



## Effect of Cinnamaldehyde as an Anti-inflammatory Agent on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Bone Substituting Purposes in Biomedicine

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**Abstract.** Combining anti-inflammatory agent derived from plant essential oil like cinnamaldehyde to bioabsorbable and osteoconductive material for bone substitute is a challenge in biomedical technology. In this study, cinnamaldehyde as a good anti-inflammatory agent with an aromatic  $\alpha$ ,  $\beta$ -unsaturated aldehyde derived from cinnamon was loaded to a composite of Plaster of Paris (POP) and hydrogel calcium carbonate (CaCO<sub>3</sub>) for bone substitute. However, it must be considered that blood-biomaterial interactions begin to occur after surgical implantation with blood protein adsorption to the biomaterial surface prior to interacting with host cell. Therefore, before the device is ready for implantation, the influence of cinnamaldehyde to the property of the composite, especially its surface characteristics, needs to be investigated. The aim of this research was to investigate the effect of cinnamaldehyde on the surface topography, contact angle, and surface roughness of POP-hydrogel CaCO<sub>3</sub> scaffold. The results indicated that cinnamaldehyde increased the contact angle, increased surface roughness of the POP-hydrogel, and seem to be homogenous in all surfaces.

**Keywords:** cinnamaldehyde; POP; CaCO<sub>3</sub> hydrogel; surface characteristics; bone substitute

### 1. Introduction

There have been a variety of ceramics used to treat bone defects ([Anzelme, 2000](#); [Chao et al., 2005](#)). One of them is calcium sulphate (CS) or POP (Plaster of Paris), known as a resorbable material that has shown the ability to enhance bone regeneration ([Cirotteau, 2001](#)). However, there is a disadvantage in using calcium sulphate related to its fast resorption rate during osteogenesis process, making it unable to provide a long-term three-dimensional framework ([Fenaroli, 2011](#); [Dewi et al., 2013](#); [Dewi et al., 2015](#)). To solve this problem, in the previous studies a biocompatible and osteoconductive hydrogel calcium carbonate (CaCO<sub>3</sub>) has been incorporated into calcium sulphate formulations ([Gomes et al., 2011](#); [Dewi et al., 2015](#)).

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From biomedical perspective, the implantation of medical devices often leads to foreign body reaction related to the accumulation and activation of inflammatory cell to the implant area. It must be noted that bone implant surgery must be considered for its increased infection risk after the procedure. Compared to bone, soft tissues are generally considered to show a more severe inflammatory response (Hallab et al., 2001; Higuera et al., 2015).

In view of the phenomenon, it would certainly be advantages if essential oil which has been known to exhibit anti-inflammatory agent, named cinnamaldehyde (CA), as described previously (Jamali et al., 2002; Kim et al., 2010) was incorporated into an implant device. Interesting results were shown when cinnamaldehyde was loaded in PLGA hydrogel (Gomes et al., 2011) and hydrogel CaCO<sub>3</sub> (Dewi et al., 2013). It was found that the incorporation of cinnamaldehyde is beneficial as an anti-microbial and anti-inflammatory agent (Dewi et al., 2015; Dewi et al., 2017). However, since cinnamaldehyde have both lipophilic and hydrophilic sides, cinnamaldehyde can affect the mechanical and surface properties of the composite when they were mixed. Meanwhile, surface properties, especially surface chemistry, hydrophilicity, and surface topography, influence the interaction between cells and substrate to the environment surrounding the material (Pal et al., 2009) because in a living host, blood plasma is the first component that contact to implant material. Further rapid adsorption of plasma protein happens onto the surface of biomaterial prior to cell attachment, spreading, proliferation, and differentiation (Jimbo et al., 2010).

Surface topography and hydrophilicity may influence the attachment of cells in different ways. Hydrophilicity, as a resultant of surface chemistry, is correlated to the wettability of the implant surface (Gittens et al., 2014). The material is categorized as hydrophilic when the contact angle between the material and water drop is lower than 90° (Yulianto and Margareta, 2014). Hydrophilic surfaces are important to promote good environment for bone formation (Boyan et al., 2017). Meanwhile, smooth surfaces may allow the cells to attach and spread more than on rough surfaces. In fact, the high wettability with microrough surface stimulates more anti-inflammatory cytokine release by macrophages than the hydrophilic but smooth surface (Hotchkiss et al., 2016).

Apart from other challenges in biomedical area (Elfani and Putra, 2013; Krisanti et al., 2019; Sahlan et al., 2019; Barleany et al., 2020), Based on the above framework, it is known that surface characteristics are critical point for the biological cascade upon implantation. In other words, the success of the implant depends on the materials surface and cells interaction. Therefore, the data on surface characteristics were significant to be investigated. The overall objective of the current study was to evaluate the effect of loaded cinnamaldehyde in hydrogel CaCO<sub>3</sub> incorporated into POP to their surface topography, contact angle, and surface roughness.

## 2. Methods

Upon the protocol development and approval, specimens were prepared and subjected for Fourier Transform Infrared (FTIR) analysis, surface topography analysis, contact angle measurement, and surface roughness analysis.

### 2.1. Specimen Preparation

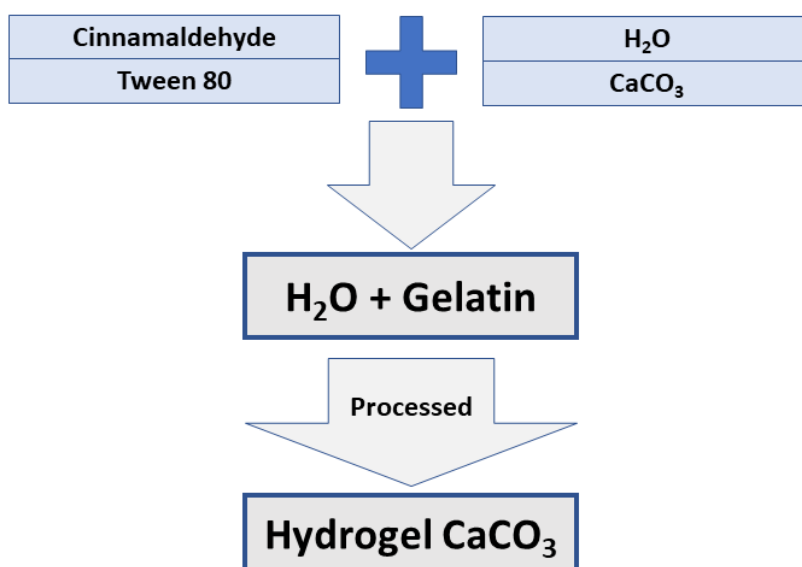
Gypsum (CaSO<sub>4</sub>.1/2H<sub>2</sub>O) or POP and calcium carbonate (CaCO<sub>3</sub>) were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Type B Gelatin was provided by Nitta Gelatin Inc., Osaka, Japan and cinnamaldehyde was provided by Merck, Germany. All other chemicals were of highest grade of commercially available ones.

Firstly, a 10ml Tween 80 solution (Sigma Aldrich, Germany) with 4ml cinnamaldehyde was stirred for 30 minutes to result 4% cinnamaldehyde. Subsequently, 40ml H<sub>2</sub>O was added in 2.5gr CaCO<sub>3</sub> (stirred for 1 hour). The 4% cinnamaldehyde solution was then added into the CaCO<sub>3</sub> emulsion. The mixture was called cinnamaldehyde-CaCO<sub>3</sub> solution. In the next step, 5gr gelatin was swelled inside 46ml H<sub>2</sub>O to prepare hydrogel.

**Table 1** Powder composition

Specimens	Powder Composition (in wt.%)	
	POP	Cinnamaldehyde crosslinked hydrogel CaCO <sub>3</sub> microsphere
POP	100	0
POP/HCin-075	75	25
POP/HCin-050	50	50

The swollen gelatin was then mixed with the cinnamaldehyde-CaCO<sub>3</sub> solution in 37° water bath continued by stirring for 2 hours. After pH was adjusted at 7.4, the solution was put into refrigerator for 24 hours at -20°C temperature and continued by freeze drying for 72 hours. Figure 1 shows the procedure of cinnamaldehyde crosslinked hydrogel preparation. The results of the hydrogel preparation were checked by FTIR spectroscopy, referred to the previous study (Dewi et al., 2013).



**Figure 1** Procedure of cinnamaldehyde crosslinked hydrogel CaCO<sub>3</sub> preparation.

Freeze dried hydrogel CaCO<sub>3</sub>-cinnamaldehyde blocks were grounded to make hydrogel beads. Through 150µm mesh, the beads were sieved and added to CaSO<sub>4</sub>.1/2 H<sub>2</sub>O powder in 25 and 50 wt.% compositions. These compositions were notified as POP/HCin-075 (25% addition of hydrogel microsphere) and POP/HCin-050 (50% addition of hydrogel microsphere), respectively. After that, the powders were applied to prepare cylindrical

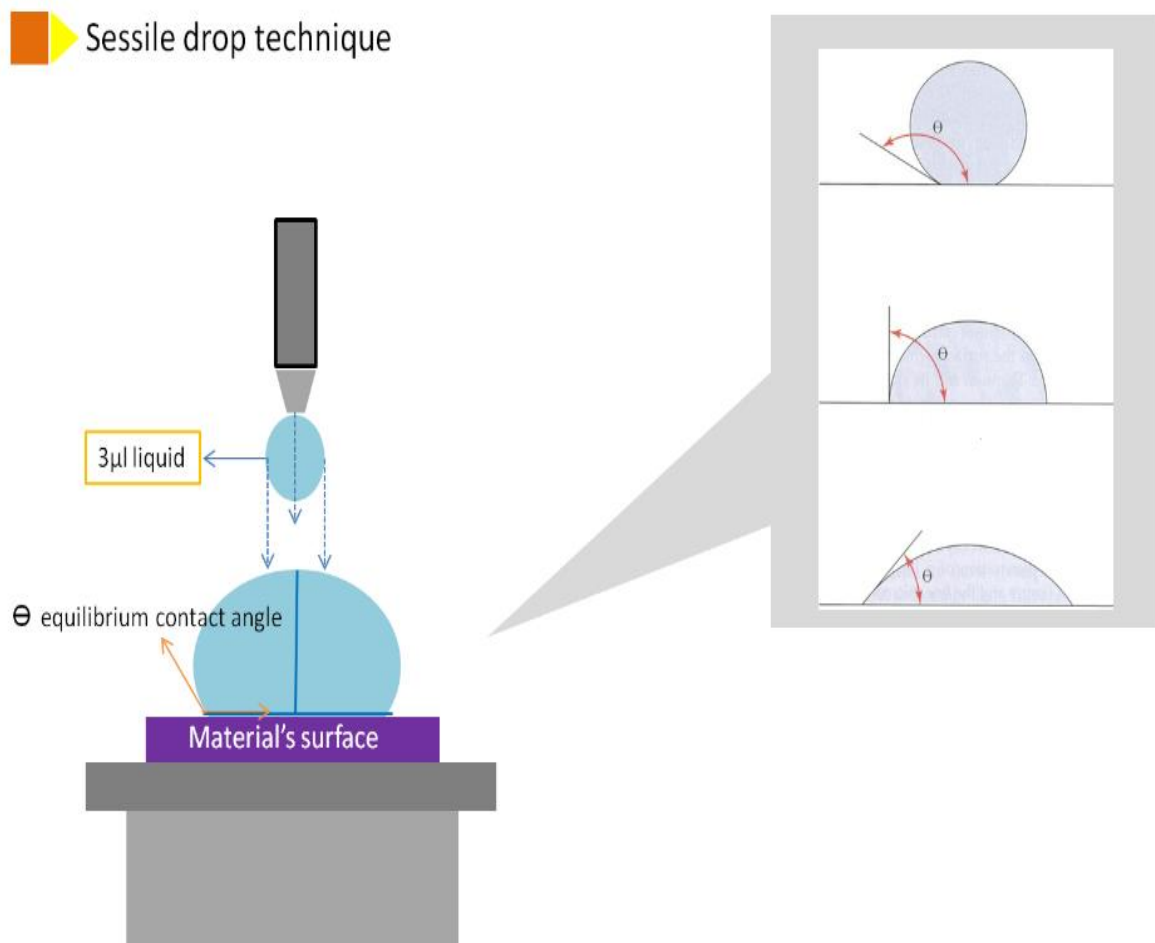
specimens for the various assays using a water/powder ratio (W/P) of 1/2. The cylindrical specimens were put in an incubator at 37°C for 24h to condition them to set completely. Table 1 shows the composition of the specimen powder.

### 2.2. Surface Topography Analysis

Microstructurally, the specimen surface was analysed by scanning electron microscopy (SEM) using a JEOL-JSM-T300 (Tokyo, Japan) at 20kV linked to an Energy Dispersive X-ray Spectrometer (EDS). The setting of 20kV accelerating voltage, approximately 20°C temperature, and the column vacuum  $7 \times 10^{-4}$  Pa were applied to visualize the surface morphology. Prior to measurement, the specimens were dried and gold layer sputter-coated.

### 2.3. Contact Angle Measurement

A sessile drop approach was implied to measure contact angle of the specimens by depositing a small drop of PBS on the composite disk (Figure 2). A customized home-made device connected with digital camera was used to capture interaction between liquid and composite disk surfaces. The image resulted from the drop profile was edited and optimized with image-J analysis software. The angle between the surface of the specimen and tangent line at the point of contact of the PBS droplet with the surface was defined as contact angle (Park and Zhao, 2004; Peng and Li, 2014) and tabulated for the purpose of data analysis.



**Figure 2** Schematic Diagram of the Contact Angle Measurement Process (Peng and Li, 2014).

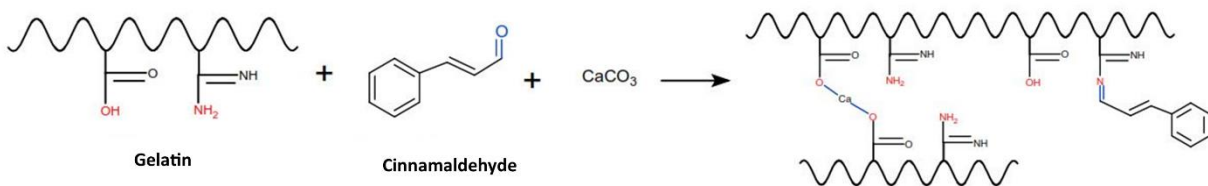
### 2.4. Surface Roughness Analysis

The surface roughness tester SJ-201P, Japan was used to measure surface roughness. Scan were performed on both sides of the samples (n=5).

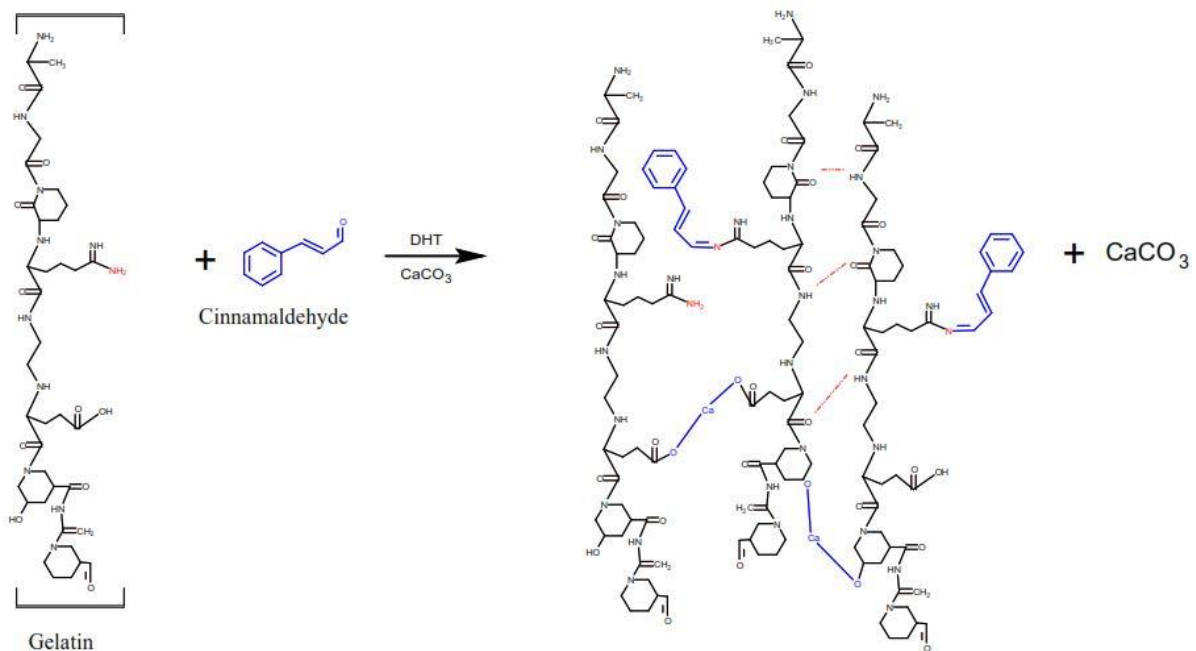
## 3. Results and Discussion

### 3.1. Hydrogel Formation

The powder composed of POP and hydrogel CaCO<sub>3</sub> were successfully developed. The composites were notified as POP/HCin-075 (25% addition of hydrogel microsphere) and POP/HCin-050 (50% addition of hydrogel microsphere), respectively. Figure 3 and 4 show the possible reactions that occur between cinnamaldehyde, CaCO<sub>3</sub>, and gelatin. Gelatin contains a hydroxyl group (OH<sup>-</sup>) and an amine group (NH<sub>2</sub>) which have an active side that can bind to the ions that are released around it. As for CaCO<sub>3</sub>, when dissolved with water, CaCO<sub>3</sub> turns into Ca<sup>2+</sup> and CO<sub>3</sub><sup>-</sup> ions. The Ca<sup>2+</sup> ions bind with double O ions from the hydroxyl group of gelatin. Oxygen element in cinnamaldehyde is released and bound to H<sup>+</sup> of the amines in gelatin, referring to a condensation reaction, so that the cinnamal which loses O forms a Schiff base imine (C = N) bond with gelatin.

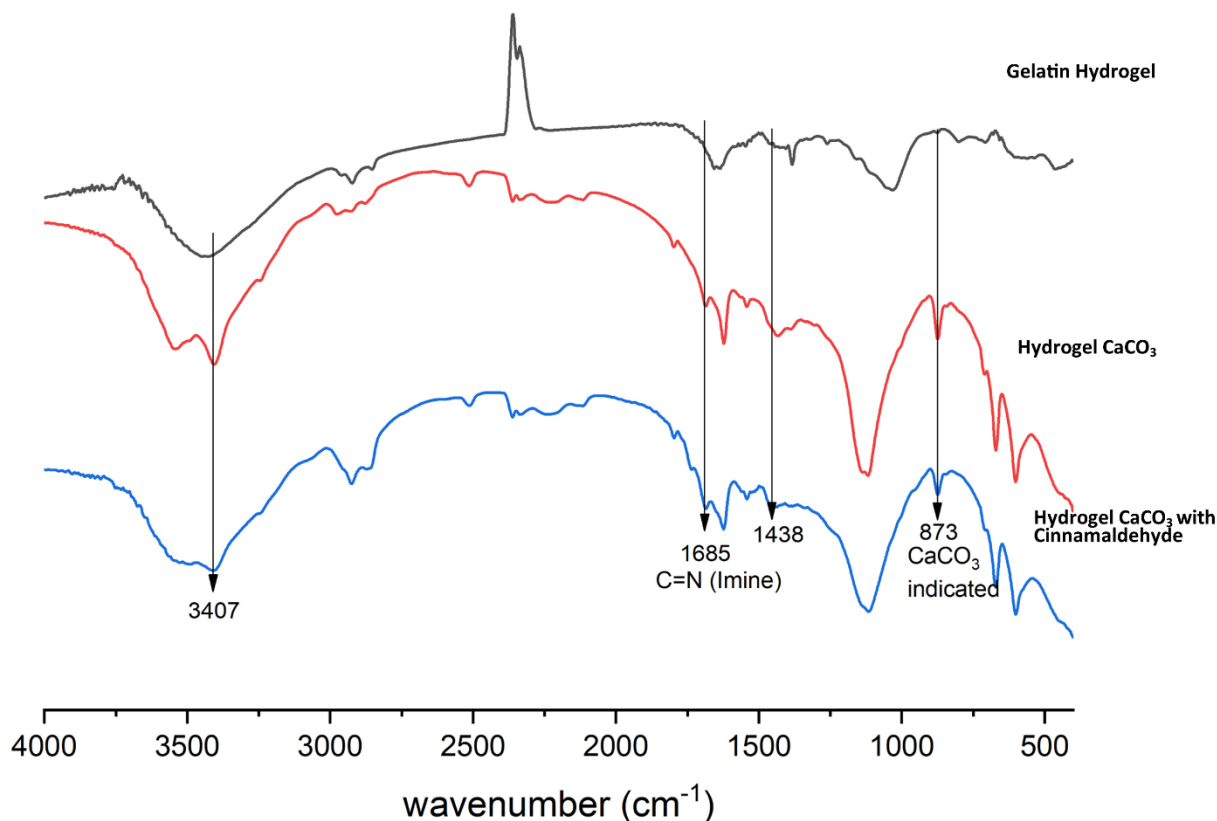


**Figure 3** Synthesis reaction between gelatin, cinnamaldehyde, and CaCO<sub>3</sub>.



**Figure 4** Synthesis reaction between cinnamaldehyde with hydrogel CaCO<sub>3</sub> continued by physical crosslinking by de- hydrothermal treatment.

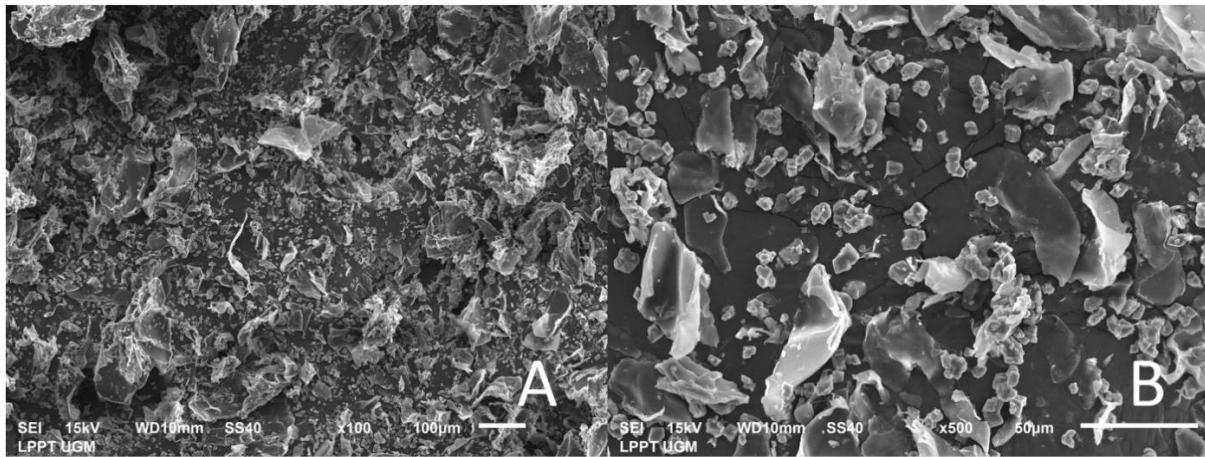
The FTIR confirmation (Figure 5) was done to analyse the results of cinnamaldehyde crosslinked hydrogel. It was shown that cinnamaldehyde is bound to hydrogel and forms an imine bond (C=N) at wave number of  $1685\text{cm}^{-1}$ . The formation of imine bond reduces the N-H stretching vibration of the gelatin as shown at  $3407\text{cm}^{-1}$  wave number. After FTIR confirmation for the hydrogel, the cylindrical specimens for the various assays using a water/powder ratio (W/P) of  $\frac{1}{2}$  were then prepared, incubated at  $37^\circ\text{C}$  for 24h to achieve complete setting, then analysed for the following results.



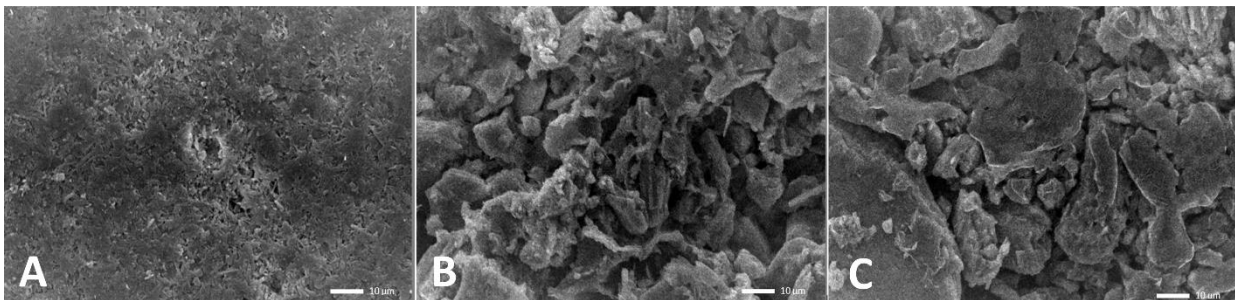
**Figure 5** FTIR spectra confirmation of the gelatin hydrogel, hydrogel CaCO<sub>3</sub>, and hydrogel CaCO<sub>3</sub> crosslinked with cinnamaldehyde.

### 3.2. Microstructure of the Composite

Figure 6 shows the micrograph of hydrogel CaCO<sub>3</sub> loaded with cinnamaldehyde, before being combined with POP. It was observed from the figure that cinnamaldehyde was dispersed homogeneously inside hydrogel system. The addition of Tween 80 seemed to be effective to homogeneously dispersed hydrophobic cinnamaldehyde. Figure 7 shows the surface topography after combining hydrogel CaCO<sub>3</sub> that loaded by cinnamaldehyde with POP. Pore size and porosity of the scaffold are two important factors that will influence cells growth in the scaffold and extracellular matrix formation (Peter et al., 2010). Scanning electron microscope showed that hydrogel calcium carbonate with cinnamaldehyde caused the POP surface topography to have rough texture. The advantage of rough texture is the increased porosity needed for cell to grow.



**Figure 6** Scanning electron microscopy of the cinnamaldehyde loaded hydrogel CaCO<sub>3</sub> at 100X (A) and 500X (B) magnitude.



**Figure 7** Scanning electron microscopy of the composite POP and hydrogel CaCO<sub>3</sub> with different ratio, POP-100 (A) POP/HCin-075 (B), and POP/HCin-050 (C), at 1000X magnitude.

### 3.3. Contact Angle

Table 2 shows the results of contact angle measurement by sessile drop method. It was not possible to measure air- water contact angle of the POP (N/A) since the sessile drop water on the surface of the POP was resorbed very fast. The result of the study showed contact angle of both POP/HC-050 and POP/HC-075 was less than  $<90^\circ$  showing hydrophilicity.

**Table 2** Contact angle of the composites

	POP	POP/HCin-075	POP/HCin-050
<b>Contact Angle</b> (Average $\pm$ SD)	N/A	$76.60 \pm 1.85$	$85.50 \pm 1.54$
<b>Surface Roughness</b> (Average $\pm$ SD)	$1.216 \pm 0.09$	$13.80 \pm 0.29$	$14.06 \pm 0.21$

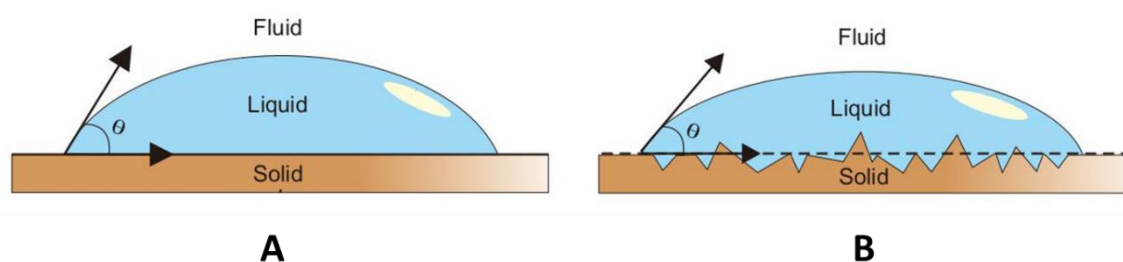
The finding corroborates with the theory that hydrogel system is known to be hydrophilic (shown by contact angle  $<90^\circ$ ). This is due to macromolecular chains of gelatin polymer (being a hydrophilic polymer since the presence of amide and carboxyl groups) is hydrolyzed quickly in the presence of water (Pogorzelskia et al., 2012). The result also showed that hydrogel addition to the POP composite enhanced water barrier properties of polymer-based film due to their hydrophobicity. The POP/HCin-075 has a slightly hydrophilic ( $76.60 \pm 1.85$ ) than the POP/HCin-050 ( $85.50 \pm 1.54$ ) but the differences were not statistically significant ( $p > 0,05$ ). This may be because cinnamon as essential oils have water barrier properties (Supova, 2009).

In view of two materials bonding or adherence, wetting is an important factor. Wetting depends on the energies or surface tension of the interfaces between two materials. Based on interfacial interaction concepts, wetting is often characterized by a liquid drop and solid surface formed contact angle. So far, a conventional method to evaluate wettability and surface energy is a drop shape analysis (Yulianto and Margareta, 2014). Wetting depends on the hydrophilicity or polarity. Hydrophilicity enables a molecule to transiently bond with water through hydrogen bonding. Oppositely, a hydrophobic substance interacts within themselves and with other substances through van der Waals forces and have low or no capacity to form hydrogen bonds (Tung et al., 2008; Youn et al., 2008; Wu et al., 2009; Yulianto and Margareta, 2014). Hydrophilicity influences the adsorption of blood protein (Vogler, 2012; Xu et al., 2016) that will promote cellular attachment onto the material surface (Thomas and Puleo, 2008).

Supova (2009) studied the contact angle between polymer and HA and the result showed that the polymers studied are found to exhibit lower contact angles ( $60^\circ$ ) on the ceramic. It is in line with the previous studies (Ojagh, 2010; Park and Zhao, 2004) which found that the hydrophilicity of the chitosan films decreased by the addition of cinnamon. The decrease of hydrophilicity might be due to moisture content value of the film caused by the loss of free amino and hydroxyl groups (Zaika, 1988).

### 3.4. Surface Roughness

The result of this study indicated that both groups showed almost the same surface roughness value. The POP/HCin-075 has a slightly rough surface ( $13.80 \pm 0.29$ ) than the POP/HCin-050 ( $14.06 \pm 2.05$ ) but the differences were not significant statistically ( $p > 0,05$ ). This indicated that adding hydrogel  $\text{CaCO}_3$ -cinnamaldehyde improved the surface to be smoother but not influenced the surface roughness significantly (Table 2).



**Figure 8** Young contact angle on ideal surface (A) and the apparent contact angle on rough surface (B).



Material surface roughness or topography is an important factor influencing cellular adhesion. Hallab and co-workers (Zdolsek et al., 2007) confirmed that cellular adhesion is correlated with the biomaterial surface roughness and surface energy. Increased cellular adhesion is associated with increased surface roughness. In this point, the data also showed that materials with lower surface energy (i.e., polymer) has higher surface roughness. Meanwhile, the higher surface energy materials like a metal has a little change in cellular adhesion strength with increased surface roughness.

As previously explained, surface topography and hydrophilicity may influence the attachment of cells in different ways (Hotchkiss et al., 2016). The wettability of a liquid in contact with a material surface plays a crucial role in many applications, such as adhesion, coating, and painting. Meanwhile, the wettability is influenced by various parameters such as porosity, surface roughness, heterogeneity, and material surface [Shupe et al., 1998]. The contact angle on ideal surface is called Young contact angle, while contact angle on rough surface is called the apparent contact angle as described in Figure 8. Accordingly, when the contact angle values decrease, the surface roughness values increase (Yorur et al., 2017). On a hydrophilic surface such as wood, more roughness often means a larger surface area for liquid to spread [Piao et al., 2010].

#### 4. Conclusions

Surface property, especially surface chemistry, hydrophilicity, and surface topography were known to influence the interaction between cells and substrate to the environment surrounding the implant material. The study demonstrated that cinnamaldehyde as an anti-inflammatory agent has been successfully loaded to hydrogel CaCO<sub>3</sub> prior to incorporation of the hydrogel into POP to form POP- hydrogel CaCO<sub>3</sub> composite. The results indicated that adding cinnamaldehyde into the hydrogel system increased the contact angle, but it was still lower than 90° (hydrophilic). The surface roughness of the POP-hydrogel CaCO<sub>3</sub> also increased accordingly. The increased contact angle and surface roughness may influence blood protein adsorption and cell attachment, thus further investigation on the *in vitro* cytotoxicity and *in vivo* animal studies are awaiting in our laboratory.

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