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Applying Design of Experiments on the Mechanical Properties of Mefenamic Acid-Loaded Transdermal Films

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Abstract

The Design-Expert® program version 11 was used to analyze and optimize the mechanical properties of mefenamic acid-loaded transdermal films. The dependent variables were ultimate tensile strength (UTS), elongation at break and folding endurance, whereas the independent variables were silicone rubber, mefenamic acid and dibutyl sebacate (DBS). While quadratic models predicted elongation at break and folding endurance more accurately, a linear model predicted the highest correlation relationship for UTS. The design of experiments (DOE) estimated that the optimal silicone rubber, mefenamic acid and DBS ratio would be 5.3:2.5:5.2. By demonstrating that the prediction value of the ratio was more than 4, the model was proved to be suitable for forecasting results inside the design space without the requirement for additional trials. Experimental values of UTS, elongation at break and folding endurance were 6.20 ± 0.50 MPa, 711.22 ± 102.00 % and 857 ± 64 folds, respectively. The percent error was determined to be 8.50, 6.70 and 9.28 %, respectively. The DOE successfully demonstrated a low percent error of prediction (less than 10 %) from the Design-Expert® approach, which was satisfactory and accepted for preparation in drug delivery systems.

Keywords: Applying design of experiments, Mechanical properties, Mefenamic acid, Transdermal films

Introduction

Mefenamic acid is classified as class II according to the biopharmaceutical classification system. It has low water solubility but high permeability. Mefenamic acid, a non-steroidal anti-inflammatory medicine, acts by inhibiting the synthesis of cyclooxygenase-2 and prostaglandin to treat moderate to severe pain and primary dysmenorrhea. It comes in tablet, pill and pediatric suspension forms. Its 2 h elimination half-life is rather short. The steady-state plasma concentration must thus be maintained by regular dosing every 6 h with oral delivery [1,2]. Mefenamic acid delivery by transdermal delivery is very attractive. The significant gastrointestinal adverse effects can be avoided by using this route, which can also deliver stable plasma levels with a single dosage and prevent hepatic 1st-pass metabolism [3,4]. The crystallization of mefenamic acid in transdermal patches is an important concern that renders the patch unstable and reduces drug delivery. Transdermal patches for mefenamic acid using ethylcellulose and Eudragit® RL as matrix layers and diethyl phthalates as plasticizer. Polyvinylpyrrolidone has been investigated and shown to be particularly effective in reducing medication crystallization. The drug: PVP K90 ratio of 1:2 has been determined to be the most effective in enhancing drug release from patch. The characterizations demonstrate homogenous patches with no crystal form of the mefenamic acid drugs, suggesting that crystallization inhibition of the mefenamic acid drug has been entirely achieved in the matrix film [3, 5]. Furthermore, mefenamic acid is produced by a complexation process with monoethanolamine, diethanolamine, triethanolamine and propanolamine, which increases the rate of skin absorption through hairless rat skin [6].

When forces are applied to the sample, it manifests physical characteristics known as mechanical properties. A material's mechanical properties are characterized as those that affect how the material responds to applied loads. When selecting a material, consideration of a material's mechanical properties helps predict how it will perform in a specific application. The mechanical characteristics of *Ganoderma applanatum* extract-containing topical films have been studied. The model, which combines the independent effects of ethyl cellulose, *G. applanatum* extracts and triethyl citrate, has been shown to accurately predict ultimate tensile strength (UTS), elongation at break and folding endurance [7]. The tensile strength, elastic modulus and elongation at break properties of domperidone maleates patches demonstrate the strength and elasticity of the film. Low values of tensile strength, elastic modulus and elongation at break signify a soft and weak polymer, whereas high values of tensile strength, elastic modulus and elongation at break signify a strong and robust polymer. Strain is another crucial factor that has been utilized to gauge the overall mechanical performance of polymer films. A good transdermal film should have a low elastic modulus but a high tensile strength, elongation at break and strain [8,9]. Anirudhnan and colleagues proposed a novel approach for increasing adhesion and improving mechanical properties of chitosan matrix-type patches by grafting chitosan with glycidyl methacrylate and then polymerizing with butyl methacrylate. Chitosan can develop higher-adhesive membranes to tissues due to the addition of catechol groups. Lidocaine, a poorly water-soluble medication used to treat neuropathic pain and presenting a series of side effects, is encapsulated in amine functionalized hyaluronic acid (via hydrophobic alteration). The encapsulated drug microparticles are then distributed throughout the grafted chitosan adhesive/matrix of the patch. As a result of this combination, the matrix has improved mechanical properties, adhesion potential, drug retention behavior and long-term storage performance [10]. As a model drug, rhodamine B is employed to create a silver hybridized porous chitosan-based matrix-type patch with high mechanical strength and drug transport efficiency. Silver metal has been identified as a potent bacterial inhibitor with potential use in preventing wound infections. Silver promoted drug release in this study by increasing the hydrophobicity of hybridized films, which was connected to an increase in stratum corneum permeability [11].

Therefore, the mechanical properties are important and necessary for the design of transdermal patches. The purpose of this experiment was to investigate the mechanical characteristics of transdermal films prepared with mefenamic acid. To select the optimum formulation, these properties will be optimized by Design-Expert® program version 11 (Stat-Ease, Inc, USA).

Materials and methods

Silicone rubber Lot no. SH1032U was received from Eton industry (Thailand) CO., LTD. Dibutyl sebacate (DBS) and mefenamic acid (95 % purity) were purchased from Sigma-Aldrich (USA). Chemical grade solvent was used.

Mefenamic acid-loaded transdermal films

Mefenamic acid, DBS and silicone rubber were dissolved in 100 mL of hexane before being thoroughly blended by a mechanical stirrer. **Table 1** provides the compositions of the transdermal films containing mefenamic acid. For 30 min, the mixed solution was sonicated to remove air bubbles. The mixed solution was then transferred into a 70.88 cm^2 Petri plate and allowed to dry overnight in a fume hood. The transdermal films containing mefenamic acid were removed from Petri dishes and stored in a desiccator until needed for physical characterization.

Table 1 Formulations of mefenamic acid-loaded transdermal films and their properties.

Formulas	Silicone rubber X_1 (g)	Mefenamic acid X_2 (g)	DBS X_3 (g)	UTS (MPa)	Elongation at break (%)	Folding endurance (Folds)
1	2	1	4	10.99 ± 1.90	478.84 ± 43.13	565 ± 16
2	6	1	4	7.15 ± 0.86	864.66 ± 82.27	778 ± 80
3	2	3	4	8.63 ± 0.92	427.58 ± 41.42	486 ± 76
4	6	3	4	5.27 ± 1.33	425.82 ± 38.72	450 ± 40
5	2	2	2	8.77 ± 0.79	707.84 ± 19.10	707 ± 20
6	6	2	2	4.86 ± 0.66	928.05 ± 77.55	902 ± 26
7	2	2	6	9.82 ± 2.12	733.76 ± 55.78	714 ± 28
8	6	2	6	6.91 ± 2.00	1077.93 ± 31.82	1000 ± 28
9	4	1	2	8.83 ± 0.54	629.32 ± 49.52	558 ± 37
10	4	3	2	5.31 ± 1.39	534.77 ± 51.53	655 ± 17
11	4	1	6	4.43 ± 0.78	688.32 ± 5.64	767 ± 34
12	4	3	6	6.08 ± 0.83	613.20 ± 26.73	844 ± 71
13	4	2	4	7.46 ± 1.24	723.55 ± 82.83	702 ± 74

Mechanical properties

To study the mechanical properties, the TA.XT Plus Texture Analyzer (Texture Technologies Corporation and Stable Micro Systems, Ltd., USA) was utilized. The testing speed was regulated at 10 mm/min and 500 g of a loaded cell were employed. Each film sample was made into a 10×60 mm^2 rectangle form. Every formula was examined. The cross-sectional testing area (width×thickness of the film, mm^2) and load cell force (N) were compared to determine the UTS of the film. The percentage of elongation at break was calculated by subtracting the length of the film at the breaking point (mm) from the beginning length (mm) [12,13].

Folding endurance

The film sample's ability to endure many folds in one spot before it breaks was investigated. The number of folds a film sample could withstand before breaking was used to calculate its folding endurance [14,15].

Optimization of properties of mefenamic acid-loaded transdermal films

The design of experiments (DOE) method, which used the Design-Expert® program version 11 (Stat-Ease, Inc., USA) in UTS, elongation at break and folding endurance of the films, predicted the ideal ratio of the 3 components.

Results and discussion

The important aim of the DOE is to use a statistical design strategy to reduce the number of trials required to find factors impacting the research findings. The DOE techniques are chosen by taking into account variables including variable interactions, variable levels, variable counts and the number of allowable experiments [16]. The mechanical characteristics of topical films containing *G. applanatum* extracts are examined under the direction of Design-Expert®. The dependent variables are UTS, elongation at break and folding endurance whereas ethyl cellulose, *G. applanatum* extracts and triethyl citrate are independent factors. The quadratic, 2FI and linear models, respectively, can better predict the best connections between UTS, elongation at break and folding endurance. It is proven that the model can accurately predict results inside the design space with no requirement for extra trials. For the development of film formulation in drug delivery systems, this is appropriate and acceptable [7].

The current investigation demonstrated the effect of silicone rubber, mefenamic acid and DBS on the mechanical properties of mefenamic acid-loaded transdermal films, including UTS, elongation at break and folding endurance. The results of UTS, elongation at break and folding endurance are presented in **Table 1**. **Figures 1** - **3** show the 3D response surface and contour plot of model conditions of UTS, elongation at break and folding endurance, respectively of mefenamic acid-loaded transdermal films. The amount of silicone rubber, mefenamic acid and DBS exhibited a linear relationship with UTS that was inversely correlated; following such an increase in amount, UTS decreased (**Figure 1**). Meaning that a high concentration of silicone rubber, mefenamic acid and DBS close to level 1 of other variables might result in a low UTS. The model's significance was verified by the UTS's ANOVA results, which had adequate precision of 5.9576. The "predicted R-squared" value of 0.9645 and the "adjusted R-squared" value of 0.9589 were both quite close to the actual result [7]. The model's *F*-value of 4.21 indicated that it was significant, and the probability of a significant "*F*-value model" owing to noise was 0.01 %. The signal-to-noise ratio is measured and the range of anticipated values at the design points is compared to the average prediction error (a ratio larger than 4 is regarded acceptable) [17]. The ratio was more than 4, confirming the model's capability for projecting results inside the design area without the need for additional trials. The following equation should be used to predict the design space.

$$\text{UTS} = 12.43519231 - 0.8771875\,(\text{Silicone rubber}) - 0.763125\,(\text{Mefenamic acid}) - 0.033125\,(\text{DBS}) \quad (1)$$

The silicone rubber, mefenamic acid and DBS had significant effects on elongation at break (**Figure 2**) and folding endurance (**Figure 3**) depending on the amount of silicone rubber, mefenamic acid and DBS used. The elongation at break and folding endurance were quadratic models. In this instance, the model parameters "silicone rubber×mefenamic acid", "silicone rubber×DBS", "mefenamic acid×DBS", "silicone rubber^2", "mefenamic acid^2" and "DBS^2" were important (**Figures 2** - **3**). The model's significance was verified by the ANOVA results, which had adequate precision of 9.5849 and 4.2353 for elongation at break and folding endurance, respectively [7]. The ratio was more than 4, indicating that the model could predict results inside the design space without the need for additional tests. The design space should be predicted using the following equations.

$$\text{Elongation at break} = 42.61 + 54.01625\,(\text{Silicone rubber}) + 941.245625\,(\text{Mefenamic acid}) - 221.7896875\,(\text{DBS}) - 48.4475\,(\text{Silicone rubber}\times\text{Mefenamic acid}) + 7.7475\,(\text{Silicone rubber}\times\text{DBS}) + 2.429375\,(\text{Mefenamic acid}\times\text{DBS}) + 8.89578125\,(\text{Silicone rubber})^2 - 209.910625\,(\text{Mefenamic acid})^2 + 25.68984375\,(\text{DBS})^2 \quad (2)$$

$$\text{Folding endurance} = 294.25 + 88.3125\,(\text{Silicone rubber}) + 618.875\,(\text{Mefenamic acid}) - 252.0625\,(\text{DBS}) - 31.125\,(\text{Silicone rubber}\times\text{Mefenamic acid}) + 5.6875\,(\text{Silicone rubber}\times\text{DBS}) - 2.5\,(\text{Mefenamic acid}\times\text{DBS}) - 0.96875\,(\text{Silicone rubber})^2 - 128.375\,(\text{Mefenamic acid})^2 + 33.21875\,(\text{DBS})^2 \quad (3)$$

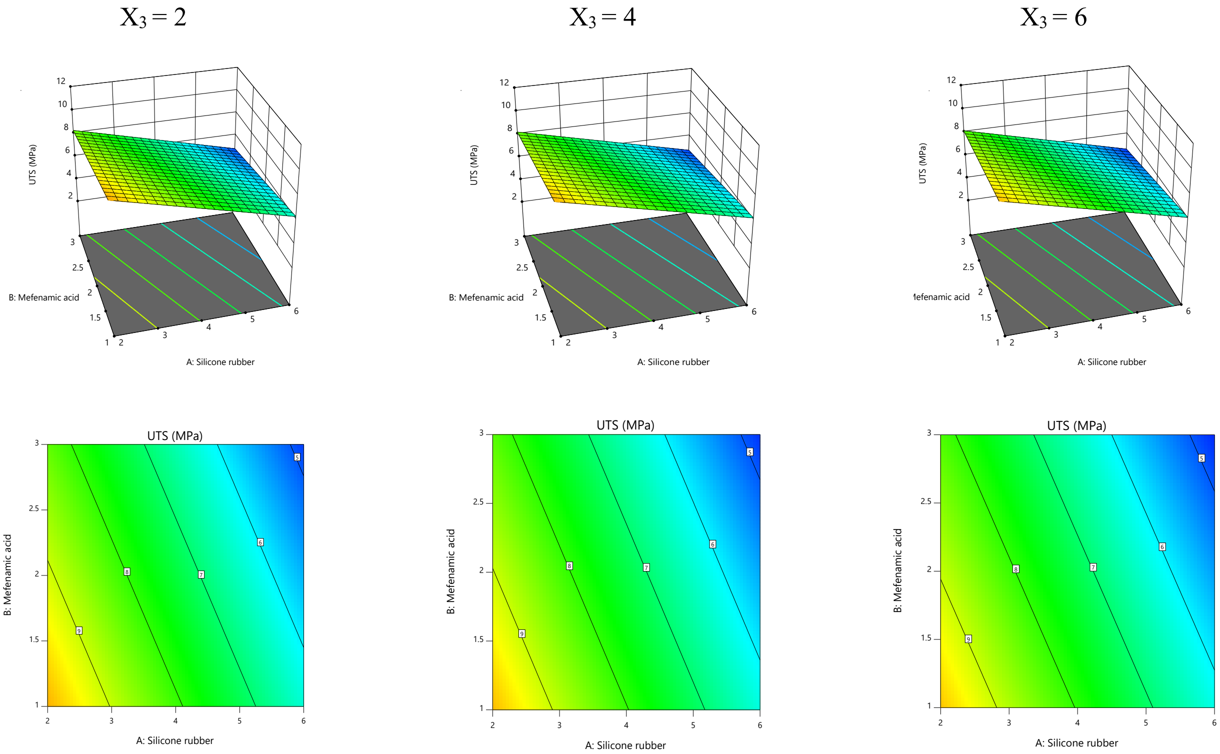

Figure 1 Model conditions of UTS of mefenamic acid-loaded transdermal films: (upper) 3D response surface and (lower) contour plot.

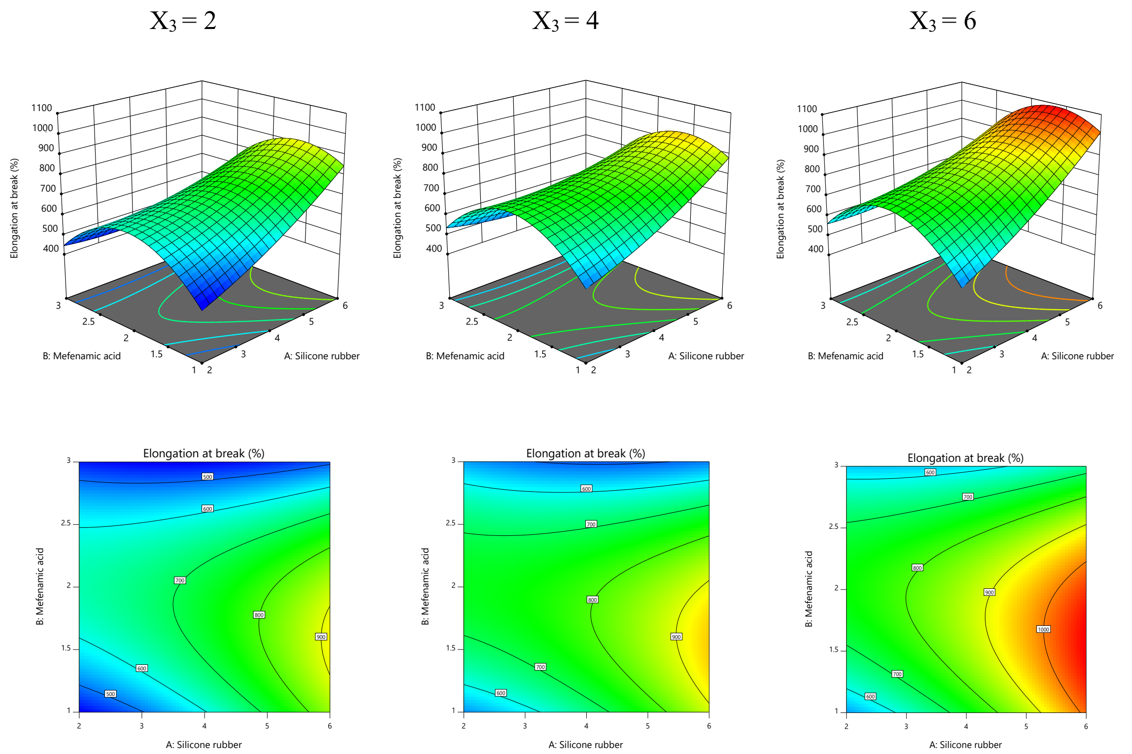

Figure 2 Model conditions of elongation at break of mefenamic acid-loaded transdermal films: (upper) 3D response surface and (lower) contour plot.

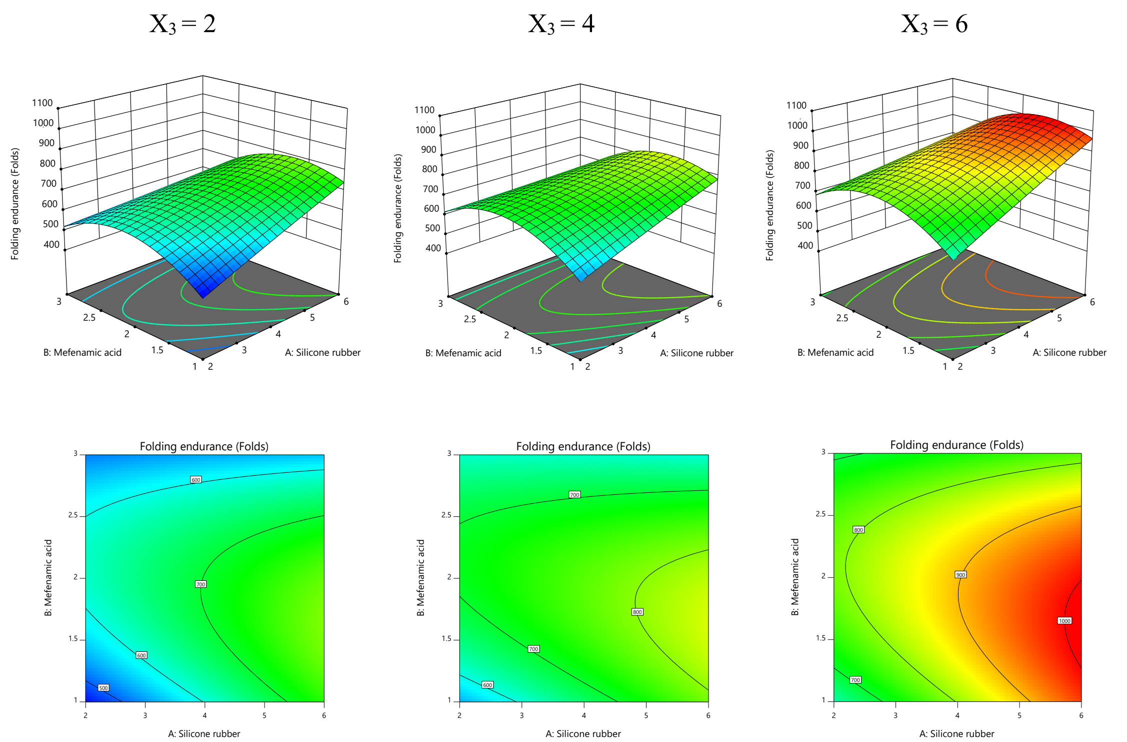

Figure 3 Model conditions of folding endurance of mefenamic acid-loaded transdermal films: (upper) 3D response surface and (lower) contour plot.

The linearity plot of the model ratios of the variables' predicted and actual values is shown in **Figure 4**, demonstrating a significant relationship.

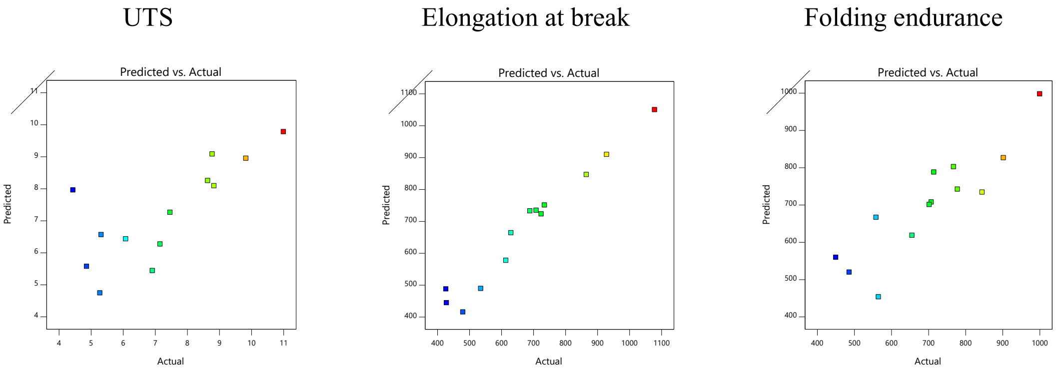

Figure 4 Predicted versus actual plots of model conditions of mefenamic acid-loaded transdermal films.

The DOE from Design-Expert® program version 11 could predict that 5.3: 2.5: 5.2 was the optimal amount of silicone rubber, mefenamic acid and DBS. UTS, elongation at break and folding endurance were all predicted to be 5.67 MPa, 758.86 % and 778 folds, respectively, for this optimized condition. The optimum amount was then made once again under the utilization conditions after that. **Figure 5**, the experimental values of UTS, elongation at break and folding endurance were 6.20 ± 0.50 MPa, 711.22 ± 102.00 % and 857 ± 64 folds, respectively. The prediction's percent errors were computed as [(Experimental value-predicted value/experimental value)×100] and were found to be 8.50, 6.70 and 9.28 %, respectively. Finally, the DOE from the Design-Expert® program was effective in proving a low percent error of prediction (less than 10 %), which was satisfactory and accepted for preparation.

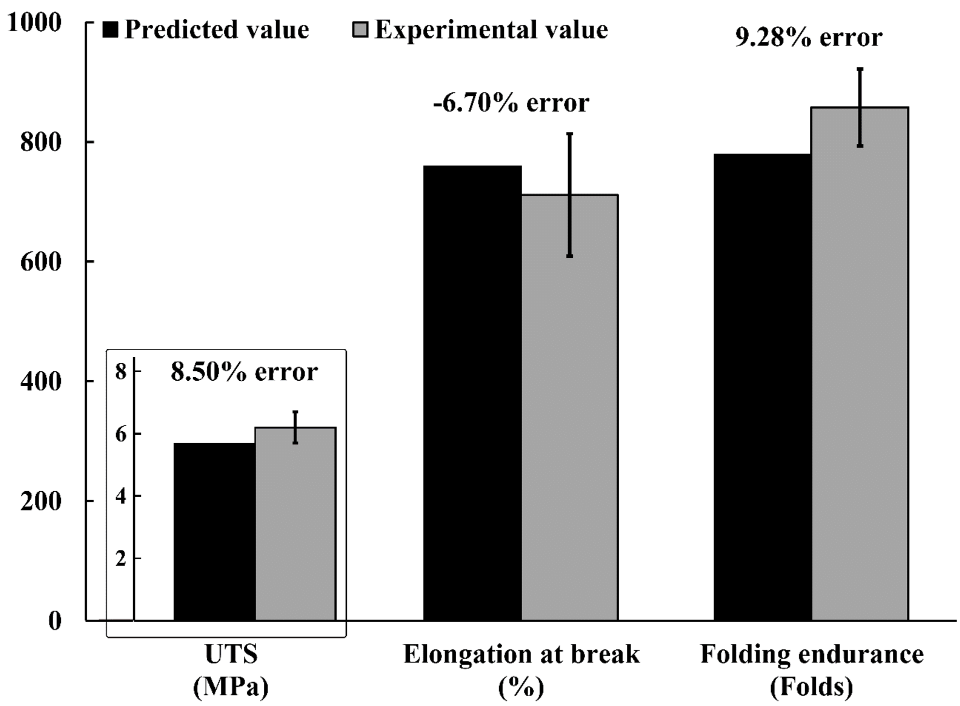

Figure 5 Predicted values, experimental values and percentage error of prediction.

Conclusions

Mefenamic acid-loaded transdermal films' mechanical properties, including UTS, elongation at break and folding endurance, were investigated and optimized by the Design-Expert® program version 11. (Stat-Ease, Inc, USA). The independent factors were silicone rubber, mefenamic acid and DBS, whereas the dependent variables were UTS, elongation at break and folding endurance. A linear model predicted the best correlation relationship for UTS with more precision, but quadratic models predicted elongation at break and folding endurance. The DOE could forecast that the optimal amount of silicone rubber, mefenamic acid and DBS was 5.3:2.5:5.2. For this ideal condition, UTS, elongation at break and folding endurance were all estimated to be 5.67 MPa, 758.86 % and 778 folds, respectively. The model's suitability for predicting outcomes inside the design space without the need for more trials was demonstrated by the ratio's value of prediction being greater than 4. The experimental findings for UTS, elongation at break and folding endurance were 6.20 ± 0.50 MPa, 711.22 ± 102.00 % and 857 ± 64 folds, respectively. It was established that the percent error was 8.50, 6.70 and 9.28 %, respectively. This formulation optimization for transdermal films containing mefenamic acid was successful and approved for preparation in drug delivery systems.

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