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Honey gel and film for burn wound

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Abstract

Honey has been used to treat infected wounds since ancient times. Antibacterial properties of honey are derived from the high sugar content which inhibits bacteria. The natural acidity of honey will inhibit many pathogens. Honey also containing glucose oxidase enzyme that produced hydrogen peroxide when diluted. But honey is still used directly to treat the wound. In this study, we try to formulate the honey to form gel and film. Polymers used are natrium carboxymethyl cellulose (Na-CMC), Aqupec 505 HV, hydroxylpropyl methylcellulose (HPMC), gelatine and polyvinyl alcohol (PVA). Selected polymer was formulated into honey film. Polymers should be combined with plasticizer to improve their properties. Plasticizers studied are polyethylene glycol 400, glycerin and propylene glycol. Evaluations for gel including general appearance, homogeneity, pH and spreadability test, washed test and skin irritation test. Film evaluations are thickness, tensile strength, elongation at break, Young's modulus and water vapour permeability. Based on general appearance and physical properties of gel and film, formula that used PVA as polymer and glycerin as plasticizer is the best formula in this study.

Keywords: Honey, gel, film, PVA and glycerin

Introduction

Honey is a natural fluid generally has a sweet taste produced by insect called a bee. Honey had been used in earlier times for its medicinal properties in many cultures throughout the world. Several studies have reported that honey is effective as a topical therapy on wound [1, 2]. Honey is antibacterial, antioxidant and has a high nutrient content which good for wound healing process [3, 4, 5]. In a study in India, honey can be used in healing burns. This is mainly because honey has a high osmolarity and content of some organic components. In addition, the content of honey also has a composition that suitable with human body, so honey is not considered as a foreign compound [6, 7].

One way of burn wound treatment is using topical antibiotic because there are many protein in the surface of burn wound that could facilitate the growth of bacteria. Honey can act as antimicrobial agents because honey contained hydrogen peroxide. Hydrogen peroxide is known as a major source of honey antibacterial capabilities. Hydrogen peroxide produced by enzyme glucose oxidase (glucosidase) reaction in honey, especially glucose. With the presence of that enzyme, glucose in honey will be converted into glucoronic acid and hydrogen peroxide. Mechanism of hydrogen peroxide as antibacterial is by ruin the outer membrane that protects the bacteria so that the bacteria will be die instantly [5, 8]. Honey has antimicrobial properties because honey has high osmolarity, acidic pH and relatively low water activity [9, 10].

Gel is defined as a semi-solid system consisting of a good dispersion composed of small inorganic particles or large organic molecules, penetrated by a fluid, can be either transparent or opaque mass is used topically [11]. Gel dosage forms have several types of advantages such as simple manufacturing; gives a sense of cold, easily leached after basting and the thin layer formed can provide protection [12]. Gel dosage form is preferred over cream which gel has a high water content so as to reduce pain at the time of application, especially to mucous membranes and in the injured tissue or burned [13]. This study used several gel-forming polymers i.e. Na-CMC, Aqupec 505 HV, HPMC, Gelatine and PVA.

In ancient time, the treatment of wounds is done by allowing the wound to dry and form a hard cover wound like a scab. Since about 30 years ago, the treatment of wound has undergone a change where it is known that the wound will heal faster when covered with a moist cover. Traditionally, gauze made of cotton was used as dressing the wound. But now we can used gels and films to cover the wound and accelerate wound healing [14]. Therefore we conducted this study to find a formula honey gel and film that can be used as wound dressing and accelerate healing of burns.

Materials and Methods

Materials

Honey was acquired from Talu, West Sumatera, Indonesia, Na-CMC, Aqupec 505 HV and Gelatine. Polyvinyl alcohol (PVA) were

bought from VWR International, Belgium. Hydroxypropyl methylcellulose (HPMC) was supplied by Sigma Chemical Co., USA. Polyethylene glycol (PEG) 400 was purchased from Fisher Scientific, U.K. Propylene glycol, glycerin, triethanolamine and methyl paraben, were acquired from R&M Chemicals,U.K.. All chemicals were used without further purification.

Methods

Preparation of Gels

Gels using Aqupec 505 HV and HPMC were prepared by cold mechanical method while gels using Na-CMC, Gelatine and PVA were prepared by hot mechanical method [12, 13, 15, 16]. The prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid.

Table 1. Honey Gels Formula

Ingredients	Formula 1 (%)			Formula 2 (%)			Formula 3 (%)			Formula 4 (%)			Formula 5 (%)		
	1a	1b	1c	2a	2b	2c	3a	3b	3c	4a	4b	4c	5a	5b	5c
Honey	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Na-CMC	4	5	6	-	-	-	-	-	-	-	-	-	-	-	-
Aqupec 505 HV	-	-	-	0,5	0,75	1	-	-	-	-	-	-	-	-	-
HPMC	-	-	-	-	-	-	4	4,5	5	-	-	-	-	-	-
Gelatine	-	-	-	-	-	-	-	-	-	2	2,5	3			
PVA	-	-	-	-	-	-	-	-	-	-	-	-	8	10	12
Propilen glikol	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Methyl paraben	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1
TEA	-	-	-	qs	qs	qs	-	-	-	-	-	-	-	-	-
Distilled water (up to)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

pH Measurements [17, 18]

The pH of all gels formula was determined by using digital pH meter.

General Appearance [11, 19]

Consistency, texture and transparency of the prepared gels were done visually.

Homogeneity [11, 17, 19]

All gels formula was tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Spreadability Test [17, 19]

0.5 g of each gel formulas was placed on a transparent glass repose graph paper, samples was let dilated at a certain diameter. Then covered with transparent plastic and given a certain load (1, 3, 5 and 7 g) for 15 seconds. Increasing of diameter measured after being given the load.

Washed Test [20]

Test was done by applied 1 g gel to the hand and then washed with a certain amount of water. Accounted for much of the water volume was used.

Skin Irritation Test [11, 17]

Test for irritation was performed on human volunteers. For each formula, five volunteers were selected and 0.1 g of formulated gel was applied on an area of 2 square inch to the back of upper hand. The volunteers were observed for lesions or irritation after 24 hours.

Preparation of Honey Film

Honey film was prepared by using selected gel formula. Honey film was prepared by drying a certain amount of honey gel in Petri dish to form a thin layer. Evaluation of film including thickness [21], tensile strength, elongation at break [22] and water vapour permeability [23].

Table 2. Honey Film Formulas

Ingredients	Formula G (%)			Formula PG (%)			Formula P (%)		
	1	3	5	1	3	5	1	3	5
Honey	10	10	10	10	10	10	10	10	10
PVA	10	10	10	10	10	10	10	10	10
Glycerin	1	3	5	-	-	-	-	-	-
Propylene glycol	-	-	-	1	3	5	-	-	-
PEG 400	-	-	-	-	-	-	1	3	5
Methyl paraben	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1
Distilled water upto	100	100	100	100	100	100	100	100	100

Film Thickness

The film thicknesses were measured using a micrometer (Digimatic micrometer, Mitutoyo, Tokyo, Japan) by the method of Yoo et al. [24] and Cao et al. [16]. Sample with air bubbles, nicks or tears and having mean thickness variations of greater than 10 % were excluded from analysis [21].

Mechanical Properties Measurements

The mechanical properties of aerosol concentrate films were evaluated using a texture analyzer (TA.XT2, Stable Micro System, Haslemere, Surrey, UK) by the method of Khan et al. [25] and Febriyenti et al. [22]. Young's modulus (E), a measure of intrinsic film stiffness (Garcia et al., 2009), can be calculated by using the equation in Martin et al. [18].

Water Vapour Permeability of Films

The rates of water vapour permeability of films were determined using the method described in USP XXIV [26] for the evaluation of moisture permeability of containers and packaging materials. Films were tied onto the mouth of small glass bottles of the same size and type (diameter = 1.6 cm) with an average volume of 25 ml ± 0.5 ml. The average area available for vapour permeation was 2.0096 cm^2. The rate of moisture permeability was calculated by using the equation:

$$\text{Rate of Moisture Permeability (mg/day/litre)} = \frac{1000}{14\ V} \times [(Tf - Ti) - (Cf - Ci)]$$

Which V is volume (ml) of the container, (Tf – Ti) is the difference (mg) between the final and initial weights of each test container, (Cf – Ci) is the average of the difference (mg) between final and initial weights of two containers (control).

And other equation by Fetisova and Tsetlin [23]:

$$\text{Water vapour permeability (mg/cm}^2\text{/day)} = \frac{1000}{14\ A} \times [(Tf - Ti) - (Cf - Ci)]$$

A is the area of the film available for vapour permeability (cm^2).

Results and Discussion

pH evaluation was done every week for 6 weeks of storage. pH value changed every week. Nevertheless the results are still within the normal skin pH range i.e. 4,2-6,5 [27] or 5-6,5 [28].

Table 3. pH of Honey Gels

Formula	pH at week						Mean ± SD
	1	2	3	4	5	6	
F1a	6,40	5,36	6,52	6,37	6,47	6,76	6,31 ± 0,49
F1b	6,68	5,66	6,55	6,54	6,83	6,64	6,48 ± 0,42
F1c	6,72	6,67	6,30	6,56	6,64	6,73	6,60 ± 0,16
F2a	5,06	5,05	5,15	5,16	5,08	5,10	5,10 ± 0,05
F2b	5,12	5,18	5,27	5,24	5,13	5,19	5,18 ± 0,06
F2c	4,90	5,19	5,21	5,19	5,18	5,17	5,14 ± 0,12
F3a	4,72	4,78	4,94	4,66	4,63	4,75	4,75 ± 0,11
F3b	4,70	4,63	4,83	4,82	4,74	4,80	4,75 ± 0,07
F3c	4,78	4,85	4,96	4,92	4,81	4,93	4,87 ± 0,07
F4a	5,56	5,27	5,61	5,62	5,57	5,63	5,54 ± 0,14
F4b	5,79	5,40	5,59	5,98	5,50	5,72	5,66 ± 0,21
F4c	5,87	5,35	5,79	5,87	5,79	5,81	5,75 ± 0,19
F5a	4,68	4,70	4,65	4,72	4,72	4,75	4,70 ± 0,04
F5b	4,72	4,70	4,75	4,70	4,72	4,78	4,73 ± 0,03
F5c	4,75	4,74	4,78	4,76	4,75	4,76	4,76 ± 0,01

Table 4 shows the results of the evaluation of general appearances, homogeneity, washed test and irritation test. Gel using Aqupec HV505 and PVA produce clear or transparent gel while the other polymer produced slightly cloudy gel. Good gel for wound dressing is transparent so it is easy to observe the condition of the wound underneath. All of the Honey gel formulas produce homogeny gel. Means that all the ingredients could be mixed with either and gel preparation method used was appropriate.

Washed test was conducted in order to measure the amount of water needed to wash up the gel smeared on the skin. Factor affecting the amount of water that is needed is the type of polymer and the viscosity of the gels. Usually, the dilute gels required less water to wash it up.

Skin irritation test was carried out on five volunteers, who performed with a close patch test and applied directly to the inside of the upper arm with a diameter of 2 cm during 24 hours. None irritate gels do not cause any reaction of erythema, edema, itching or tenderness [17]. The results showed that there are no formulas cause skin irritation.

Table 4. Honey Gel Evaluations

Gelling Agent	Conc. (%w/w)	General appearances	Homogeneity	Washed test (ml)	Irritation test
Na-CMC	4	slightly cloudy gel	Good	44.4	Nil
	5	slightly cloudy gel	Good	48.0	Nil
	6	slightly cloudy gel	Good	57.6	Nil
Aqupec 505 HV	0.5	clear gel	Good	25.9	Nil
	0.75	clear gel	Good	30.7	Nil
	1	clear gel	Good	45.0	Nil
HPMC	4	slightly cloudy gel	Good	34.3	Nil
	4.5	slightly cloudy gel	Good	36.6	Nil
	5	slightly cloudy gel	Good	43.7	Nil
Gelatine	2	slightly cloudy gel	Good	5.0	Nil
	2.5	slightly cloudy gel	Good	7.0	Nil
	3	slightly cloudy gel	Good	9.0	Nil
PVA	8	clear gel	Good	23.7	Nil
	10	clear gel	Good	24.3	Nil
	12	clear gel	Good	25.4	Nil

Spreading test aims to determine the ability of the gels to spread over the surface of the skin upon application. Spreading test was done manually by using extensometer. The principle of this test is to determine the increasing of the area that could cover by gel at a particular time after given a certain load [17]. All formula has a smaller spread than comparator.

Table 5. Spreading Test of Honey Gel

Formula	Spreading (cm)			
	1 g	3 g	5 g	7 g
Comparator	1,5215	2,0789	2,5891	2,7910
F1a	0,7693	1,0048	1,1801	1,4190
F1b	0,6986	0,8857	1,0048	1,0963
F1c	0,6633	0,7693	0,9236	1,0126
F2a	0,0157	0,1170	0,3370	0,5680
F2b	0,0157	0,0880	0,2880	0,6910
F2c	0,0078	0,0700	0,1720	0,2830
F3a	0,1480	0,4680	0,9000	1,3310
F3b	0,2010	0,3890	0,6900	1,9600
F3c	0,1250	0,4230	0,5920	0,9000
F4a	0,1300	0,5180	0,9260	1,1010
F4b	0,1070	0,4340	1,2270	1,7870
F4c	0,0620	0,1750	0,4550	0,7820
F5a	0,1710	1,9804	2,2407	2,5876
F5b	0,1579	1,7902	2,1026	2,4235
F5c	0,1456	1,6887	1,8419	2,1653

After conducting the whole test and based on the general appearance and spreading test, can be observed that the best honey gel formula was the use PVA as polymer.

Honey film was prepared by using PVA as polymer. As plasticizers were used glycerin, propylene glycol and PEG 400. Plasticizer used in three different concentrations i.e. 10%, 30% and 50 % of the polymer concentration. Films that used 30% and 50% plasticizer have the greasy surface. This result indicates that the amount of plasticizer used excess of the amount necessary to react with the polymer and improve the properties of polymers. The film for wound dressing is preferable to be sturdy but pliable [21, 25, 29] and ideally should be elastic [30]. Propylene glycol could produce film with the highest percentage of elongation at break but the lowest tensile strength. Even thought glycerin produced film with the lowest elongation at break compared with other two plasticizers, but the value of elongation at break has been more than 200%. According to Fetisova and Tsetlin [23], film for wound dressing should have minimum elongation at break 200%.

The ideal wound dressing should have several characteristics, such as ability to control gasses diffusion, maintain a moist environment around the wound, prevent further inflammation, simple and easy to use and cause little or no pain to the wound and cosmetically acceptable [31, 32, 33, 34]. A film-forming polymer is suitable for application to the injured skin should be

Table 6. Honey Film Evaluations

Formula	Thickness (mm)	Tensile Strength (N/mm2)	Elongation at break (%)	Young's modulus
FG 1	0.165 ± 0.01	9.05 ± 1.28	282.70 ± 50.49	3.24 ± 0.38
FG 3	0.225 ± 0.01	8.94 ± 1.19	339.78 ± 24.43	2.64 ± 0.35
FG 5	0.161 ± 0.02	3.09 ± 0.48	376.50 ± 52.78	0.82 ± 0.09
FPG 1	0.140 ± 0.02	7.62 ± 1.18	353.99 ± 37.57	2.19 ± 0.50
FPG 3	0.205 ± 0.01	4.49 ± 0.73	321.35 ± 65.28	1.42 ± 0.16
FPG 5	0.247 ± 0.08	5.48 ± 1.33	484.93 ± 103.95	1.14 ± 0.23
FP 1	0.157 ± 0.02	11.59 ± 2.92	288.48 ± 41.00	3.98 ± 0.64
FP 3	0.173 ± 0.02	7.30 ± 1.52	282.58 ± 31.83	2.58 ± 0.40
FP 5	0.181 ± 0.04	4.82 ± 1.51	405.04 ± 85.80	1.20 ± 0.29

permeable to water vapour to decrease the possibility of anaerobic bacterium growth in the wound vicinity. Components added to film-forming agents as a part of the formulation may affect the rate of water vapour transmission. They include the type of the film-forming polymer and plasticizer, their concentrations and the thickness of the film formed [35]. In USP XXIV [26], the materials were permeable if they have water vapour permeability more than 2000 mg/day/litre. According to Fetisova and Tsetlin [23], for the films that have water vapour permeability between 19 – 26 mg/cm^2/day or more ensure the natural aeration of the skin. The water vapour permeability test showed that films that used glycerine as plasticizer produced the best permeability when compared to films that used propylene glycol and PEG 400.

Table 7. Water vapours Permeability of Honey Film

Formula	Water Vapour Permeability	
	(mg/cm^2/day)	(mg/day/liter)
FG	15.59 ± 3.59	1958.83 ± 450.96
FPG	11.14 ± 1.07	1399.77 ± 134.98
FP	13.15 ± 2.55	1651.37 ± 320.49

Conclusion

Based on the results of physical evaluation that include general appearance, spreading test and wash test, honey gel that used PVA was better than used Na-CMC, Aqupec 505 HV, HPMC and gelatine.
Plasticizer with 10% concentration of the amount of polymer is sufficient to produce films with good elasticity. Honey films that using glycerine as plasticizer is better than that using propylene glycol and polyethylene glycol.

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