Original Article

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Preparation and characterization of lidocaine rice gel for oral application

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Summary

The objective of the present study was to prepare buccal anesthetic gels using rice as gelling agent. Rice grains of four rice varieties, Jasmine (JM), Saohai (SH), Homnil (HN), and Doisket (DS) were chemically modified. Buccal rice gels, containing lidocaine hydrochloride as local anesthetic drug were formulated using the respective modified rice varieties. The gels were evaluated for outer appearance, pH, color, gel strength, foaming property, adhesion, *in vitro* drug release and *in vivo* efficacy. It was found that the developed rice gels possessed good texture. Rice varieties showed influence on gel strength, color, turbidity, adhesive property, release property, and anesthetic efficacy. JM gel showed the lowest turbidity with light transmission of 86.76 ± 1.18% whereas SH gel showed the highest gel strength of 208.78 ± 10.42 g/cm^2. Lidocaine hydrochloride can cause a decrease in pH and adhesive property but an increase in turbidity of the gels. *In vitro* drug release profile within 60 min of lidocaine SH gel and lidocaine HN gel showed that lidocaine could be better released from SH gel. Evaluation of *in vivo* anesthetic efficacy in 100 normal volunteers indicates that both lidocaine rice gels have high efficacy but different levels. Lidocaine SH gel possesses faster onset of duration and longer duration of action than lidocaine HN gel.

Keywords: Rice gel, local anesthetic, mucoadhesive, drug release, lidocaine

1. Introduction

Many dental treatment procedures *e.g*. tooth extraction, scaling and root planing cause severe pain to the patients. These procedures therefore need an anesthetic drug to restrain the pain during the treatment. Anesthetic drug administration is generally done by injection. However, the first anesthetic injection also causes pain to the patients and makes them fear of dentistry (*1*). To reduce this pain, several methods have been used such as using a fine-gauge needle and gently pierce the needle to the target area (*2*), using a slower rate of injection in order to reduce the tissue tension (3,4), adjusting the pH or buffering the anesthetic solution in order to reduce the burning pain from the acidity of its salt solution (*5,6*), and using topical anesthetic application prior to injection (*7*). Among these methods, topical application of local anesthetic dosage form to the injection area prior to insert the needle is the most effective to overcome the pain at needle puncture. Many dentists therefore prefer to apply topical anesthetic dosage form before oral treatment with injection (*8,9*). Lidocaine has been used for local anesthesia via many routes of administration such as intradermal injection and topical application. Its anesthetic activity is due to the neuronal voltage-gated Na^+ channel blocking. This activity leads to failure in the generation or propagation of peripheral nerve action potential (*10*).

There are many dosage forms that can be applied topically in oral cavity such as disks (*11*), tablets (*12*), patches (*13*), films (*14*), ointments (*15*), and gels (*16*). Among these formulations, buccal gels are the most preferable in terms of patient compliance, comfort, and easy dispersion throughout the mucosa. Moreover,

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buccal gels show prolonging residence time at the site of drug absorption and high mucoadhesive on the absorption surface (*17*).

Gels are made of various synthetic polymers such as polyvinylalcohol, polyvinylpyrrolidone, and poly (acrylic acid). However, using chemical synthetic polymers may cause serious environmental problems. Using polymers from natural resources therefore are of better options. Recently, we reported that the gels derived from rice grain powder of some rice strains possess high mucoadhesive (*18*). In the present study, lidocaine rice gels were prepared and their characteristics and efficacy were compared.

2. Materials and Methods

2.1. *Rice materials and chemicals*

Milled rice grains of different rice varieties in Thailand, Jasmine (JM), Saohai (SH), Homnil (HN), and Doisket (DS) were used. JM and SH are white rice grains where HN and DS are reddish purple rice grains as shown in Figure 1. All rice grains used were harvested during July – September, 2014. Silver nitrate and monochloroacetic 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.

2.2. *Preparation of lidocaine rice gel*

The rice grains of each variety were modified and used as gelling agent. The rice modification procedure was done according to the method reported by Okonogi *et al*. (*19*) with some modification. Briefly, the raw rice was firstly added into sodium hydroxide methanol solution. After that, monochloroacetic acid solution was added and refluxed at 60°C for 3 h. The solid granules obtained were washed with ethanol until the silver nitrate test for chloride of the filtrate was negative. The dried solid modified rice was pulverized and the fine powder that passed an 80-mesh sieve was used for gel base preparation. Rice gel base of each rice variety was prepared using hydration method. The dispersions of the modified rice powder and water were heated to 90°C in a closed chamber for 2 h and gently stirred to obtain homogenous gels without air bubble. Lidocaine hydrochloride was exactly weighed and gradually levigated into the rice gel bases until the transparent gels of 2% lidocaine were obtained.

2.3. *pH and turbidity study of the gels*

The pH of the rice gel bases in comparison with lidocaine rice gels was measured using a pH meter with an electrode probe for semisolid samples. The turbidity of the gels was measured using a spectrophotometer (JASCO Corporation, Tokyo, Japan) at 620 nm against distilled water. Each turbidity measurement was carried out in triplicate.

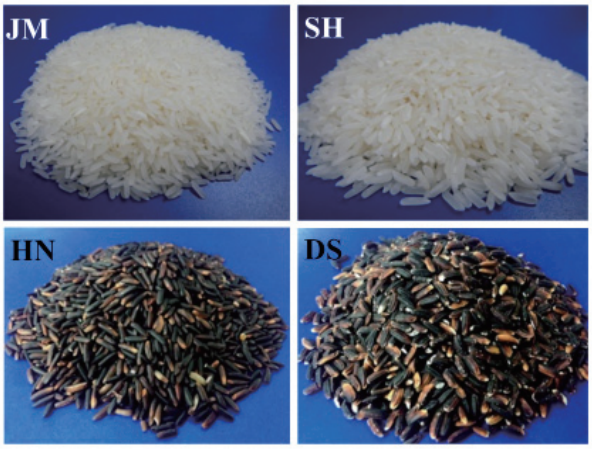

Figure 1. Outer appearance of four rice grains.

2.4. *Color measurement of the gels*

The color of lidocaine rice gels was determined using a chroma meter (Konica Minolta Optics Inc, Osaka, Japan) and Spectra-Match software, sets to lightness (L^*), redness (a^*), and yellowness (b^*) mode. The method of determination was according to the previous report (*20*). The samples were filled in a glass sample cup. Determination was performed on cross-sections of the sample. Ten determinations were performed on each gel sample. The white calibration plate was used to standardize the equipment.

2.5. *Determination of gel strength*

The gel strength of lidocaine rice gels was investigated by a method described by Zhou and Regenstein (*21*) using a texture analyzer (Stable Micro Systems Ltd., Godalming, United Kingdom). The gels were filled in a cylindrical cup (30 mm diameter × 15 mm height) and kept at 6 ± 1°C for 16-18 h. The measurement was performed using a 12.7-mm diameter plunger. The test mode was compression and the penetration speed was constant at 2.00 mm/sec and the penetration depth applied was 4 mm. The gel strength is a maximum force required in penetration. Determination was made in triplicate.

2.6. *Foam forming of the gels*

Foam forming of rice gel bases in comparison with lidocaine rice gels was measured by the method previously described (*22*) with some modification.

Briefly, the 1 mL gel sample was filled into a 10 mL graduated cylinder. The 4 mL of water was added. The cylinder was closed tightly and was vigorously shaked for 20 times. The foam volumes generated and floated over the top layer of the liquid after stop shaking (0 min) and the foam volume left after stop shaking for 15 min were recorded. Foaming properties were calculated as follow.

$$\text{Foam forming ability} = \frac{\text{Volume of foam at 0 min}}{\text{Initial volume of gel solution}}$$

$$\text{Foam stability} = \frac{\text{Volume of foam at 15 min}}{\text{Volume of foam at 0 min}}$$

2.7. *Adhesive property test of the gels*

2.7.1. *Thumb test*

This method was performed as the previous report (*23*), with some modification. Briefly, the gel sample was placed between the tips of thumb finger and middle finger and kept as such for exact time of 1 min. The qualitative adhesiveness was measured by the difficulty in separating the fingertips.

2.7.2. *Tack determination*

The 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 tack of the adhesive surface contact of the gel was measured by the rolling ball tack test. The exact amount of gel sample was applied thoroughly on the smooth surface plate with a width of 20 mm and a length of 100 mm. 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 it run on the adhesive plate until stopped by adhesive power of the gel. The length of the adhesive plate that the ball can run from the beginning of the plate to the stop point was recorded as the tack value.

2.8. *In vitro drug release property of the gels*

The *in vitro* release study was performed 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., TX, USA). The receptor compartment had a capacity of 50 mL. The dialysis bag was degassed and saturated for 30 min in receptor medium (phosphate buffer pH 7.4) before starting the experiment. The gel sample of 1 g was placed in the hydrated dialysis bag with the aid of a syringe and checked for air bubbles. The dialysis bag was tightly closed and then immersed into the medium. The receptor medium was maintained at 37 ± 1°C under constant stirring of 100 rpm. To characterize the drug release, samples were collected after 5, 10, 15, 20, 30, 40, 50 and 60 min. After sampling, the volume collected was replaced with fresh receptor medium. The amount of lidocaine released was determined by HPLC with UV detection at 230 nm. Elution was carried out at room temperature with a mobile phase consisting of phosphate buffer pH 8 (60%) and acetonitrile (40%); the injecting volume was 20 µL. The flow rate was 1.0 mL/min. In these conditions the retention time of lidocaine is 15.0 min. A calibration curve was prepared using lidocaine solution at concentrations ranging from 1 to 10 µmol/mL. In this range the method gave a linear response (r^2 = 0.9998).

2.9. *In vivo anesthetic activity of the gels*

Subjects for this study were recruited from normal volunteers of Chiang Mai University (CMU). This study was approved by the Human Experimentation Committee, Faculty of Dentistry, CMU. The anesthetics that were used in the study were two selected lidocaine rice gels. Subjects were randomly assigned to one of two groups: Each group (n = 50) received a completely blind separated lidocaine rice gel sample. An aliquot of 0.1 mL gel was placed on the tip of the tongue. The tongue was scratched using the fine gauge needle to determine the onset and duration of the anesthetic action.

2.10. *Statistical analysis*

Descriptive statistics for continuous variables were calculated and reported as a mean ± standard deviation. Data were analyzed using a one-way analysis of variance and Duncan's multiple range test ($p < 0.05$) using a SPSS software version 11.

3. Results and Discussion

3.1. *Preparation of lidocaine rice gels*

Previous reports demonstrated that rice grain composed mainly of starch (*18*). The chemical modification of rice starch under etherification used in this study could produce carboxymethyl starch. This reaction is to substitute carboxymethyl groups (CH_2COO-), which are negatively charged, for hydroxyl groups (–OH) in starch molecules (Volkert *et al*., 2004). The raw rice powders of white rice grains (JM and SH) and color rice grains (HN and DS) have slightly different in color but their modified rice powders showed similar appearance as shown in Figure 2. It is noted that the color of the modified rice powders derived from the color rice varieties was changed to almost white. The modified rice powders obtained showed good property

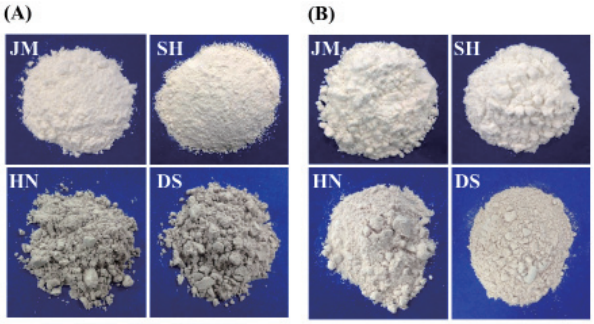

Figure 2. Outer appearance of raw rice powders (A) and modified rice powders (B).

Table 1. pH of rice gels

Rice gels	pH	
	Gel bases	Lidocaine gels
JM	7.0	6.5
SH	9.0	6.6
HN	7.8	5.9
DS	7.5	5.8

for forming gel base under simple hydration method. All rice gel bases showed good compatibility to lidocaine hydrochloride. Lidocaine rice gels obtained from these four different modified rice gel bases were further investigated for their characteristics.

3.2. *pH and turbidity of the gels*

Four rice gel bases and lidocaine loaded rice gels were compared. The pH of the gel bases was in the range of 7.0-9.0. After incorporating with lidocaine hydrochloride, the pH of the gels was slightly decreased as seen in Table 1. Lidocaine is a weak base having pKa of 7.92 at 25°C. However, the aqueous solution of its salt form with strong acid like hydrochloride form shows the weak acid to litmus. This effect therefore influenced the pH of lidocaine rice gels to be lower than their respective gel bases. Lidocaine cannot dissolve easily in water but in the form of hydrochloride, the drug solubility in aqueous system like rice hydrogel can be increased. Therefore, there was no precipitation of the drug observed in the gels. However, the gels obtained were not completely transparent. The turbidity of the gels then was measured by means of light transmission. It was found that there was a significant difference in gel turbidity among the gels obtained from different rice varieties as shown in Table 2. The highest transmission of light at 620 nm which indicated the lowest gel turbidity was found in JM gel. Lidocaine rice gels showed slightly higher turbidity than their respective gel bases. It was reported that the addition of ions might cause the increase of gel turbidity due to an increase of the aggregation of helices to form a three dimensional network (*24*). However, it was reported that the addition of small amount of calcium

Table 2. Transmission of rice gels at 620 nm

Rice gels	Transmission of light (%)	
	Gel bases	Lidocaine gels
JM	86.76 ± 1.18	58.67 ± 0.90
SH	79.19 ± 0.76	40.63 ± 0.41
HN	66.51 ± 1.07	55.27 ± 0.59
DS	72.08 ± 1.27	43.58 ± 0.12

Table 3. Color of lidocaine rice gels measured by light reflection method

Rice gels	L^*	a^*	b^*
JM	30.02 ± 0.92	– 0.23 ± 0.03	1.25 ± 0.16
SH	32.76 ± 0.61	– 0.38 ± 0.04	0.27 ± 0.03
HN	24.62 ± 0.28	3.36 ± 0.26	4.17 ± 0.63
DS	24.24 ± 0.33	3.36 ± 0.78	6.36 ± 0.47

could prevent aggregation formation of gelatin (*25*). It was also reported that the turbidity data did not reveal whether turbidity was caused by either the formation of more or larger aggregates, or both. However, in most cases, gel turbidity is caused by the scattering of light by particles entrapped inside the gel matrix (*26*). It was reported that transparent gels consisted of a molecularly homogeneous network, whereas nontransparent gels consisted of colloid particles or aggregates which larger than one quarter of the wavelength of light above 150 nm (*27*). In the present study, the addition of lidocaine hydrochloride to the rice gel bases showed a slight increase of gel turbidity. It is considered that there might be the formation of some tiny aggregates of drug molecules inside the gel network.

3.3. *Color of lidocaine rice gels*

Color of the gel is important factor in terms of general appearance and consumer acceptance. The outer appearance of lidocaine gels obtained from four different rice varieties was similar but different in color. Visual observation demonstrated that the gels derived from white rice strains were slightly white where those obtained from the color rice were slightly red purple in color. Due to different turbidity, color of the gels was measured by light reflection method using a chroma meter. This measurement reflects three color parameters; L^*, a^*, and b^*. The parameter L^* refers to the lightness of the samples, and ranges from black ($L = 0$) to white ($L = 100$). A negative value of parameter a^* indicates green, while a positive one indicates red–purple color. Positive value of parameter b^* indicates yellow while negative value indicates blue color. The results of color measurement of the gels therefore are shown as the values of L^*, a^*, and b^*. As shown in Table 3, it is found that between the two white rice gels; the color of SH gel was whiter and less yellow than JM gel. Both color rice gels showed less whiteness than white

rice gels where DS showed higher yellow than HN. The color of the rice gels observed by visualization is found to be the blend color of L^*, a^*, and b^*.

3.4. *Gel strength*

Gel strength is one of the important properties of pharmaceutical gels. Previous report showed that the gel strength of various starches depended on the type and concentration of the starches (*28*). Moreover, it was reported that the gel strength of agar extracted from the same genus but different species was significantly different (*29*). In the present study, rice gels derived from the same plant species of rice (*Oryza sativa* Linn.) but different varieties was studied. It is found that the gel strength of white rice is higher than that of color rice. The highest gel strength was obtained from lidocaine SH gel with the gel strength value of 208.78 ± 10.42 g/cm2 followed closely by JM gel with the value of 181.13 ± 13.92 g/cm^2. HN and DS gels demonstrated significantly lower gel strength values of 154.47 ± 6.11 g/cm^2 and 157.89 ± 8.49 g/cm^2, respectively. This result reveals that the plant variety also plays an important role on the gel strength.

3.5. *Foam properties of the rice gels*

Foam is a dispersion of gas bubbles in the liquid or semisolid systems. Foam formation can be easily formed during stirring certain systems containing component having activity to decrease surface tension. A desirable good appearance pharmaceutical gel should not contain any foams or air bubbles. Therefore, it is essential to investigate the possibility of foam forming and foam stability obtained by rice gels in order to avoid those undesirable foams in the formulated gels. The results showed that foam formation could be occurred in rice gel bases but in tiny amount. The ability of foam forming is depended on the rice variety as seen in Figure 3. Gel bases obtained from color rice varieties showed higher foam forming ability than those obtained from white rice varieties. The highest foam forming ability was found in HN gel with 0.1 times of the initial gel solution. Interestingly, after adding lidocaine hydrochloride in the gel bases, the foam formation was dramatically decreased. The foams of rice gels showed low stability. After 15 min of stop shaking, the foams of all gel bases decreased rapidly, particularly in the gels containing lidocaine hydrochloride as seen in Figure 4. Previous report demonstrated that adding some ions or compounds could interrupt foam forming in different mechanisms (*30,31*). The results of the present study showed that adding of lidocaine hydrochloride to the rice gel bases can prevent the formation of undesirable foam in the obtained gels.

3.6. *Adhesive property of the gels*

The adhesive property is essential for buccal drug delivery (*32*). The adhesive property of lidocaine rice gels in this study was investigated by thumb test and tack determination. The thumb test is a simple test method. The results from thumb test can roughly identify adhesiveness of the test samples. Although the thumb test may not be conclusive, it provides useful information on mucoadhesive potential. The difficulty of pulling the thumb from the adhesive gels is a function of the pressure and the contact time. Like mucin, the skin has many hydroxyl groups. It is likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesives are nonspecific and not mucin specific. The results of this study revealed that all rice gel bases as well as the lidocaine rice gel bases obtained possessed good adhesive property (data not shown). Further investigation of more precisely adhesive property was done using tack test. The result was expressed as the tack value 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 indicates the higher adhesive property of the gel. The results are shown in Table 4. From this result, it is seen that the gel bases of the white rice possessed lower adhesive strength than that of the color rice. Lidocaine

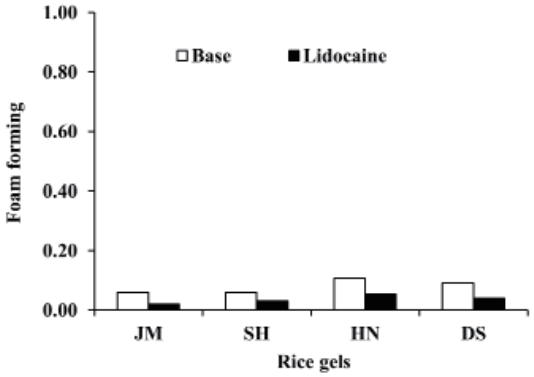

Figure 3. Foam forming ability of rice gels.

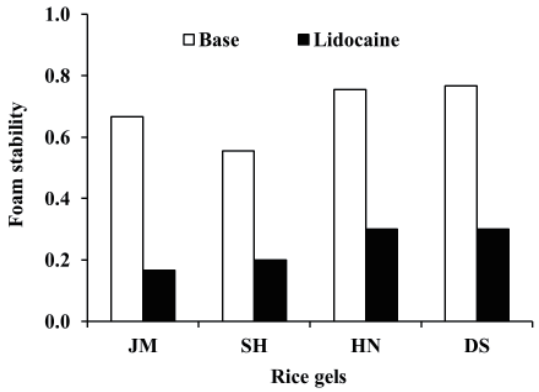

Figure 4. Foam stability of rice gels.

Table 4. Tack value of the rice gels

Rice gels	Tack value (cm)	
	Gel bases	Lidocaine gels
JM	5.20 ± 0.17	6.39 ± 0.22
SH	4.95 ± 0.20	5.62 ± 0.23
HN	3.87 ± 0.15	5.01 ± 0.30
DS	4.38 ± 0.13	6.28 ± 0.13

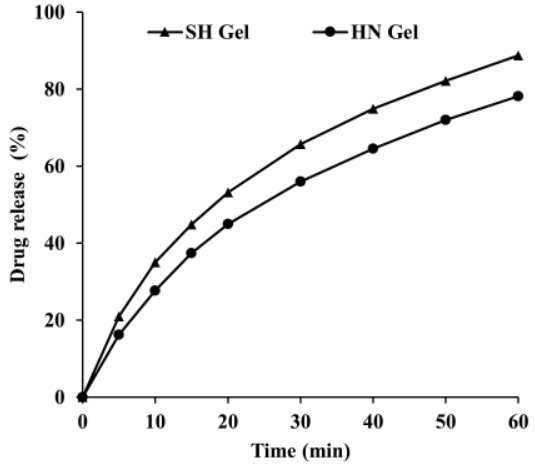

Figure 5. *In vitro* release profiles of lidocaine rice gels.

hydrochloride caused slightly higher tack value indicating slightly decrease in adhesive property of the gels.

3.7. *In vitro drug release property and in vivo efficacy of lidocaine rice gels*

In this experiment the white rice SH gel and the color HN gel were selected and their *in vitro* drug release properties as well as *in vivo* anesthetic efficacy were compared. The *in vitro* drug release tests were carried out in pH 7.4 buffer. It was observed that the release is accompanied by the dissolving of the gels. However, only the drug molecules could diffuse through the used definite MW cut-off dialysis membrane. The release profile of the two gel samples is presented in Figure 5. It is shown that SH rice gel possesses higher drug release property than HN gel. Further study in human volunteers was done in order to compare the anesthetic activity of both gels. It was found that both lidocaine rice gels possess anesthetic efficacy but in different level. Figure 6 demonstrates the results as onset and duration of action of both comparative gels. Lidocaine SH rice gel showed faster onset of action (23.96 ± 11.51 min) and longer duration of action (337.99 ± 68.55 min) than lidocaine HN gel. The onset of action of these gels is in correspondence with the results in *in vitro* release study. Lidocaine could be released from SH gel faster than from HN gel, therefore it showed faster onset of action than lidocaine HN gel. According to the difference in duration of action between these two gels,

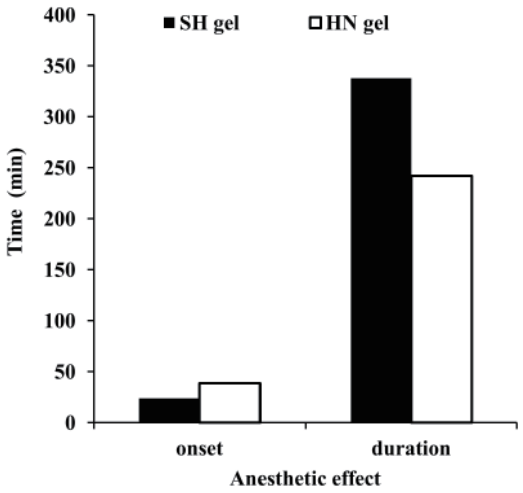

Figure 6. Onset and duration of action of lidocaine rice gels.

it is considered that there might be some interaction between the drug and the components existing in only the SH gel which could be resulted as a sustain release activity.

4. Conclusion

Lidocaine rice gel was developed. The effects of rice varieties on characteristics of lidocaine rice gels were investigated. The color of rice gels obtained was in accordance with the color of their respective rice varieties. The rice gel showed less ability of foam forming and the foams formed were less stability. White rice varieties yield the gels with higher gel strength than color rice varieties. Gel bases of white rice varieties have higher adhesive property than that of color varieties. pH of the gels obtained from both white rice and color rice varieties are similar and nearly 7.0. Incorporating the rice gel bases with lidocaine hydrochloride can cause decrease in pH and adhesive property of the gels. However, lidocaine hydrochloride increases turbidity of the gels. The developed lidocaine rice gels possess anesthetic efficacy. Lidocaine gel of white rice variety possesses higher ability of drug release, faster onset of action and longer duration of action than that of color rice variety.

Acknowledgements

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