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CASE STUDY

Environmental friendly carrier material for nifedipine as hypertension drug

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ABSTRACT

Nifedipine is a hypertension drug must be consumed three times a day due to its low oral bioavailability. One way of developing a controlled drug delivery system is making nifedipine microcapsules by using environmentally friendly polymers of polylactic acid and polycaprolactone via the evaporation method using oil-in-water solvents. Polylactic acid and polycaprolactone can be said to be environmentally friendly polymers, because they can be degraded naturally in nature both in the biotic, and abiotic environment, or microorganism. In this study, polylactic acid, Polycaprolactone, and nifedipine were dissolved in dichloromethane solvent; then, an emulsifier was added for the emulsification stage. After passing through the dispersion stage for the process of compaction of the microcapsules by solvent evaporation, the microcapsules were filtered. Microcapsules were characterized using particle size analysis, X-ray diffractometry, and scanning electron microscopy, respectively. The drug release percentage was determined by dissolving microcapsules for 55 hours using a buffer at the potential of hydrogen 1.2 and pH 7.4 as dissolution media. In this study, all variations in the composition of polyblend resulted in a percent efficiency of encapsulation ranging from 78.82%-89.84%, and percent release ranging from 6.80%-39.07%. The composition of 100% polylactic acid produces the highest percent encapsulation efficiency of 89.84% but produces the lowest percentage of drug release at 6.80%. The best composition obtained was polylactic acid: polycaprolactone 1:9 (weight per weight), with a percent release of 39.07% and percent encapsulation of 78.82%. Microcapsule solids produced are approximately 96%. Particle Size of microcapsule ranges at 0.5 µM.

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47	8	1

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INTRODUCTION

An increasing number of applications of polymers have emerged recently, including packaging, biomedical products (Davarani *et al.*, 2017), textiles, agriculture, household use, and building where biodegradable polymers and biocomposites are particularly suitable as sustainable alternatives that environmentally-friendly compared to the fossil fuel-based polymers (Anne, 2011). Therefore, now many biodegradable polymers are being developed that can provide the benefits of complete biological degradability, reduction in waste volume and compatibility in natural cycles, climate protection through reducing the amount of carbon dioxide released, and the possibility of applying agricultural resources for the production of biodegradable polymers (Ray, 2013). Thus, due to its biocompatible properties, biodegradable polymers are often utilized to be used to encapsulate drug molecules in a controlled drug delivery system, which can slowly release a drug over a certain period in order to maintain the drug concentration in the blood. Furthermore, a controlled drug delivery system is also needed to decrease the drug side effects, and increase patient compliance (Jayanthi *et al.*, 2011). Polylactic acid (PCL), is a synthetic biodegradable polyester with a monomer of lactic acid. Polylactic acid (PLA) is generally considered an environmentally friendly product because it comes from renewable energy agriculture such as corn (Sin and Tueen, 2019). Moreover, PLA is also considered as one of the most common polymers to be utilized in the drug delivery system due to its biocompatibility and the fact that it is approved by the Food and Drug Administration (FDA) (Li *et al.*, 2008). Moreover, PLA is quickly recycled into lactic acid through hydrolysis or alcoholysis processes to produce biocompatible, non-toxic metabolic products, it requires 20-55% less energy than producing other petroleum-based polymers, and has a degradation time of one year, which is quite fast compared to the other biodegradable polymers (Dorgan *et al.*, 2001; Velde and Kiekens, 2001). However, aside from its environmental and economic advantages, PLA also has weaknesses in its use such as being fragile and having an inert side chain (Rasal *et al.*, 2010), resulting in PLA being often used in its copolymer form. To overcome this problem, PLA is often paired with other polymers that have different properties and characteristics, such as polycaprolactone (PCL) and polyglycolic acid (PGA). PCL is very hydrophobic, semi-crystalline, dissolves easily at room temperature, and is easily processed because of its low melting point and glass transition (Deshmukh *et al.*, 2017), and high copolymer compatibility; these traits have urged researchers to learn about potential applications, especially in the biomedical field (Nair and Laurencin, 2007). PCL has a slow degradation rate of more than 2 years (Lu and Chen, 2004) and high permeability so it is useful for applications such as long-term implants and drug delivery systems (Sinha *et al.*, 2004). However, PCL can be degraded by living organisms such as bacteria and fungi through enzymatic degradation processes through esterase and other types of lipases that these organisms possessed (Tokiwa and Suzuki, 1977; Nishida and Tokiwa, 1993). Therefore, this research utilized PLA-PCL polyblend to take advantage of PLA character which has a faster degradation time which is certainly beneficial for the environment and PCL character which has a high permeability to support a good drug delivery system. Nifedipine, an anti-hypertension drug, works by orally inhibiting calcium from entering cells (Young *et al.*, 2001). Inhibition of the entry of Calsium (Ca^{2+}) through L-type which is dependent on calcium channel tension, opened by depolarizing stimulation in vascular smooth muscle cells (Godfraind, 1994) which results in a vasodilator effect (dilation/relaxation of blood vessels) to facilitate blood flow (Salomone *et al.*, 1996). This calcium channel blocker drug can effectively lower blood pressure, although several side effects, such as hypotension, myocardial ischemia, and peripheral edema, may occur during the treatment (Elliot, 2011). The normal dose used for this medicine is 10 mg every 8 hours (Javed *et al.*, 2014) thus, it is taken three times a day. However, repeated consumption may cause fluctuations of the drug concentration, and increasing the risk of patient noncompliance (Bhowmik *et al.*, 2012). Therefore, a controlled drug delivery system is needed to encapsulate the nifedipine so that the drug can release slowly over a certain period so that the concentration of the drug in the blood is maintained. This method may stabilize the drug concentration in blood, maintain the therapeutic effects, decrease the side effects, and increase patient compliance (Jayanthi *et al.*, 2011). In this research, the PLA-PCL polyblend was used to encapsulate nifedipine using the oil-in-water (o/w) solvent evaporation method.

The microcapsule was formed with the varied PCL and PLA composition to obtain the optimum results in nifedipine encapsulation. In theory, the increase of PCL composition in the polymer will increase the percentage release of nifedipine due to PCL possesses a higher permeability than PLA. Moreover, both Span 80 and Tween 80 were utilized as emulsifiers in this research to stabilize the emulsion in forming microcapsules, resulting in a uniform size and spherical shape of microcapsules, high percentage of encapsulation, and high percentage of drug release. This study was entirely conducted in the Organic Chemistry and Biochemistry Research Laboratory, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Indonesia in 2019.

MATERIALS AND METHODS

Materials

PLA (Mw= 137.000 g/mol) and PCL (Mw= 150.000 g/mol) were obtained from Changchun Foliaplast Bio-Tech Co. Ltd., China. Nifedipine was purchased from PT. Ferron Par Pharmaceutical Bekasi, Indonesia. Moreover, Span 80 was purchased from Evonik Industries AG, while Tween 80 Merck, $KH_2PO_4.3H_2O$ Merck, K_2HPO_4 Merck, NaCl Merck, 37% HCl Merck, and dichloromethane Merck from Germany

Preparation of polyblend solutions

About 0.5 g of mixtures of PLA and PCL with compositions of PCL: PLA (% w/w) of 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, and 10:0 were dissolved in 10 mL of dichloromethane (DCM) and stirred using a magnetic stirrer at a speed of 400 rpm for 10 minutes.

Preparation of nifedipine microcapsules

In this step, 60 mg of nifedipine was added to polyblend solutions. Span 80 with a concentration of 1% (v/v; 0.1 mL) was added to the polyblend solution. For the emulsion step, a beaker containing polyblend, drug, and Span 80 was stirred with a stirring speed of 700 rpm for 1 hour. After that, the solution was put into a spray bottle. In the dispersion step, the solution was sprayed into 100 mL of distilled water containing 0.025% (v/v) Tween 80, which was stirred at a speed of 900 rpm for 1 hour to form microcapsules. The resulting microcapsules were then filtered and washed with 5 mL of methanol and dried in an oven at a temperature of 38–40°C for two nights, to evaporate the remaining DCM solvents and methanol. The surfactant concentration, stirring speed, and stirring time parameters were chosen based on the optimum conditions obtained from (Wati *et al*., 2018).

Determination of encapsulation efficiency

About 10 mL of the filtrate obtained from the dispersion step was taken, followed by taking 1 mL aliquots and diluting the filtrate 20 times. The results were then measured for the absorbance at the maximum wavelength of nifedipine (λ = 238 nm) (Prathusha *et al*., 2015), obtained using an ultraviolet-visible (UV-Vis) spectrophotometer with distilled water as a blank.

Dissolution test

First, the microcapsules were immersed in 900 mL of a buffer solution with pH 1.2, and then they were stirred for 3 hours. Samples were taken after 1, 2, and 3 hours. After 3 hours, the microcapsules were moved into a buffer solution with pH 7.4, and sampling was taken each hour up to the 55th hour. The concentration was determined at the maximum wavelength of nifedipine (λ = 238 nm) using a UV-Vis spectrophotometer.

Characterization of the microcapsule profile

The microcapsules were measured by a Fourier transform infrared (FT-IR) spectrophotometer to determine the chemical bonding in these microcapsules. Furthermore, to determine the size and crystallinity of the microcapsules, the measurements were carried out using particle size analysis (PSA) and X-ray diffraction (XRD), respectively. Finally, an optical microscope (OM) was used to observe the morphology of the microcapsules before and after the dissolution test and scanning electron microscope (SEM) was used to observe the morphology cross-section of microcapsules.

RESULTS AND DISCUSSION

Food is in the human digestive system around 24-72 hours (Kirarli, 1995), it will be removed from the body. Microcapsules that act as a drug-carrying matrix will also be removed from the body through feces. This is one of the advantages of choosing biodegradable materials, where microcapsule waste will be easily degraded naturally without endangering the environment. PLA can be degraded

in a biotic or abiotic environment well but does not show degradation with the help of microbes (Agarwal *et al*., 1998). In contrast to PLA, PCL can be degraded by living microorganisms such as bacteria (Motiwalla, 2013). In general, the degradation of PLA and PCL is almost the same, starting from the diffusion of water into the amorphous region, followed by the hydrolytic separation of the ester bond, which results in damage to the long macromolecular chain (Agarwal *et al*., 1998; Woodruff and Hutmacher, 2010). The degradation time of the polymer depends on the molecular weight, the degree of crystallinity because what will be degraded first is the amorphous part of the polymer, and the morphology of the polymer (Leja and Lewandowicz, 2010). Based on these facts, the PLA-PCL polyblend can be utilized as an environmentally-friendly material for drug delivery system, since both of the polymers, in fact, are also biocompatible as well. The oil-in-water (o/w) solvent evaporation method was chosen to produce nifedipine microcapsules with low solubility in water (Li *et al*., 2008). In this research, nifedipine drug was incorporated into environmentally friendly copolymer PCL/ PLA dissolved in 10 mL of DCM solvent. DCM was chosen as the solvent due to its nonpolar characteristics, enabling it to dissolve PLA and PCL well. Furthermore, DCM possesses a low boiling point (39.6°C) (Cayot *et al*., 2016), making the hardening process of the microcapsule easier (Li *et al*., 2008). After the mixture of drug and polymer became homogenous, a surfactant of Span 80 was added to help stabilize the emulsion of o/w when this organic phase was dispersed in the continuous phase (Narang *et al*., 2007). Span 80, which is a hydrophobic phase, will create a reverse micelle with its head facing inside and tail facing outside. The tail of Span 80 will act as an anchor that holds the drug so that it will be well incorporated into the copolymer

Fig. 1: Microcapsule of nifedipine

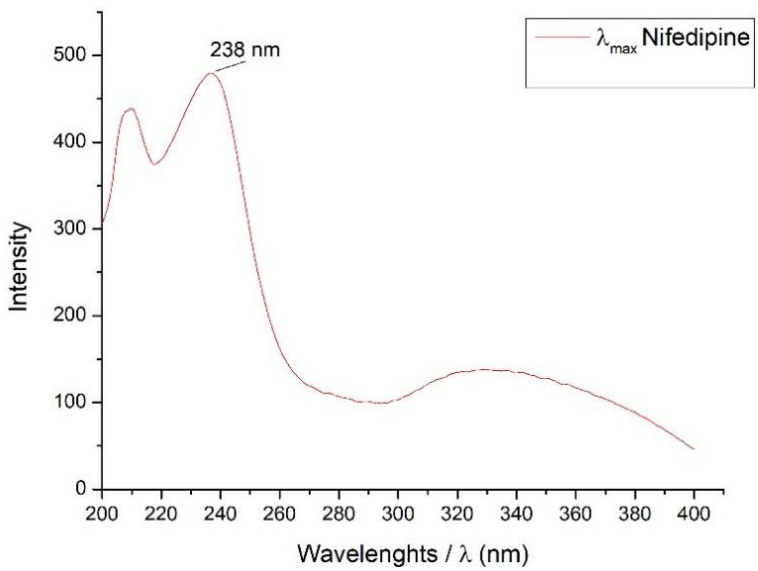

Fig. 2: The maximum wavelength of nifedipine (λ = 238 nm) using a UV-Vis spectrophotometer

matrix of PLA and PCL. The second step is dispersion of the organic phase into the continuous phase of 0.025% (v/v) Tween 80 solution. This step is a droplet-formation step (Tiwari and Verma, 2011). When the organic phase was dispersed into the continuous phase, the hydrophobic tail of Span 80, which is the sticking place of copolymer and nifedipine, rotated inward so that the copolymer and nifedipine were inside the micelle (Swarbrick *et al*., 2006). Along with the rotation of the tail and head of Span 80, the micelle composition was rearranged with Tween 80 in the continuous phase. The micelle droplets were more stable due to the combination of these two surfactants. The third step was evaporation of the DCM solvent and microcapsule solidification. The mechanism of solvent evaporation was composed of two stages. In the first stage, the solvent was diffused from emulsion droplets to the continuous phase, and then it was continued by the evaporation of solvent to the air (Li *et al*., 2008). The concentration of microcapsules was denser along with the evaporation of solvent, making it solid. The last step was separation of the microcapsule produced in its continuous phase by filtration. Microcapsule solids (Fig. 1) were kept and dried in a 40°C oven. Meanwhile, the continuous phase of the filtrate was kept for efficiency testing of nifedipine microcapsule encapsulation by using the UV-Vis spectrophotometer on a wavelength of 238 nm (Fig. 2).

This study emphasizes optimization of the best polyblend composition of PLA:PCL as Nifedipine coating. The component variation of PLA:PCL used is 10:0 (N1), 9:1 (N2), 8:2 (N3), 7:3 (N4), 6:4 (N5), 5:5 (N6), 4:6 (N7), 3:7 (N8), 2:8 (N9), 1:9 (N10) and 0:10 (N11).

Fig. 3 shows the categorization result of the nifedipine microcapsule morphology based on the optimization of polyblend composition by OM utilization. An interesting result came along with the increase of PCL composition in the microcapsule, which resulted in the formation of holes in the microcapsule's morphology. The number of holes created in the microcapsule was increased along with the higher concentration of PCL. This occurrence was caused by the free volume phenomenon in the polymer. PCL possesses a low glass transition temperature of −60°C (Lu and Chen, 2004), which causes it to take a rubber form at room temperature.

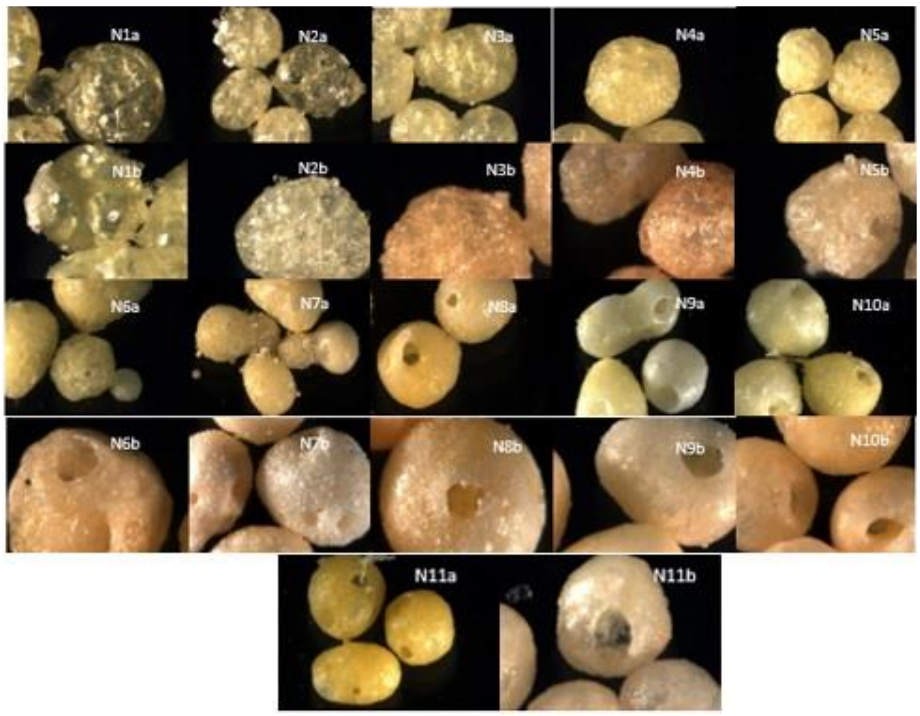

Fig. 3: Morphology of nifedipine microcapsule PLA:PCL (%w/w) (a) before dissolution 25x (b) after dissolution 50x

Free volume is a space in solids or liquids that is not occupied by polymer molecules; in other words, it is the "empty space" between molecules. The more empty spaces a substance has, the less polymer glass transition occurs because the movement of the polymer chain will be more flexible. In liquid form, the amount of free volume is high, which enables moving the polymer chain relatively easily. This phenomenon occurs due to the empty space, which enables the molecules to move and change their conformation independently (Young and Lovell, 2011). As mentioned before in terms of microcapsule production, a polyblend of PCL and PLA is first dissolved by DCM, which makes the free volume of polyblend higher and creates holes in the microcapsule's morphology when solidification occurs. PLA possesses a relatively high temperature of glass transition, which is 60°C (Lunt, 1998). As a result, at room temperature, it will be glassier (solid and rigid) (Ahmed and Varshney, 2011) and possess low free volume. This is what makes N1 and N2 microcapsules more transparent and holeless.

Based on the results displayed in Table 1, the more the PCL composition was within the nifedipine microcapsule, the less efficient the nifedipine encapsulation became. Sample N10 had the lowest encapsulation efficiency, which was 78.82 ± 0.68%, due to the existing holes on the microcapsule. The holes allowed the medicine to diffuse out from the microcapsule during solidification. Moreover, Table 1 displays the percentage of the acquired microcapsule solids based on the optimization of the polyblend composition. From the data, there was no significant difference between the percentage of microcapsule solids acquired by different polyblend compositions. This was because the concentration of the polyblend solution remained the same, which was 5%, even though the compositions of PLA and PCL had changed, representing 0.5 g of polyblend dissolved

Table 1: Nifedipine microcapsule encapsulation efficiency results

Samples	PLA	PCL	Encapsulation Efficiency (%)	Yield of Microcapsules (%)
N1	10	0	89.84±0.06	96.79±0.92
N2	9	1	87.25±0.37	96.48±1.07
N3	8	2	85.95±2.35	96.98±1.68
N4	7	3	83.74±0.35	96.46±0.64
N5	6	4	80.75±0.63	96.03±2.43
N6	5	5	83.85±0.75	96.62±0.74
N7	4	6	80.30±1.98	95.76±1.25
N8	3	7	80.73±0.96	95.27±1.54
N9	2	8	80.68±1.96	95.86±0.28
N10	1	9	78.82±0.68	96.36±0.37
N11	0	10	80.28±0.10	95.69±0.49

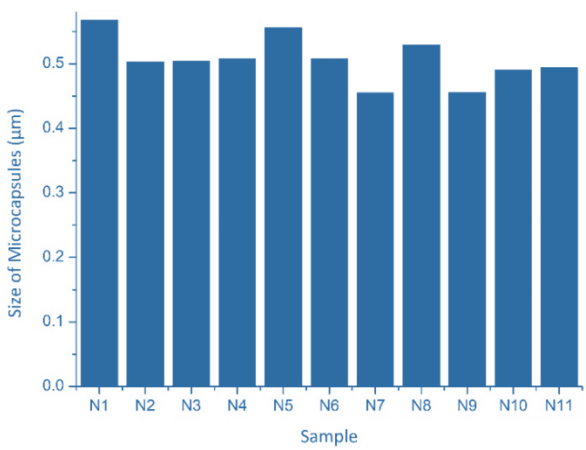

Fig. 4: Microcapsule size acquired from the optimization of the polyblend composition of nifedipine microcapsule

in 10 mL of DCM. Because the concentration and viscosity of the polyblend remained the same, so did the percentage of the resulting microcapsule solids. This basis explains the formation of microcapsule particles with similar sizes (Fig. 4) despite the change in the compositions of PLA and PCL. As stated by Sharma *et al*. (2016) in their research, polymer types and composition do not affect the particle size because the parameters affecting the size the most are concentration and viscosity.

Dissolution testing has become an important parameter in vitro tests to determine the quality of oral drugs. Although the main evaluation of drug performance must involve testing in humans, a simple in vitro dissolution test can provide an initial picture of the potential problem of the bioavailability of a product. For example, if a certain drug product shows a very slow dissolution rate, it could mean that there are several factors in the formulation or production process of the drug that might indicate a problem. This underlies, the dissolution of testing has been widely accepted as a quality control (QC) parameter for monitoring the quality of medicinal products (Mehta, 1993). The dissolution test was conducted against 11 samples with varied optimized polyblend compositions of PLA and PCL for 55 hours to determine the best optimization in terms of medicine release. Dissolution was done continuously, where the microcapsule was dissolved in pH 1.2 (simulated gastric fluid), representing the acidity of gastric liquid, in the first 3 hours. Afterward, dissolution was continued for the remaining hours at pH 7.4 (simulated intestinal fluid), representing the acidity of colon liquid. Dissolution was performed for 55 hours to represent how long it takes in humans from the beginning of digesting food to when it is excreted from the body.

Based on the data displayed in Fig. 5, burst release occurred in the dissolution with pH 1.2. This effect was quite significant, reaching 15% for sample N10. The burst release effect is a high-speed medicine release that occurs dissolution. According to Yeo and Park (2004), it is caused by two factors, which are as follows: 1) the presence of bonded active substance in the surroundings of the microcapsule surface or non-encapsulated active substance on the microcapsule surface; and 2) the microcapsule's morphology, consisting of sufficiently large pores or fissures formed during the solidification of the microcapsule. The burst release effect that occurred in this research was likely caused by the holes on the microcapsule, as displayed in the figure, causing the medicine to diffuse rapidly to the dissolution medium, with a pH of 1.2, at the beginning of the dissolution. Park (1994) stated that one of the factors affecting the medicine release is polymer molecule weight; the heavier it is, the more structured the polymer structure is, preventing medicine release. Heavier molecules add greater duration for the degradation of polymer; this is because a heavier

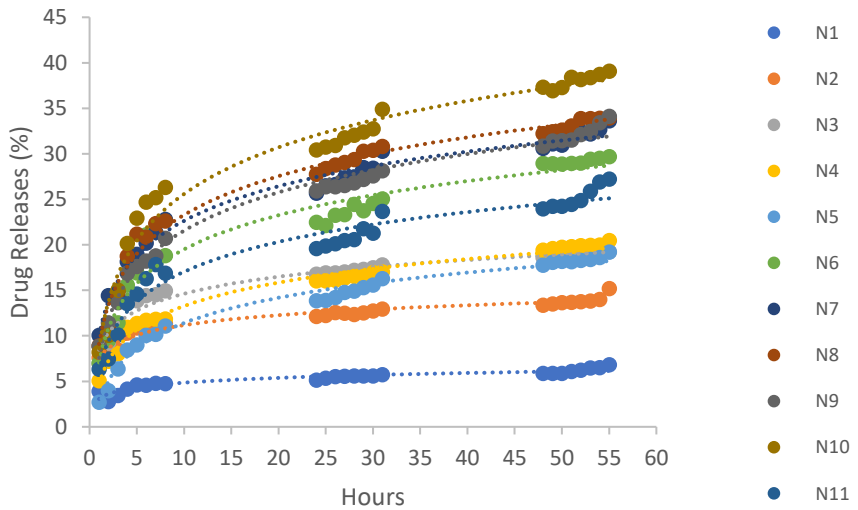

Fig. 5: Dissolution profile of nifedipine microcapsule with varied optimized polyblend composition of PLA and PCL

weight indicates that the molecule has a longer chain. That said, 55 hours of dissolution were assumed to be insufficient for degrading PLA, with its molecular weight of 137,000 Da, not to mention PCL, for which the semi-crystalline structure weighs 150,000 Da. Insignificant degradation could be observed from the microcapsule's morphology, with no evident difference between the ones before and after the dissolution. Furthermore, heavy polymer molecules also affect pore formation on microcapsules. A heavy microcapsule has poor porosity due to rapid solidification during the continuous phase (Yeo and Park, 2004). Poor porosity can affect medicine release, especially in the case of hydrophobic medicine, which is almost insoluble in water. The smaller the pores become, the harder it is for the medicine to diffuse in the matrix to the dissolution of the medium. This research used hydrophobic polymer PLA and PCL, a hydrophobic medicine, as the distributor of the drug nifedipine. The similarity between the polyblend and the medicine in the research was also a challenge during the dissolution stage. Medicine bound more strongly to the matrix than the dissolution medium with polarity did. This explains the cause of the small percentage of the acquired medicine. Microcapsules made by hydrophilic polymer matrix can facilitate the water absorption from the dissolution medium to the matrix wall, making it easier to release medicine (Yeo and Park, 2004). From the explanation, it is predicted that the mechanism of the medicine release is by diffusion rather than polymer degradation. Based on the medicine release percentage, the polyblend with the best composition was N10, that is, PLA:PCL 10:90 (%w/w). Sample N10, with its 90% PCL composition, still had original PCL characteristics, which involved low Tg (−60°C) (Lu and Chen, 2004). Under Tg, the polymer will be in a glass state, which involves limited mobility and a low rate of diffusion. Above Tg, the polymer will be inelastic, allowing a higher mass transfer rate of water to escape from the matrix (Liechty *et al*., 2010).

Fig. 6A and Fig. 6B show the cross-sectional

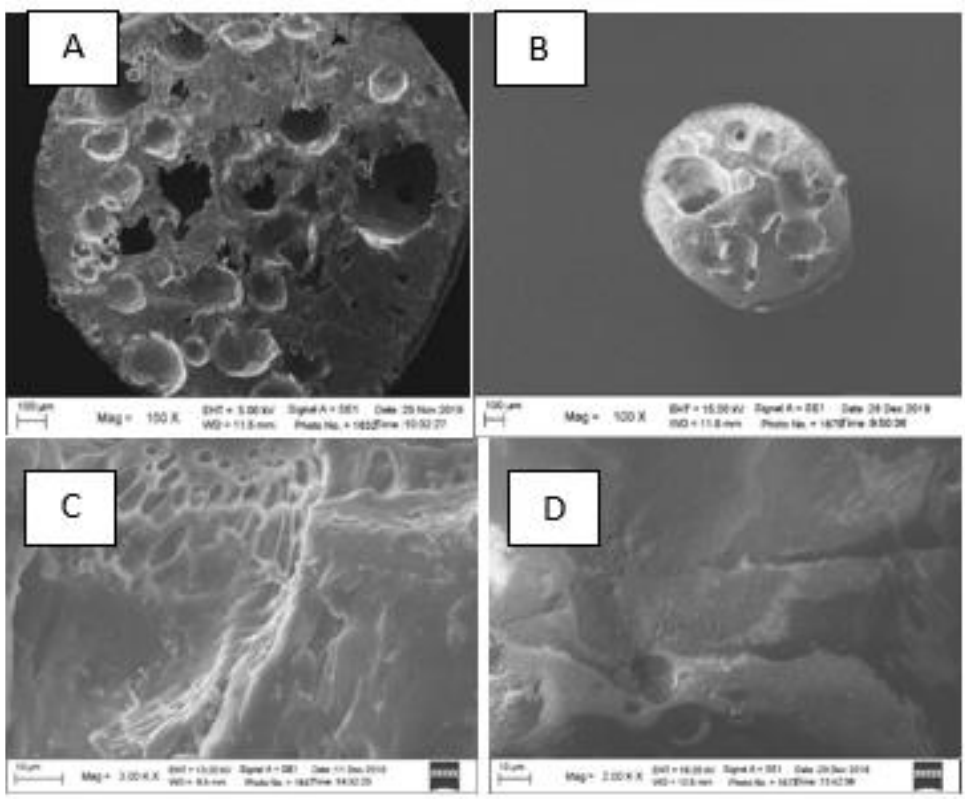

Fig. 6: Morphology cross section of nifedipine microcapsule PLA:PCL (%w/w) (A) N10 150x (B) N1 100x (C) N10 3000x (D) N1 2000x

morphology of the nifedipine microcapsule. From the pictures, it can be observed that the inside of the microcapsule contains small cavities. This cavity is the part occupied by organic solvents (DCM) in making microcapsules; when solidification occurs, the solvent diffuses out of the microcapsules to form a hole or cavity on the inside of the microcapsules (Shi *et al*., 2018). In the scanning electron microscopy (SEM) cross-section results at 3,000x magnification for N10 (Fig. 6C), it was found that a higher PCL composition could increase the rate of drug release. This was due to the higher permeability characteristics of PCL, which tends to produce pores in the microcapsules. Permeability is closely related to porosity, pore size, pore shape, morphology, and pore structure. Porosity tends to be linearly related to the logarithm of permeability. Therefore, it can be said that the higher the permeability of a material is, the greater is the porosity that will be produced (Cole, 1983). In contrast, for N1 (Fig. 6D), in the nifedipine microcapsule consisting of 100% PLA, there are no visible pores at all.

Based on Fig. 7A, the absorption band on the microsphere spectrum at wavelengths of 2923/cm

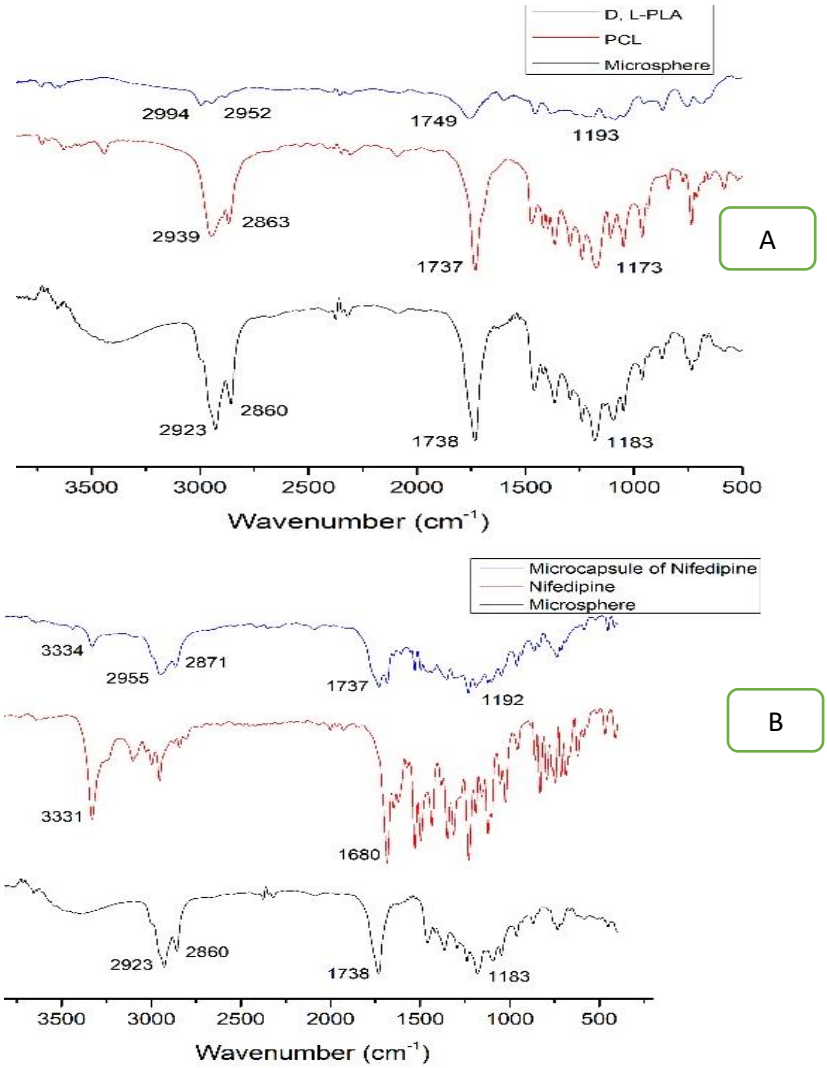

Fig. 7: Spectrum FT-IR of (A) PLA, PCL, microsphere (B) microcapsule of nifedipine, nifedipine, microsphere

and 2860/cm shows the presence of a stretching vibration of the C-H group. Moreover, the absorption band at the 1738/cm wavelength shows the presence of a stretching vibration of the C=O carbonyl group (ester) (Jackson *et al*., 2017). The crest shown in the 1183/cm wavelength is an absorption band of the C-O-C group. The FT-IR spectrum ratio between PLA and PCL in the microspheres in Figure 6A does not show a loss or increased absorption band, which means there are only a physical interaction and no chemical reaction between PLA and PCL in the microsphere (Kemala *et al*., 2012). The physical interaction of PLA and PCL could be a hydrogen bond between oxygen atoms of the PCL carbonyl group and hydrogen atoms of the PLA hydroxyl group, or it could be dipole-dipole interactions between oxygen atoms (δ−) of the PCL carbonyl group and carbon atoms (δ+) of PLA carbonyl group. The lowest physical interaction between PLA and PCL is a Van der Waals interaction. Based on Fig. 7B, it can be observed that the spectrum of nifedipine microcapsules is a combination of the microsphere and nifedipine spectra. This occurs because all the absorption bands of the microsphere and nifedipine are also possessed by the nifedipine microcapsule spectrum without experiencing decreasing and increasing numbers of absorption crest, although it experiences slight shifting. Nifedipine, with the functional group of N-H, possesses a wavelength number of 3300/cm. When a pure sample of nifedipine was tested under a UV-Vis spectrometer, a similar wavelength, 3301/cm, resulted from the process. Not only that, but the microcapsule was also detected to have nifedipine with a similar wavelength. In other words, the interaction between the drug nifedipine and polyblend of PLA and PCL is a physical interaction without any chemical interaction. The nifedipine microcapsule spectrum above also shows that the drugs were incorporated well in the matrix. Few microcapsules taken for FT-IR characterization could represent the nifedipine presence inside the microcapsule.

A possible factor in determining the release profile of active compounds is the polymer structure, which is influenced by the molecular weight, crystallinity, melting point, and glass transition temperature (Ge *et al*., 2000). As explained in the previous subchapter, the best release profile is the drug with polyblend composition of 90% PCL, but the release percentage obtained from the research is still low (39.07%). Bikiaris (2011) researched the crystallinity effect of polyester in terms of the drug release tendency. They found that poly(propylene adipate) (PPAd), which has a low molecular weight and low temperature of glass transition, possessed the slowest drug release due to its high crystallinity. High crystallinity of the matrix may have a negative effect on the drug release rate because lamellae can act as a barrier during the drug diffusion process (Bikiaris, 2011). Because PCL possesses semi-crystalline characteristics, it is necessary to study the crystallinity of the matrix

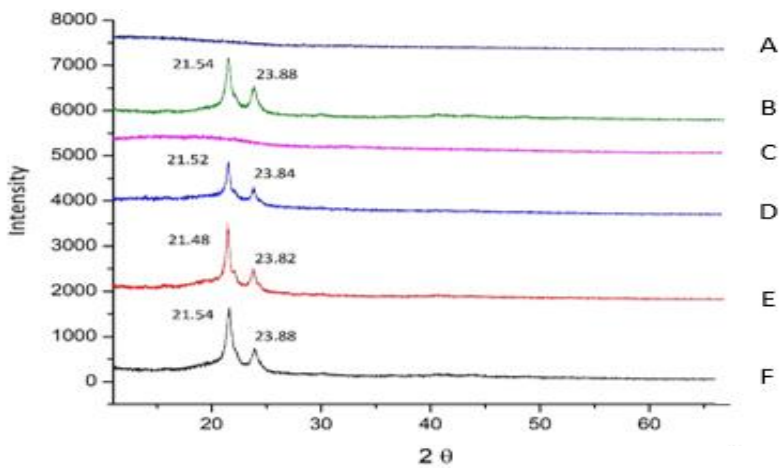

Fig. 8: XRD spectrum of (A) PLA, (B) PCL, (C) N1 microcapsule, (D) N5 microcapsule, (E) N10 microcapsule, (F) N11 microcapsule

and the microcapsules formed. Based on Fig. 8, it can be illustrated that PLA (Fig. 8(A)) does not show a specific crystallinity crest, indicating the amorphic characteristics of PLA, in line with previous research by Chen *et al.* (2003). Meanwhile, there are two specific crests of PCL (Fig. 8(B)) at 2θ 21.54° and 23.88°. These data are in line with research by Ge *et al*. (2000), who found two specific crests at 2θ 21.54° and 23.75°, and Chen *et al*. (2003), who reported that the crests at 21.42° and 23.83° were specific crests for PCL. The N1 microcapsule, coated by a 100% PLA matrix, did not show a specific crest (Fig. 8C) because the real characteristics of PLA are amorphic. Microcapsule samples of N5, N10, and N11 (Figs. 8D, 8E and 8F) showed PCL-specific crests on 2θ despite experiencing a shift caused by the presence of PLA in the polyblend. This was proven by the lower composition of PLA, making the specific degree of PCL approach the specific degree of pure PCL, as shown in N11, which possesses a specific crest of 2θ. The XRD characterization result also showed that the polymer still carried its proper characteristics despite experiencing dissolution, microcapsule solidification, and physical interaction with one another.

CONCLUSION

Polylactic acid and polycaprolactone are biodegradable dan environmentally friendly polymers that are proven safe for the environment, because they can be degraded naturally in nature. The hydrolysis of the two polymers results in a biocompatible product that is safe for the body, and of course also safe for the environment. This study uses polylactic acid and polycaprolactone as a nifedipine carrier matrix, and the best polyblend composition in coating nifedipine is determined. In this study, it was found that the efficiency of microcapsule encapsulation, which was synthesized by various PLA: PCL polyblend compositions, showed a value of 78.82 to 89.84%. The highest efficiency, 89.84%, belongs to N1, with a PLA: PCL 10: 0 polyblend composition. The absence of PCL inside the microcapsules, causes no holes to form on the surface of the microcapsules so that the drug cannot diffuse out of the microcapsules and the drug is encapsulated much more. The holes formed on the surface of the microcapsules are caused by the character of PCL which has a Tg −60°C. A low Tg tends to provide a large movement space for the polymer chain so that a large free volume is formed in the polymer. In the dissolution test, the percentage of drug release for all variations of the polyblend composition was 4.8-39.07%. The highest percentage of drug release, 39.07%, belongs to the composition of the N10 polyblend with a ratio of 1: 9 from PLA: PCL. The composition of PCL which dominates within the microcapsule causes the character of PCL to also dominate the microcapsules. PCL has high permeability properties, so the more PCL composition in the microcapsules, the permeability of the microcapsules will also increase. High permeability causes the drug to easily diffuse out of the microcapsule. Therefore, the best ratio of the polyblend composition of PLA: PCL to nifedipine is a 1: 9 ratio. Microcapsule solids produced are approximately 96%, and Particle Size of microcapsule ranges at 0.5 µm.

AUTHOR CONTRIBUTIONS

E. Budianto led the study and analyzed the data, S.H. Astuti designed the background of the study and conducted the literature review.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been completely observed by the authors.

ABBREVIATIONS

δ-	Delta negative
δ+	Delta positive
λ	Lamda

Θ	Theta
^oC	Degree Celsius
Ca^{2+}	Calsium
C	Carbon
cm	centimeter
Da	Dalton
DCM	Dichloromethane
FDA	Food and Drug Administration
Fig.	Figure
FT-IR	Fourier transform infrared
g	gram
HCl	Hydrochloric acid
H	Hydrogen
HLB	Hydrophilic lipophilic balance
K_2HPO_4	Dipotassium phosphate
KH_2PO_4	Potassium dihydrogen phosphate
mg	miligram
mL	milliliter
Mw	Molecular weight
µm	micrometer
N1	PLA:PCL 10:0 (w/w)
N2	PLA:PCL 9:1 (w/w)
N3	PLA:PCL 8:2 (w/w)
N4	PLA:PCL 7:3 (w/w)
N5	PLA:PCL 6:4 (w/w)
N6	PLA:PCL 5:5 (w/w)
N7	PLA:PCL 4:6 (w/w)
N8	PLA:PCL 3:7 (w/w)
N9	PLA:PCL 2:8 (w/w)
N10	PLA:PCL 1:9 (w/w)
N11	PLA:PCL 0:10 (w/w)
NaCl	Sodium chloride
N	Nitrogen
O	Oxygen
OM	Optical microscope
o/w	oil-in-water
PCL	Polycaprolactone
PGA	Polyglycolic acid
pH	Potential of hydrogen
PLA	Polylactic acid
PSA	Particle size analysis
QC	Quality control
rpm	Revolution per minute
SEM	Scanning Electron Microscopy
Tg	Glass Transition
UV-Vis	Ultraviolet-Visible
v/v	Volume per volume
w/w	Weight per weight
XRD	X-ray Diffractometry

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