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Original Article

PREPARATION AND CHARACTERIZATION OF MODIFIED COLORED RICE AS A GELLING CARRIER FOR BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT

Objective: The present study was to prepare and characterize the chemically modified rice from the colored rice grains as a gelling agent for buccal gel preparation.

Methods: The colored rice grains from two different varieties, Homnil (HN) and Kum-Doisket (KD), were compared. The chemically modified rice was prepared by etherification. The obtained modified samples were investigated for their solid structure using scanning electron microscope and X-ray diffractometer. The solubility and swelling property in water were also investigated. Rice gel bases and drug loading gels were prepared by hydration and levigation methods, respectively. The obtained gels were evaluated for rheological, adhesive, and drug release properties.

Results: The HN and KD rice varieties yielded modified rice powders with different morphology, crystallinity, aqueous solubility, and swelling characteristics. The amylose content in different rice variety significantly affected the internal crystalline structure of the rice powders and adhesive as well as rheological properties of the respectively derived gels. Rheological behavior of the colored rice gels was pseudoplastic non-Newtonian flow. The drug release property of HN and KD gels was influenced by swelling property of the gel base. Different gel properties reflected the different rice varieties used for gel preparation.

Conclusion: The variety of rice can affect the properties of the gelling agent from colored rice grains. The chemical modified colored rice grain can be feasible to be the good gelling agents in Pharmaceutical buccal gel preparation.

Keyword: Rice variety, Rice gel, buccal gel, Amylose content, Carbamide peroxide

INTRODUCTION

Buccal drug delivery is receiving increased attention as for avoidance of acid hydrolysis in the gastrointestinal tract and hepatic first-pass effects [1, 2]. Among the various transmucosal routes, buccal mucosa has an excellent accessibility and is suitable for administration of controlled release dosage forms [3, 4]. Buccal drug delivery has a high patient acceptability compared to other non-oral transmucosal routes of drug administration. Additionally, rapid cellular recovery of the buccal mucosa is another advantage of this route [5]. Gel is one of the most preferable among several local dosage forms used in buccal cavity because of its excellent adhesiveness, comfort, and easy dispersion throughout the mucosa. Preparation of gels is generally achieved by using wide molecular weight ranges of synthetic polymers as a gelling agent.

However, such chemical synthetic materials can cause serious environmental problems. Gel bases derived from natural polymers are of increasing interest because of their less toxicity and green sense of natural use with biodegradable properties. Many natural polymers such as chitosan, alginates, and their derivatives, therefore, have been recently used as the alternative natural gelling agents [6-9]. However, the properties of these materials are sometimes limited and suitable for only certain drug molecules. Searching for a more natural gelling agent from the other natural resources is the necessary. A poly glucan like starch is one of the interesting natural polymers. Many plant fruits and cereal seeds like rice grains contain mainly starch. Modification of starch of different origin has been shown to access various valuable features [10, 11]. However, there are few reports on pharmaceutical applications particular as a gelling agent. Therefore, it is interesting to investigate this application of rice.

Rice (*Oryza sativa* L.) is an important and economic plant as rice grains are the principal staple food for people in many countries [12]. It is well documented that consumption of rice bran can produce a hypocholesterolemic effect as well as antioxidant activity according to the presence of gamma-oryzanol and tocotrienols [13, 14]. Various rice varieties have been grown in different countries, however, can be classified according to the rice grain color into 2 groups, white rice and colored rice or pigmented rice varieties. Colored rice grains exhibit specific color, e. g., red, purple, and black whereas white rice grains are white or pale yellow. White rice has been widely consumed by most people. However, the colored rice recently becomes more popular due to the health-promoting effects of important bioactive anthocyanins and phenolic compounds [15]. Anthocyanins are natural colorants that belong to the group of flavonoids. The most commonly occurring anthocyanin aglycones are cyanidin, peonidin, malvidin, and pelargonidin [16]. It is reported that purple-black rice contains an acetylated procyanidin, a common anthocyanin with free radical scavenging activity [17]. Moreover, investigation of colored rice from many countries reveals that several anthocyanins, such as cyanidin-3-glucoside, cyanidin-3-rhamnoside, cyanidin-3-rutinoside, cyanidin-3, 5-diglucoside, peonidin-3-glucoside, and malvidin-3-galactoside, are found in Japanese, Korean, Canadian and American colored rice varieties [18-21]. Phenolic acids are typically located in the outer layers of rice grains. It is reported that purple rice contains protocatechuic acid as a major phenolic acid [15, 22]. Hence, the products derived from colored rice have more advantages on biological activities for health promotion than that from white rice. Moreover, less investigation on the pharmaceutical application has been found with the colored rice. Therefore, the present study is emphasized on the colored rice in order to attempt of utilization in pharmaceutical fields as drug carrier gels in the buccal cavity.

MATERIALS AND METHODS

Rice materials and chemicals

Milled rice grains of two colored varieties in Thailand, Homnil (HN) and Kum-Doisket (KD), harvested in the northern part of Thailand during April–September 2014 were purchased from the local market in Chiang Mai province, Thailand. These rice varieties are the most popular rice in Thailand. The color of HN is black-purple whereas that of KD is purple. Both HN and KD varieties provide pleasant aromatic odor after cooking. Carbamide peroxide, silver nitrate, and mono chloroacetic acid were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Methanol and glacial acetic acid were from RCI Lab-scan Co., Ltd. (Bangkok, Thailand). Lidocaine hydrochloride (99.9% purity) was from Gufic Biosciences (Mumbai, India). All other chemicals and solvents were of AR grade or the highest grade available.

Analysis of rice composition

The raw milled grains of HN and KD were subjected to the analysis of the main composition of protein, fat, carbohydrate, and ash using the method of the AOAC guidance [23]. Determination of protein was done by Kjeldahl nitrogen method which could determine the crude protein content with the nitrogen-to-protein conversion factor of 6.25. Determination of fate content was performed using BUCHI Soxhlet extraction with petroleum ether as a solvent. The extraction was done over a period of 2 h. The ash content was determined using dry incineration in a muffle furnace at 550 °C for 24 h. Carbohydrates content was approximately determined by subtraction from the contents of the other components.

Determination of moisture and amylose content

The raw milled grains of HN and KD were subjected to a Kett F-IA moisture balance with halogen heating. The heating temperature was set at 105 °C. The rice sample was weighed before and after being heated to a constant weight. The amount of moisture contained in each sample was calculated and expressed as a percentage of moisture content and loss on drying. According to amylose content determination the raw rice powder was used, and the determination was according to the method previously described by Juliano [24].

Preparation of modified rice

The powder samples of raw HN and KD milled rice were subjected to a chemical modification method described previously [25] with some modification. Briefly, the raw rice powder was dispersed in methanol-water mixture in a 500-ml three-necked round-bottom flask, equipped with a motor-driven stirrer. A 1:4 mixture of 50% sodium hydroxide and methanol was added and mixed. The Proper amount of mono chloroacetic acid was subsequently added. The mixture was refluxed with continuously stirred at 60°C for 3 h. The solid rice granules obtained were collected and washed several times with 95% ethanol until the silver nitrate test for chloride of the filtrate was negative. The solid product was dried and pulverized. The modified rice powder that passed 80-mesh sieve was used for characterization.

Solid structure of rice powders

The solid external structure of HN and KD rice powders was investigated by scanning electron microscopy (SEM) using a JEOL JSM-5410LV (Japan) equipped with a large field detector. The acceleration voltage was 10-20 kV under low vacuum mode (0.7–0.8 torr). The solid internal structure of the rice powders was characterized by means of X-ray diffractometry (XRD) using a Siemens D-500 X-ray diffractometer with Cu Kα radiation at a voltage of 30 kV and an electric current of 15 mA. The samples were scanned between 2θ = 5-60° with a scanning speed of 5°/min. Prior to the test, the rice samples were dried at 50°C for 24 h and stored in a desiccator.

Aqueous solubility and swelling property

The aqueous solubility and swelling property of the raw and modified rice powders of HN and KD were compared. The solubility test was performed using the method previously described [26] with some modification. Rice powder sample (1 g) was gradually dispersed in 250 ml water and continuously stirred at 100 rpm. After 1 h the solution was filtered through a Whatman (No. 1) filter paper and the weighed portion of the filtrate was dried at 60 °C under vacuum until a constant weight was reached. The solubility was calculated and expressed as the solubilization index which is the percentage ratios of the solubilized rice/initial weighed rice. The higher of the index value indicated, the higher aqueous solubility of the samples.

The swelling property was measured according to the previously described method [27] with a slight modification. The rice sample was packed in a suitable labeled test tube to obtain the tapped volume of 1 ml. Sufficient water was added and the mixture was well stirred before adjusting the volume with water to 10 ml. The samples were centrifuged at 4,000 rpm for 15 min. The rice mass sedimentation volume was recorded. The swelling property was calculated as Vt/Vo, where Vo is the initial sedimentation volume at once after stop centrifugation (t = 0) and Vt is the sedimentation volume at 5, 24, or 48 h standing at room temperature after centrifugation.

Gel preparation

The modified rice powders of HN and KD were weighed and dispersed in distilled water to obtain 10% w/w rice dispersion. The dispersions were heated to 90°C in a closed chamber for 2 h and gently stirred to obtain homogenous gels and avoid air bubble formation. The physical appearance of the gels was observed visually.

Rheological behavior of the gels

The colored rice gels obtained were investigated for their rheological behavior using a Brookfield rheometer R/S-CPS (USA) with a parallel plate and plate gap of 1000 µm. The gel sample was gently loaded onto the rheometer plate using a micro spatula. The rheological behavior of the samples was characterized over a range of 0-1000 s^{-1} for a period of 3 min. The measurements were made at 30±2°C. The rheological profile of the gels was obtained from a plot of the shear stress versus its respective shear rate under the above experimental conditions. The average apparent viscosity of the gels was calculated by using Rheo3000 program.

Adhesive property of the gels

The adhesive property of the colored rice gels was determined according to the tack principle. Tack is the ability of a gel sample to bond under conditions of light contact pressure and a short contact time. In the present study, the track of the gels was measured by the rolling ball tack test. The exact amount of gel sample was applied thoroughly on the smooth surface plate of 20 mm wide and 100 mm long. This plate was laid horizontally next to the inclined plate. A 15-mm diameter glass ball was released from the top of the inclined plate (angle 30°) with a running length of 200 mm and let to continue to run on the horizontal adhesive plate until stop by adhesive power of the gel. The length of the adhesive plate that the ball could run from the beginning of the plate to the stop point was recorded as the track value.

***In vitro* drug release property**

In this experiment, carbamide peroxide (CP) was used as a model drug. The drug was gradually added to the rice gel bases by levigation until the desired drug concentration was reached. The *in vitro* drug release property of the gel samples was done using dialysis bag with a molecular weight (MW) cut-off at 12,000 daltons (Cellu Sep® T4 regenerated cellulose tubular membrane, Membrane Filtration Products, Inc.). Phosphate buffer solution (PBS) pH 7.4 was used as a receptor medium. The dialysis bag was degassed and saturated for 30 min in the receptor medium before loading with 1 g of CP loaded rice gel. The open end of the bag was subsequently tightly closed before immersing into the medium at 37±1 °C under constant stirring of 100 rpm. The samples were collected periodically after 5, 10, 15, 20, 30, 40, 50 and 60 min. The fresh medium was replaced after each sampling. The drug released concentration was determined by HPLC with UV detection at 225 nm.

Statistical analysis

All data were reported as mean±SD for triplicate experiments. To determine statistical difference between means ($p<0.05$), a one-way analysis of variance and Duncan's multiple range tests ($p<0.05$) using SPSS software version 11 was used.

RESULTS AND DISCUSSION

Rice composition

It is well known that rice grain is composed mainly of starch, a polysaccharide that functions as a carbohydrate store and is an important constituent of the human diet. However, it was demonstrated that the rice composition is mainly affected by rice varieties and the cultivated area [28]. Previous reports on white rice demonstrated that the grains of three different rice varieties showed total carbohydrate content of 82-83%, whereas the examination in six colored rice varieties revealed lower carbohydrate content [29, 30]. Sompong *et al.* reported that the carbohydrate content of red rice strains was 75-79% whereas that of the black rice varieties showed 74-75% [28]. The two native colored rice varieties used in the present study showed carbohydrate content of approximately 86-87% as shown in table 1, significantly higher than that previously reported. The protein content of both HN and KD was also higher than the previous reports who worked with the Thai white rice varieties and reported their protein contents of 7.0-7.5% or less [31, 32]. This was considered to be due to the difference in rice varieties. Fat content for both colored rice grains in the present study was in the range between 2.7-2.8% which was in good agreement with the previous reports on the colored rice [28], while ash content of our colored rice samples ranged between 0.2-0.4% which was significantly lower than that of the colored rice varieties reported previously [33].

It is necessary to know the moisture content of rice as moisture migration can cause physical, chemical and biological changes in materials [34]. The results showed that the moisture content of HN was 6.77±0.15% whereas that of KD was the higher value of 8.07±0.21%. The moisture content of raw rice influences its storage properties as it was related to the water activity of microorganisms [35]. The results in the present study suggested that attention should be paid to the storage of rice with high moisture content such as KD because of the high risk of microorganism contamination. The results from amylose determination demonstrated that the amylose content of KD is 15.24±0.08%, significantly higher than that of HN (11.47±0.07%).

Table 1: Composition of the raw colored rice powders

Composition* (%)	Rice varieties	
	HN	KD
Carbohydrates	87.29±0.15	86.84±0.16
Lipids	2.72±0.17	2.85±0.01
Proteins	8.58±0.13	9.09±0.02
Ash	1.27±0.01	1.46±0.05

* Values are expressed as mean±SD, n=3

Modification of rice

The raw rice starch has a pharmaceutical limitation on gel preparation according to its low water solubility. Modification of rice starch based on physical, chemical, and biological reactions has been suggested to solve this problem [36]. Chemical modification of rice starch was reported to cover a wide range of pharmaceutical application and biomedical fields [37]. In the present study, therefore, the powder sample of the raw colored rice was firstly subjected to the chemical modification based on carboxymethylated etherification in order to modify the starch structure and to obtain better property of rice starch. The color of the obtained modified rice powders of the two varieties was light gray while that of the color of the original raw rice powders was dark gray as shown in fig. 1. The color of modified HN is brighter than that of modified KD.

Fig. 1: Outer appearance of the raw (A) and modified (B) rice powders

Solid structure of rice powders

The solid external structure of raw rice powders in comparison with their respective modification examined under SEM was shown in fig. 2. In this figure, the particle morphology and approximate size of the rice powders were demonstrated. It was found that the raw rice particles displayed an irregular polygonal shape with several obvious sharp edge surfaces. The morphology of raw rice shape resulted in the present study were similar to those previously reported [38], but the size of the rice particles was slightly different. This was considered to be due to the effect of rice varieties and the method of rice powder preparation. It was noted that after modification, there was a slightly change in the rice particle shape. The modified rice particles were swollen, and the surface edges are slightly blunt. The particles size of the modified rice was larger than the raw rice. The morphological change of modified KD was more obviously seen than that of modified HN. A previous report revealed that the extent of rice swelling after the modification was due to the amylose content [38]. In the present study, KD rice which contained significantly higher amylose demonstrated higher swelling and microstructural change than the lower amylose content, HN. Our result, therefore, was in good agreement with the previous report.

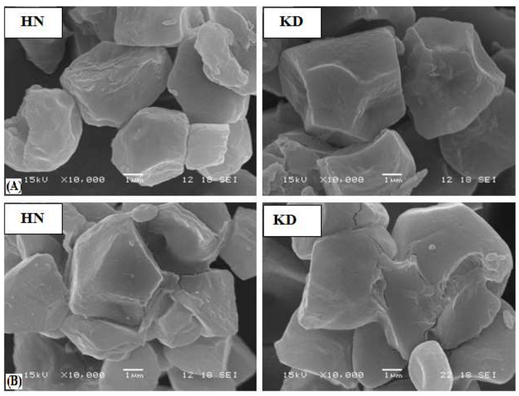


Fig. 2: SEM morphology of the raw (A) and modified (B) rice powders

Internal solid structure of rice particles

XRD analysis is a standard tool to characterize the internal crystalline structures of solid particles [39]. Lattice formation of crystalline starch is due to the arrangement of amylose and amylopectin molecules which can be classified to A-, B-, and C-type by XRD pattern analysis [40]. Starch of A-type shows strong diffraction peaks at 15° and 23° with unresolved doublet at 17° and 18°. However, B-type starch gives an identical peak at 6° and 17° with several small peaks at 15°, 20°, 22°, and 24°. The B-type starch was reported to possess higher resistant power against enzyme hydrolysis than A-type starch [41]. A mixture of A-and B-type starch is call C-type, which shows the total diffraction peaks of A-type and B-type. The C-type that is composed of higher content of A-type than B-type is called CA-type where that contains higher B-type than A-type is called CB-type. The XRD patterns of two raw colored rice samples were shown in fig. 3. It was found that all raw rice samples displayed strong reflections with different diffraction angles. Raw HN exhibited the diffraction peaks around 14.7, 17.7°, and 22.5° where raw KD presented the identical peaks at 14.9, 16.7°, and 22.7°. These XRD peaks were considered to be the A-type crystalline arrangement. The XRD results of raw HN and KD found in the present study were in good agreement with the previous Blazek and Gilbert, who reported that starches from cereals presented A-type structure [40]. After modification, the solid internal structure of both HN and KD was changed but slightly different as seen in fig. 3. The XRD result of the modified HN was a halo pattern suggesting that the crystalline structure of HD was completely destroyed and changed to an amorphous form. Tiny crystalline peak was observed at about 17° in the XRD pattern of the modified KD indicating some crystalline structure still remained. However, most part of the pattern could be seen as the halo pattern indicating that most of the internal structure the modified KD was also amorphous form. The results from XRD and SEM suggested that the condition of chemical modification used in the present study caused the complete loss of crystallinity in HN rice variety but not totally for KD rice. As the amylose content in HN and KD was different, it was considered that the crystalline solid structure of the lower amylose rice powders was easier destroyed by chemical modification than the rice with higher amylose content. Some small peaks remaining in the XRD patterns of the modified rice of the higher amylose KD indicated the difficult destruction of the double amylose helices.

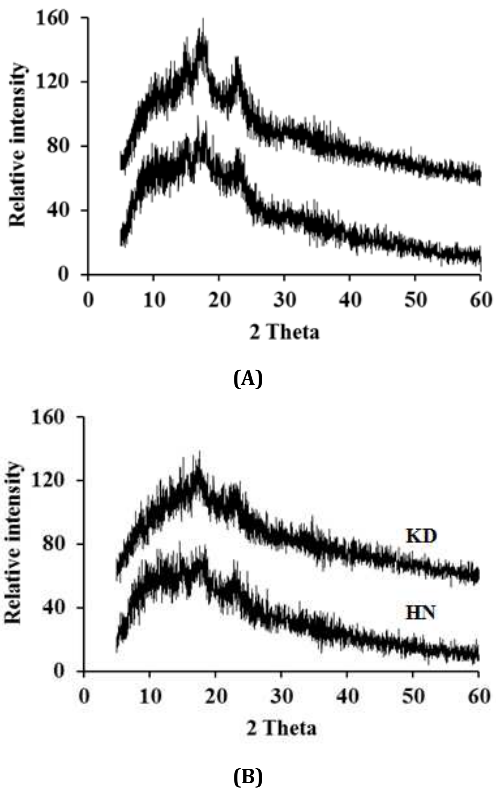


Fig. 3: XRD diffractograms of the raw (A) and modified (B) rice powders

Aqueous solubility and swelling property

Gelling agents should have high water solubility in order to provide hydrophilic gels with the desirable characteristic of high transparency. The result in table 2 demonstrated that the solubility of the raw and modified rice powders of HN and KD was significantly different. It was clearly seen that the modified rice powders had extremely higher aqueous solubility than their respective raw rice. The result suggested that chemical modification by etherification could enhance the water solubility of the rice. It was reported that water solubility of rice samples depended on their amylose content [42]. In the present study, the water solubility of the higher amylose content KD was less than that of the lower amylose content HN. It was noted that the modified HN, which the internal structure was more complete amorphous, demonstrated significantly higher water solubility than the modified KD.

It was therefore considered that amorphous structure of the rice played the important role on the water solubility enhancing the property of the modified colored rice. It was noticed that when the rice powder contacted to the water, a greater portion of the raw rice remained in the sediment whereas the some portion of the modified rice began to swell and almost ready to form the gel. The swelling property of the modified rice of both HN and KD was significantly higher than their respective raw rice. Fig. 4 showed that the swelling behavior of the modified rice was time-dependent. It was found that the modified KD showed significantly higher swelling property than the modified HN. It could be concluded from these results that higher amylose content such as KD provided lower solubility but higher swelling property which was in agreement with solid structure of rice powders part above.

Table 2: Solubility index of the rice powders

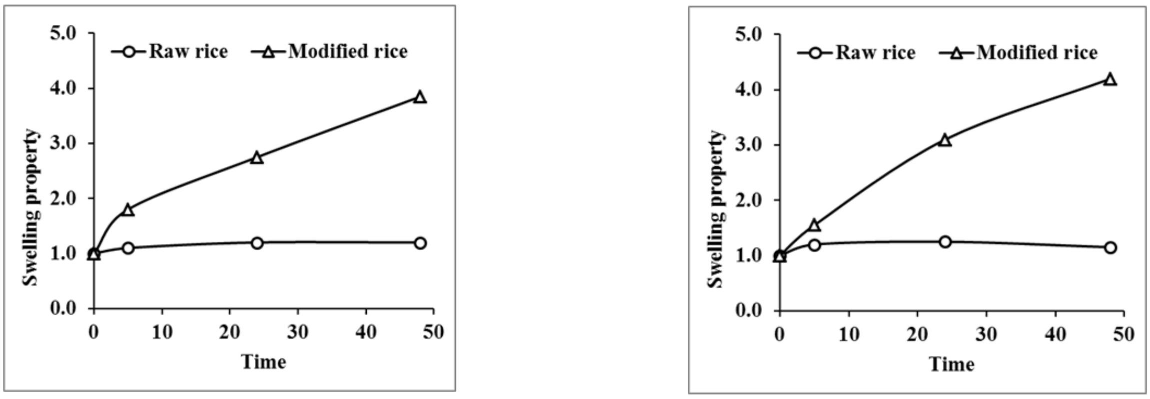
Rice variety	Solubility index* (%)	
	Raw rice	Modified rice
HN	0.3±0.1	98.2±0.2
KD	0.2±0.1	95.4±0.4

* Values are expressed as mean±SD, n=3

Appearance and rheological behavior of rice gel

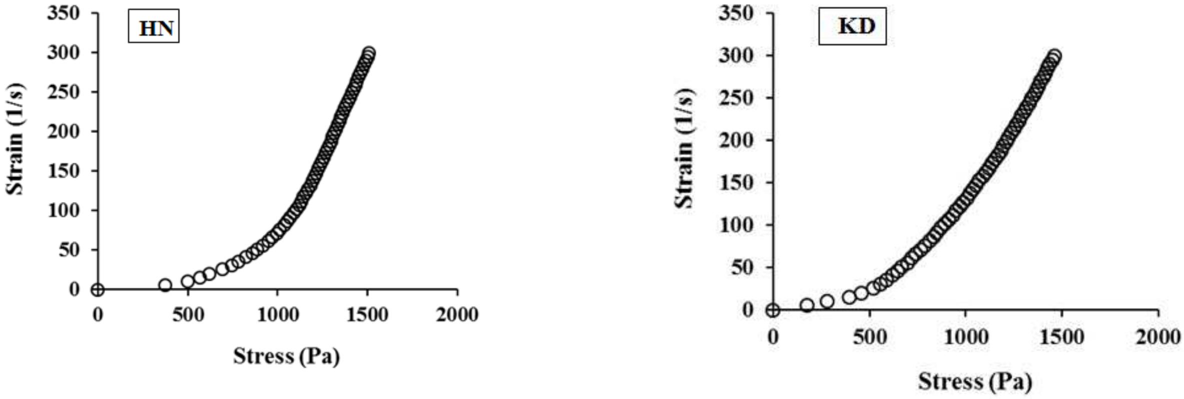
Rice gels may be prepared by thermal pre-gelatinization, however, the gels obtained gradually retrograde during storage. The retro gradation in rice gels can be avoided by using chemical modified rice [43]. The chemical modification of rice starch under etherification used in the present study was to substitute carboxymethyl groups (CH_2COO^-), which were negatively charged, for hydroxyl groups (–OH) in rice starch molecules and produce carboxymethyl starch [44]. The modified rice powders of HN and KD showed good property for forming gel under simple hydration method. Both gels were similar in outward appearance as transparent semisolids and had a homogeneously desirable external structure with light purple color. After incorporating with carbamide peroxide, both gel bases showed good compatibility to the drug. The rheological behavior of the rice gels is shown in fig. 5. It was seen that the stress-strain relationship was not linear for both gels indicating that the rheological behavior of the gels was a pseudo plastic non-Newtonian flow.

The viscosity of the gels was changed when the gels were sheared. In pharmaceutical fields, it is very important to know the viscosity of the gel formulations particularly for buccal application in order to desire the suitable packaging and administration. It was found that the average viscosity of HN gel was 12.2±0.1 Pas, significantly higher than that of KD gel (9.4±0.2 Pas). It was reported that the rheological behavior and viscosity of rice gels developed by thermal gelatinization were influenced by amylose content [45]. In the present study, the amylose content of HN and KD was significantly different. This was considered to affect the rheological property of the obtained gels.



A B

Fig. 4: Swelling property of HN (A) and KD (B) rice powders, Values are expressed as mean±SD, n=3



A B

Fig. 5: Rheogram of rice gel bases, HN (A) and KD (B)

Adhesive property of rice gels

The adhesive property is essential for buccal drug delivery [46]. Buccal gels with high adhesive property can be retained in the application area for the desired duration of action. The buccal gels with low adhesive property are easily washed away and removed by saliva. Therefore, adhesive property is an important issue for buccal gels. The adhesive property of rice gels in this study was investigated by tack test. The result expressed as the tack value was shown in which represented the length of the adhesive plate (covered with the gel sample) that the ball could run from the beginning of the adhesive plate applied with the rice gel sample to the stop point. Therefore, the lower tack value indicated, the higher adhesive property of the gel. The adhesive property of the rice gel bases in comparison with drug loaded rice gels was shown in table 3.

From this result, it is seen that the adhesive strength of HN gel was higher than that of KD gel. This might result from the higher viscosity of HN than KD. After loading with carbamide peroxide, the adhesive power of both rice gels was decreased. The results in the present study indicated that adhesive property of rice gels is affected by rice variety and drug incorporation.

Table 3: Track value of the rice gels

Rice gels	Track value* (cm)	
	Gel bases	Carbamide gels
HN	3.87±0.15	5.01±0.30
DS	4.38±0.13	6.28±0.13

* Values are expressed as mean±SD, n=3

***In vitro* drug release property**

The *in vitro* drug release tests were carried out in pH 7.4 buffer. It was observed that the release was accompanied by the dissolving of the gels. However, only the drug molecules could diffuse through the used definite MW cut-off (12,000-dalton) dialysis membrane. The release profile of the two gel samples was presented in fig. 6. It was shown that both HN and KD rice gels demonstrated similar drug release profile, however slightly different level. It was noted that both gels presented the fast release within 10 min. KD gel showed complete drug release within 30 min, whereas the drug release from HN was found to be 40 min. Highly gel swelling was observed in the KD gel. This swelling permitted water molecules to enter into the gel matrix and to dissolve the drug inside the gel. While the gel was swelling, its consistency was decreased. The dissolved drug could easily pass through the less consistency gel matrix. Therefore, the drug released from KD gel was higher than that from the less swelling HN gel.

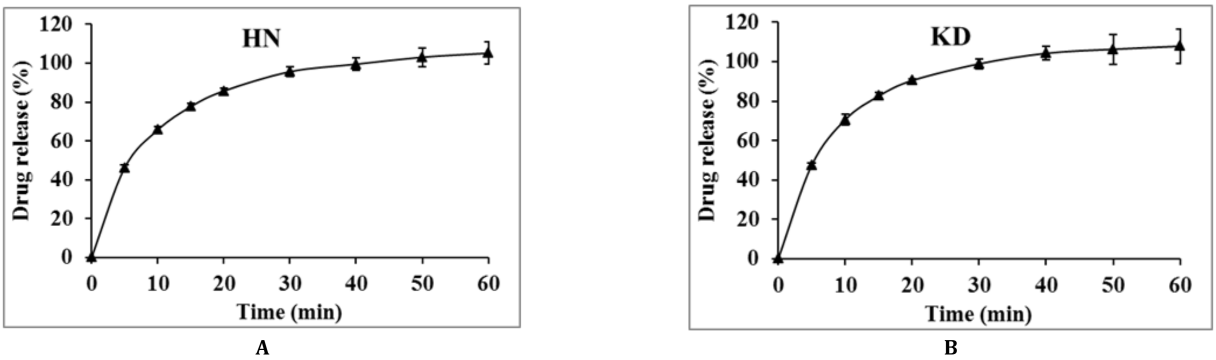


Fig. 6: Release profiles of drug loading rice gels, HN (A) and KD (B), Values are expressed as mean±SD, n=3

CONCLUSION

The effects of rice varieties on the physicochemical characteristics of colored rice powder and properties of the derived gels obtained from the respective modified rice powders are explored in this study. The colored rice grains yield modified rice powders with different morphology, crystallinity, aqueous solubility, and swelling characteristics. The amylose content in the rice significantly affects the internal crystalline structure of the rice powders and adhesive as well as rheological properties of the respectively derived gels. Rheological behavior of the colored rice gels is pseudoplastic non-Newtonian flow. The drug release property of both colored rice gels is influenced by swelling property of the gel base. Different gel properties reflect the different rice varieties used for gel preparation. The results suggest that the chemical modified colored rice powders can be feasible to be the good gelling agents in Pharmaceutical buccal gel preparation.

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CONFLICTS OF INTERESTS

All authors have none to declare

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