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Preparation and In Vitro Evaluation of a New Fentanyl Patch Based on Acrylic/Silicone Pressure-Sensitive Adhesive Blends

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In this study, the influence of the ratio of silicone (Si) to acrylic pressure-sensitive adhesive (PSA), polyvinyl pyrrolidone (PVP), and lauryl alcohol (LA) % (wt/wt) on the properties of a drug in adhesive patch containing 4% (wt/wt) fentanyl as model drug was evaluated. The dependent variables selected were drug solubility, in vitro drug release in the platforms as well as adhesion properties including peel strength and tack value. By using the central composite design of Design Expert software, it was found that the effect of each factor was different, yet all had influenced dependent variables significantly ($p < .05$). Quadratic model generated for various response variables using backward regression analysis was found to be statistically significant ($p < .05$). It was deduced that the presence of PVP and Si displayed similar trends on drug solubility and release. Each role played by Si with LA and PVP in release rate was separately investigated, and it was found that the presence of PVP and LA in lowering the amount of drug released was more dominant compared with that of Si. The release patterns at the early and later stages follow the Higuchi and semiempirical models, respectively. Effect of PVP as well as Si and LA were similar on tack value. The influence of LA compared to peeling characteristics of Si system was more pronounced.

Keywords fentanyl; patch; central composite design; blend; pressure-sensitive adhesive

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INTRODUCTION

Fentanyl, a potent narcotic analgesic, is used clinically to relieve acute postoperative and chronic cancer pain. Fentanyl was developed in 1960s in a search for an intravenous anesthetic agent. It was a synthetic opioid in the phenyl piperidine series and is most closely related to meperidin. Fentanyl is 100 times more potent than morphine (Bagheri Haghi, Khalilian, & Rouini, 2006; Consuelo, Falson, Guy, & Jasques, 2007; Evaristo, & Fabio, 2003; Huynh, Tyrefors, Ekman, & Johansson, 2004; Mehdizadeh, Ghahremani, Ruini, & Toliate, 2006; Mehdizadeh, Toliate, Ruini, Abaszadeh, & Dorkoosh, 2004; Roy, Gutierrez, Flymn, & Clearly, 1991; Sloan, Moulin, & Hays, 1998). Transdermal drug delivery systems (TDDSs) may offer an attractive alternative for the delivery of drugs such as fentanyl, which undergoes a presystemic metabolism in the gastrointestinal intolerance, reduce the first-pass liver metabolism, and eliminate the need for intravenous access (Mehdizadeh et al., 2006). Several factors should be considered before choosing an appropriate design for a particular device: drug solubility, release rate, and adhesion properties. Preparation of TDDSs consists of three basic designs: membrane control or reservoir patches, matrix patches (MPs), and drug in adhesive patches (DIAPs). For a number of years, fentanyl TDDS has been on the market. This system is of the type known as reservoir system. In this specific case (Duragesic® TTS), fentanyl is in solution in a mixture of ethanol and water. However, reservoir systems have a major disadvantage, namely that in the event of a leakage (e.g., a simple mechanically induced damage, a cut or tear, and splitting of the weld seam) in the pouch containing the active substance formulation, the active substance may come into

contact with the skin over a large area and as a consequence of this contact, it may be absorbed in excessive doses. Specially, in the case of fentanyl and the fentanyl analog derivatives, it is potentially fatal, as an overdose leads very rapidly to respiratory depression and hence fatal incidents (Muller, 2004).

Fentanyl DIAPs or MPs are preferred because they are relatively simpler to manufacture (Miranda & Sablotosky, 1999); overall function is achieved by bringing together the required functions into a single component of an adhesive polymer and more comfortable to wear compared with reservoir-type devices (Goulding, 1994; Guyot & Fawaz, 2000).

All TDDS include a pressure-sensitive adhesive (PSA) layer to hold the patches on the skin (Mehdizadeh et al., 2006). PSAs adhere to a substrate by application of a light force and leave no residue when removed (Miller, Govil, & Bhatia, 2006). Choosing a suitable PSA for TDDS is not simple because several requirements should be met. These requirements include no skin irritation or sensitization or residue when peeled off from skin and easy removal from the skin without causing pain. The physicochemical characteristics of a drug-adhesive combination such as solubility in adhesive may be determined by selecting a suitable adhesive for the drug (Kandavilli, Nair, & Panchagnula, 2002; Miranda & Sablotosky, 1999). Usually, the PSAs used for TDDs are based on acrylic, silicone (Si), and poly(isobutylenes) (PIBs). Acrylic and Si PSAs have several desirable features such as resistance to oxidation, permeability for water vapor and oxygen, good tack behavior, and moderate cost. Although Si group of adhesives has an outstanding combination of biocompatibility and ease of fabrication for hydrophilic drug (Colas, Gary, Valencia, & Thomas, 2005; Kandavilli et al., 2002; Lin, Durfee, Ekeland, Vie, Schalau, 2007), PIBs show chemical inertness and good resistance to weathering, ageing, heat, and chemicals. The structure of the close and unstrained molecular packing leads to the low air, moisture, and gas permeability of PIBs. The higher the molecular weight of the PIB, the lower would be its permeability. PIBs are, therefore, preferred for drugs with low solubility parameters (Tan & Pfister, 1999).

Polyvinyl pyrrolidone (PVP) is commonly used to form solid dispersion pharmaceutical systems, and it is reported that more than 60 different types of drugs have been dispersed in this polymer (Ford, 1986). PVP inhibits crystallization in both solution and amorphous solid dispersion (Sekikawa, Nakano, & Arita, 1978; Yoshioka, Hancock, & Zografi, 1995). Lauryl alcohol (LA), as a skin permeation enhancer, has the best performance in fentanyl TDDS (Evaristo & Fabio, 2003).

In new generation of DIAPs, the blend of at least two polymers is used. The advantages of these systems are small size, proper adhesion, and low irritation. However, there are some patents that have evaluated the effect of acrylic/Si composition PSA blends on the release behavior of hydrophilic and hydrophobic drugs (Dunbar & Sharma, 2000; Miranda & Sablotsky, 2001). To the best of our knowledge, there is no report published up till now on the effect of acrylic/Si composition of PSA blend on release behavior of fentanyl and adhesion properties of these systems.

The aim of this research was to study the effect of formulation variables on the design of an acrylic/Si-based PSA blend for transdermal delivery system of fentanyl as a model drug. For this purpose, the effects of acrylic, Si, PVP, and LA concentrations on the drug solubility, release rate, and adhesion properties are evaluated using Design Expert 6.0.6 software.

MATERIALS AND METHODS

Materials

PVP k27/23 (Rahavard Tamin Co., Tehran, Iran), Gelva 737 acrylic adhesive (Solutia Inc., St. Louis, MO, USA), Si Adhesive 7-4503 (Dow Corning Corporation, Midland, MI, USA), poly(ethylene terephthalate) as a backing layer with thickness of 80 μm (Daro Pat Shargh Co., Tehran, Iran), LA (Fluka, St. Louis, MO, USA), fentanyl base (Diosynth B.V., Kloosterstraat, the Netherlands), and all other materials were of high-performance liquid chromatography (HPLC) grades.

Sample Preparation

A general method employed for sample preparation was as follows: According to Table 1, an appropriate amount of acrylic PSA and PVP were mixed first. Then, Si PSA, fentanyl, and LA were added to the above mixture (samples for evaluating fentanyl solubility were prepared without drug) and mixed together in a rotary mixer. The formulation was coated onto a backing layer by film applicator (elcometer 3580 SPRL 75 mm) to a controlled dried thickness (70 μm). The coated product was then placed in an oven at 50°C for 45 min to drive off volatile solvents, which were all the component parts of the adhesives (isopropanol, ethylacetate, and n-heptane).

Drug Solubility in Adhesive

Adhesive films without drug were prepared with specified thickness by the method described earlier. These films were immersed in the fentanyl-saturated free base solution in pure water at 32°C for at least 2 weeks to reach equilibrium. Then, each film was removed from the solution, and the exposed surface was rinsed with buffer (pH 6) solution and dried. Based on the obtained saturation concentration value of fentanyl in buffer solution (104 ppm) and sink condition (Roy et al., 1991), the dried film was transferred to a glass bottle and 15 mL of fresh phosphate buffer (pH 6) was added to release the absorbed drug from the adhesive. The solution was stirred for 48 h to facilitate the release of the drug into buffer medium. A 5-mL sample was withdrawn and evaluated by HPLC. To eliminate all the existing drug component of the patches, the above patch samples were placed into the blank solution of buffer (pH 6) for a long time before each HPLC test. The solubility of fentanyl in

TABLE 1
Independent Variables Percentage (% wt/wt)

	Factor 1		Factor 2		Factor 3
	A : Si (wt/wt) %		B : PVP (wt/wt) %		
Run	a[1]	b[2]	a[3]	b[4]	C : LA (wt/wt) %
1	75.6	90	0	0	12
2	41.4	50	6.3	15	6
3	79.7	90	1.3	15	6
4	41.4	50	6.3	15	6
5	83.5	90	2.9	30	0
6	7.9	10	10.7	15	6
7	6.5	10	17.8	30	12
8	45	50	0	0	6
9	7.5	10	20.1	30	0
10	44.6	50	6.6	15	0
11	8.4	10	0	0	12
12	41.4	50	6.3	15	6
13	9.6	10	0	0	0
14	41.4	50	6.3	15	6
15	38.7	50	11.7	30	6
16	41.4	50	6.3	15	6
17	39	50	5.8	15	12
18	73.3	90	2.4	30	12
19	86.4	90	0	0	0
20	41.4	50	6.3	15	6

All formulations contain 4 (%, wt/wt) fentanyl.
[1]Si percentage in the formulation.
[2]Si percentage is based on the Si/acrylic PSA blend.
[3]PVP percentage in the formulation.
[4]PVP percentage is based on the acrylic PSA.

each sample was determined from the total amount of drug released into buffer divided by the geometrical volume of the patch.

Drug Analysis

Fentanyl released from DIAPs was determined by HPLC (Younglin, SDV30) with UV detector at 207 nm. HPLC separation system consisted of a PerfectSil Target (column 150 × 4.6 mm; i.d., 5 μm), equipped with a guard column. The mobile phase consisted of 10 mM MeCN/K_2HPO_4 (in the ratio 80 : 20), which was adjusted to pH of 6.0 ± 0.1 by the addition of H_3PO_4. The flow rate of mobile phase was 1 mL/min. For preparing the standard curve, solutions of 0.5, 1, 2, 3, 4, 5, 6, 8, and 10 μg/mL of fentanyl were prepared by spiking of materials at nine aforementioned concentrations and drawing the linear calibration curve (R^2 = .9998). The specificity for assay was established using the three sequential replicates of solution, which were used in standard curve.

Drug Release

The release of fentanyl from DIAPs was measured in a hydrodynamically well-characterized Chien permeation system at 37°C (Perme Gear Inc., Bethlehem, PA, USA). A sodium phosphate buffer (pH 6) was prepared and heated to 37°C before being tested as a release medium. For the determination of the fentanyl release profile, each sample was mounted in the orifice of a half-cell of the Chien permeation system. At different intervals, from 0.25 to 48 h, the release medium was completely withdrawn and immediately replaced with a fresh solution and assayed by an HPLC-UV method.

Probe–Tack Test

Tack tests were carried out for adhesive tapes with different thicknesses according to ASTM D3121 by using Chemie Instruments Probe-Tack PT-500 (Fair field, OH, USA) for at least four samples.

Peel Strength Measurement at 180°

Peel tests were carried out according to the ASTMD3330 on adhesive-coated tapes with 25 mm width. After preparation of PSA tape/stainless-steel joints, they were stored at room temperature for 20 min. Peel force in 180° directions was measured at a peel rate of 5 ± 0.2 mm/s at room temperature using Chemie Instruments adhesive/release tester AR-1000. The test was accomplished at least three times for each sample.

Experimental Design

The response surface methodology using central composite design with $\alpha = 1$ was designed to estimate the coefficient of a quadratic model for some experimental formulations that were needed to run only three levels of each factor (Bostedt, Fischer, & Leichs, 2004). For this study, Design Expert software (version 6.0.6; State Ease Inc., Minneapolis MN, USA) was used. Good fit of the model was tested using analysis of variance, the prediction multiple correlation coefficient (prediction R^2), adjusted R^2, and the lack of fit, provided by Design Expert software, were used as factors for selection of adequate models (Jovanovic, McKenna, & Dubé, 2004; Kim et al., 2007; Singh, Chakal, & Ahuja, 2006). The quadratic was selected as a good fit for the model. The effect of Si (A), LA (B), and also PVP (C) concentrations on the solubility, release, tack as well as the peel values were evaluated. A polynomial model including interactions and quadratic terms was given as

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2,$$

where Y is the measured response associated with each factor level combination and β_0 is an intercept representing the arithmetic average of all quantitative data obtained by 20 runs. β_1–β_{33} are regression coefficients, and X_1, X_2, and X_3

are independent variables. Positive or negative signs before the coefficient in quadratic models indicate a synergistic effect for the factor. The dependent and independent variables selected are shown in Table 1 along with their low, medium, and high levels selected for this study. Table 2 summarizes an account of 20 experimental runs studied with independent variable and corresponding responses.

RESULTS AND DISCUSSION

Solubility Studies

The solubility of fentanyl in 20 experimental formulations was determined and summarized in Table 3. In this work, the drug released was modeled with backward regression starting with a special quadratic model. There was no lack of fit for this model. The adjusted R^2 was .87 and the prediction R^2 was .78. *A*, *B*, *C*, A^2, B^2, and *AC* were the significant terms of model ($p < .05$). The final model for fentanyl solubility in the samples followed as the equation:

$$\begin{aligned}\text{Drug solubility} = {} & +39.01172 + 1.62578\,(\text{Si}) - 6.53833(\text{PVP}) \\ & + 0.4812\,(\text{LA}) - 0.01582\,(\text{Si}^2) \\ & + 0.2052\,(\text{PVP}^2) + 0.02604\,(\text{Si})\,(\text{LA}).\end{aligned}$$

TABLE 2
Normalized Response Values

Run	Response 1 (Peel)	Response 2 (Release)	Response 3 (CP)	Response 4 (Tack)
1	13	67	98	8
2	74	65	38	100
3	65	60	20	67
4	65	60	29	90
5	65	83	54	1
6	100	55	10	78
7	43	62	54	43
8	65	78	100	70
9	52	75	44	7
10	50	80	39	55
11	35	69	58	9
12	74	66	30	90
13	65	75	50	14
14	74	65	30	100
15	74	70	73	78
16	68	66	38	100
17	26	68	60	60
18	43	64	74	7
19	30	100	50	7
20	72	66	38	89

TABLE 3
Drug Solubility Data and Their Normalized Values

Run	C_p (μg/cm$^{3)}$	Normalized C_p
1	36,748	98
2	14,250	38
3	7,500	20
4	10,875	29
5	20,249	54
6	3,750	10
7	20,249	54
8	37,500	100
9	16,500	44
10	14,625	39
11	21,750	58
12	11,250	30
13	18,750	50
14	11,250	30
15	27,375	73
16	14,250	38
17	22,500	60
18	27,750	74
19	18,750	50
20	14,250	38

The response surfaces and contour plots in Figure 1 show the effect of Si, PVP, and LA on drug solubility in the blends. The same plots in Figure 1 also show that when the Si percentages in the blend are increased up to 70%, fentanyl solubility in the polymer matrices increases. At higher concentrations of Si, the solubility values of blends are decreased. Addition of LA to Si has had a synergistic effect and therefore the solubility is increased. At lower percentages of PVP of 0–15% (wt/wt), the rate of solubility is lowered and by higher amount of PVP up to 30% (wt/wt), the solubility of fentanyl is increased in the matrix. The formulations that contained 70 and 12% (wt/wt) of Si and LA have shown maximum solubility values. Minimum solubility was observed in the formulation that included 10% (wt/wt) Si with no PVP and LA. Possible interactions were investigated by FT-IR spectroscopy (Equinox 55; Bruker, Ettlingen, Germany) on every two components of the patch system. As most of the patch components had similar functional groups that could enter into hydrogen bonding, it would have been impossible to distinguish the source of bonding in mixtures with more than two components by FT-IR spectroscopy. Figure 2 shows FT-IR spectroscopy (Equinox 55; Bruker) recorded at room temperature for neat PVP, LA, and fentanyl and a series of PVP/fentanyl, fentanyl/LA, and PVP/LA mixtures, respectively.

Taking into account the chemical structure of the pure PVP, which possesses the absorption band close to 1654 cm^{-1} is called amide-I, and is a combined mode with the contribution of

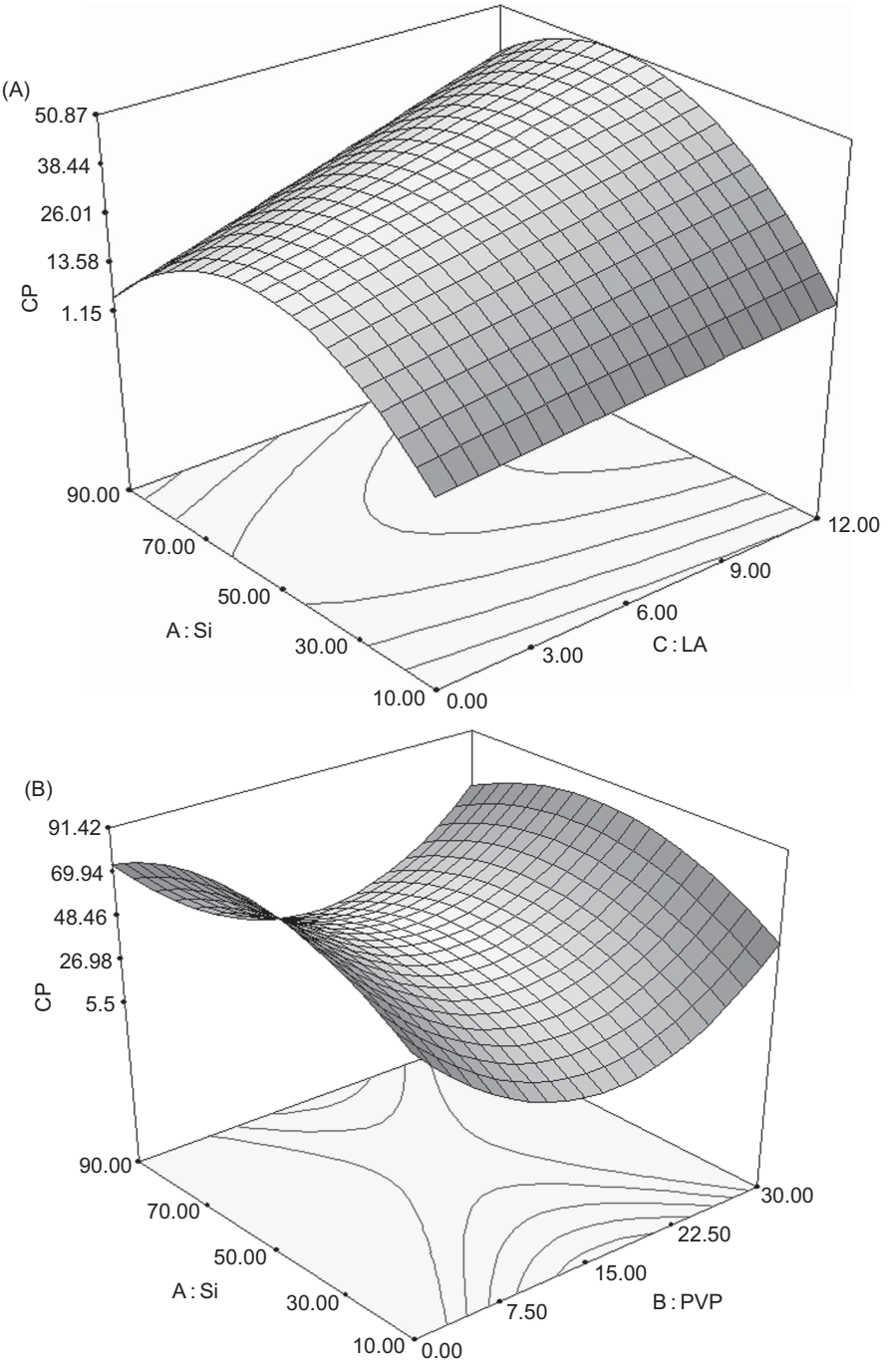

FIGURE 1. Response surfaces and contour plots of drug solubility (A) versus Si and LA in PVP = 15% and (B) versus Si and PVP in LA = 6%.

C=O and C–N stretches. Owing to this combination mode, the band occurred at a lower wavenumber than expected for pure ester carbonyl band (1,700–1,750 cm^{-1}) (Lau & Mi, 2002). The reason that the carbonyl stretching band of neat PVP obviously broadens and shifts to a lower frequency is because of the strong self-association of PVP molecules.

The stretching band of fentanyl's carbonyl amide groups is observed at 1,657 cm^{-1}. FT-IR spectroscopy of mixture of PVP/fentanyl shown implies that there is no interaction between PVP and fentanyl because there was no shift in the main peaks of the mixture compared to the pure material.

The absorption band at near 3,380 cm^{-1} in the spectrum of LA in Figure 2 belongs to hydroxyl group of LA. As it is seen in spectrum of PVP/LA, there are two peaks at 3,360 and 1,664 cm^{-1} that can be attributed to the hydrogen-bonded hydroxyl group of LA and carbonyl group of PVP. The

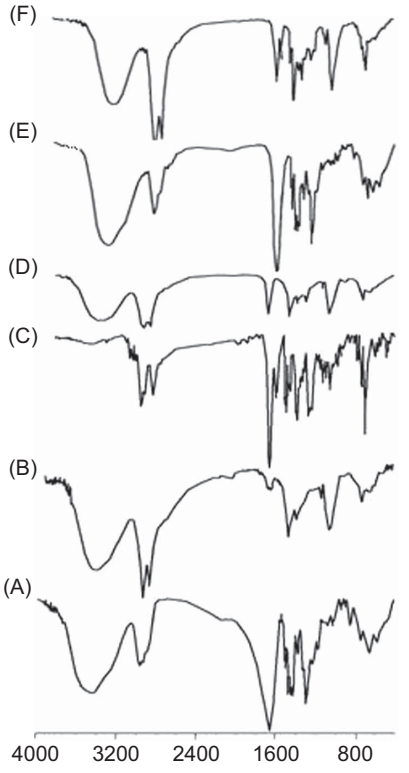

FIGURE 2. FT-IR spectrum of (A) PVP, (B) LA, (C) fentanyl, (D) PVP/LA, (E) PVP/fentanyl, and (F) fentanyl/LA mixtures.

TABLE 4
Cumulative Drug Released Data and Their Normalized Values

Run	Release[a] (μg)	Normalized Release
1	518	67
2	503	65
3	464	60
4	464	60
5	643	83
6	425	55
7	479	62
8	603	78
9	580	75
10	619	80
11	534	69
12	511	66
13	580	75
14	503	65
15	541	70
16	511	66
17	526	68
18	495	64
19	773.7	100
20	511	66

[a]Cumulative release recorded at 48 h.

absorption peaks at 3,360 and 1,639 cm^{-1} in the spectrum of fentanyl/LA are attributed to the hydrogen-bonded hydroxyl group of LA and carbonyl group of fentanyl. FT-IR studies confirm hydrogen bonding between LA and fentanyl, which is an indication of higher solubility of the drug in the adhesive by the addition of LA.

Regarding PVP, it has been suggested that a polymer such as PVP, with a high T_g (Yoshioka, Hancock, & Zografi, 1995), will raise the T_g of the mixture, and therefore, it decreases the mobility of the phase. As a result it reduces the tendency to crystallization of drug as an antinucleating agent, and hence it plays a significant role in improving the solubility of the drug in TDDSs (Taylor & Zografi, 1997). According to Figure 1B, PVP initially decreases the solubility of fentanyl in the adhesive, which can be related to the decrease in concentration of free PVP. Because PVP at the higher concentration reacts with LA through hydrogen bonding, at the constant amount of LA, however, free PVP is increased and it improves the drug solubility in the adhesive system.

In Vitro Drug Release Studies

In vitro drug release from 20 formulations containing 4% (wt/wt) fentanyl was studied, and the results are summarized in Table 4 and related profiles are shown in Figure 3. The drug release values and the effect of Si, PVP, and LA are determined by the same method and their response surfaces and contour plots are shown in Figure 3. By using backward regression with quadratic model, there is no lack of fit for this model. The adjusted R^2 and prediction R^2 are .89 and .73, respectively, and parameters of A, B, C, A^2, B^2, C^2, and AC are statistically significant. The final model for drug release is as follows:

$$\begin{aligned}\text{Drug release} = {} & 71.45 + 0.7076\,(\text{Si}) - 1.364\,(\text{PVP}) \\ & - 3.203\,(\text{LA}) - 5.198\text{E}(-3)\,(\text{Si}^2) \\ & + 0.22727\,(\text{LA}^2) + 0.036364\,(\text{PVP}^2) \\ & - 0.016146\,(\text{Si})\,(\text{LA}).\end{aligned}$$

Data obtained from release studies were fitted to various kinetic equations such as the kinetic models of zero-order equation ($Q_t = Q_0 - K_0 t$), Higuchi equation ($Q_t = K_h t^{0.5}$), and Korsmeyer Peppas equation, log Q_t versus log t, where Q_t is the cumulative amount of drug released at time t per unit of exposed area; Q_0, the initial amount of drug in fentanyl patch; K_0, the zero-order release rate constant; K_h, the diffusion rate

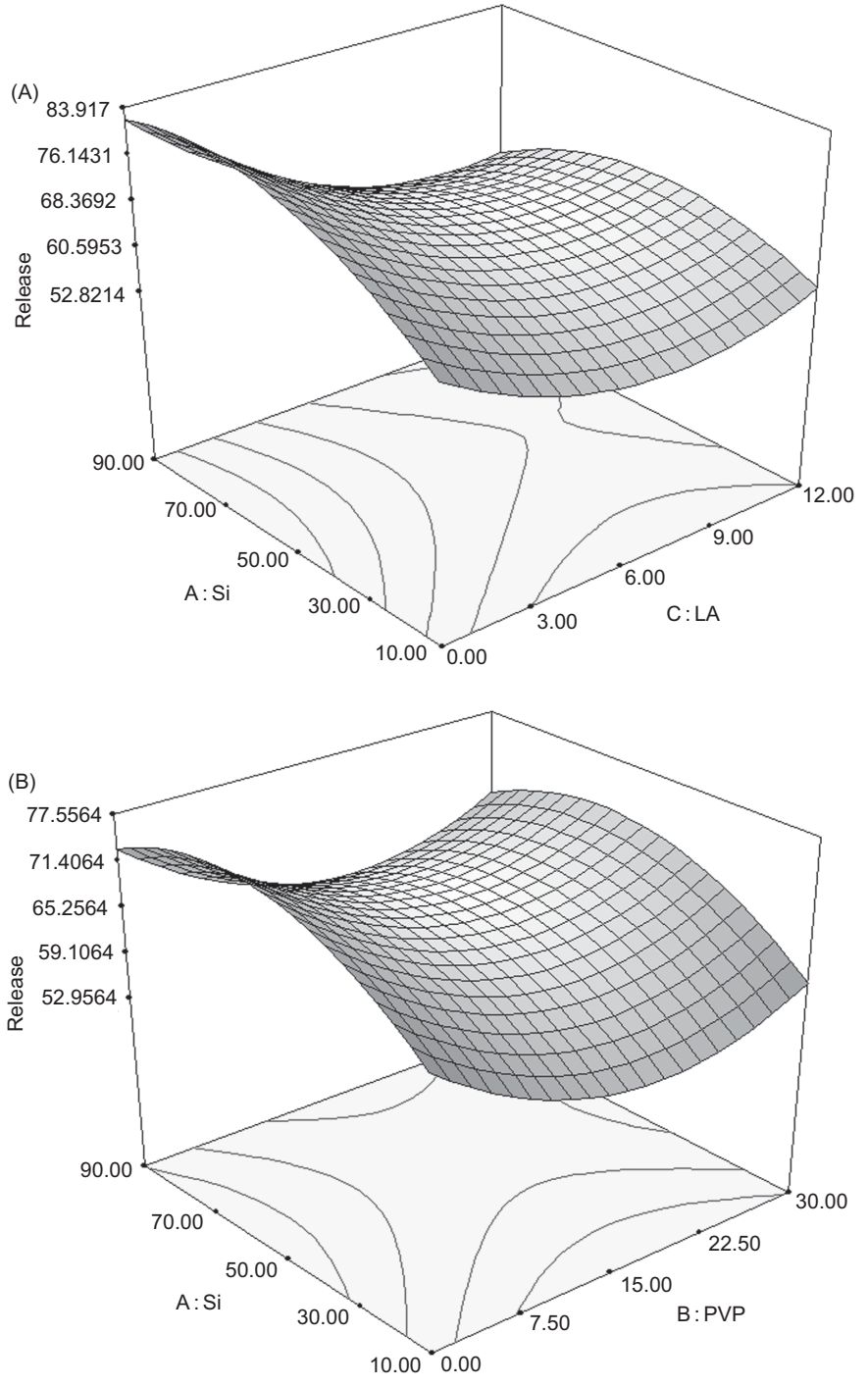

FIGURE 3. Response surfaces and contour plots of drug released (A) versus Si and LA in PVP = 15% and (B) versus Si and PVP in LA = 6%.

constant; and K_p the Korsmeyer Peppas release rate constant. The R^2 for these equations are shown in Table 5.

By further investigation, it was also found that the formulations follow Higuchi equation after at most 4 h of release time and then would follow Korsmeyer Peppas equation, as shown in Table 6. The amount of drug released from the matrix device can be predicted from the Higuchi Eq. 1 for large (C_0/C_p) (Papadokostaki & Petropoulos, 1997):

$$Q_t = (2DC_pC_{0t})^{0.5}\frac{1-C_p}{6C_0}, \quad (1)$$

TABLE 5
Results of Kinetic Model Fitting for Different Formulations of Fentanyl Patch

No. of Formulations	Higuchi R^2	Korsmeyer Peppas R^2	Zero-order R^2
1	.75	.83	.59
2	.74	.80	.71
3	.83	.90	.67
4	.84	.80	.71
5	.89	.75	.74
6	.82	.87	.66
7	.73	.85	.56
8	.84	.92	.67
9	.90	.94	.76
10	.90	.95	.75
11	.75	.86	.59
12	.84	.80	.71
13	.93	.95	.79
14	.84	.80	.45
15	.84	.89	.70
16	.84	.80	.71
17	.84	.88	.68
18	.77	.87	.60
19	.98	.97	.87
20	.84	.80	.71

R^2, determination coefficient.

TABLE 6
Results of Kinetic Model Fitting for Different Formulations of Fentanyl Patch

	Higuchi		Korsmeyer Peppas		
No. of Formulations	R^2	K_h ($\mu g/cm^2/h^{0.5}$)	R^2	K_p ($\mu g/cm^2/h^n$)	n
1	.990	149	.990	149	0.10
2	.993	100	.991	103	0.18
3	.998	137	.995	122	0.14
4	.992	98	.992	102	0.18
5	.993	85	.996	122	0.20
6	.999	121	.999	133	0.14
7	.990	163	.990	155	0.10
8	.985	88	.98	159	0.13
9	.998	76	.999	117	0.19
10	.998	88	.997	122	0.19
11	.992	120	.990	166	0.10
12	.991	101	.992	104	0.18
13	.997	68	.991	103	0.24
14	.994	100	.997	132	0.15
15	.998	128	.997	132	0.15
16	.991	102	.993	104	0.18
17	.989	122	.992	129	0.15
18	.990	108	.993	145	0.10
19	.998	74	.997	92	0.34
20	.992	102	.991	104	0.17

K_h, the diffusion rate constant; K_p, the Korsmeyer Peppas release rate constant; n, the release exponent; and R^2, determination coefficient.

where Q_t is the cumulative amount of drug released at time t per unit of exposed area, D is the constant diffusion coefficient, and C_0 and C_p are the drug loading and drug solubility in the polymer matrix, respectively (Papadokostaki & Petropoulos, 1997).

Drug solubility is the most important parameter in drug release. According to Higuchi equation, the drug released (Q_t) is directly proportional to drug solubility C_p. According to Korsmeyer Peppas equation, the drug released (Q_t) was directly proportional to $K_{p,}$ which is the function of C_p (Kiortsis, Kachrimanis, Broussali, & Malamataris, 2004).

By considering the response surfaces and contour plots in Figure 3, it is observed that the addition of Si PSA increases the amount of drug released. Figure 3 illustrates that the increase in Si percentage from 10 to 90% (wt/wt) does facilitate the solubility of fentanyl in the matrix (C_p) and mediate drug release (Q_t) in conformity with Eq. 1.

This study was also designed to evaluate the effect of PVP and LA on solubility and drug release, and the results are shown in Figure 3A and B. It was found that the addition of PVP initially reduces the solubility as well as drug release and then releasing was being mediated, because it provided greater solubility of drug in the blend.

By the addition of LA from 0 to 6% (wt/wt), the drug release was dropped although the solubility of drug was increased. At the higher percentages (6–12%, wt/wt) of LA, the degree of the solubility and also drug release were increased. Generally, by addition of LA, lower quantity of drug is being released. Hence, one may conclude that the presence of LA induces greater hydrophilicity of the system; therefore the hydrophilicity of donor and receptor phases are brought closer to each other so that the affinity of fentanyl for release is lowered. Figure 3A and B illustrate that the maximum release is around 70% (wt/wt) of Si PSA. Investigation of the role played by Si with PVP and LA separately reveal that, in cases where the system includes 15% (wt/wt) PVP, even in region where the concentration of Si is as high as 70% (wt/wt), the release rate is decreased. This trend is also observed in consideration of Si PSA effect with LA. Therefore, it is concluded that the presence of LA in lowering the released drug is more dominant than Si in increasing the drug release. Generally, PVP and LA decrease the drug release. Maximum drug release has been observed at the point containing 70% (wt/wt) Si in such a way that it was increased twofolds and minimum drug release in the formulation, which has included 10, 15, and 12% (wt/wt) of Si, PVP, and LA, respectively.

Tack and Peel Studies

For modeling of tack behavior, a quadratic model with backward regression was used. The model showing the best fit was the special quadratic model as follows:

$$\begin{aligned} E\,(\text{tack}) = {} & -18.181 + 1.92794\,(\text{Si}) + 4.25736\,(\text{PVP}) \\ & + 10.98509\,(\text{LA}) - 0.017688\,(\text{Si}^2) \\ & - 0.11911\,(\text{PVP}^2) - 0.97166\,(\text{LA}^2) \\ & - 0.014727\,(\text{Si})\,(\text{PVP}) + 0.080177\,(\text{PVP})\,(\text{LA}). \end{aligned}$$

The results are summarized in Table 5. There is, however, no lack of fit for this model either. Adjusted R^2 and prediction R^2 are .93 and .77, respectively, and A^2, B^2, C^2, and AB are significant parameters ($p < .05$). As shown in Figure 4 by the addition of Si, LA, and PVP up to their middle point, the tack values are increased, and in their higher percentages the tack values are reduced (Table 7).

PSA tack is an adhesive property related to bond formation and is a very interesting behavior. Tack is defined as the ability to instantaneously stick to a substrate under low pressure and be easily removed by adhesive separation (without leaving any

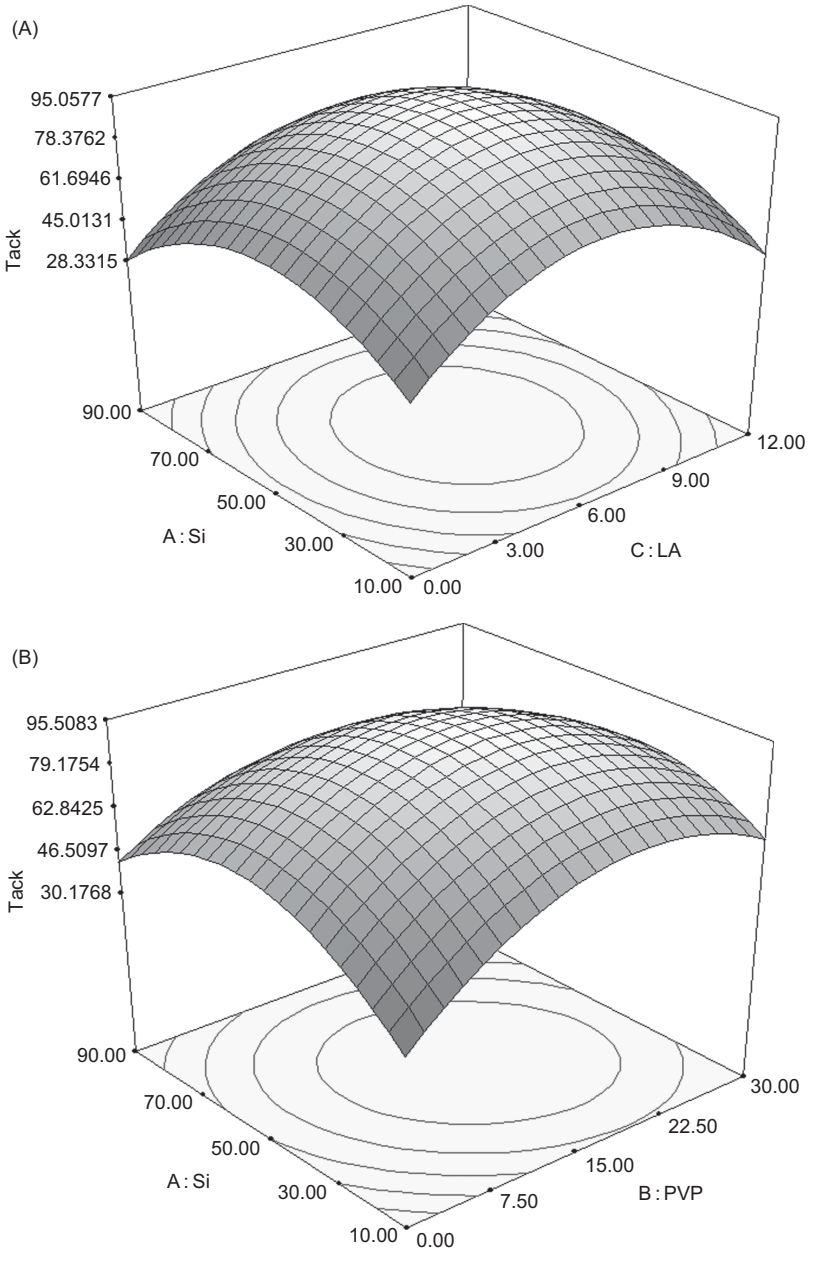

FIGURE 4. Response surfaces and contour plots of tack value (A) versus Si and LA in PVP = 15% and (B) versus Si and PVP in LA = 6%.

TABLE 7
Tack Data and Their Normalized Values

Run	Tack (N/mm^2)	Normalized Tack
1	0.38	8
2	4.70	100
3	3.17	67
4	4.30	90
5	0.04	1
6	3.70	78
7	2.00	43
8	3.30	70
9	0.33	7
10	2.60	55
11	0.42	9
12	4.30	90
13	0.66	14
14	4.70	100
15	3.70	78
16	4.70	100
17	2.80	60
18	0.33	7
19	0.33	7
20	4.20	89

TABLE 8
Peel Data and Their Normalized Values

Run	Peel (N/25 mm)	Normalize
1	3.12	13
2	17.80	74
3	15.60	65
4	15.60	65
5	15.60	65
6	24.00	100
7	10.30	43
8	15.60	65
9	12.50	52
10	12.00	50
11	8.40	35
12	17.80	74
13	15.60	65
14	17.80	74
15	17.80	74
16	16.80	68
17	6.20	26
18	10.30	43
19	7.20	30
20	17.30	72

residue at the substrate surface). Indeed, for viscoelastic materials to be tacky, adhesion must be developed during the bonding step and cohesion during the debonding step (Ben-Zion, Karpasas, & Nussinovitch, 2003; Chau & Swei, 2004). Tack is not a simple property such as density or modules, but it is rather a complex response of the adhesive characteristics of the surface chemical and bulk physical properties upon being brought into contact with another material (Moon, Chiche, Forster, Zhang, & Stafford, 2005). In this respect, the molecular weight, temperature, and morphology have also significant effects on tack behavior of polymers (Aymonier, Papon, Castelein, Brogly, & Tordjeman, 2003; Yang et al., 2006). PSA tack and bond formation, in general, ultimately involve molecular interactions at the adhesive/adherent surface.

According to Figure 4, it seems that by the addition of LA, the viscosity of the adhesive is reduced and bonding stage occurs easier and the tack value is increased. With higher percentages of LA, the tack value has decreased because of the decrease in the loss modulus of adhesive. Considering the effect of PVP concentration on tack, it seems that the free hydroxyl group increases by the addition of PVP initially but with higher concentration of PVP due to increase in viscosity of the system, the bonding step is more difficult to occur. Also the concentration of adhesive is reduced in the interface by surface migration of PVP, and therefore the tack value is decreased.

The results of peel strength are listed in Table 8. By using the similar model as well as tack value, the best predictions are obtained as follows:

$$\begin{aligned}\text{Epeel} = 72.50 &- 0.92406\,(\text{Si}) \\ &- 0.26917\,(\text{PVP}) + 10.42500\,(\text{LA}) \\ &+ 5.07812\text{E-}003\,(\text{Si}^2) - 1.01042\,(\text{LA}^2) \\ &+ 0.014583\,(\text{Si})\,(\text{PVP}).\end{aligned}$$

There was also no lack of fit for this model either. The adjusted $R^2$and prediction R^2 were .91 and .81, respectively, and A, B, C, A^2, C^2, and AB were significant.

It is observed in Figure 5 that the addition of Si has had a negative effect on peel strength. The enhancer LA initially causes the peel values to increase and then beyond 6% (wt/wt) of LA the peel strength is decreased. As illustrated in Figure 5, the PVP had a positive effect on peel strength and addition of PVP between 15 and 30% (wt/wt) to the system decreased the effect of Si and finally caused peel values to increase. The high peel values were observed for blends richer in Si and PVP .The lowest peel strength was obtained in the formulations including 90, 12, and 0% (wt/wt) of Si, PVP, and LA, respectively, which gave rise to the lowest adhesion strength.

Comparison of Si PSA with PVP and LA in peel strength, referring to Figure 4A and B, shows that Si and PVP have identical effect in lowering and increasing the peel strength; however, changes in peel strength by LA are more pronounced than that of Si.

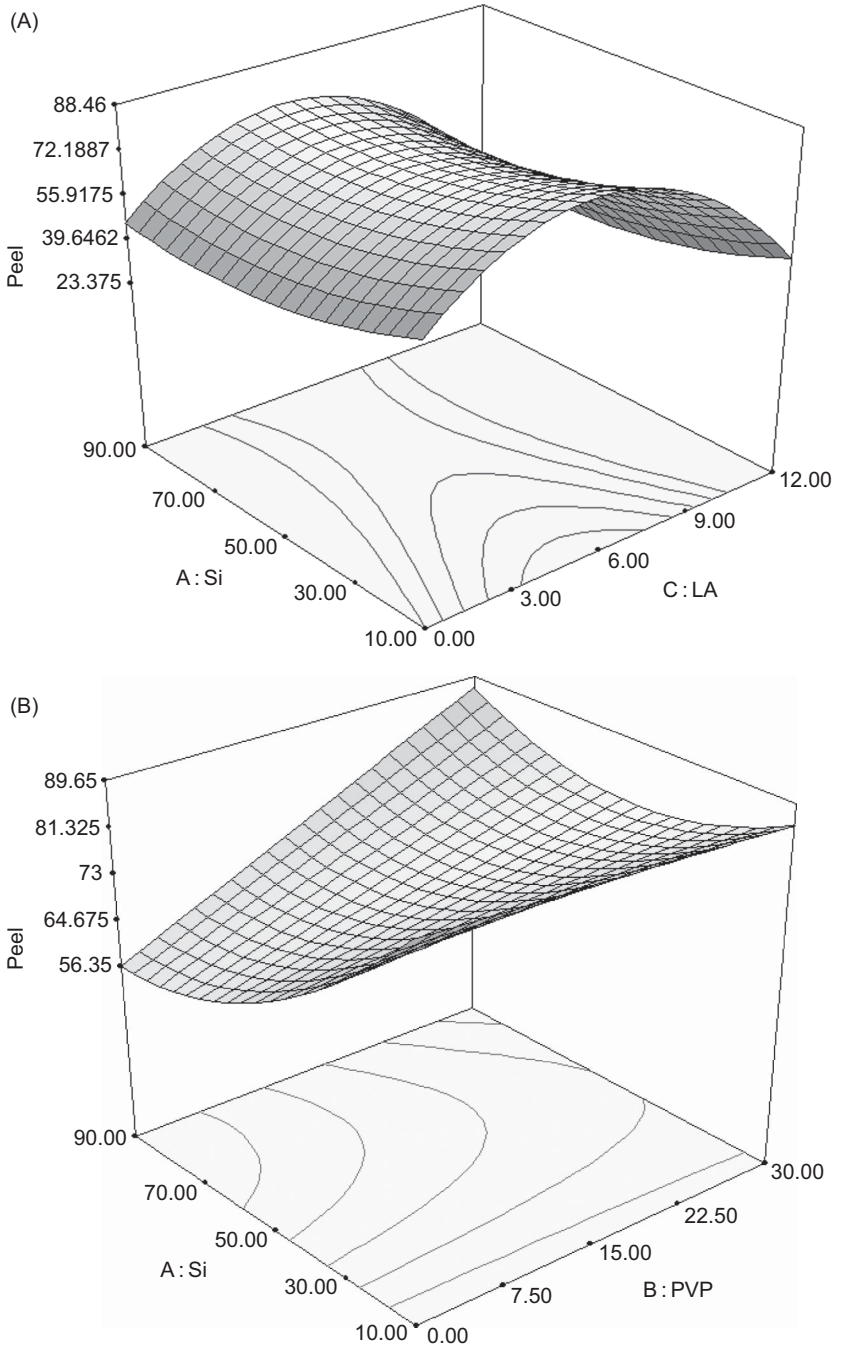

FIGURE 5. Response surfaces and contour plots of peel strength (A) verus Si and LA in PVP = 15% and (B) verus Si and PVP in LA = 6%.

CONCLUSION

This study is generally related to TDDSs and, more particularly, to a transdermal drug delivery composition where in a blend of polymers was utilized to affect the rate of drug delivery and adhesion properties of the composition containing fentanyl as a model drug. More specifically, a plurality of Si and acrylic base PSAs including soluble PVP and the LA as a permeation enhancer having different solubility parameters, immiscible with each other, balancing the solubility of fentanyl in a polymeric adhesive system formed by the blend, affect the drug solubility and have modulated the delivery of drug from the platforms as well as adhesion properties of the blends. It was found that drug solubility, cumulative amount of drug released, and adhesion properties of fentanyl DIAPs were influenced by Si as well as LA and PVP concentrations in the matrix. LA and Si PSA had a synergic effect on drug solubility.

Generally, PVP and LA had a negative effect on the drug released. Addition of Si to the system resulted in increasing drug

release values, in such a way that the amount of drug release was increased twofolds with approximately 70% Si, in comparison with the case where the system had only acrylic PSA.

Investigating the separate role played by Si with PVP and LA revealed that, in a case where the system contained 15% (wt/wt) PVP, the release rate was decreased even in the region where the concentration of Si was as high as 70% (wt/wt). This trend was also observed in the case of Si PSA with LA present. Also it was observed that the all systems follow Higuchi equation after at most 4 h of release time and then would follow Korsmeyer Peppas equation. According to in vitro evaluation, it was found that by increasing the amount of Si in the system by up to 70% (wt/wt), patch size can be reduced, which is an important factor as far as application is concerned.

Regarding adhesion properties, it was observed that generally by the addition of PVP to the system, the peel strength was increased, whereas Si reduced it. But the role played by PVP at higher percentages for increasing the peel strength was enhanced by the presence of Si at higher concentrations.

The effects of PVP as well as Si and LA were similar on tack value in such a way that the maximum value of tack appeared to be in the medium ranges. On the basis of all responses, no single point was found, where all responses showed the maximum values. Thus, the design for final performance might involve a trade-off between certain properties. On the other hand, this situation can be used to our advantage if one of the properties of fentanyl DIAPs performance is favored for a particular application.

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