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Research Article

Fabrication and Characterization of Ibuprofen and Ceftriaxone loaded Electrospun Cellulose Acetate Nanofiber Layers as a Model of Targeted Drug Delivery System

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ABSTRACT

This study aims to study the process of fabricating and characterization of nanofibers based on cellulose acetate polymer filled with ceftriaxone and ibuprofen using the electrospinning method as a model for a targeted drug delivery system. Cellulose acetate has been successfully fabricated into nanofibers using the electrospinning method and filled with ceftriaxone and ibuprofen. The resulting nanofibers have an average diameter in the range of 412.5 – 558.5 nm under the conditions of the electrospinning process, namely 22 kV voltage, 15 cm distance, and flow rate. 0.005 mL/min using acetone/DMAc (2:1). Based on the data generated from the FTIR test, homogeneity, and drug release test, it is known that the resulting nanofibers, namely cellulose acetate, cellulose acetate-ceftriaxone, and cellulose acetate-ibuprofen, have good morphological characteristics, homogeneity, and release rate so that they have the potential to be used as a targeted drug delivery system.

Keywords: nanofiber, cellulose acetate, ceftriaxone, ibuprofen, model, drug delivery system

1. Introduction

Drug delivery systems develop to achieve the desired therapeutic effect. It has many advantages over the conventional methods such as increasing the drug compounds activity, dissolution rate, and minuscule cytotoxicity, and can pass the first degree of metabolic activities, controlling the pharmacokinetics, way of distribution, and reducing the drug delivery intervals [1 – 5].

The drug delivery system is a field that has received much attention, and it has many development techniques carried out in various fields of science. [6] Drug delivery systems using nanofibers are one of the methods attracting much attention because they have many advantages. Such as easy encapsulation of the drug molecules or even forming composites with nanofiber polymers, stability, and keeping of the morphological structure of drugs that are stored in the long term, increased surface area against volume ratio, flexibility to control and modify the desired morphological specifications, superior mechanical performance for various uses in the biomedical field [1, 2, 4, 7-9].

Electrospinning is a method to produce nanofibers widely applied as a drug delivery system [9]. Nanofiber resulting from the electrospinning method called electrospun has advantages such as high surface area, pore structure construction with large porosity making it suitable for variations in drug loading models, modified diameter range as a drug release factor in wound tissue, easy to use, inexpensive, and versatile. [5], 10] The electrospun has a wide variety of applications as a delivery system containing medicinal compounds and natural active ingredients such as naproxen, indomethacin, ibuprofen, and sulindac [11], acetylsalicylic acid, and nicotine [12], bupivacaine [13], ibuprofen [4, 14], Vitamins A and E [10], Bioactive Sambong Oil [15], Myrtle essential oil [16], and crude annatto extract [17].

The size of drug particles has a significant influence on bioavailability and the speed of drug action. Mixing drugs in the polymer before electrospinning will produce a nanofiber-drug layer with a scale ranging from micrometer to nanometer, providing a positive value on the bioavailability and performance of the drug, which may decrease the dose value that should give [18]. The utilization of electrospun that's coating with drugs may decrease the dose of administration of the drugs 18 to 25 times lower than oral methods with a higher level of effectiveness oral methods [19].

Cellulose is an abundant natural polymer with a range of 40-60% on each plant and is stable in nature, has low toxicity, is biodegradable, biocompatible, renewable, and easy to modify chemically are fundamental advantages as biomaterials and exploited as a drug delivery system [4, 20]. Cellulose uses in various medical applications such as scaffolds for tissue engineering, synthetic implants, membranes, and composites [21]. As a drug delivery medium, cellulose can maintain drug release for up to ten months by forming a tight fiber network to influence the diffusion properties of the drug preparation contained therein [1, 2].

However, the biggest challenge to producing nanofibers using cellulose polymers is the type of solvent. The presence of inter-and intramolecular hydrogen bonds in the cellulose structure makes it difficult to dissolve and only soluble in certain solvents [10]. The manufacture of cellulose nanofibers using the electrospinning method made with various solvents [11, 12, 22, 23]. The electrospun is used as a delivery system with good release capability and varies on the type of content carried [11, 12].

Cellulose acetate is an ester of cellulose, a natural polymer that is very abundant in existence, sustainable, and can be naturally degraded [24]. Cellulose acetate has a reasonably high attractiveness due to its biodegradable nature so it is environmentally friendly, biocompatible, has good affinity with other substances, and has good modulus, flexural strength, and tensile strength. Cellulose acetate is also hydrophobic and has properties that are easy to shape, not easy to wrinkle, and have high stability and has been variously used in the pharmaceutical and biomedical fields such as antimicrobial membranes, bladder matrix materials, nanocomposites, biosensors, and drug delivery systems [10, 25].

Ceftriaxone, a third-generation cephalosporin commonly used for surgical prophylaxis in Indonesia, modulates the glutamate neurotransmitter system in the central nervous system. Cephalosporins are derived from the fungus *Cephalosporium acremonium* and are members of the *β-lactam* antibiotic family, with the common feature of β-lactam rings. They are broad-spectrum bactericidal antibiotics (kill bacteria). The bactericidal effect of Ceftriaxone results from the inhibition of bacterial wall synthesis. Ceftriaxone has high stability against beta-lactamases, both against penicillins and cephalosporins produced by gram-negative and gram-positive bacteria [26, 27].

Ibuprofen is one of the NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), a group of anti-inflammatory, analgesic, and antipyretic functions. Ibuprofen is a nonselective inhibitor of cyclooxygenase (COX) required for the synthesis of prostaglandins via the arachidonic acid pathway. COX is required to convert arachidonic acid to prostaglandin H2 (PGH2), so inhibition of COX enzymes results in a decrease in the body's production of prostaglandin enzymes [28].

The fabrication of nanofibers-loaded drug particles such as Ceftriaxone and ibuprofen can be an alternative in non-invasive targeted drug delivery systems to minimize side effects and increase the effectiveness of the treatment.

2. Materials and Methods

2.1. Materials

The cellulose used is an ester of cellulose, i.e., cellulose acetate with a molecular weight of 30.000 with the content of 38% wt acetyl, (99%, Sigma-Aldrich), Ibuprofen (Sigma-Aldrich), Ceftriaxone (Kalbe Farma), Phosphate Buffer Saline (PBS) (Biogear).

2.2. Methods

Ceftriaxone and ibuprofen dissolved in Cellulose Acetate solution 17% using DMAc/Acetone 2:1, stirred the solution until all bubbles appeared utterly gone. The content and release tests of ceftriaxone and ibuprofen were tested using UV-Vis at wavelengths 200-400 nm. The release test used a Phosphate Buffer Saline (PBS) solution with 1 hour, 2 hours, 3 hours, and 4 hours of dissolution time.

3. Result and Discussion

3.1. Morphology

The best morphology of nanofibers at 22 kV, a distance of 15 cm, and 0.005 mL/min flow rate. The fiber morphology observation using a scanning electron microscope (SEM) Hitachi SU3500, Hitachi MCI000 sputter ion, and coating process of fiber sample by platinum, the result shown in **Figure 1** below.

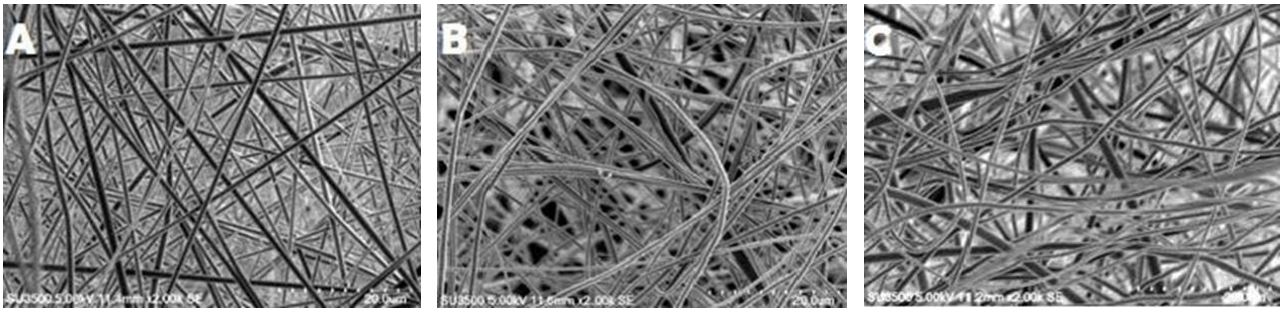

Figure 1. Photo of SEM results at 2000x magnification for cellulose acetate fibers (A), cellulose acetate-ceftriaxone fibers (B), and cellulose acetate-ibuprofen fibers (C) at 22 kV, 15 cm, and 0.55 mL/min.

The optimization process performs by varying the flow rate and the distance of the needle with the collector. The cellulose acetate concentration referred to in a study conducted by Rodrıguez et al. [29] is 17% w/v using a mixture of acetone and DMAc with a ratio of 2:1 v/v. Cellulose acetate is highly soluble in acetone, the addition of DMAc reduces the volatility levels of acetone. The use of a rapidly evaporating solvent leads to an impasse process at the tip of the needle so that the electrospinning process will often stop for the needle cleaning process. The addition of DMAc helps improve the electrospinning ability of the Cellulose Acetate solutions in acetone–DMAc [30].

Ceftriaxone is a water-soluble substance (hydrophilic), and it is capable of dissolving in polar organic solvents. In this study, the cellulose acetate-ceftriaxone polymer solution was dissolved first the ceftriaxone in DMAc [31], followed by cellulose acetate polymers and acetone at a composition ratio of 2:1. Electrospinning process stages obtained the best fiber at 22 kV voltage conditions with a distance of 15 cm, and the flow rate is 0.005 mL/min.

The process of cellulose acetate-ibuprofen solution has no constraints because ibuprofen is a hydrophobic drug type that is easily soluble. The optimum condition of cellulose acetate-ibuprofen fibers is obtained at a 22 kV voltage condition with a distance of 15 cm, and the flow rate is 0.005 mL/min. The subsequent observations were made at 20,000x magnification to see the surface morphology and pores on the fiber bars. The surface of the fiber can represent the homogeneity of mixing and dissolving processing of the composite between cellulose acetate polymer with ceftriaxone and ibuprofen, as shown in **Figure 2**. following:

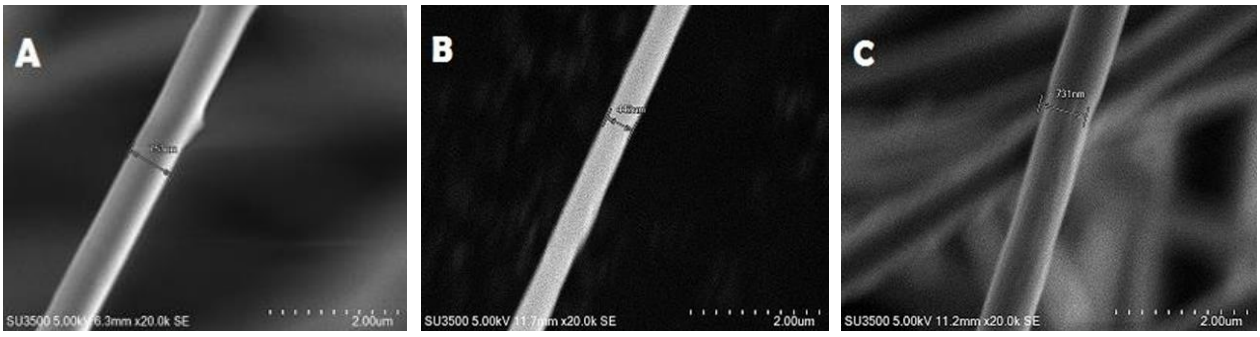

Figure 2. The photographs of SEM results at 20,000x magnification for cellulose acetate fibers (A), cellulose acetate-ceftriaxone fiber (B), and cellulose acetate-ibuprofen fibers (C) at 22 kV, 15 cm, and 0.005 mL/min.

The SEM, EDAX, and mapping result was excellent without beads or spots, elongated, continuous fibers, and a layered matrix structure. The drug particles did not show in the fiber matrix, which indicated that there had been good dissolution and blended with the cellulose acetate polymer in nanofiber.

The diameter of cellulose acetate fiber is not uniform; the diameter of the fiber is mainly 700-799 nm and evenly 300-699 nm. Fiber cellulose acetate-ceftriaxone evenly in 400-499 nm and almost evenly in 99-499 nm. Cellulose acetate-ibuprofen fibers are common at 500-599 nm and evenly at 100-899 nm. The results showed that cellulose acetate fibers had an average diameter of 558.5 nm, cellulose acetate-ceftriaxone had an average diameter of 412.5 nm, and cellulose acetate-ibuprofen had an average diameter of 533.5 nm, as shown in **Fig. 3** below.

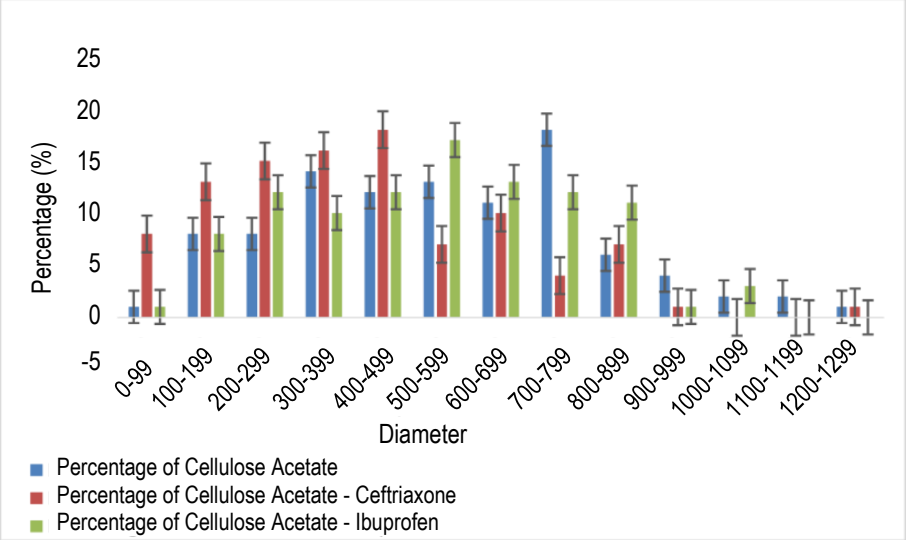

Figure 3. Diagram of fiber diameter distribution

The diameter of different sizes is affected by many factors such as solution conditions, processes, and the surrounding environment. The selection and composition of the solvent used and the flow rate regulation during the electrospinning process significantly affect the fiber size, diameter distribution, and geometric structure of the cellulose acetate fiber produced [29].

3.2. FTIR Characterization

Observations of cellulose acetate fibers using the Fourier Transform Infra-Red (FTIR) Prestige 21 Shimadzu; to determine the specific functional groups, shifts, and changes in the intensity of cellulose acetate fibers' absorption band before and after the addition of ceftriaxone and ibuprofen. The results of FTIR analysis for cellulose acetate fiber compared with cellulose acetate-ceftriaxone and cellulose acetate-ibuprofen, as shown in **Figure 4.** below.

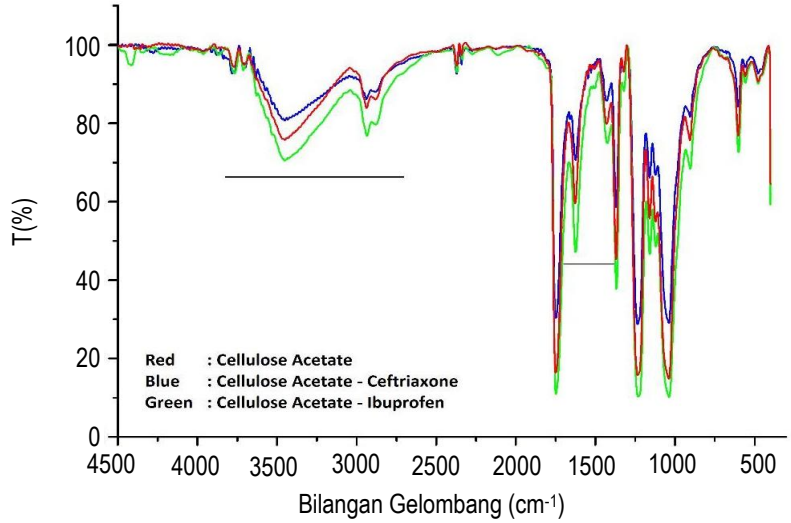

Figure 4. FTIR results from cellulose acetate (red), cellulose acetate-ceftriaxone (blue), and cellulose acetate-ibuprofen (green) samples

The FTIR test result is known that there is a minor change at the peak, but not specifically from the cluster contained therein either by the wavelength or the infrared energy transmission percentage value used. The data showed a reaction

between cellulose acetate with ceftriaxone and cellulose acetate with ibuprofen that has been added to the cellulose acetate solution before the electrospinning process. However, the reaction does not show interactions that change the structure of cellulose acetate as the carrier matrix of ceftriaxone and ibuprofen particles. It will not affect the activity and therapeutic effect of ceftriaxone and ibuprofen.

3.3. Homogeneity and Release Test

Homogeneity is closely related to the dissolution process of drug particles in the polymer solution; a good dissolution process causes the drug particles to be spread evenly in the polymer solution to produce a uniform distribution in the formed fibers. The homogeneity of drug particle distribution has been seen from the observation and mapping using SEM, no visible particle of the drug in the matrix structure of the fiber formed, and from the mapping results obtained information that every atomic drug component constituent compound has been unified and spread evenly in each fiber strands produced.

The homogeneity test to determine the distribution of drug particles in the fiber shown by the drug release test result within a drug mass is 1% w/w. The samples were taken randomly with a length of 5 cm. A release test was taken using Phosphate Buffer Saline (PBS) with pH 7,3 at 1 hour, 2 hours, 3 hours, and 4 hours periods.

The homogeneity test analyses with Lavene Test obtained a significance value of 0,085 for ceftriaxone and 0,385 for ibuprofen. The significance value indicates that cellulose acetate-ceftriaxone and cellulose acetate-ibuprofen fiber samples based on the ceftriaxone and ibuprofen release profile of fiber are homogeneous. The release graphic of ceftriaxone and ibuprofen are in **Fig. 5** and **Fig. 6** below.

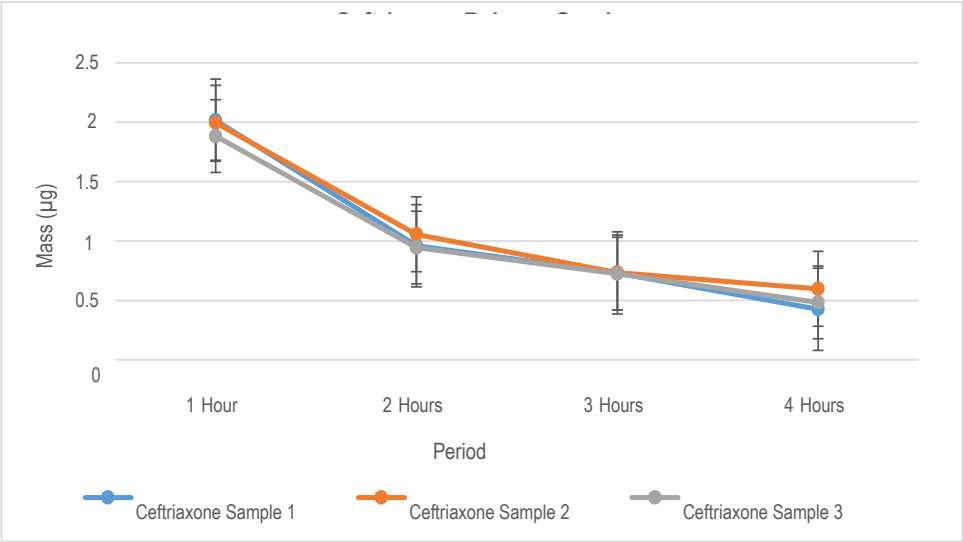

Figure 5. Ceftriaxone release graph

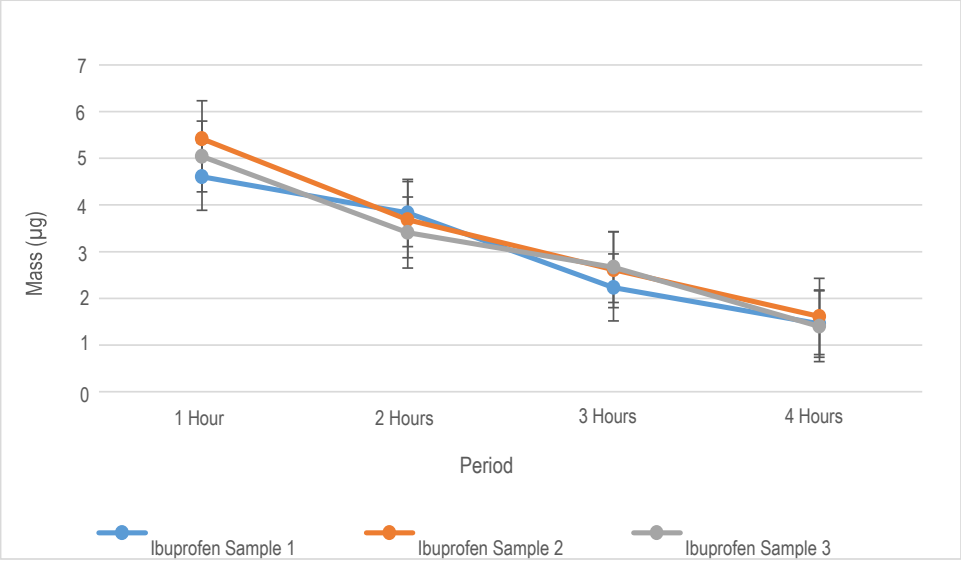

Figure 6. Ibuprofen releases graph

Ceftriaxone and ibuprofen have different solubility properties from each other. Ceftriaxone is hydrophobic and requires a special polar solvent to dissolve it. Ibuprofen is hydrophilic and is easy to dissolve in a variety of commonly used solvents. The dissolution kinetics of the two types of drug compounds will be different due to different solubility properties. Generally, when a hydrophilic drug is incorporated into a matrix, the release occurs quickly by diffusion, compared to a hydrophobic drug. The release of hydrophobic drugs is often associated with matrix erosion. The differences in solubility, the factors that determine solubility, and the involvement of different processes explain why the same drug behaves differently when incorporated into a polymer matrix.

Based on calculations using four models of drug release kinetics, that drug release from nanofiber tended to follow Higuchi kinetics. This kinetics describes drug release from the nanofiber matrix depending on time and takes place by diffusion. For cellulose acetate-ceftriaxone and cellulose acetate-ibuprofen, values for Korsmeyer-Peppas release kinetics are more likely to be in the range of $0.45 < n < 0.89$, indicating that the release follows a non-Fickian diffusion that promotes controlled drug release mechanism describes the integrated mechanism of diffusion and erosion of polymeric materials

4. Conclusion

Based on experimental data, it is known that the fabrication of nanofibers using the electrospinning method using cellulose acetate polymer succeeded in producing nanofibers filled with ceftriaxone and ibuprofen as drug particles with different solubility properties. Cellulose acetate, cellulose acetate-ceftriaxone, and cellulose acetate-ibuprofen nanofibers had similar morphology with no different mean diameters and did not show significant changes based on FTIR data.

Based on the homogeneity test data, the distribution of ceftriaxone and ibuprofen particles in the cellulose acetate polymer showed promising results, and the particles were evenly distributed on the nanofibers. The drug release test showed that the drug particles in the nanofibers were released based on the effect of diffusion and the erosion effect of the cellulose acetate polymer. Based on the data, cellulose acetate has the potential to be fabricated into a drug delivery system using the electrospinning method by producing nanofibers capable of being filled with both hydrophilic and hydrophobic drug particles with good morphological characteristics, and homogeneity.

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