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# FORMULATION AND PHYSICAL EVALUATION OF TOPICAL PATCH CONTAINING *DERRIS SCANDENS*

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**Abstract**: Formulation of topical patch containing *Derris scandens* extracts (DSE) for topical and transdermal drug delivery systems were developed and their physical properties including drug release were investigated. The topical patches of DSE were prepared by solvent casting evaporation technique using various proportions of DSE concentration (A), the polymer proportion of HPMC E4M and E15LV (B) and the amount of PEG 400 (C). Central composite design was adopted to determine the effect of the above formulation factors on the tensile strengths of the patches. It was found that tensile strengths were in the range of 151.88±46.58 g/cm$^2$ to 902.89±101.05 g/cm$^2$, demonstrating the patches with suitable hardness and brittleness. The mathematical equation was used to relate independent variables with tensile strength. The optimization model predicted the desired tensile strength with A, B, and C levels of 0.6 g, 48:52 and 40 %, respectively. This optimum composition resulted in suitable tensile strength of 571.28 ± 37.61 g/cm$^2$ and showed a good correlation between predicted and observed value. The *in vitro* drug release from the DSE patches were studied in 10%w/v ethanol in phosphate buffer saline and 50% w/v ethanol. Maximum concentrations of drug released obtained within 12 hours and 1 hour for 10 % w/v ethanol in phosphate buffer saline and 50% w/v ethanol, respectively. The release rates were found to decrease with the increase in polymer proportion of HPMC E4M and E15LV. The drug releasee kinetics of Higuchi models fit well to DSE release data of optimized patches. Hence DSE patches have a potential as an alternative dosage form to oral preparation and could be further developed for the study of *in vitro* skin permeation of DSE.

**Keywords**: *Derris scandens* extract, topical patches, topical drug delivery system

**บทคัดย่อ:** การพัฒนาสูตรตำรับแผ่นแปะผิวหนังซึ่งบรรจุยาสมุนไพรสกัดเถาวัลย์เปรียง (DSE) โดยประเมินคุณสมบัติทางกายภาพและความสามารถในการปลดปล่อยยาออกจากแผ่นแปะผิวหนังซึ่งสามารถเตรียมแผ่นแปะโดยวิธี solvent casting evaporation technique โดยใช้สัดส่วนที่ต่างกันของเถาวัลย์เปรียง (A) สัดส่วนของพอลีเมอร์ HPMC E4M:E15LV (B) และสารเพิ่มความยืดหยุ่น PEG400 (C) ใช้ central composite design เพื่อพิจารณาหาผลของปัจจัยที่เกี่ยวข้องกับสูตรตำรับข้างต้นที่มีผลต่อ tensile strengths ของแผ่นแปะ จากการทดลองพบว่าค่า tensile strengths อยู่ในช่วง 151.88 ± 46.58 g/cm$^2$ ถึง 902.89 ± 101.05 g/cm$^2$ โดยให้ความแข็งแรงและยืดหยุ่นเป็นที่น่าพอใจ สร้างสมการทางคณิตศาสตร์ที่แสดงความสัมพันธ์ระหว่างตัวแปรอิสระกับ tensile strengths ใช้ optimization model ที่สร้างขึ้นทำนายค่า tensile strength ที่ต้องการได้ จากค่าของ A, B และ C ที่ 0.6 g, 48:52 และ 40% ซึ่งส่วนประกอบดังกล่าวจะให้ผลเป็นที่น่าพอใจคือแสดงค่า tensile strengths 571.28 ± 37.61 g/cm$^2$ และให้ความสัมพันธ์ที่สอดคล้องกันระหว่างค่าที่ทำนายและค่าที่ได้จริง การศึกษาการปลดปล่อยยาในระดับ *in vitro* drug release โดยใช้เครื่อง Franz diffusion cells ในสารละลาย 2 ชนิด ได้แก่ 10% w/v ethanol in phosphate buffer saline และ 50% w/v ethanol แสดงให้เห็นว่ามีลักษณะของการปลดปล่อยยาที่ความเข้มข้นสูงสุดที่ 12 ชั่วโมง สำหรับ 10% w/v ethanol in phosphate buffer saline และ 1 ชั่วโมง สำหรับ 50% w/v ethanol พบว่าอัตราการปลดปล่อยยาจะลดลงเมื่อเพิ่มสัดส่วนของพอลีเมอร์ HPMC E4M ต่อ E15LV โดยลักษณะทางจลนศาสตร์ของการปลดปล่อยยาเข้ากันได้ดีกับโมเดลของ Higuchi สำหรับแผ่นแปะที่ได้จาก optimization ดังนั้นการศึกษาการซึมผ่านผิวหนังในระดับ *in vitro* skin permeation เพิ่มเติมนั้นจะทำให้ทราบถึงศักยภาพของแผ่นแปะ DSE ที่จะเป็นรูปแบบยาเตรียมทางเลือกอื่นนอกจากการให้ทางปาก

**คำสำคัญ:** สารสกัดเถาวัลย์เปรียง แผ่นแปะผิวหนัง ระบบนำส่งยาผ่านทางผิวหนัง

## INTRODUCTION

*Derris scandens* (Roxb.) Benth. (Fabaceae) or Thao-Wan-Priang (Thai-name) is known as herbal medicine in the South-East Asia and has been traditionally used as a diuretic, antitussive, expectorant, anti-dysentery and muscle pain treatment. It is also claimed as cancer prevention, and health promotion herb in cardiovascular patients and postmenopausal women (Sriwanthana and Chavalittumrong, 2001; Kuptniratsaikul *et al*., 2011). Active ingredients of *Derris scandens* for anti-inflammatory effect are genistein glycoside derivatives (isoflavones). Current evidence suggested that *Derris scandens* might be considered as a potential alternative for nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of musculoskeletal pain. The use of *Derris scandens* as alternative medicine might be safer than NSAIDs in long-term use (Puttarak *et al*., 2016).

The term of topical drug products referring to all formulations applied to the skin except transdermal delivery systems (TDS) or transdermal patches that will be addressed separately (Pharmacopeial Forum, 2009). Topical patch formulation is the alternative medicine apart from oral therapy. In contrast to conventional topical formulations, such as creams, gels and sprays, topical patch provides a defined dose to a defined area for an extended period time. In addition, application of the patch is devoid of the messiness or staining of the skin that may occur while applying creams or gels. Sun Hwa Lee et al. (2016) studied the hydrocolloid patch including genistein and daidzein to deliver them through the skin. It was confirmed that the patches are helpful for the drugs to be absorb much and more deeply than the cream due to the occlusive effect of patch. In this study, the topical patch consisted of *Derris scandens* extracts (DSE) was developed as alternative drug delivery. Aim of this study is to investigate the drug released and evaluate the physical properties of the formulation of topical patches.

## MATERIALS AND METHODS

### *Materials*

*Derris scandens* extract (PSU pharmacognosy laboratory), Genistein standard (Sigma®, Thailand), Hydroxypropyl methylcellulose grade E4M and E15LV (P.C. Drug Center, Bangkok, Thailand), Polyethylene glycols 400 (P.C. Drug Center, Bangkok, Thailand). 95% Ethanol, AR grade (Lab-Scan®, Bangkok, Thailand), Aluminium Chloride AR grade (Sigma®, Thailand)

### *Methods*

### *Experimental design*

The central composite design was adopted to optimize the formulation factors, i.e. DSE concentration, polymer proportion of HPMC E4M and E15LV and percentage of PEG 400 and to evaluate their effects on a response of the tensile strength of the patches. All the factors and the response variables are mentioned in Table 1.

**Table 1.** Variables and their levels in central composite experimental design

| Variables | Levels | | | | |
|---|---|---|---|---|---|
| | -1.68 | -1 | 0 | 1 | 1.68 |
| *Independent factors* | | | | | |
| A = DSE **(g)** | 0.064 | 0.2 | 0.4 | 0.6 | 0.736 |
| B = HPMC E4M:15LV **(%)** | 22 | 33.33 | 50 | 66.67 | 78 |
| C = PEG400 **(%)** | 13.18 | 20 | 30 | 40 | 46.82 |
| *Dependent response* | | | | | |
| Tensile strength **(g/cm$^2$)** | | | - | | |

Statistical analysis for the present study was performed by Design-Expert software (Version 10, Stat-Ease Inc., Minneapolis, MN, USA). Experimental design of different runs (formulations) of topical patch is presented in Table 2.

**Table 2.** Central composite design for the preparation of different formulations

| Runs | Factors with levels | | |
|---|---|---|---|
| | DSE (g) | HPMC E4M (%) | PEG400 (g) |
| 1 | 0.2 | 33.33 | 20 |
| 2 | 0.6 | 33.33 | 20 |
| 3 | 0.2 | 66.67 | 20 |
| 4 | 0.6 | 66.67 | 20 |
| 5 | 0.2 | 33.33 | 40 |
| 6 | 0.6 | 33.33 | 40 |
| 7 | 0.2 | 66.67 | 40 |
| 8 | 0.6 | 66.67 | 40 |
| 9 | 0.064 | 50 | 30 |
| 10 | 0.736 | 50 | 30 |
| 11 | 0.4 | 22 | 30 |
| 12 | 0.4 | 78 | 30 |
| 13 | 0.4 | 50 | 13.18 |
| 14 | 0.4 | 50 | 46.82 |
| 15 | 0.4 | 50 | 30 |
| 16 | 0.4 | 50 | 30 |

***Preparation of the herbal medicine patch***

The 16 formulations of topical patches (Table 2) were prepared by solvent casting evaporation technique. Initially, the 3% HPMC solution containing water and HPMC in varied proportions of E4M and E15LV were prepared. The HPMC polymers were dispersed and thoroughly hydrated in about 20-30 % of the required amount of water. The water was heated to 80 -90 °C, and then the polymers were added with stirring action. Sufficient cold water then was added to produce the required volume while continuing to stir. Required quantities of DSE and PEG 400 were added slowly to previously prepared HPMC solutions while cooling followed by mixing them thoroughly. The matrix solutions were poured on to a petri dish. The solvent casting was evaporated at 45 °C for 24 hours. The dried DSE films were cut into 40 cm$^2$ and wrapped in aluminum foil before being kept in a desiccator 2-8 °C (Rabinarayan and Padilam, 2016).

### *Evaluation of physicochemical properties of the patch*

#### *1) Thickness and weight variation*

The thickness of patch was measured three times by Teclock® dial thickness gauge. Weight variation studies were carried out with selected the three patches )40 $cm^2$ (from each run using analytical balance (Rabinarayan and Padilam, 2016).

#### *2) pH measurement*

The pH of patches solution (n=3) were measured by pH meter (Professional Benchtop pH meter BP3001 Trans Instruments., Singapore).

#### *3) Swelling index*

The dried patches supported by stainless steel mesh were immersed in a beaker containing 25 ml distilled water at room temperature. At the $2^{nd}$ minute time interval the swollen samples with the pre-weighed mesh were weighed after removal of excess surface water by blotting lightly with a filter paper. The experiment was discontinued when the patches began to disintegrate or dissolve. To quantify the swelling index, percentage was calculated as follows:

$$\text{Swelling index} = \frac{(W_s - W_d) \times 100}{W_d} \quad (1)$$

Where; $W_d$: the weight of the dried patch
$W_s$: the weight after swelling

#### *4) Mechanical properties*

For the measurement of mechanical properties as tensile strength ($g/cm^2$), % elongation at break (EB) and elastic modulus (EM), the patch specimen of specific dimension (4 × 2 cm) was fixed between two clamps of texture analyzer (TA. XT plus, Stable MicroSytems Ltd, USA). The test condition were ; test speed of 10 mm/min, target load of 5 kg, holding time of 5 seconds, and trigger force of 5 g (Rabinarayan and Padilam, 2016). The mechanical properties were determined as follows:

Tensile strength ($g/cm^2$) = Breaking force (g) / area of the film ($cm^2$) (2)

#### *5) Drug content*

A 1x1 $cm^2$ of each patch (n=3) was dissolved in 10 ml of 95 % ethanol and sonicated for 30 minutes. Then 0.5 ml of each sample solution, 1.5 ml of 95 % ethanol, 0.1 ml of 1 M aluminium chloride and 2.9 ml of distilled water were thoroughly mixed to obtain the completely dissolved solution. Sample blank was prepared in similar way by replacing 1M aluminium chloride with distilled water. All prepared solution was filtered through 0.45 µm. filter paper before measuring. The samples and blank solution were measured by UV-VIS spectrophotometer (UV-1800, SHIMADSU) at 382 nm. Genistein standard as marker for DSE was used to make the calibration curve **(**Isabela da Costa César *et al*., 2008).

#### *6) In vitro release study*

The three suitable patch formulations from the physical properties evaluation were selected to continue the *in vitro* drug release study. The *in vitro* evaluation was carried out in Franz diffusion cell. The cellulose dialysis membranes (molecular weight cut-off 12,000 to 14,000 Da, Spectra/ Por®, Spectrum Labs, Rancho Dominquez, CA, USA) was mounted between the donor and receptor compartment of the diffusion cell. The membrane was previously soaked for 2 hours in receptor fluid of 10 % w/v ethanol in phosphate buffer saline

(PBS) and 50% w/v ethanol. The 1.77 $cm^2$ patches were placed over the membrane. The receptor compartment of the diffusion cell was filled with 12 ml of the receptor fluid. The solution in the receptor compartment was constantly and continuously stirred using magnetic bar at 500 rpm; the temperature was maintained at 31 ± 0.5 °C. Samples were withdrawn (1 ml) at predetermined time intervals (0, 5, 15, 30, 45, 60, 120, 240, 360 and 720 minutes) and replaced with an equal volume of receptor fluid. The genistein content in these samples was determined by UV-VIS spectrophotometer at 382 nm.

### *7) Statistical analysis*

In the study of physical evaluation of topical patch**,** polynomial models including linear, interaction, quadratic and cubic were generated for all the response variables using multiple linear regression analysis. Equations were derived and coefficients of interactions were calculated to determine the effect of each variable on the formulation characteristics. Statistical validity of the model was established on basis of analysis of variance (ANOVA) using various statistical parameters such as p-value, coefficient estimate, determination coefficient ($R^2$), adjusted determination of coefficient (Adjust $R^2$) by the Design Expert Software Version 10 (Stat-Ease Inc., Minneapolis, MN, USA.).

In the study of drug release, the dissolution data of various formulations were fitted with the different mathematical models to determine the drug release kinetics, i.e., zero order, first order and Higuchi's model.

## RESULTS AND DISCUSSION

### *Evaluations of physicochemical properties and mechanical parameter of DSE patches*

The physicochemical properties of DSE patches such as, thickness variation, weight variation, pH and genistein content were measured and presented in Table 3. The genistein content of all patch were found to be in the range of 4.52 ±0.23 to 42.72 ±1.34 mg/40 $cm^2$. The thickness of all patches was varied between 0.085 ±0.008 to 0.177 ±0.027 mm. The variation of weight ranged from 561.0 ±31.15 mg to 771.2 ±30.41 mg. The pH of solution ranged from 8.48 ±0.03 to 8.86 ±0.01. Mechanical parameters such as tensile strength (TS), % elongation at break (EB) and elastic modulus (EM) are shown in Table 4. which indicated the hardness and brittleness of prepared patches. Tensile strength values were found to be in the range of 151.88 ±46.58 g/$cm^2$ to 902.89 ±101.05 g/$cm^2$, as a resulting of the formulation factors, i.e., DSE concentration, polymer proportion and amount of plasticizer as further discussed by using response surface plots.

**Table 3.** Results of physicochemical properties of DSE patches

| Runs | Thickness (mm) | Weight (mg) | pH | Amount of genistein in patch (mg) |
|---|---|---|---|---|
| 1 | 0.121 ±0.024 | 751.7 ±15.4 | 8.86±0.01 | 12.37 ± 0.31 |
| 2 | 0.085 ±0.008 | 591.6 ±1.7 | 8.85±0.01 | 34.70± 0.17 |
| 3 | 0.151 ±0.014 | 688.3 ±10.1 | 8.55±0.04 | 12.12± 0.24 |
| 4 | 0.102 ±0.006 | 610.4 ±12.0 | 8.86±0.01 | 34.91 ± 0.23 |
| 5 | 0.099 ±0.006 | 716.8 ±9.7 | 8.50±0.01 | 12.41 ± 0.05 |
| 6 | 0104 ±0.009 | 718.3 ±19.4 | 8.50±0.01 | 34.57 ± 0.27 |
| 7 | 0.094 ±0.005 | 718.6 ±30.1 | 8.59±0.02 | 12.94 ± 0.16 |
| 8 | 0.098 ±0.010 | 711.9 ±10.9 | 8.55±0.01 | 35.07 ± 0.22 |
| 9 | 0.103 ±0.015 | 708.7 ±11.5 | 8.47±0.03 | 4.52 ± 0.23 |
| 10 | 0.086 ±0.011 | 561.0 ±31.1 | 8.54±0.03 | 42.72 ± 1.34 |
| 11 | 0.113 ±0.029 | 711.2 ±5.3 | 8.53±0.03 | 26.57 ± 0.04 |
| 12 | 0.177 ±0.027 | 562.0 ±14.4 | 8.51±0.04 | 26.50 ± 0.20 |
| 13 | 0.091 ±0.005 | 620.1 ±7.9 | 8.52±0.04 | 26.76 ± 0.35 |
| 14 | 0.114 ±0.015 | 771.2 ±30.4 | 8.55±0.04 | 27.48 ± 0.31 |
| 15 | 0.101 ±0.020 | 688.1 ±15.1 | 8.59±0.04 | 27.71 ± 0.54 |
| 16 | 0.105 ±0.011 | 718.0 ±4.3 | 8.48±0.03 | 27.86 ± 0.29 |

**Table 4.** Results of mechanical parameters of DSE patch

| Runs | Tensile strength ($g/cm^2$) (TS) | % Elongation at break (EB) | Elastic modulus (MPa) (EM) |
|---|---|---|---|
| 1 | 829.34±38.35 | 114.49 | 7.10 |
| 2 | 447.26±35.84 | 92.48 | 4.74 |
| 3 | 902.89±101.05 | 56.23 | 14.29 |
| 4 | 377.23±40.13 | 18.18 | 22.60 |
| 5 | 422.65±58.07 | 79.51 | 4.18 |
| 6 | 470.95±41.40 | 75.34 | 6.45 |
| 7 | 469.85±60.75 | 122.41 | 4.43 |
| 8 | 439.11±19.03 | 96.25 | 4.47 |
| 9 | 443.08±6.29 | 81.67 | 5.26 |
| 10 | 355.43±19.97 | 84.63 | 7.37 |
| 11 | 709.84±58.90 | 92.70 | 4.69 |
| 12 | 151.88±46.58 | 67.81 | 5.14 |
| 13 | 880.42±166.31 | 100.76 | 7.72 |
| 14 | 573.49±61.34 | 64.90 | 2.29 |
| 15 | 562.74±57.21 | 77.94 | 8.98 |
| 16 | 635.65±9.02 | 70.08 | 9.19 |

Swelling indexes of all patches which indicate the swelling properties are shown in Figure 1. The result implied that the low polymer proportion of HPMC E4M and E15LV as seen from runs 1,2,5,6 had higher swelling index than those of the high polymer ratio patches from runs 3,4,7,8. It could be explained that the water uptake by the patches increased as amount of HPMC E15LV increased because HPMC E15LV was more hydrophilic and easily leached from the patch and left behind a porous structure and thereby increased penetration of water. Consequently, the portion of HPMC E4M in the patch imbibed more water to swell. In addition, DSE concentration had also agonist effect on swelling property. The patches with composition of high DSE concentration and high polymer proportion had lower swelling

index as seen from runs 13, 14, 15 and 16. The patch with the lowest DSE concentration as seen in run 9 had the highest swelling index.

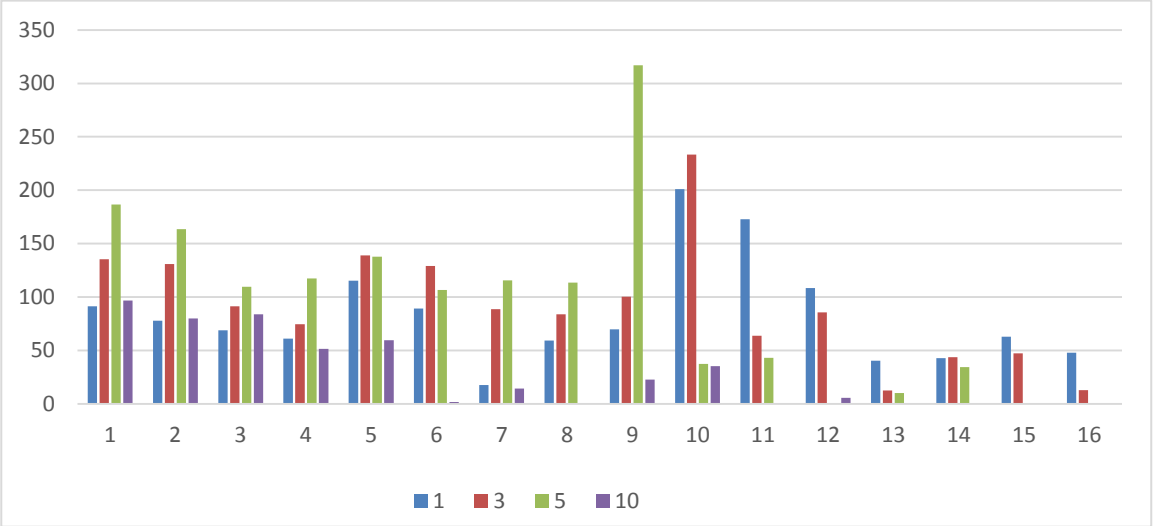



**Figure 1.** The swelling (%) at 1st, 3rd, 5th and 10th minutes of runs 1-16.

***Analysis of suitable mathematical model***

In a statistical design, the essential components include defining output response and input variables, design of experiment, running experiment, statistical analysis and optimization of formulation (suitable combination of independent variables). In the current study, the combined effect of process variables such as DSE concentration, proportion of HPMC E4M and E15LV and PEG 400 concentration at different levels on dependent variable (tensile strength) were studied using central composite design method. Experimental data were fitted to different polynomial models including linear, quadratic and cubic models and statistical tests such as sequential model sum of squares and model summary were performed to determine the adequacy of models (Table 5 and 6).

**Table 5.** Model Summary Statistics

| Source | Std.dev. | $R^2$ | Adjusted $R^2$ |
|---|---|---|---|
| Linear | 176.72 | 0.4087 | 0.2609 |
| Quadratic | 143.67 | 0.8046* | 0.5115 |
| Cubic | 53.11 | 0.9911 | 0.9332 |

**Table 6.** ANOVA for Response Surface Quadratic model

| Model | Coefficient estimate | P value |
|---|---|---|
| Model | 596.24 | 0.1159 |
| A-DSE | -75.90 | 0.0987 |
| B-HPMC | -67.40 | 0.1337 |
| C-PEG400 | -93.09 | 0.0537 |
| AB | -27.70 | 0.6052 |
| AC | 115.79 | 0.0629 |
| BC | 1.36 | 0.9795 |
| $A^2$ | -63.56 | 0.2268 |
| $B^2$ | -52.38 | 0.3096 |
| $C^2$ | 52.30 | 0.3103 |

### *Effect of formulation variables on tensile strength of DSE patch*

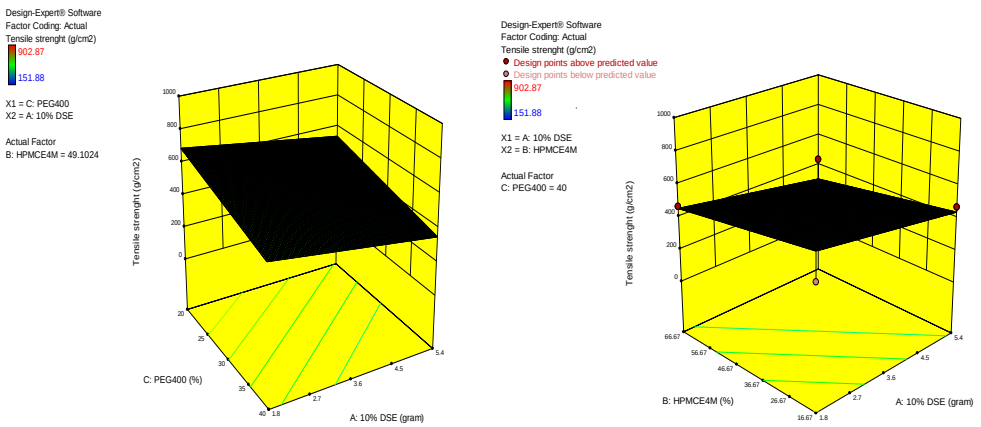
The experimental data was evaluated by ANOVA and the significance was measured by the corresponding p-value of the regression coefficients as shown in Table 5. Quadratic model was found to be fitted for the response tensile strength with $R^2 = 0.8046$. All terms were selected for model and generated quadratic equation is given to:

$$\text{Tensile strength } (g/cm^2) = 596.24 - 75.90A - 67.40B - 93.09C - 27.70AB + 115.79AC + 1.36BC - 63.56A^2 - 52.38B^2 + 52.30C^2 \quad (3)$$

The equation shows that factors A and C have negative effects on the tensile strength of patches. However, the coefficient value of -93.09 for factor C indicates its higher influence on the patch's tensile strength than factor A, having coefficient value of -75.90. The interaction factor (AC) has synergistic effect on decreasing tensile strength due to their positive coefficient value. In addition, the influences of patch formulation variables on the tensile strength can be further explained by using response surface plots based on this model. The values of three factors (A, B and C) were substituted in the polynomial equation to calculate the theoretical value of the response (tensile strength). The theoretical (predicted) values and observed values were mostly in agreement as shown in Table 7.

**Table 7.** Observed and predicted values of response tensile strength

| Runs | Factor 1 A = DSE (g) | Factor 2 B = HPMC E4M (%) | Factor 3 C = PEG400 (g) | Response Tensile strength ($g/cm^2$) | Predicted Tensile strength ($g/cm^2$) |
|---|---|---|---|---|---|
| 1 | 0.2 | 33.33 | 20 | 829.34±38.35 | 858.44 |
| 2 | 0.6 | 33.33 | 20 | 447.26±35.84 | 530.47 |
| 3 | 0.2 | 66.67 | 20 | 902.89±101.05 | 779.32 |
| 4 | 0.6 | 66.67 | 20 | 377.23±40.13 | 337.55 |
| 5 | 0.2 | 33.33 | 40 | 422.65±58.07 | 437.97 |
| 6 | 0.6 | 33.33 | 40 | 470.95±41.40 | 573.14 |
| 7 | 0.2 | 66.67 | 40 | 469.85±60.75 | 361.28 |
| 8 | 0.6 | 66.67 | 40 | 439.11±19.03 | 385.65 |
| 9 | 0.064 | 50 | 30 | 443.08±6.29 | 544.37 |
| 10 | 0.736 | 50 | 30 | 355.43±19.97 | 289.34 |
| 11 | 0.4 | 22 | 30 | 709.84±58.90 | 561.63 |
| 12 | 0.4 | 78 | 30 | 151.88±46.58 | 335.15 |
| 13 | 0.4 | 50 | 13.18 | 880.42±166.31 | 900.25 |
| 14 | 0.4 | 50 | 46.82 | 573.49±61.34 | 587.46 |
| 15 | 0.4 | 50 | 30 | 562.74±57.21 | 596.24 |
| 16 | 0.4 | 50 | 30 | 635.65±9.02 | 596.24 |




(a) (b)

**Figure. 2** Response surface plots showing the effects on the tensile strength of three formulation factors (a) between DSE concentration (A) and amount of plasticizer (C); (b) between DSE concentration (A) and polymer proportion (B)

The 3D response surface plots were shown in Figure 2. The effect of DSE concentration (A) and amount of plasticizer (C) at mid-point of factor B on the response tensile strength was exhibited in Figure 2a. Both factor A and C adversely affected the tensile strength. The results were found that the increase in DSE concentration and amount of plasticizer resulted in a substantial decrease in tensile strength. The effect of DSE concentration (A) and polymer ratio (B) at mid-point of factor C on the response was also shown in Figure 2b and implied that both factor A and B had negative effect on tensile strength. It could be suggested that the DSE concentration, amount of plasticizer and polymer proportion had the optimal levels to use in the patch formulation.

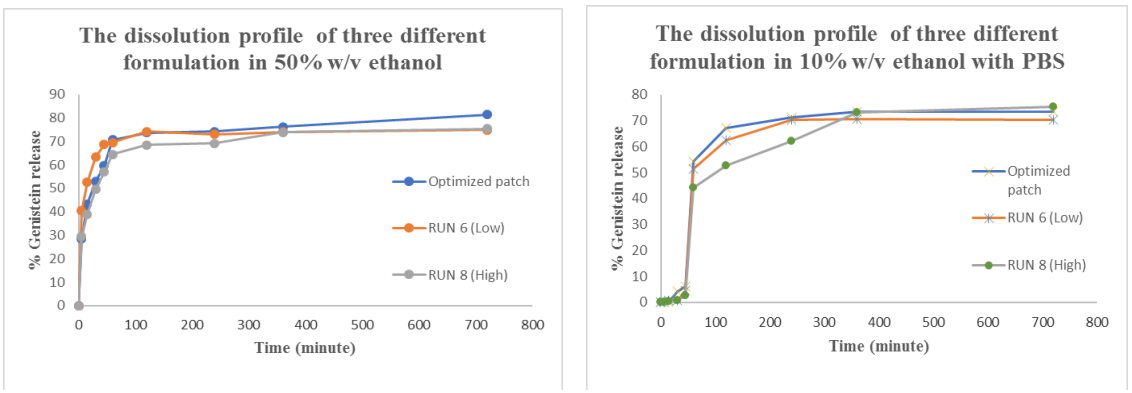
### *Optimization of DSE patch formulation*

Derringer's desirability function methodology was used for optimization of DSE patch formulation. Table 4 shows the mechanical properties of the DSE patch. Higher values of tensile strength (TS) are desirable for mechanical resistance. The elongation at break (EB) is a measure of the ductility of a patch which defines the ability of a patch to deform before failure occurs whereas the elastic modulus (EM) is a key indicator of the stiffness of the patch. The tough patch should have low EM, moderate TS and high EB. The TS was selected as the key parameter to be optimized. The desirability was designed to have high DSE content and varied the polymer proportion and amount of plasticizer to obtain the moderate TS. The optimum compositions were found to be 0.6 g for DSE, 48:52 % for proportion of HPMC (E4M:E15LV) and 40 % for PEG 400 which predicted that value of TS would be 550 g/cm$^2$ with desirability value of 0.999. The experiment was performed to prepare the DSE patch as according to the optimized composition for validation purpose. The average optimized patches (n=5) values of 571.28 ±37.61 g/cm$^2$ for TS and 83.5 % for EB and 6.71 MPa for EM were obtained. The result of TS was closely related with the data predicted from the above numerical optimization technique using desirability methodology and EB value was high whereas EM value was low, indicating that the optimized patch had the required mechanical property. The result was also in accordance with the study of Rabinarayan and Padilam (2016) who use the response surface methodology to investigate the mechanical properties of the transdermal patch of simvastatin. It was reported that high drug

concentration (2%), medium polymer ratio (50%) and high amount of plasticizer (40%) resulted in mechanical properties of high EB (85.33%) and low EM (20.39 MPa). The optimized composition was used to prepare DSE patch for the *in vitro* drug release study.

***In vitro drug release study***

The *in vitro* drug release of DSE patches were carried out using 10% w/v ethanol in phosphate buffer saline and 50% w/v ethanol. The dissolution profiles of three different formulations, i.e., optimized patch, run 6 (low polymer proportion), run 8 (high polymer proportion) in different media are shown in Figure 3. The results showed that maximum concentrations of drug released were obtained at the 1$^{st}$ hour and 12$^{th}$ hour for 50% w/v ethanol and 10% w/v ethanol in phosphate buffer saline, respectively. From Figure 3a, it was found that all patches released genistein rapidly in 50% w/v ethanol medium. The percent release at the 60$^{th}$ minute of optimized, low and high polymer proportion patch were 70.76 %, 69.52 % and 64.44 % respectively due to the high solubility of genistein in this medium. From Figure 3b, it was found that all patches released genistein more slowly in 10% w/v ethanol in phosphate buffer saline. The percent release at the 240$^{th}$ minute of optimized, low and high polymer proportion patch were 67.28, 70.28 and 62.17 % respectively. In both cases, the release of drugs from the patch is governed by the diffusion of solute which dissolved initially by the medium within the matrix phase and continuously decreasing when the concentration gradient is smaller. Therefore, the higher drug solubility could facilitate higher drug release from the patches. To explain the drug release kinetics of genistein from the topical patchs, the mean dissolution curves included the fraction between 10-90% of drug release was calculated by linear regression analysis of various mathematical models but neither one of the models could provide good coefficients of determination except Higuchi's ($R^2$ 0.962, 0.534 and 0.899) which gave $R^2$ close to 1 as tabulated in Table 8 for the test run in receptor fluid of 10% w/v ethanol in PBS. Hence, the release mechanism of genistein from the topical patches is governed by diffusion process. The $R^2$ of the DSE patch with low polymer proportion is lower than that with high polymer proportion. It might be explained that the patches composed of the more proportion of hydrophilic polymer, leading to high erosion of the patches and thereby facilitating rapid drug release from the patches by dissolution. According to this fact, the release rates were found to decrease with increase in polymer proportion of HPMC E4M and E15LV. The results of the swelling index supported the drug release in the corresponding manner.




(a) (b)

**Figure 3**. The *in vitro* drug release profile of 3 different patch formulations in 50% w/v ethanol (a) and 10% w/v ethanol with PBS (b)

**Table 8.** Coefficient of determination from linear regression analyses of various mathematical models

| DSE patches | Zero order $Q_t = K_0t + Q_0$ | First order $LogQ_t = K_1t + LogQ_0$ | Higuchi $Q_t = K_Ht^{1/2}$ |
|---|---|---|---|
| Receptor fluid; 50% w/v ethanol | | | |
| Optimized | 0.665 | 0.393 | 0.639 |
| Run 6 | 0.831 | 0.464 | 0.452 |
| Run 8 | 0.815 | 0.453 | 0.641 |
| Receptor fluid; 10% w/v ethanol in PBS | | | |
| Optimized | 0.674 | 0.735 | 0.962 |
| Run 6 | 0.468 | 0.490 | 0.534 |
| Run 8 | 0.774 | 0.822 | 0.899 |

## CONCLUSION

Formulation of *Derris scandens* extracts (DSE) for topical patches were developed and evaluated for the physical properties and drug release. The optimum compositions were found to be 0.6 g for DSE, 48:52% for proportion of HPMC (E4M:E15LV) and 40 % for PEG, resulting in the tensile strength of 571.28 g/cm$^2$ and high elongation at break of 83.5 %. It indicated that the patch was tough and inherited a good mechanical property. The release rates were found to decrease with increase in polymer proportion of HPMC E4M and E15LV. The drug release kinetics of Higuchi models ($R^2$ 0.962, 0.534 and 0.899) fit to DSE release data better than the others. However, the optimized patch has the potential as an alternative to oral preparation and could be developed further for the study of *in vitro* skin permeation of DSE.

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