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Preparation and Characterization of Curcumin-Based Coating Material on Co-Cr Alloy

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Abstract. Commonly used as a stent-based material, cobalt-chromium (Co-Cr) alloy requires drug coating on its surface for prevention of restenosis risk; this is known as the drug-eluting stent (DES). In this research, *curcumin* was investigated as a drug coating material with biodegradable polymer PLLA (poly-L lactic acid) as a drug carrier and mildly fabricated on the surface of Co-Cr alloy by using an ultrasonic spraying method. Three kinds of concentrations were equipped — low (~62.5 µg), moderate (~125 µg), and high (~250 µg) concentration. This study also investigated the coating with *curcumin* only that may be used as the exploration to develop the drug coating stent without using polymer. The characterization of the coating specimens was analyzed by Fourier-transform infrared spectroscopy (FT-IR), analytical scanning electron microscope (SEM) together with energy dispersive X-Ray spectroscopy (EDS). Results showed that *curcumin* and PLLA were relatively homogeneous blended in order to be formulated as the coating material. Further, the *curcumin*/PLLA and the *curcumin* only were also affecting the topography of the surfaces on the specimens coated. Moreover, the in vitro study result showed that the drug release of all *curcumin* concentrations indicated a mildly sustained release profile without any apparent burst release within the period of the measurements.

Keywords: Co-Cr; Coating; Curcumin; PLLA

1. Introduction

Coronary heart disease (CHD) is one of the most considerable health problems which can be the leading cause of death worldwide (Khan *et al.*, 2020). It is caused by the narrowing of blood vessels or other abnormalities, primarily due to plaque formation known as atherosclerosis, which can lead to a heart attack. Atherosclerosis can be overcome by installing a stent. Stent aims to support the coronary vessel wall so it does not easily recoil after being dilated with a balloon (Grabow *et al.*, 2010). It is mostly made of metal such as stainless steel, platinum alloys-chromium (Jorge and Dubois, 2015), or cobalt-chromium (Co-Cr), then formed into a small pipe, originally known as bare metal stent

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(BMS). Co-Cr alloys have high density, which is advantageous to radio-opacity, and have high elastic modulus, which limits recoil, and tensile strength properties that allow stent designs with thinner struts (Poncin *et al.*, 2005).

Besides the promising role of Co-Cr stents for minimization of coronary remodeling, restenosis risk remains a critical concern. Restenosis could occur due to blood clotting, called thrombosis, which can lead to the proliferation of vascular smooth muscle cells (VSMC) (Foerst *et al.*, 2013). Besides the promising role of Co-Cr stents for the minimization of coronary remodeling, restenosis risk remains a critical concern. Restenosis could occur due to blood clotting called thrombosis, leading to the proliferation of vascular smooth muscle cells (VSMC) (Foerst *et al.*, 2013).

The VSMC proliferation and intracellular matrix synthesis in response to stent-implanted inflammatory reaction are broadly believed as the major mechanisms of restenosis, and it needs a drug to prevent it (Bennet and Michael, 2001). However, orally administered drugs may have inadequate local drug concentration and can cause toxic reactions from excessive drug doses. Therefore, a drug delivery system is needed to control drug release (Imani *et al.*, 2022). The drug delivery system works by preserving the drug and restraining the drug release; therefore, the drug can reach its action site appropriately by enhancing and/or reducing the drug circulation (Barleany *et al.*, 2020). To deal with this issue, drug coating stents which are globally known as drug-eluting stents (DESs), become the answer by releasing pharmacological agents to inhibit the response of restenosis (Bennet and Michael, 2001).

Previously, DES, which releases anti-proliferative drugs such as *sirolimus* (*rapamycin*) and *paclitaxel* with synthetic polymer coatings, has opened up a new paradigm for the treatment of in-stent restenosis (ISR), known as first-generation DES. Advantageously, these drug-coating stents can provide luminal scaffolding that eventually eliminates the recoil and remodeling of vascular coronary. However, the released drug from the coating can achieve high local drug concentration, cellular proliferation prevention, or thrombus formation (Waksman *et al.*, 2006). Furthermore, the residual synthetic polymer coating remains in the body, which may lead any complications such as an over-inflammatory response and *neointimal hyperplasia* at the implant site (Ranade *et al.*, 2004). To avoid these unavailing effects, it is urgent to build a drug-coating stent with a biodegradable and biocompatible coating. One kind of biodegradable polymer that has good mechanical properties is Poly-(L lactic acid) (PLLA). This polymer is known to be the most desirable biocompatible and biodegradable polymer obtainable from starch in a high yield (Ni'mah *et al.*, 2019). PLLA is widely used in biomedical devices such as orthopedic surgery and other surgery fields where bioresorbable sutures are needed, as well as used for drug-delivering implants (Zilberman and Eberhart, 2006). Because of its superior mechanical strength, PLLA can be a good candidate as a drug carrier for stent coatings.

Curcumin is a *polyphenolic* compound commonly derived from the dried rhizomes of *Curcuma longa* L. (Basile *et al.*, 2009), presents low intrinsic toxicity and shows a wide spectrum of pharmacological properties, including anti-oxidation, anti-inflammation, anti-thrombus and anti-proliferation activities (Chen *et al.*, 2015). These promising characteristics suggest that *curcumin* could be applicable as a therapeutic agent for DES.

By considering these biomaterials, the preparation of the curcumin-based coating using Poly-(L lactic acid) (PLLA) as the drug material, along with the in vitro characteristics in this study, were reported. To our knowledge, the preparation of *curcumin* coating by using PLLA to be coated on Co-Cr alloy has not been investigated.

2. Methods

2.1. Materials

The material used in this study was Co-Cr alloy (Dentaurum GmbH & Co. KG, Ispringen, Germany). The composition (wt%), as provided by the manufacturer, was 60.5% *cobalt* (Co), 28% *chromium* (Cr), 1.5% *silicon* (Si), 9% *tungsten* (W), other elements were *manganese* (Mn), *nitrogen* (N), *niobium* (Nb), and *iron* (Fe) were less than 1%, and free from nickel (Ni), beryllium (Be), and gallium (Ga). The coating material was *curcumin* (Merck KGaA, Darmstadt, Germany) that had a purity above 96% and PLLA (30% wt. in H_2O) (L1875–Sigma Aldrich, Massachusetts, US). All other reagents used in this research were analytical grade.

2.2. The Curcumin-based Coating Preparation

Firstly, the Co-Cr tube was shaped into a platted disk by a mold casting machine. The materials were polished and then were cleaned ultrasonically with acetone (Merck KGaA, Darmstadt, Germany), ethyl alcohol (Merck KGaA, Darmstadt, Germany), and distilled water sequentially. The cleaned materials were preserved under a vacuum to evaporate the residual water (Pan *et al.*, 2006). Next, curcumin, which was previously dissolved in absolute ethanol at different concentrations, was mixed with 1% wt. of PLLA using a homogenizer for at least 3 minutes. The solutions were then sprayed onto cleaned materials using the ultrasonic spraying method, with each sample sprayed for at least 1 minute. It was remarked parenthetically that the solutions sprayed to all samples were about 0.5 ml with about 3µm thickness of the coating severally. Those sprayed mass of coating on the sample surface could be obtained by calculating the solution concentration. Three coating concentrations of *curcumin* were prepared at low concentration (~62.5 µg), moderate concentration (~125 µg), and high concentration (~250 µg). There were two kinds of control samples prepared. The first one was with only polymer, and the second one was with *curcumin* with the same concentration and the same method of coating.

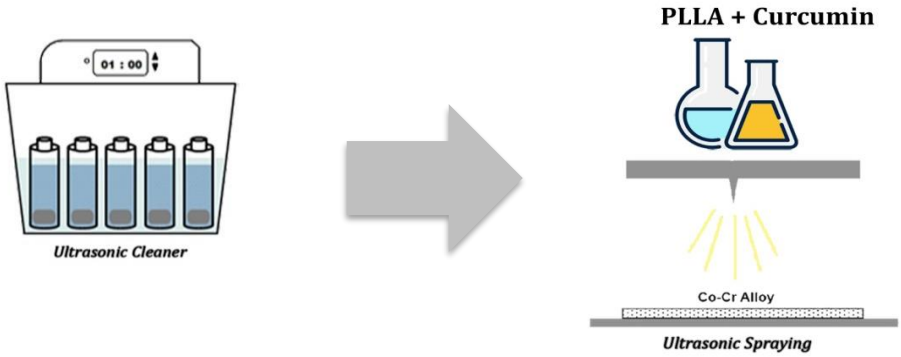

Figure 1 Schematic of Material Preparation using Ultrasonic Cleaner and Ultrasonic Spraying

2.3. Fabrication of the coating films

To cast a thin polymer film, a one wt.% solution PLLA was prepared by dissolving the solution in ethyl acetate (Merck KGaA, Darmstadt, Germany), then placed on a cleaned watch glass dish 10 cm. The films were slowly dried in hot air until the solvent evaporated to obtain the films. The films were then preserved to evaporate the residual solvent. The curcumin coating films were prepared in two different ways. First, curcumin with high concentration dissolved in ethanol was mixed with dissolved PLLA in ethyl acetate, and the second was dissolved curcumin in ethanol only. Both of them were evaporated and were treated in the same manner as such polymer films.

2.4. Structure analysis of the coating films

The structure of PLLA, curcumin, and curcumin/PLLA films was analyzed by the FTIR system (FTIR type SHIMADZU IR-Prestige 21, Japan) to determine the chemical compounds. Further, curcumin powder was also examined for additional control data. The scanning of the FT-IR range equipped with an attenuated total reflectance accessory for wavenumbers from 4,000 cm^{-1} to 300 cm^{-1}, approximately 20 scans were performed for each film with 1 cm resolution.

2.5. Morphology of curcumin-based coating

The surface morphology of curcumin-based and PLLA coatings was investigated using analytical scanning electron microscopy (SEM-EDX JEOL JSM-6510LA, JEOL Ltd., Japan), operated at SEI with 20 kV accelerating voltage. In addition, energy-dispersive X-ray spectroscopy (EDS) analysis was also performed to determine the abundance of the specific chemical elements of each sample.

2.6. Curcumin Release Profile

The release profile of the curcumin from the samples was examined in vitro by immersing each sample in a medium consisting of phosphate-buffered saline (PBS, pH=7.4) (Invitrogen by Thermo Fisher Scientific, Massachusetts, US) with 10% ethanol at 37^{O}C because the solubility limit of the curcumin in water that makes it difficult to be investigated in buffer (Alexis *et al.*, 2004). At specific intervals, the medium of the PBS solution was removed completely and replaced with the fresh medium. The removed medium was then measured using a UV-Vis spectrophotometer (VWR®^{V} V-1200, UV–1600PC Spectrophotometer UV-Vis, England) at wavelength 425 nm to determine the amount of released curcumin. The results were obtained accumulatively in micrograms (µg) and percentages (%) of released curcumin. Moreover, in order to investigate the drug release mechanism, it was applied by using the equation of Ritger & Pappas (see Equation 1) as below:

$$k.t = \frac{M_t}{M_\infty} \quad (1)$$

where M_t was the amount of *curcumin* released at the time (t), M_∞ was the total amount of *curcumin*, and k was a constant parameter of the release exponent (Kharaziha *et al.*, 2015).

3. Results and Discussion

3.1. FTIR Analysis

FTIR spectra of *curcumin*, PLLA, *curcumin* coating film, and *curcumin/*PLLA coating film are shown in Figure2. A transmission band related to *curcumin* was observed at 3448 cm^{-1}. This was attributable to the stretching vibrations of the phenolic O-H group. However, this band could not be distinguished from other peaks in *curcumin* coating film and so *curcumin*/PLLA coating film. A sharp peak was seen at 1597 cm^{-1}, corresponding to the stretching of the C = C bond of the benzene ring. Another sharp peak was seen at 1512 cm^{-1}. It was related to the olefin bending vibrations of the C-H bond to the benzene ring of *curcumin*. Those peaks were shifted to 1620 cm^{-1} and 1520 $cm^{-1,}$ respectively, in *curcumin* coating film, as well in *curcumin*/PLLA coating film to 1589 cm^{-1} and 1517 $cm^{-1,}$ respectively. Further, the peak from pure *curcumin* at 817 cm^{-1} and 1280 cm^{-1}, assigned for vibration of C–O in –C–OCH_3 of the phenyl ring, were shifted and only detected at 1288 cm^{-1} in *curcumin* coating film and at 1285 cm^{-1} in *curcumin*/PLLA coating film.

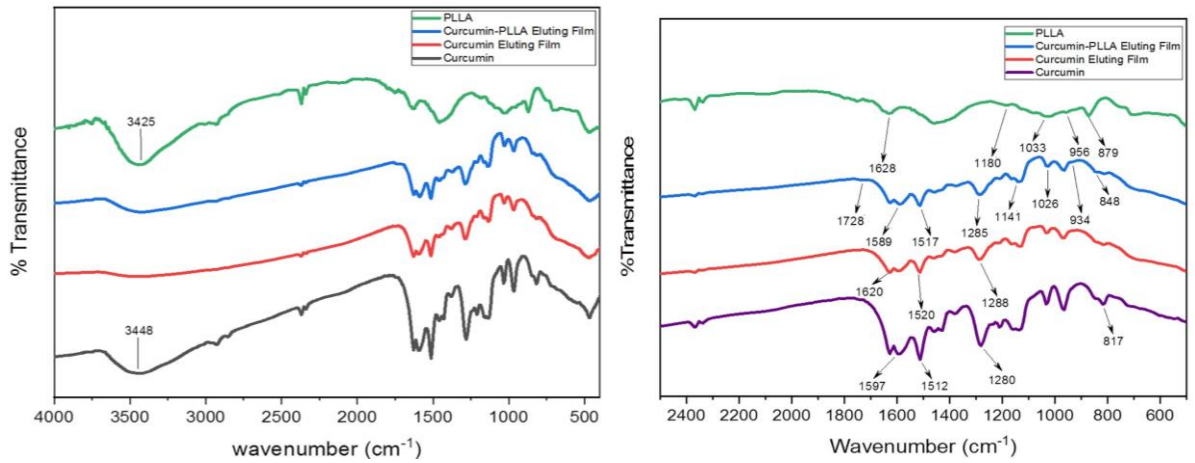

Figure 2 Result of the FTIR Analysis of Pure Curcumin and PLLA, Curcumin Film, and Curcumin/PLLA film

Similarly, with the curcumin-related band, a valley-like peak at 3425 cm^{-1} was seen in PLLA film. This was probably ascribable to hydroxyl stretching OH bending. Other characteristic peaks of PLLA and their shift in curcumin/PLLA were also identified. A blunt peak at 1628 cm^{-1} is assigned as carbonyl stretching C=O in the –CO–O– group of PLLA and was observed vaguely at 1728 cm^{-1} at curcumin/PLLA. Another hollow-like peak was seen at 1180 cm^{-1}. This corresponds to the stretching vibrations of the symmetric CH bending in the –CH–O– chains of PLLA, and it shifted to 1141 cm^{-1} in the case of curcumin/PLLA. Additionally, a mountainous triplet peak at 1033; 956; and 879 cm^{-1} that were ascribable to the C–O bond vibration in –CO–O– group in PLLA chains shifted accordingly to 1026; 934; and 848 cm^{-1} respectively in curcumin/PLLA.

Based on the peak shifts shown in the FTIR data (Figure 2), it can be confirmed that curcumin and PLLA were adequately bound together. Meanwhile, the peak at 879 cm^{-1} in PLLA, which was ascribable to the C–O bond vibration in the –CO–O– group in PLLA chains, shifted to 848 cm^{-1} in *curcumin*/PLLA. That shifting could be confusing with the vibrations of the phenyl ring C–O in –C–OCH_3 from *curcumin*. Nevertheless, this confusion can lead to the certainty that *curcumin* and PLLA were perfectly blended. Furthermore, a peak at 1628 cm^{-1} that was identified as carbonyl stretching C=O in the –CO–O– a group of PLLA then shifted to 1728 cm^{-1} at *curcumin*/PLLA, indicating weak hydrogen bond formation between the carbonyl group of PLLA and the hydroxyl group of *curcumin*. This finding was reinforced by the peak shift of the symmetric CH bending of PLLA in *curcumin*/PLLA, from 1180 cm^{-1} to 1141 cm^{-1}. C–H groups that showed symmetric CH bending were the neighboring groups to C = O in PLLA. The changes in vibrational frequency indicated by the peak shift were probably the consequence of interaction between the C = O group of PLLA with the O–H group of *curcumin*.

3.2. SEM-EDS Analysis

SEM images were taken on the top surface where *curcumin*, *curcumin*/PLLA, and PLLA were coated on Co-Cr Alloy. Those images are shown in Figure 3, Figure 4, and Figure 5 to evaluate the morphology of the coating. There are two types of analyzed samples for SEM, first, the samples that were only coated with *curcumin*, *curcumin*/PLLA, and PLLA on Co-Cr Alloy, and the second were the coated samples with release treatment with PBS (phosphate buffer saline) for about 20 hours.

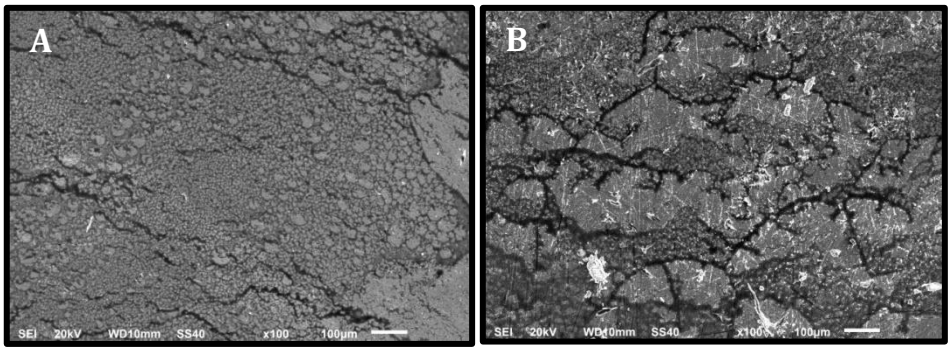

Figure 3 SEM Images of *curcumin* coated before (A) and after (B) PBS treatment

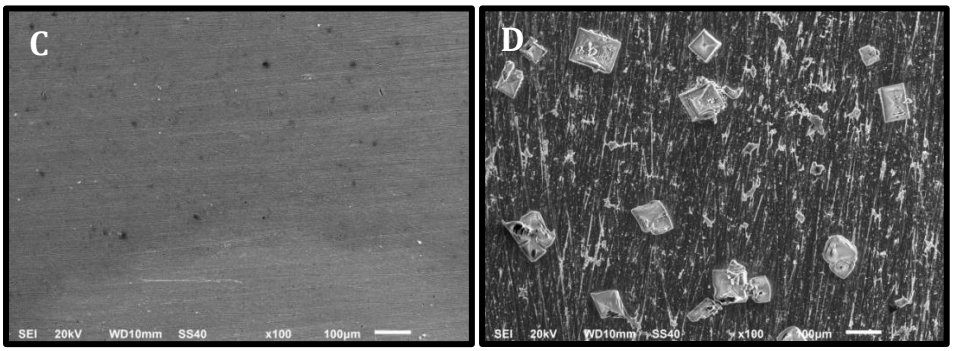

Figure 4 SEM Images of PLLA coated before (C) and after (D) PBS treatment

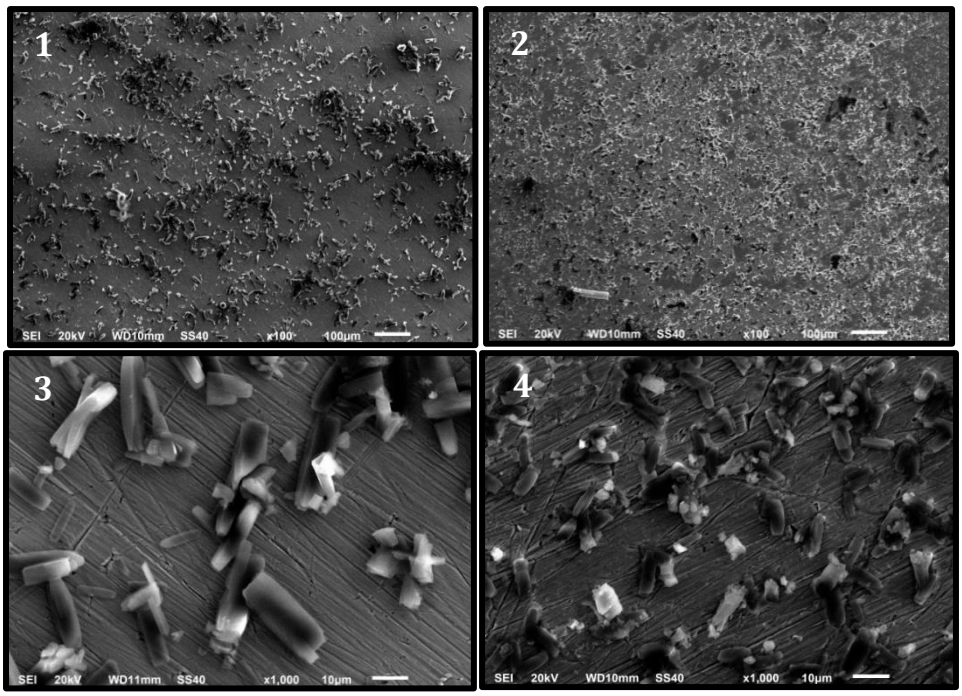

Figure 5 SEM Images of *curcumin*/PLLA coated before (1, 3) and after (2, 4) PBS treatment

A considerably smooth surface was observed on the surface where the sample was coated with PLLA only. It could be indicated that the PLLA was coated perfectly with Co-Cr. However, after giving the release treatment with PBS, it was shown that the PLLA surface formed some cuboid shape particles that claim the PLLA surface has a deformation on its particles. On the other hand, A rough surface with circular shaped particles was seen on a sample that was coated with *curcumin* only. It is indicated the distribution of the *curcumin* particle on the material surface. Further, a fractured surface was then observed after the

coating was treated with PBS. At fractured surface condition shows that the *curcumin* was released and formed a deformation on the surface. Surprisingly, on the SEM images of the curcumin/PLLA coated surface revealed the presence of numerous tubular-shaped particles on the surfaces. Those deformations on *curcumin*/PLLA particles could be caused by the adsorption of the *curcumin* onto PLLA. *curcumin*/PLLA coating surface after treatment with PBS.

In the other images of the *curcumin*/PLLA coatings, there was a sloughed area on the coated sample surface which was treated by PBS. Those indicated that the *curcumin*/PLLA coating which was treated by PBS, was released well at almost one day of releasing time. In addition, it can be vaguely seen that there were some shrinking particles on the Table 1.

Table 1 Element composition (wt%), measured using energy-dispersive spectroscopy (EDS), of the surface of the cobalt-chromium (CoCr) alloy coated with PLLA, *Curcumin*, and *Curcumin*/PLLA

Sample Treatment	Element Composition Mass (wt.%)						
	Co	Cr	W	Si	C	H	O
PLLA Coating	53	26	8	1	9	0	2
Curcumin Coating	40	19	6	1	28	0	6
Curcumin/PLLA Coating	39	20	7	1	27	0	5

The result of the surface topography of the coated specimens analyzed using energy-dispersive spectroscopy (EDS) was barely perceptible in the spectrum images of EDS analysis (data was not shown). In spite of the spectra analysis of the EDS, the result of the element composition mass of the specimens had some differences discernibly. On the top surface of the PLLA coated specimen, the composition mass of the Co-Cr alloy such as Co, Cr, W, and Si was the highest among other coating treatment samples. It could be argued that the PLLA coating film on Co-Cr alloy only slightly affect the element composition of the material. However, on the *curcumin*-only coating and *curcumin*/PLLA coating, there were obviously increments in the composition of the coating elements. Among the three specimens, the *curcumin*/PLLA coating sample had the lowest amount of mass of the Co-Cr element composition, whereas the *curcumin* coating sample had the most sizeable amount of coating composition of elements. The coating elements, which were C, H, and O, were adapted from *curcumin* ($C_{21}H_{20}O_6$) and PLLA ($C_3H_6O_3$)

3.3. The Release Profile of Curcumin

Generally, drug release quantification and the following biodegradation mechanism from drug coating biomaterial attached to the body are essential to formulate effectively the time-released drug (Sternberg *et al.*, 2007). Therefore, the *in vitro* release profile of *curcumin* from *curcumin*/PLLA coated samples was investigated to optimize the coating condition.

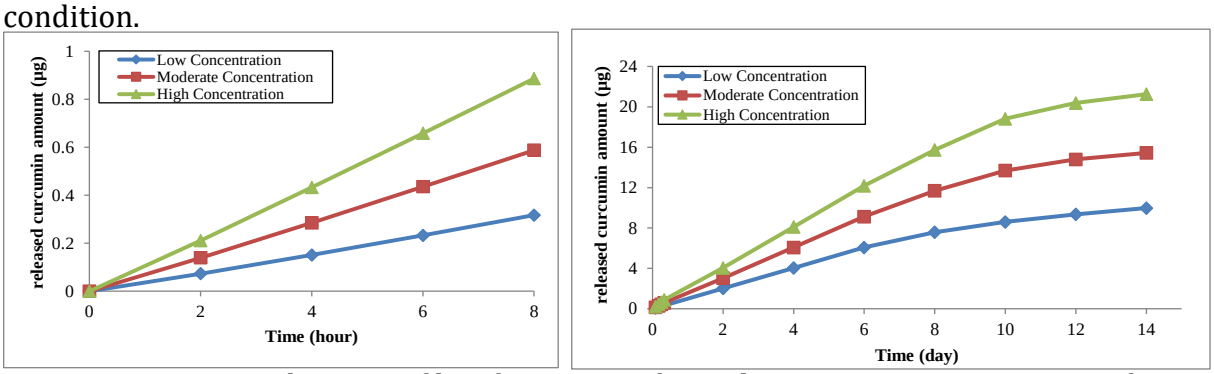

Figure 6 *In vitro* release profile of *curcumin* from three concentration types of coated materials; the cumulative amount of *curcumin*

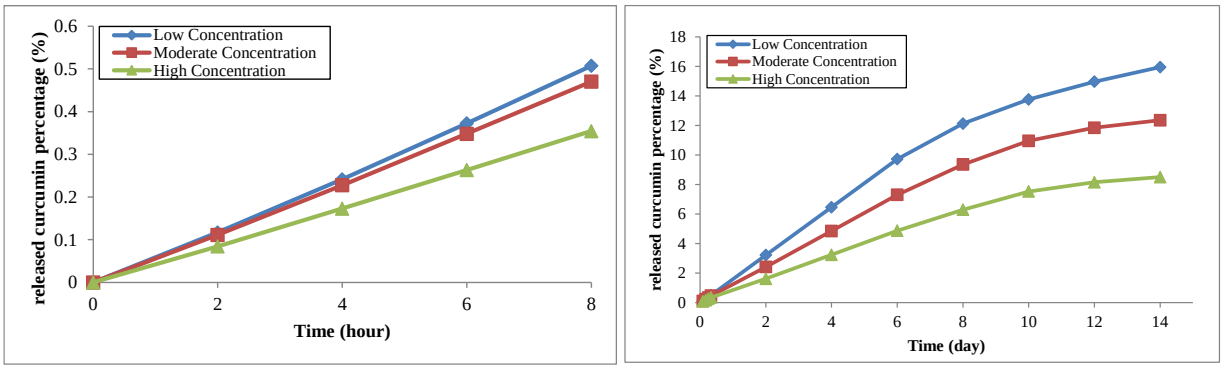

Figure 7 *In vitro* release profile of *curcumin* from three concentration types of coated materials; the percentage weight of released *curcumin*

The release of the drug from the matrix paired with the polymer begins with the presence of an initial burst release (Dinarvand *et al.*, 2005). Therefore, tests were carried out in two different types of time intervals, the fast release period in the first hour for 8 hours after treatment with PBS, then followed by a moderate-slow release period of observation for 14 days. Based on the results in Figure 6, all specimens coated with *curcumin*/PLLA in each treatment showed a nearly linear controlled-release profile with no significant burst release observed during the first hour period up to 14 days of the test. Theoretically, the controlled release of anti-restenosis drugs is required to prevent the migration and proliferation of vascular smooth muscle cells (VSMC) for at least one month after stenting implantation (Puranik, Dawson, and Peppas, 2013). From the *curcumin* release profile graph in Figure 6, the average release of the controlled rate at low concentrations is ±1.42 µg per day (2.27% wt.), at moderate concentrations ±2.21 µg per day (1.76% wt.), and ±3.03 µg per day (1.21%) at high concentrations. Furthermore, based on the average rate of *curcumin* release, it could be decided that the duration of *curcumin*-controlled release is ±44 days for *curcumin*/PLLA low concentration, ±57 days at moderate concentration, and for ± 82 days at *curcumin*/PLLA high concentration. All of the concentrations overall met the criteria for drug release for at least 30 days (one month). Additionally, the Ritger and Peppas equation (Equation 1) was also applied to evaluate the mechanism of *curcumin* release (Kharaziha *et al.*, 2015). The results showed that the release of *curcumin* in the *curcumin*/PLLA coating in this study occurred through a diffusion mechanism. The treatment of replacing the release medium at successive day intervals resulted in a significant gradient of *curcumin* concentration between *curcumin*/PLLA with the release medium, causing the formation of barely constant linear lines from the diffusion of the drug, as shown in Figure 6. Diffusion-sustained drug delivery systems can arrange the delivery of drugs for several weeks and give a special capability to control the kinetics of drug release (Acharya and Park, 2006). In addition, the diffusion of drug molecules through the polymer matrix depends on the solubility of the drug in the polymer, as well as the medium surrounding the drug as the diffusion coefficient and concentration gradient of the drug to the polymer. Therefore, it can provide an indication that if the diffusion of *curcumin* is faster than the degradation of the polymer matrix, it means that the mechanism of releasing *curcumin* occurs through the diffusion mechanism (Mohammadi *et al.*, 2019).

4. Conclusions

In conclusion, based on the results obtained in this research suggested that *curcumin*-based coating had the potential to become a coating material for improving drug-eluting stents. *Curcumin* could be blended with PLLA at the molecular level as coating material

using ultrasonic spraying as shown by SEM images. In addition, *curcumin* could be indicated to disperse in the PLLA matrix according to FTIR results. *Curcumin* also can be potential material for drug eluting stents as it showed the mildly sustained release profile without any apparent burst release. The slightly drawback of *curcumin* release profile which is needed to be reviewed is to find the moderate amount of curcumin concentration that can be released no more than 30 days in order to release at the appropriate duration.

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