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Original Article

Application of hydroxypropylated crosslinked starch from the grains of *Oryza sativa* L. as potential disintegrant in compressed solid dosage form

[Aplicación de almidón reticulado hidroxipropilado de los granos de *Oryza sativa* L. como desintegrante potencial en forma de dosificación sólida comprimida]

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Abstract

Context: The modification of starch from the grains of NSICRc222 rice variety may provide a new material with enhanced disintegrating functionality in compressed solid dosage forms.

Aims: To synthesize hydroxypropylated crosslinked rice starch that may possess characteristics of a good disintegrant.

Methods: Starch was isolated by the wet milling method. The crosslinking was performed using trisodium trimetaphosphate as crosslinking agent, and successively hydroxypropylated by using phosphorous oxychloride. The evidences of chemical modifications were determined by FTIR, TGA, and DSC. The application of modified rice starch as a disintegrant was evaluated by determining the dissolution profile, and was compared to the performance of commercially available disintegrants. The compatibility of modified rice starch was employed using FTIR, and the stability of the formulation was subjected to an accelerated stability study.

Results: The changes in infrared spectra and thermogram confirmed successful chemical modification of rice starch. Allopurinol and modified starch mixture staged from 0 to 3 months showed no significant changes in the infrared spectra, which suggest compatibility of HCR with allopurinol. The dissolution rate of allopurinol tablets at pH 1.2, pH 4.5, and pH 6.8 with various superdisintegrants were comparable to the dissolution rate that utilized hydroxypropylated crosslinked rice starch as disintegrant. The accelerated stability study showed no significant changes from 0th to 3rd month, and no degradation products were detected in the HPLC analysis.

Conclusions: The chemical modification of rice starch through crosslinking and hydroxypropylation yielded a novel material comparable to the commercially available superdisintegrants.

Keywords: crosslinking; disintegrant; hydroxypropylation; immediate release; NSIC Rc222-Tubigan 18; rice starch.

Resumen

Contexto: La modificación del almidón de los granos de la variedad de arroz NSIC RC 222 puede proporcionar un nuevo material con una funcionalidad de desintegración mejorada en formas de dosificación sólidas comprimidas.

Objetivos: Sintetizar almidón de arroz reticulado hidroxipropilado que pueda poseer características de un buen desintegrante.

Métodos: El almidón se aisló por el método de molienda húmeda. El entrecruzamiento se realizó con trimetafosfato trisódico como agente de entrecruzamiento, y sucesivamente se hidroxipropiló utilizando oxicloruro de fósforo. Las evidencias de modificaciones químicas fueron determinadas por FTIR, TGA y DSC. La aplicación de almidón de arroz modificado como desintegrante se evaluó determinando el perfil de disolución y se comparó con el desempeño de los desintegrantes disponibles comercialmente. La compatibilidad del almidón de arroz modificado se empleó mediante FTIR y la estabilidad de la formulación se sometió a un estudio de estabilidad acelerado.

Resultados: La caracterización por FTIR reveló una modificación exitosa del almidón de arroz según los cambios de espectros. Los cambios en los termogramas confirmaron la modificación exitosa del almidón de arroz. La mezcla de alopurinol y almidón modificado en etapas de 0 a 3 meses no mostró cambios significativos en los espectros infrarrojos, lo que sugiere compatibilidad de HCR con alopurinol. La velocidad de disolución de las tabletas de alopurinol a pH 1,2, pH 4,5 y pH 6,8 con varios superdesintegrantes fue comparable a la velocidad de disolución de HCR. El estudio de estabilidad acelerada no mostró cambios significativos del mes O al 3, y no se detectaron productos de degradación en el análisis HPLC.

Conclusiones: La modificación química del almidón de arroz a través de la reticulación y el hidroxipropilado produjo un material novedoso comparable a los superdesintegrantes disponibles comercialmente.

Palabras Clave: almidón de arroz; desintegrante; hidroxipropilado; liberación inmediata; NSIC Rc222-Tubigan 18; reticulado.

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INTRODUCTION

Drug discovery is a scientific discipline that has undergone continuous evolution over the years. It is no longer only focused on the discovery and development of new drugs and active principles but also on the discovery and development of new excipients. The increasing demand for drugs requires the need to increase production and, thus, leads to the problem of the availability of inert materials. Coupled with this, is the problem of supply for raw materials that are used in the production of excipients.

Pharmaceutical excipients are substances other than pharmacologically active substances that play an essential role in the drug development process and the formulation of stable oral solid dosage forms (Furrer, 2013). They are often added for several purposes – i.e., to make drug products more palatable (flavorants), to enhance appeal (colorants), to prevent microbial growth and decomposition (preservatives), to dissolve drug substances (solvents or vehicles), to improve stability (stabilizers), to increase bulk formation (bulking agents), to reduce friction (lubricants), to help free-flowing of granules (glidants), to prevent surface adhesion (anti-adherents), to enhance adhesion (binders), and to promote moisture penetration and dispersion (disintegrants) (Karthik, 2016). Thus, for every single dosage form, excipients contribute to the primary qualities of the drug and influence its physical form, texture, stability, overall appearance, and bioavailability.

Disintegrant is one of the primary excipients added to tablets to facilitate dispersion and breakup of the tablets into their primary components for faster dissolution upon coming in contact with the dissolution medium. The disintegrants help in the fast breakdown of oral dosage forms upon ingestion to promote intestinal absorption and bioavailability of active ingredients. Moreover, superdisintegrants are used in the formulation of orally disintegrating tablets, dispersible tablets which are used at lower concentrations of about 1% to 10% by weight compared to simple disintegrants (Kar et al., 2019). Traditionally, starch has been the disintegrant of choice in tablet formulations. Starch is the most widely used disintegrant as these are easily available, blend well with other excipients, and are pharmaceutically elegant. However, the concentration of starch as a disintegrant in solid dosage forms is high, typically 15% w/w (Hausler et al., 2009). This presents difficulty in tablet compaction as a result of elastic deformation and consequently yields tablet defects such as chipping and capping.

Rice is one of the most abundant sources of starch in Asian countries, especially the Philippines. The Philippine Rice Research Institute (PhilRice) is promoting high-yielding rice varieties to help farmers increase their production, one of which is NSICRc222 (Tubigan 18). A novel excipient with improved and value-added functionality may be achieved through chemical modification of the starch derived from the NSICRc222 variety. Furthermore, chemically modified substances are used as superdisintegrants made by crosslinking (Xiao et al., 2012); and hydroxypropylation may be introduced to the crosslinked material to produce modified starch (Rahaju et al., 2014). Modified starches and starch derivatives swell extensively with minimal gelling and optimum concentration levels of 4%-6% by weight. The starch forms a sticky and gelatinous matter that continues to aid the disintegration process. It also helps to hold and keep the tablet particles together due to their high swelling capacity even in low concentrations (Pahwa and Gupta, 2011). Acetylation and hydroxypropylation as individual modification techniques have been applied to rice and other starches that are carried out to overcome undesirable characteristics and improve their physico-chemical properties (Colussi et al., 2014; Granza et al., 2015; Shen et al., 2021). Additionally, acetylation improves paste clarity, flow properties, and increased swelling capacity (Lawal, 2004), while carboxymethylation of starch may increase water solubility, lowered gelatinization temperature, and paste stability (Kunle, 2019). While, dual-modified rice starches enhance the thermostability, enzyme resistance, and functional property (Iftikhar and Dutta, 2019). Crosslinking and hydroxypropylation of starch are both used to improve the stability and hardness of gels obtained from starch materials (Ravenelle and Rahmouni, 2006). These successive modifications may provide value-added functionality to the material, including disintegration characteristics in a compressed solid dosage form. Superdisintegrant is an important excipient in the formulation of the immediate-release compressed solid dosage form as it facilitates faster disintegration, thereby increasing the dissolution rate of active material in the drug preparation. Modifying the chemical structure of starch can provide new functionality and could act as a superdisintegrant due to enhanced wetting capacity and hydrophilicity brought about by crosslinking and hydroxypropylation. Moreover, the study aims to address the scarcity of raw materials as they may be more effective in lower concentrations as compared to unmodified starch, which in effect can improve functionality and minimize material cost.

Immediate release (IR) dosage forms are still popular due to economic and pharmacokinetic reasons. It may improve compliance, solubility, stability, bioavailability, allows high drug loading, cost-effective, adaptable, and amenable to existing processing and packaging machinery, and decreased disintegration and dissolution times (Neha, 2017). Superdisintegrant is important in IR dosage form, and developing novel material that can be used as an excipient is vital in formulation development, which could potentially solve the problem of material scarcity, patient and regulatory compliance. Allopurinol (ALO) is one of the drugs that exhibit dissolution difficulty. ALO is practically insoluble in water, resulting in poor bioavailability after oral administration (Runa et al., 2013). The drug belongs to the biopharmaceutics Classification System (BCS) class IV category at the 300 mg dosage strength (NDA, 2017) with poor aqueous solubility and permeability (Radhakrishnan et al., 2020). Moreover, several researches reported that allopurinol tablets failed to meet dissolution compendia requirements (Changdeo et al., 2011; Dai et al., 2020; Runa et al., 2013). Hence, utilizing allopurinol as an active material can provide insights into the utility of hydroxypropylated crosslinked rice starch as a disintegrant in formulating compressed solid dosage form.

This study modified the rice starch through crosslinking and hydroxypropylation. The potential application as a disintegrant was assessed by determining the dissolution profile of allopurinol 300 mg tablet that is formulated with the modified rice starch, as compared to its native rice starch form and commercially available superdisintegrants. The comparative dissolution behavior of the hydropropylated crosslinked rice starch toward other commercially available disintegrants can provide good insights into its utility as a novel disintegrant in comparison to its native form and other superdisintegrants.

MATERIAL AND METHODS

The plant material, NSIC Rc222 (Tubigan 18) variety of *Oryza sativa* L. and its certificate of authenticity was obtained from the Philippine Rice Research Institute, Los Baños, Laguna. All chemicals, reagents, and solvents that are used in this study were purchased from Alysons' Chemical Enterprises, Inc., Quezon City, Philippines. Trisodium trimetaphosphate and propylene oxide were obtained from Sigma-Aldrich Co., United States. Lactose monohydrate (Pharmatose 50 M) and magnesium stearate were obtained from DFE Pharma, Germany. Sodium starch glycolate was obtained from Yung Zip Chemical Ind. Co. Ltd. Taiwan, crosslinked polivynylpyrrolidone (crospovidone) was obtained from BASF Pharmaceutical Ingredients, Metro Manila, Philippines. Crosslinked sodium carboxymethylcellulose (croscarmellose) was obtained from Amit Hydrocolloids, Mumbai, India. Allopurinol (pharmaceutical grade) was used as received from Yixing City Xingyu Pharmaceuticals Co., Ltd., Jiangsu, China. Allopurinol USP reference standard was procured online from USP Store, Inc.

Synthesis of hydroxypropylated crosslinked rice starch

Isolation of starch

The alkali steeping process developed by Bindar et al. (2013) was employed to isolate starch from the rice. Rice grains were milled to facilitate greater surface area contact between alkali solution and solid plant material. The milled rice was steeped in five volumes of 0.40% sodium hydroxide solution for 24 h at 25°C to soften the endosperms of the rice. Then, the mixture was filtered using 100 mesh nylon cloth to obtain the rice residues. After which, the residues were pressed using mortar and pestle to rupture the cellular structure. The steeping process was repeated 10 times, in which the filtrate became negative for the presence of protein using the Biuret test. Ten drops of 0.01% sodium metabisulfite solution (Usman et al., 2014) were incorporated in each steeping stage to prevent microbial growth.

The crude rice starch was purified by suspending it in distilled water until sediments are completely formed. The residue was collected through decantation and filtration using a 200-mesh nylon filter cloth. The procedure was repeated until the filtrate was no longer alkaline. The liquid alkalinity was determined by using a phenolphthalein indicator. The purified starch was dried in ambient conditions for 5 days.

Qualitative test for starch

One gram of rice starch was suspended in 2 mL of water (room temperature). Then 15 mL of boiling water was added to produce a smooth mixture. The mixture was boiled for two minutes and allowed to cool until a translucent, whitish gelatinous mixture was obtained. A few drops of iodine solution were added to the mixture. A positive result for the presence of starch yields a reddish violet, which upon cooling turns into deep blue color (Tiwari, 2015).

Crosslinking and hydroxypropylation of NSICRc222 rice grain starch

NSICRc222 rice grain starch (RGS) was crosslinked and hydroxypropylated with some modifications following the procedures according to Lenaerts et al. (2003). Two hundred grams of RGS were subjected to crosslinking and hydroxypropylation. About 370 mL

of deionized water were added to 200 g of RGS containing 0.30 g sodium hydroxide and 16 g of sodium sulfate. The slurry was then maintained at 30°C for 1 h. After which, 2.0 g trisodium trimetaphosphate, a crosslinking agent, was added to the mixture and allowed to react for 3 h with constant stirring.

The crude mixture was transferred into the round bottom flask, heated to 40°C for 30 min, and purged with nitrogen. After 30 s, 12 mL of propylene oxide were added. The reaction mixture was kept at 40°C and under a nitrogen blanket for 20 h. After which, pH was adjusted to 5.5 using 0.1 N sulfuric acid in 1:2 v/v. The slurry was then washed with 370 mL of deionized water and the mixture was allowed to suspend until sediments are completely formed. The residue was collected after decantation and filtration (Whatman No. 5) and dried in an oven at 160°C for 48 h.

Characterization of hydroxypropylated crosslinked rice starch

Fourier transformed infrared (FTIR) spectroscopy

The samples were analyzed using an FTIR spectrometer (Shimadzu IRAffinity-1S, Japan). A few mg of rice starch, crosslinked rice starch, and hydroxypropylated crosslinked rice starch was added to pure potassium bromide powder (approximately 200 mg) and grounded using mortar and pestle. The finely grounded sample was then put in the sample holder ready for scanning in Fourier Transform Infrared or FTIR spectrometer (Shimadzu IRAffinity-1S, Japan) in the range 4000 to 400 cm^{-1}. The method was adopted from Changdeo et al. (2011) with modifications.

Thermogravimetric analysis (TGA)

The samples were analyzed using Perkin Elmer TGA 4000. About 1 mg of sample was placed in a standard aluminum pan then analyzed at a heat range of 25 to 850°C at a rate of 10°C/min under an atmosphere of dry nitrogen. The method was adopted from Xie et al. (2019) with modifications.

Differential scanning calorimetry (DSC)

The samples were analyzed using Perkin Elmer DSC 4000. The sample was weighed to about 5 mg and placed in a standard aluminum pan. The parameters for DSC were set to heat range from 25 to 250°C at a rate of 10°C/min under an atmosphere of dry nitrogen (Hu et al., 2014; Zaidul et al., 2008).

Compatibility of hydroxypropylated crosslinked rice starch

A mixture of hydroxypropylated crosslinked rice starch (HCR) and allopurinol (ALO) was triturated at a 1:1 ratio to produce a total weight of 10 mg. Then, the mixture was added with 3 mL of deionized water and triturated to form a uniform wet mass. The damped mass was dried in an oven for 12 h at 70°C. The dried powder mixture was placed on an enclosed bottle and then stored in a desiccator. A sample is withdrawn at 0^{th}, 1^{st}, 2^{nd}, and 3^{rd} month for FTIR Analysis. The FTIR spectra of allopurinol and hydroxypropylated crosslinked rice starch were also obtained to serve as a reference in determining the absorption peaks in the sample. The method was adopted from Prathyusha and Murthy (2013) with modifications.

Approximately 1-2 mg of the sample was added to pure potassium bromide powder (approximately 200 mg) and grounded using mortar and pestle. The finely grounded sample was then put in the sample holder ready for scanning in Fourier Transform Infrared or FTIR spectrometer (Shimadzu IRAffinity-1S, Japan) in the range 4000 to 400 cm^{-1}.

Tablet compression of allopurinol 300 mg IR tablets

Allopurinol (ALO) powder blends were prepared with various disintegrating agents. The weight of ALO was maintained at 300 mg as the labeled amount. Table 1 shows the composition of the formulation. The filler, binder, and lubricant used in the formulation were based on the commercially available preparation of allopurinol immediate-release tablets, including the innovator drug product (Casper Pharma LLC, 2018).

The binder solution was prepared by dissolving 50 g of povidone in 100 mL of purified water and set aside before use. This was a preparation of solution which was utilized in 10 to 15 min after being prepared. Seven hundred fifty grams of (750 g) allopurinol and 145 g of lactose monohydrate were sifted in Mesh No. 14 before mixing through V-blender (2-kg maximum capacity) for 10 min. The powder blend was unloaded and kneaded mechanically with the povidone solution until homogenous wet mass was achieved. The wet mass was screened in Mesh No. 14 to form a narrower granule size. Then, the wet granules were dried in an oven at 70°C for about 15 h. After drying, the granules were screened in Mesh No. 14, to break down agglomerated particles. Then, the previously sifted (Mesh No. 30) 50 g disintegrants and 5 g magnesium stearate were added sequentially for 5 and 3 min, respectively, in V-blender. The powder blends were stored at 25°C and tightly sealed in a

Table 1. Unit dose formulation for allopurinol tablet using various disintegrating agents.

Component	Unit dose (mg)					
	A_1	A_2	A_3	A_4	A_5	A_6
Allopurinol	300	300	300	300	300	300
Lactose monohydrate	58	58	58	58	58	58
Povidone	20	20	20	20	20	20
Hydroxypropylated crosslinked rice starch	20					
Rice starch		20				
Corn starch			20			
Sodium starch glycolate				20		
Croscarmellose					20	
Crospovidone						20
Magnesium stearate	2	2	2	2	2	2
Total	**400**	**400**	**400**	**400**	**400**	**400**

polyethylene bag before compaction. A 1 kg batch was prepared in all of the formulations. In addition, the manufacturing procedure and parameters were maintained constant in all of the trials.

The powder blends were compressed in a 10-station rotary tablet press machine (Zp10b rotary tablet press machine, Shanghai Famo Machinery Manufacture & Trade Co., Ltd., China) using 10 mm punches and dies. The average tablet weight and thickness were targeted at 400 mg and 3.65 mm, respectively. The tablets were tested for weight variation, thickness, dissolution, and assay according to USP-NF 2021 methods.

Determination of tablet weight

Each of twenty (20) tablets were weighed individually using an analytical balance and the average tablet weight was calculated; the requirements were met if not more than 2 tablets show ± 5% weight variation (USP- NF, 2021; Troy and Beringer, 2006).

Determination of tablet thickness

Twenty (20) tablets were measured in diameter using digital caliper; the requirements were met if all tablets are within ± 5% variation based on the average thickness value (USP- NF, 2021; Troy and Beringer, 2006).

In vitro dissolution study

Six (6) tablets, weighed accurately, were suspended in each of 6 vessels of a USP type 2 (paddle type) dissolution tester containing 900 mL of 0.01 N HCl preheated at 37 ± 0.5°C and rotated at a speed of 75 rpm; 2 mL aliquot portions were withdrawn after 45 min, filtered immediately (Whatman No. 1), diluted to 50 mL with the dissolution medium and read for absorbance at 250 nm; a 0.1 mg/mL USP allopurinol reference standard in the dissolution medium is also read at 250 nm; the amount of allopurinol that dissolves after 45 minutes was calculated. The requirements were met if at least 75% of allopurinol in each of the 6 tablets dissolved after 45 min (USP- NF, 2021).

Tablet assay

Twenty (20) tablets were assayed for allopurinol content using a Shimadzu Prominence HPLC unit with a photo-diode array detector at 250 mm; separation was accomplished using Inertsil ODS-3 (C18, 4.0 × 300 mm, I.D., 5 µm) at 40°C at an injection volume of 15 µL using as mobile phase an isocratic run of methanol: 0.05 M ammonium phosphate (95:5, v/v) at flow rate of 2 mL/min. The method was adopted in USP - NF (2021) with some modifications.

Determination of dissolution profile

The procedure for the dissolution experiment was adopted from guidance for industry dissolution testing of immediate-release solid oral dosage forms (US FDA, 2019). The dissolution medium for 12-sample runs at pH 1.2, pH 4.2, and pH 6.8. About 900 mL of the dissolution medium were transferred in the dissolution vessel and preheated to 37 ± 1°C. One tablet of allopurinol was loaded into each dissolution vessel. About 5 mL of the sample were withdrawn at 5, 10, 15, 20, 30, 45, and 60 min time periods. Five mL of dissolution medium were replaced in each sample withdrawal. The amount of allopurinol dissolved was determined by UV-vis spectrometry at 250 nm.

Accelerated stability study

Before subjecting the sample in stability study, the sample was blister packed in PVC and aluminum foil (10 × 10's) and contained in cartoon boxes. Samples of the allopurinol tablets were stored at 40 ± 2°C and 75% RH ± 5% RH and withdrawn every month for 3 months and tested for assay and dissolution. The method was adopted from ASEAN Guideline on Stability of Drug Product (2005).

Statistical analysis

All analytical methods conducted in this study were performed in triplicate per batch. Replicate measurements were expressed as mean ± standard error of the mean. The one-way analysis of variance (ANOVA) was used to demonstrate if there were significant changes in the data obtained from stability testing.

RESULTS AND DISCUSSION

Synthesis and characterization of hydroxypropylated crosslinked rice starch

A white odorless rice starch powder was obtained after the isolation. Identification for the presence of starch was determined by the iodine test. The average percentage yield of starch in NSICRc222 (Tubigan 18) was 85.5 ± 0.8%. A white odorless powder was obtained after crosslinking and hydroxypropylation with an average percentage yield of 95.8 ± 1% after 5 batches.

Fourier Transform Infrared (FTIR) Spectroscopy

Infrared spectroscopy was employed to determine the bond vibration due to the absorption of infrared waves. The intensities and frequency absorptions of the samples were used to track the changes in modifying starch. Fig. 1 shows the infrared spectra of rice starch, crosslinked rice starch, and hydroxypropylated crosslinked rice starch. The important changes were tabulated in Table 2. The spectrum of rice starch did not significantly change after crosslinking, and only subtle differences can be accounted for the changes in the spectrum. This was however consistent with the studies conducted by several researchers. In the study conducted by Liu et al. (2013), no significant changes were detected in infrared spectra after crosslinking maize starch, except for the absorbance at 1017 cm^{-1}, in which the absorption intensity was a little bit greater than the native starch. Singh and Nath (2011) observed slight shifting of peak frequencies and intensities after crosslinking. In the study of Feng and Wen (2017), slight changes in peaks were observed, however, a disappearance of peak at 2900 to 3000 cm^{-1} were observed as a result of peak broadening in the region 3000 to 3600 cm^{-1} due to O-H stretching. Li et al. (2020) crosslinked carboxymethyl starch, wherein a slight difference in the intensities of O-H stretch was observed, whereas, the absorption peak at 1021 cm^{-1} was significantly enhanced. In this study, changes in the peak intensities and shifting of absorption frequency were observed as a result of crosslinking. The O-H stretch of rice starch at 3468 cm^{-1} shifted to 3443 cm^{-1} when it was crosslinked. The intensity of the O-H stretch increases slightly. This can be seen through the relative intensity of the neighbor absorption peak at 2930 ± 2 cm^{-1}. As can be noticed, the distance in the peak in terms of % transmission increases on the crosslinked rice starch. Moreover, the crosslinked rice starch bears a broader signal than the rice starch. This is evident in the adjacent peak at 3050 to 3060 cm^{-1}, in which a slight disappearance of the peak on the crosslinked rice starch is observed. The broadening of the peak due to O-H stretching vibration suggests that hydrogen-bonding was enhanced in the crosslinked rice starch. This was probably due to force interaction of the hydroxyl groups as a consequence of closer proximity to hydrogen bond acceptor obtainable through crosslinking. Another noticeable change can be seen at the signal due to the C-H stretch, the signal slightly shifted from 2928 to 2930 cm^{-1} after crosslinking. The characteristic peak of rice starch at 1675 cm^{-1} shifted to 1680 cm^{-1}.

Table 2. Characterization of rice starch, crosslinked rice starch, and hydroxypropylated crosslinked starch via infrared spectroscopy.

Characteristic absorption (cm^{-1})			Functional groups and types of vibration
Rice starch	Crosslinked rice starch	Hydroxypropylated crosslinked rice starch	
3468	3443	3313	O-H stretch
3050	3060	-	C-H stretch
2928	2930	2932	C-H stretch
1675	1680	1640	
1153	1153	1130	O-C stretch, anhydroglucose ring
1088	1090	1070	

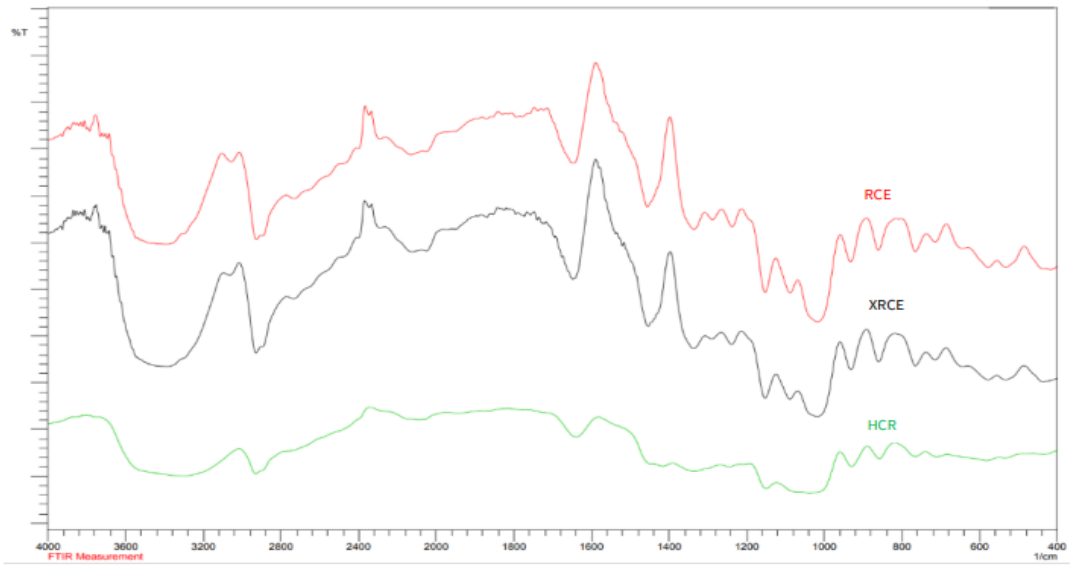

Figure 1. Infrared spectra of rice starch (RCE), crosslinked rice starch (XRCE), and hydroxypropylated crosslinked rice starch (HCR).

The hydroxypropylation of crosslinked rice starch caused significant changes in the spectra. The signal due to the O-H stretch becomes more pronounced and broader, which indicates that hydroxypropylation was successfully synthesized. The broadening of the peak suggests that hydrogen bonding was enhanced, and this was due to the incorporation of hydroxypropyl groups in the starch. The hydroxypylation extended the O-H group on the outward portion of the starch molecular structure, thereby, enhancing the hydrogen bonding in its adjacent molecule. Moreover, the signal shifted to 3314 cm^{-1} and the peak due to the stretch at 3050 cm^{-1} disappeared due to the broadening of the signal. Furthermore, the signal due to the C-H stretch at 2930 cm^{-1} shifted to 2932 cm^{-1} and became sharper. The characteristic peak at 1675 cm^{-1} shifted to 1640 cm^{-1} and the O-C stretch due to anhydroglucose ring shifted to 1130 and 1070 cm^{-1}. All these changes suggest successful chemical modification of rice starch.

Thermogravimetric analysis (TGA)

The thermograms shown in Fig. 2 show the thermal decomposition of rice starch (A), crosslinked rice starch (B), and hydroxypropylated crosslinked rice starch (C). The differences in the thermal decomposition of the samples indicated that chemical modification was successfully made. In Fig. 2, the TGA thermogram exhibits three-stage mass loss in all of the samples. The first stage appeared in the range of 28 to 50°C, which is associated with the loss of water present in the sample. The second stage in the range 280 to 350°C is a mass loss due to thermal decomposition. The third stage in the range of 410 to 510°C is due to the glowing combustion. These stages were consistent in the TGA thermograms conducted by Liu et al. (2013; 2014; 2016) in characterizing thermal degradation of corn starch and crosslinked cornstarch samples. The onsets of thermal degradation of 298.87, 300.10, and 279.68°C were obtained for the samples rice starch, crosslinked rice starch, and hydroxypropylated crosslinked rice starch respectively as shown in Table 3, which indicates that modification in the chemical structure of rice starch was made. The changes in their thermal decomposition as a result of chemical modification in the rice starch molecule can be illustrated in the first derivative peak temperature (T_{peak}). T_{peak} of 319.08°C was obtained from the rice starch sample. This decreases to 314.95°C as a result of crosslinking the starch, and up to 301.96°C upon hydroxypropylation. Moreover, the improvement in thermal stability can be assessed further on the temperature by which 50% of the mass has degraded (T50% mass loss). An increase of T50% indicates an improvement in thermal degradation. The T50% mass loss obtained from rice starch was 316.44°C. This increased to 320.66°C for crosslinked rice starch, and 318.84°C for hydroxypropylated crosslinked rice starch. A 1.33% increase in thermal stability can be calculated for crosslinked rice starch, which is consistent with the calculated value using assessing the first derivative peak temperature. An improvement of 0.75% for the hydroxypropylated crosslinked starch can be calculated based on T50% mass loss. This is a significant difference relative to the computed increase in thermal stability on the first derivative peak temperature. The weight loss of the sample in the

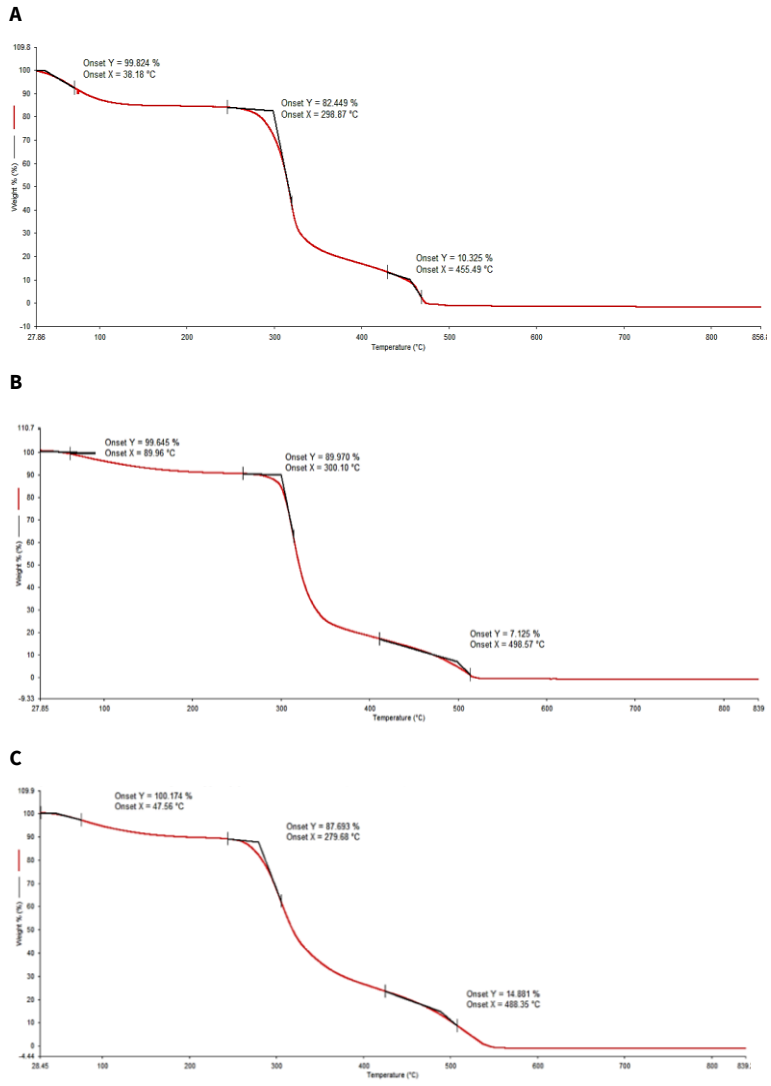

Figure 2. TGA thermograms of **(A)** rice starch; **(B)** crosslinked rice starch; **(C)** hydroxypropylated crosslinked rice starch.

Table 3. TGA thermograms of rice starch, crosslinked rice starch, and hydroxypropylated and crosslinked rice starch.

Sample	Inflect temp. (°C)	T50% mass loss (°C)	T_{Peak} (°C)	% Mass change (280-350°C)	Residue (%)
Rice starch	298.87	316.44	319.08	57.57	10.33
Crosslinked rice starch	300.10	320.66	314.95	63.97	7.13
Hydroxypropylated crosslinked rice starch	279.68	318.84	301.96	45.86	14.88

decomposition stage in the range 280 to 350°C corresponds to the breakdown of the starch polymeric chain, crosslink bond, and thermal decomposition of glucose units (Zhao et al., 2008). A mass change of 57.57% was obtained from rice starch, and a significant increase in mass change was obtained from the crosslinked rice starch with 63.97%. This increase can be associated with the bulk decomposition of polymer chains chemically connected as a result of crosslinking. And as a result, a residue of 7.13% was obtained, which was relatively smaller in amount compared to the other two samples. On the other hand, the mass change of the hydroxypropylated crosslinked rice starch was way lower compared to the rice starch. This can be attributed to the hydroxypropylation, which somehow could have weakened the crosslinked bonds and resulted in a higher residue, which may be somehow a moiety with higher crosslink density and lesser hydroxypropylation.

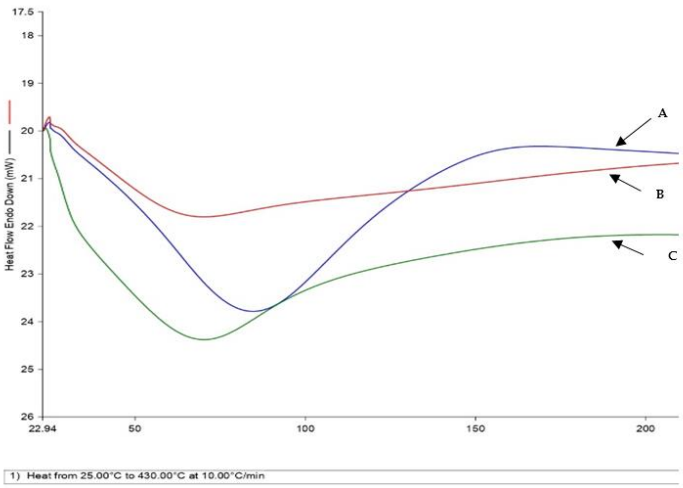

Figure 3. DSC thermograms of **(A)** rice starch; **(B)** crosslinked rice starch; **(C)** hydroxypropylated crosslinked rice starch

Table 4. DSC endotherms of various samples

Sample	Endothermic peak (°C)
Rice starch	84.39
Crosslinked rice starch	69.37
Hydroxypropylated crosslinked rice starch	68.71

Differential scanning calorimetry (DSC)

Fig. 3 shows the DSC thermograms of rice starch (A), crosslinked rice starch (B), and hydroxypropylated crosslinked rice starch (C). All the curves show a similar trend, that is, an endothermic peak was observed in all samples. The endothermic peak corresponds to the gelatinization temperature of the samples (Hu et al., 2014; Zaidul et al., 2008). The gelatinization temperature decreased as a consequence of chemical modification as shown in Table 4. A gelatinization temperature of 84.39°C was derived from rice starch. The crosslinking of rice starch caused the gelatinization temperature to decrease to 69°C; whereas, a gelatinization temperature of 68.71°C was obtained from the hydroxypropylated crosslinked rice starch. Moreover, the endothermic peak of the crosslinked rice starch differs significantly from the unmodified rice starch. This change in the peak was significant and indicated that the rice starch was modified. Moreover, the endothermic peak became more pronounced again after hydroxypropylation, which could be attributed to the introduction of hydroxypropyl groups in the starch.

Compatibility of HCR with allopurinol

Fig. 4A shows the infrared spectra of allopurinol, hydroxypropylated crosslinked rice starch, and allopurinol-hydroxypropylated crosslinked rice starch mixture (at 0^{th} month). The allopurinol showed C-H stretch at 3000 cm^{-1} due to the pyrimidine ring. Imbedded in the signal, is a weak N-H stretching band at 3356 cm^{-1}. A characteristic peak at 1711 cm^{-1} was also detected due to the C-O stretch from the keto form of 4-hydroxytautomer. The hydroxypropylated crosslinked rice starch showed a characteristic peak enumerated in Table 5. Shifting and merging of peaks were observed in the physical mixture of allopurinol and hydroxypropylated crosslinked rice starch as shown in the graph (0^{th} month) in Fig. 4A. A union of peaks due to the C-H stretching of the pyrimidine ring in allopurinol 3000 cm-1 and O-H stretching of hydroxypropylated crosslinked rice starch at 3314 cm^{-1} created a very wide band of signal between 3600 and 2400 cm^{-1}. The signal at 1711 cm^{-1} due to C-O stretching in the keto form of 4-hydroxytautomer in allopurinol has slightly shifted to 1707 cm^{-1}. The O-C stretching in the anhydroglucose ring of hydroxypropylated crosslinked rice starch shifted from 1070 and 1130 to 1079 and 1022 cm^{-1}. The shifting of peaks was due to the interaction of these groups with the other molecule. Fig. 4B shows the allopurinol-hydroxypropylated crosslinked rice starch mixture staged from 0-3 months in a desiccator at room temperature. No significant changes in the infrared spectra were observed, which suggests that the mixture is stable and no chemical change transpired as a consequence of their chemical interactions after 3 months.

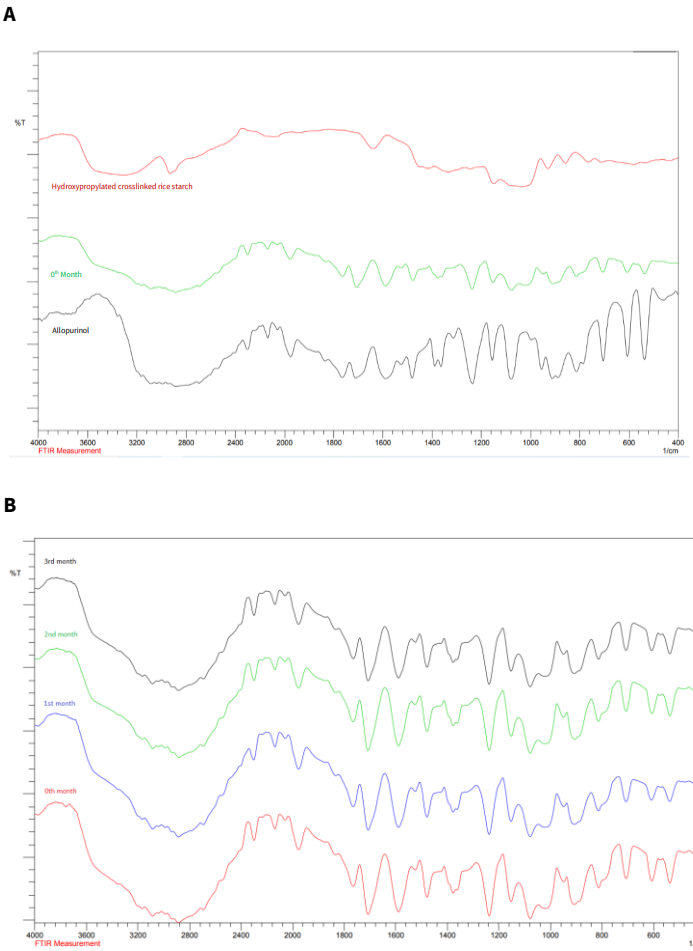

Figure 4. (A) Infrared spectra of allopurinol, hydroxypropylated crosslinked rice starch, and allopurinol-hydroxypropylated crosslinked rice starch mixture (at 0th month); **(B)** Allopurinol-hydroxypropylated crosslinked rice starch mixture at 0th, 1st, 2nd, and 3rd month.

Table 5. FTIR spectral data of allopurinol, hydroxypropylated crosslinked rice starch, and allopurinol-hydroxypropylated crosslinked rice starch mixture.

Sample compound	Frequency (cm^{-1})	Assignment
Allopurinol	3356	N-H stretching band
	3000	C-H stretching, pyrimidine ring
	1711	C-O stretching, keto form of 4-hydroxytautomer
Hydroxypropylated crosslinked rice starch	3314	O-H stretching, very broad, hydrogen-bonded hydroxylpropyl group
	2932	C-H stretching
	1640	C-O bending associated with OH group
	1070 and 1130	O-C stretching, anhydroglucose ring
Allopurinol and hydroxypropylated crosslinked rice starch mixture	3600 to 2400	Union of peaks due to O-H stretching, strong and broad, hydrogen-bonded hydroxylpropyl group (in HCR) and C-H stretching, pyrimidine ring (in allopurinol)
	1707	C-O stretching, keto form of 4-hydroxytautomer (signal due to allopurinol)
	1022 and 1078	O-C stretching, anhydroglucose ring

Determination of dissolution profile

Table 6 shows the calibration curve equation for determining the allopurinol content in tablet samples. A good linear fit was obtained in all of the methods with a coefficient of determination (R^2) of 0.9999 for UV-vis spectrophotometry at solution pH of 1.2, and 1.000 at pH 4.5 and 6.8. The detection limit (Cm) and quantitation limits (CQ) for the UV-vis spectrophotometry were determined to establish measurement merits in quantifying the amount of dissolved allopurinol in the dissolution profile experiment. Table 7 shows Cm and CQ values. All of the measurements conducted in the experiment were above CQ. Prior to analysis the assay of all samples was determined as shown in Table 8.

Fig. 5A shows the dissolution profile of allopurinol tablets at pH 1.2. The formulation that utilizes corn starch (CRN) and rice starch (RCE) exhibited very slow dissolution relative to the formulation that utilizes super disintegrants. At 45 min, only 6.10 ± 1.00 and 10.65 ± 2.12% were dissolved for CRN and RCE, respectively, and both formulations did not exceed over 20% dissolution at 120 min. Among the three superdisintegrants, crospovidone (XPV) revealed a faster dissolution rate compared to sodium starch glycolate (SSG) and croscarmellose sodium (XCM). A relatively slower rate was observed in SSG with a dissolution rate of 20.13 ± 3.60% at 45 min and 35.19 ± 4.27% at 120 min, followed by XCM with a dissolution rate of 36.93 ± 3.61% at 45 min and 62.30 ± 5.38% at 120 min. The dissolution rate behaviors of these three superdisintegrants were consistent with the available literatures. The swelling capacity of some disintegrants is pH-dependent (Desai et al., 2016) and the sedimentation volume of crosslinked starch and cellulose were affected by pH, whereas crospovidone and pregelatinized starch were unaffected (Shangraw et al., 1980). Chen et al. (1997) reported that the disintegration rate of tablets containing sodium starch glycolate and croscarmellose sodium decreased in acidic media but the tablets containing crospovidone were unaffected. Moreover, SSG and XCM contain sodium that interferes with the disintegration at low pH. Its performance is affected due to the ionization pattern of the excipients (Zarmpi et al., 2020). In addition, the electrostatic interaction between sodium and the chloride ions present in the dissolution medium creates a thin layer of ions on the tablet surface; thus, hindering the entry of water into the tablet. This phenomenon slowed down the swelling of the tablet, and ultimately manifested a slower dissolution. Interestingly the dissolution characteristic of the allopurinol tablet with hydroxypropylated and crosslinked rice starch (HCR) was at par with the one formulated using crospovidone (XPV). The tablet formulated with crospovidone exhibited the fastest dissolution (60.77 ± 5.01% at 45 min, and 79.20 ± 5.52% at 120 min); while HCR dissolved 56.68 ± 4.49% at 45 min, and 78.63 ± 3.93% at 120 min. The crosslinking and hydroxypropylation brought a significant enhancement in the disintegration of the tablet, which resulted in a faster dissolution of the active ingredient.

The dissolution rate of CRN and RCE at pH 4.5 remained slower and about 20% active material dissolved at 120 min as shown in Fig. 5B. The dissolution rate of the hydroxypropylated and crosslinked rice starch (HCR) was significantly enhanced with the dissolution of 55.14 ± 4.82 % at 45 min, and 73.71 ± 3.07 % at 120 min. The dissolution behavior of HCR was comparable to that of SSG (48.33 ± 7.35% at 45 min, and 77.57 ± 8.31% at 120 min) and XPV (50.57 ± 6.58% at 45 min, and 73.82 ± 6.50% at 120 min). The fastest dissolution was observed on the formulation utilizing croscarmellose sodium (XCM) with 64.49 ± 5.56% dissolved at 45 min, and 82.45 ± 3.11% dissolved at 120 min. This confirmed that the dissolution rate of tablet that utilizes croscarmellose sodium and sodium starch glycolate were impeded at low pH.

Table 6. Calibration curve equation in determining the allopurinol content in tablet samples using UV-vis spectrophotometry.

Parameter	pH 1.2	pH 4.5	pH 6.8
Calibration Equation	y = 0.0587x + 0.0107	y = 0.0599x – 0.0006	y = 0.0584x + 0.0016
R^2	0.9999	1.000	1.000

Where: y is the instrument response, x is the allopurinol concentration, and R^2 is the coefficient of determination.

Table 7. Detection quantitation limits of UV-Vis analytical method at different solution pH.

Solution pH	Detection Limit, C_m (µg/mL)	Quantitation Limit, C_Q (µg/mL)
1.2	0.0822	0.1895
4.5	0.0806	0.1858
6.8	0.0827	0.1576

Table 8. Percentage assay of allopurinol tablet samples.

Sample	% Assay
A_1	99.89 ± 1.80
A_2	101.14 ± 1.09
A_3	99.55 ± 1.75
A_4	100.68 ± 1.04
A_5	99.32 ± 1.68
A_6	101.02 ± 1.61

Allopurinol tablets containing: A_1= hydroxypropylated crosslinked rice starch; A_2 = rice starch; A_3 = corn starch; A_4 = sodium starch glycolate; A_5 = croscarmellose; A_6 = crospovidone

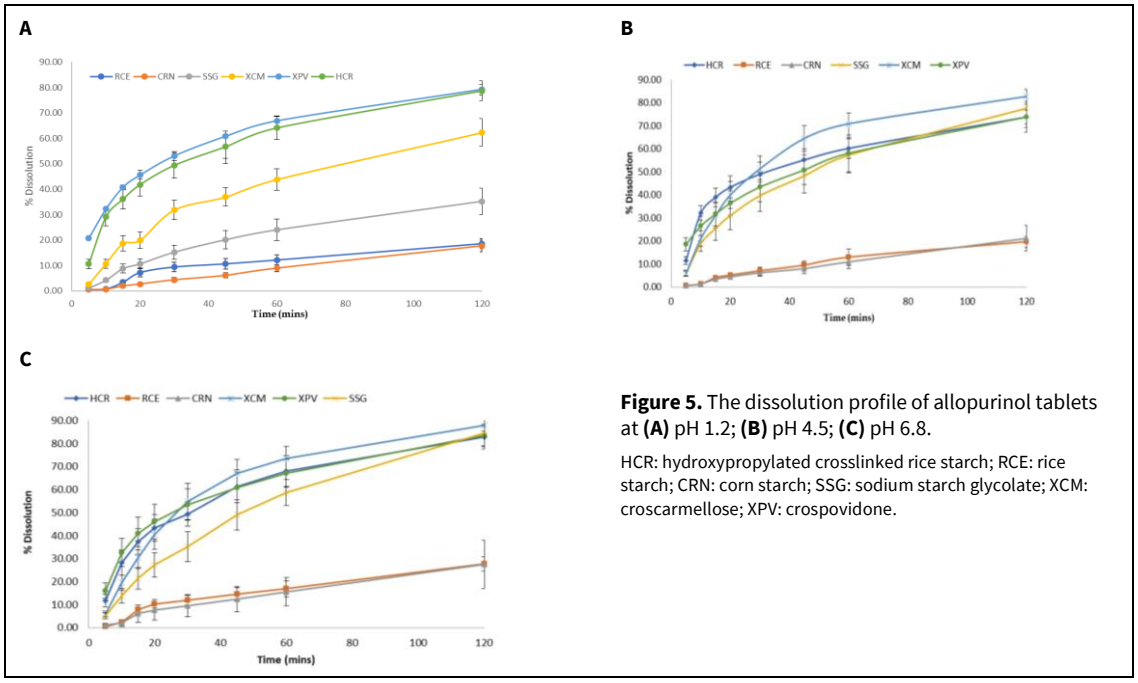

Figure 5. The dissolution profile of allopurinol tablets at **(A)** pH 1.2; **(B)** pH 4.5; **(C)** pH 6.8.

HCR: hydroxypropylated crosslinked rice starch; RCE: rice starch; CRN: corn starch; SSG: sodium starch glycolate; XCM: croscarmellose; XPV: crospovidone.

Fig. 5C shows the dissolution profile of allopurinol tablets at pH 6.8. The dissolution rate of the allopurinol with corn starch and rice starch as a disintegrant was consistent to bear the slowest dissolution rate (about 27% was dissolved at 120 min). An improvement in the HCR was also observed at this pH with 61.36 ± 7.06% dissolved at 45 min, and 82.77 ± 5.27% dissolved at 120 min. The dissolution rates of the superdisintegrant were consistently higher relative to the starch and are comparable to the dissolution rate of HCR. The fastest dissolution was observed in XMC with a dissolution rate of 66.94 ± 6.21% at 45 min and 87.93 ± 2.79% at 120 min.

Accelerated stability study

Table 9 shows the mean values of allopurinol tablet formulations with hydroxypropylated crosslinked starch as disintegrant. It was observed that the mean values obtained from allopurinol tablets staged from 0 to 3 months have no significant changes. The statistical analysis (ANOVA) showed that there are no significant differences in the values in all parameters, as shown in Table 10. This suggests that the formulation was stable and no physical and chemical changes transpired.

Fig. 6A-D shows the chromatograms of assay performed on the 0th to 3rd month. The retention time of allopurinol was observed at 4.420 to 4.427 minutes in all the tablet samples. On the other hand, the retention time of standard solutions was observed at 4.420 to 4.429 min, as shown in Fig. 7. In addition, no other peak was observed in the chromatogram of all tablet samples, which indicates the absence of degradation product.

Table 9. Mean values of tablet formulation utilizing hydroxypropylated crosslinked rice starch (HCR) weight, thickness, hardness, % dissolution, assay stability (0^{th}, 1^{st}, 2^{nd}, 3^{rd} data at 40°C/ 75% RH months).

Month	Weight, W (g)	Thickness, X (mm)	Hardness, H (kg_f)	Dissolution (%)	Assay (%)
0^{th}	400.77 ± 6.34	3.68 ± 0.05	10.49 ± 1.02	56.21 ± 5.27	99.70 ± 1.47
1^{st}	401.80 ± 7.51	3.67 ± 0.05	10.51 ± 1.02	52.75 ± 4.66	100.60 ± 1.89
2^{nd}	399.13 ± 6.63	3.67 ± 0.05	10.63 ± 1.00	54.31 ± 5.10	100.21 ± 1.32
3^{rd}	401.50 ± 6.63	3.67 ± 0.05	10.62 ± 0.89	57.25 ± 5.28	99.41 ± 1.42

Table 10. Statistical analysis (ANOVA) on the weight, thickness, hardness, % dissolution, assay of the allopurinol tablets with hydroxypropylated crosslinked rice starch (HCR).

HCR	F	F_{crit}	Remarks
Weight (W)	0.6020	2.6828	$F < F_{crit}$, no significant difference
Thickness (X)	0.5794	2.6828	$F < F_{crit}$, no significant difference
Hardness (H)	0.1567	2.6828	$F < F_{crit}$, no significant difference
% Dissolution	0.9269	3.0984	F < Fcrit, no significant difference
Assay	0.3526	4.0662	F < Fcrit, no significant difference

F= F value; F_{crit} = F critical value.

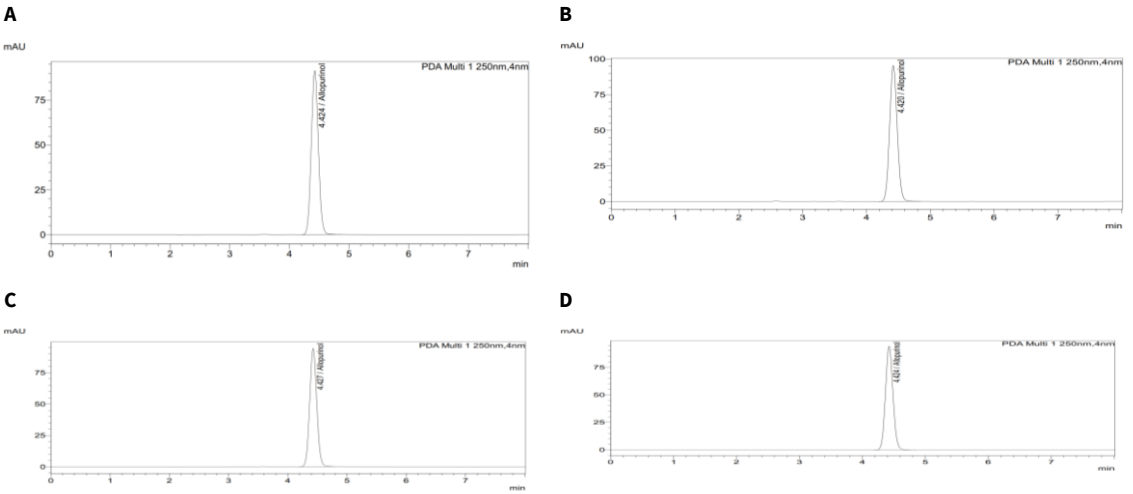

Figure 6. Chromatograms of allopurinol tablets produced with hydroxypropylated crosslinked rice starch subjected under stability study at 40°C. **(A)** 0^{th} month, **(B)** 1^{st} month, **(C)** 2^{nd} month, and **(D)** 3^{rd} month.

CONCLUSION

Rice starch was successfully modified by crosslinking and hydroxypropylation. The evidence of crosslinking and hydroxylpropylation was demonstrated by the changes in infrared spectra and thermograms (by DSC and TGA characterization) in every step of chemical modification. The dissolution of allopurinol tablet was significantly enhanced when the rice starch was modified. The dissolution of rice starch at pH 1.2, 4.5 and 6.8 at 45 min was 10.65, 9.45, 14.52%; wherein the modified rice starch was 20.13, 48.33, 48.99%, respectively. The performance of rice starch was found to be comparable to the commercially available superdisintegrants in terms of dissolution profile.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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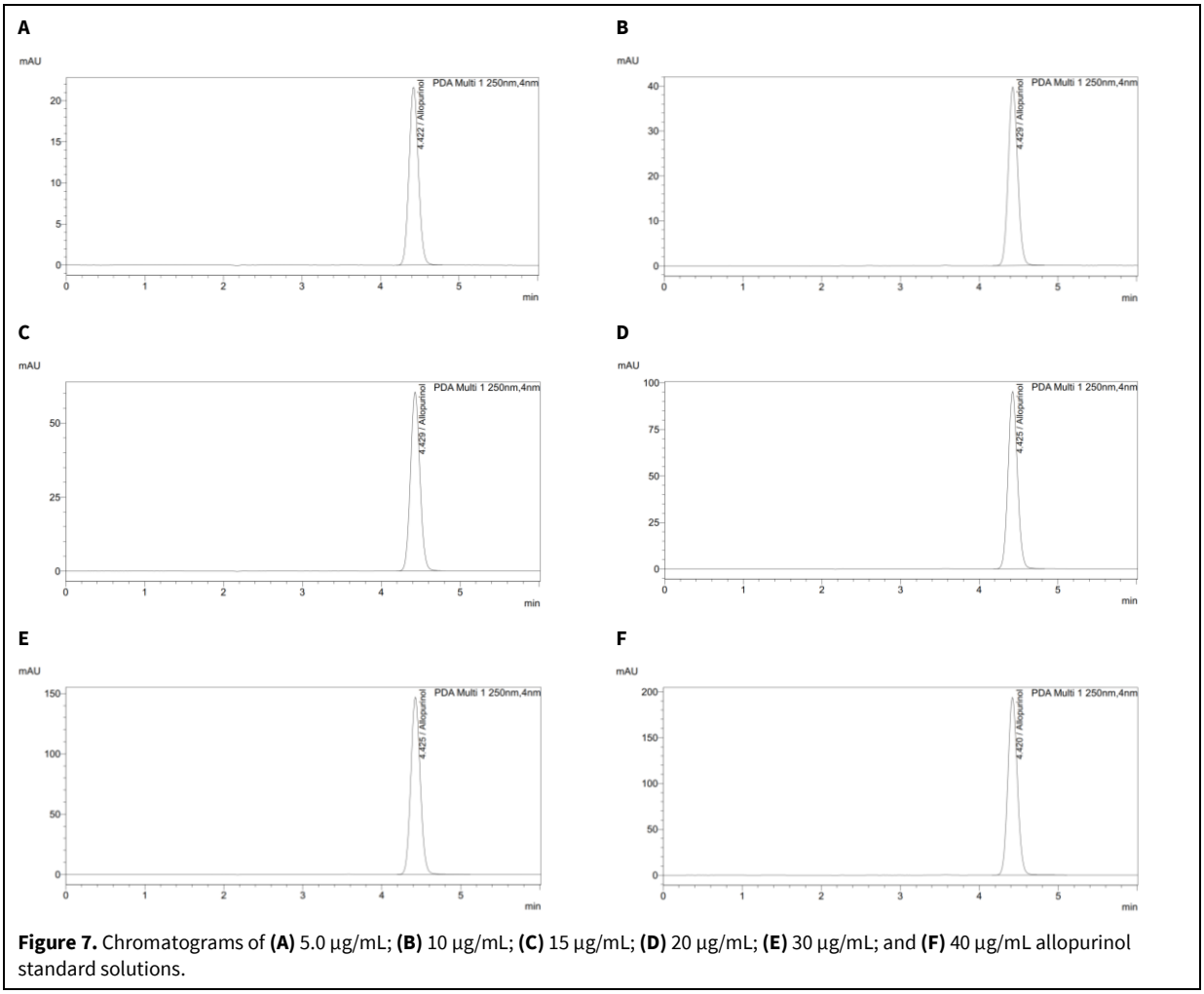

Figure 7. Chromatograms of **(A)** 5.0 µg/mL; **(B)** 10 µg/mL; **(C)** 15 µg/mL; **(D)** 20 µg/mL; **(E)** 30 µg/mL; and **(F)** 40 µg/mL allopurinol standard solutions.

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AUTHOR CONTRIBUTION:

Contribution	Elizabeth AP	Judson Lowie TR	Gerard QDG
Concepts or ideas	x		x
Design	x	x	x
Definition of intellectual content	x	x	x
Literature search	x	x	x
Experimental studies	x	x	
Data acquisition	x		
Data analysis	x	x	x
Statistical analysis	x	x	
Manuscript preparation	x	x	x
Manuscript editing	x	x	x
Manuscript review	x	x	x

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