Interprof. J. Health Sci. 2020,18(1): 01-14.
ISSN (online) 2672-9423 ISSN (print) 2672-9628

EVALUATION AND CHARACTERIZATION OF A PVA-DURIAN HULL GUM WOUND DRESSING CONTAINING CENTELLA ASIATICA EXTRACT (ECA233)

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Received 9 October 2019; Accepted 15 August 2020

Abstract: Durian hull gum (DG) is isolated from the fruit-hulls of durian (*Durio zibethinus*), a biproduct of the food industry. DG has antibacterial properties, and can be used as an effective film-forming agent in the preparation of film-based wound dressings. *Centella asiatica* is a medicinal herb that has been used in Asia for over-two thousand years, however, the development of dosage forms has been limited. In this study we present the development and formulation of a wound dressing that contains a *Centella asiatica* extract (ECa233), produced by a film casting method using polyvinyl alcohol (PVA) 8% w/v as a polymer base combined with DG in various ratios (0.5%,1%, 3%). Each formulation was evaluated for its physical and chemical characteristics. Our results demonstrate that PVA supplemented with DG 3.0% w/v provided the best swelling capacity. Combination of PVA with DG at a ratio of 8.0:1.0% w/v resulted in the highest tensile strength. Increased concentration of DG, resulted in increased Young's modulus, a measure of material stiffness, but decreased the % elongation at the materials breaking point. The study also found that PVA combined with DG resulted in higher levels of controlled release, and dressing swelling capacity than the control (PVA alone).

Keywords: Durian hull gum, Wound dressing, *Centella asiatica* extract (ECa233), PVA

INTRODUCTION

Durian is an economically important seasonal tropical fruit grown throughout Southeast Asia and is one of the most expensive fruits in the region. There are nine edible species of durian with over 300 named varieties in Thailand alone (Baraheng and Karrila, 2019; Ketsa, 2018). Currently only *Durio zibethinus* L. is extensively farmed and harvested commercially. Only around a third of the durian fruit is edible and durian hulls/ seeds are a bioproduct of this food industry which have historically been discarded (Penjumras et al., 2014; Amid and Mirhosseini, 2012). Durian hull gum (DG) isolated from fruit-hulls of durian contain a polysaccharide gel (PG) which can be used as an efficient film forming agent to prepare film-based wound dressings. DG displays antibacterial properties against *Staphylococcus aureus* and *Staphylococcus epidermidis*, present on the human skin surface, which are common causes of wound infection. In an *in vivo* study, DG-based wound dressing-treated wounds showed increased rapidity of wound closure, and lower tissue reactions to those derived from pig skin, a medium which has been increasingly employed over the last decade due to its ability to reduce infection, reduce pain sensation and to reduce water loss.

Centella asiatica (Linn.) (Also known as Asiatic pennywort, Indian pennywort, gotu kola [China], and mandukpani/ jahbrahmi [India]) has been used as a traditional medicine for

over 2000 years. Several pharmacological effects relating to wound healing have been ascribed to *C. asiatica*, including: anti-inflammatory, antipsoriatic, antiulcer, antibacterial, and antifungal effects. Traditional uses in wound healing are now being backed by modern research which indicates that the principal active compounds of *C. asiatica* are triterpenoids (Saponins) and their sapogenin derivatives which inhibit collagen production at the wound site (Ruszymah et al., 2012; Azis et al., 2017). The *Centella asiatica* extract ECa233 contains triterpenoid glycosides as the major active compounds of which more than 80% are asiaticoside and madecassoside (1.5 ± 0.5:1.0). Use of a ECa233 gel preparation for treatment in wound healing has previously been reported (Koranit Wannarat1 MHT, 2009). However, this preparation was limited due to difficulty in controlling dosage.

Polyvinyl alcohol (PVA, also known as PVOH, or PVAL) is a synthetic hydrogel polymer. It is odorless, solvent-resistant, biocompatible and toxicologically safe. It has been used as an excipient (vehicle) in a range of pharmaceutical products. However, it has some limitations, in terms of control of drug release, air permeation and exudate absorption. (Kataria, 2014). Combination of PVA and other hydrogel polymers could significantly improve these limitations.

Use of wound dressings as a topical dosage form for controlled drug release, improved patient compliance, enhanced absorption of wound exudate and decreased local irritation from an antiseptic solution. It has been reported that such wound dressings can reduce the wound healing rate (Yang, 2010).

In this study, we aimed to develop and formulate a PVA- and DG-based wound dressing incorporating *Centella asiatica* extract (ECa233), using a film casting method, and to evaluate its physical and chemical properties.

MATERIALS AND METHODS

Materials

ECa233 was kindly provided by Assoc. Prof. Mayuree H. Tantisira Ph.D. (Faculty of Pharmaceutical Science, Burapha University, Chonburi, Thailand). Durian hull was donated from the Chonburi market, Chonburi, Thailand. PVA Mw 130,000 (99% hydrolyzed) was purchased from Sigma-Aldrich. HPLC reagents and solvents were Analytical Reagent (AR) grade and obtained from Honey Well.

Preparation of Durian Hull Gum (DG)

Polysaccharide form durian hull was extracted using a modified method as described by Sanya Hokputsa et al. (Hokputsa et al., 2004). Briefly, clean durian hulls were ground, and oven dried at 60 °C. The resultant durian hull powder was then extracted with water and adjusted to pH 4.5 with citric acid, followed by heating for 20 min at 90-100 °C. The mucilage was then filtered and evaporated using a solvent evaporator at 70 °C until completely desiccated. Three fold volumes of acidified ethanol **(**pH3**.**5**)** was then used to precipitate the extracts by acid-ethanol precipitation. The obtained extract was collected and washed with 75% non-acidified ethanol twice followed by a single wash with 95% non-acidified ethanol. After drying at 70 °C for 4 h, the extracts were grinded with blender. Figure 1 illustrates the appearance of the final product.

Figure 1. Durian hull gum after being dried and ground.

Preparation of Films

Wound dressings were prepared using a film casting method, as follows. A PVA solution 8% (w/v) was prepared by dissolving PVA in distilled water and heating at 110 °C for 3 h. DG was then added to the PVA solution at either 0.5, 1 or 3% w/v as indicated. ECa233 1% (w/v), and glycerin 5% (w/v) which was used as plasticizer, were then added. A fixed volume (15 ml) of the final polymeric solution was incorporated with ECa233 and the plasticizer, and was then poured into a glass petri dish and oven dried at 50 °C for 12 h. All wound dressing formulations tested are indicated in Table 1 and Table 2.

Table 1. Wound dressing composition.

Formula	F00	F01	F02	F03
PVA (% w/v)	8.0	8.0	8.0	8.0
DG (% w/v)	-	0.5	1.0	3.0
Glycerin (% w/v)	5.0	5.0	5.0	5.0
Methylene blue	qs	qs	qs	qs
Water qs to (ml)	100	100	100	100

Table 2. Composition of wound dressings containing ECa233.

Formula	FA00	FA01	FA02	FA03
PVA (% w/v)	8.0	8.0	8.0	8.0
DG (% w/v)	-	0.5	1.0	3.0
Glycerin (% w/v)	5.0	5.0	5.0	5.0
Ethanol (% w/v)	5.0	5.0	5.0	5.0
ECa233 (% w/v)	1.0	1.0	1.0	1.0
Water qs to (ml)	100	100	100	100

Determination of Physical Appearance

The color, homogeneity, and smoothness of the wound dressings were examined by visual inspection. The morphology of the surface area of the film was analyzed by scanning electron microscope (SEM; LEO/1450 VP-EDS, UK).

Determination of Compatibility

Differential Scanning Calorimetry (DSC; Model DSC 822, Mettler Toledo, LLC, Germany) analysis was performed for PVA, DG, ECa233 and the mixture of PVA, DG and ECa233. Fourier transform infrared (FTIR) spectroscopy (Nicolet 6700, Thermo Scientific, UK) was used to characterize the functional groups present within the wound-dressing films.

Determination of Mechanical Properties

The tensile strength and the percentage of elongation at the films breaking points were measured using a tensile tester (Testometric Micro 350, Rochdale, UK). The film was cut into strips of 1 x 5 cm^2 size and each batch was measured for thickness at five different points. Test strips were mounted onto a tensile tester with an initial grip separation of 3.0 cm. Following application of a force of 50 N at a speed of 100 mm/min, the tensile strength, % elongation of the sample at the breaking point and Young's modulus were obtained from the average values of at least three independent samples. These values were calculated from equations 1, 2 and 3, respectively (see below).

$$\text{Tensile strength } (N/mm^2) = \frac{\text{Break force (N)}}{\text{Initial cross section are of the sample } (mm^2)} \qquad \text{Equation 1}$$

$$\%\ \text{Elongation at break} = \frac{\text{Increase in length} \times 100}{\text{Original length}} \qquad \text{Equation 2}$$

$$\text{Young's modulus } (N/mm^2) = \frac{\text{Force} \times \text{Length}}{\text{Extension} \times \text{Area}} \qquad \text{Equation 3}$$

Determination of Swelling Properties

The method to determine the swelling index of the wound dressings was modified from Shabbir et al. (Maryam Shabbir, 2017). Preweighed patches 2x2 cm^2 diameter representing each formulation were placed into phosphate buffer pH 6.8 in 10cm^2 petri dishes. After the indicated defined time intervals, the excess phosphate buffer on the patch-surface was removed. The swollen patches were then weighed accurately and the percentage swelling index was calculated according to equation 4:

$$\textbf{\%}\ \text{Swelling index} = \frac{(W_2 - W_1) \times 100}{W_1} \qquad \text{Equation 4}$$

where W_1 is initial weight of patch and W_2 is weight of patch after water absorption at the indicated time point. All swelling tests were performed in triplicate. Data are presented as the mean ± standard deviation (SD).

Determination of In Vitro Drug Release

In vitro drug release was calculated using the method from Mendes *et al.* (Mendes AC, 2016). Each wound dressing formulation was cut into a 2x2 cm^2 diameter patch, which was then immersed into 25 ml of phosphate buffer pH 6.8 and shaken at 100 rpm on an orbital shaker (NB-101M; Benchmark Scientific, Edison, NJ, USA) for 6 h**.** Drug release into the sampling solution was analyzed by HPLC (Agilent Technologies, Inc., CA, USA) at the indicated time points, at a wavelength of 220 nm (Namviriyachote et al., 2019).

RESULTS AND DISCUSSION

Analysis of Wound Dressing Physical Appearance

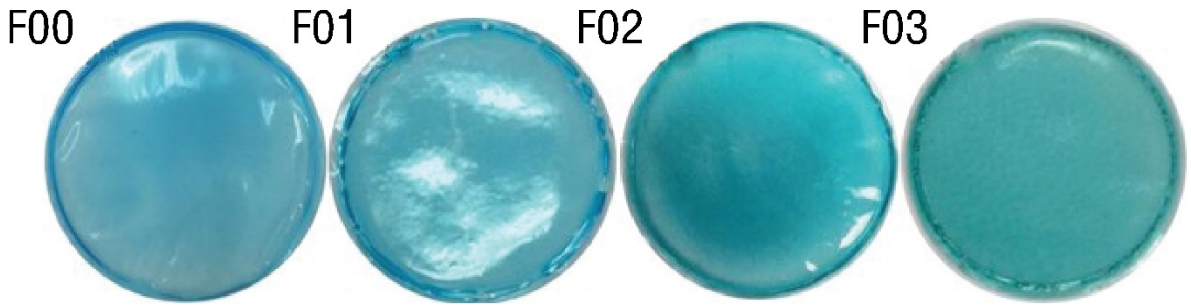

Figure 2. Physical Appearance of Wound Dressing Formulations.

Figure 3. Physical Appearance of Wound Dressings Containing ECa233.

Comparison of the texture morphology between the PVA film and the DG/PVA formulations, indicated that the clear, flat and homogenous properties of the PVA film were not altered by the addition of DG at lower concentrations. They were however altered in the F03 formulation producing a film that was opaque and exhibited PVA-DG separation resulting in small spots on the film (Figure 2).

Following addition of Eca233 into the DG/PVA formulations, the FA00-FA02 films remained clear and unaltered without precipitation of the added extract as observed in the control. The resulting FA03 film however, was opaque and the surface was not smooth. Furthermore, under the high DG concentration conditions, the DG and Eca233 separated resulting in Eca233's immediate precipitation, a phenomenon known as salting out. This is likely the result of DG's property as a hydrophilic polymer, acting to pull water molecules towards itself. As a result, when the concentration of DG is increased, the remaining water volume in the Eca 233solution system will decrease, resulting in sedimentation of Eca233 (Ebrahimi et al., 2018). Additionally, the elevated (3%) DG concentration resulted in increased viscosity during film preparation, such that it was difficult to prepare a smooth polymeric film.

Analysis of Wound Dressing Surface Morphology

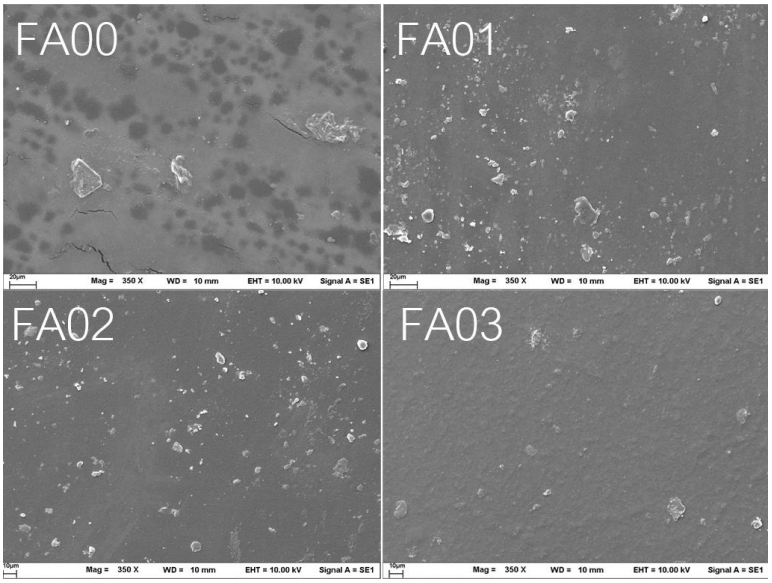

Figure 4. SEM images of FA00, FA01, FA02 and FA03 wound dressing formulations.

The morphology of the surface areas of the wound dressing formulations were analyzed by scanning electron microscopy (SEM). SEM images are shown in Figure 4. The surface morphology of the PVA only film (FA00) displayed noticeable cracking, while formulations in which PVA was combined with DG (FA01-03) displayed less surface cracking. This was likely a result of the increased flexibility of the films composed of more than one polymer. These data are consistent with previous reports demonstrating that combination of natural polymers with PVA results in a stronger film (Sarwar et al., 2018; Bano et al., 2019). Moreover, these data develop this technology as a potentially viable sustained drug delivery system.

Chemical Compatibility of Wound Dressing Film Components

The chemical compatibility of PVA and DG within the wound dressing films was analyzed by differential scanning calorimetry (DSC). These data indicate that PVA and DG are compatible, and that there are no interactions between these polymers and Eca233. The DSC thermograms also indicated that there was no significant change in melting point of the mixed polymer versus the single PVA polymer formulation. These data were confirmed by independent analysis of the samples with Fourier-transform infrared spectroscopy (FTIR) which indicated consistent findings (See Figures 5 and 6 and tables 3 and 4).

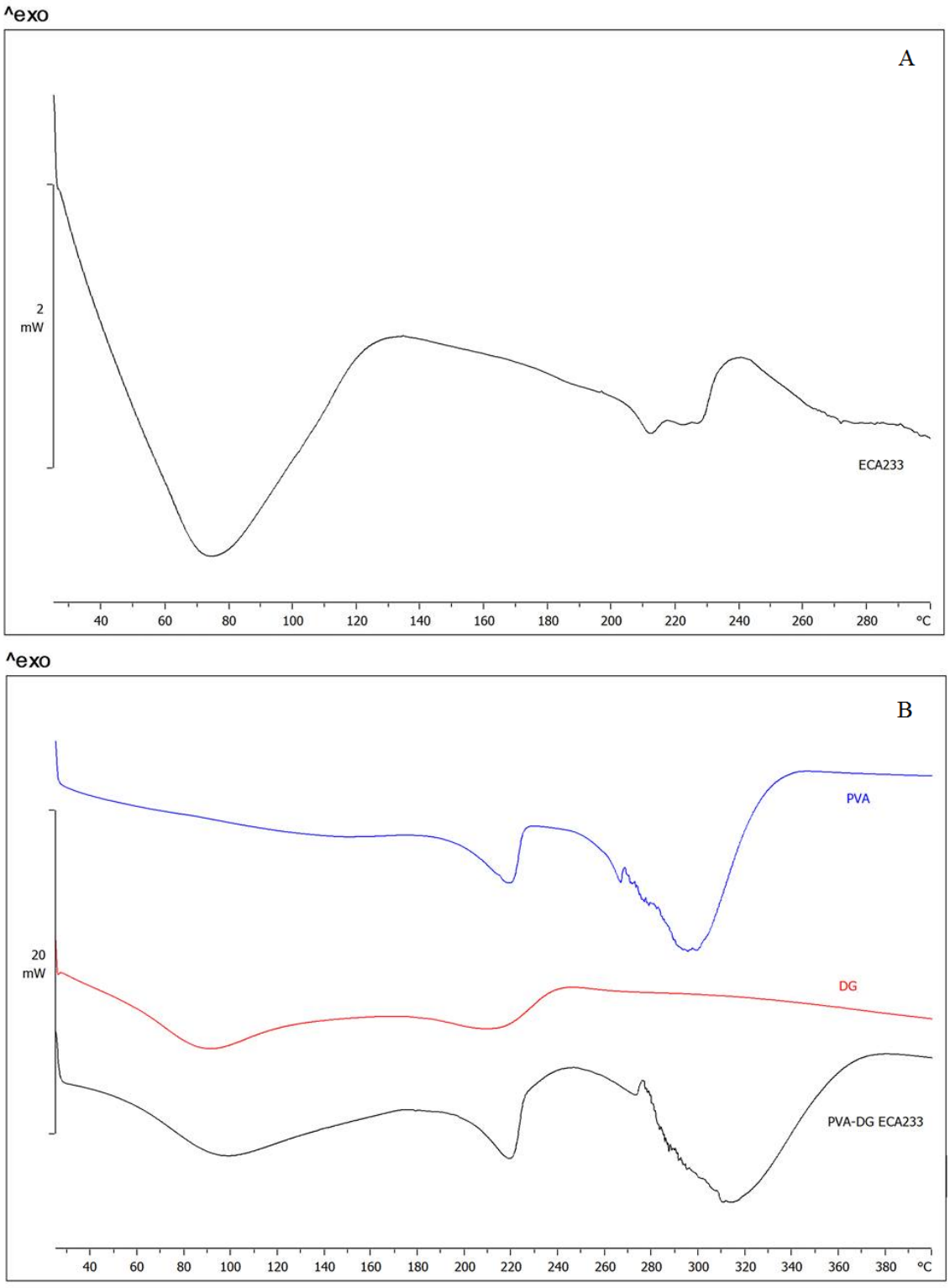

Figure 5. Differential scanning calorimetry (DSC) thermograms of films containing PVA, DG and ECa233.

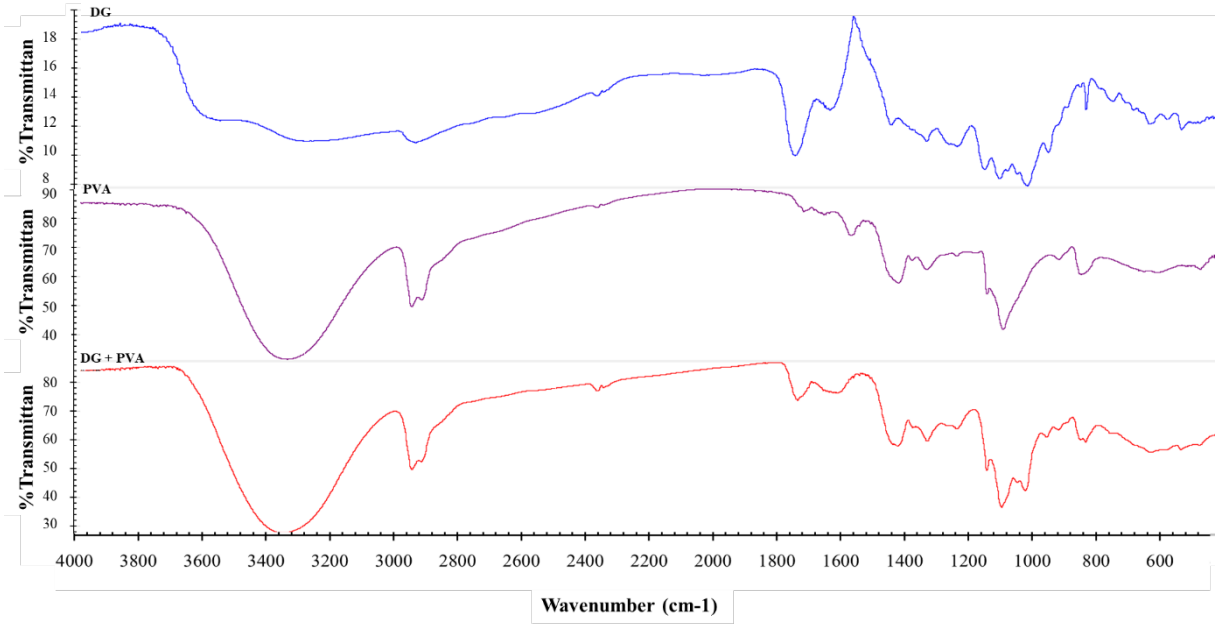

Figure 6. FTIR Spectrums of DG, PVA and DG + PVA.

Table 3. Characteristic FTIR peaks of PVA

Absorption $^{-1}$	Group
3331	O-H stretching
2941	C-H stretching
1419	C-H bending
1092	C-O stretching

Table 4. Characteristic FTIR peaks of DG

Absorption $^{-1}$	Group
3269	O-H stretching
2929	C-H stretching
1743	C=O stretching of carboxylic
1331	C-O stretching of carboxylic acid
1235	C-O-C stretching
1149	C-O stretching

Our studies clearly indicated that the quality of the wound dressing films was better when both DG and PVA were mixed together. To establish if the physical differences between the formulations were due to interaction between the two compounds, the films were analyzed by FTIR spectroscopy. The extracted DG polymer from durian is an acidic polysaccharide (Penjumras et al., 2014; Amid and Mirhosseini, 2012), resulting in the presence of carboxylic acid in its FTIR spectrum. Comparison of the mixed PVA/DG versus single DG polymers (Figure 6), indicated that the carboxylic acid group (C=O) at wavelength 1,600-1,700 and hydroxyl group (O-H) at wavelength 3,000-3,500 appeared at the expected wavelength in both formulations, and did not demonstrate any noticeable wavelength shift. If the PVA had undergone a chemical reaction with DG, the O-H peak intensity would have been expected to decrease and the carboxylic group (C=O) peak would shift following reaction between the two groups, resulting in formation of an ester group (COOR). This demonstrated that any changes

in the composition of the wound dressing films were of a physical nature and not due to chemical bonds being broken or formed (Pichayakorn et al., 2012).

Mechanical Properties of the Wound Dressing Patches

Table 5. Mechanical properties of the wound dressing patches

Formulation	Tensile strength (N/mm^2)	% Elongation (% ± SD)	Young's modulus (N/mm^2)
FA00	5.00 ± 1.60	45.79 ± 8.91	30.50 ± 2.12
FA01	4.53 ± 2.87	48.14 ± 5.54	36.58 ± 11.92
FA02	7.30 ± 3.06	45.08 ±15.16	40.75 ± 20.75
FA03	5.26 ± 2.10	22.16 ± 13.46	63.12 ± 25.28

Assessment of the physical properties of the PVA/DG wound dressing film versus that of the PVA single polymer film indicated that mixture of DG and PVA resulted in strengthening of the film at the expense of reduced flexibility. This was quantified by analysis of Young's modulus. Consistent with our observations, as the relative quantity of DG increased within the wound dressing film, the flexibility decreased. The reason for this change in the physical properties of the film is likely that the addition of DG disturbed the physical structure of the PVA matrix resulting in loss of flexibility. A similar phenomena occurs upon the combination of ethyl cellulose with hydroxyl propyl methyl cellulose (Verma et al., 2014) in which, addition of ethyl cellulose strengthens the film and allows it to be developed in to a sustained release system, but if excessive amounts of ethyl cellulose are added, the film loses flexibility.

Swelling Properties of the Wound Dressing Patches

The swelling profiles of the various wound dressing formulations are shown in Figure 7. The highest percentage swelling index (indicating highest degree of phosphate buffer absorption) was observed for the formulation in which PVA was combined with the highest concentration of DG (3%). This resulted in a swelling index which displayed a statistically significant difference between that of the other formulations ($p<0.05$). The data demonstrated a positive correlation between increased percentage of swelling index and increased concentration DG in the wound dressing formulation. These data show a similar trend to a previous studies using hydrophilic polymers in which a direct relationship was observed between the swelling index and the quantity of polymer in the formulation (Larsson et al., 2017; Okeke and Boateng, 2016). The swelling of the polymer can be explained by the presence of hydroxyl group within the polymer molecules. The hydrophilic nature of the polymer increases the water absorption of the wound dressing; consequently, the swelling rate and the degree of swelling are increased.

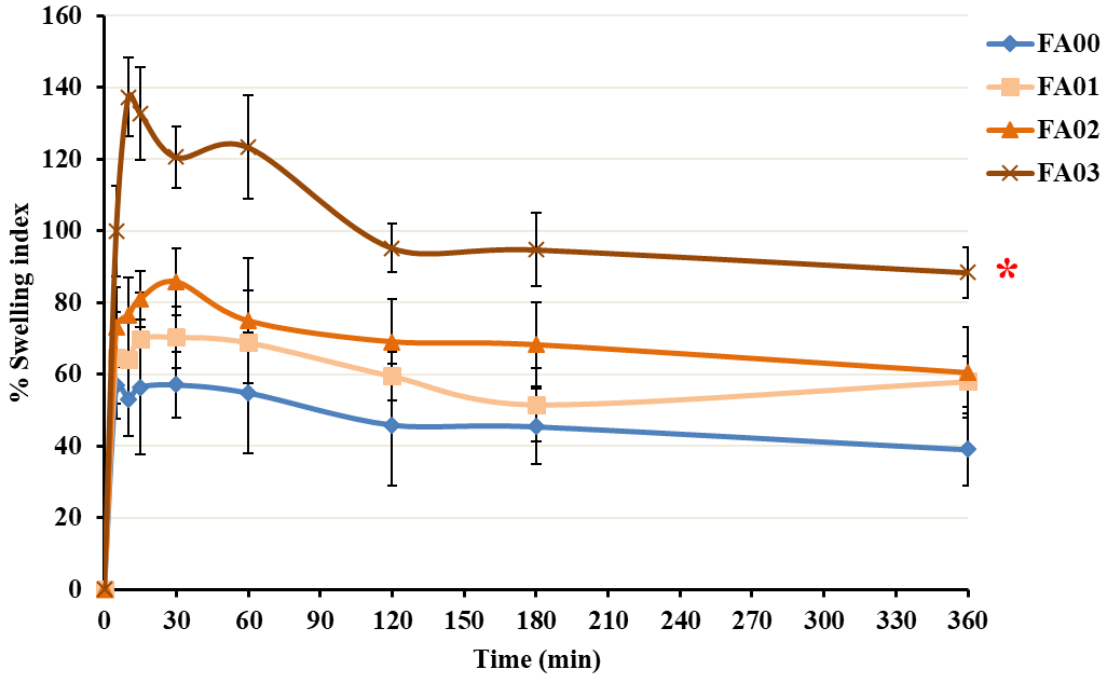

Figure 7. Percentage of swelling index of wound dressing formulations. Values represent mean values ± SD (n=3). The swelling index for FA03 was determined to be statistically significantly different to the other formulations ($p<0.05$)

In Vitro Drug Release of the Wound Dressing Patches

In vitro release of ECa233 from the wound dressing formulations was assessed. In particular, this study sought to ascertain the degree of release of madecassoside and asiaticoside, the major active components. Following immersion in phosphate buffer pH 6.8 with agitation the amount of drug released from the wound dressing film was assessed using HPLC. Madecassoside and asiaticoside peaks were evaluated at 4.357 min and 4.888 min, respectively and quantity assessed as the area beneath the curve at the respective peak height (Figure 8). **%** Drug release was calculated from**:**

Amount of drug release (mg) = Concentration (mg/ml) × Dissolution volume Equation 5

$$\text{Percent release (\%Drug release)} = \frac{\text{Cumulative release at the each time}}{\text{Initial dose}} \times 100 \qquad \text{Equation 6}$$

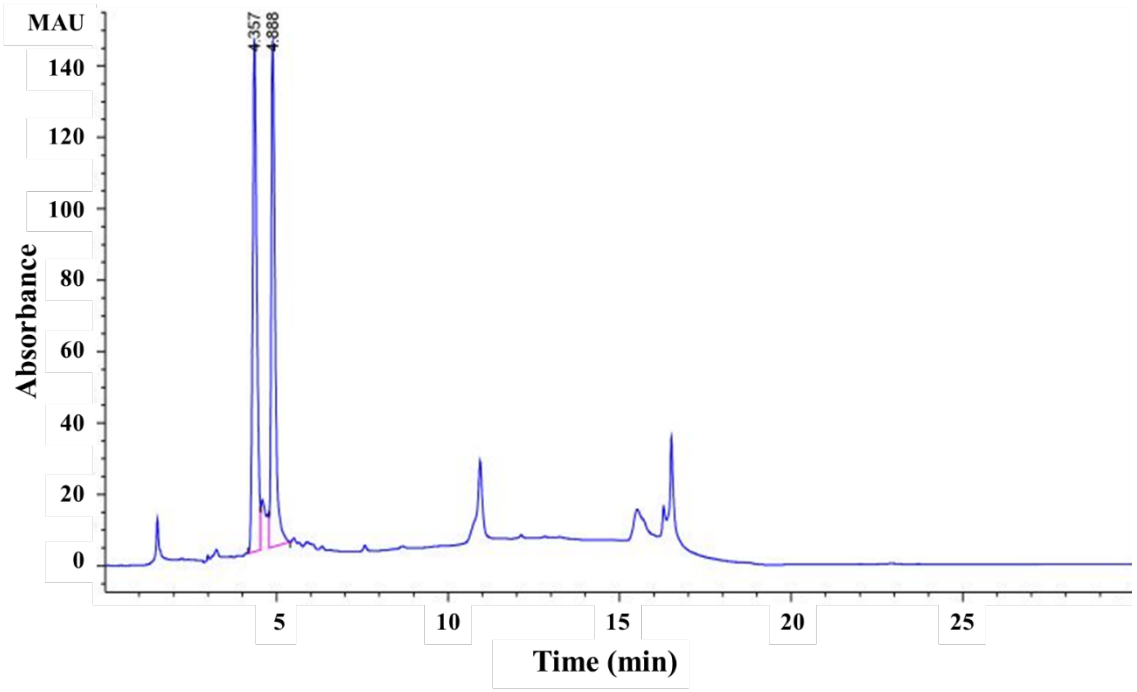

Figure 8. Chromatogram of Eca233 (4.357 min = madecassoside, 4.888 min = asiaticoside)

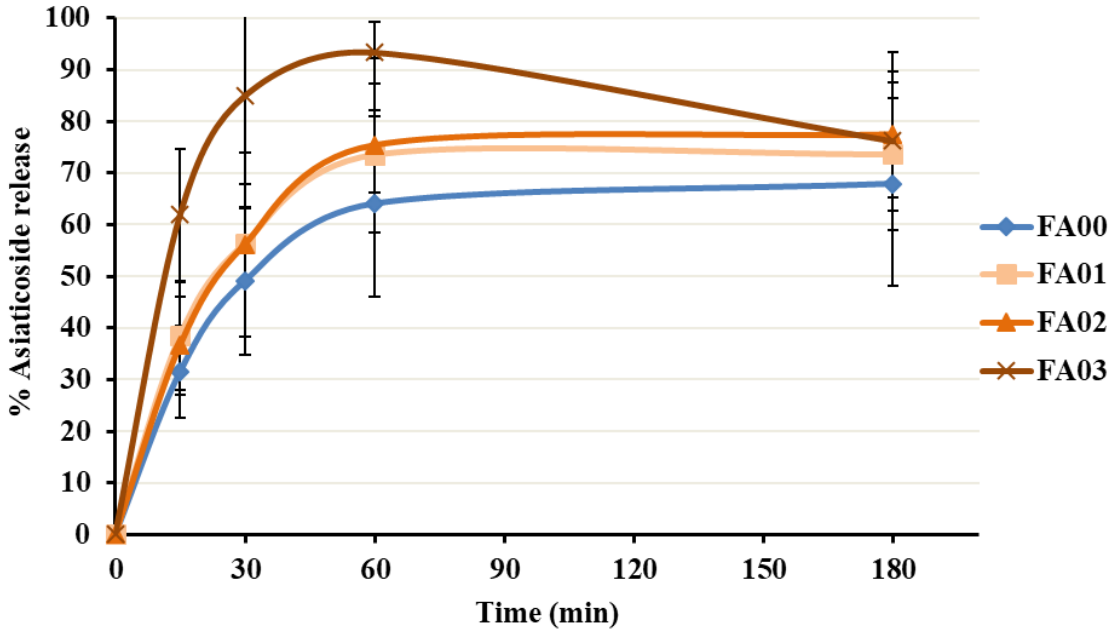

Figure 9. Asiaticoside release profile over 180 min. Values represent the mean ± SD (n=3).

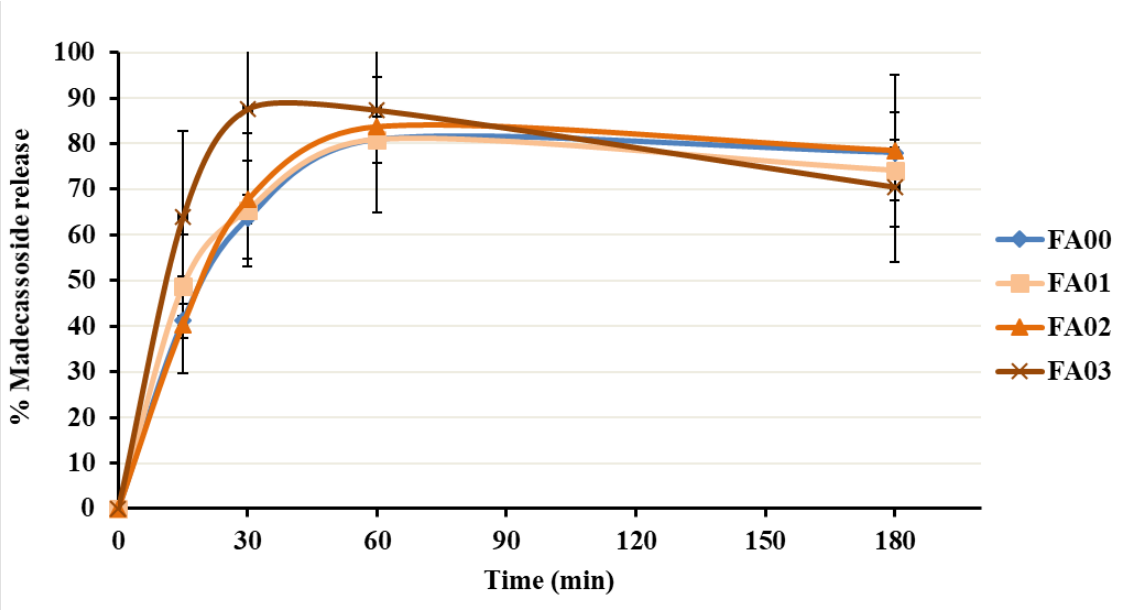

Figure 10. Madecassoside release profile over 180 min. Values represent the mean ± SD (n=3).

Madecassoside and asiaticoside are the major active compounds within the ECa233 *Centella asiatica* extract. The aim of this *in vitro* release study was to establish which wound dressing formulation was most effective in delivering these active compounds. The most effective formulation for drug delivery was the one containing 3% DG which released almost 100% of both major substances. This is likely a result of the presence of the hydroxyl groups in the hydrophilic DG polymer, which were responsible for its high water-swelling properties. As a result, when the wound dressing film contacts water (in this case within the phosphate buffer), the DG will rapidly swell resulting in the breakdown of the film at the molecular level and release of the active components. As such, the % DG within the wound dressing formulation directly correlated with drug release, consistent with the direct correlation with swelling index (Figure 7). Our data indicate that alteration of the % DG within the formulation facilitates fine-tuning of drug release an important consideration within a sustained release drug delivery system. While the 3% DG formulation provided maximum release, the formulation containing 1% DG allowed sustained slow release. The release profile for PVA combined with 1% DG was inferior to that containing 3% DG but was superior to that of PVA alone. This is a consequence of the formation of new hydrogen bonds between PVA and hydrophilic polymer, which results in a looser structure at the molecular level. Consequently, water can diffuse more easily within the DG-containing film, resulting in improved drug-release (Kazsoki et al., 2018; Teodorescu et al., 2019).

CONCLUSION

Our results demonstrate that addition of a hydrophilic DG polymer to PVA results in significant alteration in its physical properties, increasing its suitability for use as a wound dressing and facilitating controlled drug-release. Wound dressings comprised of PVA combined with 3% DG (formulations F03 and FA03) displayed the best swelling capacity (145.64% ± 16.51 and 137.27% ± 23.82 swelling index, significant $p < 0.01$). Consistent with improved swelling capacity, mixture of PVA with DG also resulted in increased, controlled release of ECa233 compared with PVA alone. However, the 3% DG formula resulted in a nonhomogeneous formulation, and while it provided optimal drug-release, lower DG% resulted

in a more suitable dressing both in terms of physical appearance and in terms of sustained drug-release. Increased DG concentration also resulted in higher tensile strength but also decreased the percentage of elongation at the dressing's breaking point. As such, addition of DG to PVA results in a trade-off of increased swelling and drug release properties versus physical homogeneity and integrity. Ultimately, the ideal formulation comes as a compromise and is comprised of a lower DG to PVA ratio. These data demonstrate the benefit of addition of DG polymer to PVA for the formulation of wound dressings, future studies will continue optimization to provide the optimal dosage form.

ACKNOWLEDGMENTS

The *Centella asiatica* extract (ECA233) was kindly provided by Assoc. Prof. Mayuree H. Tantisira Ph.D., Faculty of Pharmaceutical Science, Burapha University. We thank her for her support throughout this study.

CONFLICT OF INTEREST

The authors declare the absence of any conflicts of interest.

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