Asia-Pacific Journal of Science and Technology: Volume: 29. Issue: 05. Article ID.: APST-29-05-13. Research Article

APST

Asia-Pacific Journal of Science and Technology

https://www.tci-thaijo.org/index.php/APST/index

Published by the Research Department,
Khon Kaen University, Thailand

Evaluation of transdermal patches made from *Garcinia mangostana* Linn. peel extract and natural rubber

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Received 18 May 2023
Revised 5 March 2024
Accepted 25 April 2024

Abstract

Transdermal drug delivery systems (TDDS) are a popular research focus in pharmaceutical technology and a commonly produced pharmaceutical product worldwide. Utilizing these systems helps mitigate the disadvantages of other administration methods, such oral and parenteral. The aim of this study was to evaluate the properties of transdermal patches containing *Garcinia mangostana* Linn. peel extract with natural rubber content. Formula 1-4 (F1-4) transdermal patches with natural rubber were produced with hydroxypropyl methylcellulose (HPMC) and low protein rubber (LPR). The patches were examined to evaluate physicochemical properties and drug release characteristics. The casting evaporation method was utilized to produce transdermal patches that are smooth, dry, and white in color. pH values ranged between 5.8-6.2, and tensile strength values were 2.35 – 3.75 N/mm. The patches exhibited a thickness range of 0.47-0.55 mm. The weight values were in the range of 2.2-2.5g. and percent moisture and protein content ranged between 4.01-6.74 and 1.32-3.25 respectively. F-2 patches exhibited the highest drug entrapment capacity (71.02 %) and release efficiency (26.96% over 360 minutes). Therefore, the findings of the study suggest that F-2 patches can be developed as commercial alternative pharmaceutical products.

Keywords: Transdermal patch, Natural rubber, Physical characterization, *Garcinia mangostana* Linn.

1. Introduction

A skin patch, also known as a transdermal patch, is an adhesive patch that delivers a specific dose of medication into the lower layers of the skin and the bloodstream. Transdermal drug delivery systems (TDDS) offer several advantages such as circumventing issues related to drug absorption in the gastrointestinal tract, providing an alternative to oral medication administration, bypassing the first-pass effect, avoiding the inconvenience of parenteral therapy, and enabling fast termination of drug effects [1]. The natural latex extracted from *Hevea brasiliensis* contains a colloidal polymer (cis-1,4-polyisoprene) and possesses useful physical characteristics, including high elongation, high tensile strength at break, excellent resilience, and impermeability to liquids and gases [2]. Currently, natural rubber latex is frequently utilized as a raw material in medical and pharmaceutical applications, however, it can result in allergic reactions due to the presence of certain proteins in field latex, such as Hev b1-Hev b14. Allergic symptoms can range from mild to severe, including skin irritation, erythema, rhinitis,asthma and anaphylaxis [3]. Enzymatic digestion is necessary to remove the proteins from natural rubber latex and reduce protein allergies [4], therefore, use of an alternative low protein rubber may be advantageous.

Mangosteen (*Garcinia mangostana* Linn.) is one of the most delicious tropical fruits. The extract of mangosteen fruit is used for applications in cosmetics and food supplements, while the extract of its peel has been employed in traditional medicines. Mangosteen peel contains a variety of chemical substances such phenolic acid,

tannins, anthocyanins and xanthones [5]. Mangosteen exhibits anti-inflammatory [6], antimicrobial and anti-oxidant [7] activities. Mangosteen peel and the phytochemical compounds found in it, particularly the group of xanthones, have a wide range of pharmacological properties, especially anti-inflammatory effects [8].

The objectives of our study were to improve the efficacy and physical characteristics of transdermal patches by utilizing a blend of hydrophilic and hydrophobic polymers. To achieve this, we employed the evaporation casting method to develop transdermal patches infused with mangosteen peel extract (ME). These patches were formulated by combining hydroxypropyl methylcellulose (HPMC) and low protein rubber (LPR) at various ratios, and their physical properties were evaluated. Additionally, we investigated the capacity for drug entrapment and release from the transdermal patches.

2. Materials and methods

2.1 Chemicals

Hydroxypropyl Methylcellulose (HPMC) was purchased form ShimEtsu (Japan). Natural rubber was purchased form Rungart (Thailand). Distilled water was purchased form Lab valley (Thailand). Methanol, ethanol, polyethylene glycol 400 (PEG 400) and Folin-Ciocalteu reagent were purchased form Merck (Germany). Bovine Serum Albumin (BSA), KAO Protease and α-Mangostin ≥ 98% (HPLC) were purchased from Sigma-Aldrich (USA).

2.2 Plant material and extract preparation

Mangosteen peel (MP) was obtained from a folk medicine drugstore located in Nakhon Sri Thammarat, Thailand, in May 2022. To prepare the extract, 500 g of dried mangosteen peel was ground and macerated with 1,000 mL of 95% ethanol, then stored for 3 days at 25°C. The solution was then subjected to evaporation using a rotary evaporator (Buchi, Switzerland). The resulting extract was stored in airtight glass bottles in a dark location until further use.

2.3 Preparation of LPR

The preparation of LPR was conducted following a previously described method [9]. In brief, 10% of natural rubber was mixed with 5% KAO Protease and stirred at room temperature for 24 hours at a speed of 50 rpm. The content of the low protein solution was quantified using the Lowry method, and the solution was then stored in glass bottles at 4°C for future use.

2.*4 Formulation of transdermal patches*

Four formulations of transdermal patches containing mangosteen peel extract were prepared. To produce the transdermal patches, we used a combination of MP, HPMC, and LPR with a total polymer weight of 610 mg for each formula, as outlined in Table 1. Initially, the HPMC was dissolved in 10 mL of methanol with the assistance of a magnetic stirrer. Subsequently, the LPR was added to the HPMC solution, and thorough homogenized. Next, we added 20 milligrams of ME to the solution and homogenized it for 10 minutes to form solution. PEG400 was then added to the previously prepared mixture. We then poured 10 milliliters of the resulting solution onto a plate and oven-dried it at 50°C for 24 hours. Finally, the transdermal patches were collected in a desiccator until needed for analysis.

Table 1 Transdermal patches formulations.

Ingredients	Code			
	F-1	F-2	F-3	F-4
MP (mg)	5	5	5	5
HPMC (mg)	500	450	400	350
LPR (mg)	50	100	150	200
PEG400 (mg)	55	55	55	55

2.5 Physical characterization

2.51 Organoleptic

The organoleptic evaluation of the patches involved observing and documenting their shape, odor, color, and texture [10].

2.5.2 Thickness

After cutting the patches to a size of 1.5 x 1.5 cm^2, the thickness of the patches was measured at three different locations on each patch using a digital micrometer. This measurement was repeated three times [10].

2.5.3 pH

After cutting the patches to a size of 1.5 x 1.5 cm^2, they were immersed in 1 mL of distilled water at room temperature for 3 hours at 25°C. The pH of the solution was analyzed using a pH meter [10].

2.5.4 Weight

After cutting the patches to a size of 1.5 x 1.5 cm^2, the average weight of each patch was determined by weighing three patches from each formula [10].

2.5.5 Moisture content

To determine the moisture content percentage in the patches, the patches were weighed and then placed in a hot air oven for 24 hours at 45°C. After 24 hours, the patches were reweighed [10].

$$\text{Moisture content (\%)} = \frac{\text{Intitial weight-Final weight}}{\text{Initial weight}} \times 100 \quad (1)$$

2.5.6 Tensile strength

The tensile strength, following ASTM D412C standards, was determined using a Shimadzu Autograph (AG-X) tensile tester. Patches measuring 5 x 1 cm^2 were prepared and positioned between the cell clamps. Gradual force was applied to the film until it reached the breaking point. The resulting tensile strength was measured in kilograms based on the dial reading. The following formula was utilized for calculation [10].

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross-section area}} \times 100 \quad (2)$$

2.5.7 Protein content

To determine the percentage of protein content in the patches, 0.2 g patches were cut and incubated in 3 mL of distilled water for 2 hours. Protein concentrations in the samples were exanimated by comparing the obtained absorbance values with those in the standard curve [10].

$$\text{Protein content (\%)} = \frac{\text{Intitial protein-Final protein}}{\text{Initial protein}} \times 100 \quad (3)$$

2.6 Drug entrapment study

The patches were cut to a size of 1.5 x 1.5 cm^2 and extracted in methanol under sonication for 2 hours. After extraction, the solution was diluted and adjusted to the specified volume. The concentration of α-mangostin that was entrapped in transdermal patches was analyzed using a high-performance liquid chromatography HPLC instrument (Shimadzu SCL-10A, UV-vis detector SPD-10A, Rheodyne injector fitted with a 20 µL loop and C-18 column (4.6 x 250 mm, 5 µm size). The analyzed α-mangostin that was analyzed was compared to the peak area of the standard curve's linearity. The assessment of drug content in transdermal patches was conducted in triplicate. The drug entrapment efficacy of α-mangostin in transdermal patches was determined by calculating the percentage of the analyzed α-mangostin content in the patch compared to the theoretical α-mangostin content [11].

2.7 Drug release study

The drug released from the patches was measured using the modified paddle-over-disk method. The patches were positioned within an aluminum disk and subjected to a dissolution medium consisting of 300 mL of pH 6.9 phosphate buffer solution. The medium was stirred at 100 rpm and maintained at a temperature of 37°C. At predetermined time points (0, 10, 20, 30, 60, 120, 240 and 360 minutes), 3 mL of the medium solution was

withdrawn and replaced with an equal volume of fresh medium. The concentration of α-mangostin in each sample was determined using an HPLC assay and compared to the calibration curve [12].

2.8 Statistical analysis

Results for all three experiments are shown as mean ± SD. One-way ANOVA was used with 95% confidence. SPSS 20.0 (IBM Corp., Armonk, New York) was used for statistical analysis.

3. Results and discussion

3.1 Physical characterization of transdermal patches

In the study, the transdermal patches were characterized using polymers, which included HPMC and LPR. The mangosteen peel extract was combined with different ratios of each polymer form, and the formulation of transdermal patches was studied to evaluate various properties. The organoleptic evaluation of four formulas indicated that each of them exhibited smoothness, dryness, elasticity, and white and transparent characteristics. The mangosteen peel extracts using natural rubber transdermal patches are shown in Figure 1. The prepared transdermal patches were evaluated for various parameters, including thickness, pH, tensile strength, weight, moisture content percentage and percentage protein content. The results of these evaluations are presented in Table 2.

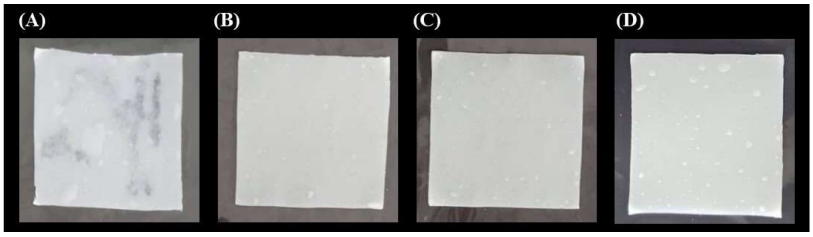

Figure 1 Mangosteen peel extract natural rubber transdermal patches: (A) F-1, (B) F-2, (C) F-3, and (D) F-4.

The transdermal patches exhibited weights ranging from 2.2 to 2.5 g. The study showed that when the ration of LPR was increased, there was a corresponding increase in the weight of the transdermal patches. When incorporated into the mixture, natural rubber, as an organic and hydrophobic polymer, has the potential to increase the weight of the patch. The HPMC is hydrophilic polymer and has the ability to absorb water, resulting in an increase in the weight of the transdermal patches. The transdermal patches displayed thickness values ranging from 0.47 to 0.55 mm. The thickness of the prepared dermal patch conforms to the specified requirements of being less than 1 mm [13]. The pH range of the transdermal patches is between 5.8-6.2, which is similar to the pH range of 5-7 commonly found in skin products [14]. Therefore, the transdermal patches are suitable for application on the skin. The transdermal patches were found to have a percentage moisture content ranging from 4.01-6.74. High humidity leads to microbial contamination. Additionally, the polymers used in the formulation may provide a suitable environment for microbial growth [15]. Reducing the amount of moisture and preservatives is necessary to prevent microbial contamination [16]. The tensile strength and percentage elongation of the transdermal patches ranged from 2.35-3.75 N/mm^2 and 135-161 respectively. The higher concentration of LPR in the transdermal patches impacts their mechanical and flexibility characteristics. An increase in the level of LPR was discovered to impact patch elongation. When rubber, a polymer resembling a chain or network, is stretched, bonds form between the chains. Hence, increasing its flexibility [17]. The application of protease enzymes was employed to decrease the protein content, leading to a threefold reduction in comparison to the initial protein content. The study revealed that the percentage protein content ranged from 1.32-3.25, Reducing, the protein content would also affect incidence of protein allergy from the used of the skin transdermal patches [18].

Table 2 Physical characterization of transdermal patches.

Code	pH	Tensile strength (N/mm^2)	Thickness (mm)	Elongation (%)	Weight (g)	Moisture content (%)	Protein content (%)
F-1	6.20±0.21[a]	2.35±0.05	0.47±0.01[a]	135±0.75[a]	2.2±0.04[ab]	6.74±0.62	1.32±0.24
F-2	5.80±0.15[a]	3.15±0.04	0.48±0.02[a]	136±0.32[a]	2.3±0.10[abc]	5.21±0.23	1.94±0.13[a]
F-3	6.10±0.30[a]	3.54±0.03	0.51±0.01	154±0.71	2.4±0.02[bcd]	4.32±0.21[a]	2.14±0.34[a]
F-4	6.20±0.24[a]	3.75±0.02	0.55±0.01	161±0.34	2.5±0.02[cd]	4.01±0.37[a]	3.25±0.23

[a-d] The data marked by different letters in each column indicate a statistically significant difference (SPSS version 20.0, $p \leq 0.05$)

3.2 Drug entrapment study

The drug entrapment study conducted on the prepared transdermal patches revealed that the F-2 formulation exhibited the highest entrapment efficacy, with a percentage of 71.02±5.1, but the values were not significantly different at the confidence level of $p < 0.05$ when compared with other formulas in Figure 2. The results exhibited that the *α*-mangostin could be distributed evenly in F-1 to F-4 of transdermal patches. Drug entrapment from the transdermal patches depends on the chemical bonding or interaction between *α*-mangostin and the polymer of the patch [19].

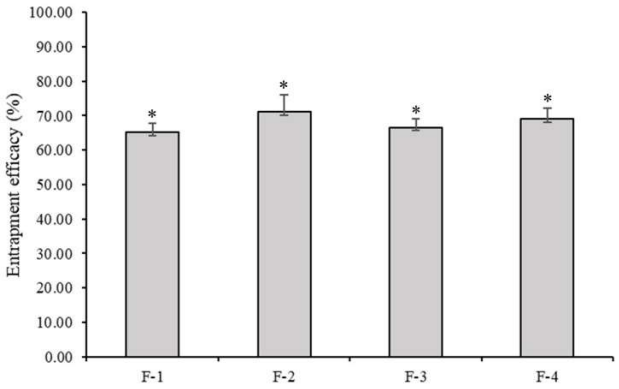

Figure 2 Percentage of drug entrapment efficacy. * The analysis revealed no significant differences ($p < 0.05$).

3.3 Drug release study

The studies investigating the release of *α*-mangostin from transdermal patches prepared using HPMC and LPR polymer found that an increase in HPMC content led to enhanced release of *α*-mangostin. In Figure 3, the cumulative percent *α*-mangostin release from the patch at 360 minutes ranged from 21.84 % - 26.39%. HPMC resulted in faster and greater release, while polymers with high LPR concentrations exhibited slower and less. The surface area exposed to air or solvent during medication dissolution may affect the rate of drug release. The choice of solvent and surface area dimensions are important factors in patch formulation [20]. Therefore, the release study serves as the foundation for future research and development of a transdermal patch targeted for commercial use.

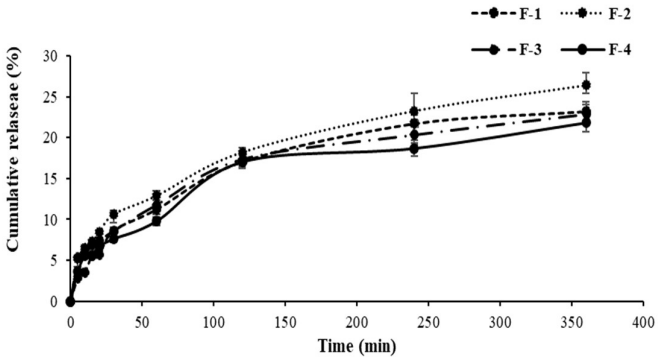

Figure 3 The cumulative release percentages of *α*-mangostin from transdermal patches.

4. Conclusion

In this study, transdermal patches were developed from low protein rubber extracted from mangosteen peels, using hydrophilic and hydrophobic polymers. Subsequently, a comprehensive assessment of different properties was performed. The results demonstrated that transdermal patches formulated with varying composition of HPMC and LPR exhibited good physical drug entrapment and drug release properties. Notably, the F-2 formula demonstrated the highest effectiveness all the formulations tested. This study represents an initial investigation

into transdermal patches and serves as a preliminary assessment. Further research is necessary to conduct safety studies, establish product standards, and evaluate their efficiency for human use. The transdermal patches have the potential to be further developed as a viable alternative product for commercial use.

5. Acknowledgements

This work was financially supported by Fundamental Fund; FF (2022), Rajamanjala University of Technology Srivijaya (Nakhon Si Thammarat Campus).

6. References

[1] Alkilani AZ, Donnelly RF. Beneath the Skin: A Review of Current Trends and Future Prospects of Transdermal Drug Delivery Systems. Pharmaceutics. 2022;14(6):1152.
[2] Lehman N, Kalkornsurapranee E. Influence of Non-Rubber Components on the Properties of Unvulcanized Natural Rubber from Different Clones. Polymers. 2022;14(9):1759.
[3] Xu L, Amin, S. Polymer Colloids for Cosmetics and Personal Care. Polymer Colloids. 2019;9:399.
[4] Yusof NH, Ibrahim S, Tan KS, Ab Rahim R, Mohd Rasdi FR. Soluble protein-free natural rubber latex prepared using guanidine hydrochloride as a denaturant. J Rubber Res. 2023;26:99-109.
[5] Rohman A, Windarsih A. Chemical composition and antioxidant studies of underutilized part of mangosteen (*Garcinia mangostana* L.) fruit. J Appl Pharm Sci. 2019;9(8):47-52.
[6] Astuti KW, Putra P. S. A. Anti-inflammatory activity of mangosteen (*Garcinia Mangostana* Linn.) rind extract nanoemulgel and gel dosage forms. Biomed Pharmacol J. 2019;12(04):1767-1774.
[7] Rizaldy D, Fidrianny I. Chemical compounds and pharmacological activities of mangosteen (*Garcinia mangostana* L.) Updated review. Biointerface Res Appl Chem. 2021;12(5):2503-2516.
[8] Feng Z, Lin L. Xanthones, a promising anti-inflammatory scaffold: Structure, activity, and drug likeness analysis. Molecules. 2020;25(3):598.
[9] Suksaeree J, Pichayakorn W. Improving the hydrophilic properties of deproteinized natural rubber latex films for lidocaine transdermal patches by starch blending. J Polym Environ. 2022;30:1574-1586.
[10] Putri F, Sahumena M. A. Formulation and physical characterization of curcumin nanoparticle transdermal patch. Int J Appl Biol Pharm. 2019;11(6):217-221.
[11] Monto. C, Suksaeree J. Herbal transdermal patches made from optimized polyvinyl alcohol blended film: Herbal extraction process, film properties, and in vitro study. J Drug Deliv Sci Technol. 2022;69:103170.
[12] Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol. 2016;7:1-13.
[13] Morais R, Marino C E. Skin interaction, permeation, and toxicity of silica nanoparticles: Challenges and recent therapeutic and cosmetic advances. Int J Pharm. 2022;614:121439.
[14] Jacob L, Saju J. Formulation and Evaluation of Transdermal Patches of Selegiline. Asian J Pharm. 2022; 12(2):96-100.
[15] Corrêa G D O P, Isaac V L B. *In vitro* evaluation of the cytotoxicity and eye irritation potential of preservatives widely used in cosmetics. RBCF. 2022;58:e20039.
[16] Chauhan SB, Naved T, Parvez N. Effect of hydrophilic and hydrophobic polymer matrix on the transdermal drug delivery of ethinylestradiol and medroxyprogesterone acetate. Int J Appl Pharm. 2019;11:210-215.
[17] Supapvanich C, De Vocht F. Evaluation of proteins in natural rubber latex gloves and pulmonary function amongst female nurses in two tertiary hospitals in southern, Thailand. Asian Pac J Allergy Immunol. 2022; 40(3):240-246.
[18] Puyathorn N, Phaechamud T. Natural rubber-based pressure sensitive adhesive as a drug carrier. Mater. Today: Proc. 2023;75:9-14.
[19] Latif M S, Alhashem Y N. Formulation and Evaluation of Hydrophilic Polymer Based Methotrexate Patches: *In Vitro* and *In Vivo* Characterization. Polymers, 2022;14(7):1310.
[20] Schroeder I Z, Franke P, Schaefer U F, Lehr C M. Development and characterization of film forming polymeric solutions for skin drug delivery. Eur J Pharm Biopharm. 2007;65(1):111-121.