

## Formulation of Acne Patch from *Garcinia mangostana* L Peel Extract With a Combination of Chitosan Polymer and HPMC Against *Propionibacterium acnes* Bacteria

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### Abstract

*Garcinia mangostana* or Mangosteen has main compounds derived from xanthenes, one of them was alpha mangosteen known having antibacterial activity. The purpose of this study was to formulate an acne patch preparation from mangosteen peel extract with a combination of chitosan and HPMC polymer against *Propionibacterium acnes* bacteria. Acne patches were made by solvent evaporation by using oven at 70 °C. Acne patch preparation was evaluated for physical characteristics, and tested for its antibacterial effectiveness activity. The acne patch formulation was made with the ratio of Chitosan :HPMC: mangosteen peel extract at F1 (800 mg: 400 mg: 120 mg), F2 (900 mg: 300 mg: 120 mg), F3 (800 mg: 400 mg: 240 mg), F4 (900 mg: 300 mg: 240 mg). All formulas have good organoleptic properties, thickness 0,7-0,9 mm, folding resistance >300 times, low vapor transmission rate 0,0030-0,0078 g.cm<sup>2</sup>/hour, moisture absorption capacity 13-23%, content moisture <10% and uniform active substance ingredient. The patch preparation has antibacterial effectiveness with strong inhibition in the range of 10-20 mm. F1 (800 mg: 400 mg: 120 mg) and F3 (800 mg: 400 mg: 240 mg) have the strongest inhibition with 11,2 and 11,0 mm respectively.

**Keywords:** acne patch; chitosan; HPMC; mangosteen peel extract; *propionibacterium acnes*

### 1. INTRODUCTION

Acne vulgaris or acne is a chronic multifactorial skin disease that affects millions of people worldwide. The pathophysiology of acne consists of several mechanisms such as hyperseborrhea, hyperkeratinization of pilosebaceous units (hair follicles and oil glands), proliferation of acne bacteria, hyperandrogenism, changes in sebum content and the occurrence of inflammatory processes. In this regard, the main cause of acne development and the severity of acne lesions make the selection of active substances and the development

of dosage forms for anti-acne become essential. *Propionibacterium acnes* is one of the gram-positive microorganisms on human skin involved in the pathophysiology of acne (Ghasemiyeh et al., 2022)

Topical and oral antibiotics such as erythromycin and clindamycin can be used in the treatment of mild to severe acne. However, the topical and oral use of macrolide antibiotics is no longer recommended due to the resistance of *Propionibacterium acnes* to macrolides, thus reducing the effectiveness of this antibiotic group (Baghaie et al., 2017). The use of natural ingredients can serve as an

alternative in acne treatment. *Garcinia mangostana* L., or Mangosteen, is a plant commonly found in Asian countries, including Indonesia. Mangosteen contains primary compounds called xanthone derivatives, which include  $\alpha$ -mangosteen,  $\beta$ -mangosteen,  $\gamma$ -mangosteen, 8-deoxygartanin, garcinone E, mangostanol,  $\beta$ -mangostin, tovophyllin A and B, mangostenin, mangostenone C, D, and E, garcinion E, and gartanin. It is known to exhibit antifungal, antimicrobial, antioxidant, anti-inflammatory, and cytotoxic effects (Ansori et al., 2020).

Topical and oral therapy of antibiotics such as erythromycin and clindamycin can be used in the treatment of mild to severe acne but topical and oral use of this macrolide class is no longer recommended because *Propionibacterium acnes* is resistant to macrolides, reducing the effectiveness of this macrolide antibiotic (Baghaie et al., 2017).

The use of natural ingredients can be an alternative in the treatment of acne. *Garcinia mangostana* L or Mangosteen is a plant that is found in many Asian countries including Indonesia. Mangosteen has the main compounds of xanthone derivatives consisting of  $\alpha$ -mangosteen,  $\beta$ -mangosteen,  $\gamma$ -mangosteen, 8-deoxygartanin, garcinone E, mangostano 118,  $\beta$ -mangostin 19, tovophyllin A and B20, mangostenin21, mangostenone C, D, and E, garcinion E, and gartanin are known to have activities as antifungal, antimicrobial, antioxidant, anti-inflammatory and anti-cytotoxic (Ansori et al., 2020).

Antiacne cream containing 1-2% chitosan-mangosteen peel extract nanoparticles can inhibit the growth of *Propionibacterium acnes* equivalent to antiacne products with antibiotic active formulation with HPMC polymer as film has more optimum bioadhesivity (Latif et al., 2022)

The purpose of this study was to formulate acne patch from mangosteen peel extract with a combination of chitosan

ingredients. Another study showed that mangosteen extract is effective in treating mild to moderate acne comparable to 1% clindamycin gel without causing severe side effects (Lueangarun et al., 2019) Currently, an alternative acne treatment is being developed in the form of acne patch. Patch are dosage forms that can be given by the percutaneous route of administration in direct contact with the skin in a closed manner. Patch are well accepted by patients because they are non-invasive when used, the bioavailability of the active substance is guaranteed, can be in prolonged contact with the skin so as to maximize drug delivery and therapeutic effects (Kesarwani et al., 2013).

Polymers are the basis for percutaneous drug delivery systems. One of the polymers that can be used in patch is chitosan. Chitosan is a natural polysaccharide that is biocompatible, biodegradable and has low toxicity (Crendhuty et al., 2021). Chitosan is able to help tissue healing or in this case can help the skin repair process of acne scars (Crendhuty et al., 2021) (Cacicedo et al., 2020).

Formulation using chitosan as film in previous studies showed successful drug delivery with higher penetration in the skin and produced good physical patch characteristics (Crendhuty et al., 2021) (Crendhuty et al., 2021). The ideal patch must also be able to quickly adhere and have optimum adhesion strength. HPMC is one of the polymers that often used in percutaneous drug delivery in controlled drug delivery systems, cosmetic product and good adhesive materials because of its non-toxic, non-irritating and compatible with various active substances and excipients. Previous research shows that

and HPMC polymers against *Propionibacterium acnes* bacteria, determine the physical characteristics and patch preparations of mangosteen peel extract (*Garcinia mangostana* L) and its antibacterial effectiveness.

## 2. METHODS

### Tool

Analytical balance (OHAUS PX224), magnetic stirrer (Thermo Fisher Scientific SP88857105), caliper, incubator (Mettler IN110), homogenizer (Cimarec), desiccator, UV-Vis spectrophotometer (Thermo Scientific), oven (Mettler), autoclave (Tomy SX-500), Laminar Air Flow, pH indicator, beaker glass, measuring cup, petri dish, bunsen.

### Materials

The materials used were mangosteen peel extract (Lansida®), *Propionibacterium acnes* Bacterial Culture (Microbiology Laboratory, University of Indonesia), chitosan (Nitra Kimia), HPMC (Nitra Kimia), DMSO (Nitra Kimia), Propylene Glycol, Ethanol 96%, Distilled Water, Blood Agar Media (Nitra Kimia), Acetic Acid (Nitra Kimia), Calcium Chloride

(Nitra Kimia), and Potassium Chloride (Nitra Kimia).

### Formulation Acne Patch of Mangosteen Peel Extract

Mangosteen peel extract, 12 mg, was dissolved in 50% ethanol. Chitosan, 800 mg and 900 mg respectively, was dissolved in a 1% acetic acid solution at a ratio of 1:10 until completely dissolved. HPMC, 400 mg and 300 mg respectively, was dissolved in distilled water at a ratio of 1:20. The dissolved chitosan and HPMC were each homogenized using a homogenizer at 400 rpm for 30 minutes and then allowed to stand for 24 hours to remove foam from the solution. The chitosan solution, HPMC solution, DMSO, propylene glycol, and mangosteen peel extract, mixed in a beaker, were stirred until homogeneous. The mixture was then poured into molds and oven-dried at 70°C for 15 hours, followed by standing at room temperature (25°C) for 24 hours (Auliya dkk, 2019).

**Table 1. Formulation Design of Mangosteen Peel Extract Acne Patch**

Ingredients	Formula (w/w)						Roles
	K1	K2	F1	F2	F3	F4	
Mangosteen Peel Extract	-	-	120 mg	120 mg	240 mg	240 mg	Antibacterial
Chitosan	800 mg	900 mg	800 mg	900 mg	800 mg	900 mg	Polymer
HPMC	400 mg	300 mg	400 mg	300 mg	400 mg	300 mg	Polymer
DMSO	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	Enhancer
Propylene Glycol	4 mL	4 mL	4 mL	4 mL	4 mL	4 mL	Plasticizer
Ethanol (50%)	4 mL	4 mL	4 mL	4 mL	4 mL	4 mL	Solvent

### Note:

K1=Chitosan:HPMC (800 mg:400 mg)

K2=Chitosan:HPMC (900 mg:300 mg)

F1 =Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:120mg)

F2 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:120 mg)

F3 =Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:240 mg)

F4 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:240 mg)

### Physical Characteristics Evaluation of Mangosteen Peel Extract Patches Organoleptic

The patch formulations were visually observed, encompassing color, shape, and surface texture (Latif et al., 2022).

#### Thickness

Three patches were taken from each formulation, then their thickness was measured on three different sides using a caliper, and the average was calculated. (Ramadhani, 2017)

#### Weight Uniformity

Three patches from each formula were weighed, and their averages were calculated. The weight of each patch should not deviate significantly from the average by more than 5% (Ramadhani, 2017)

#### Folding Endurance Test

Samples of patches were taken from each formula, and then a folding endurance test was conducted by repeatedly folding the patches until they broke. The number of folds indicates the folding endurance of the patches (Ramadhani, 2017).

#### Moisture Absorption Test

Samples of patches were taken from each formula and weighed as the initial weight. They were then placed in a desiccator at room temperature for 24 hours. Afterward, they were re-weighed as the final weight, and the moisture absorption percentage was calculated. Moisture absorption was calculated using the equation (Ramadhani, 2017):

$$\% \text{ Daya Serap Lembab} = \frac{(\text{bobot akhir} - \text{bobot awal})}{\text{bobot awal}} \times 100$$

#### Moisture Content Test

The moisture content test was conducted by taking several patch samples, which were then weighed as the initial weight. The patches were stored in a desiccator containing silica gel at room temperature

for 24 hours. Afterwards, they were re-weighed as the final weight (Latif et al., 2022).

$$\text{Kandungan lembab} = \frac{(\text{bobot awal} - \text{bobot akhir})}{\text{bobot awal}} \times 100\%$$

#### Acidity Test

Samples of patches were taken from each formula and immersed in containers containing 10 mL of distilled water. They were then left to stand for 1 hour at room temperature, and the pH was measured using pH indicator (Nurmesa dkk., 2019).

#### Vapor Transmission Test

The vapor transmission test was conducted using vials containing anhydrous calcium chloride as the transmission medium. Patches were affixed onto the transmission medium using adhesive patches and weighed as the initial weight. The cells were left in a desiccator for 24 hours, which contained potassium chloride. The cells were weighed as the final weight. (Ramadhani, 2017).

$$\text{Laju transmisi uap} \left( \frac{\text{gram} \cdot \text{cm}^2}{\text{jam}} \right) = \frac{\text{bobot akhir} - \text{bobot awal}}{\text{waktu}} \times \text{area}$$

### Antibacterial Test of Mangosteen Peel Extract Patches

#### Preparation of Bacterial Suspension

A total of 1-2 colony-forming units (CFU) of *Propionibacterium acnes* bacteria were extracted and suspended in a 0.9% NaCl solution until turbid according to the 0.5% McFarland standard or equivalent to  $10^8$  (CFU)/mL. The bacteria were gently swabbed onto bacterial growth media (Aziz, 2010).

#### Antibacterial Effectiveness Test

Blood Agar media as much as 10 grams was weighed and dissolved in 250 mL of aquadest, the solution is heated on a hot plate stirrer until homogeneous, media that has been homogeneous is stored in a sterile 250 mL Erlenmeyer then sterilized using an autoclave at a

temperature of 121°C with a pressure of 2 atm during sterilized using an autoclave at 121°C with a pressure of 2 atm for 15 minutes. The solution was poured into a petri dish approximately 10 mL used for growth media. A total of 1-2 ose of *Propionibacterium acnes* bacterial culture was taken and suspended in 0.9% NaCl solution until cloudy according to the standard of 0.5% McFarland standard or comparable to 108 (CFU)/mL. Bacteria were streaked slowly on the growth media. The Acne Patch with a diameter of 0.6 mm was placed on media previously inoculated with *Propionibacterium acnes* bacteria with 3 replication, then incubated at 37°C for 24 hours.

The antibacterial effectiveness was indicated by the diameter of the inhibition zone formed. In this test, the inhibitory effect of the acne patch formulation containing mangosteen peel extract was compared to that of the patch without extract (Aziz, 2010).

### Data Analysis

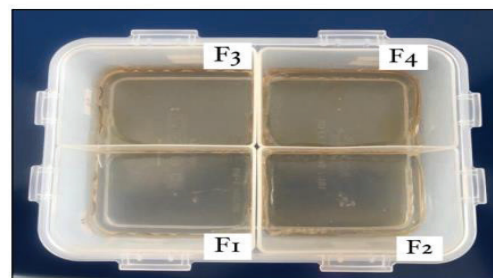
The data from experiments on thickness, weight uniformity, folding endurance, vapor transmission rate, moisture content, and antibacterial effectiveness were statistically analyzed. If normally distributed and homogeneous, they underwent One Way ANOVA; significant results ( $P \leq 0.05$ ) led to Tukey's HSD test for inter-formula significance. Non-normally distributed data underwent Kruskal-Wallis testing; significant results ( $P \leq 0.05$ ) were followed by the Mann-Whitney post hoc test.

## 3. RESULTS AND DISCUSSION

### Organoleptic

Based on visual observations, the patches appear transparent, brownish, light brown, film-shaped, odorless, and exhibit different textures. F1 and F3 represent formulas with Chitosan: HPMC polymer ratios of 800mg:400mg, while F2 and F4 represent formulas with Chitosan: HPMC polymer

ratios of 900mg:300mg. The color differences are a result of variations in the amount of extract in the formulations, where F1 and F2, containing 1% extract, exhibit a transparent colour, while F3 and F4, containing 2% mangosteen peel extract, have a light brown colour. The utilization of polymer combinations aims to ascertain the differences in the characteristics of acne patch formulations. A higher concentration of Chitosan in the formulation results in a slightly wet texture of the patch. This is due to Chitosan's narrow pores, resulting in lower absorption capacity, thus the solvent is not fully absorbed (Cacicedo et al., 2020). The utilization of a higher concentration of HPMC results in the formulation of a more adhesive patch. This is attributed to the adhesive properties of the HPMC polymer, which possess optimal adhesion. (Latif et al., 2022).



**Figure 1. Acne Patches of Mangosteen Peel**

### Note :

F1 =Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:120mg)

F2 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:120 mg)

F3 =Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:240 mg)

F4 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:240 mg)

### Thickness

The results of the testing in Table 2 reveal that the patches' thickness in this study falls within the range of 0.7 to 0.9 mm. The thickness of the patch significantly influences user comfort. According to the test findings, all patches meet the specified requirements, where an ideal patch should

have a thickness ranging from 0.5 to 1.0 mm. This suggests that the formulation maintains consistent thickness, avoiding extremes of thinness or thickness. Thin patches may be fragile, whereas thick patches can compromise comfort during use and hinder the permeability process of active substances through the film. Moreover, thicker films tend to diminish the permeability of active substances and the coefficient of drug permeability through the film.

**Table 2. Thickness of Mangosteen Peel Extract Patches**

Formula	Mean ± SD Thickness (mm)
F1	0.92± 0.010
F2	0.82± 0.035
F3	0.77± 0.035
F4	0.87± 0.015

#### Acidity

The pH testing was conducted by immersing the patch in a container containing 10 mL of distilled water, then left to stand for 1 hour at room temperature, and the pH was measured using a pH indicator. The pH testing results of all formulations indicated a pH of  $5 \pm 0.02$ . The slightly acidic pH of the formulations may be attributed to the influence of chitosan polymer dissolved in 1% acetic acid. The pH of the formulations can be considered to meet the requirements of skin pH, which ranges from 4.5 to 6.5. pH that is too acidic or too alkaline can cause skin irritation (Nurmesa dkk., 2019).

#### Weight Uniformity

The factors influencing the weight uniformity of the patches are the solvent evaporation process and polymer concentration. The formulation weight will be uniform if the solvent evaporates completely and evenly. Statistical test results indicate no significant differences between formulas; all have uniform weights without deviation exceeding 5%.

**Table 3. Weight Uniformity of Mangosteen Peel Extract Patches**

Formula	Mean ± SD Weight Uniformity (g)
F1	8.11± 0.03
F2	8.10± 0.07
F3	8.28± 0.18
F4	8.07± 0.03

Overall, the patch weight ranges around 8 grams (as seen in Table 3). Weight variations in the patches are influenced by the physicochemical properties of the polymers used. Previous studies indicate that an increase in the amount of HPMC leads to an increase in the formation of a gel layer, which affects the weight of the patch formulation (Inayah dkk., 2018).

#### Folding Endurance

All formulated patch preparations exhibit folding endurance that meets the criteria, where all formulations have fold endurance exceeding 300 folds, with no significant differences between them. Folding endurance can be influenced by the use of polymer combinations, with the combination of Chitosan and HPMC potentially enhancing the folding endurance of the patch preparation. Overall, the average formula observed in Table 4 indicates that the acne patches have folding endurance exceeding 200 folds. This is supported by previous research indicating that the folding endurance of a patch can be considered good if the preparation remains intact and does not crack after folding testing exceeding 200 times. (Misnamayanti, 2019). Research on other types of patches also supports the notion that a patch has good folding endurance if it does not tear easily upon application to the skin, typically exhibiting fold endurance exceeding 200 folds (Thakur et al., 2016).

**Table 4. Fold Endurance of Mangosteen Peel Extract Patches**

Formula	Mean ± SD Fold Endurance (times)
F1	353± 2,51
F2	367± 2,51
F3	360± 6,02
F4	357± 8,62

**Absorption Capacity and Content of Moisture**

Moisture absorption testing was conducted to determine the moisture absorption capacity of the skin, indicating the level of water absorption in the formulation during use. The test results revealed that the moisture absorption capacity of the formulated acne patches ranges from 13-23% (Table 5). The comparison of chitosan: HPMC polymers (800 mg: 400 mg) exhibits higher water absorption capacity compared to chitosan: HPMC (900 mg: 300 mg). This is related to the hygroscopic properties of the polymers, where HPMC has higher hygroscopicity compared to chitosan, resulting in higher moisture absorption capacity as the concentration of HPMC increases (Auliya dkk, 2019). Moisture absorption in the range of 13-23% in this formulation does not affect the physical quality of the patch. Supported by fold endurance test exceeding 200 folds, it indicates that moisture absorption in this range does not cause the patch to become easily damaged or torn. The patch's ability to absorb moisture affects the diffusion of active substances, where the process of water absorption in tissues facilitates the release of the extract (Misnamayanti, 2019).

**Table 5. Absorption Capacity and Content of Moisture of Mangosteen Peel Extract Patches**

Formula	Mean ± SD Absorption Capacity (%)	Mean ± SD Moisture Content (%)
F1	19% ± 0,04	5,08% ± 0,007
F2	13% ± 0,04	4,49% ± 0,008
F3	23% ± 0,02	4,57% ± 0,005
F4	17% ± 0,01	3,08% ± 0,003

The test results show that all acne patch formulas have an eligible % moisture content of <10% (table 5). The percent moisture result is also influenced by the hygroscopicity of the polymer. F1 and F3 have a higher percent moisture content than F2 and F4. The ability to absorb moisture affects the diffusion of active substances where the the process of water absorption in the tissue will facilitate the diffusion of active substances (Misnamayanti, 2019) . Previous research shows that the higher the concentration of HPMC, the greater the moisture content, this is related to the hygroscopic nature of HPMC or easily absorbs moisture (Auliya dkk, 2019).These results are supported by antibacterial effectiveness test data where the preparation has a strong inhibition against bacteria *Propionibacterium acnes* (Misnamayanti, 2019).

**Vapour Transmission Rate**

Vapour transmission rate is the amount of water vapor lost or transmitted per unit hour per unit area of the film. Vapor transmission rate testing affects the permeability of patch formulations, where the value of vapour transmission rate is inversely related to moisture content; higher moisture content tends to slow down the vapour transmission rate of mangosteen peel extract patch formulations(Ramadhani, 2017) (Ramadhani, 2017) (Ramadhani et al., 2017). The lower the vapour transmission rate, the better the permeability and physical characteristics of the formulation.

The results of the vapour transmission rate can be seen in **Table 6**.

**Table 6. Vapour Transmission Rate of Mangosteen Peel Extract Patches**

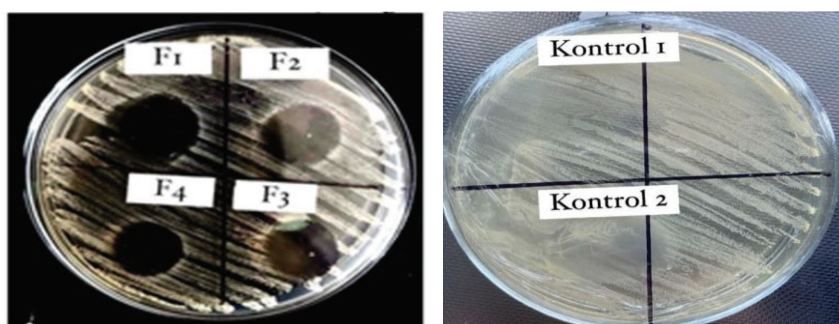
Formula	Mean ± SD Vapour Transmission Rate (g.cm <sup>2</sup> /hour)
F1	0,0039± 0,013
F2	0,0078± 0,013
F3	0,0030± 0,019
F4	0,0052± 0,013

**Antibacterial Activity Against *Propionibacterium acnes***

The extract of mangosteen peel contains a compound called alpha-mangosteen, which is the main compound of xanthone derivatives known for their antibacterial activity against *Propionibacterium acnes* (p-value <0.05). These results suggest that patch formulations containing 1-2% mangosteen peel extract exhibit strong inhibitory activity against *Propionibacterium acnes*. Conversely, patch formulations without extract or

activity. Alpha-mangostin can induce damage to bacterial membranes by disrupting the integrity of the cytoplasmic membrane, thereby resulting in cell damage or cell death (Koh et al., 2013). This study was conducted by comparing a patch formula containing active ingredients extracted from mangosteen peel with a formula without the extract. The aim was to determine the effectiveness or inhibitory activity of the patch containing 1-2% mangosteen peel extract. Strong inhibitory activity is characterized by inhibition zones of 10-20 mm, while weak inhibitory activity is indicated by inhibition zones < 5 mm. (Susanto, dkk., 2013). The statistical test results indicate significant differences (p-value < 0.05) that F1>F3>F4>F2, with inhibition zone ranges falling within the significant range of 10-20 mm. Negative controls show no inhibition zones. Therefore, it can be concluded that the antibacterial activity against *Propionibacterium acnes* originates from the mangosteen peel extract.

**Figure 2. Antibacterial Activity of Acne Patches from Mangosteen Peel Extract**



K1=Chitosan:HPM

C (800 mg:400 mg)

K2=Chitosan:HPMC (900 mg:300 mg)

F1 =Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:120mg)

F2 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:120 mg)

F3 =Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:240 mg)

F4 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:240 mg)

**Table 7. Antibacterial Activity of Mangosteen Peel Extract Patches**

Formula	Mean ± SD Inhibition Zone (mm)
K1	0
K2	0
F1	11.2 ± 0.45
F2	10.0 ± 0.30
F3	11.0 ± 0.28
F4	10.1 ± 0.26

**Note:**

K1=Chitosan:HPMC (800 mg:400 mg)

K2=Chitosan:HPMC (900 mg:300 mg)

F1 = Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:120mg)

F2 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:120 mg)

F3 = Chitosan:HPMC:Mangosteen Peel Extract (800mg:400mg:240 mg)

F4 =Chitosan:HPMC:Mangosteen Peel Extract (900mg:300mg:240 mg)

**4. CONCLUSION**

Mangosteen Peel Extract Patches with Chitosan:HPMC:Mangosteen Peel Extract ratios in F1 (800 mg: 400 mg: 1%), F2 (900 mg: 300 mg: 1%), F3 (800 mg: 400 mg: 2%), F4 (900 mg: 300 mg: 2%) exhibit good physical properties and characteristics. Organoleptic tests show that F1 and F2 are transparent, while F3 and F4 are brown. All patch formulations have a thickness of 0.7-0.9 mm, folding endurance >300 times, vapour transmission rate ranging from 0.0030-0.0078 g.cm<sup>2</sup>/hour, moisture absorption of 13-23%, moisture content <10%, uniform

active ingredient content, and weight. The strongest antibacterial activity is found in F1 (11.2 + 0.45 mm) and F3 (11.0 + 0.28 mm).

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