PROGRESS IN APPLIED SCIENCE AND TECHNOLOGY
Faculty of Science and Technology
Rajamangala University of Technology Thanyaburi
Vol.11 No.1 (2021): 38–45
ISSN (Print): 2730-3012
ISSN (Online): 2730-3020
https://ph02.tci-thaijo.org/index.php/past

Received 25th November 2020,
Revised 6th January 2021,
Accepted 8th January 2021

DOI: 10.14456/past.2021.1

Fabrication of pH-Sensing Sodium Alginate Films Containing *Clitoria Ternatea* Linn. Extract and Drug Release Characteristics

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Abstract

Halochromic property of the sodium alginate films containing *Clitoria ternatea* Linn. flower extract (SA/CT) was studied. Gallic acid (GA) with pK_a of 4.4 and resorcinol (RC) with pK_a of 9.3 as the model drugs were loaded into the SA/CT films, and their halochromic behaviors were investigated. The color change of the films was influent by the pH of solutions and pK_a of drugs. The release profiles of either GA or RC from the films were determined by the total immersion and transdermal diffusion through pig skin method at 37°C for 24 h in three types of media, including an acetate buffer (pH 5), a phosphate buffer (pH 7), and a borax buffer (pH 9) solutions. For the total immersion method, the burst release of drugs at the initial time of release followed by the gradual release until reaching a plateau was observed. The maximum cumulative amounts of drug release were in a range of about 17-29%. The amounts of drug release depended on the pH of the solutions and the pK_a of drugs. The more polar molecules exhibited higher amounts of drug release. The slower release and the lower maximum cumulative amounts of drug release in a range of 5-21% were obtained for the transdermal diffusion method. Like the total immersion method, the amounts of drug release depended on the solutions' pH and the pK_a of drugs. However, the less polar molecules exhibited higher amounts of drug release.

Keywords: Alginate, *Clitoria ternatea* Linn., Drug release, Gallic acid

1. Introduction

Wound healing is a process for the regeneration of destroyed tissue by living tissue. The pH value is one of the important parameters to indicate whether the wound is healed or infected. An alkaline pH was found to worsen wound by encouraging pathogenic bacteria's growth and becoming chronic wound (1). In contrast, an acidic pH can support tissue oxygenation, promoting the wound healing process, and suppressing pathogenic bacteria's growth. The pH values of chronic and infected wounds were found to be above 7.3 (1). Using pH strips to determine wounds' pH values is not convenient and can cause patients' suffering. The halochromic wound dressings that show different colors with pH values changing can provide more benefit as they act as both wound dressing materials and indicators for pH values. The halochromic substances' color is altered with the surrounding pH values because of their pH-sensitive chromophore groups. For biomedical applications, natural dyes have more advantages than synthetic dyes. Anthocyanins are the pH indicators extracted from various types of plants and fruits, such as purple cabbage, berries, black rice, purple cauliflower, and butterfly pea flower. They also exhibited interesting properties including, anti-inflammatory (2), antioxidant (3-4), and antimicrobial properties (5-6). *Clitoria ternatea* Linn. (CT), also known as butterfly pea, blue pea, or Asian pigeonwings, is in the Fabaceae family and is widely found in tropical and subtropical regions (7). CT flowers are an interesting source of anthocyanins because they are inexpensive, easily obtainable, and exhibit outstanding biological properties. Anthocyanins extracted from CT petals showed the highest pH sensitivity and the most increased antioxidant activity among various kinds of plants, including red cabbage, roselle, sweet potatoes, husks, and peelings from mangosteen, and red dragon fruit (8). Changes in the color of anthocyanin are due to different chemical structures. Flavylium cation (red color) predominately exists in acidic solution. However, the conjugation of double bonds of flavylium cation is disrupted in basic condition (8). As a result, its structure absorbs photons in a higher wavelength and shows different colors, such as green, blue, and purple. The properties of the films containing CT extracts were investigated

for use in food packaging (8) but not widely in wound dressing applications.

Hydrogels have been widely used as wound covering materials because of their ability to keep moisture contents for wounds. Sodium alginate (SA) is a derivative of alginic acid, which is a linear copolymer of (1,4)-linked *β*-D-mannuronic (M) and its C-5 epimer *α*-L-guluronic (G) acids (9). It is extracted from a cell wall of brown algae. Crosslinking of carboxylic groups of SA molecules allows hydrogel formation that can be swollen but not soluble in water. SA is bio-based and biocompatible hydrogels that have been studied extensively in biomedical applications, including tissue engineering (10) and carriers for the controlled drug release in wound healing (11-13).

In this research work, CT extract was prepared by sonication extraction and was blended with the SA solution. The SA/CT films were fabricated and studied for their halochromic properties. Drug-loaded SA/CT films were prepared using two types of drugs with different pK_a values, including gallic acid (GA) and resorcinol (RC). Gallic acid or 3,4,5-trihydroxy benzoic acid, classified as a polyphenol compound, is naturally found in various types of vegetables and fruits (14). GA reveals excellent antioxidant (15), anti-inflammatory (16), and antibacterial activities (15, 17). Resorcinol (RC), or 1,3-dihydroxybenzene, is widely used as an active ingredient in pharmaceutical and cosmetics, especially in acne treatments and skin diseases (18). The antioxidant property of RC was also reported (19). A number of researches in the drug-controlled release have utilized GA (15, 20) and RC (21) as model drugs to investigate the release behaviors. In this work, the halochromic properties of the drug-loaded SA/CT films were investigated. The release characteristics of GA and RC were studied by total immersion and transdermal diffusion through pig akin methods under acidic, neutral, and alkaline conditions. The degree of swelling of the drug-loaded SA/CT films was also examined to explain the drug release behaviors.

2. Materials and Experiment

2.1 Materials

Clitoria ternatea Linn. (CT) flower was collected from Pathumthani province, Thailand. Sodium alginate (SA), gallic acid (GA; $C_7H_6O_5$), and resorcinol (RC; $C_6H_6O_2$) were purchased from Acros Organics (USA). Glycerol ($C_3H_8O_3$), ethanol (CH_3CH_2OH), glacial acetic acid (CH_3COOH), sodium acetate trihydrate ($CH_3COONa•3H_2O$), disodium hydrogen phosphate (Na_2HPO_4), sodium dihydrogen phosphate (NaH_2PO_4), disodium tetraborate decahydrate (borax; $Na_2B_4O_7•10H_2O$), boric acid (H_3BO_3) were purchased from Carlo Erba (Italy). Sodium hydroxide (NaOH) and calcium chloride ($CaCl_2$) were purchased from Ajax Finechem (Australia). All chemicals were analytical grade and were used without further purification.

2.2 Extraction of CT flower

Sun-dried CT petals were grounded into powder using a blender. The powder was added to 100 mL of 95% ethanol:water at a 70:30 v/v ratio (8). The ratio of CT powder and solvent was 50 mL solvent:5 g powder. The mixture was ultra-sonicated at 40 kHz for 60 min. The extract was collected after removing the solid part out of the mixture by filtration. The extract was kept in a closed container at 18°C.

2.3 Fabrication of drug-loaded SA films containing CT extract

Sodium alginate (SA) solution was prepared at 2% w/v by mixing SA powder with water and stirring the mixture for one h. For 100 mL of SA solution, 4.5 g of glycerol and 2 mL of CT extract were added, and the mixture was stirred. 20 g of the obtained solution was poured into a petri dish with a diameter of 10 mm. The film was obtained after drying in an oven at 45°C for 24 h. Crosslinking alginate molecules was performed by immersing the film in 15 mL of 2% w/v $CaCl_2$ solution for 5 min. Later, the film was rinsed with a large amount of distilled water and dried at room temperature for 24 h. The obtained film was designated as SA/CT film.

The drug-loaded SA/CT film preparation, either GA or RC powder, was mixed into the SA/CT solution at 1% w/v. The drug-loaded solution was stirred until the homogeneous solution was obtained. The similar solution casting and crosslinking methods, as mentioned earlier, were carried out. The obtained films were designated as GA-loaded SA/CT film and RC-loaded SA/CT film.

2.4 Preparation of buffer solutions

Various buffer solutions with different pH ranging from 3-10 were prepared using the formulas shown in Table 1. The buffer solutions were prepared by dissolving these components in distilled water and adjusting the final volume to be 1 L. The pH of the obtained solution was measured using a pH meter. Few drops of 1 M hydrochloric acid or 1 M sodium hydroxide solution could be added to adjust the final pH. However, for the phosphate buffer with pH 6 and 7, calcium chloride was added into the solution at 0.05 M to prevent the breaking of crosslinking of alginate molecules according to the replacement of calcium atoms by sodium atoms that presented in the buffer solution.

2.5 Halochromic property of films

Each type of film, including SA/CT, GA-loaded SA/CT, and RC-loaded SA/CT, was cut into a square shape with 2x2 cm^2. Five drops of various buffer solutions with different pH ranging from 3-10 were dropped on the films. The films were dried at room temperature for 5 min. Photographs of the films were taken. The quantitative color data as RGB values of these photographs were determined using Adobe Photoshop software.

Table 1 Formulas for preparation of 1 L of buffer solutions

Chemicals	Amounts of chemicals		
	pH 3.0	**pH 4.0**	**pH 5.0**
CH3COONa•3H2O (MW:136.09 g/mol)	1.22 g	2.45 g	9.53 g
CH_3COOH (MW:60.05 g/mol)	8.20 g	7.39 g	2.70 g
	pH 6.0	**pH 7.0**	
Na_2HPO_4 (MW:141.96 g/mol)	1.94 g	8.20 g	
NaH_2PO_4 (MW:119.98 g/mol)	10.36 g	5.07 g	
	pH 8.0	**pH 9.0**	**pH 10.0**
$Na_2B_4O_7•10H_2O$ (MW:381.43 g/mol)	2.86 g	7.63 g	9.54 g
H_3BO_3 (MW:61.84 g/mol)	4.33 g	1.24 g	-
NaOH (MW:40.00 g/mol)	-	-	3.44 g

2.6 Standard curves of GA and RC in buffer solutions

Either GA or RC solutions with various concentrations in acetate buffer (pH 5), phosphate buffer (pH 7), and borax buffer (pH 9) were prepared and measured for their absorbance using a Hanon I-3 UV-vis spectrophotometer at the wavelength (λmax) of 259 nm and 275 nm, respectively. The standard curves plotted between absorbance and concentration was constructed.

2.7 Degree of swelling

Each type of film, including SA/CT, GA-loaded SA/CT, and RC-loaded SA/CT, was cut into a square shape with 2x2 cm^2. The film was immersed in 40 mL of buffer solution at 37°C for six h. The weights of the film before and after immersion were measured as M_i and M, respectively. The degree of swelling was calculated according to Eq. (2.1).

$$Degree\ of\ swelling\ (\%) = \frac{M-M_i}{M_i} \times 100 \qquad (2.1)$$

The degree of swelling of the films was determined in 3 types of buffer solution, including acetate buffer (pH 5), phosphate buffer (pH 7), and borax buffer (pH 9).

2.8 Release characteristics of GA and RC as determined by the total immersion method

The release profiles of GA from GA-loaded SA/CT films and RC from RC-loaded SA/CT films were studied in 3 types of buffer solutions with different pH in the range of acid, neutral, and base. The acetate buffer (pH 5), phosphate buffer (pH 7), and borax buffer (pH 9) were used as media in this study. Either GA-loaded SA/CT or RC-loaded SA/CT films with a square shape of 2x2 cm^2 was immersed in 40 mL of buffer solution at 37°C. At each releasing time point ranging between 0 and 24 hours, 1.0 mL of releasing medium was withdrawn and was diluted with certain amounts of buffer solution. An equal amount of fresh buffer solution (1.0 mL) was refilled in a medium to keep a constant solution volume. Later, the diluted releasing solution's absorbance was measured using a UV-vis spectrophotometer at the drugs′ λmax. The amount of drug release from the film sample was calculated from the absorbance by comparing it with the drug's pre-determined standard curves in each buffer solution type.

2.9 Release characteristics of GA and RC as determined by transdermal diffusion through pig skin method

The release characteristics of either GA from GA-loaded SA/CT film or RC from RC-loaded SA/CT film were also investigated by transdermal diffusion through the pig skin method. Abdomen pig skin was treated by removing epidermal hairs and subcutaneous fat. The final thickness of pig skin was about 1-1.2 mm. Each type of buffer solution, including acetate buffer (pH 5), phosphate buffer (pH 7), and borax buffer (pH 9) was filled up in a Franz diffusion cell. The treated pig skin was placed on the cell, followed by a piece of the film sample. The Franz diffusion cell volume was 9.0 mL, and the diameter exposed to the pig skin was 13 mm. The experiments were carried out at 37°C. At each releasing time point ranging between 0 and 24 hours, 0.3 mL of releasing medium was withdrawn and diluted with certain buffer solutions. An equal amount of fresh buffer solution (0.3 mL) was refilled into a Franz diffusion cell. Finally, the diluted releasing solution's absorbance was determined and calculated into the amounts of drug release.

3. Results and Discussion

3.1 pH-sensing SA/CT films

The halochromic behaviors of each film, including the SA/CT, the GA-loaded SA/CT, and the RC-loaded SA/CT films, were studied. Figure 1a shows the SA/CT films' photographs after moistened by different pH solutions and their color data as RGB values. The colors of CT extract under acid to the basic condition are changed from red to blue and green. Under acid conditions (pH 3-6), the SA/CT films had red-blue color. The films became blue at pH 7 and became blue-green under basic conditions (pH 8-10). The change of color according to the change of pH can be visually observed. Moreover, the RGB values of photographs can also be used to distinguish the color change. However, the consideration of only a single-color value cannot tell much information. The differences in color values, such as green versus red values (ΔGR), blue versus red values (ΔBR), and green versus blue values (ΔGB), can be noticed and used to explain the results. ΔGR and ΔBR were notably more significant with

increasing pH. In other words, Blue and green were more predominant, whereas red was declined.

To investigate the effect of the acidity or basicity of drug to the color change of the films, two types of drugs with the different pK_a, including GA (pK_a 4.4) (22) and RC (pK_a 9.3) (23) were loaded into the films. Their halochromic behaviors were also studied. Figure 1b and Figure 1c show the photographs of the GA-loaded SA/CT and the RC-loaded SA/CT films, respectively, after moistened by different pH solutions along with their RGB values. For the GA-loaded SA/CT films, the color of visually observed films was not much changed with pH. By varying pH from acid to base conditions (pH 3-10), films' color turned from red-blue to blue color. It was found that the red values were not dropped, even though ΔGR was more significant when pH was increased. The GA-loaded SA/CT films had quite similar colors with high red values for all pH ranges due to a high acid strength of GA that can be noticed from its pK_a.

For the RC-loaded SA/CT films, the films' color had changed from red-blue to blue and to green when the pH was adjusted from acid to base conditions. However, this type of film exhibited more green color than that of the GA-loaded SA/CT films due to RC's higher pK_a, which express fewer acidity of drug molecules. The ΔGB and ΔGR were larger with increasing pH.

These results demonstrated that the SA/CT films could be used in wound dressing applications to monitor the change of pH by visually observing the films' color or detecting the films' RGB values. However, the color of SA/CT films was influent by the type of the loaded drugs. Drugs with high acid strength (low pK_a) would govern films' color to be redder. While the low acid strength (high pK_a) drugs would govern the films' color to be more green.

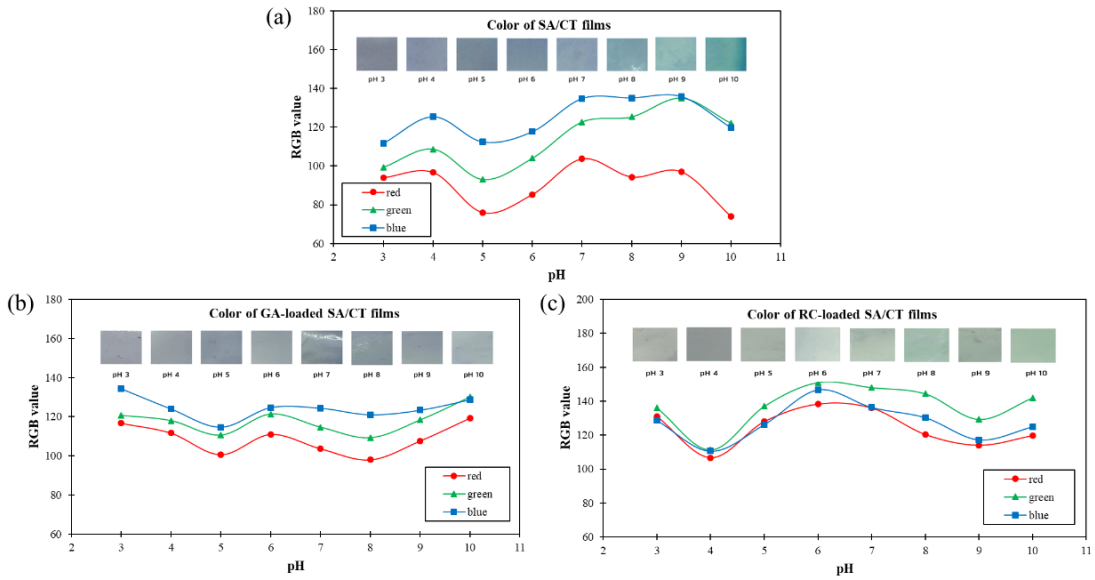

Figure 1 Photographs and RGB values of (a) SA/CT films, (b) GA-loaded SA/CT films, and (c) RC-loaded SA/CT films after immersion in different pH buffer solutions.

3.2 Standard curves of GA and RC in buffer solutions

To calculate the amounts of drug release from the drug-loaded SA/CT films in the next part, the standard curves of either GA or RC in each type of buffer were constructed and used in the calculation. For all kinds of buffer solution, including acetate buffer (pH 5), phosphate buffer (pH 7), and borax buffer (pH 9), the linear function between drug concentration and absorbance was observed as explained by the Beer-Lambert law. The standard curves, the linear equations, and the coefficient of determination (R^2) were presented in Figure 2. High values of R^2 that determined the best fit of data and equation were achieved.

3.3 Degree of swelling

The degree of swelling was examined in this study because it was one of factors that influent to the drug release behaviors. The degree of swelling of all types of films were determined at 37°C after immersion in the buffer solution for 6 h. Three types of buffer solutions in range of acid, neutral, and base were used. Figure 3 shows the degree of swelling of the SA/CT, the GA-loaded SA/CT and the RC-loaded SA/CT films in acetate buffer (pH 5), phosphate buffer (pH 7), and borax buffer (pH 9) solutions. At pH 5, 7, and 9, the degree of swelling of the SA/CT films were 358.9 ± 6.4, 326.6 ± 4.3, and 306.9 ± 7.4%, respectively. The values of the GA-loaded SA/CT films were 328.4 ± 3.7, 313.4 ± 3.2, and 303.2 ± 4.5%, respectively.

The values of the RC-loaded SA/CT films were 350.4 ± 1.8, 323.5 ± 2.5, and 304.2 ± 6.6%, respectively.

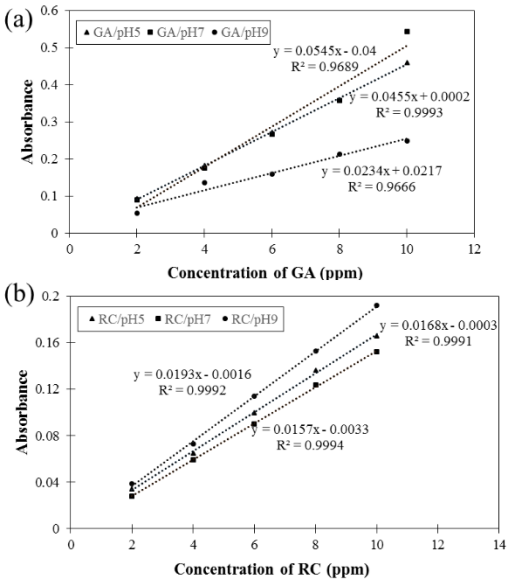

Figure 2 Standard curves plotted between concentrations of (a) GA and (b) RC solutions at pH 5, 7, and 9 and absorbance at *λmax*.

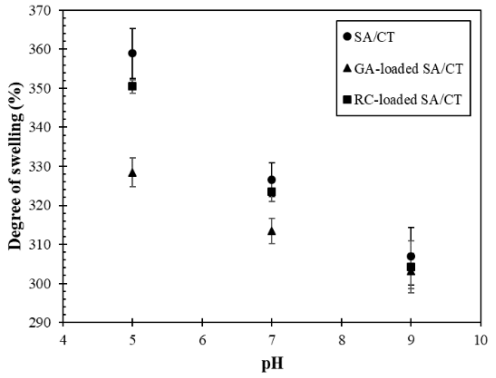

Figure 3 Degree of swelling of the SA/CT, the GA-loaded SA/CT, and the RC-loaded SA/CT films after immersion in different pH buffer solutions for 6 h.

It was found that the degree of swelling of all types of films was increased with decreasing pH of the solution. At low pH in which high amounts of proton in solutions have existed, proton could probably substitute calcium atoms in crosslinking regions of alginate molecules. Therefore, the crosslinking is destroyed. It is well known that the degree of swelling would be increased with a decrease in the degree of crosslinking of substances (24). When comparing the degree of swelling among the various types of films at the same pH, these values of the drug-loaded SA/CT films were lower than that of the neat SA/CT films. The presence of either GA or RC could disturb the water absorption of the crosslinked alginate molecules. Drug molecules that might be trapped in space between the crosslinking junctions could hinder water molecules from entering or being absorbed. Therefore, the GA-loaded SA/CT and the RC-loaded SA/CT films revealed a lower swelling degree than that of the neat SA/CT films.

3.4 Release characteristics of GA and RC

The release behaviors of either GA from the GA-loaded SA/CT or RC from the RC-loaded SA/CT films were investigated by total immersion and transdermal diffusion through pig skin methods in 3 types of buffer solutions 37°C for 24 h.

3.4.1 Total immersion method

In the total immersion method, the burst release of GA (Figure 4a) and RC (Figure 4b) from the films was noticed at the initial release time. Later, the gradual release of drugs until reaching the plateau was observed. For the release of GA, the maximum amounts of GA released (at 1440 min) under pH of 5, 7, and 9 were about 21, 22, and 29%, respectively. From the fact that the degree of swelling of the GA-loaded SA/CT films at low pH was more significant than those at high pH, the release amounts of GA from the films at low pH should be more significant than that of high pH. However, the release amounts of drugs were not correlated with the degree of swelling. The polarity of drug molecules is another important factor that affected the amount of release. According to a high polarity of water, the main component in buffer solution, the more polar molecules can be more released into media. With pK_a of 4.4 at 25°C (22), GA would be presented in more ionized form, as a basic form, at pH larger than its pK_a (25). As higher pH, the greater amounts of ionized GA molecules, which are polar, would more exist. Therefore, the greater release amounts of GA were observed at high pH.

For RC release, the maximum amounts of RC released (at 1440 min) under a pH of 5, 7, and 9 were about 31, 28, and 17%, respectively. In this case, pK_a of RC has less effect than GA, as mentioned earlier. RC with pK_a of 9.3 (23) would appear in an acid form or a non-ionized form at pH lower than its pK_a (25). Therefore, RC molecules have similarly existed in a non-ionized form in all types of buffer solutions (i.e. pH 5, 7, and 9). However, the amounts of RC release can be explained along with the films' degree of swelling (see Figure 3). The degree of swelling of the RC-loaded SA/CT films under pH 5 was more significant than pH 7 and 9, respectively. The more swollen matrix would allow more RC molecules to diffuse out. Furthermore, even though RC molecules were in an acid form in all types of buffer

solutions, they were more protonated under a lower pH. They were more convenient to be released in polar media.

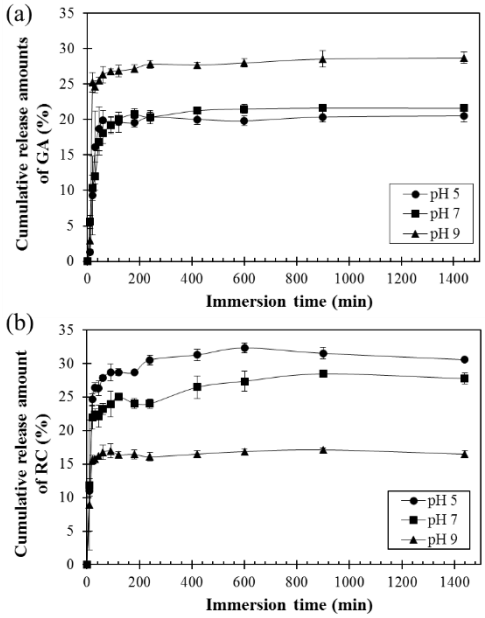

Figure 4 Cumulative release profiles of (a) GA from the GA-loaded SA/CT films and (b) RC from the RC-loaded SA/CT films after immersion in different pH buffer solutions.

3.4.2 Transdermal diffusion through pig skin method

The transdermal diffusion also investigated either GA or RC's release characteristics from the films through the pig skin method. Comparing to the total immersion method, the slower release and lower maximum amounts of drug release were observed from the transdermal diffusion method (Figure 5). For the release of GA, the maximum amounts of GA released (at 1440 min) at pH of 5, 7, and 9 were about 15, 11, and 5%, respectively (Figure 5a). According to the structure of mammal skins, lipid bilayers presented in the epidermis layer (26) act as a non-polar membrane that allows non-polar substances to diffuse or penetrate conveniently (27). Oppositely, the polar molecules will be more difficult to penetrate a non-polar skin membrane. At pH 5, an acid form or non-ionized form of GA molecules was more dominant. As increasing pH of the solution, a basic form or ionized form of GA molecules would be dominant. Therefore, the non-ionized or non-polar GA molecule primarily existed in pH five could diffuse through skin conveniently and reveal a high release amount. The more ionized GA molecules that presented at pH 7 and 9 contributed to the lower amounts of GA release. The effect of the degree of swelling of the GA-loaded SA/CT films was also in agreement with GA release results. As the higher degree of swelling of the films observed at pH 5, GA can easily diffuse out of the films compared to pH 7 and 9, respectively.

For RC release, the maximum amounts of RC released (at 1440 min) at pH 5, 7, and 9 were about 5, 14, and 21%, respectively (Figure 5b). RC molecules were presented in an acid form for all types of buffer solutions (pH 5, 7, and 9) because the pH was lower than its pK_a. However, protonation of RC molecules could occur more at a lower pH. Therefore, the more ionized or more polar structure of the protonated RC molecules that existed at pH 5 showed less ability to diffuse through the non-polar skin than those at pH 7 and 9.

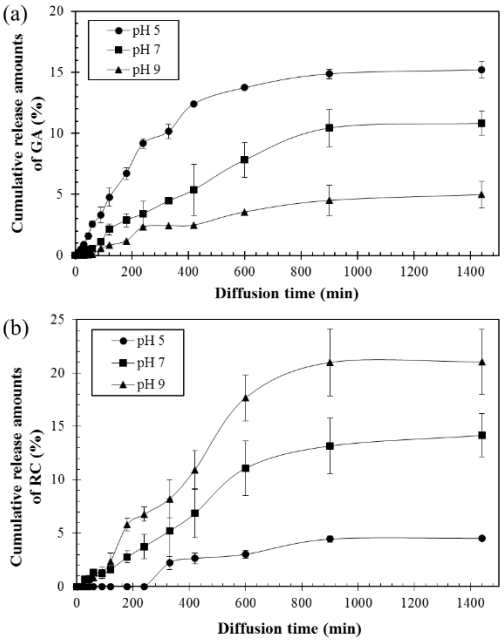

Figure 5 Cumulative release profiles of (a) GA from the GA-loaded SA/CT films and (b) RC from the RC-loaded SA/CT films as determined by transdermal diffusion through pig skin method different pH conditions.

Many factors affected the amounts of drug release from specimens, including the weight loss of the matrix (15), the degree of swelling of the matrix (28), and solubility of the substance in medium (29). In this study, the specimen's degree of swelling is one of the important factors to determine the amounts of drug release. However, the pH and pK_a of the release substance which determine the solubility of substance in medium seemed to play more important role than the effect of the degree of swelling. The controlled release system will be achieved when these parameters are well understood.

4. Conclusions

The sodium alginate films containing *Clitoria ternatea* Linn. flower extract (SA/CT) was successfully fabricated. In wound dressing application, the wound's pH is an important parameter to signify the wound's recovery. The wound dressing materials that assist in monitoring the change of pH will be useful and valuable. Two types of drugs, GA and RC, were chosen as the model drugs to be loaded into the SA/CT films in this study. The study of halochromic properties of these films revealed that the films' color change was influenced by the pH of solutions and pK_a of drugs. The release characteristics of both drugs from the films were determined by the total immersion and transdermal diffusion through pig skin method at 37°C for 24 h in three types of media, including an acetate buffer (pH 5), a phosphate buffer (pH 7), and a borax buffer (pH 9) solutions. The degree of swelling of these films was also studied to see whether it affect the release behaviors. The degree of swelling of all types of films was lower with the increasing pH of the solution. The addition of drugs into the films was found to lower the degree of swelling of the films.

For the release study, as determined by the total immersion method, the burst release of drugs at the initial time of release followed by the gradual release until reaching a plateau was observed. The maximum cumulative amounts of drug release were in a range of about 17-29%. The amounts of drug release depended on the pH of the solutions and the pK_a of drugs. The molecules of drug can be either an ionized or a non-ionized form according to the changing of pH of solution and therefore the polarity of drug would be changed. The drug molecules with higher polarity exhibited higher amounts of drug release.

For the transdermal diffusion through pig skin method, the slower release and the lower maximum cumulative amounts of drug release in a range of 5-21% were observed. Like the total immersion method, the amounts of drug release depended on the pH of solutions and drugs' pK_a. However, the less polar molecules revealed higher amounts of drug release because the skin is considered as a non-polar membrane. The degree of swelling of the films in various pH conditions also affected the amounts of drug release, but it had less influence than the pK_a of drugs.

The SA/CT films can be the promised material for use as a pH-sensing wound dressing material from this study. Moreover, by understanding the nature of the loaded drugs and the degree of swelling of the films, the drug release behaviors could be predicted or controlled.

Acknowledgments

The authors acknowledge the support received from the Faculty of Engineering, Thammasat University.

Declaration of conflicting interests

The authors declared that they have no conflicts of interest in the research, authorship, and this article's publication.

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