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COLON SPECIFIC DELIVERY OF FUCOIDAN BY INCORPORATION OF ACIDIFIER IN ENTERIC COATING POLYMER

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ABSTRACT:

The aim of the study was to design a colon drug delivery system for fucoidan, a recently discovered material from ocean, useful in treatment of human colon cancer cells. Initial core tablets using polyethylene oxide (PEO) as a matrix former were prepared, and then, were coated with a coating formulation based on Kollicoat MAE 100P, a film former used in the pharmaceutical industry for the production of enteric coatings for solid dosage forms. Citric acid was incorporated into the above polymer coating formulation with a notice that the amount of citric acid was very crucial in preparation of the coating formulation. Interestingly, the drug release profile of coated tablets with citric acid showed sustained drug release behaviors over 15 h, expressing a promising colon specific drug delivery system; whereas, the coated tablets without citric acid showed the conventional drug release rate of an enteric film coated dosage form. In order to elucidate the effects of citric acid on the drug release rate, swelling and erosion studies, scanning electron microscopy (SEM), and Fourier transform infrared (FTIR) spectroscopy were conducted.

Key words: fucoidan, citric acid, Kollicoat MAE 100P, film coating, colon drug delivery system

INTRODUCTION

Current thriving high technologies - based pharmaceutical drug delivery allow delivery of drugs at desired release kinetics for extended periods of time, and hence, leading to the improvement of the drug therapeutic index. The development of targeted drug delivery system is one of the attractive strategies facilitating the field. Targeted drug delivery is considered as smart drug delivery because it delivers concentrated medication to the diseased tissues of interest while reducing the relative concentration of the medication in the remaining tissues. While the absorption of the drug occurs across a biological membrane for the conventional drug delivery system, the drug is released in a dosage form for the targeted release system. Thus, the main advantages of targeted release system can be seen in (a) improving clinical efficacy with the reduction in the frequency of the dosages taken by the patient, and (b) minimizing drug-originated systemic toxic effects.

Colonic drug delivery for targeted drug release into the colon have gained much interest by researchers because it has been applied for chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction [1]. It is highly desirable for not only the local treatment of colon cancer and inflammatory bowel diseases [1, 2] but also for the systemic delivery of proteins and therapeutic peptides [3]. The transit time through the gastrointestinal tract varies. Normally, it is about 2 h in the stomach, around 3 h in the small intestine and 20–30 h in the colon [4]. For this delivery, the stomach and the small intestine are not the places where the release and absorption of drug are expected to occur. Thus, the delivery system should be designed to prevent the drug from degradation in those dissolution sites so that the optimal released and absorbed behaviors of drug could take place once the system reaches the colon [5]. To protect drug release during its transfer to colon, several approaches have been developed including formation of a pro-drug,

multicoating time-dependent delivery systems, coating with pH-sensitive polymers, pressure dependent systems, and the use of biodegradable polymers [6, 7]. Polymeric coating techniques have been widely used in pharmaceutics for controlled release of drugs [8]. One of the conventional methods is to coat the dosage forms with enteric polymers for colonic delivery. However, if the coating solution is only composed of the conventional components including the enteric polymer, a plasticizer, other excipients, the thickness of the coating film has to be increased into a certain level to achieve successful colonic delivery [4]. In this study, citric acid, an acidifier, was incorporated in the polymer coating solution to modulate an efficient retardation for targeting drug to the colon site due to the control of microenvironmental pH. Kollicoat MAE 100P which has been known as film-formers in the pharmaceutical industry for the production of enteric coatings for solid dosage forms was selected as the model in the study. It is a copolymer derived from methacrylic acid/ ethyl acrylate, the two monomers being bound in the molar ratio of 1:1. The advantages of Kollicoat MAE 100P include the easy dispersion of the polymer powder into water facilitating the reproductive preparation of the coating solution, the use of water instead of organic solvent avoiding the risks of environmental hazards. However, polyethylene oxide (PEO)-based matrix tablets had been prepared before introducing them into the coating process. PEO is a water-soluble, controlled release polymer capable of forming swellable hydrophilic matrices widely used to modify drug release and dissolution [9, 10]. When a PEO-based dosage form is exposed to an aqueous environment, PEO will hydrate and swell to form a hydrogel layer inducing further liquid penetration into the matrix. Hence, the drug molecules can be diffused out of the dosage form [11, 12]. The hydrogel layer formation slows down the rate of water intake while decline and prolong that of drug release. This formation generally occurs through three stages 1) initial hydrogel layer thickness increases due to polymer swelling; 2) maintenance of constant gel layer thickness between swelling and dissolution front; 3) reduction in gel layer thickness due to gel dissolution or erosion of polymer [9, 13, 14].

Figure 1 shows the schematic illustration of coated tablets without (Fig. 1A.) and with (Fig. 1B.) acidifier at pH 1.2 and pH 6.8. Both of the coated tablets are intact from the pH 1.2 medium, ensuring the inhibition of drug release at the upper gastrointestinal tract. At pH 6.8, the coating film containing citric acid can resist dissolution to be dissolved for hours meanwhile the film without the acid gets dissolved immediately after passing through pH 1.2.

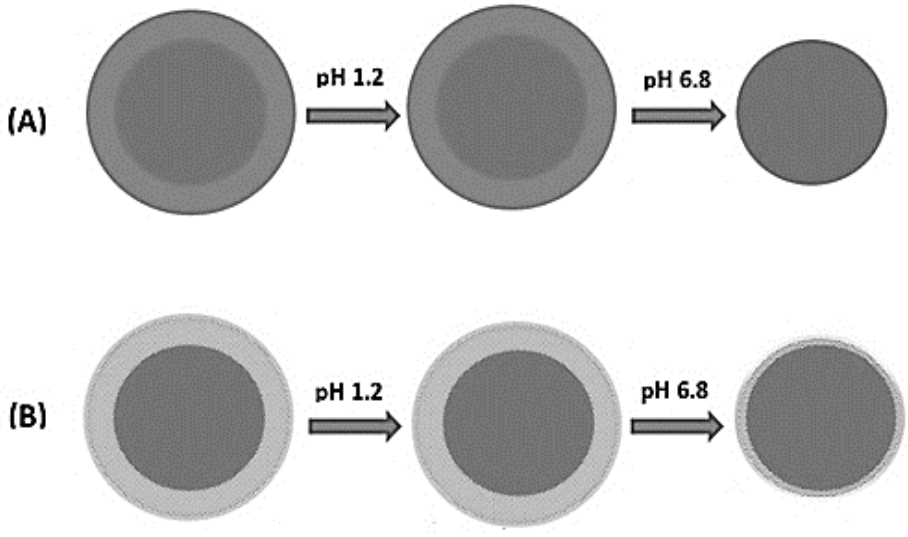

Fig. 1. Schematic illustration of coated tablet in different pH conditions. (A) – without acidifier in coating polymer, (B) – acidifier in coating polymer.

Fucoidan is a recent discovery from ocean that has attracted attention of many scientists for medical treatment. It is a sulfated polysaccharide found in brown algae having substantial percentages of L-fucose and sulfate ester groups [15]. It has been extensively studied due to its numerous interesting biological activities [16]. Recently, it has been determined that fucoidan inhibits growth and induces apoptosis in human colon cancer cells [17]. Because of its chemical structure, fucoidan is

soluble in water and acidic solutions [18] and thus it may not safely reach to the colon with a concentration for treatment of diseased colonic site. In this study, we designed a sustained drug delivery system of fucoidan for targeting to the colon. The release rate of the drug was characterized in the gastric fluid (pH 1.2) and the intestinal fluid (pH 6.8). The molecular interaction of acidifier and enteric coating polymer was also investigated using Fourier transform infrared (FTIR) spectroscopy. The surface morphology of the coated films was characterized by scanning electron microscopy (SEM).

MATERIALS AND METHODS

Materials

Polyethylene oxide N-60K (PEO) was provided by from Dow Chemical Company (USA). Microcrystalline cellulose (Avicel PH 102) was kindly supplied from Brenntag Group (Germany). Fucoidan 80% (FU) was kindly supplied by Nha Trang Institute of Technology Research and Application. Magnesium stearate was purchased from Nitika Pharmaceutical Specialities Pvt. Ltd (India). Citric acid monohydrate was purchased from Xilong Group (China). Polyethylene glycol 6000 (PEG 6000) was purchase from Sino-Japan Chemical Co., Ltd. (Taiwan). Kollicoat MAE 100P was purchased from BASF (Germany). All other chemicals were of analytical grade and were used without further purification.

Methods

Analysis of fucoidan

FU concentration was determined by conductometric titration method. Solution of $BaCl_2$ 0.01 M was prepared to use as titrant. Samples were diluted in the concentration range of 5-50 µg/ml for titration. The conductometric titrations were performed by measuring the specific electrical conductivity of a FU solution as a function of the volume of added $BaCl_2$ solution. The equivalence point is the point at which the conductivity undergoes a sudden change.

Preparation of sustained release tablet

FU was blended with PEO, microcrystalline cellulose (MCC) and finally magnesium stearate. The mixture was directly compressed into 300-mg tablet containing 100 mg FU by round punches and dies with a 10-mm diameter. The hardness was controlled at 90 ± 5N. The detailed composition of the formulations is described in Table 1.

Table 1: Formulation compositions of sustained release tablets of FU

Codes	F1	F2
Fucoidan 80% (mg)	125	125
PEO (mg)	80	160
MCC (mg)	92	12
Magnesium stearate (mg)	3	3
Total (mg)	300	300

2.2.3. Preparation of coating solutions

Kollicoat MAE 100P was initially dispersed in the sufficient amount of distilled water. Plasticizer and acidifier were separately dissolved in a small amount of distilled water. When Kollicoat MAE 100P was completely dispersed in water, the solution of plasticizer and acidifier was then incorporated. The detailed formulation compositions of coating solutions are shown in Table 2.

Table 2: Formulation compositions of coating solutions. The concentration of citric acid was calculated based on amount Kollicoat MAE 100P.

Codes	C1	C2	C3	C4
Kollicoat MAE 100P (g)	60	60	60	60
PEG 6000 (g)	6	6	6	6
Citric acid (g)	0	0.6	1.2	3
Water (g)	1000	1000	1000	1000

Tablet coating process

The coating process was carried out using a film coater (BYC-400, Taiwan) under the following conditions: air supply temperature (60°C), pan speed (12 rpm), peristaltic pump (2 rpm) and air pressure (20 psi). The tablets were sampled at regular intervals and weighed to determine the coating levels based on the weight gains of tablets. When the required coating weight gain was achieved, spraying of the solution was stopped, and the coated tablets were then dried in the coating drum for another 10 min before the samples were taken out. Tablets with coating levels at 5% (w/w) weight gains were obtained and stored at room temperature until use.

Dissolution studies

The sustained tablets and coating tablets were exposed to 900 mL dissolution media using the USP apparatus I (100 rpm, 37°C). Dissolution of sustained core tablets was performed in enzyme-free simulated intestinal fluid (pH 6.8) for 24 h. Dissolution of coating tablets was performed in enzyme-free simulated gastric fluid (pH 1.2) for 2 h. At the end of 2 h, the tablets were moved to

enzyme-free simulated intestinal fluid (pH 6.8). Dissolution testing was continued for 24 h. Samples were withdrawn at predetermined intervals and replaced with an equivalent amount of fresh medium to maintain a constant dissolution volume. The concentrations of FU were analyzed as described above.

Swelling and erosion studies

The coating tablets (C1 and C2 formulations) were accurately weighed (W_0) and placed in the basket of apparatus I USP dissolution tester. Baskets were then immersed in 900 mL of dissolution medium with rotating at 100 rpm. Samples were firstly placed in simulated gastric fluid (pH 1.2) in 2 h and subsequently moved to simulated intestinal fluid (pH 6.8) at 37 ± 0.5 °C. After 2, 4, 6 h in pH 6.8, tablets were removed from the basket, lightly blotted with tissue paper to remove excess test liquid and then reweighed (W_t). The experiments were performed in triplicate. The degree of swelling (S) was calculated from the following equation [19]:

$$S = \frac{W_t - W_0}{W_0} x100$$

After the swelling studies, the wet tablets were then dried in an oven at 60 °C until constant weight was achieved (W_d). The tablet erosion (ES) at different times was estimated from the following equation [20]:

$$ES = \frac{W_0 - W_d}{W_0} x100$$

Fourier transform infrared spectroscopy (FTIR)

A FTIR spectrophotometer (Bruker Vertex, Germany) was used to investigate the spectra of citric acid, dried coating polymer with and without citric acid. The wavelength was scanned from 500 to 4000 cm^{-1} with a resolution of 2 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr.

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to characterize surface morphology of tablets. The samples were examined using scanning electron microscope JSM-6480LV (Jeol, Japan). Results and discussion

Dissolution study

Dissolution profiles of sustained-released core tablets

The formulation of hydrophilic matrix-based tablets with high gelling capacity is of particular interest in the field of designing a sustained release dosage form. Various types of polymers are used as the gel forming agent in matrices such as methylcellulose (MC), hydroxyl propylmethyl-cellulose (HPMC), hydroxypropylcellulose (HPC) and sodium carboxymethylcellulose (Na CMC). In some cases where the amount of water sorbed by polymer is desired to be limited, the limited swelling hydrophilic polymers such as poly(vinyl alcohol) (PVA); poly (2- hydroxyl –ethyl methacrylate) (PHEMA) or poly(ethylene oxide) (PEO) have been used to retard the drug delivery. Structure of the polymers consists of the substitution of some hydrophilic monomer by hydrophobic monomer. For instance, PEO has a structure in which some monomers of ethylene oxide are changed by propylene oxide into poloxamers [21]. In this study, firstly the PEO matrix-based core tablets were prepared. Figure 2 shows dissolution profiles of the sustained-release core tablets of F1 and F2 in 24 h at pH 6.8. The core tablet will be coated with enteric coating polymer to prevent drug release at pH 1.2, i.e. the core tablets were exposed to the medium after the coated tablets passed through the stomach. Therefore, only medium of pH 6.8 was used for dissolution test of sustained-release core tablets. F2 dissolution profile shows a higher capability of sustaining drug release compared to that of F1. It has been clearly expressed through the percentage of drug release since 4 h. At 4h, the release of drug from F1 and F2 was 40% and 10%, respectively. Almost 100% of drug released from F1 could be reached at 12 h; whereas approximately 80% of drug content was released from F2 at this time. One hundred percent of drug content of F2 only accomplished the release at 24 h. The result was attributed to the 2-fold greater amount of PEO of F2 compared to that of F1. The hydrogel layer formation from the hydration and swelling of PEO will slow down the rate of water intake while decline and prolong that of drug release. This formation generally occurs through three stages (1) initial hydrogel increase due to polymer swelling; (2) maintenance of constant gel layer thickness between swelling and dissolution front; (3) reduction in gel layer thickness due to gel dissolution or erosion of polymer [9, 10, 13, 14]. The increase in PEO proportion retarded the water uptake by the matrix core, consequently prolonged the drug diffusion and dissolution from the dosage forms. In the formulation of PEO-based core tablets, a suitable amount of MCC was accompanied to assist PEO in the compression for preparation of strong tablets because PEO was

shown to consolidate via viscoelastic behavior and fusion, and showed very poor tabletability characteristics. MCC is known to have a high compactibility which can improve manufacturability. Other reasons for choosing MCC are that its fibrousness and hydrophilic property which also promote water uptake, improve matrix integrity and provide for modulation of matrix erosion rate [22].

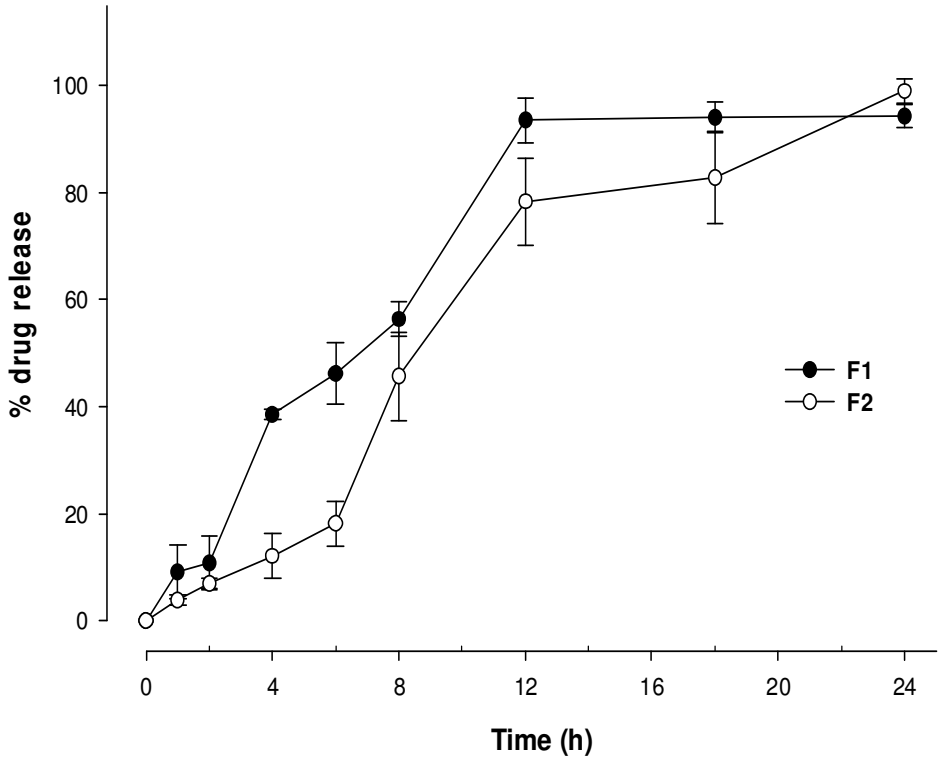

Figure. 2. Dissolution profiles of FU from sustained release tablets at pH 6.8.

Dissolution profiles of coated tablets

Tablet coatings serve a protective function for drug release within the body. Since the variation in coating thickness is limited in some cases due to formation of cracks at lower coating levels, changes of components in coating formulation can play a major role in adjustment of drug release profiles. In this study, Kollicoat MAE 100P was selected as the model coating polymer. The neutralized carboxyl groups in the powder make it easy to redisperse in water. The polymer has an anionic character and is a weakly acidic copolymer that dissolves at a pH above 5.5. In other words, drug is released from the dosage form coated by this polymeric film when the dosage form reaches at the site of the gastrointestinal tract at which the pH is above pH 5.5. To achieve the local therapy for colon-related disease, the film-coated tablets should prevent drug release in the upper GI tract. The incorporation of citric acid in the coating formulation composition was supposed to retard the drug release and thus sustain it for a longer time as compared to the one without citric acid. Also, the citric acid amount in the coatings should be sufficient to ensure that most of the drug is released in the targeted site. Figure 3 shows the dissolution behaviors of drug release from the coated dosage forms which were tested in simulated gastric fluid (pH 1.2) and then transferred to simulated intestinal fluid (pH 6.8). At 4h, approximately 10% of drug released from C1 formulation which has no citric acid; whereas, almost no drug released from C2 and C3 formulations which have 1% and 2% of citric acid content, respectively. At 10h, while 40% of drug released from C1 formulation, only 10% of drug released from C2 and C3 formulations. At 14h, the percentage of drug release from C1 could reach at 70% meanwhile that from C2 and C3 formulations were about 40%. At 21h, almost 80% of drug released from C1 formulation and about 70% of that from C2 and C3 formulations; however, it's not much significantly different among them. After 24 hrs, the drug release from all of the coated dosage forms was 100%. Thus, the sustained release behavior could be observed most before the time of 21h occurred. Although the drug sustained

release behaviors of C2 and C3 formulations were quite similar, the spraying gun was blocked sometimes during the coating process of the C3 formulation. Besides, the C4 formulation in Table 2 couldn't be used to coat the core dosage form because there was sedimentation in the preparation of the coating solution. Therefore, C2 could be considered the optimal coating formulation for the purpose of sustaining drug release rate. In other words, the percentage of citric acid content used in the coating formulation should below 2% (w/w). The addition of citric acid in the coating film may readily facilitate greater acidic pH of the film, and hence, prolonging the time that the coated tablets travel to the site having pH 5.5. Thus, it prolongs the time of dissolving the film in the media as illustrated in Fig.1. The interesting point herein is that it seemed impractical to add any acidifier into the coating solution of Kollicoat MAE 100P because the manufacturer instructed that due to its partial neutralisation, the polymer can be directly dispersed in water without the need for alkaline additives such as sodium hydroxide. It means that the dispersion of the polymer powder in water is easy for users since approximately 6 mole % of the co-polymer has been neutralised by sodium hydroxide and it is not if users lower its pH to acid. However, the study indicated that by adjusting a sufficient amount of citric acid which does not exceed 2% (w/w), the enteric coating formulation is still be possible and can be utilized to prolong drug release for concentrating drug at the targeted colonic site. Also, the instruction of the manufacturer is not wrong when the amount of citric acid in the coating formulation is over 2% which leads to uneasy dispersion of the polymer in water for spraying. The swelling and erosion behaviors of the coated tablets in the following discussion may contribute to a clearer explanation of the drug release rate.

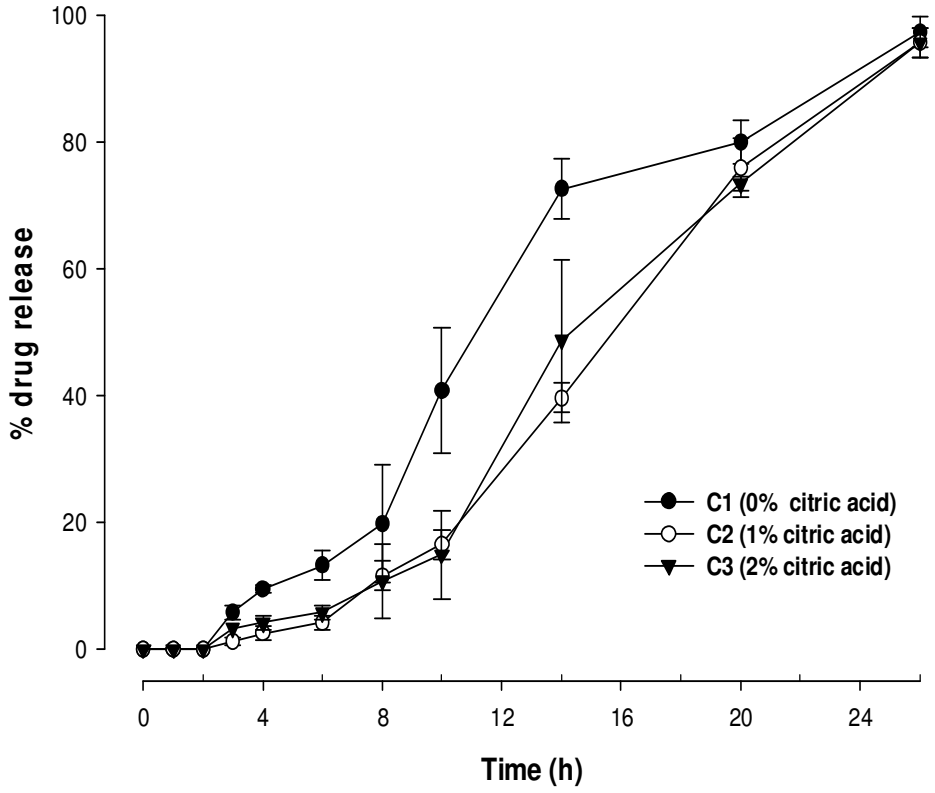

Figure. 3. Dissolution profiles of FU from coating tablet at pH 1.2 up to 2 h and at pH 6.8 from 2h to 26 h.

Swelling and erosion studies

Because the penetration of the dissolution medium and the erosion of the hydrated tablets may affect drug release, swelling and erosion behaviors of the coated tablets were determined. The fact that the level of swelling and erosion of the coated tablets at pH 1.2 was almost nil is reasonable because the coating formulation was designed to prevent drug release at the upper part of the

gastrointestinal tract for targeting drug concentration at the colonic site. The coating formulation without citric acid (C1) and the optimal coating formulation containing 1% of citric acid (C2) were introduced to the test. Data of swelling and erosion rate of the coated tablets at pH 6.8 only, thus, is shown in this report. The percentage increase in weight of the C1 and C2 at various time intervals up to 6 h at pH 6.8 are shown in Figure 4. Simultaneously, the degree of polymer erosion was also measured (Figure 5). It has to emphasize herein that data of the tablets in Figure 4 and Figure 5 was received after the tablets had passed through the pH 1.2 medium. So, the tablets only showed significant swelling and erosion rate after spending 4hrs total at both pH 1.2 (2 h) and pH 6.8 (2 h). The degree of swelling and erosion is dependent on the citric acid presence in coating formulations. It also matches the above dissolution results (Figure 3). At 2 h at pH 6.8, the percentage of swelling and erosion was higher in the case of C1 coated tablets without citric acid, inducing the higher release rate of drug from C1 formulation. More precisely, the higher erosion of C1 caused the higher drug release from C1. At 4 h and 6 h at pH 6.8, in contrary, the percentage of swelling was higher and the percentage of erosion was lower in the case of C2. This result explained why drug release from C2 could be sustained. Citric acid presence in the coating formulation helped to create thicker swellable layer but delay the erosion so that it could sustain the drug release. When a polymer has ability of swelling in aqueous media, it means that they can absorb significant amounts of water. The increased hydrophilicity of the polymer will lead to the more increased interaction between water and hydrogel, facilitating water diffusion and greater swelling. A balance among osmotic, electrostatic and entropy-favored dissolution forces facilitated polymer behaviors in water, driving the absorption or swelling process. A certain amount of elastic forces will be a more favorable condition for swelling of the ionic polymers at a more entropy-favored process as compared to the non-ionic ones. The increasing number of ions within the hydrogel will create more and more osmotic and electrostatic forces and hence, compelling it to behave thermodynamically as more space of the surroundings are taken up [23]. Moreover, a swellable polymer starts to erode when hydration is at a severely high swollen state because the interchain intermolecular forces will no longer be able to resist any external forces. Once it erodes, more surfaces of the dosage form will be exposed to the fresh swelling medium and facilitate more drug to release [24].

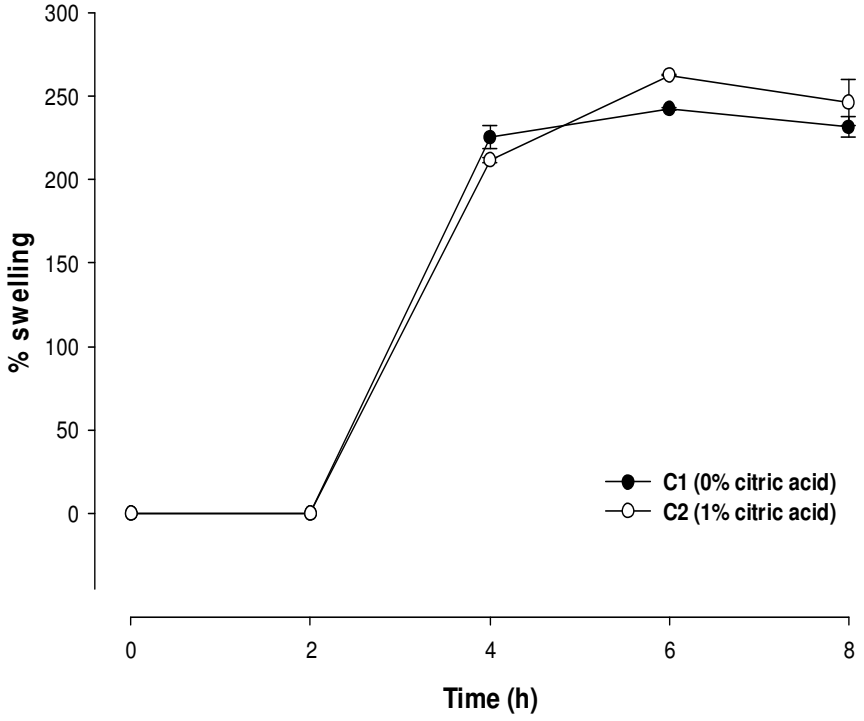

Figure. 4. Swelling percent of tablet without (C1) and with (C2) citric acid in coating polymer after 2h at pH 1.2 and 4h, 6h, 8h at pH 6.8.

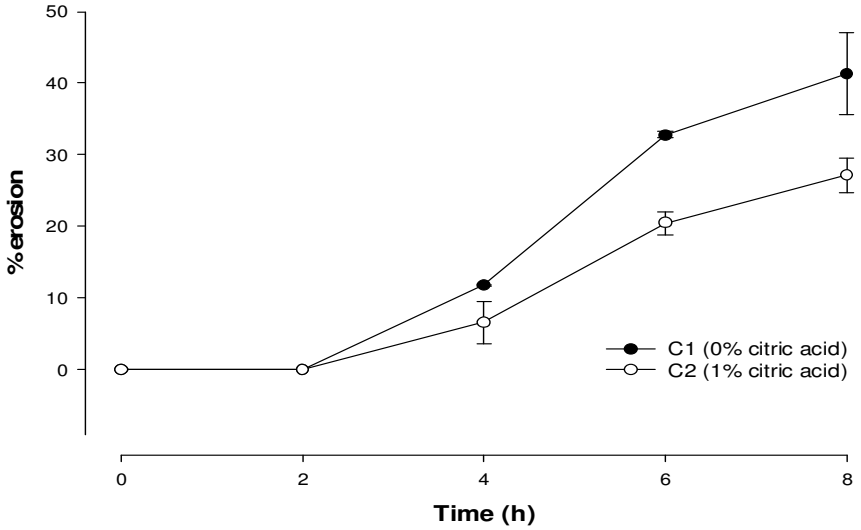

Figure. 5. Erosion percent of tablet without (C1) and with (C2) citric acid in coating polymer after 2h at pH 1.2 and 4h, 6h, 8h at pH 6.8.

Physicochemical characterization using instrumental analyses

FTIR spectroscopy often supplies information about the molecular interactions among functional groups, reflecting the structural behaviors of the samples [8, 25]. In this study, the FTIR spectra of the coated films were used to figure out if there's any interaction between citric acid and other components that may affect the drug release rate (Figure 6). Samples used in this analysis were film coatings of C1 and C2 tablets compared to pure citric acid as a reference. The spectrum of the pure citric acid has a stretching band at 1,625 cm^{-1} attributed to the C=O in the dissociated carboxylic acid, while it is 1,730 cm^{-1} when not dissociated. Compared with the spectrum of pure citric acid, there were no significant changes of the characteristic peaks of citric acid in the spectra of C2 containing citric acid, indicating no strong coordination of citric acid to other components of the coating formulation. Therefore, the sustained drug release rate from C2 was not caused by any chemical interaction between citric acid and other components.

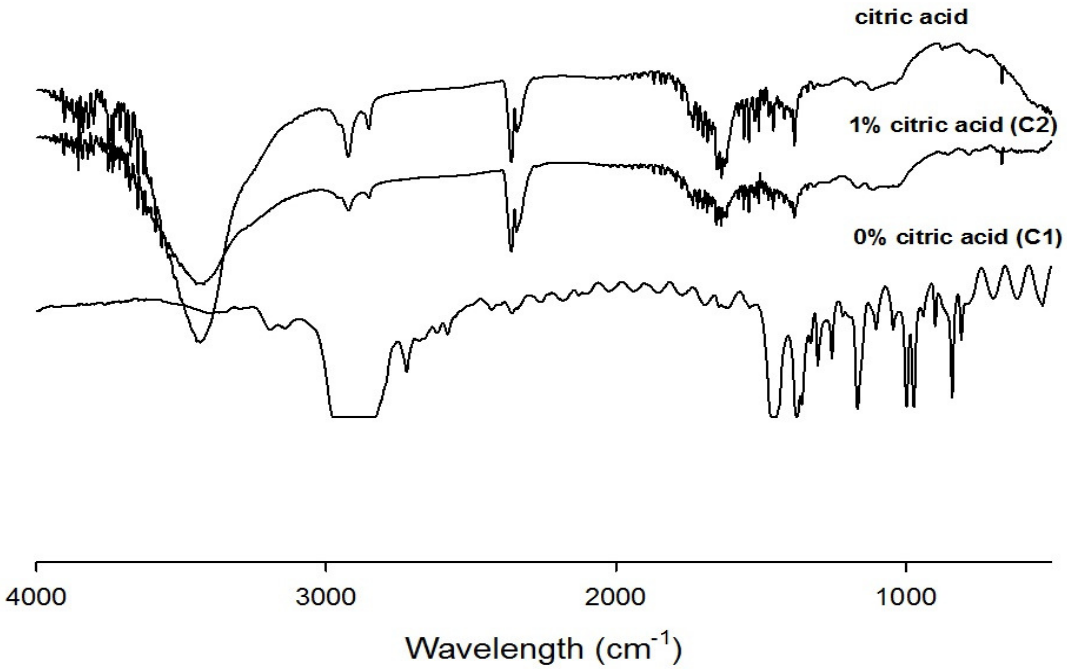

Figure. 6. FTIR spectra of acid citric, dried coating polymer without (C1) and with (C2) citric acid.

Since the scanning electron microscope (SEM) first became available for practical applications, it has been widely used for biomedical and pharmaceutical researches because it provides vivid, seemingly 3-dimensional images. Thus, it is a very useful imaging technique for mostly yielding information about the surface of a sample.

Figure 7 shows the surface morphology of the coated films of the C1 and C2 tablets using SEM. The surface morphology of the coated film C1 was more homogenous and smooth; meanwhile, the resulting undefined large lumps and the rough surface of the coated film C2 which may retard the dissolved time of coating film to exhibit slower erosion of C2 coated tablets [26].

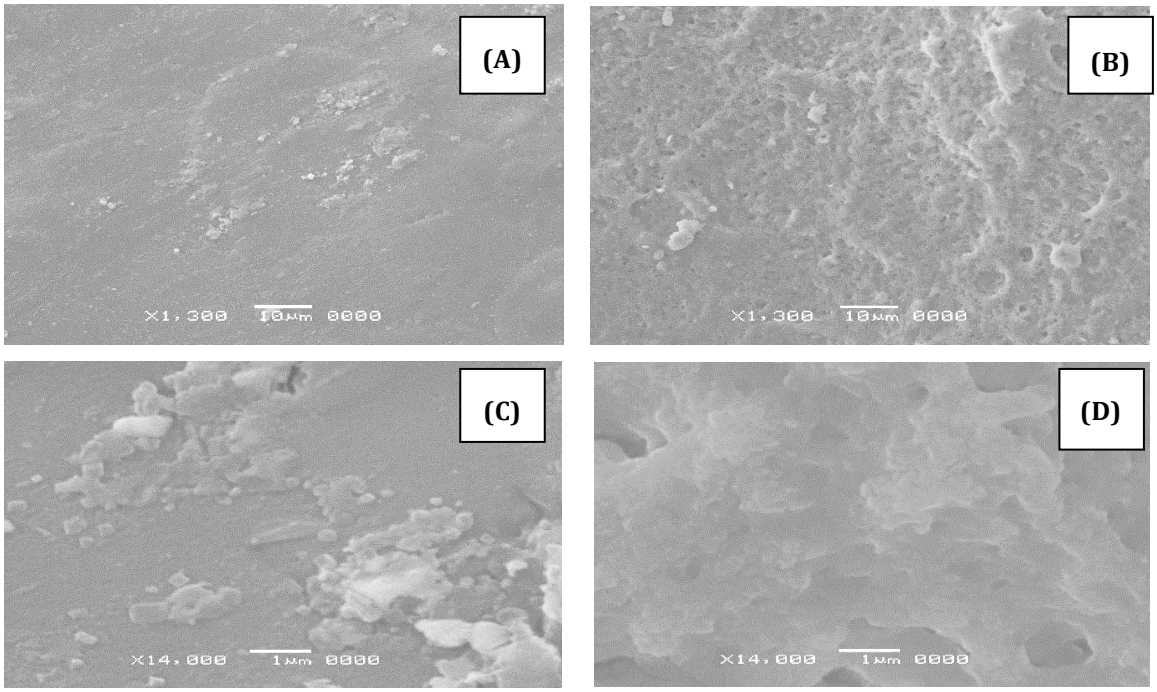

Figure. 7. SEM images of tablet without (A, C) and with (B, D) citric acid in coating polymer.

Therefore, only SEM analysis expressing the presence of citric acid which creates a rough surface with lumps of the C2 coating film elucidates the sustained drug release. Further, the FTIR spectra also helped to confirm that no chemical reaction between citric acid and other components participated in reasons for the sustained drug release.

CONCLUSION

The addition of citric acid with a sufficient amount in the Kollicoat MAE 100P coating solution was found out to be an interesting solution to achieve the sustained release of drug. It worked by curbing a common dissolving rate of the Kollicoat MAE 100P coating film for hindering drug release upon a higher swelling and slower erosion rate. The lumpy and rough coating film (observed through high resolution SEM images) is also a likely factor that may have contributed to be one of the reasons for the sustained drug release from the dosage form. However, chemical interaction between citric acid and other agents of the coating formulation should not be considered as a reason to explain this sustained drug release. The current study can be used to deliver drugs which are needed to target the colon with a concentrated amount for an effective treatment of colonic diseases.

ACKNOWLEDGEMENTS

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