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Preparation and Physicochemical Properties of Transdermal Patch Bases using Chitosan Matrix

[1] Nindita Clourisa Amaris Susanto, [2] Fadhila Diva Haninda, [3] Dian Eka Ermawati, [4] Sholichah Rohmani, [5] Heru Sasongko, [6] M Fiqri Zulpadly, [7] Annisa Diyan Meitasari, [8] Ulfa Afrinurfadhilah Darojati, [9] Meta Kartika Untari

[1, 2, 3, 4, 5, 6, 7, 8, 9] Department of Pharmacy, Universitas Sebelas Maret, Indonesia

Corresponding Author: **Nindita Clourisa Amaris Susanto**

Abstract

Transdermal patches are a dosage form with several advantages, such as being easy to use, no external contamination, and no residue. One of the critical components in making transdermal patches is the polymer used as the base of the patch. This polymer will influence the release of the drug from the transdermal patch. The investigation of the physicochemical properties of transdermal patches can involve organoleptic, weight uniformity, pH, patch thickness, and patch fold resistance tests. In this study, the transdermal patch bases have been successfully prepared using chitosan polymer with various concentrations of 1, 1.5, 2, 2.5, and 3% w/v (F1, F2, F3, F4, and F5, respectively). Based on the evaluation of the physicochemical properties, F1 and F2 with 1.5 % and 1.5 % w/v chitosan met all parameters of physicochemical properties.

Keywords: Patch, Transdermal, Chitosan, Physicochemical

Introduction

A patch is a medicated adhesive placed on the skin to deliver a dose of medication into the bloodstream to close wounds. The patch preparation is chosen because it is easy to use, can control drug delivery, and can obtain the right concentration to provide a therapeutic effect on the affected area (Nitiariksa and Sukmawati, 2021) [8]. The patch is effectively employed for wound healing in the proliferation phase because it can increase the rate of tissue epithelialization and accelerate tissue autolysis (Primadani and Nurrahmantika, 2021) [10]. The patch composition consists of polymer, adhesive layer, backing layer, plasticizer, penetration enhancer, and active substances (Baharudin and Maesaroh, 2020) [3]. An essential component in the patch is the polymer, which will be the basis and control the release of the drug from the patch (Alexander *et al*., 2012) [2].

One of the polymers that can be used in making this patch is chitosan because it has antibacterial activity, inhibiting infection and speeding up wound closure and healing (Susilowati *et al*., 2020) [13]. Chitosan has several advantages of being biocompatible, non-toxic, bioactive, antifungal, hemostatic, and analgesic (Marieta and Musfiroh, 2019) [7]. The antibacterial ability of chitosan is due to the presence of the NH_3 glucosamine group, which can interact with the negatively charged surface of bacterial cells to interfere with bacterial growth (Eldin *et al*., 2008) [4].

The disadvantage of using chitosan is that the resulting patch is stiff, brittle, and less elastic, so glycerin must be added as a plasticizer to increase elasticity. Besides, the hydrophobic nature of chitosan causes a low water resistance value, so it is necessary to add citric acid as a crosslink, causing an increase in the –OH content so that the water resistance of the patch increases.

This study aimed to prepare the transdermal patch bases using chitosan polymer with various concentrations to determine the effect of chitosan addition on the physicochemical properties. The physicochemical properties of the transdermal patches include organoleptic, weight uniformity, pH, patch thickness, and patch fold resistance tests.

Materials and Methods

Tools

The tools used in this research were an ATC 2011 pH meter (OEM, Indonesia), digital analytical balance (KERN ABJ, d = 0.1 mg; Balingen, Germany), oven (Memmert; Schwabach, Germany), glassware (Pyrex, Germany), magnetic stirrer (IKA C-MAG HS 7, Germany), refrigerator (Samsung, Indonesia), Teflon mold (Happy Call, Korea), caliper (TOKI, Japan), and desiccator (Duran, Germany).

Material

The materials were fennel leaves (Boyolali, Indonesia), distilled water (OneMed, Indonesia), $AgNO_3$ powder (Merck KgaA, Germany), chitosan (Repacking by CV. ChiMultiguna, Indonesia), glycerin (Repacking by GHD, Indonesia), acetic acid (Merck, Germany), and citric acid (Merck, Germany).

Preparation of 1% Acetic Acid Solution

To produce a 1% v/v acetic acid solution, 1 mL of glacial acetic acid was dropped into a 100 mL measuring flask using a dropper pipette. Next, distilled water was added up to the flask's limit mark. The glacial acetic acid was diluted in distilled water (Riesca, 2012).

Preparation of 1% Glycerin Solution

Glycerin 98% pf 0.51 mL was put into a 50 mL volumetric flask. Next, distilled water was added until the limit mark and glycerin was diluted.

Preparation of 1% Citric Acid

Citric acid powder of 0.5 g was put into a 50 mL beaker. Next, 50 mL of distilled water was added and stirred until homogeneous.

Preparation of Patch Base

Table 1: Patch Base Formulation with Various Chitosan Concentrations

Material	Patch Base Formulation					Function
	F1	F2	F3	F4	F5	
	1%w/v	1.5%w/v	2%w/v	2.5%w/v	3%w/v	
Chitosan	0.5 g	0.75 g	1 g	1.25 g	1.5g	Polycationic polymer, preservative
Acetic Acid 1% w/v	33.3 mL	33.3 mL	33.3 mL	33.3 mL	33.3 mL	Solvent
Glycerin 1%w/v	8.3 mL	8.3 mL	8.3 mL	8.3 mL	8.3 mL	Plasticizers
Citric Acid 1%w/v	8.3 mL	8.3 mL	8.3 mL	8.3 mL	8.3 mL	Crosslinking polymer

Table 1 presents the patch base formulation with various chitosan concentrations. For preparing the patch base, 33.3 mL of 1% acetic acid solution was mixed with 8.3 mL of 1% citric acid solution and stirred until homogeneous, producing the acid solution. Then, 8.3 mL of 1% glycerin solution was mixed with the acid solution. Afterward, chitosan with various concentrations, represented by the weights of 0.5 g, 0.75, 1, 1.25, and 1.5 g, was added to the solution and stirred for ± 2 hours using a magnetic stirrer. The patch base solutions with a pale white chitosan variation were kept overnight to remove bubbles. They were then poured into a Teflon mold and dried in an oven at 50˚C for 48 hours. Finally, the constructed patch bases were tested for their physicochemical properties, including organoleptic, weight uniformity, pH, thickness, folding resistance, drying shrinkage, and moisture absorption tests.

Physicochemical Test of Chitosan Patch

Organoleptic Test

The organoleptic examination was done to observe the patches' shape, color, and smell (Baharudin and Maesaroh, 2020) [3].

Weight Uniformity Test

This test was conducted by weighing all patches with various chitosan concentrations and then calculating their average weight (Baharudin and Maesaroh, 2020) [3]. From the calculation, the standard deviation (SD) was determined. The patch weight was considered uniform if the SD value was ≤ 0.05 (Wardani and Saryanti, 2021) [15].

pH Test

pH testing was completed by adding 10 ml of distilled water to the patches and leaving them for 2 hours. Then, the pH values of the solution were measured using a pH meter (Baharudin and Maesaroh, 2020) [3]. The pH value requirement for the skin was 4.5-6.5 (Tiensi, 2018) [14].

Thickness Test

Thickness testing was done by measuring the thickness of the resulting patch using a caliper. The measurement was completed at three points on each patch, then the average thickness was calculated in micrometers (Baharudin and Maesaroh, 2020) [3]. Thickness plays a role in the physical properties of the patch. Thin patches will be easier to use (Wardani and Saryanti, 2021) [15].

Folding Resistance Test

Patch folding resistance was determined by repeatedly folding a patch in the same place until it broke or folding it up to 300 times manually to produce good patch properties (Baharudin and Maesaroh, 2020) [3]. A patch is considered good if it has a fold resistance value of more than 300 folds (Bharkatiya *et al*., 2010).

Drying Shrinkage Test

Drying shrinkage testing was done by weighing the patches and storing them in a desiccator for 24 hours containing silica. After that, the patch was re-weighed, and the drying shrinkage percentage was determined. The drying loss value required for patch preparations is not absolute (Wardani and Saryani, 2021) [15].

Moisture Absorption Test

Moisture absorption testing was performed by weighing patches and storing them at room temperature in a desiccator for 24 hours. They were then exposed to a temperature of 40°C for 24 hours and re-weighed. Previous research stated that the percent value of moisture absorption ranged from 3.52-9.79% w/v (Wardani and Saryani, 2021) [15].

Results and Discussion

The chitosan patch bases were made with various chitosan concentrations to determine the effect of chitosan addition as a polymer on the physicochemical properties of the patch preparation. The formulation of the patch bases with different chitosan concentrations is shown in Table 1. Chitosan is biocompatible, non-toxic, and has antibacterial capabilities. It is used as a polymer and a natural preservative. Chitosan also functions as an adsorbent, adhesive, additive for paper and textiles, and pure water purifier. Besides, it also has the advantages of accelerating wound healing, reducing cholesterol levels, and improving color-binding properties. Chitosan is a unique biopolymer with cationic characteristics and is positively charged in

acidic solutions. Nevertheless, chitosan also has the disadvantage of low water-holding capacity, so crosslinking is needed to increase the water-holding capacity (Zhuang *et al*., 2020) [16]. Chitosan efficiency can be increased by modifying it using a crosslinking agent.

Besides chitosan, several additional ingredients used to prepare patch bases in this study included glycerin, acetic acid, citric acid, and distilled water. Citric acid is a crosslinking agent that can be crosslinked with chitosan because of its excellent biocompatibility, non-toxicity, and antibacterial and antioxidant properties. It can also prevent damage to the active ingredients encapsulated in chitosan (Primadevi and Nafi'ah, 2020) [11]. Acetic acid is employed as a solvent because chitosan can dissolve in acidic conditions to form polycationic chitosan, which dissolves well in 1-2% acetic acid solution, which is a suitable solvent for chitosan. An acetic acid concentration of 1% w/v is the right concentration so that chitosan can dissolve completely.

Acetic acid is known to have a good effect as an antibacterial and can provide good absorption values for water flux and function as a crosslink former, strengthening the resulting layer. Using a mixture of weak acid solvents between citric acid and acetic acid has excellent absorption capacity and good quality. Besides, combining citric acid and acetic acid can dissolve chitosan properly, even though the resulting surface is not as good as acetic acid.

Citric acid is used as a chitosan crosslink because it is non-toxic, has no strong odor, and does not change color. The hydrophobic characteristics of chitosan can cause the resulting patch to be stiff and have a low water resistance value. Thus, it is necessary to add glycerin, which functions as a plasticizer to produce a patch preparation with good elasticity and flexibility. Moreover, the addition of citric acid as a crosslink also affects the drying shrinkage and strength test results. Patch moisture absorption increases because it causes more –OH content to be produced.

A. Physicochemical Properties of Patch Bases

1. Organoleptic Test

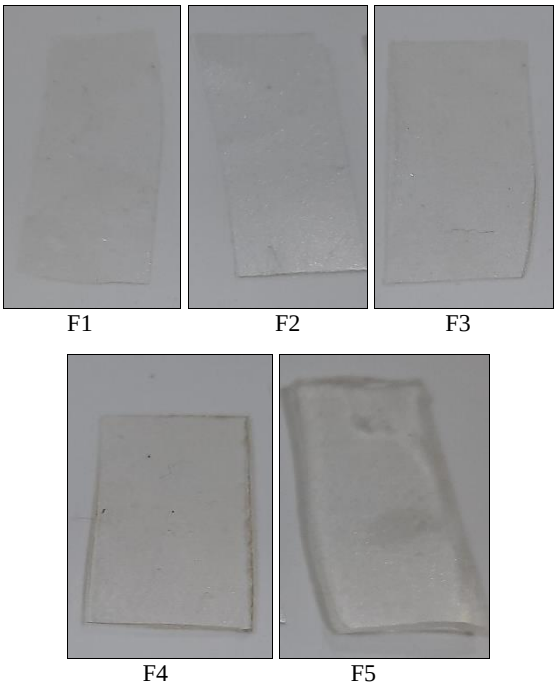

Fig 1: The physical characteristics of Patch Bases

The organoleptic test was performed visually by observing the resulting patch's shape, color, smell, and surface condition. The physical characteristics and results of organoleptic observations can be seen in Figure 1 and Table 2.

The results reveal that the resulting patch bases were circular with a surface diameter of about 4 cm according to the Teflon mold used. F1 and F2 samples were thin layers with a typical odor. Besides, their surface condition was dry, without cracks, and clear in color. F3 was in the form of a relatively thick layer with a typical odor. Further, the surface condition was dry and clear in color without cracks. Meanwhile, F4 and F5 formed thick layers with a distinct smell. Moreover, the surface condition was dry and clear in color without cracks.

Based on the observations, the patch bases also had a smooth, strong, and elastic texture. These strong and elastic properties were obtained due to the use of chitosan as a polymer and the presence of crosslinks, which produce strong interactions, especially hydrogen bonds, causing chitosan to have high strength, elasticity, and flexibility.

All patch bases with various chitosan concentrations had a typical sour-like aroma due to the use of acetic acid solvents and citric acid polymers. All bases were clear because they had not been mixed with active substances. The clear color and uniform typical odor in the five patch bases were because they did not contain active substances except acetic acid and citric acid solvents.

Table 2: Organoleptic Test Results of Patch Bases

Samples	Thickness	Smell	Surface Conditions	Color
F1	Thin layer	Typical	Dry and not cracked	+
F2	Thin layer	Typical	Dry and not cracked	+
F3	Relatively thick layer	Typical	Dry and not cracked	++
F4	Thick layer	Typical	Dry and not cracked	+++
F5	Thick layer	Typical	Dry and not cracked	+++

Information:
+: Clear ++: Slightly cloudy +++: Quite cloudy

2. Weight Uniformity Test

This test was carried out to determine the weight uniformity of each patch base and ensure that the resulting patch base corresponds to the desired weight. This test was conducted by weighing each sample having 3 replications and then calculating the average weight and standard deviation (SD).

The results of the weight uniformity test can be seen in Table 3. The results revealed that the five patch bases met the SD criteria of ≤ 0.05 (Baharudin and Maesaroh, 2020) [3]. Nevertheless, there was an increase in patch weights between different samples due to different chitosan concentrations. The higher polymer concentration can be related to the greater patch weight because the patch experiences a low shrinkage rate and has low water mass. Pachisia *et al*. (2012) [9] showed that the higher polymer concentration, using chitosan, induced a greater patch weight.

Table 3: Weight Uniformity of Patch Bases

Samples					
Replication	**F1**	**F2**	**F3**	**F4**	**F5**
R1	0.04 g	0.11 g	0.15 g	0.2 g	0.22 g
R2	0.07 g	0.13 g	0.13 g	0.18 g	0.27 g
R3	0.05 g	0.09 g	0.1 g	0.14 g	0.2 g
Mean ± SD	0.05 ± 0.015	0.11 ± 0.02	0.13 ± 0.025	0.17 ± 0.031	0.23 ± 0.037
Information	MS	MS	MS	MS	MS
Good Standard Deviation (≤ 0.05) (Baharudin, 2020) [3]					

MS: Qualified, TMS: Unqualified

The weight uniformity of the patch base can influence the resulting therapeutic effect. Several factors can cause the patch weight to be less uniform, including incomplete solvent evaporation or uneven pouring of the patch mixture into the mold. If, during the drying process, all the solvents can evaporate completely, then the patch weight will be uniform. However, conversely, the patch weight will increase if a solvent has not evaporated completely.

3. Folding Resistance Test

The folding resistance test was done to determine the flexibility and elasticity of the patch bases after being folded at the same angle. This test was carried out manually by folding the patch base on one side repeatedly until it broke or folding it up to 300 times. The number of folds made without showing any damage indicates the value of the folding resistance of the patch base. Increasing the folding resistance of the patch base demonstrates that it has good consistency so that it does not break or tear easily during storage (Wardani and Saryanti, 2021) [15].

Table 4: Folding Resistance values of Patch Bases

Formulas					
Replication	**F1**	**F2**	**F3**	**F4**	**F5**
R1	>300	>300	>300	<300	<200
R2	>300	>300	>300	<300	<250
R3	>300	>300	>300	>300	<200
Information	MS	MS	MS	TMS	TMS
Requirements for good folding durability (≥ 300 folds) (Anisa, 2019) [7]					

MS: Qualified, TMS: Unqualified

The results of the folding resistance test are listed in Table 4. It shows that the folding resistance values of F1, F2, and F3 were more than 300 times folded, so it can be considered good. It is because the patch base was still in good condition, not damaged, and not cracked during the test. Meanwhile, F4 and F5 had a folding resistance of less than 300 times, so they did not meet the folding resistance criteria. It might be caused by the preparation's physical results or the preparation's texture and the poor surface condition of F4 and F5, making the patch base easily damaged and not last long.

A good patch must have strong and elastic properties. The integrity of the patch when applied to the skin is demonstrated by good fold resistance, so it is hoped that the patch will not tear easily during its usage. Patches tearing easily indicate their fragile nature. Adding chitosan produces hydrogen bonds from crosslinking, making chitosan not easily torn. Adding plasticizers to the patch formula also affects flexibility and good physical characteristics. The combination of chitosan as a polymer and glycerin as a single plasticizer produces an elastic layer and good adhesion to the skin membrane. The greater polymer concentration in making the patch induces higher patch thickness and lower folding resistance of the patch produced. Thus, it can be concluded that the difference in polymer concentration in the patch affects the durability of the fold.

4. Thickness Test

Table 5: Thickness values of Patch Bases

Formulas					
Replication	**F1**	**F2**	**F3**	**F4**	**F5**
R1	0.2 mm	0.4 mm	0.55 mm	0.7mm	0.8mm
R2	0.3 mm	0.5 mm	0.45 mm	0.85mm	0.95mm
R3	0.25 mm	0.45 mm	0.5 mm	0.8mm	1mm
Mean ± SD	0.25 ± 0.05	0.45 ± 0.05	0.5 ± 0.05	0.78 ± 0.076	0.92 ± 0.1
Information	MS	MS	MS	TMS	TMS
Good Standard Deviation: ≤0.05 (Baharudin, 2020) [3]					

MS: Qualified, TMS: Unqualified

The thickness test aimed to determine the uniformity of the resulting patch base thickness. Thickness plays a role in the physical properties of the patch. A thin patch base will be easier to use. Besides, the patch's thickness affects the drug's permeability to penetrate the patch. A thicker patch will reduce drug permeability and the drug permeability coefficient through the patch. Patch thickness affects fragility, where too-thin patches are easily torn and brittle (Ermawati *et al*., 2022) [5].

Thickness testing in one patch can be done by measuring the thickness at three points using a caliper. The average thickness and SD were then calculated to obtain the uniformity of patch thickness (Boddeda *et al*., 2016). The thickness of the patch bases is written in Table 5. It exhibits that F1, F2, F3, F4, and F5 had average thicknesses of 0.25 mm, 0.45 mm, 0.5 mm, 0.78 mm, and 0.92 mm, respectively. The thickness of the five samples follows the patch thickness requirements of >1 mm. If the patch is too thick, releasing the active substance won't be easy. However, only F1, F2, and F3 met the SD requirement of ≤ 0.05, indicating that the interfacial thickness of these patches was uniform. Meanwhile, the SD values of F4 and F5 did not meet the requirements of ≤ 0.05.

Increasing the concentration of chitosan causes the resulting patch base solution to become thicker so that the thickness of the resulting patch base increases. Factors that cause differences in thickness in one patch can be the pouring technique of the patch solution into the mold and the drying process of the patch, including drying time and temperature. Other factors are the mold's area, the solution's volume, and the total amount of solids in the solution (Suryani, 2017). The ideal patch is thin but does not tear quickly, so it is comfortable to use.

5. Test pH

The pH testing aimed to determine whether the pH of the resulting patch base met the tolerable requirements so that it is safe and cannot irritate the skin when applied. The standard pH value meeting the requirements is about 4.5 – 6.5. Meanwhile, the required pH value that does not irritate the skin is about 5 – 9. The pH values of three replicated samples for each formula were measured using a pH meter. Then, the mean pH and SD were calculated. Table 6

presents the pH values of all patch samples. F1, F2, F3, F4, and F5 had pH values that met pH requirements for the skin, so they are safe for topical usage.

Table 6: pH values of Patch Bases

Samples					
Replication	**F1**	**F2**	**F3**	**F4**	**F5**
R1	4.83	4.82	4.97	4.94	4.73
R2	4.5	4.9	5.24	5.31	5.53
R3	4.97	5.12	5	4.73	4.88
Information	MS	MS	MS	MS	MS
The pH meeting the requirements is 4.5 – 6.5 (Anisa, 2019) [7]					

MS: Qualified, TMS: Unqualified

The different pH values in the five formulas were due to the use of acidic solvents, storage factors, and the influence of environmental temperature. Nevertheless, the pH values of all patch bases have met the requirements. If the pH is too acidic, it can irritate the skin, whereas if it is too alkaline, it can cause the skin to become scaly (Wardani and Saryanti, 2021) [15].

6. Drying Shrinkage Test

The drying shrinkage test aimed to determine the amount of drying shrinkage and the moisture content after 24-hour storage in a desiccator. A good patch should not be too damp because it will tear easily. However, it also should not be too dry because it can break easily. There is no absolute value for the amount of drying shrinkage required. However, based on previous research, a good patch drying shrinkage value was < 9.29%w/v (Fatmawaty *et al*., 2017) [6]. Table 7 demonstrates the drying shrinkage percentages of all patch bases. It shows that F1 and F2 had drying loss values of 6.67% w/v and 7.69% w/v, respectively, where these values met the requirements for good drying loss of < 9.29%w/v. Meanwhile, based on the values, F3, F4, and F5 did not meet the requirements.

Table 7: Drying Shrinkage Values of Patch Bases

Samples				
F1	**F2**	**F3**	**F4**	**F5**
6.67% w/v	7.69% w/v	10%w/v	11.11%w/v	13.64%w/v
MS	MS	TMS	TMS	TMS
Good drying loss is <9.29%w/v (Fatmawaty *et al*., 2017) [6]				

MS: Qualified, TMS: Unqualified

Table 7 exhibits that the water content in the patch preparation was truly stable with a low %w/v value. It benefits from protecting the patch from contamination or microbial contamination (Wardani and Saryanti, 2021) [15]. The high drying shrinkage value may also be due to the difficulty in controlling the moisture content using solvent evaporation in making patches. A physically good patch must be flexible, thin, smooth, homogeneous, and have low drying shrinkage (Fatmawaty *et al*., 2017) [6].

7. Moisture Absorption Test

The moisture absorption test aimed to determine the water absorption level from patches conditioned at 40°C for 24 hours. Moisture absorption capacity is a response parameter to specify the patch's ability to absorb moisture. Application of the patch's moisture absorption capacity to the skin indicates the water absorption level in the patch during usage. The patch's resistance to moisture, where it absorbs a lot of moisture, will affect the quality of the patch, which can affect the elasticity of the patch so that it can tear easily. A low percentage absorption value will produce a relatively stable patch, and the patch will be protected from microbial contamination. Previous research stated that the percent value of good moisture absorption ranged from 3.52-9.79% w/v.

Table 8: Moisture Absorption Values of Patch Bases

Samples				
F1	**F2**	**F3**	**F4**	**F5**
7.14%w/v	8.33%w/v	11.11%w/v	12.5%w/v	15.79%w/v
MS	MS	TMS	TMS	TMS
Good moisture absorption capacity is <9.79%w/v (Fatmawaty *et al*., 2017) [6]				

MS: Qualified, TMS: Unqualified

Table 8 shows the moisture absorption values of the five patch bases. It demonstrates that the moisture absorption values for F1 and F2 met the requirements for good moisture absorption, namely < 9.79% w/v. Meanwhile, F3, F4, and F5 did not meet the requirements. The percent moisture absorption of the film will increase with increasing polymer concentration. This is because chitosan contains hydroxyl groups (OH groups), which are hydrophilic and can promote higher water absorption (Afif *et al*., 2018) [1]. The greater chitosan concentration induces more hydroxyl groups, causing the moisture absorption capacity to increase. A physically good patch must be flexible, thin, smooth, homogeneous, and have low moisture absorption (Fatmawaty *et al*., 2017) [6].

Conclusion

This study has successfully prepared transdermal patch bases using the chitosan polymer matrix with various concentrations and observed their physicochemical properties. F1 and F2 containing 1 % w/v and 1.5 % w/v chitosan met all physicochemical test parameters. F3 met the test parameters for weight uniformity, folding resistance, and thickness. Meanwhile, F4 and F5 with chitosan at 2.5 % w/v and 5 % w/v, respectively, only met the weight uniformity parameter. A transdermal patch base was selected that completed all test parameters. The greater chitosan concentrations made the patches thicker, so they did not meet the folding resistance test. The chitosan's hydrophilic nature influenced the drying shrinkage and moisture absorption test results.

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