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Effect of Several Factors on the Mechanical Properties of Pressure-Sensitive Adhesives Used in Transdermal Therapeutic Systems

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ABSTRACT The effects of coating thickness, type of adhesive, and type and concentration of enhancer on the mechanical properties of two acrylic pressure-sensitive adhesives (PSAs) were investigated using a 2^4 factorial design and an optimization technique. Sixteen formulations containing 0% or 10% of either caprylic acid or methyl laurate in two different PSAs, namely Duro-Tak® 87-2196 and Duro-Tak® 87-2097, were prepared. The adhesive properties of these laminates were evaluated by applying the 90^0 Dynamic Adhesive Strength Peel Test (90^0 DASPT) and 180^0 Release Liner Peel Test (180^0 RLPT). Coating thickness, concentration of enhancer, and type of adhesive did affect the 90^0 DASPT. For the 180^0 RLPT, the most significant factors were coating thickness and concentration of enhancer, with a strong interaction observed between the two. Coating thickness and concentration of enhancer were also used to create mathematical models that correlated these factors with the mechanical properties of the PSAs. For this purpose, the optimization technique 3^2 was applied. It was found that the correlation of the above factors can be adequately described with polynomial equations, which can be used for predicting the mechanical properties of the laminates containing the above PSAs and methyl laurate (0%-10%).

KEYWORDS: Transdermal Drug Delivery, Pressure-Sensitive Adhesives, Penetration Enhancers, Factorial Design, Peel Force

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INTRODUCTION

Pressure-sensitive adhesives (PSAs) are materials that adhere to a substrate by application of light force and leave no residue when removed. PSA products are widely used for medical, hospital, first aid, athletic protection, and related applications. Hospital tapes, the oldest PSA application, are used to restrict movement or hold dressings in place. Other uses of PSA products include electrocardiagram and ostomy mounts; occlusive dressings; burn dressings; surgical drapes; protective pads, including various protective foot products; and grounding pads for electrosurgery. PSAs are also important components of transdermal drug delivery systems (TDDS), because they ensure intimate contact between the drug-releasing area of a TDDS and the skin surface, which is critical for controlled release of the drug [1].

Choosing a suitable PSA for a TDDS is not simple because the requirements are more demanding than those for a simple medical tape. PSAs are examined for their potential to produce skin irritation or sensitization. Another requirement is that PSAs must leave no residues when peeled off from either the release liner or the skin. Furthermore, the TDDS must be easy to remove from the release liner and from the skin, without causing pain that might discourage patients from using these products. In addition, PSAs must hold the TDDS at the appropriate body site for long periods of time. The above-described characteristics are strongly dependent on the mechanical properties of the PSAs [2].

Several materials have pressure-sensitive adhesive properties, but the major classes of PSA polymers are acrylics, silicones, and polyisobutylenes [3]. The acrylic PSAs have several desirable features, such as resistance to oxidation thermal degradation and moderate cost. They are permeable to water vapor and oxygen and generally exhibit good tack. In addition, their properties can be easily modified by incorporating different monomers during polymerization [4].

The properties of the PSA layer in a TDDS depend on the incorporated drug, the components of the TDDS (eg, backing film), the excipients (eg, penetration enhancers, solubilizers), and the chemical composition of the PSA. For a particular drug, the mechanical properties of the TDDS depend on the type and concentration of enhancer, the type of PSA, and the coating thickness. Several physical tests measure the adhesive properties of TDDS (eg, peel adhesion to stainless steel). The choice of the most appropriate test depends on patch design and components of the formulation [5].

The most common and necessary excipients of almost any formulation used for transdermal delivery are penetration enhancers, which are used to increase the permeation of drug molecules through the skin. The selection of an enhancer for a transdermal product should be based on its efficacy, lack of toxicity, and compatibility with other components of the TDDS [6,7].

The objective of this study was to investigate the effect of the coating thickness, type of adhesive, and type and concentration of enhancer on the mechanical properties of two acrylic PSAs using a 2^4 factorial design and an optimization technique.

MATERIALS AND METHODS

Materials

The following acrylic PSAs were used in this study: Duro-Tak® 87-2196 and Duro-Tak® 87-2097 (National Starch and Chemical Co, Bridgewater, NJ); caprylic acid (Sigma Chemical Co, St. Louis, MO); methyl laurate (Henkel, Germany); siliconized polyester film (Rexam Release, Netherlands); and polyethylene monolayer film CoTran® 9720 (3M Drug Delivery Systems, St. Paul, MN).

Factorial design

The factorial design [8,9] is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses. In this study, a 2^4 factorial plan was used to determine the effects of coating thickness, type of adhesive, and type and concentration of enhancer on the mechanical properties of two acrylic PSAs. The four factors and their levels are shown in **Table 1.** The levels for each factor are represented by a (-) sign for the low level and a (+) for the high level. The matrix of the factorial design is depicted in **Table 2.**

Table 1. Factors and Levels Used for the 2^4 Factorial Design

Factors	Levels*
(A) Coating thickness	(-) 0.127 mm
	(+) 0.381 mm
(B) Concentration of enhancer	(-) 0%
	(+) 10%
(C) Type of enhancer	(-) Methyl laurate
	(+) Caprylic acid
(D) Type of PSA	(-) Duro-Tak® 87-2196
	(+)Duro-Tak® 87-2097

*(-) = low level; (+) = high level.

Table 2. Matrix of the 2^4 Factorial Design

Formulation	Factor				90^0 DASPT	180^0 RLPT
(Patch)	A	B	C	D	Peel Force (gf/cm)	Peel Force (gf/cm)
(1)	(-)	(-)	(-)	(-)	387.7 (3.6)	4.599 (1.675)
(A)	(+)	(-)	(-)	(-)	555.7 (3.5)	6.388 (8.284)
(B)	(-)	(+)	(-)	(-)	342.4 (2.1)	4.117 (2.473)
(AB)	(+)	(+)	(-)	(-)	402.4 (2.8)	4.245 (5.508)
(C)	(-)	(-)	(+)	(-)	387.7 (3.6)	4.599 (1.675)
(AC)	(+)	(-)	(+)	(-)	555.7 (3.5)	6.388 (8.284)
(BC)	(-)	(+)	(+)	(-)	233.5 (6.9)	3.262 (3.720)
(ABC)	(+)	(+)	(+)	(-)	478.6 (9.5)	4.490 (6.860)
(D)	(-)	(-)	(-)	(+)	250.9 (5.0)	4.546 (6.245)
(AD)	(+)	(-)	(-)	(+)	250.9 (7.6)	6.779 (7.075)
(BD)	(-)	(+)	(-)	(+)	165.6 (7.3)	3.889 (4.514)
(ABD)	(+)	(+)	(-)	(+)	251.4 (10.0)	3.926 (10.655)
(CD)	(-)	(-)	(+)	(+)	250.9 (5.0)	4.546 (6.245)
(ACD)	(+)	(-)	(+)	(+)	250.9 (7.6)	6.779 (7.075)
(BCD)	(-)	(+)	(+)	(+)	188.3 (7.5)	3.595 (6.096)
(ABCD)	(+)	(+)	(+)	(+)	292.0 (6.2)	4.647 (10.859)

The levels of the factors were selected so that their relative difference would have a detectable effect on the response. A guide in choosing these levels is to consider the extremes of their useful range [9] and their practical application

Preparation of the matrices

The formulations were prepared according to a 2^4 factorial design. Sixteen formulations containing 0% or 10% of either caprylic acid or methyl laurate in two different PSAs, Duro-Tak® 87-2196 and Duro-Tak® 87-2097, were prepared. The release liner (siliconized polyester film) was held in place on a flat surface. A sample from each formulation was placed across the top edge of the release liner. The mixture was casted onto the release liner by drawing a multiple clearance film applicator AR 5315 (Pacific Scientific, Silver Spring, MD) with 0.127- or 0.381-mm clearance. The wet adhesive film was then dried in an oven (WTB binder, Germany) at 80^0C for 20 minutes. Then the backing film (polyethylene monolayer film) was placed on the top of the coatings. Rectangular patches of 10 cm^2 were die-cut and used for the measurements.

Evaluation of the adhesive properties

Several methods have been used to evaluate the adhesive properties of PSAs. According to Peterson et al [5], peel adhesion tests are commonly performed to determine the adhesion of a transdermal patch. The adhesive properties of the patches were evaluated using the Instron 4411 apparatus (Instron, UK) and by applying the 90^0 Dynamic Adhesive Strength Peel Test (90^0 DASPT) and 180^0 Release Liner Peel Test (180^0 RLPT) according to the American Standard Test Methods.

The objective of the 90^0 DASPT is to determine the peel force, in gram force per cm (gf/cm), needed to remove the TDDS from a standard stainless steel surface using a 90^0 peel angle with constant peel rate of 30.48 cm/min at constant temperature and relative humidity.

The objective of the 180^0 RLPT is to determine the peel force, in gram force per cm (gf/cm), needed to

remove the TDDS from the release liner using a 180^0 peel angle with constant peel rate of 30.48 cm/min at constant temperature and relative humidity.

Data analysis

Statistical evaluation of the data was performed applying one-way analysis of variance (ANOVA) at the 0.05 significance level using a commercially available software package (Statgraphics® Plus 4 Professional, Manugistics Inc, Rockville, MD.).

RESULTS AND DISCUSSION

Sixteen different formulations were prepared as described above.

The levels of factor A (coating thickness) represent the maximum and the minimum thickness normally used in TDDS manufacturing. The levels of factor B (concentration of the penetration enhancer) were chosen to examine the effect of enhancer incorporation into the system. The levels of factor C (type of enhancer) represent two enhancers from different chemical categories. Finally, for factor D (type of PSA), two commonly used acrylic adhesives with different chemical composition were chosen.

The adhesive properties of the patches were evaluated using the 90^0 DASPT and the180^0 RLPT; the average load/width (gf/cm) for each formulation is depicted in **Table 2.** In all cases the coefficient of variation for the peel force was less than 10.8%.

The main effects of the factors on the peel force and their interactions were calculated using Statgraphics® Plus 4 Professional. The results obtained for 90^0 DASPT and 180^0 RLPT are shown in **Table 3.** For the 90^0 DASPT, three factors were found to be statistically significant (P<0.05): coating thickness, concentration of enhancer, and type of PSA. The interactions between factors were not statistically significant.

Table 3. Main Effects or Interactions of the Factors on Mechanical Properties of PSAs

	90^0 DASPT		180^0 RLPT	
Factor	Main Effect or Interaction	P Value	Main Effect or Interaction	P Value
A	103.8	0.0052*	1.319	0.0003*
B	-67.0	0.0285*	-1.566	0.0001*
C	3.8	0.8688	-0.014	0.9257
D	-180.3	0.0004*	0.068	0.6549
AB	19.8	0.4089	-0.691	0.0049*
AC	25.4	0.3009	0.256	0.1360
AD	-56.4	0.0503	0.086	0.5747
BC	3.8	0.8688	-0.014	0.9257
BD	40.5	0.1254	-0.100	0.5168
CD	12.0	0.6089	0.138	0.3806

*Significant at P<0.05.

In the case of the 180^0 RLPT, two effects were statistically significant (P<0.05): coating thickness and concentration of enhancer. A statistically significant interaction was also observed between coating thickness and concentration of enhancer.

For both test methods, it was found that an increase in the amount of adhesive, which results from laminates with greater coating thickness, causes an increase in peel force for the same backing film (**Table 3**). The reason is that the peel force is directly proportional to the amount of adhesive under deformation and to the energy required to deform the backing film [10].

It is also evident from **Table 3** that the presence of penetration enhancer affected peel force, while the type of the enhancer did not. Wilking et al [11] reported that the inclusion of penetration enhancers in a matrix with acrylate or polyisobutylene or silicone PSAs often affects the mechanical properties of the system because enhancers act like plasticizers [12].

Furthermore, for the 90^0 DASPT, the use of Duro-Tak® 87-2196 rather than Duro-Tak® 87-2097 caused a decrease in peel force, as shown in **Table 3.** Both PSAs are acrylate-vinylacetate copolymers, but only Duro-Tak® 87-2196 has carboxylic acid groups as functional groups. Satas [10] has reported that the presence of carboxylic acid groups improves the adhesive bond between the adhesive and the substrate. The mechanism of this action is not clear, but it is assumed that the presence of the carboxylic acid groups helps to wet the adherent surface and causes hydrogen bonding between the PSA and the surface [10]. For the 180^0 RLPT the change in type of PSA had no effect on the peel force, probably because the polyester surface of the release liner used was more difficult to wet than the stainless steel surface employed in the case of 90^0 DASPT.

Panaitescu et al [13] studied the effect of coating thickness and type, and concentration of the penetration enhancer on the mechanical properties of an acrylic PSA, Duro-Tak® 87-2353. They too concluded that coating thickness and concentration of the enhancer had a statistically significant effect on the mechanical properties of the PSA for both tests.

Coating thickness and concentration of enhancer were also used to construct mathematical models that correlate these factors with the mechanical properties of the PSAs. For this purpose, the optimization technique 3^2 was applied [8].

For each PSA (Duro-Tak® 87-2196 and Duro-Tak® 87-2097), 9 formulations containing 0%, 5%, and 10% of methyl laurate were prepared as previously described and coated using 0.127 mm, 0.254 mm, and 0.381 mm wet thickness. The adhesive properties were evaluated by applying 90^0 DASPT and 180^0 RLPT. The results were further analyzed with multiple regression analysis using Statgraphics® Plus 4 Professional. The polynomial equations obtained correlate the coating thickness (X_1) and the concentration of methyl laurate (X_2) with the 90^0 DASPT and 180^0 RLPT peel force (Y):

- Laminates with Duro-Tak® 87-2196 and methyl laurate:

90^0 DASPT

$$Y = -95.4*\mathbf{X}_1-3.9*\mathbf{X}_2+1445.6*\mathbf{X}_1^2+0.3*\mathbf{X}_2^2-42.5*\mathbf{X}_1*\mathbf{X}_2+388.2$$

$r = 0.984$, SE = 21.4, $P<0.05$ **(Eq. 1)**

180^0 RLPT

$$Y=107.798*\mathbf{X}_1+1.89*\mathbf{X}_2-197.139*\mathbf{X}_1^2-0.183*\mathbf{X}_2^2-0.663*\mathbf{X}_1*\mathbf{X}_2-6.165$$

$r = 0.997$, SE = 0.364, $P<0.05$ **(Eq. 2)**

- Laminates with Duro-Tak® 87-2097 and methyl laurate

90^0 DASPT

$$Y = 913.6*\mathbf{X}_1-13.6*\mathbf{X}_2-1846.6*\mathbf{X}_1^2-0.1*\mathbf{X}_2^2+27.5*\mathbf{X}_1*\mathbf{X}_2+184.7$$

$r = 0.909$, SE = 31.2, $P<0.1$ **(Eq. 3)**

180^0 RLPT

$$Y = 8.037*\mathbf{X}_1+0.880*\mathbf{X}_2-8.349*\mathbf{X}_1^2-0.083*\mathbf{X}_2^2-0.868*\mathbf{X}_1*\mathbf{X}_2+4.260$$

$r = 0.854$, SE = 1.347, $P<0.1$ **(Eq. 4)**

The surface plots for equations 1 through 4 are shown in **Figures 1 through 4**, respectively.

Figures 1 and **3** show that peel force for 90^0 DASPT decreased while concentration of enhancer increased. Maximum peel force from laminates containing Duro-Tak® 87-2196 was obtained with 0.381-mm coating thickness and 0% concentration of methyl laurate, whereas maximum peel force from laminates containing Duro-Tak® 87-2097 was obtained for 0.254 mm coating thickness and 0% concentration of methyl laurate.

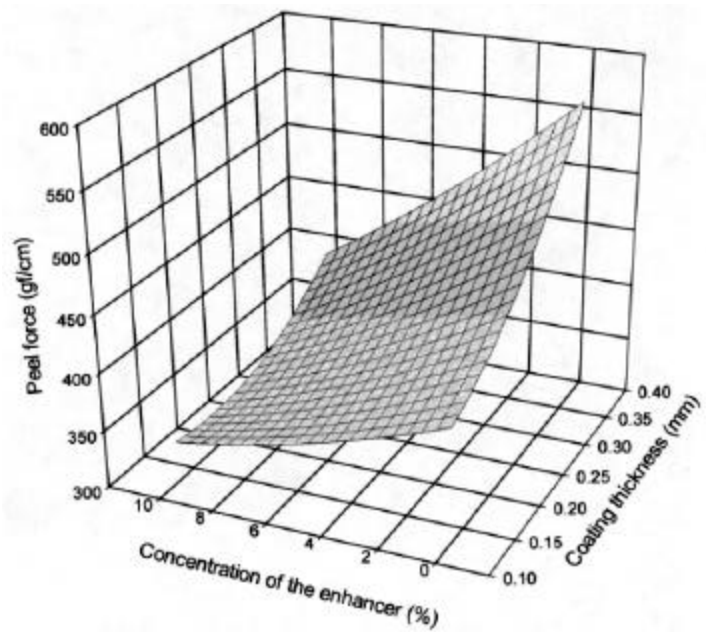

Figure 1. Effect of concentration of penetration enhancer and coating thickness on peel force (90⁰ DASPT) from patches with Duro-Tak® 87-2196 and methyl laurate.

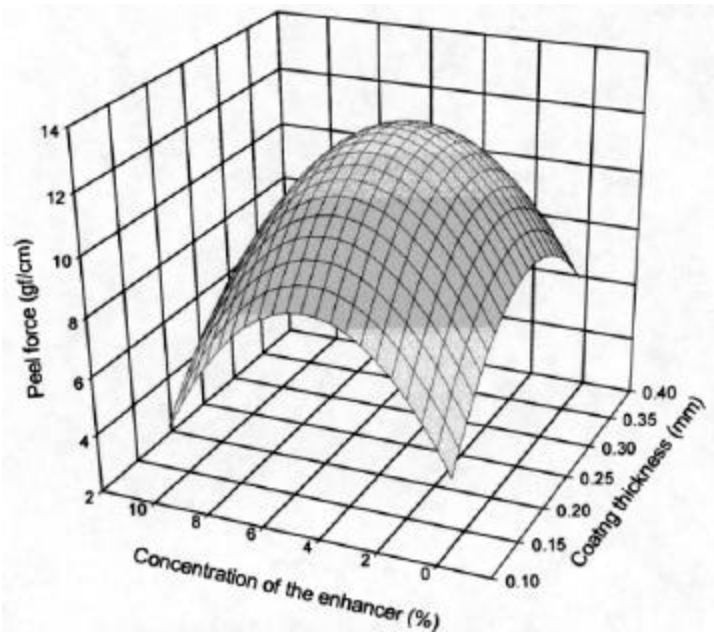

Figure 2. Effect of concentration of penetration enhancer and coating thickness on peel force (180⁰ RLPT) from patches with Duro-Tak® 87-2196 and methyl laurate.

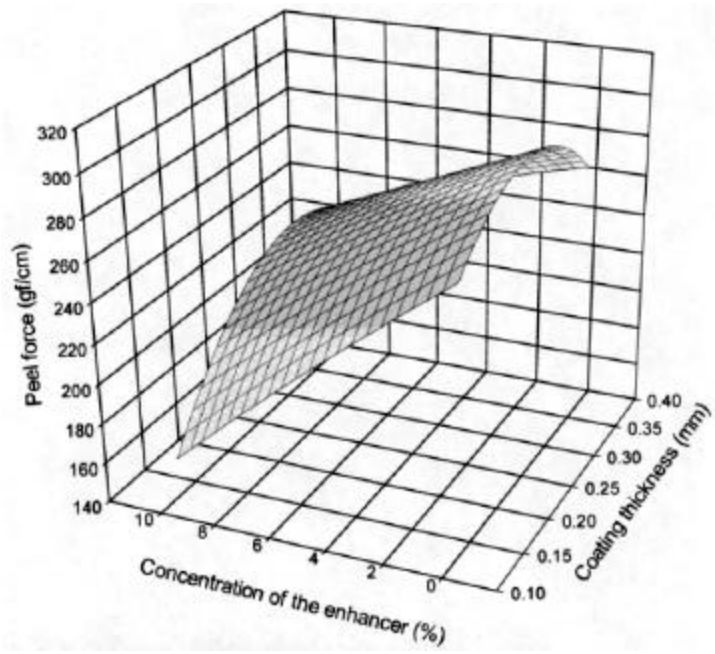

Figure 3. Effect of concentration of penetration enhancer and coating thickness on peel force (90⁰ DASPT) from patches with Duro-Tak® 87-2097 and methyl laurate.

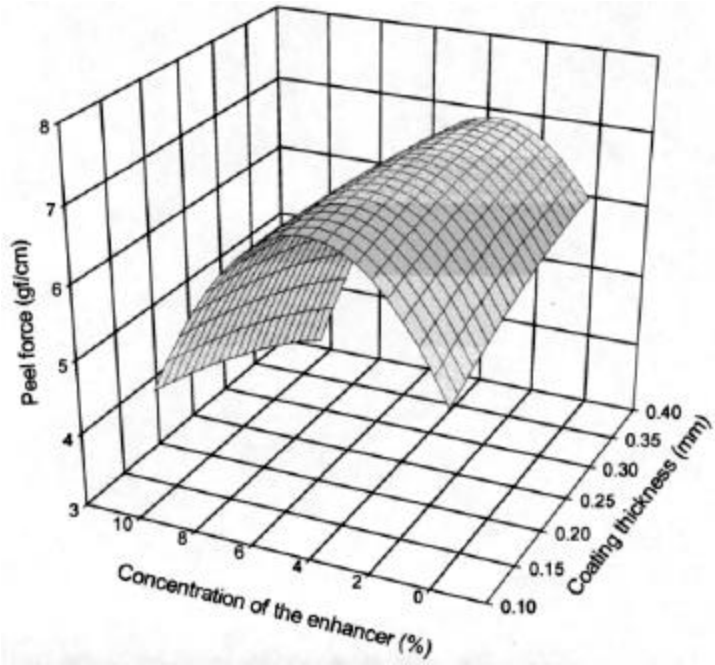

Figure 4. Effect of concentration of penetration enhancer and coating thickness on peel force (180⁰ RLPT) from patches with Duro-Tak® 87-2097 and methyl laurate.

Figures 2 and **4** show that the peel force for 180^0 RLPT increased when the concentration of methyl laurate increased from 0% to 5% and decreased when the concentration increased from 5% to 10% for both PSAs. For 180^0 RLPT, maximum peel force from laminates containing Duro-Tak® 87-2196 was obtained for 0.254-mm coating thickness and 5% concentration of methyl laurate, while for laminates containing Duro-Tak® 87-2097, maximum peel force was obtained for the 4% concentration of methyl laurate and 0.254-mm coating thickness.

To assess the reliability of the above-described equations, a series of additional experiments were conducted that varied the two independent variables (ie, coating thickness (X_1) and concentration of the penetration enhancer (X_2)) and estimated the dependent variable (ie, peel force (Y)). For each PSA (Duro-Tak® 87-2196 and Duro-Tak® 87-2097), two formulations containing 2.5% and 7.5% of methyl laurate were prepared and coated using 0.254-mm wet thickness. The adhesive properties were evaluated using 90^0 DASPT and 180^0 RLPT. The results are shown in **Table 4**, in which the experimental values are compared with the predicted values gained from equations 1-4. This table shows that there is good agreement between the predicted and the experimental values.

Table 4. Comparison Between Experimental and Theoretical Values (n = 5)*

Formulation	90^0 DASPT		180^0 RLPT	
	Experimental	Theoretical	Experimental	Theoretical
Duro-Tak® 87-2196 and 2.5% methyl laurate	431.8 (3.4)	422.2	9.744 (7.812)	11.657
Duro-Tak® 87-2196 and 7.5% methyl laurate	378.9 (2.8)	362.5	10.828 (3.926)	11.108
Duro-Tak® 87-2097 and 2.5% methyl laurate	239.4 (5.9)	280.2	5.894 (7.619)	6.891
Duro-Tak® 87-2097 and 7.5% methyl laurate	201.0 (1.8)	240.2	5.071 (0.472)	6.017

*Numbers in parentheses correspond to the coefficient of variation.

CONCLUSIONS

For the 90^0 DASPT, coating thickness, concentration of enhancer, and type of PSA affected the adhesive properties of the laminates. The interactions between the factors were not statistically significant. For the 180^0 RLPT, coating thickness, concentration of enhancer, and their interactions were statistically significant. These findings suggest that all the above factors should be considered during the developmental phase of TDDS. The choices of appropriate type and concentration of enhancer and coating thickness are extremely important because they determine the release profile of the drug from the system.

Furthermore, the correlation between coating thickness and concentration of penetration enhancer can be sufficiently described with polynomial equations. The validation of the equations showed that they can be used for predicting the mechanical properties of the laminates containing Duro-Tak® 87-2196, Duro-Tak® 87-2097, and methyl laurate (0%- 0%) with 0.127–0.254 mm coating thickness.

Finally, the application of experimental design techniques, such as factorial design and optimization, was useful for identification and correlation of the significant factors that affect the mechanical properties of the TDDSs.

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