Kinetical Release Study of Copper Ferrite Nanoparticle Incorporated on PCL/Collagen Nanofiber for Naproxen Delivery

by Mochamad Zakki Fahmi

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Abstract

Nanofiber has become one of tissue engineering examples and has extensive application on medical field, particularly as a wound healing and wound dressing. In this research, nanofiber composite based on polycaprolactone and collagen was successfully obtained via electrospinning process and further developed as host of naproxen as anti-inflammatory agents. Addition of copper ferrite ($CuFe_2O_4$) nanoparticles on the nanocomposite becomes an advance part on this study to control of naproxen release. Several characterizations were furnished to prove the design composite nanofiber and its drug release analysis performed to find out the kinetic model and naproxen release mechanism from nanofibers. $CuFe_2O_4$ nanoparticles have potential to be used to control naproxen release in nanofiber that lead to decrease level of drug released, where mostly follow the Korsmeyer-Peppas model. The release of naproxen was certainly influenced by pH value, in which the drug was easier to release on base, instead of acid or neutral condition. Varied naproxen and nanoparticle compositions were prepared to reach optimum formulation of the release. This study provides fundamental data for the effect of magnetic nanoparticle on drug release process.

Keywords Nanofiber · Drug delivery system · Magnetic nanoparticle · Naproxen · Kinetic of drug release

1 Introduction

Controlled drug delivery is one of the most investigated research due to the advantages compared with the conventional dosage forms such as enhanced therapeutic efficacy and reduced toxicity by delivering drugs at a controlled release rate [1]. From those aspects, innovation design of material for excellent delivery agent became a crucial part to be considered, where it must be good in protecting the drug inside, biodegradable, and perform controllable release. Some drug-delivering agents have been reported on various nanomaterial forms including nanoparticles [2, 3], cast films [4, 5], and nanofibers. Nanofibers have performed to be an efficient system on providing sustained release of drug

compared the others [6]. Electrospinning was recently a common way of preparing nanofiber and reached potential applications on filtration, protective dressing, and biological applications (tissue engineering scaffolds and drug delivery devices) [4, 7]. Compared on its potential applications, drug delivery emerged as its most promising application. The high loading capacity, high encapsulation efficiency, simultaneous delivery of diverse therapies, ease of operation, and cost-effectiveness are appealing features for electrospinning used in drug delivery [3, 5].

The simple process in preparing nanofiber via electrospinning is also supported by other advantages like cost-effective, versatile process along with non-toxic degradation in the body and sustained release of encapsulated drugs [8, 9]. Thus, the electrospinning process is a promising technique for many biomedical applications. In particular, composite nanofiber of polycaprolactone (PCL)/collagen was reported as great candidate for tissue engineering applications [10]. PCL is a semicrystalline polymer with hydrophobic properties and high molecular weight [1]. PCL is largely used for tissue scaffolding, drug delivery, and guided bone regeneration [8, 11]. PCL has also good mechanical properties and slow degradability [9, 10]. In order to obtain multi-purpose nanofiber, techniques have been developed by load one or more of active agents on

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nanofiber, like growth factors [12], vitamins [13], proteins [14], genes [15], nanoparticles [16], natural compounds [17], anticancer [18], and antibacterial, to encourage healing processes [9, 19]. On most of above purposes, nanofiber acted as vessel for delivering or transferring those active agents. Therefore, combining magnetic nanoparticle on nanofiber can be envisaged as one of intriguing ways on design of controllable nanofiber. It was well-documented on several reports that combination of spinel ferrite nanoparticle on nanofiber gave magnetic-response effect of the fiber [16–18]. However, utilization of spinel ferrite nanoparticle on expedites drug leaching from nanofiber was not much explored. Recently, Haroosh and Dong [8] reported new drug delivery system for tetracycline hydrochloride (TCH) antibiotic from nanofibrous membranes based on PLA/PCL incorporated with magnetite (Fe_3O_4) nanoparticles as member of spinel ferrite, where these nanoparticles serve as controller for TCH release from nanofibers. Unfortunately, the studies on combining nanofiber with spinel ferrite were mostly using Fe or magnetite-based nanomaterial.

In this study, we deal on incorporating copper ferrite ($CuFe_2O_4$) nanoparticles onto PCL/collagen nanofiber. Copper ferrite has attracted an increasing interest as nanocomposite because of its good biocompatibility, large surface areas, super strong paramagnetic properties, low toxicity, and high adsorption ability [20]. Those reasons made this kind of spinel ferrite applied as antibacterial [21], catalyst [22], sensor [23], and cancer therapy [24]. The composited nanofiber will further load naproxen. Naproxen is one of non-steroidal anti-inflammatory drugs with analgesic and antipyretic properties, and widely used for the treatment of osteoarthritis, rheumatoid osteoarthritis, and acute pain in musculoskeletal disorders [25]. The addition of naproxen as drug material is used to treat inflammation and pain of wound areas for wound healing application. The effect of $CuFe_2O_4$ nanoparticle and the role of naproxen release are the main parts of this study that are never been explored before. The aim of the controlled release system on drug containing nanofiber is to maintain drug concentration in the blood or target tissue at desired value as long as possible, so as to exert control duration and drug release rate. Generally, controlled release systems initially release part of drug doses contained to achieve effective therapeutic of drug concentrations. The drug release kinetics follows rules that have been defined to supply the drug dosage requirements needed to attain the desired drug concentration [26]. Therefore, beside to investigate effects of $CuFe_2O_4$ nanoparticles addition on morphology, structure, and cytotoxicity, this paper also focused to investigate drug release profile of naproxen from PCL/collagen nanofibers. The investigation of PCL/collagen blended with $CuFe_2O_4$ nanoparticles may create new drug delivery system, which enables to directly deliver drugs to the targeted area of the body using external magnetic field.

2 Experimental

Materials PCL with average molecular weights (Mw) of 80.000 g.mol^{-1}, NaOH, chloroform, acetone, benzyl ether, oleylamine, copper(II) acetylacetonate and iron(III) acetylacetonate, and sodium naproxen were purchased from Sigma-Aldrich, USA. Bovine collagen was purchased from commercial products of Gelita, Brazil. For medium of buffer solutions (pH 4 and pH 9), phosphate-buffered saline (PBS) was purchased from Merck, Germany. All of chemicals were directly used without particular purification.

Synthesis of CuFe$_2$O$_4$ Nanoparticles The preparation of $CuFe_2O_4$ nanoparticles was adopt from previous report, with some modifications [27]. Experimentally, about 2 mmol of $Fe(acac)_3$ and 1 mmol of $Cu(acac)_2$ were mixed with 15 mL benzyl ether and 15 mL oleylamine. This material mixture was heated and stirred at a temperature of 270 °C for 2 h. After cooled on room temperature, the obtained nanoparticle was then washed with ethanol 90% and separated from the supernatant using centrifugation for 25 min at 4000 rpm.

Preparation of Dope Solutions The varied dope solution was prepared by dissolving PCL, collagen, and other components following Table 1. Pointy for regular dope solution, PCL 30% (w/v) was dissolved in chloroform at room temperature and bovine collagen 20% (w/v) was dissolved in water at the same room temperature with PCL. Both of these polymer solutions are further blended with addition of acetone to form a single-phase solution. The blended polymers were stirred for 1 h until homogenous solutions are obtained. About 20% (w/v) of naproxen solution on NaOH 0.1 N was then added into blended solutions following with stirred process for 1 h. After naproxen addition, $CuFe_2O_4$ nanoparticles were added into dope solutions and continually stirred for 1 h.

Electrospinning Process The dope solutions were transferred into 10 mL syringe equipped with 21 G metallic needle with inner diameter of 0.80 mm. The parameters were set with flow rate of polymer solutions at 0.01 μL/h for 3 h, and using drum collector. The electrospinning process was carried out under ambient conditions with 25 °C of temperature and relative humidity about 63%. The electrospinning high voltage was set at 26 kV. Drum collector covered with aluminum foil was placed 10 cm from the needle tip. On this study, several compositions of nanofiber were prepared with dope solution following Table 1.

In Vitro Drug Release and Kinetic Analysis On this analysis, dried nanofiber samples were prepared with adjusted shape and weight. The samples were transferred to dialyzed tube (MWCO 15,000 kDa, Orange Inc.) and further immersed in 100 mL of DI water placed in a beaker and set above a

Table 1 Varied composition of dope solution prepared for nanofiber

Nanofiber sample	Polycaprolactone (%)	Collagen (%)	Naproxen (%)	CuFe$_2$O$_4$ (mg)
Polycaprolactone (PCL)	30	0	0	0
Polycaprolactone-collagen (PC)	30	20	0	0
Polycaprolactone-collagen-naproxen (PCN)	30	20	20	0
Polycaprolactone-collagen-naproxen-with 2.5 of CuFe$_2$O$_4$ (PCNM 2.5)	30	20	20	2.5
Polycaprolactone-collagen-naproxen-with 7.5 of CuFe$_2$O$_4$ (PCNM 7.5)	30	20	20	7.5
Polycaprolactone-collagen-naproxen-with 12.5 of CuFe$_2$O$_4$ (PCNM 12.5)	30	20	20	12.5

magnetic stirrer, without using a spin bar, to give magnetic induction on the samples. At certain times, 1 mL of sample solutions was taken from the beaker glass and further measured with UV-Vis spectrophotometer (Shimadzu 1800, Japan) to determine the naproxen concentration by comparing maximum wavelength of naproxen (330.5 nm) with calibration curve. The total DI water in this system was maintained by adding fresh DI water after taking sample solution, and the actual concentration is determined by following equation [28].

$$C_t = C_m + \frac{v}{V}\sum_{0}^{t-1} C_t \qquad (1)$$

where C_t is the corrected concentration at time t, Cm is the measured concentration at time t, v is the volume of the aliquots taken, and V is the total volume of the buffer (100 mL). The calibration curve will be used to calculate cumulative release of naproxen into water medium from nanofibers. The pH effect on naproxen release and kinetic parameter results were also observed using above step with modifying pH value of DI water and time variation.

For kinetic study, there are four drug release models used, the equation is showed below, with kinetic parameter obtained by regression using Microsoft Excel software.

$$\text{Zero order}: Q = Q_0 - K_0 t \qquad (2)$$

$$\text{First order}: \log Q = \log Q_0 - K_1 t/2.303 \qquad (3)$$

$$\text{Higuchi}: \log Q = \frac{1}{2}\log t + \log K_H \qquad (4)$$

$$\text{Krosmeyer–Peppas}: \log\left(\frac{M_t}{M_\sim}\right) = n\log t + \log KKP \qquad (5)$$

where Q_0 and Q are the loaded naproxen content and naproxen released from nanofibers after time t, respectively. K_0, K_1, K_H, and K_{KP} confirm to the constant parameters of zero order, first order, Higuchi, and Korsmeyer-Peppas equations, respectively. $Mt/M_\sim$ is the fraction of released naproxen at time t, and n confirms the diffusional coefficient [29].

Cytotoxicity Evaluation This observation was firstly carried out by culturing HeLa cells on Eagle's minimum essential medium (EMEM) supplemented with L-glutamine, antibiotic antimycotic formulation, and fetal bovine serum. On the evaluation step, cells were seeded in a six-well plate containing adjusted shape nanofiber with 2 mL of culturing medium, then incubated for 24 h cells. After those treatments, the cells were washed three times with PBS and added with 1 mL of MTT solution (0.1 mg/mL) followed by incubation of the treated cells for 4 h at 37 °C. Then, the resulted formazan dyes were dissolved by DMSO solution and quantified by using ELISA reader at a wavelength of 570 nm [30].

Characterizations The XRD measurements were performed by Bruker Discover 8 Advance Diffractometer (Germany) with Cu-Kα radiation (λ = 1.5406 Å) and scanning rate of about 0.05°/s. XRD data was collected in the range of 2θ from 5° to 65°. Size and zeta potential of CuFe$_2$O$_4$ nanoparticles were measured by dynamic light scattering (DLS, Nano-Zetasizer-HT, Malvern, UK). Samples of transmission electron microscopy (TEM, JEOL 3010, Japan) were prepared with layering of CuFe$_2$O$_4$ solution onto copper grids (200-mesh) dried to remove its organic solvent. The hysteresis loop of CuFe$_2$O$_4$ was performed from vibrational sample magnetometer (VSM, Lake Shore Cyrotronic, USA) at room temperature in a magnetic field range of − 8 to + 8 kOe. Nanofiber morphology was observed using scanning electron microscope (SEM, Bruker, USA) with accelerating voltage of 20 kV and sputtered with gold film. The diameter of the fiber was determined from SEM images using image analysis tool by Image J software with sample sizes at least 50 fibers per SEM micrograph. Conductivity measurements of fiber solutions were carried out using conductivity meter (JP Selecta CD-2004, Spain) at room temperature.

3 Results and Discussion

Preparation of CuFe$_2$O$_4$ Nanoparticles The copper ferrite nanoparticle on this study was synthesized via solvothermal

process, wherein both $Cu(acac)_2$ and $Fe(acac)_3$ took part as Cu and Fe source on the nanoparticle. The existence of benzyl ether and oleylamine made the obtained nanoparticles become hydrophobic nanoparticle, wherein benzyl ether acted as solvent of reaction and oleylamine performed as capping ligand for the spinel ferrite. The amine site of oleylamine creates chemical bond leaving hydrocarbon tile as new surface on the nanoparticle. Crystal structure observation of the obtained nanoparticle was carried out by XRD. Figure 1a represented the XRD pattern of synthesized copper ferrite nanoparticles that shows presence of three peaks of 2θ as highest intensity at 35.3869°, 42.9721°, and 62.6159°. These three peaks follow JCPDF 25-0283 indicating formation of copper ferrite nanoparticles. However, the broad "hump" curve on the diffractogram confirms amorphous region of the spinel ferrite nanoparticle due to capping ligand on surface of each nanoparticle. In addition, improvement of XRD data can predict particle size of nanoparticle via the Scherrer equation, where average diameter of the copper ferrite closes to 12.97 nm. The TEM images (Fig. 1b.) clearly furnished morphological

apparent of $CuFe_2O_4$ nanoparticles. On its high magnification image (insert of Fig. 1b), the shape of resulted nanoparticles is close to spherical crystal structure.

Further improvement on diameter size distribution was performed by DLS (Fig. 2a). The DLS data complements previous observations on adjusting average size of $CuFe_2O_4$ nanoparticle with maximum on 18.75 nm. DLS data also informs size range of nanoparticle on range 6–40 nm. DLS analysis was also carried to consider the loading efficiency of the nanoparticles onto nanofibers. Figure 2b shows the hysteresis loops of $CuFe_2O_4$ nanoparticles as a function of the magnetic field. The magnetization value of $CuFe_2O_4$ nanoparticles is 80.56 emu g^{-1} with very small coercivity value (26.5 G). This kind of magnetic property is categorized as superparamagnetic material as a commonly magnetic nanoparticle that has lower magnetization value than its bulk form (less than ~92 emu g^{-1}) [31].

Preparation of Composite Nanofiber Electrospinning is the main process in this study in preparing nanofiber. The

Fig. 1 **a** XRD pattern of $CuFe_2O_4$ nanoparticles compared with standard XRD data of copper ferrite. **b** TEM images of $CuFe_2O_4$ nanoparticles. Insert: higher magnification image of red box area
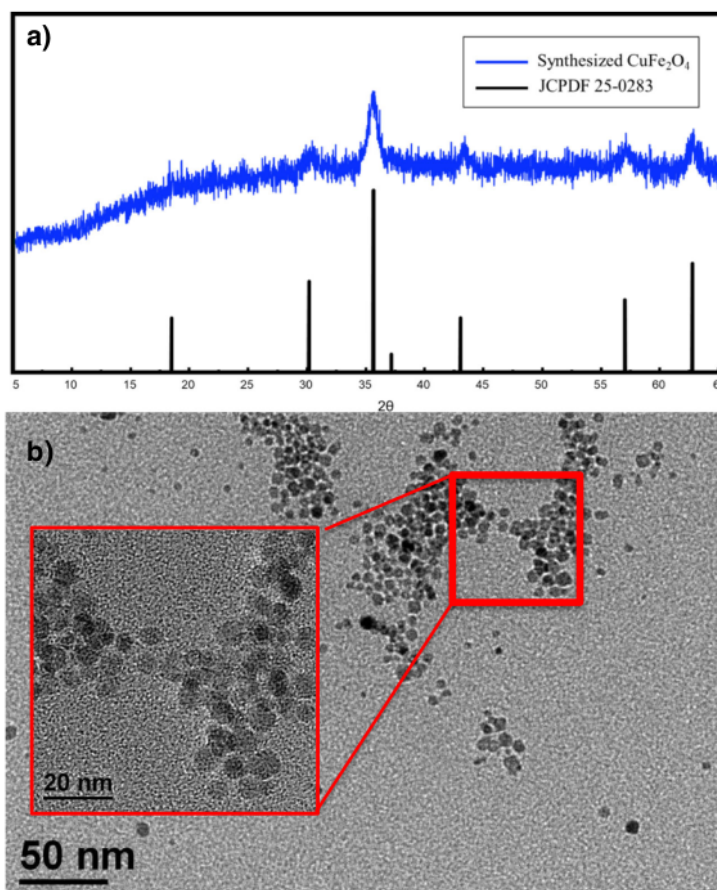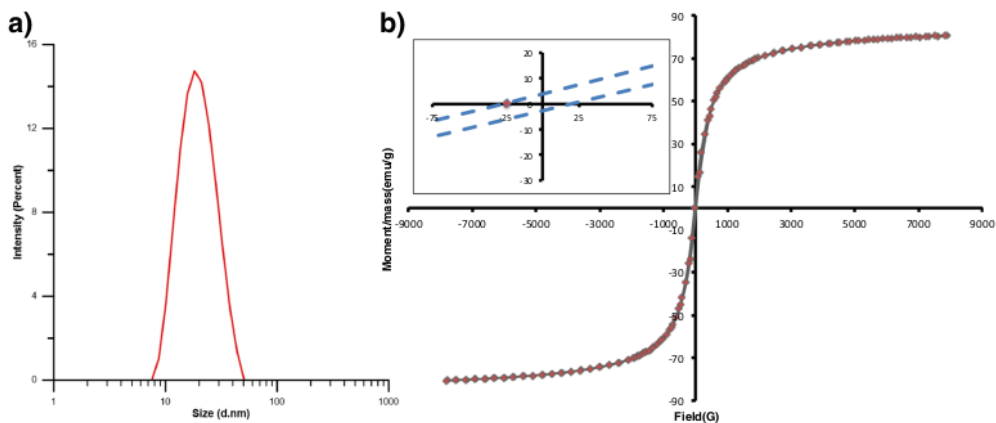
Fig. 2 **a** Dynamic light scattering (DLS) data of obtained $CuFe_2O_4$ nanoparticles. **b** Vibration sample magnetometer plot of nanoparticle. Insert: zoomed plot to show its coercivity value

designed nanofiber was described on Scheme 1, in which electrospinning will combine four components to composite nanofiber (regarding Table 1). PCL that is commonly applied on tissue and biomedical engineering will be the backbone of the nanofiber due to its excellent mechanical properties, whereas collagen can provide good conjugation between cell tissue and the nanofiber when it is further applied on wound healing. Even attraction between PCL and the collagen is just mediated by physical interaction; technical process on electrospinning will make them compact with each other because they got solvent leaving at same time [32]. It was considered to make collagen well dispersed on PCL by firstly dissolving collagen in the water and PCL in chloroform. These two clear solutions were further mixed by adding acetone to ensure all of solvents can mix to one another. Even the

mixed solution becomes cloudy, mean collagen and PCL cannot mix well, and there is absence of precipitation of collagen and PCL indicating they are dispersed in the mix solution. Moreover, naproxen acts as a drug proposed to release from the nanofiber. This semi-polar compound can easily incorporate with both PCL and collagen via hydrogen bonding, van der Waals, and phi-phi bonding attractions. Meanwhile, the hydrophobic $CuFe_2O_4$ nanoparticle will come close to PCL to attribute magnetic responsiveness of the fiber.

The SEM analysis was next carried out to determine the surface morphology and adjust nanofiber diameter by using Image J software. Figure 3 shows the morphology of nanofiber formation of each sample. The average diameter measurement, furnished on Table 2, proves that addition of collagen, even to naproxen and nanoparticle, results to smaller diameter
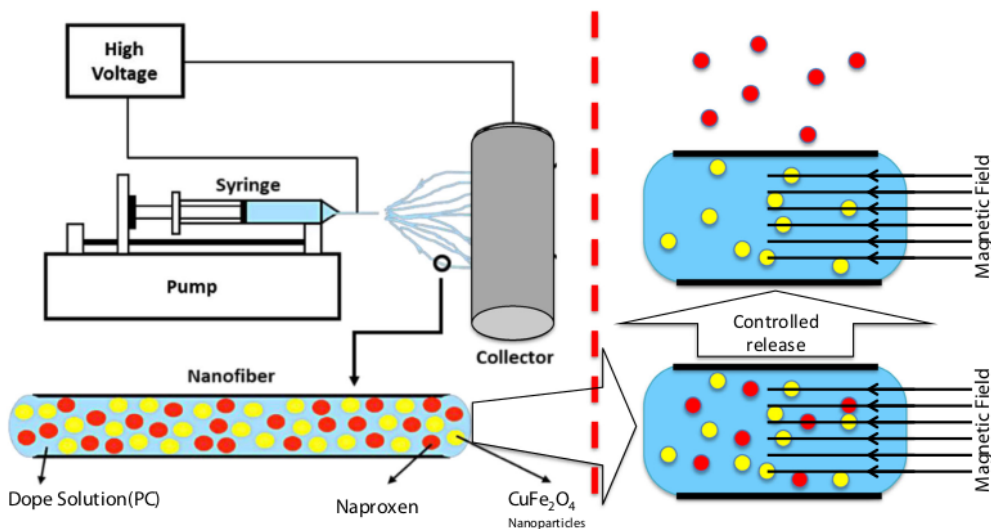
Scheme 1 Schematic image preparation of nanofiber PCNM

compared with bare PCL. Reducing PCL viscosity after addition of collagen was major responsible for this finding. Tan et al. (2005) reported that decreasing viscosity of polymer solution for electrospinning will affect on reducing fiber diameter [33]. Furthermore, addition of naproxen and $CuFe_2O_4$ nanoparticles into PC made the diameter become smaller. The viscosity still be the major reason on adding those component. In particular, addition of magnetic material also gave significant decrease of nanofiber diameter. The conductivity investigation of nanofiber supported the above statement (Table 2), in which addition of collagen, naproxen, and magnetic nanoparticle increases conductivity to higher values, respectively. The addition of magnetic nanoparticles enhanced conductivity up to 12.5 $\mu S.cm^{-1}$ and produced more electric charge that gave more thrust of the polymer jets to reach the target during electrospinning process. Thus, increasing these thrust effects on the diameter of the nanofiber resulted. These conditions are similar with addition of gold nanoparticle on the nanofiber, where increasing electric charge by gold nanoparticles will produce a higher repulsion force on the polymer jet, so that the polymer jet will elongate to form a longer and more stretch fiber structure due to the influence of the electric field [34].

The morphology of PCL nanofiber, Fig. 3, formed irregular fiber structure, slightly contrast to PC nanofiber. While SEM image of PCN nanofiber shows beads-formed structure, even overall fiber is still uniform. We speculate to say that the formation of beads-formed fibers caused drug materials aggregation of naproxen added into nanofiber. The beads formation can also occur due to slow evaporation of solvents on the
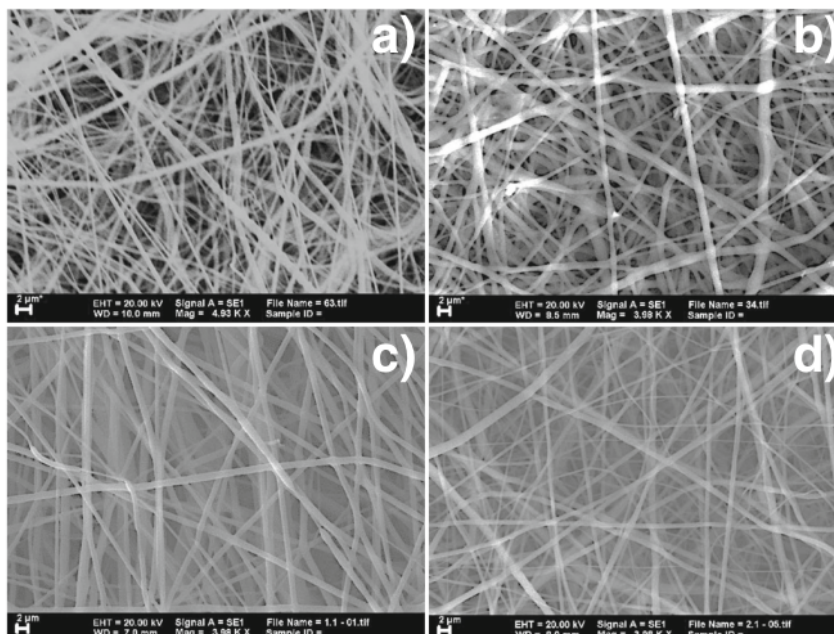
Table 2 Average diameter size of nanofiber ($n = 50$)

Nanofibers	Diameter (nm)[a]	Conductivity ($\mu S.cm^{-1}$)
PCL	1179 ± 20	–
PC	878 ± 35	4.2
PCN	898 ± 42	7.7
PCNM 7.5	481 ± 12	12.5

[a] All data were presented as mean ± SD ($n = 50$)

polymer jet during electrospinning process. Another factor that may influence the beads formation is the electrical surge affecting the elongation of polymer jet to become unstable as well. In contrast to PCN, PCNM 7.5 shows more uniform morphology, when it was compared with others.
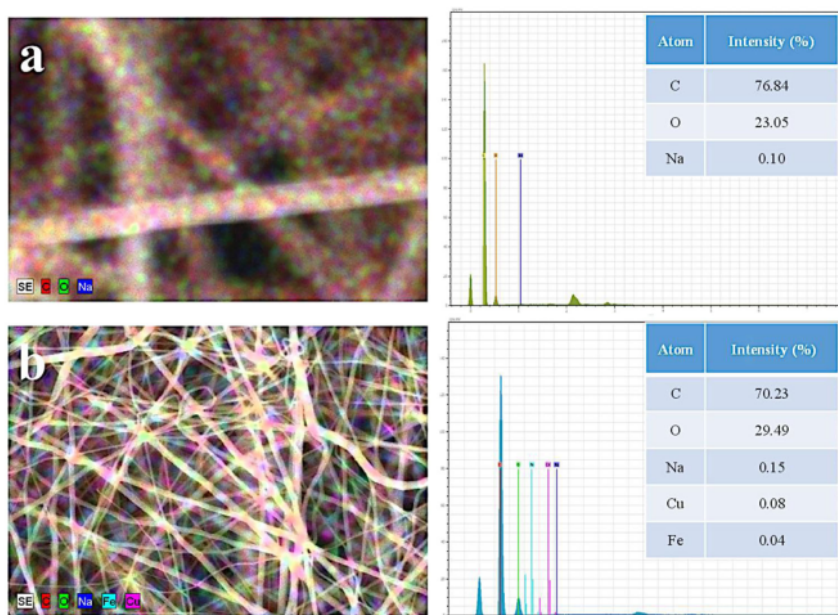
On deeper morphology analyses, SEM-EDX was also carried out to determine the elements contained on nanofiber, showed in Fig. 4. The SEM-EDX analyses prove the existence of naproxen on PCN by signaling of sodium element on the PCN because naproxen used on this study is in salt form. The nanofiber with the magnetic nanoparticle addition (PCNM 7.5) has also copper (Cu) and iron (Fe) elements on its EDX, instead of carbon and oxygen element as main components of PCL, collagen, and naproxen. In detail on comparing each element, SEM-EDX data showed the differences by increasing percentage of oxygen element in PCN and PCNM 7.5 from 23.05 to 29.49%, whereas the percentage of carbon is decrease. The accumulation of O element in nanofiber

Fig. 3 SEM morphology of nanofibers: **a** PCL, **b** PC, **c** PCN, and **d** PCNM 7.5

Fig. 4 SEM-EDX screening of PCN (**a**) and PCNM 7.5 (**b**)

Atom	Intensity (%)
C	76.84
O	23.05
Na	0.10

| Atom	Intensity (%)
C	70.23
O	29.49
Na	0.15
Cu	0.08
Fe	0.04

occurred due to the presence of copper ferrite nanoparticles, which contribute more oxygen atoms on the nanofiber.

Naproxen Release and Kinetic Study The drug release kinetics describes the level of drug-released concentration of a system for a certain time. Information of drug release kinetics is needed in understanding the mechanism of drug release. In this study, four kinetics of drug release modeling were carried out, namely zero order, first order, Higuchi, and Korsmeyer-Peppas. These four kinetics models were used to observe the

mechanism and rate of naproxen release from nanofiber mats. Thus, it can determine the effect of $CuFe_2O_4$ nanoparticles addition against naproxen release from the nanofibers.

Kinetics parameter data of naproxen release are shown in Fig. 5, where all of investigated nanofibers perform burst release on the first 50 min indicating accumulation of drug on the surface of nanofiber. The release rate further decrease and close to stable over 150 min that means the naproxen at the inner of fiber diffuses on the polymer. Figure 5 also informs that addition of $CuFe_2O_4$ nanoparticle tends to inhibit release

Fig. 5 Comparison of naproxen release from PCN (filled circle), PCNM 2.5 (filled triangle), PCNM 7.5 (filled square), and PCNM 12.5 (filled diamond). Kinetic release models for each nanofiber performed with zero order (red lines), first order (green lines), Higuchi (yellow lines), and Korsmeyer-Peppas (blue lines) models
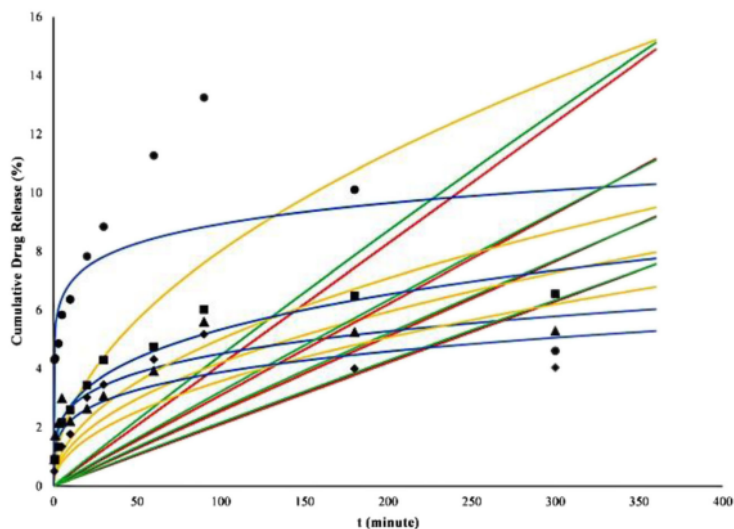
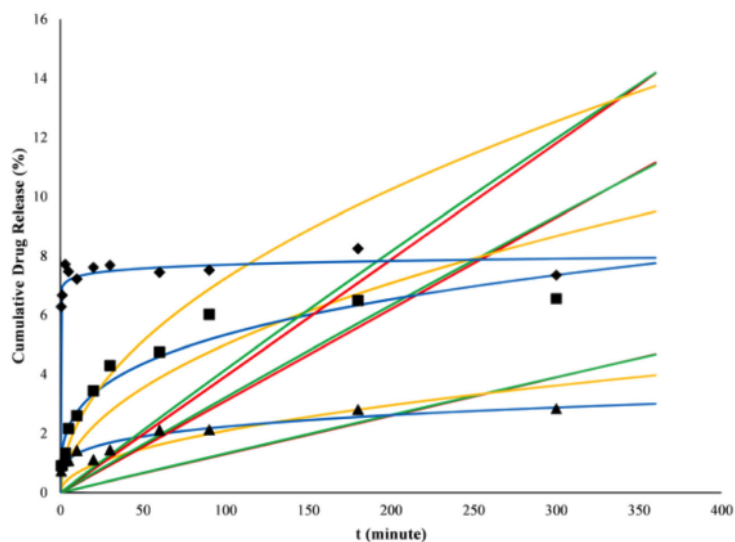**Table 3** The kinetic parameters of naproxen release at neutral pH

Nanofibers	Kinetic rules			
	Zero order	First order	Higuchi	Korsmeyer-Peppas
PCN	$k = 0.000413$ $R^2 = 0.019886$	$k = 0.000455$ $R^2 = 0.024935$	$k = 0.801324$ $R^2 = 0.152717$	$k = 5.357946$ $R^2 = 0.345848$ $n = 0.110984$
PCNM 2.5	$k = 0.000255$ $R^2 = 0.628004$	$k = 0.000267$ $R^2 = 0.636334$	$k = 0.419865$ $R^2 = 0.814413$	$k = 1.580530$ $R^2 = 0.878070$ $n = 0.227448$
PCNM 7.5	$k = 0.000310$ $R^2 = 0.662688$	$k = 0.000327$ $R^2 = 0.673229$	$k = 0.500560$ $R^2 = 0.879667$	$k = 1.389688$ $R^2 = 0.952648$ $n = 0.292045$
PCNM 12.5	$k = 0.000210$ $R^2 = 0.389130$	$k = 0.000218$ $R^2 = 0.395938$	$k = 0.357830$ $R^2 = 0.643433$	$k = 1.268624$ $R^2 = 0.788892$ $n = 0.242398$

of naproxen. The higher the $CuFe_2O_4$ nanoparticle contained on nanofiber, the less is the release of naproxen. It can be understandable due to the nanoparticle properties that increase the hydrophobic phase of nanofiber and the diffusion of hydrophilic naproxen will get obstacle from this. At the highest nanoparticles' component (PCNM 12.5), naproxen release cannot perform sustained release and it can be predicted due to the massive inhibition of the nanoparticles. However, compared with PCN, the release pattern of PCNM is well ordered and it can be confirmed from its coefficient value (R^2) and k values from Table 3. The absence of nanoparticles made nanofiber getting uncontrolled release process; thus, all naproxen released before 300 min. Table 3 also explains that all of nanofiber samples tend to follow Korsmeyer-Peppas rules, based on its highest coefficient determination value (R^2).

PCN, PCNM 2.5, PCNM 7.5, and PCNM 12.5 have R^2 values following Korsmeyer-Peppas model, which were 0.35, 0.89, 0.95, and 0.79, respectively. The highest R^2 for PCNM 7.5 also indicates it was the best composition on the nanofiber design.

The Korsmeyer-Peppas model explained drug release from a polymer system [35] and it was in good agreement with the polymeric system on this study. Furthermore, the diffusion coefficient values (n) on all of nanofiber samples were $n < 0.45$, which confirms the mechanism of naproxen release following Fickian diffusion. Fickian diffusion is a mechanism explaining that molar flux is proportional to its concentration gradient. In this case, naproxen release occurred due to the swelling effect of the PCL polymer matrix. This swelling can cause opening of pores in the entire nanofiber matrices,

Fig. 6 Naproxen release of PCNM 7.5 at 4 (filled triangle), 7 (filled square), and 9 (filled diamond). Kinetic release models for each sample performed with zero order (red lines), first order (green lines), Higuchi (yellow lines), and Korsmeyer-Peppas (blue lines) models

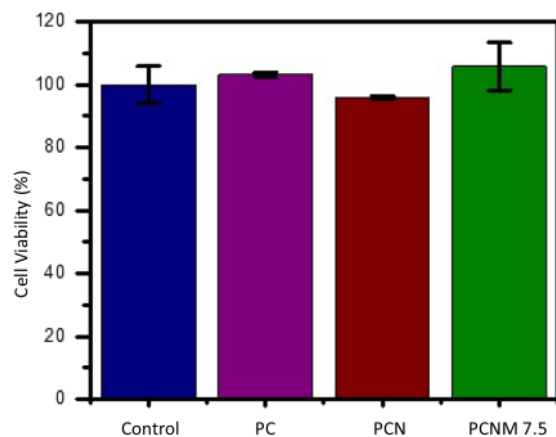**Table 4** The kinetic parameters of naproxen release against varied pH

pH value	Kinetic rules			
	Zero order	First order	Higuchi	Korsmeyer-Peppas
4	$k = 0.000130$	$k = 0.000133$	$k = 0.209009$	$k = 0.766647$
	$R^2 = 0.809471$	$R^2 = 0.813082$	$R^2 = 0.930139$	$R^2 = 0.920454$
				$n = 0.231748$
7	$k = 0.000310$	$k = 0.000327$	$k = 0.500560$	$k = 1.389688$
	$R^2 = 0.662688$	$R^2 = 0.673229$	$R^2 = 0.879667$	$R^2 = 0.952648$
				$n = 0.292045$
9	$k = 0.000394$	$k = 0.000425$	$k = 0.724654$	$k = 6.912822$
	$R^2 = 0.116968$	$R^2 = 0.123156$	$R^2 = 0.243998$	$R^2 = 0.479947$
				$n = 0.023494$

so that drug molecules will move out from fiber matrices into a place with a lower concentration.

Application of PCNM as wound healing material compels this nanofiber to have good stability properties under complex organ systems and adapt to various conditions especially pH of the human body. Therefore, the pH effects on the character of naproxen release become important to be observed. From Fig. 6, it can be decided that higher pH value accelerates increasing naproxen release. PCL and collagen of nanofiber contain many electronegative species that, on high pH, will emerge the repulsion of one each other resulting in pore opening of the fiber.

Moreover, the character of naproxen that also poses electronegative species makes naproxen easy to leave nanofiber on high pH. On further discussion in Fig. 6, it can be seen that the high pH effect makes the nanofiber getting extremely burst release on very early time and those conditions are unwanted for controlled release nanofiber.

The kinetic parameters of naproxen against pH values were shown in Table 4, which explained the kinetic models followed by each sample. From Table 2, it is also informed that nanofiber samples tested in neutral and base media tend to follow Korsmeyer-Peppas rules with n values of 0.292045 and 0.023494, respectively. Meanwhile, the nanofiber tested in acidic medium tends to follow Higuchi's model, which explained the release profile of dispersed drugs in an insoluble matrix as a diffusion process. The mechanism of drug release following Higuchi's model occurs through diffusion. Higuchi's model described the linear relationship between drug concentration released and time root [35]. Similar with Fickian diffusion, diffusion mechanism of Higuchi rules also occurs due to the swelling effect of polymer matrices.

Cytotoxicity Assessment Regarding bioapplication of the fiber, cytotoxicity evaluation of the nanofiber is an important part to be investigated. Cytotoxicity test was carried out with MTT assay to determine the percentage of HeLa cell viability. Figure 7 shows that PC, PCN, and PCNM 7.5 nanofibers did not decrease the cell viability (over 80%), indicating non-toxic properties attributed on these nanofibers. These finding is in similar agreement with previous report that claims composite material of PCL and collagen performs good cytotoxicity [32] and can be strong data on supporting these nanofibers for wound healing material.

4 Conclusions

In summary, a novel drug delivery system has been successfully made from composite nanofiber modified with $CuFe_2O_4$ nanoparticles for controlled drug release. The addition of naproxen and 7.5 mg of copper ferrite nanoparticles affects the formed nanofiber with smaller diameter and controlled release compared to its bare composition (PCL and PC nanofibers). The drug release kinetics model of naproxen tends to follow the Korsmeyer-Peppas model. In drug release profile analysis, more addition of copper ferrite nanoparticles leads to

Fig. 7 Cell viability of HeLa cell upon 24 h incubation with the nanofibers. All of MTT data were represented with mean ± SD ($n = 3$)

decrease naproxen released from the nanofiber. The results of naproxen release showed that the percentage of naproxen had higher release in the base medium with good cytotoxicity. The reports showed that the nanofibers have potential to be used in biomedical applications.

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