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Effect of Cinnamaldehyde, an Anti-Inflammatory Agent, on the Surface Characteristics of a Plaster of Paris – $CaCO_3$ Hydrogel for Bone Substitution in Biomedicine

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Abstract. Combining an anti-inflammatory agent derived from a plant essential oil, such as cinnamaldehyde, with bioabsorbable and osteoconductive material as a bone substitute is a challenge in biomedical technology. In this study, cinnamaldehyde, a good anti-inflammatory agent with an aromatic α, β-unsaturated aldehyde derived from cinnamon, was loaded in composites of plaster of Paris (POP) and calcium carbonate ($CaCO_3$) hydrogel as a bone substitute. However, during blood–biomaterial interactions, which start after surgical implantation, blood protein adsorption to the biomaterial surface occurs prior to interaction with host cells. Therefore, before a device is ready for implantation, the influence of cinnamaldehyde on the property of the composite, especially its surface characteristics, needs to be examined. The aim of this research was to investigate the effect of cinnamaldehyde on the surface topography, contact angle, and surface roughness of a POP–$CaCO_3$ hydrogel scaffold. The results indicate that cinnamaldehyde increased the contact angle and surface roughness of the POP hydrogel, which seemed to be homogenous on all surfaces.

Keywords: Bone substitute; $CaCO_3$ hydrogel; Cinnamaldehyde; POP; Surface characteristics

1. Introduction

A variety of ceramics have been used to treat bone defects (Anzelme, 2000; Ooms et al., 2002; Orsini et al., 2004; Chao et al., 2005). One of them, calcium sulfate (CS) or plaster of Paris (POP), known to be a resorbable material, has shown the ability to enhance bone regeneration (Cirotteau, 2001). However, a disadvantage of using CS is related to its fast resorption rate during the osteogenesis process, making it unable to provide a long-term three-dimensional framework (Fenaroli, 2016; Dewi et al., 2013; Dewi et al., 2015). To solve this problem, in previous studies, biocompatible and osteoconductive hydrogel calcium carbonate ($CaCO_3$) has been incorporated into CS formulations (Gomes et al., 2011; Dewi et al., 2015).

From a biomedical perspective, the implantation of medical devices often leads to a foreign body reaction related to the accumulation and activation of inflammatory cells in

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the implant area. Although there is an increased risk of infection after bone implant area. Although there is an increased risk of infection after bone implant surgery, compared to bone, soft tissues are generally considered to show a more severe inflammatory response (Hallab et al., 2001; Higueras et al., 2015).

In view of the phenomenon, it would be advantageous if cinnamaldehyde (CA), previously described as an essential oil and known to be an anti-inflammatory agent (Jamali et al., 2002; Kim et al., 2010, Jakethia et al., 2010), could be incorporated into an implant device. Interesting results have been found when CA was loaded in a PLGA hydrogel (Gomes et al., 2011) and a $CaCO_3$ hydrogel (Dewi et al., 2013). It was found that the incorporation of CA is beneficial as an anti-microbial and anti-inflammatory agent (Dewi et al., 2015; Dewi et al., 2017). However, since CA can be both lipophilic and hydrophilic, this can affect the mechanical and surface properties of a composite. Additionally, surface properties, especially surface chemistry, hydrophilicity, and surface topography, influence the interactions between cells and substrates in the environment surrounding implanted material (Pal et al., 2009) because in a living host, blood plasma is the first component to contact implant material. Further rapid adsorption of plasma protein occurs on the surface of biomaterial prior to cell attachment, spreading, proliferation, and differentiation (Jimbo et al., 2010).

Surface topography and hydrophilicity can influence the attachment of cells in different ways. Hydrophilicity, a result of surface chemistry, is correlated to the wettability of an implant surface (Gittens et al., 2014). A material is categorized as hydrophilic when the contact angle between the material and a water droplet is <90° (Yulianto and Margareta, 2014). Hydrophilic surfaces are important for promoting a good environment for bone formation (Boyan et al., 2017). Additionally, smooth surfaces allow cells to attach and spread more than rough surfaces, and high wettability combined with a microrough surface stimulates more anti-inflammatory cytokine release by macrophages than a hydrophilic but smooth surface (Hotchkiss et al., 2016).

Apart from other challenges in the 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 for biological cascade upon implantation. In other words, the success of an implant depends on the surfaces of the materials and cell interaction. Therefore, it is important to investigate surface characteristic data. The overall objective of the current study was to evaluate the effect of CA-loaded $CaCO_3$ hydrogel incorporated into POP on surface topography, contact angle, and surface roughness.

2. Methods

After protocol development and approval, specimens were prepared and analyzed by Fourier transform infrared (FTIR) spectroscopy for surface topography and surface roughness, and the droplet contact angle was determined.

2.1. Specimen Preparation

Gypsum ($CaSO_4.1/2H_2O$) or POP and $CaCO_3$ (Wako Pure Chemical Industries Ltd. (Osaka, Japan), Type B gelatin (Nitta Gelatin Inc., Osaka, Japan), and CA (Merck, Germany) were used for the sample preparation. All other chemicals were of the highest commercially available grade.

First, a 10 ml Tween 80 solution (Sigma Aldrich, Germany) with 4 ml CA was stirred for 30 min to obtain a 4% CA solution. Then, 2.5 g $CaCO_3$ was emulsified with 40 ml H_2O by stirring for 1 hour. The 4% CA solution was then added to the $CaCO_3$ emulsion, creating a

$CA–CaCO_3$ solution. In the next step, 5 g gelatin was swelled in 46 ml H_2O to prepare a hydrogel.

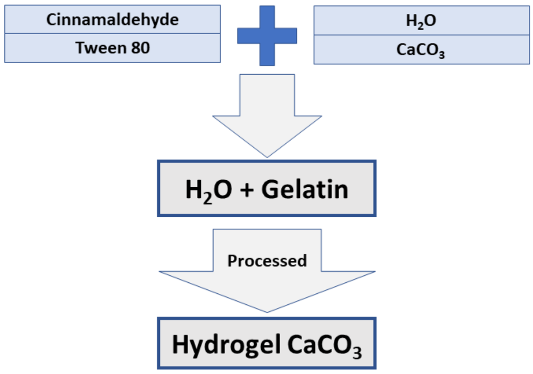

Figure 1 Procedure for incorporating cinnamaldehyde in a $CaCO_3$ hydrogel preparation

The swollen gelatin was then mixed with the $CA–CaCO_3$ solution in a 37°C water bath and stirred for 2 hours. After adjusting the pH to 7.4, the solution was refrigerated for 24 hours at −20°C and then freeze dried for 72 hours. Figure 1 shows the procedure used to prepare the hydrogel. The results of the hydrogel preparation were checked by FTIR spectroscopy, as described in a previous study (Dewi et al., 2013).

Table 1 Powder compositions

Specimen	Powder Composition (wt%)	
	Plaster of Paris (POP)	Cinnamaldehyde-loaded $CaCO_3$ hydrogel microspheres
POP	100	0
POP/HCin-075	75	25
POP/HCin-050	50	50

The freeze-dried $CA–CaCO_3$ hydrogel blocks were ground to make hydrogel beads. After sieving through 150-µm mesh, 25 and 50 wt% of the hydrogel microspheres were added to two separate $CaSO_4.1/2H_2O$ powders. These compositions were labeled POP/HCin-075 (25 wt% addition of hydrogel microspheres) and POP/HCin-050 (50 wt% addition of hydrogel microspheres), respectively. The powders were then used to prepare cylindrical specimens for the various assays using a water to powder ratio (W:P) of 1:2. The cylindrical specimens were placed in an incubator at 37°C for 24 h to completely set them. Table 1 shows the compositions of the specimen powders.

2.2. Surface Topography Analysis

The specimen surfaces were microstructurally analyzed by scanning electron microscopy (JSM-T300; JEOL, Tokyo, Japan) at 20 kV linked to an energy dispersive X-ray spectrometer. An accelerating voltage of 20 kV, ~20°C, and a 7×10^{-4} Pa column vacuum were applied to visualize the surface morphology. Prior to measurement, the specimens were dried and gold-layered by sputter coating.

2.3. Contact Angle Measurement

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

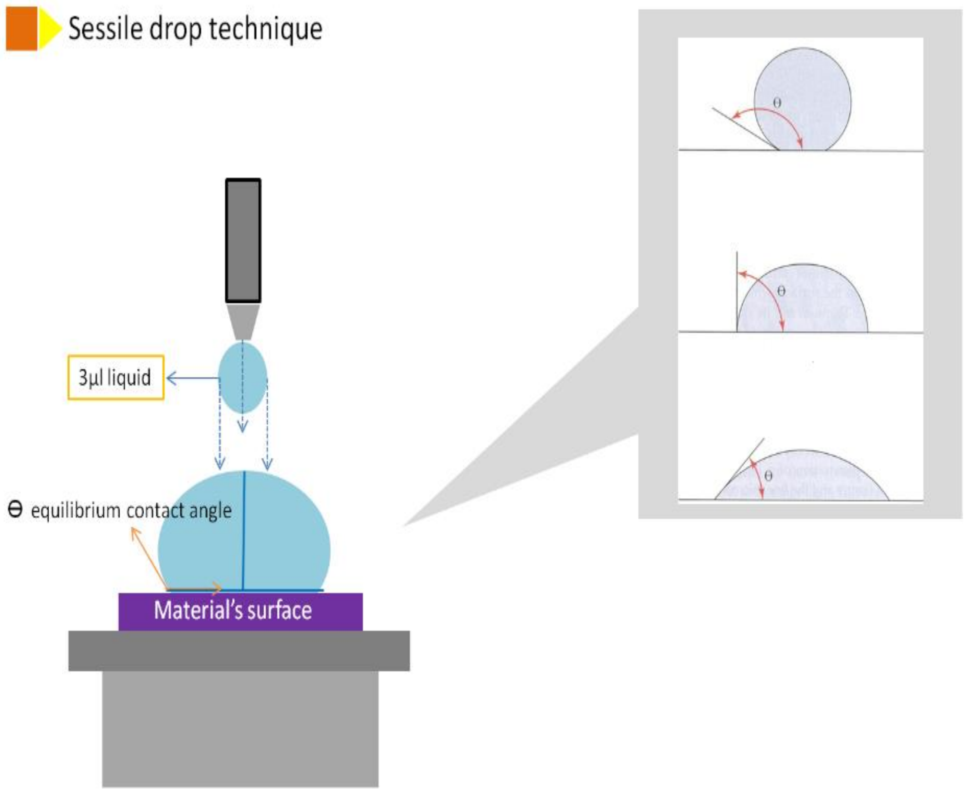

Figure 2 Schematic of the contact angle measurement process (after Peng and Li, 2014)

2.4. Surface Roughness Analysis

A surface roughness tester (SJ-201P; Mitsutoyo Co., Japan) was used to measure the surface roughness. Both sides of the samples were scanned (n = 5).

3. Results and Discussion

3.1. Hydrogel Formation

Plaster of Paris–$CaCO_3$ hydrogel powder was successfully developed. Figures 3 and 4 indicate the possible reactions between CA, $CaCO_3$, and gelatin. Gelatin contains a hydroxyl group and an amine group, which have active sites that can bind to ions. When $CaCO_3$ is dissolved in water, Ca^{2+} and CO^{3-} ions are produced. The Ca^{2+} ions bind with double-bonded O ions from the gelatin hydroxyl group. The oxygen in the CA is released and bound to the hydrogen ions (H^+) in the gelatin amines, known as a condensation reaction, so the CA, which loses O, forms a Schiff-base imine (C=N) bond with the gelatin (Da Silva et al., 2011).

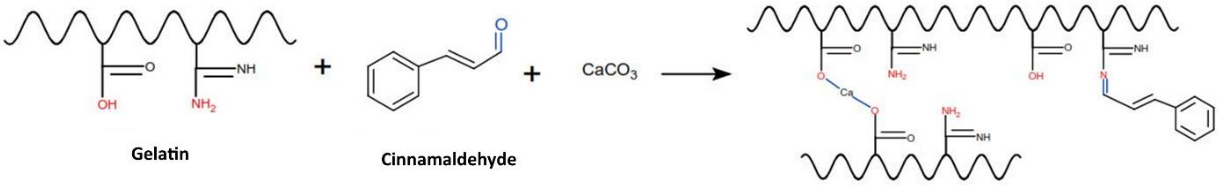

Figure 3 Synthesis reaction between gelatin, cinnamaldehyde, and $CaCO_3$

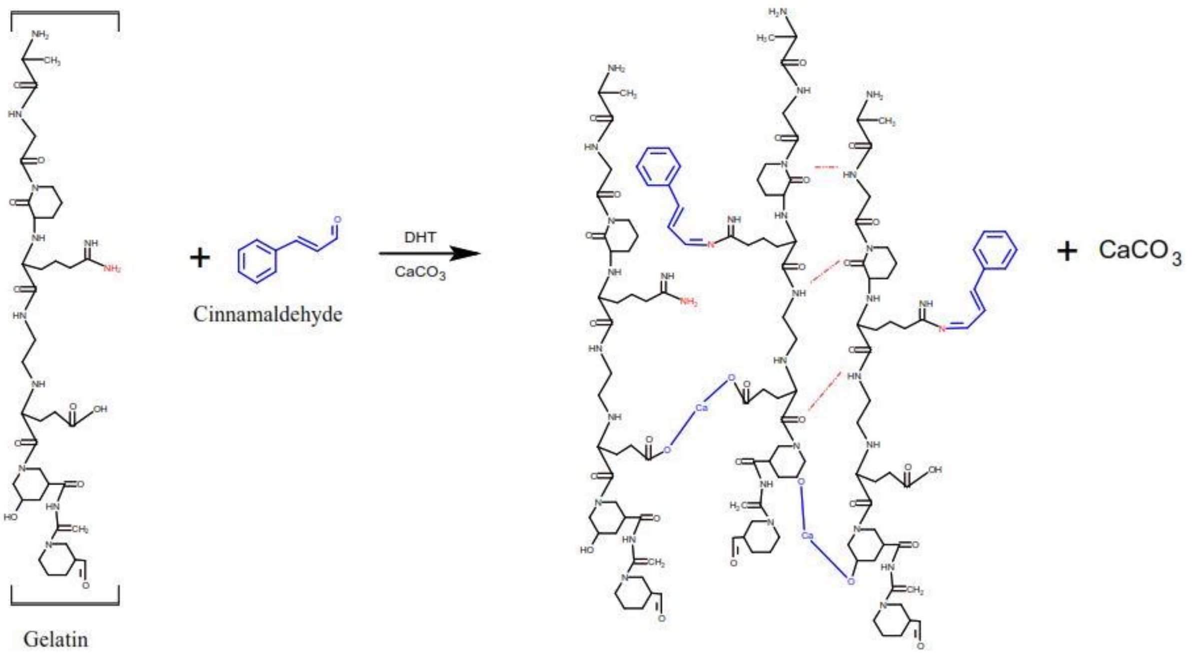

Figure 4 Synthesis of cinnamaldehyde and $CaCO_3$ hydrogel, continued by physical crosslinking through de-hydrothermal treatment

To analyze the results of the CA-crosslinked hydrogel, FTIR confirmation was undertaken (see Figure 5). The CA, bound to the hydrogel, formed an imine bond (C=N), seen at 1685 cm^{-1}. The formation of the imine bond reduced the N-H stretching vibration of the gelatin seen at 3407cm^{-1}. After FTIR confirmation of the hydrogel, cylindrical specimens using a W:P of 1:2 for the various assays were prepared and incubated at 37°C for 24 h for complete setting. They were then analyzed as follows.

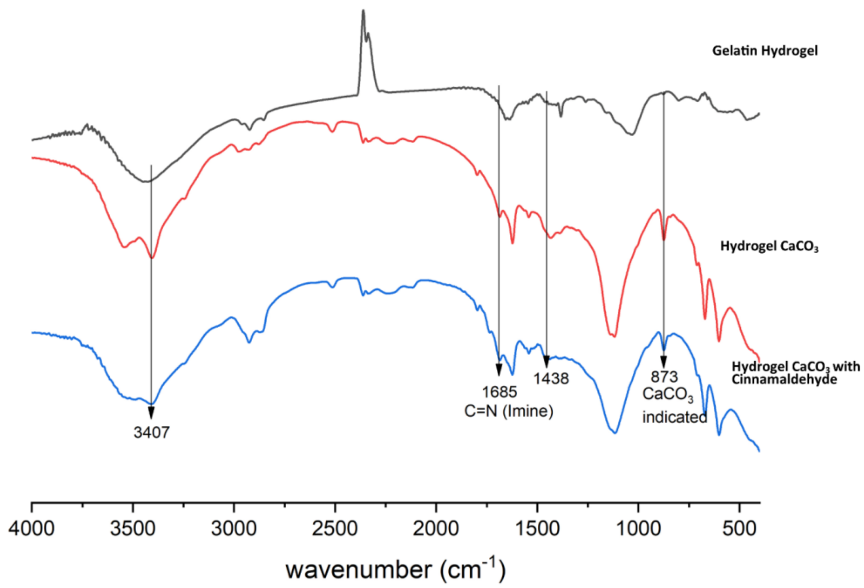

Figure 5 Fourier transform infrared spectroscopy spectra confirmation of the gelatin hydrogel, $CaCO_3$ hydrogel, and $CaCO_3$ hydrogel crosslinked with cinnamaldehyde

3.2. *Composite Microstructures*

Figure 6 shows a micrograph of the CA-loaded $CaCO_3$ hydrogel before being combined with POP. The CA was homogenously dispersed inside the hydrogel system. The addition of Tween 80 seemed to have effectively homogenously dispersed the hydrophobic CA. Figure 7 shows the surface topography after combining CA-loaded $CaCO_3$ hydrogel with POP. Scaffold pore size and porosity are two important factors that influence cell growth in scaffolds and the formation of an extracellular matrix (Peter et al., 2010). Scanning electron microscopy showed that the CA-loaded $CaCO_3$ hydrogel resulted in a rough POP topographic surface. The advantage of a rough texture is that it increases the porosity required for cell growth.

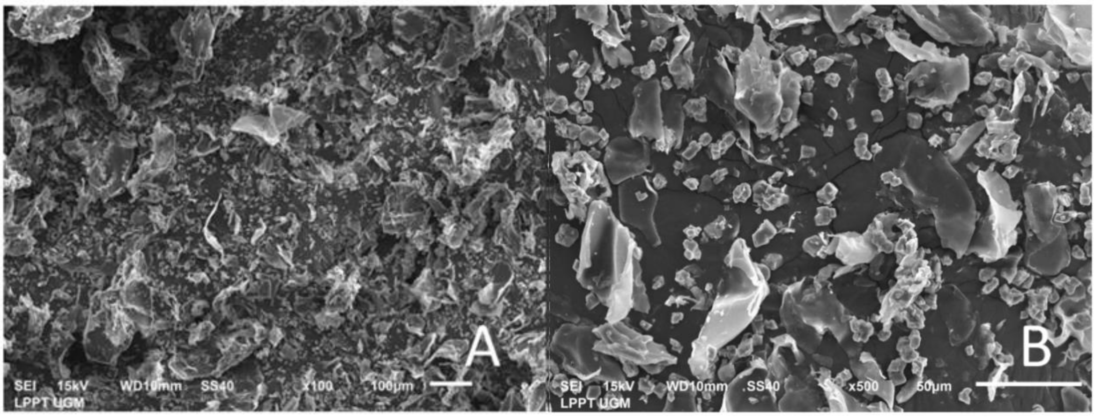

Figure 6 Scanning electron microscopy of the cinnamaldehyde-loaded $CaCO_3$ hydrogel at (A) 100× (B) and 500× magnification

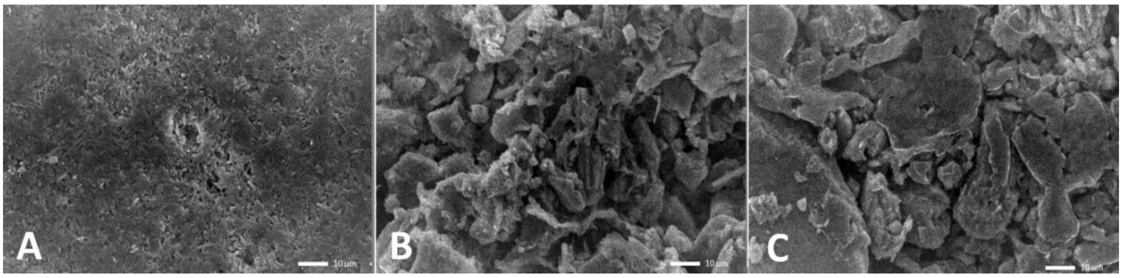

Figure 7 Scanning electron microscopy of the plaster of Paris composites containing different ratios of $CaCO_3$ hydrogel. (A) POP-100, (B) POP/HCin-075, and (C) POP/HCin-050 at 1000X magnification

3.3. *Contact Angle*

Table 2 shows the results of the contact angle measurements by the sessile drop method. It was not possible to measure the air–water contact angle of the POP because the sessile water drop was rapidly resorbed on the surface of the POP. The results showed that the contact angles of both POP/HCin-050 and POP/HCin-075 were <90°, indicating hydrophilicity.

Table 2 Contact angles of the composites

	Plaster of Paris (POP)	POP/HCin-075	POP/HCin-050
Contact Angle (Average ± SD)	N/A	76.60 ± 1.85	85.50 ± 1.54
Surface Roughness (Average ± SD)	1.216 ± 0.09	13.80 ± 0.29	14.06 ± 0.21

This finding corroborates the theory that the hydrogel system is hydrophilic (shown by a <90° contact angle). This is due to the rapid hydrolyzation of gelatin polymer macromolecular chains in the presence of water. Gelatin is a hydrophilic polymer because of the presence of amide and carboxyl groups (Pogorzelskia et al., 2012). The results also showed that the addition of the hydrogel to the POP composites enhanced the water barrier properties of the polymer-based film due to its hydrophobicity. The POP/HCin-075 was slightly more hydrophilic (76.60±1.85) than the POP/HCin-050 (85.50±1.54), but the differences were not statistically significant ($p>0.05$). This may have been because cinnamon, as an essential oil, has water barrier properties (Supova, 2009).

Wetting is an important factor for the bonding or adherence of two materials. Wetting depends on the energies or surface tensions at the interface between two materials. Based on concepts of interfacial interaction, wetting is often characterized by the contact angle between a liquid drop and a solid surface. Currently, the conventional method used to evaluate wettability and surface energy is drop shape analysis (Yulianto and Margareta, 2014). Wetting depends on hydrophilicity or polarity. Hydrophilicity enables a molecule to transiently bond with water through hydrogen bonding. In contrast, a hydrophobic substance interacts with itself and other substances through van der Waals forces, and they 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., 2014), which promotes cellular attachment to a material's surface (Thomas and Puleo, 2009).

Supova (2009), studying the contact angles between polymers and HA (hydroxyapatite), showed that the polymers exhibited lower contact angles (60°) on a ceramic. This is in line with previous studies (Ojagh et al., 2010; Park and Zhao, 2004) that found that the hydrophilicity of chitosan films decreased with the addition of cinnamon. This decrease in hydrophilicity might be due to the moisture content of the film caused by the loss of free amino and hydroxyl groups (Zaika, 1988).

3.4. Surface Roughness

The results of this study indicated that both groups exhibited almost the same surface roughness. The POP/HCin-075 had a slightly rougher surface (13.80±0.29) than the POP/HCin-050 (14.06±2.05), but the differences were not statistically significant ($p>0.05$). This indicated that adding CA-loaded $CaCO_3$ hydrogel improved the surface by making it smoother but did not significantly influence the surface roughness (Table 2).

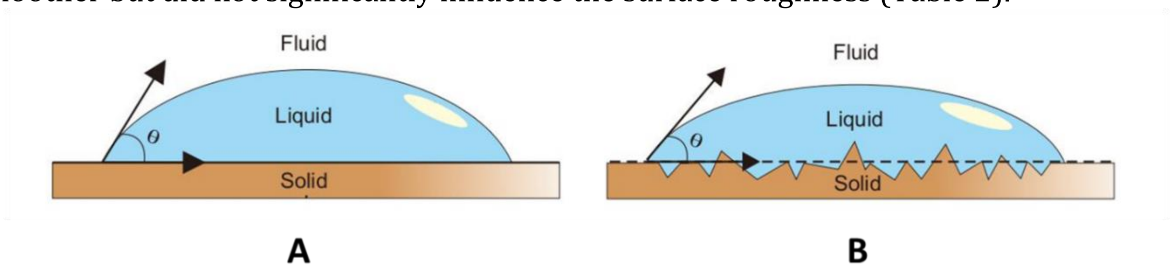

Figure 8 (A) Young contact angle on an ideal surface and (B) the apparent contact angle on a rough surface

Material surface roughness or topography is an important factor that influences cellular adhesion. Hallab and co-workers (Zdolsek et al., 2007) confirmed that cellular adhesion is correlated to biomaterial surface roughness and surface energy. Increased cellular adhesion is associated with increased surface roughness. The data from the current study showed that the materials with low surface energies (i.e. polymers) have higher surface roughness (Mazor et al., 2011; Mazzola et al., 2012). However, higher surface energy materials, such as metals, show little change in cellular adhesion strength with increasing surface roughness.

As discussed, surface topography and hydrophilicity can influence cell attachment (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, and wettability is influenced by various parameters, such as porosity, surface roughness, heterogeneity, and the material surface (Shupe et al., 1998). The contact angle on an ideal surface is called the Young contact angle, while the contact angle on a rough surface is called the apparent contact angle, as shown in Figure 8. Accordingly, when the contact angle decreases, the surface roughness increases (Yorur et al., 2017). On a hydrophilic surface, such as wood, greater roughness often means a larger surface area for liquid spreading (Meiron et al., 2004; Piao et al., 2010).

4. Conclusions

Surface properties, especially chemistry, hydrophilicity, and topography, are known to influence the interaction between cells and substrates in the environment surrounding implanted materials. This study demonstrated that CA as an anti-inflammatory agent can be successfully loaded into $CaCO_3$ hydrogel prior to the incorporation of the hydrogel into POP to form POP–$CaCO_3$ hydrogel composites. The results indicated that adding CA to a hydrogel system increased the contact angle, but it was still $<90^o$ (i.e. hydrophilic). The surface roughness of the POP–$CaCO_3$ hydrogel was also increased. Increased contact angle and surface roughness may influence blood protein adsorption and cell attachment; therefore, we propose carrying out investigations of the *in vitro* cytotoxicity and *in vivo* animal studies in our laboratory.

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