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Synthesys and Characterization of PLA-CNC Matrix for Antidiabetic Drug Release Applications

Nufus Kanani[1,a*], Yenny Meliana[2,b] , Endarto Yudo Wardhono[3,c], Rahmayetty[4,d], Sri Agustina[5,e], and Alia Badra Pitaloka[6,f]

[1*]Department of Chemical Engineering, University of Sultan Ageng Tirtayasa, 42435 Cilegon, Banten Indonesia

[2]Research Centre for Chemistry, Indonesian Institute of Sciences, Indonesia

[3-6]Department of Chemical Engineering, University of Sultan Ageng Tirtayasa, 42435 Cilegon, Banten Indonesia

[a*]nufus.kanani@untirta.ac.id, [b]yenn001@lipi.go.id, [c]endarto.wardhono@untirta.ac.id, [d]rahmayetty@untirta.ac.id, [e]sriagustina@untirta.ac.id, [f]aliabp@untirta.ac.id

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Abstract. Recently, drug nanoparticles formulation using Poly Lactic Acid-Cellulose nanocrystal (PLA-CNC) have been introduced. PLA-CNC were prepared by emulsion method for antidiabetic drug delivery applications. PLA is one of polymer which potentially used as raw material of drug delivery because it has the ability to bind and carry drugs into cell target, but the hydrophilic character of PLA can cause the degradation of PLA in the body run slowly, so it is necessary combining PLA with CNC to improve its property. In this study, special attention has been given to the modification of PLA-CNC as a drug delivery matrix to obtain the optimum drug release of antidiabetic drugs. In this study drug release analysis was conducted at 35-39 ^{0}C and pH range 3 to 9 with varied of time dissolution 0 to 180 min. PLA-CNC matrixs were characterized using FTIR and SEM, its drug loading capacity, encapsulation efficiency and in vitro drug release behavior was determined by using UV spectrophotometer. It gave the initial burst release at the first hour at 37 ^{0}C pH 3.

Introduction

Diabetes Mellitus type II (DM) is a chronic metabolic disease. Diabetics cannot produce sufficient amounts of insulin, and the body cannot also use insulin effectively. Some ways to control sugar levels in body can be done by diet, exercise and consume some medicine to control sugar level such as Metformin Hydrochloride (Metformin HCl). Metformin HCl is an antidiabetic with high solubility in water [1].

Recently, biodegradable material matrix such as Poly Lactic Acid (PLA) is one of the most well-known bioabsorbable polymers, non-toxic and with good biodegradability, biocompatability useful in several food packaging and biomedical application [2].

PLA is a one of biodegradable polymer from natural resources, it is biocompatible and biodegradable [2]. It can be produced from lactic acid derived include sugar, starch and glycerin. It is known as non-carcinogenic compounds, widely used in food and biomedical packaging application [3]. In vivo, PLA has the ability to bind and carry drugs to cells target through the transport channel and release. PLA can also be dissolved and removed from the body through the secretion system, so it does not interfere with the existing metabolic system, but PLA has high crystallinity and low hydrophylity which causes slow degradation in human body.

PLA Modification by bending with other hydrophilic polymers can facilitate the drug to be degraded and excreted. Commonly polymers combined with PLA such as polyethylene glycol (PEG), Polyhydroxybutyrate (PHB), polycaprolactone (PCL), polybutylene adipate-co-terephthalate (PBAT), chitosan and Cellulose Nano Crystals (CNC) [4].

CNC has a high crystalline structure, good tensile strength properties and elongation at break. CNC commonly used to strengthen polymer materials. Modification of CNC-CTAB used as a binder of drug delivery, it can control drug release for 2 days and CNC-CHX matrix can control drug release for more than 48 hours even using very small dosage [5, 6].

This work focused on the preparation of PLA-CNC matrix and percentage released of Metformin HCl using PLA-CNC matrix in different temperature and different pH conditions.

Material

Poly lactic acid (PLA) with specific gravity 1.24 g/cm^3 and Cellulose nanocrystals (CNC) were purchased from Huaian Ruanke Trade, China, Metformin Hydrochloride (Metformin HCl) with dosage 500 mg were purchased from drug store, demineralized water produced by purification chain was used for all experiments, all the reagents and chemicals are used as a laboratory grade without further purification.

Methods

PLA-CNC matrix formulation. The PLA-CNC matrix formulation was performed by adding 5 gr of PLA and 150 ml of chloroform. 5 gr of PLA was dissolved into 150 ml chloroform. 5 gr of CNC were then added to the PLA and chloroform suspension. This mixture continued being stirred at 900 rpm, the temperature was maintained at room temperature for 4 hours. The gels formed from the materials were poured into dishes and dried using oven at 60 ^{0}C for about 24 hours.

Microcapsules synthesis. The microcapsules synthesis of Metformin HCl using PLA-CNC matrix ware produced by adding Metformin HCl (dosage 500 mg) solution and polyvinyl alcohol (PVA) solution. The Metformin HCl solution was formed by dissolved 0.25 gr Metformin HCl into 30 ml demineralized water and the polyvinyl alcohol solution was conducted by dissolving 0.25 gr PVA into 50 ml demineralized water.

Metformin microcapsules was then formed by pouring and mixing Metformin solution, PVA solution and PLA-CNC solution. the solutions were then be blended at 80 ^{0}C and 30 minutes. Finally, the materials were poured into dishes and dried using oven. the temperature was maintained at 60 ^{0}C and 24 hours

Drug release analysis. Drug release was measured using a UV-VIS Cary 60 instrument spectrophotometer. Firstly, an initial scanning was performed to determine the wavelength at which the readings would be carried out the wavelength 235 nm as selected. 0.2 grams of microcapsules were dissolved into 900 mL of buffer solution (pH 3 to 9). 5 ml of the samples were then taken in interval 15 minutes and diluted until 10 ml. Finally, the solution was measured by UV-Vis spectrophotometer instrument Cary 60 with 50 rpm for 3 hours. For each sample, 6 scans were recorded.

Characterization. FTIR analysis was conducted to analysis the function groups present in the PLA, CNC and PLA-CNC matrix. The measurements were taking in range from 500 cm^{-1} to 4000 cm^{-1}.

Results and Discussions

Calibration set. Figure 1 shows that the amount of concentration of Metformin HCl (ppm) is presented by x-axis, and absorbance is presented by y-axis. It appears the most samples lie close to the theoretical line. An indication of the accuracy of the curve model is provided by the root-mean-square error ($R^2 > 99$).

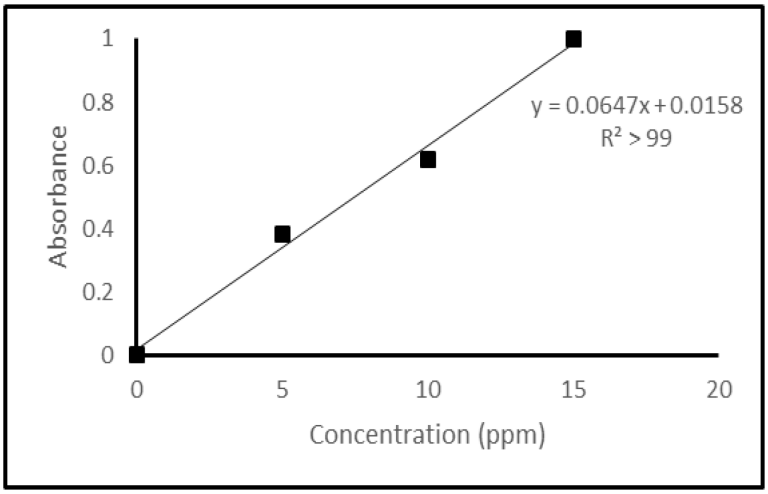

Figure 1. Calibration set for different concentration

Chemical structure. FTIR spectroscopy analysis was conducted to investigate the changes of chemical structure materials before and after treatments. The spectra of PLA and CNC as raw materials and also PLA-CNC matrix as products are shown in figure 2.

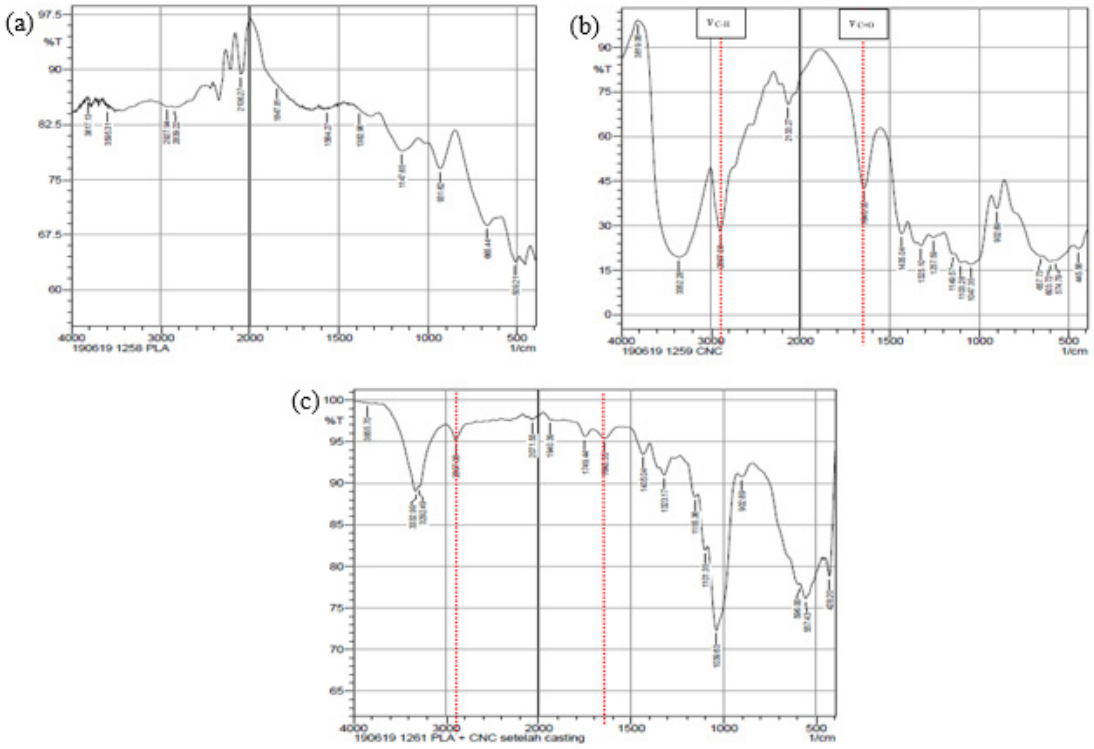

Figure 2. FTIR spectra of (a) PLA; (b) CNC; (c) PLA-CNC matrix

FTIR analysis showed that the chemical structures of all raw materials unchanged during the PLA-CNC matrix formulation processed. FTIR displayed the wave number of functional groups absorption intensities are between 500 cm^{-1} to 4000 cm^{-1} [7]. It also displayed the broad peak in the 3640-3630 cm^{-1} was assigned to O-H stretching vibrations [8, 9], which are characteristic of the hydroxyl groups generally present in cellulose, water and lignin. The absorbtion at about 3352.28 cm^{-1} can be assigned as O-H stretching vibration of CNC.

Table 1. Result of FTIR analysis of PLA, CNC and PLA-CNC matrix

Sample	Chemical structure	Stretching vibration (cm^{-1})
CNC		
	OH	3352.28
	C-H	2897.08
	C-O	1435.04-657.73
Polylactid Acid (PLA)		
	C=O	1847.81
	C-O	1147
	CH3	2927.94 dan 2839.22
PLA-CNC		
	C=O	1749.44
		1643.35
	C-O-C	1155.36
	CH3	2897.08

The vibration band between 1435 to 650 cm^{-1} corresponded to C-O stretching vibration. from the figure 2 (a), (b) and (c) showed that the stretching vibration are 1435.04-657.73 cm^{-1}; 1147 cm^{-1}; and 1749.44 cm^{-1}, it can be assigned as C-O stretching vibration of, CNC, PLA and PLA-CNC matrix.

Drug release analysis. Figure 3 shows the percentage of drug release versus pH profile from metformin HCl in PLA-CNC matrix at pH range 3 to 9. The drug release showed an initial burst release at pH 3 followed by pH 4 to 9. The fraction release of Metformin HCl at lower pH was higher because the reaction will be more reactive at lower pH, the active material on the matrix surface will be more easily released at lower pH, so it can cause a significant uncontrolled burst release of Metformin HCl.

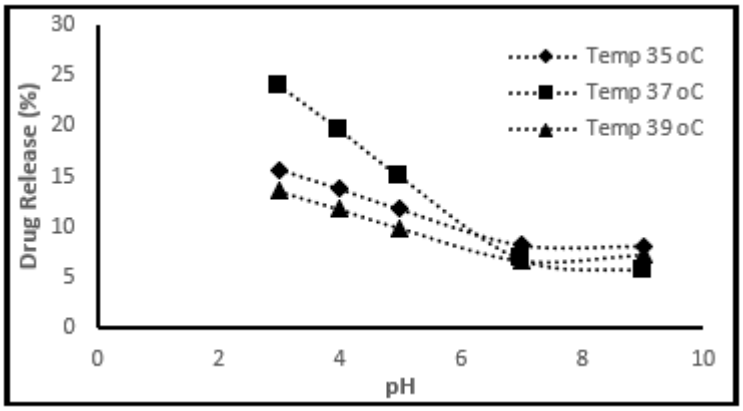

Figure 3. Relationship between drug release % and pH (of Metformin using PLA-CNC matrix) for different temperature

The percentage of drug release at lower pH has higher percentage than other higher pH. The PLA-CNC matrix more reactive at lower pH, it can cause the filler (Metformin HCl) will be easily release. Burst release of Metformin HCl occur at pH 3,4 and 5, then decrease at pH 6. However at pH 7 and 9 gave fairy constant release of Metformin HCl, it means that at high pH does not occur burst release because the PLA-CNC matrix surface gave a constant drug release.

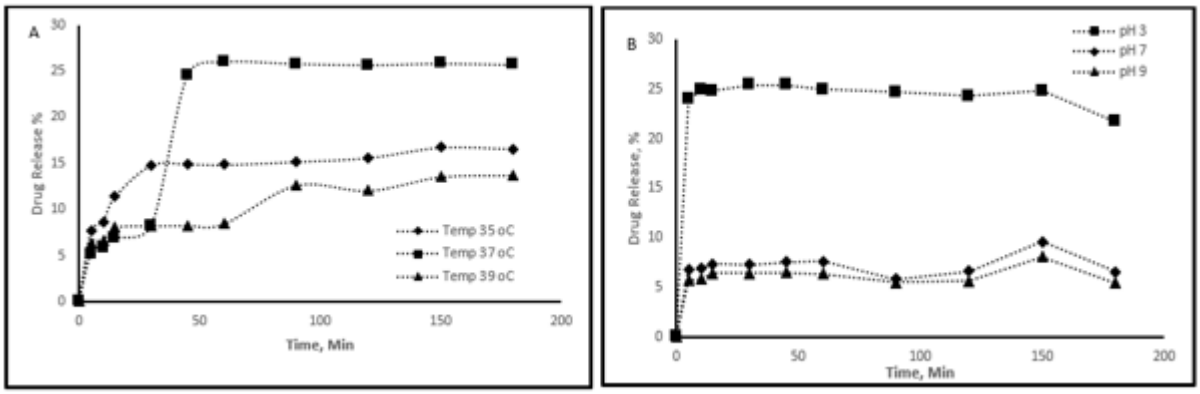

Figure 4. Relationship between % release of Metformin using PLA-CNC matrix and time (A) for different temperature (B) for different pH

Figure 4 presents the percentage of drug release versus time profile from metformin HCl in PLA-CNC matrix at temperature range 35 to 39^{0}C and pH range 3 to 9. Percentage drug release of Metformin HCl ranging from an immediate release to a substantially prolonged release, that approximately 26% of Metformin was released within the first hour, followed by slower but sustained release.

From Figure 4a the higher release of metformin is denoted at temperature 37 ^{0}C at the first hour and Figure 4b shows the release of Metformin HCl at different pH. At the lower pH, percentage of metformin release showed an initial burst release because PLA-CNC matrix has high reactivity.

Conclusion

Biodegradable material matrix such as Poly Lactic Acid (PLA) is one of the most well-known bioabsorbable polymers, non-toxic and with good biodegradability, biocompatability useful in several biomedical application such as drug delivery. CNC has a high crystalline structure, good tensile strength properties and elongation at break, commonly used to strengthen polymer materials. PLA Modification by bending with CNC can facilitate the drug to be degraded and excreted. The report of drug release from such drug delivery system shows that Matformin HCl is mainly released and prolonged through PLA-CNC matrix.

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