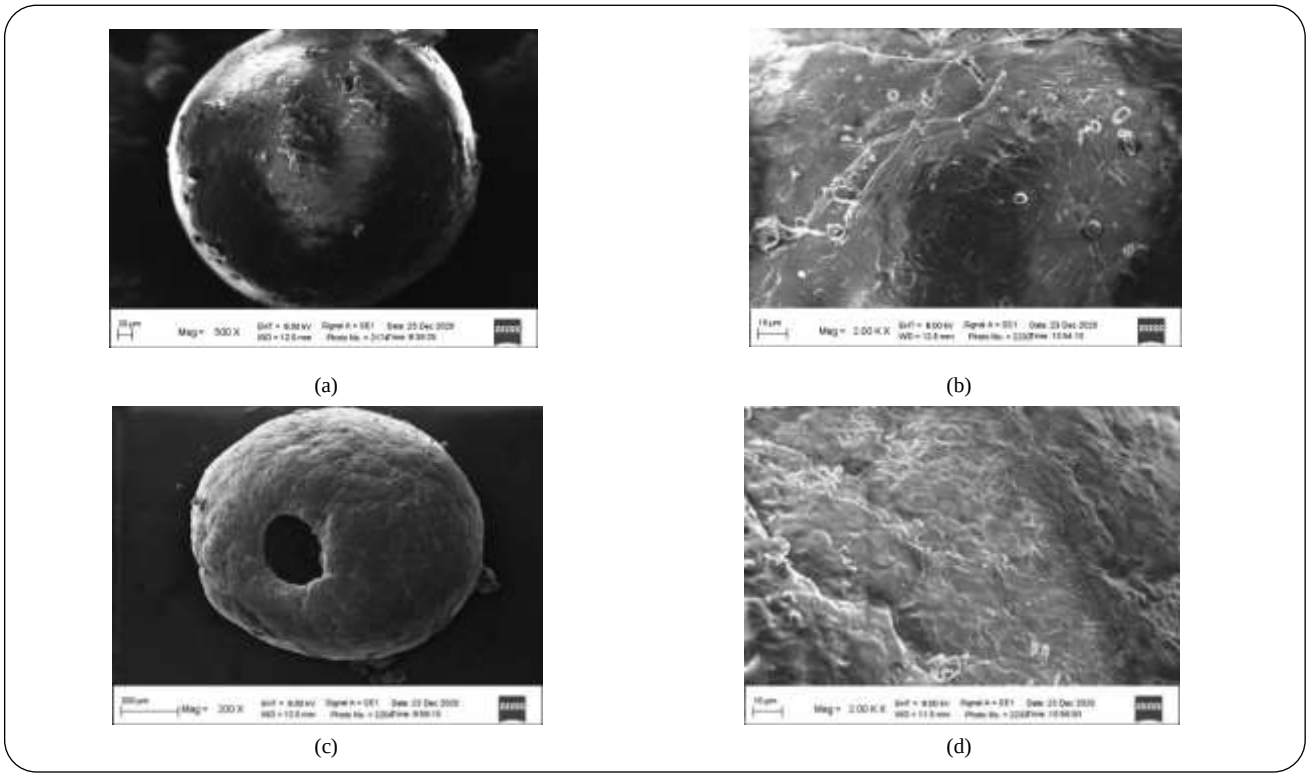


Fig. 13: SEM images of (1) PDLLA/PEG$_{600}$ (9/1) microcapsule with (a) 500x and (b) 2,000x magnification and (2) PCL/PEG$_{35000}$ (7/3) with (c) 200x and (d) 2000x magnification after dissolution.

In the composition of PEG in the polyblend resulted in a slight decrease in encapsulation efficiency. In addition, a high molecular weight of PEG increased encapsulation efficiency to some extent. A continuous release of the drug was achieved for 55 h in acidic and basic media. Our finding suggested that microcapsules with PDLLA/PEG$_{600}$ 9/1 (%w/w) composition had the best drug release of 43.2% with an encapsulation efficiency of 91.96% whereas microcapsules with PCL/PEG$_{400}$ (7/3) had the highest drug release of 44% with an encapsulation efficiency of 90.64%. The higher the molecular weight of PEG was, the lower drug release could be obtained. The surface of the microcapsules after dissolution had few pores and smoother textures. Further study in the future is needed in respect of adjusting PEG concentration as well as its molecular weight to improve the drug release.

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