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EVALUATION OF MICROSPHERE OF POLY(LACTIC ACID) AS CELECOXIB CARRIER

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Abstract

Celecoxib, cyclooxygenase-2 inhibitor approved for the management of rheumatism and osteoarthritis. Celecoxib is a Biopharmaceutics Classification System (BCS) class II compound whose oral bioavailability is highly limited owing to its poor aqueous solubility. Microencapsulation is very helpful to increase the solubility and slow the release of drugs. For the drugs of BCS Class-II, we use this technique which enables us to get more solubility and increase dissolution profile. The present study aims to reduce the drug's negative effect and boost its bioavailability. Poly(lactic acid) (PLA) a biodegradable polymer microsphere that can be synthesized to encapsulate celecoxib, was prepared by solvent evaporation with chloroform were used. The characterized surface morphology, drug entrapment efficiency (DDE), and in vitro drug release. Morphology was studied by scanning electron microscopy (SEM), crystallinity was studied using an X-ray diffractometer (XRD), and drug release was spectrophotometer UV-Vis. The results were observed to indicate there were microspheres homogeneous in the distribution of celecoxib in the polymer matrix. Formulations indicated that DEE was between 55.80 and 70.70% with prolonged length microspheres in the 10-30 μm range. Study in vitro drug release, when placed in phosphate buffer (pH 7.4) containing 2% w/w Tween 80 solvent, there was an initial burst of drug release within the first two hours followed by constant drug release. The PLA microsphere can release the confined celecoxib gradually but does not follow a controlled diffusion mechanism, but rather a mechanism of expansion and erosion of the microsphere matrix.

INTRODUCTION

Microsphere technology is one of the alternative pharmacotherapy treatments that are not directly related to the gastrointestinal system but are treated through direct injections into diseased parts of the body. Next, the drug formulation confined in the microsphere will be slowly released in the diseased part of the body. Microspheres are solid particles of 1-1000 μm in size that do not change their properties and functions, Microspheres have a wide field of applications, depending on the type of confinement and confined material, such as for applications in medicine, agriculture, and industry. Microsphere polymers and microcapsules as carriers of active substances make it possible to achieve controlled or sustained release. The difference between the two is seen in the shape of the microsphere with no visible walls or sheaths [1] and [2].

Biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and its derivatives can be degraded through hydrolysis in the body and excreted within a few months. This biodegradable polymer also does not poison the body (*biocompatible*). It is widely used in the field of medicine such as for drug delivery systems (*drug delivery system*, DDS) [3], and surgical threads, so the development of PLA-based microspheres is exciting to carry out [4] and [5]. *Rheumatoid arthritis* (RA) is an autoimmune disease that attacks the joints because the cells in the immune system do not function properly. RA attacks the body's equipment, especially the wrists, fingers, and feet. Pharmacotherapy for RA is the use of non-steroidal anti-inflammatory drugs (NSAIDs) given

early to address joint pain due to inflammation. The limitation of the use of NSAIDs is their toxicity.

The most common toxicity of NSAIDs is gastrointestinal side effects such as nausea, abdominal cramps, continuous bowel movements, decreased appetite, and heartburn [6] [7]. For sensitive patients, NSAIDs preparations are used in the form of suppositories or enteric coating forms. This preparation has less effect on the gastric mucosa than ordinary preparations, but it has systemic effects, especially in patients with gastroduodenal disorders. Celebrex is paired with celecoxib, which is an NSAIDs drug that is effective in reducing pain and inflammation in RA patients [8]. The dosage form with a controlled drug release system is an alternative that can be used to maintain a continuous level of drug therapy gradually. However, development to obtain other ingredients that are more stable and can deliver drugs to the target precisely is still needed. One alternative is to use biodegradable polymers of PLA as microspheres.

EXPERIMENT

The research conducted is an experimental method consisting of several stages, namely the manufacture of PLA microspheres using the solvent evaporation method in water and the in vitro performance of PLA microspheres [1].

Material

PLA pellets (Wako-Japan) with molecular weight 39000, potassium hydroxy phosphate (KH_2PO_4) 0.2 M, sodium hydroxide (NaOH) 0.2 M, polyvinyl alcohol (PVA) with BM 72000 obtained from Merck, buffer phosphate (pH 7.4), Tween-80, and antiarthritis drug Celebrex 200 mg.

Instruments

The equipment used in the process is divided into 3 groups, namely those related to the PLA microsphere synthesis, including glass equipment, stirrers, dryers, and filters. Equipment for the feature includes SEM Philip Type 505, XRD Shimadzu. Equipment for the release test is a Buchi incubator shaker, an Eppendorf centrifuge, and a Shimadzu-UV 1700 spectrophotometer.

Procedure

Synthesis PLA Microsphere

Microspheres are made by the method of evaporation of solvents in water (solvent evaporation method). 0.1 g of celecoxib drug powder is added to a 10% PLA solution. The mixture is emulsified into 10 mL of 5% PVA using a stirring motor at 1000 rpm for 5 minutes. The emulsion was dispersed into a 1 L cup containing 500 mL of aqueduct while stirring using a stirring motor at a rotational speed of 1000 rpm. Stirring is carried out for 60 minutes to evaporate the chloroform. After that, the mixture is decanted until the formed PLA microsphere precipitates. The precipitate was washed with 300 mL of aqueduct to remove PVA adhering to the microsphere surface. After that, the microsphere deposits are centrifuged and filtered to separate them from the water, then rinsed three times with an aquifer. The resulting PLA microspheres are air-dried for 24 hours and dried in an oven at 40 ^oC for 60 minutes to remove any unwanted solvent residues that may still be attached to the microsphere. The resulting drug microsphere is MS 0.10, MS 0.25, and MS 0.50 for drug concentrations of 0.10 each; 0.25, and 0.50 g, and comparators made microspheres without drugs (empty microspheres (MSo)). The drained PLA microspheres are then used for in *vitro performance of microspheres* [1].

PLA Microsphere Characterization

A few mg of the microsphere are dried until they are free of water and other molecules that can evaporate when electrons are fired, and then the microspheres are placed on an aluminum plate that has two sides. Then the mixture is coated with a 48 nm thick gold layer. The samples that have been observed use SEM with a voltage of 22 kV and magnification of 1250 and 2500 times. Crystallinity was analyzed to determine the characteristics of the microsphere produced using XRD.

Drug Entrapment Efficiency (DDE)

Some microspheres were weighed and suspended into 0.1 N HCl and incubated for 24 hours. This solution is dispersed into chloroform by shaking to extract celecoxib. The organic extract is evaporated until dry and the residue is dissolved in methanol. The absorbance of the resulting solution was measured at a wavelength of 250 nm using the Shimadzu-UV 1700 spectrophotometer to determine the amount of celecoxib present in the microsphere [2].

$$\text{Drug Entrapment Efficiency (\%)} = \frac{amount\ of\ drug\ actually}{amount\ of\ drug\ theoretical} x\ 100\% \quad (1)$$

In Vitro Drug Release from Microspheres

Celecoxib release from the microsphere is determined using phosphate buffer (pH 7.4) containing 2% b/b Tween-80 as the drug release medium. Some microspheres were weighed which was equivalent to 2.5 mg celecoxib, dissolved in 50 mL of the solution medium in a 100 mL goblet glass, and stirred at a speed of 50 rpm in a thermostat bath at a temperature of 37°C. Two milliliters of samples were taken at intervals of 0, 1, 2, 4, and 24 hours and centrifuged at 5000 rpm. Supernatants were taken as much as 0.5 mL diluted 10x, and the absorbance of the resulting solution was measured at a wavelength of 250 nm, with a medium solution (buffer phosphate + Tween-80) as a blank [3] and [4].

RESULT AND DISCUSSION

Celebrex

Celebrex drugs contain active ingredients such as celecoxib and fillers. The drug was extracted with methanol to produce celecoxib active ingredients and its crystallinity was measured using XRD (**Figure 1**). Typical peaks of celecoxib based on XRD measurement results show 14.8, 16.0, 21.6, 22.3, 23.5, and 25.4° according to the report [8].

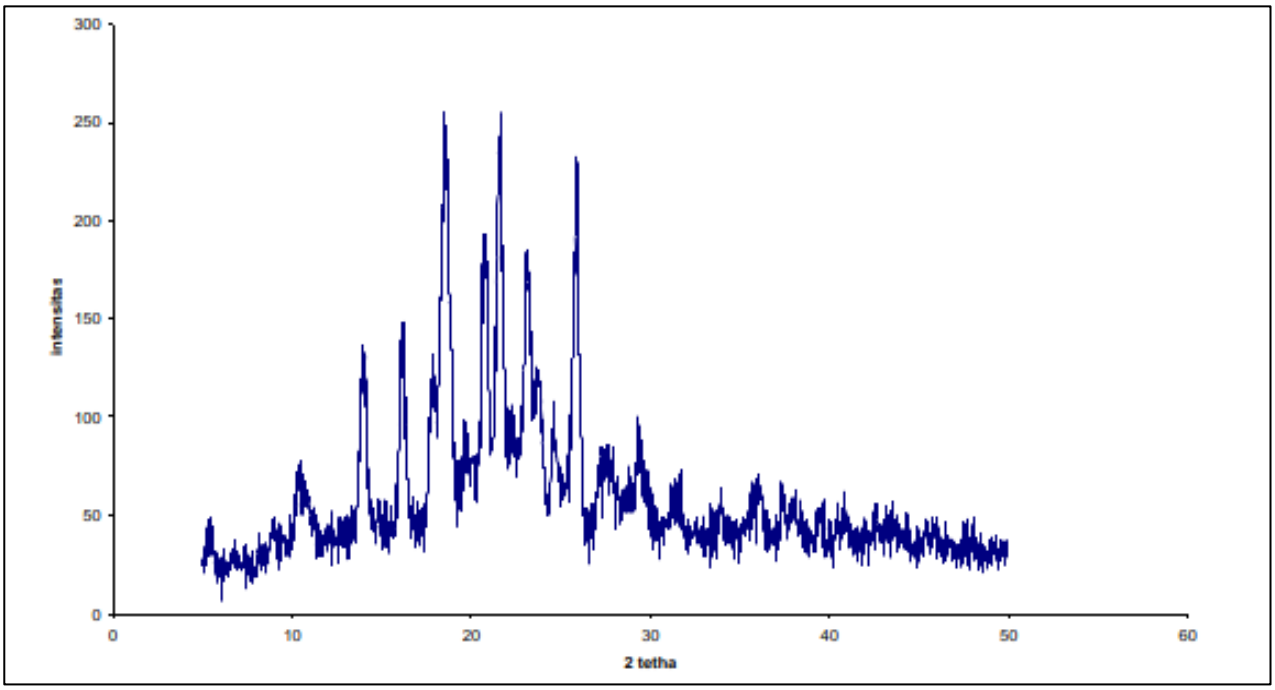

Figure 1. XRD pattern of Celecoxib.

The photo using a *Scanning Electron Microscope* (SEM) is seen in **Figure 2**, **Figure 3**, and **Figure 4**. **Figure 2** is the morphology or texture of the drug. The Celexocib used has a size of > 10 µm. **Figure 3** is the morphology or texture of the active ingredient of celecoxib measuring ± 10 µm, and **Figure 4** is the filling material of > 10 µm. All measurements are enlargements of the SEM 2500X.

Crystalline celecoxib has high solubility when recrystallized from acetone at -20 °C and during three months of storage, celecoxib shows no change in crystallinity [8]. Celebrex is paired with celecoxib, which is an NSAIDs drug that is very effective in reducing pain and inflammation in RA patients, but the most common toxicity of NSAIDs is gastrointestinal side effects such as nausea, abdominal cramps, continuous bowel movements, decreased appetite, and heartburn.

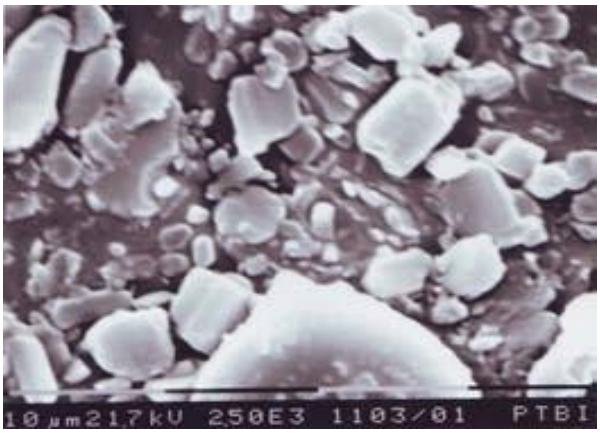

Figure 2. Celebrex drugs.

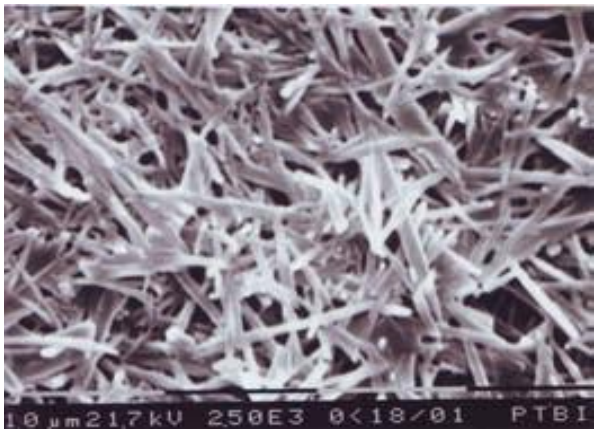

Figure 3. Celecoxib.

Figure 4. Filler of celebrex.

Microsphere PLA

Microspheres are small particles with diameters in the micrometer ranges of 1-1000 µm without changing their properties and functions. The materials used must meet the requirements, including contact time, control release, increase the therapeutic effect, have properties that can protect drugs, can reduce toxicity, are biocompatible, relatively stable, and have good solubility in water. The processes are carried out in a liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. Solvent evaporation involves the formation of an emulsion between a polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous [1].

The microspheres PLA are generally round and have a smooth surface (**Figure 5**). The morphology and distribution of microsphere size with stirring for 5 minutes and a rotation speed of 1000 rpm results in a round and flat microsphere shape, without wrinkles and holes, and has a size of 10-100 µm (**Figure 5**). Microsphere quercetin-alginate size has a size of 5-15 µm for the colon. It is well known that the ideal particle size for drug localization in the colon [9]. The size plays a role in gastrointestinal performance: microparticles under 800 µm get through the pylorus without the influence of gastric emptying, thus eliminating the interpersonal and intrapersonal (nutrition-based) differences. Particles larger than 100 nm stay at the site of administration until phagosomal clearance. Lymphatic uptake and node accumulation are most significant between 10–80 nm [2]. While research from [10] reported that the Ramipril microspheres ranged in size from 25.7 to 49.2 µm, on average. Ramipril an antihypertensive medicine has a 28 percent oral bioavailability and is promptly eliminated from the body through the kidneys. Varying alginate concentrations produce different microsphere sizes. Increasing alginate concentration causes a rise in alginate viscosity, which slows down the movement of polymer molecules, making it more difficult for them to spread out. As a result, larger microspheres were formed. Quersetin-alginate microsphere sizes were 6.53 ± 0.91 to 8.34 ± 0.46 µm with drug entrapment efficiency $68.97 \pm 7.67\%$ to 76.77 ± 5.18 %. Variations in alginate concentration did not significantly affect entrapment efficiency. This result is likely caused by the lack of calcium ions in the microsphere system, resulting in a poorer polymer bond and decreased drug trapped in the microsphere [11].

Figure 5. Microsphere PLA. 1250X SEM magnification.

For the application of the microsphere as an encapsulation in a DDS that is injected directly through a vein or into a sick target, a homogeneous microfloral size is required, so the sample is screened using a mesh of 100. The powder may be injected with several 18 or 20 needles and must consist of spherical particles measuring less than 125 microns. The difficulty of removing the

microspheres from the site is one of the disadvantages of using them for controlled release parenteral. Minimum drug content (max 50 percent). Microspheres can potentially cause the drug to shrink. During microsphere processing, the drug undergoes a change in shape to crystal or polymorphism [12].

The size of the microsphere is affected by the concentration of PLA, PVA, the ratio of water volume to solvent, and the speed of stirring. The high concentration of PLA is affected by the increase in viscosity in the dispersed phase, so the merger of dispersed granules is very easy to form. High PVA concentrations make it possible to form tightly packed micelles around the PLA microsphere, therefore the microsphere size is smaller [11]. Polymer EudragitRL100 and ethyl cellulose used for the microsphere were in the range size of 25.7 to 49.2 m. The size of the microsphere increased along with the concentration of crosslinking of the polymers, and it also shrank with an increase in the stirring rate [10]. The amount of PVA as an emulsifying agent did not influence the drug loading and entrapment efficiency of microspheres however the particle size of microspheres is seen to be dependent on the PVA concentration in the continuous phase [13].

Microencapsulation is a technology for the protection of solid, liquid, and gaseous material, in small capsules that release their contents at a controlled rate over a long period [14]. Microsphere formulations with celecoxib of 0.10 g (MS 0.10), 0.25 g (MS 0.25), and 0.50 g (MS 0.50) resulted in spherical microsphere shapes, smooth surfaces, and slight pores, but did not affect the size distribution of microspheres particle. These results are supported by [15] i.e. poly(DL-laktida-co-glycoside) (PLLGA) and poly(L-laktida-co-glycoside) (PDLLGA) copolymer microspheres without drugs have a spherical and non-porous shape, and microspheres with spherical and slightly porous drugs, do not show significant differences in distribution their particle sizes with different molecular weights (the DL-LA/GA ratio is 80/20). An increase in the concentration of the drug by up to 50% results in a non-smooth microsphere surface that drug crystals or broken drug particles may even cover.

The size of the particles is affected by the molecular of the polymer and the interaction between the drug and the polymer. The size of the empty particles obtained is larger than that of particles containing drugs, especially in drugs that are less soluble in water. This is because the hydrophobicity of polymers or drugs affects the aggregate number of particles. Further explained, the change in the size of the drug-containing particles occurs due to a change in the amount of polymer aggregate or a change in the weight of the polymer type, so that there is an increase in the interaction between the drug and the polymer which causes the particle shape to be denser and thicker. Then, the small size of the drug particles results in very high drug confinement and the presence of excess drugs does not cause the expansion of the polymer matrix.

The very high encapsulation of drugs is due to the interaction between drugs and polymers, so no drugs are water-soluble, washed out at the time of particle creation. The results of this study show that the size of the microsphere containing celecoxib varies depending on the number of drugs confined. The typical peaks of PLA are 16.7 and 18.96º, while the typical peaks of celecoxib are 14.8, 21.5, 22.36, 23.45, 25.25, and 25.39 º (**Figure 6**).

The results of this study indicate that the size of the microspheres containing celecoxib varies depending on the amount of drug encapsulated. The diameter of MS 0.10 and MS 0.25 has a size of 10-30 ⌈m because the speed and rotation time in the emulsification and evaporation processes remain the same. On the other hand, MS 0.50 has a smaller microsphere size because the amount of drug added is increasing. In addition, there is an interaction between the drug and the polymer, in the form of a hydrogen bond between the -C=O group of PLA and the -NH_2 group of celecoxib so that the size of the microspheres is smaller.

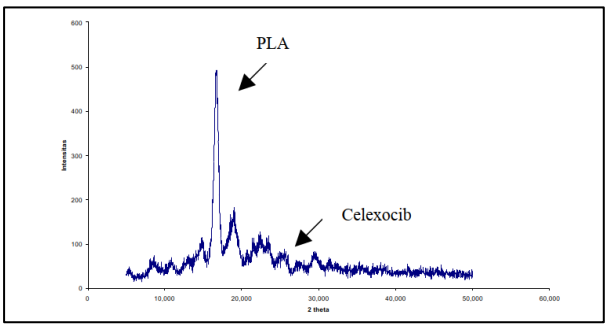

Figure 6. XRD pattern of microspheres containing Celecoxib.

Drug Encapsulation Efficiency (DDE)

Entrapment efficiency is generally expressed in the percent of drug absorption [16]. The range of the entrapment efficiency was 58.60-70.70% (**Table 1**). As stated by [14] and [17], the efficiency of entrapment is affected by the

solubility of the drug in the solvent and the crosslinking concentration rose.

Table 1. Entrapment efficiency (%) microspheres.

Sample	Efficiency (%)		
	Theoretical	Result	Efficiency
MS 0.10	9.09	5.51	60.60
MS 0.25	20.00	11.72	58.60
MS 0.50	33.33	23.54	70.70

In contrast, the result of the efficiency value shows that the more drugs are added, the more drugs are confined in the microsphere. This is because celecoxib has low solubility in water but is soluble in its organic solvents, namely chloroform and methanol [9]. According to [1] the process of synthesis of microspheres by emulsifying oil/water (w/o) is more widely used for the encapsulation of fat-soluble drugs (*lipid-soluble*). The emulsion between PLA and the drug is thicker so that it can prevent the dissolution of celecoxib in the internal phase.

In vitro Drug Release

The process of drug release of microparticulate, produced by special manufacturing technologies and/or possibly containing special excipient(s), is the result of various phenomena and mechanisms (dissolution/diffusion, osmotically driven release, erosion) [2].

The results of in vitro drug release showed an increase in celecoxib release from the PLA microsphere in a pH 7.4 phosphate buffer medium at 1, 2, 4, and 24 hours incubation time. The first hour of drug release occurs exponentially and tends to be stable until the 24-hour incubation period (**Figure 7**).

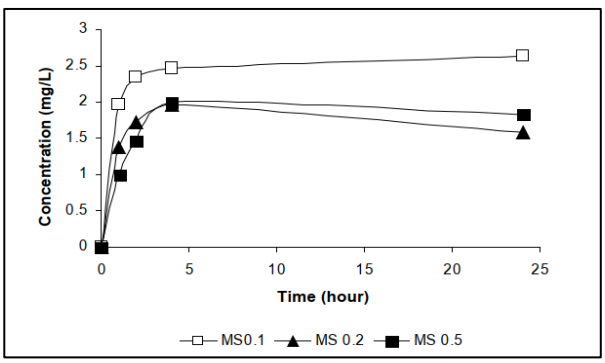

Figure 7. Drug release microsphere MS 0.10; MS 0.25 and MS 0.5.

The results of the celecoxib release test of MS 0.10 from 1 hour to 24 hours increased exponentially, namely 1.966 to 2.636 mg/L, indicating the release of the ruptured drug (burst) at the beginning and followed by slowing down. The dissolution of celecoxib was studied in 900 mL of sodium phosphate dibasic anhydrous buffer with 1% sodium lauryl sulfate at 37 ± 0.5 °C, stirred at 50 rpm for 120 minutes. At 30 minutes, the dissolution of celecoxib was 97.3% at the condition, according to [8]. These results can be seen from the SEM image which shows that the process of drug release from the microspheres has surface erosion, after two to three hours of incubation (**Figures 8, Figure 9,** and **Figure 10**).

Figure 8. Distribution of microsphere particles MS 0.10.

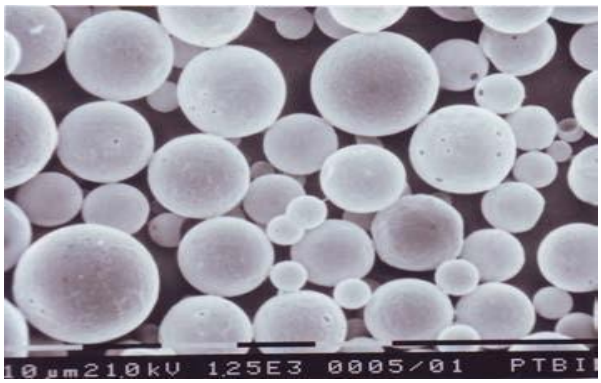

Figure 9. Distribution of microsphere particles MS 0.25, after 5-hour release.

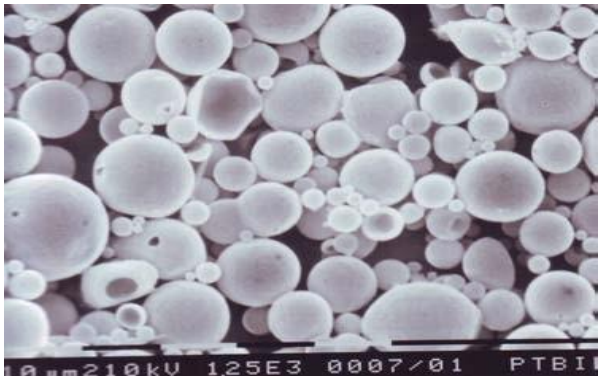

Figure 10. Distribution of microsphere particles MS 0.50, more than 5-hour release.

On the other hand, the drug release decreased as the PLA increased, and the concentration of celecoxib. The most attractive and commonly used biodegradable polymers are polyesters such as poly(lactic acid) (PLA). These materials are commercially available in different compositions and molecular weights, allowing the control of polymer degradation. For biodegradable polymers two different erosion mechanisms can be suggested: homogeneous or bulk erosion, and heterogeneous or surface erosion. The difference between both is that, in the case of bulk erosion, degradation is observed all over their cross-section because the penetration of water into the polymer bulk is faster than the degradation of the polymer [18] and [19].

In addition, the ratio of concentration between the drug and the polymer and the solubility of the drug affect the controlled release of the drug. The weak bond between the drug and PLA and the level of microsphere porosity allows the drug to escape quickly [15] reported that the mechanism of microsphere surface degradation occurs through two processes, namely direct destruction of the microsphere surface and the rupture of the initial microsphere to form a new microsphere. From the results of the research [10], the rupture of the initial microsphere is more dominant than the process of direct destruction on the surface of the microsphere. This is because the surface of the microsphere is porous, PLA can absorb water, causing the level of porosity to increase because there is passive diffusion of water into the microsphere so that physically the size of the microsphere becomes large because of swelling, the bonds between PLA molecules become weak and finally break so that pores appear that make it easier for drugs to come off. In contrast to the results [11], of microsphere size alginate, increasing alginate concentration caused a significant decrease in drug loading.

The result is likely caused by the lack of calcium ions in the microsphere system, resulting in a poorer polymer bond and decreased drug trapped in microspheres. The amount of PLA in MS 0.10 is more than that of confined celecoxib drugs, so the porosity nature causes the diffusion of drugs from the microsphere to be more controlled because the drugs are released gradually. The degree of porosity does not affect the degradation of PLA. The degradation of PLA BM 39000 occurred over 12 weeks. MS 0.25 shows that the longer the incubation time, the exponential increase in the concentration of drugs in the media, which is from 1.381 to 1.967 mg/L. However, at the 24-hour incubation time, there was a decrease in the concentration of the drug by 0.377 mg/L (1.967 to 1.590 mg/L). The microsphere surface of MS 0.25 shows that there is some drug that sticks to the surface and may come off during washing and drying, which is seen from the presence of small holes in the surface of the microsphere.

The efficiency value of 58.6% of the amount of drugs that are confined is only part of the drugs added, some of which can be lost during washing. The porosity level of MS 0.25 is small based on the small number of pores as a result of which water absorption is small, microsphere bulging is also small, so the drug is released little. In addition, the pharmacokinetic properties of the drug celecoxib have a half-life (t1/2) of 11 hours so that at 24 hours of incubation the drug has been converted into a compound, the absorption value decreases so that the concentration also decreases. The MS 0.50 formula shows the same picture as MS 0.25; at 24-hour incubation, the concentration decreased by 0.173 mg/L. The efficiency value was 70.6%, and the number of drugs confined was more than MS 0.10 and MS 0.25. The decrease in concentration can be caused by the drug being converted after 24 hours of incubation because it passes the half-life of the drug, which is 11 hours. In addition, the microsphere has fewer pores because the microsphere is slightly inflated due to the absorption of water by PLA less, so fewer drugs are released than MS 0.10. According to [20] stated that a high value of % of infinement efficiency indicates a decrease in drug release compared to a low value of % efficiency.

The DDE can be observed by increasing the lactic acid ratio, so that the hydrophobic properties increase, but in this study, the lactic acid ratio was not calculated. The solubility of the polymer or the small size of the polymer in water gives the surface tension lower, this affects the increase in the release speed of the drug. After the process of imbibition water into PLA microparticles, the drug dissolves and breaks through hydrolysis, forming an unstable/balanced ester bond. Then simultaneously, the drug diffuses outside the matrix according to the concentration gradient. Drug diffusion can occur mainly through polymer matrixes, water-filled pores, and through both. In addition, the porosity of particles also affects drug diffusion and polymer degradation [11]. Drug molecules can still be released by diffusion through closed holes or pores. The presence of pores and the high absorption of poly(ethylene oxide)-poly(lactide-co-glycoside) PEO-PLGA particles indicate the permeability of

the drug in the polymer matrix. Quick release and entrapment within 5 hours [10]. The magnitude of the initial drug release value from the microsphere indicates the easy release of drug crystals that adhere to the surface of the microsphere. The results of the analysis of celecoxib-release kinetics from the microsphere (**Table 2**).

Table 2. Entrapment of determination (*R2*) from microspheres.

Sample	Entrapment of determination (*R2*)	
	Order of zero	First Order
MS 0.10	0.292	0.575
MS 0.25	0.070	0.078
MS 0.50	0.305	0.210

The celecoxib release of MS 0.10, MS 0.25, and MS 0.50 had an *R2* value between 0.070 and 0.575. The value is less than 1, meaning that it does not follow the kinetics of the zero and first-order releases, but tends to occur exponentially. This suggests that after the initial release, the release of the drug from the microsphere is not followed by a controlled diffusion mechanism, but the mechanism may be due to the swelling and erosion of the polymer matrix and is followed by the release of the drug simultaneously.

CONCLUSION

The microspheres formed in this study are between 10 to 30 μm in size with a spherical shape and a smooth surface. The confinement efficiency is 50-70%. The PLA microsphere can release the confined selecoxib gradually but does not follow a controlled diffusion mechanism, but rather a mechanism of expansion and erosion of the microsphere matrix.

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