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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DESIGN AND EVALUATION OF PROPOLIS-LOADED BUCCAL PATCHES

PROPOLİS YÜKLÜ BUKKAL YAMALARIN TASARIMI VE DEĞERLENDİRİLMESİ

Ali ALAZZO[1]*, Amina Mudhafar AL-NIMA[1], Mohammed Nooraldeen AL-QATTAN[2]

[1]Mosul University, Faculty of Pharmacy, Department of Pharmaceutices, Mosul, Iraq
[2]Nineveh University, Faculty of Pharmacy, Department of Pharmaceutical science, Mosul, Iraq

ABSTRACT

Objective: *Propolis is highly recommended in aphthous stomatitis, a condition that requires a proper delivery tool to achieve an efficient treatment. For this indication, a buccal patch that provides prolonged mucosal contact and protection would be beneficial. Accordingly, in this study, we designed propolis-loaded buccal patches, composed of three polymers (alginate, carboxymethylcellulose, and polyvinylpyrrolidone) of complementary properties, and the proper combination of them to produce the patch of optimum properties.*
Material and Method: *Nine patches of different polymer ratios were prepared by casting method and evaluated by assessing their swelling, adhesion time and strength, and dissolution rate. Then the patches properties were correlated using artificial neural network analysis.*
Result and Discussion: *The results showed that all patches were smooth, translucent, and flexible with surface pH between 6.5 and 7.4. The correlation between polymer composition and measured properties was complex and non-linear. Therefore, an artificial neural network was used to analyze these properties and optimize them. The model of this analysis provides higher weights for favorable tensile and adhesion strengths while considering swelling, rigidity, and fast dissolution rate as unfavorable. According to summation analysis, the combination of CMC% and PVP% of 15.5 and 13, respectively, provides the best score of 3.5.*
Keywords: *Alginate patches, buccal patches, mucoadhesive polymers, propolis*

ÖZ

Amaç: *Etkili bir tedaviye ulaşmak için uygun bir uygulama aracı gerektiren bir durum olan aftöz stomatitte propolis kesinlikle önerilir. Bu endikasyon için uzun süreli mukozal temas ve koruma sağlayan bukkal yama faydalı olur. Buna göre bu çalışmada, tamamlayıcı özelliklere sahip üç polimerden (aljinat, karboksimetilselüloz ve polivinilpirolidon) oluşan propolis yüklü bukkal yamaları ve bunların optimum özelliklere sahip yamayı üretmek için uygun kombinasyonu tasarlanmıştır.*
Gereç ve Yöntem: *Döküm yöntemiyle farklı polimer oranlarına sahip dokuz yama hazırlanmış, şişme, yapışma süresi ve gücü ile çözünme hızı açısından değerlendirilmiştir. Sonra yamaların özellikleri yapay sinir ağı analizi kullanılarak ilişkilendirilmiştir.*
Sonuç ve Tartışma: *Sonuçlar, tüm yamaların pürüzsüz, yarı şeffaf ve esnek ile yüzey pH'ının 6,5 ile 7,4 arasında olduğunu göstermiştir. Polimer bileşimiyle ölçülen özellikler arasındaki korelasyon karmaşık ve doğrusal değildir. Bu nedenle bu özellikleri analiz ve optimize etmek için yapay sinir ağı kullanılmıştır. Bu analizin modeli, uygun çekme ve yapışma gücü için daha yüksek ağırlıklar*

* **Corresponding Author / Sorumlu Yazar:** Ali Alazzo
e-mail / e-posta: alialazzo@uomosul.edu.iq, **Phone / Tel.:** +9647517014655

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sağlarken şişme, sertlik ve hızlı çözünme oranını olumsuz olarak değerlendirir. Toplama analizine göre, sırasıyla 15,5 ve 13'lük CMC% ve PVP% kombinasyonu, en iyi 3,5 puan sağlar.
Anahtar Kelimeler: *Aljinat yamalar, bukkal yamalar, mukoadezif polimerleri, propolis*

INTRODUCTION

Propolis, a bee product, is a traditional remedy with many health benefits. It contains different flavonoids and cinnamic acid derivatives that have several biological effects, including anti-bacterial, anti-fungal, antiviral, anti-inflammatory, antioxidant, and immune modulation effect [1–3]. Propolis, therefore, has been used successfully for many therapeutic purposes, particularly in dentistry and oral health. For example, it was effectively applied in the treatment of aphthous stomatitis and other ulcerative disorders of the mouth cavity [4]. Interestingly, the clinical outcomes in these medical conditions are highly reliant on the modes of delivery with best outcomes being associated with prolonged duration of action and good mucosal protection. Thus, using a controlled strategy of good mucosal adhesion, such as buccal patches, for the administration of propolis is thought to be advantageous.

The concept of buccal drug delivery is gaining increased attention in pharmaceutical science for its local and systemic advantages. It is a readily accessible route, provides prolonged contact with the oral mucosa, and relatively rapid absorption with efficient avoidance of the first-pass effect [5,6]. Many studies, therefore, have attempted to formulate various buccal delivery systems such as tablets, patches, strips, and gels [7,8]. However, buccal patches have shown good flexibility, accurate dosing, and better toleration by patients than other formulations. Also, patches provide a good physical barrier for protecting the oral mucosa from irritation, which is beneficial in many cases, mainly aphthous and mouth ulceration [9]. However, a variety of factors affect proper buccal drug delivery such as saliva flow, shearing forces due to tongue movements, and loss of adhering vehicle. Thus, such factors should be considered in the design of such dosage forms [10].

Buccal vehicles need to possess enhanced and extended adhesive properties. Hence, different mucoadhesive polymers, natural and synthetic, should be evaluated in designing buccal patches such as sodium alginate, hydroxypropyl methylcellulose, and poly acrylic acid. Many of these mucoadhesive polymers, although possessing excellent adhesive properties, have a high swelling ratio and poor mechanical properties [9], which reduce the adhesion time of buccal patches. However, the proper combination of polymers may be helpful to overcome these limitations.

Therefore, in this study, we aim to investigate the effect of various combinations, of sodium alginate, carboxymethylcellulose, and polyvinylpyrrolidone, on swelling ratio, adhesion strength, adhesion time, and dissolution rate for the propolis buccal patches. Due to the possible complex interaction between the polymers, an artificial neural network was used to correlate the ratios of polymers in combination with the measured properties.

MATERIAL AND METHOD

Materials

Propolis samples were collected from hives of honeybees in Babylon City / Iraq. Sodium alginate (SAG), LR- moderate viscosity grade, was obtained from Thomas Baker, Mumbai, India. Carboxymethylcellulose sodium salt (CMC) and polyvinylpyrrolidone (PVP K-30) were procured from Quzhou Ebright Chemicals, China. Glycerin was purchased from Scharlab S.L., Spain. Ethanol was purchased from (Tedia Company, USA). All other used chemicals were obtained from BDH chemicals, UK**.**

Extraction of Propolis

The extraction procedure aimed to remove the waxy impurities, such as beeswax from the major active ingredients of propolis. Before starting the extraction, a frozen propolis was divided into small pieces using ordinary kitchen knife and ground into a fine powder using an electric grinder (Royal-Japan) for about 5 minutes at room temperature [2]. For extraction, 300 ml of 70% (v/v) ethanol were

mixed with 45g of the grounded propolis, shaked manually for 10 minutes, and left in a refrigerator for 3 days to ensure complete extraction. Then, the mixture was filtered, poured into glass Petri dishes, and allowed to dry at room temperature. The obtained propolis extract was then collected, weighed, and kept in a closed container in the refrigerator [3].

Formulation of Propolis-loaded Patches

The solvent casting method was used for the preparation of nine formulations of patches containing propolis (F1- F9) which were prepared by dissolving the calculated amounts of polymers in 25 ml distilled water. The dispersion of the three polymers was stirred using a magnetic stirrer (Fisher Scientific, Korea) for nearly 4 hours with the assistance of heat (50°C) at 350 rpm, and glycerin as plasticizer was also added under constant stirring. After cooling, the polymer dispersion was left overnight to allow air bubbles to be expelled. The 65 mg of propolis extract was weighed, dissolved in 1 ml of 90% ethanol, and added to the polymer dispersion under stirring (350 rpm, 1 hour) until a homogeneous mixture was formed. The final mixture was poured into glass Petri dishes having 9.4 cm diameter, which were kept in the oven at 35 ± 5°C for 24 hours. Finally, these dishes were wrapped with aluminum foil and stored at room temperature [7].

Evaluation of the General Properties of the Formulated Propolis-loaded Patches

All the measurements were carried out on three different pieces of each formulation; each piece had an area of 1.8 cm^2.

Thickness and Uniformity of Mass

Thickness was measured using a digital micrometer caliper (Ditron, China), while the mass measurements were performed by Equinox Analytical and Semi-Micro Balances from ADAM Scales and Balances [11].

Folding Endurance Test

Each formulated patch was repeatedly folded until breaking or folding up to 300 times, which is considered acceptable to reveal good patch properties [7].

Surface pH

Each patch's formulation was allowed to swell by keeping it in contact with 3-5 ml of distilled water for 1 hour at room temperature. The pH was measured by dipping the electrode into the swollen patch and allowing it to stand for 1 minute. The tests were carried out in triplicate, and average values were reported [12].

Evaluation of Mucoadhesive Strength

The adhesion strength of all the formulated patches (F1-F9) was evaluated by a texture analyzer (HD plus, Stable Micro System, Surrey, UK) using a surface of gelatin (6.67% w/v) covered with mucin solution (2% w/v) to represent the buccal mucosa surface [13]. Briefly, the propolis-loaded patch of size 1.8 cm^2 was fixed to the arm of the texture analyzer using cyanoacrylate adhesive (Hopson Chemical Industry Limited, China) and the exposed surface of the patch was kept in contact with the gelatin surface for 60 sec before starting the test for initial hydration and adhesion. The force, required to detach the patch from the gelatin surface, was considered to assess the adhesion strength [14].

***In vitro* Adhesion Time**

The *in vitro* adhesion time was measured for all the formulated patches (F1-F9) using a modified device consisting of a magnetic stirrer (Fisher Scientific, Korea) with a heating jacket supplied at about 37 ± 0.5°C. The medium was phosphate buffer, pH 6.8. A piece of silicone rubber (4 cm width and 1.5 cm length) was attached vertically to the inner surface of a 250 ml beaker. The formulated buccal patch was hydrated from one surface using a few drops of phosphate buffer, and attached to the silicone rubber. The magnetic stirrer was then started (125 rpm, 37.0±0.5°C), with the formulated patch completely immersed in the buffer. The time required for each patch to erode or separate from the silicone

rubber was recorded [15].

Swelling Study

A pre-weighed square-shaped glass slide (2×2) cm^2 was used to weigh a formulated propolis-loaded patch with a diameter of 1.3 cm (all formulations F1-F9 were tested). It was kept in a Petri dish covered with 50 ml of pH 6.8 phosphate buffer. After every 5 min, up to 30 min, the glass slide was removed and weighed using a stopwatch. The percentage of weight increment due to absorption of water and swelling of the propolis-loaded patch was recorded as a swelling percent [14].

Tensile Testing

The tensile properties of the formulated propolis-loaded patches were analyzed using a texture analyzer. The patches were cut into strips of fixed length using a template shaped like a dumbbell. Then, they were fixed on the texture analyzer and evaluated using a stretching speed of 2mm/sec. The elongation at break (%), tensile strength, and elastic modulus were calculated using the following equations [16].

$$\textbf{Percent of elongation at break} = (L_f - L_i)/L_i * 100 \quad \ldots\ldots\ldots (1)$$

$$\textbf{Tensile strength} = F/A \quad \ldots\ldots\ldots (2)$$

$$E = \sigma/\epsilon \quad \ldots\ldots (3)$$

Where **Lf** is the length of the specimen when it breaks, **Li** is the initial length of the specimen, **F** is the peak force at break, **A** is the cross-sectional area of the specimen, **E** is the elastic modulus, σ is the stress, ϵ is the strain.

***In vitro* Release Study**

The release of propolis was evaluated using the paddle dissolution apparatus. The propolis-loaded patch (1.8 cm^2) was applied to a glass disk and fixed at the bottom of the dissolution vessel. The experiment was performed using phosphate buffer (400 ml, pH 6.8) at 37 ± 0.5°C and a rotation speed of 50 rpm. At each time interval, samples of 3 ml were collected and replaced with phosphate buffer pH (6.8). Then the samples were filtered and measured spectrophotometrically at 278 nm [17].

Use of Artificial Intelligence to Find Correlations Between Observations and Settings and Training of Neural Networks

Using Matlab R2017b, an individual feed-forward neural network was trained to reproduce each of the individual physical measures. Each network is composed of the input layer, hidden layer, and output layer. For all networks, the input layer is composed of two neurons to accept the values of PVP% and CMC%, while the output layer is composed of a single neuron to provide the value of a particular physical measurement. The number of hidden neurons was varied to be 5, 6, 7, and 10 for the networks that reproduce force of adhesion, dissolution rate, rigidity-tensile strength, and water-alcohol swelling, respectively. The network was trained with a learning rate of 0.3. The activation functions for hidden and output neurons were Log-sigmoid and linear functions, respectively. The dataset used for training was randomly divided to include 90% of the data for training and 5% of data for each testing and validation. Due to the small dataset size (nine formulations), it was difficult to reproduce the same surface of correlation from the same neural network in repeated training runs. Therefore, to get a consistent surface of correlation, the training process was repeated 10 times and the average trained weights were used.

RESULT AND DISCUSSION

Good adhesion and mechanical properties are very important for buccal patches intended for mouth ulcers to provide long mucosal contact and good physical protection. Therefore, and because the properties of patches are a function of the type and concentration of their components, three polymers, namely SAG, CMC, and PVP were selected in this study to formulate propolis-loaded buccal patches as these polymers have complementary properties.

A natural polysaccharide, SAG, was used to build up the backbone of the patches. It is a safe, biocompatible, biodegradable, and hydrophilic polymer; however, its properties include low cell adhesion and mechanical strength [18,19]. On the other hand, CMC, an ether derivative of cellulose, has shown very good adhesion properties but its water solubility and swelling ratio is high and should be controlled for good buccal patch properties [11]. PVP is a synthetic polymer of good flexibility and mechanical strength. It has considerable hydrophobic groups and, therefore, a low swelling ratio, which helps it improve the patch's mechanical characteristics and regulate CMC's swelling ratio [7].

Formulation of Propolis-loaded Patches

Nine propolis-loaded patches of different polymer compositions are provided in Table 1. The physical dimensions of the prepared patches were consistent and had a narrow range of thickness (0.29 ± 0.03 mm) and mass (79.7 ± 8.5 mg) as shown in Table 2. All the patches showed the desired appearance of smoothness, translucency, flexibility, uniformity, and folding endurance (more than 300 times). The surface *p*H values for all the patches were between 6.5 and 7.4, which suggests that they had a good likelihood of causing no irritation to the buccal mucosa.

Table 1. Composition of the formulated propolis buccal patches with their assigned batch codes

	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Propolis (mg)	65	65	65	65	65	65	65	65	65
***SAG (mg)**	1000	1000	1000	1000	1000	1000	1000	1000	1000
***CMC (mg)**	50	150	250	50	150	250	50	150	250
***PVP (mg)**	50	50	50	250	250	250	400	400	400
Glycerin (mg)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25

*SAG: sodium alginate, *CMC: carboxymethylcellulose, *PVP: polyvinylpyrrolidone

The physical measurements of the nine propolis-loaded patches are provided in Table 2. Principally, patches of low PVP content showed a higher force of adhesion compared to other patches. The first three patches (F1-F3) of low PVP composition showed higher force and time of adhesion relative to the other patches. The composition of 150 mg of CMC showed the highest force of adhesion of all patches.

Table 2. The general properties and mechanical measurements of the formulated propolis-loaded patches

	Thickness (mm)	**Mass (mg)**	**pH**	**Force of adhesion (N)**	**Adhesion time (min)**	**Tensile strength (g/mm^2)**	**% of elongation**	**Modulus of elasticity**
F1	0.30	83.1	7.4	0.81	117.5	55.5	83.0	56.2
F2	0.30	94.3	6.6	0.92	130.0	111.1	133.0	79.7
F3	0.32	85.7	7.4	0.84	145.0	130.2	92.0	125.5
F4	0.24	69.9	6.5	0.69	55.0	83.3	197.0	33.2
F5	0.29	73.0	7.1	0.72	140.0	137.9	200.0	64.5
F6	0.26	67.6	7.3	0.66	70.0	179.4	180.0	95.3
F7	0.32	79.5	7.2	0.78	30.0	52.1	158.0	24.3
F8	0.30	85.3	7.0	0.84	25.0	100.0	155.0	61.6
F9	0.31	78.8	7.4	0.77	25.0	86.0	88.0	84.6

The adhesion is a function of the interaction and entanglement of hydrophilic polymer chains with mucosal mucus [20]. Considering the fact that the carbonyl group in PVP is a strong proton acceptor that can easily interact with other polymers and forms complexes [21], then the interaction of PVP with CMC and SAG would possibly lower the mobility and flexibility of these polymers and so their entanglement with mucin. These results were in line the data reported by Patel et.al [22], who studied

the effect of PVP on the physicochemical properties of chitosan buccal patches. They found that the increasing the concentration of PVP produces patches with less adhesion force and time. A similar effect of PVP was also reported with buccal patches composed of Carbopol 934 and Eudragit-100 [23].

Regarding the mechanical properties, the tensile strength was increased with increasing concentration of CMC, except for F9, which had a high concentration of PVP. Also, F5 and F6 of intermediate PVP concentration showed the highest tensile strength. Similarly, the highest elongation was reported with F4 - F6 having intermediate concentrations of PVP. It was clear that the elasticity modulus was directly proportional to the concentration of CMC and inversely proportional to the concentration of PVP. These parameters determined the softness, hardness, and flexibility of the patches and are directly related to the intermolecular forces between the polymer's network [24]. The findings suggest that the introduction of PVP resulted in a noticeable increase in the elasticity of the patches. Conversely, the incorporation of CMC led to a transformation of the patches into a stiffer material with a higher modulus of elasticity.

The effect of the polymers on the swelling of the patches is shown in Figure 1. The highest swelling index was observed at F5, which had an intermediate concentration of PVP and CMC. It can be noted that the first three patches, F1-F3, with low PVP concentration and low elasticity, presented a low swelling index as these patches showed a high degree of erosion during the swelling study. Also, the swelling of high PVP patches, F8 and F9, significantly increased after 20 min, which is more likely related to the high elasticity of these patches that maintains the patches intact and able to accommodate more water without erosions over the swelling study in contrast to the low PVP patches of low elasticity and high degree of erosion during the swelling study. This effect of PVP is useful to provide good physical protection for the mouth ulcer; however, with a shorter adhesion time. These patches, with high PVP patches, have matrices of more polymers' interaction or cross-linked points and less free polymer chains, which would result in weak adhesion properties.

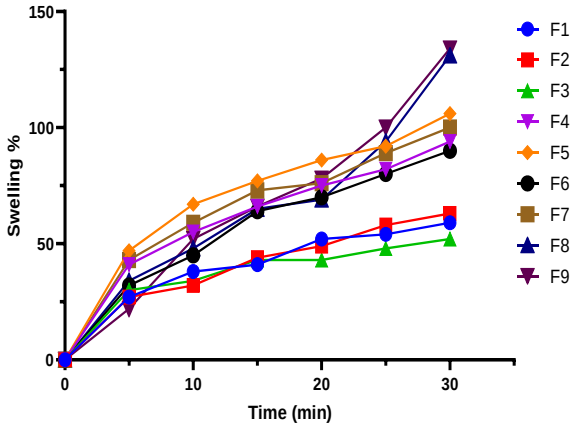

Figure 1. Swelling index of the formulated propolis-loaded patches

Furthermore, the release of propolis from different patches is shown in Figure 2. The patches with high PVP concentration achieved a slower release than the others. The release of drugs from buccal patches is function to several factors. One key factor is the swelling rate, the hydrophilic polymers such as PVP, CMC, and SAG facilitate the wettability, water absorption, and then swelling, which allow the loaded drug to dissolve and diffuse out. However, this can be regulated by the polymers entanglement and crosslinking of the polymers, which affect the relaxation and, consequently, the swelling of the patches. Another key factor that should be considered is the susceptibility of the patch matrix to erosion [25,26].

Therefore, the slow release of propolis obtained with high PVP patches is likely due to the tightly crosslinked polymers of these patches and the slower erosion rate as suggested by the mechanical measurements. In contrast, the patches with loosely bound polymers, such as low PVP patches, were readily eroded, allowing the easy release of propolis.

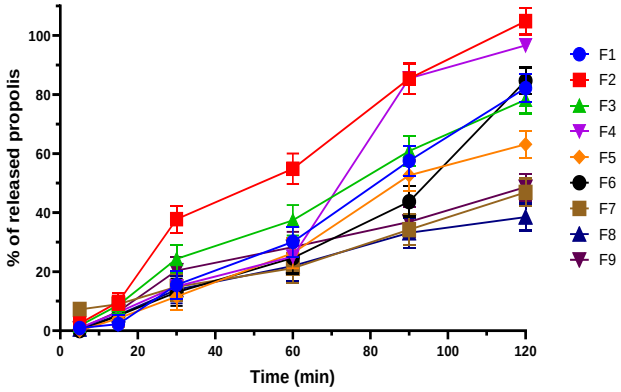

Figure 2. The percentage of propolis released from different patches

Correlation of Patch Composition with Experimentally Measured Physical Values Using Neural Networks

Correlations between composites and physicochemical measures are valuable in optimizing pharmaceutical formulations. This optimization is a multi-objective problem, where multiple properties need to be simultaneously adjusted. Accordingly, neural networks can perform well in such tasks to find linear as well as non-linear correlations that can be used to predict, characterize, and optimize pharmaceutical formulations [27]. Neural networks have found application in formulations of solid, liquid, and other dosage forms [28]. The applications include optimizing stability, loading power, dissolution, particle size, drug release, etc. during the formulation of different pharmaceutical dosage forms [29]. Recently, the neural network approach has been applied in the formulation of topical patches and hydrogel to predict drug release[30], viscosity, and sol-gel transition time [20].

The correlation between patch polymer composition and physically measured properties was thought to be complex and non-linear due to the possible intermolecular interactions [31,32]. Therefore, a neural network was trained to simulate the correlation between patch composition and each of the force of adhesion, tensile strength, rigidity, dissolution rate as well as swelling in water. The trained neural networks were used to visualize correlation surfaces for experimental data and provide predictions for an optimum formulation.

As illustrated in Figure 3, the correlation surface for tensile strength shows that the PVP% of 15 provides the best measure which is improved by increasing CMC%. While rigidity correlates with CMC%; however, it decreases as PVP% is increased. The patch swelling after 30 min was increased mainly by increasing PVP% and the highest release rate of 1.45 was expected to occur at PVP% and CMC % of 28.5 and 19, respectively. For tensile strength, the optimum value of 185 is expected to occur at PVP% and CMC% of 17.3 and 14.4, respectively. For dissolution rate after 60 min, the ratio of CMC to PVP of 0.6 provides the highest release of 29% propolis content of patches compared to other ratios.

This could indicate the formation of a specific intermolecular arrangement at this composite ratio that has a lower interaction with propolis extract. In order to incorporate all the observed correlations in guiding future formula design, a summation graph was calculated, Figure 4. The graph was obtained by normalizing z values of individual graphs to be between 0 and 1 before making a summation of matrices using the following model.

Summation = 2TS + 3AS - 1S - 1R - 1DR

Where TS is the tensile strength, AS is the adhesion force, S is the swelling in water, R is the rigidity of the patches, and DR is the dissolution rate.

The model provides higher weights for favorable tensile and adhesion strengths while considering water swelling, rigidity, and dissolution rate as unfavorable. According to the summation graph, the combination of CMC% and PVP% of 15.5 and 13, respectively, provides the best score of 3.5 on the graph.

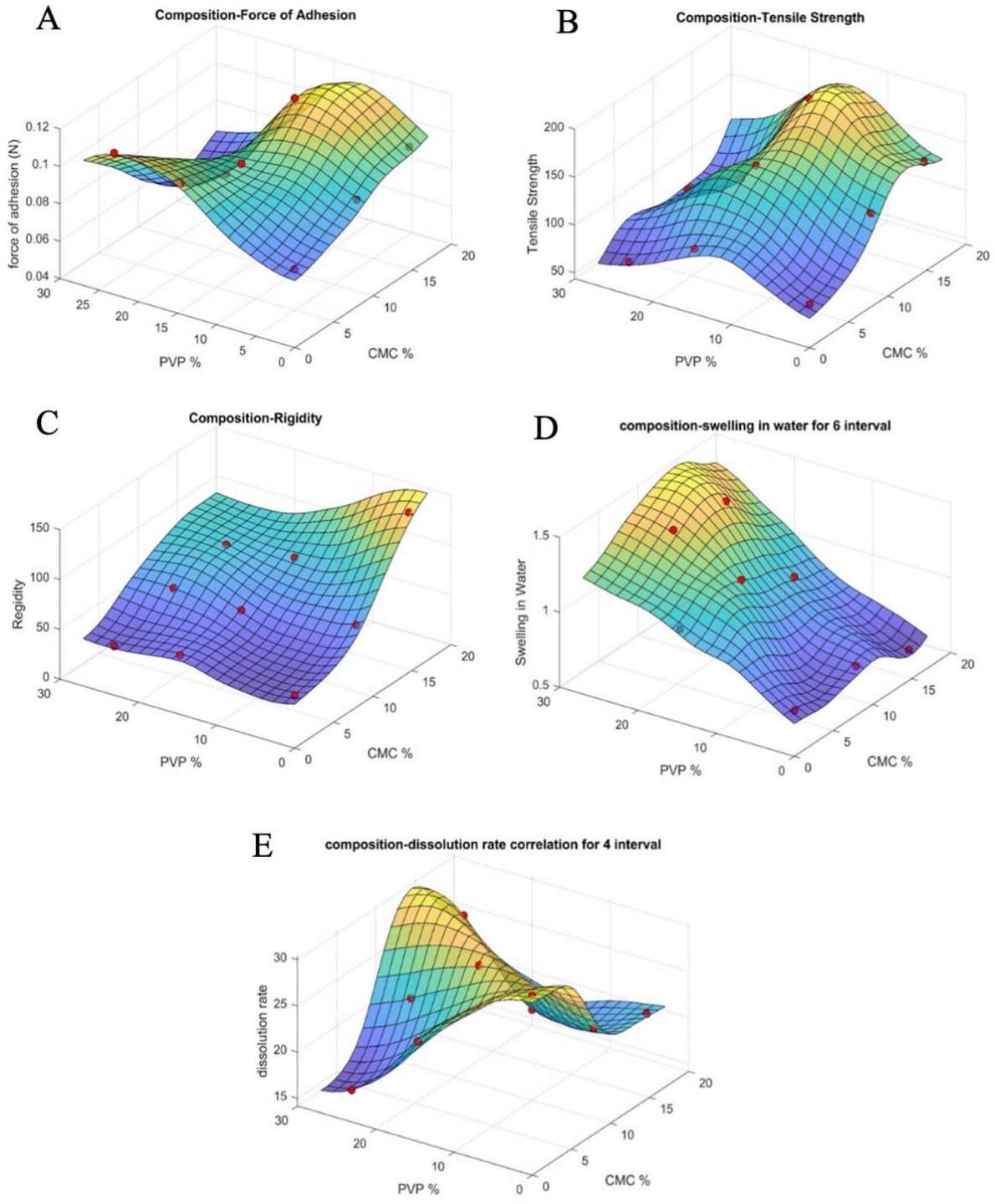

Figure 3. The predicted correlations between patch composition (only percentages of CMC and PVP are shown) and (A) the force of adhesion, (B) the tensile strength, (C) the rigidity of patches, (D) the swelling in water, and (E) the dissolution rate. The red dots represent the experimentally measured values used to train the neural network which in turn was used to construct the correlation surface

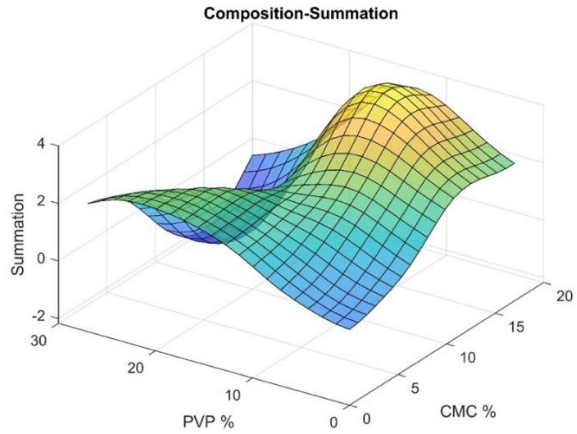

Figure 4. The predicted surface of correlation to find optimum formulation composition. The surface represents the summation of wanted properties (tensile strength, force of adhesion) minus the summation of unwanted properties (water swelling, dissolution rate, rigidity)

In summary, in this research we examined in this research the impact of different polymer combinations, including SAG, CMC, and PVP, on the physical characteristics of propolis-loaded patches. Overall, our findings indicate that higher CMC concentration improved adhesion properties, while PVP resulted in more flexible and durable patches. However, the relationship between polymer ratios and measured properties was complex and not easily assessed using conventional analysis tools. Consequently, we utilized neural network analysis to optimize the patches we prepared. The analysis revealed that a combination of 15.5% CMC and 13% PVP achieved the highest score of 3.5. Therefore, this particular combination offers the optimum adhesion and mechanical protection, as well as prolonged release of propolis.

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AUTHOR CONTRIBUTIONS

Concept: A.A., A.M.; Design: A.A., A.M., M.N.; Control: A.A.; Sources: A.A., A.M., M.N.; Materials: A.A., A.M., M.N.; Data Collection and/or Processing: A.A., A.M., M.N.; Analysis and/or Interpretation: A.A., A.M., M.N.; Literature Review: A.A., A.M., M.N.; Manuscript Writing: A.A., A.M., M.N.; Critical Review: A.A., A.M., M.N.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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