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Evaluation of PVA-Seaweed Cottonii Hydrogel Patch for Melasma Treatment with Incorporation of Snail Mucin and *Glycyrrhiza glabra*

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Abstract

Melasma is a chronic hyperpigmentation disorder that mostly occurred in women and linked to the limitations and complications of the conventional treatment methods like the use of hydroquinone and chemical peeling. The problem associated with the study was the absence of a safe and effective system for the sustained delivery of depigmenting and antimicrobial functions of the treatment. The aim of the study was to design and assess the use of hydrogel patch containing natural bioactive components in the treatment of melasma. In this study, the approach included the formulation of a PVA-based hydrogel layer with added seaweed extract, snail mucin, and *Glycyrrhiza glabra*, optimized via Design of Experiment (DOE), with the subsequent testing of the pH and tensile strength. The study revealed the optimized hydrogel patch to be pH compatible with the skin and sufficient mechanical strength. Future studies should be focused on antibacterial, antioxidant, in vivo evaluation, long-term stability analysis, and clinical validation to further establish the effectiveness and safety of the patch for the management of melasma.

1. Introduction

Melasma is the chronic form of hyperpigmentation that impacts up to 30% of females and has been known to have severe psychosocial and quality of life implications, primarily in darker skinned females [1]. The existing treatment options of choice for melasma include hydroquinone, azelaic acid, and chemical peeling [2]. However, it has been noted to be coupled with dermatitis, rebound hyperpigmentation, and lack of efficacy in many situations, thereby leading to reduced compliance among patients [3]. The reason for the increase in the use of plant-derived actives is their cumulative depigmenting, antioxidant, and antimicrobial properties. Seaweed polysaccharides have moisturizing and ROS-scavenging activity, snail mucin offers a hydrated viscoelastic substrate and ROS-neutralizing peptides, whereas the licorice extract flavonoids (glabridin and liquiritin) noncompetitively inhibit tyrosinase and melanosomes [4].

The current melasma treatments are mainly cream formulations that do not possess mechanical strength, sustained release, or occlusive barrier function, hence having low loading capacity, instability, or poor adhesion to the facial skin [5]. Therefore, there is a need for creating a polyvinyl alcohol polymer-based PVA hydrogel core

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that incorporates with bioactive agents. Failure to fill this gap could lead to patients being reliant on irritant chemicals and having suboptimal treatment outcomes, whereas a successful hydrogel patch system could provide a non-invasive and multi-functional treatment solution.

This study aimed to find out the best formulation of seaweed extract, snail mucin, and licorice extract that can deliver a patch with skin-compatible pH approximately 5.5 – 7.5 and a tensile strength within the target range around 3 – 5 MPa. To achieve these aims, Box-Behnken Design of Experiments was used to approximately vary the concentration of the three extracts for optimizing the values of pH and tensile strength.

2. Methodology

2.1 Material

The hydrogel patch was made up of polyvinyl alcohol (PVA) as base polymer, *Eucheuma cottonii* seaweed extract, snail mucin powder from *Eulota similaris Ferussac* species, *Glycyrrhiza glabra* (licorice) extract, and distilled water. This preparation required an analytical balance, a magnetic stirrer with heating, a speed mixer, molds for shaping, oven for drying, calibrated pH meter with electrode, and universal testing machine (UTM) for tensile strength. To plan and optimize the formulation, Design-Expert software was used. Fig. 1 shows the flowchart of the preparation of the hydrogel.

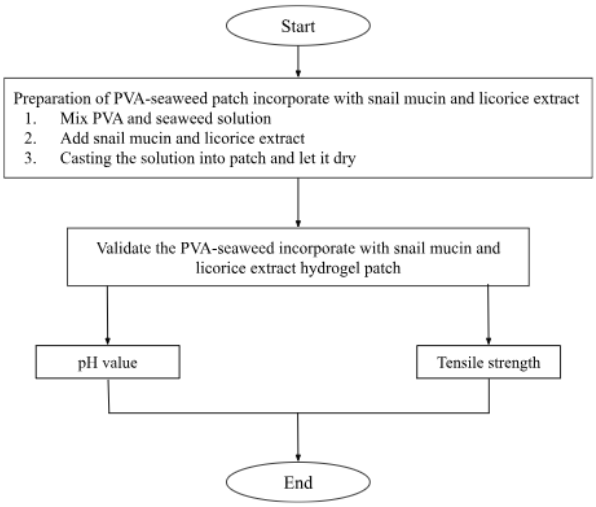


Fig. 1: A flowchart of the preparation of hydrogel patch.

2.2 Design of Experiment (DOE) by Design-Expert

A Box-Behnken response surface design was developed in Design Expert 13 for optimization of hydrogel formulation. Three quantitative variables, namely seaweed extract (1-5 wt%), snail mucin (2-8 wt%), and licorice extract (0.5-3 wt%), with two response variables, pH and tensile strength (MPa). The software predicted a set of 17 experimental runs comprising 12 edge points and 5 nominal centre points. As the centre-point formulation was prepared and characterised as a single preparation, only 13 unique factor-level combination were used to analyzed ANOVA for significance, and for locating the optimal formulation.

2.3 Preparation of Combined PVA-Seaweed Polymer Solution

10g of *Eucheuma cottonii* was weighed and boiled in 100 mL distilled water at a temperature of 80 – 95 ˚C for 1 hour until it was totally dissolved. In another experiment, 10g PVA was dissolved in 100 mL distilled water with a temperature of 90 ˚C under magnetic stirring for 25 minutes. It was then reduced to 40 ˚C and then slowly added into the seaweed solution with a speed mixer at 3000 rpm for 20 minutes with the purpose of obtaining a homogeneous polymer blend.

2.4 Incorporation of Bioactive Compounds

Snail mucin powder was added to the PVA-seaweed mixture and stirred for 30 minutes. After that, licorice extract was added and stirred until dissolved and homogeneous (20 min). The suspension was first degassed under vacuum for 10 min to remove the entrapped air, then casting into 1 mm films and subjected to five freeze-thaw

cycles which means 12 hours at -20 ˚C followed by 12 hours at room temperature. The final films were then stored at 4 ˚C until testing.

2.4.1 pH Testing

Approximately 0.5g samples were added to 20 mL pre-boiled distilled water, and vortexed for 2 min and allowed to equilibrate for 10 min. A pH meter calibrated with buffers pH 7.01 and 4.01 was used. The electrode was placed in 5 mL solution and allowed to reach equilibrium before recording the value (≈ 5s).

2.4.2 Tensile Testing

All samples were cut in rectangular strips which approximately 25mm × 150mm that based on ASTM D882 geometry. Measured with condition at 23 ˚C/50% RH for 30 min, then clamped to a universal testing machine with 100N load cell at a rate of 100mm min^{-1}. Force and extension measurements enabled calculation of tensile strength at break.

3. Results and Discussion

3.1 pH of the Hydrogel Patch Formulation

The pH of all hydrogel patch formulations was found to range from 6.89 to 7.30 (Table 1), with four formulations marginally acidic, one exactly neutral, and the remaining eight marginally alkaline. All thirteen formulations therefore fell within the targeted skin-compatible window of 5.5 -7.5, and this near-neutral range is generally well tolerated in topical application. According to previous studies, hydrogel patches having a pH approaching the neutral value are very well tolerated as well as found to stabilize during their use [6]. Some of the formulations had a pH level around 7.23, which represented a neutral condition. Although a neutral pH is more comfortable for the user and non-irritating, it might not be the most optimal for the treatment of melasma, since normal skin is slightly acidic. Also, the acidic mantle of the skin is a crucial component in protecting it from infection, and its deviation towards alkalinity might impair its natural barrier and result in pigmentation disorders [7].

The lowest pH recorded was 6.89 (sample 8), which was within the ideal range for dermatological use. Slightly acidic pH is ideal for the treatment of melasma because it promotes skin barrier function and suppression of overactive melanocytes. The decrease in pH seen in some formulations can be attributed to the addition of addition of bioactive ingredients like snail mucin and plant extracts, which have an acidic nature and lower pH of the entire system of hydrogel formulations [6]. It can be observed from Table 1 that the pH values are within a range demonstrating a skin-friendly pH to treat melasma. The pH range between 6.9 to 7.3 is desirable because, by being neither too high nor too low, these patches are not only pleasant for use, but there will be fewer associated hazards, as in the case of highly basic creams. Such results establish that the designed hydrogel patches are Ph compatible for use on the skin.

Table 1: pHh value results

No. of samples	Extract seaweed (wt%)	Snail Mucin (wt%)	Extract licorice (wt%)	pH value
1	3	5	1.75	7.23
2	5	5	3.00	6.91
3	3	8	3.00	7.18
4	3	2	0.50	7.30
5	5	5	0.50	7.00
6	3	8	0.50	6.98
7	1	2	1.75	7.26
8	1	8	1.75	6.89
9	1	5	3.00	6.96
10	3	2	3.00	7.18
11	1	5	0.50	7.11

12	5	2	1.75	7.13
13	5	8	1.75	7.04

Table 2: ANOVA for quadratic model describing pH

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.2025	7	0.0289	7.11	0.0231	significant
A-Extract seaweed	0.0647	1	0.0647	15.90	0.0105	
B-Snail mucin	0.0761	1	0.0761	18.71	0.0075	
C-Extract licorice	0.0145	1	0.0145	3.57	0.1175	
AB	0.0196	1	0.0196	4.82	0.0795	
BC	0.0256	1	0.0256	6.30	0.0539	
A^2	0.0723	1	0.0723	17.79	0.0083	
C^2	0.0182	1	0.0182	4.49	0.0877	
Residual	0.0203	5	0.0041			
Cor Total	0.2228	12				

Analysis of variance for the quadratic model for pH is presented in Table 2. This model proved statistically significant (F = 7.11, p = 0.0231), which means the response surface accurately represented the pH changes within the design space. Snail mucin (B, p = 0.0075) and seaweed extract (A, p = 0.0105) had the greatest influence, along with a notable curvature in seaweed extract (A^2, p = 0.0083). The linear term for licorice extract (C) remained in the model to preserve its structure, as the BC interaction and the C^2 quadratic term were included, even though its individual impact was not statistically significant (p = 0.1175). The BC interaction (p = 0.0539), the C^2 term (p = 0.0877), and the AB interaction (p = 0.0795) were close to the 5% significance level. Therefore, these results are considered suggestive rather than conclusive. The negative coefficient for snail mucin matches the mild acidity of the mucin fraction. Conversely, the positive linear coefficient for seaweed extract, tempered by a significant negative quadratic term, suggests that the anionic polysaccharide fraction raises pH until an intermediate concentration of about 2.5 - 3 wt% is reached, after which the effect reverses. Licorice extract's limited effect on pH is beneficial for formulation, allowing its concentration to be adjusted to improve the depigmenting action of glabridin and liquiritin without significantly altering the patch's skin-compatible pH [4].

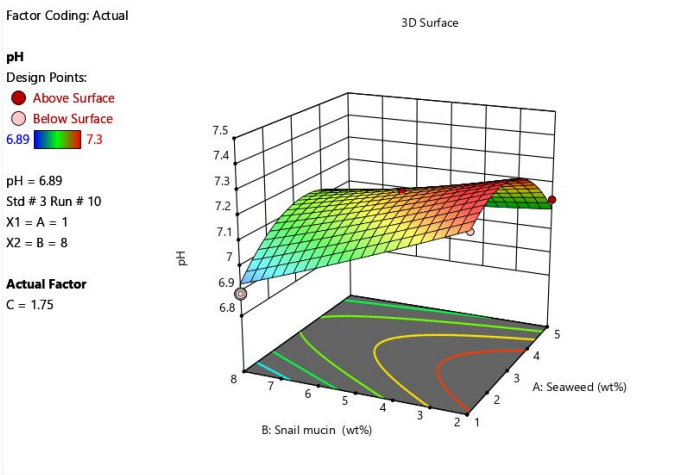


***Fig. 2*:** Response surface 3D graph for pH

The response surface plot in 3D illustrates the interaction between seaweed concentration (Factor A) and snail mucin concentration (Factor B) on pH value. As illustrated in Fig. 2, which presents the surface at a fixed licorice extract level of 1.75 wt% , the measured pH ranged from 6.89 to 7.30 across the design space, remaining near-neutral throughout. Overall, the surface was even and did not have sudden slope changes, which showed that the

pH shifted slowly and predictably throughout the design area. As confirmed by the analysis of variance, the primary factors controlling this change were the individual influences of seaweed extract and snail mucin, along with the curvature of seaweed extract, instead of their combined effect. This suggests that within the studied design space, the formulation system was relatively stable and suitable for controlled pH adjustment.

A noticeable trend from the response surface is that lower seaweed concentrations combined with higher snail mucin concentrations resulted in lower pH values. The region of minimum pH was found at Factor A of approximately 1 wt% and Factor B of around 8 wt%, for a pH value of about 6.89, within the acceptable limits for skin uses. This is attributed to the mildly acidic nature of the snail mucin fraction. The influence of seaweed extract is not monotonic: owing to the significant negative quadratic term, pH increases with seaweed loading up to approximately 2.5 - 3 wt% and declines thereafter, so that the highest pH within the design space occurs at an intermediate seaweed content combined with a low snail mucin loading.. Similar reports were made in pH-sensitive hydrogel systems where the ratio of the different polymers controlled the pH value without affecting the material properties, and thus this optimization supports the applicability of the approach [8].

3.2 Tensile Strength of the Hydrogel Patch Formulations

Values of tensile strength ranged from 3.21 MPa to 7.62 MPa, reflecting the mechanical strength dependence of hydrogel patches on formulation composition (Table 3). The lowest value of 3.21 MPa was recorded for sample 1, the centre-point formulation, indicating a softer and more flexible hydrogel structure. Such tensile strength values are appropriate for applications that require contact with the skin, as they allow for better conformity with facial contours due to the lower risk of discomfort or irritation when worn [9]. In contrast, samples having higher tensile strength values greater than 6 MPa manifested increased rigidity, which enhances tear resistance but may decrease flexibility and skin adaptability.

A moderate tensile strength of 3.0 MPa to 5 MPa is ideal for hydrogel patches that ensure a proper balance between strength and flexibility that is found in hydrogel patches for dermal application. Only two formulations fell within this window, namely sample 1 (3.21 MPa) and sample 8 (4.55 MPa), whereas the remaining eleven formulations exceeded 5 MPa and would therefore be expected to exhibit greater stiffness and reduced conformity to facial contours. It should be noted that the freeze-thaw crosslinking regime was held constant at five cycles for all formulations, so that the observed differences in stiffness are attributable to biopolymer loading rather than to the degree of crosslinking. Previous studies have nevertheless reported that more densely crosslinked networks yield stiffer samples less suited to biomedical patch application, whereas moderate crosslinking affords a more favourable balance of properties [10].

Table 3: Tensile strength results

No. of samples	Extract seaweed (wt%)	Snail Mucin (wt%)	Extract licorice (wt%)	Tensile Strength (MPa)
1	3	5	1.75	3.21
2	5	5	3.00	7.17
3	3	8	3.00	5.93
4	3	2	0.50	5.15
5	5	5	0.50	7.62
6	3	8	0.50	5.89
7	1	2	1.75	6.79
8	1	8	1.75	4.55
9	1	5	3.00	7.38
10	3	2	3.00	6.75
11	1	5	0.50	5.28
12	5	2	1.75	5.65
13	5	8	1.75	7.60

Table 4: ANOVA quadratic model for tensile strength

Progress in Engineering Application and Technology Vol. 7 No. 2 (2026) p. 108-115

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	20.83	9	2.31	599.78	0.0001	significant
A-Extract seaweed	6.91	1	6.91	792.09	0.0001	
B-Snail mucin	12.30	1	12.30	596.63	0.0002	
C-Extract licorice	5.44	1	5.44	410.01	0.0001	
AB	4.39	1	4.39	1137.54	< 0.0001	
AC	1.63	1	1.63	421.33	0.0003	
BC	0.6084	1	0.6084	157.68	0.0011	
A^2	8.56	1	8.56	2218.12	< 0.0001	
B^2	2.30	1	2.30	595.38	0.0002	
C^2	6.74	1	6.74	1747.49	< 0.0001	
Residual	0.0116	3	0.0039			
Cor Total	20.84	12				

Analysis of variance for the tensile strength response is presented in Table 4. The quadratic model returned a highly significant F-value (599.78, p = 0.0001) and all nine model terms were significant, with the quadratic terms C^2 (F = 1747.49) and A^2 (F = 2218.12) and the AB interaction (F = 1137.54) making the largest contributions.

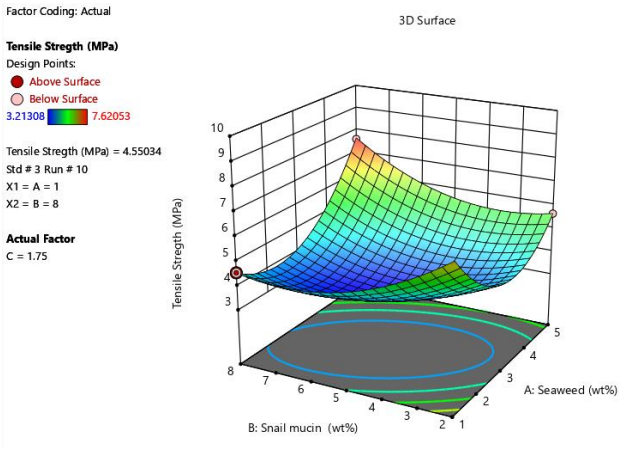


Fig 3: Response surface 3D graph for tensile strength

The 3D response surface graph, which used a set licorice extract level of 1.75 wt%, shows that the hydrogel patch's tensile strength results from the combined effect of several formulation variables. This means it has a clear curve and factor interaction, not just one variable acting independently. The surface appears convex, dropping to its lowest point with intermediate compositions and rising towards the highest or lowest values of both factors. The lowest tensile strength, 3.21 MPa, occurred at the center point (3 wt% seaweed extract, 5 wt% snail mucin). In contrast, the highest value, 7.60 MPa, was achieved when both factors were at their upper limits (5 wt% and 8 wt% respectively). This likely happens because poly(vinyl alcohol) crystallite formation is interrupted during freeze-thaw cycles when there's a medium amount of biopolymer. However, with low biopolymer amounts, the PVA network mostly stays together. With high amounts, the extra hydrogen bonding from the polysaccharide and mucin components adds a reinforcing effect. Such variation has been demonstrated in PVA-based hydrogels, as proper levels of PVA concentration have been shown to be imperative to facilitate tensile properties [11].

More importantly, the response surface indicates that maximal tensile strength is obtained towards the extremes of the design space rather than at intermediate compositions, whilst the region of minimum tensile strength coincides with the centre of the design space. In this study, the hydrogel network can distribute stress by hydrogen bonding and physical crosslinking, which enhances its mechanical stability with relatively good flexibility. In contrast, a reported optimisation study observed superior tensile properties for hydrogels at intermediate formulation conditions rather than at the extreme compositions [12], which suggests that the direction of the compositional effect is dependent upon the polymer system and the crosslinking route employed. Thus, the response surface plot verifies that controlled optimization of the formulation is necessary to obtain a hydrogel patch that possesses adequate mechanical durability for facial applications while maintaining the comfort and conformity required for contact with the skin.

3.3 Formulation Optimization

Numerical optimization was performed in Design-Expert 13 to find the optimised sample from the 13 generated samples. Since a mildly acidic surface is generally preferred for dermal application, the pH response was set to be minimised, while the tensile strength response was targeted to the range of 3 – 5 MPa. On this basis, the software computed the optimum formulation of 1.00 wt% seaweed extract, 8.00 wt% snail mucin, and 0.85 wt% licorice extract, with predicted responses of pH 6.84 and tensile strength 4.96 MPa. Thus, this optimised formulation from this study can be further improved by adding citrate buffer as one of the factors to reducing the pH to further match the skin acid mantle.

4 Conclusion

A PVA-based hydrogel patch for melasma treatment has been successfully designed and developed by combining seaweed extract, snail mucin, and licorice extract. The proposed design, aimed to offer mechanical support and a biocompatible environment for application on human skin. Additionally, a Design of Experiment (DOE) approach has been developed for optimizing the designed system by considering the significant factors that influence the properties of the hydrogel. On the analysis done by the DOE, numerical optimization identified an optimal composition made of 1.00 wt% seaweed extract, 8.00 wt% snail mucin, and 0.85 wt% licorice extract, with predicted responses of pH 6.84 and tensile strength 4.96 MPa. More optimisations can be done based on this formulation such as formula improvement, antibacterial, antioxidant, and irritation test to confirm the patch's suitability for melasma therapy.

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Conflict of Interest

Authors declare that there is no conflict of interests regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Nur Hanis, Aliff Hisyam; data collection: Nur Hanis; analysis and interpretation of results: Nur Hanis, Aliff Hisyam; draft manuscript preparation: Nur Hanis, Aliff Hisyam

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