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Research Article

QUALITY BY DESIGN (QBD) TO OPTIMIZATION OF SEMI-SOLID SUSPENSION TYPE OF CAPTOPRIL TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Introduction: In recent year, USFDA and EMA have issued the guideline on Quality by design (QBD). PAT and DOE are the essential tolls for QBD to evaluate the product. Focusing on the insight provided in these guideline as initiative was taken for the development of captopril transdermal system.
Objective: Optimization of the penetration enhancer, drug delivery and in-vitro adhesion of captopril transdermal system by QBD.
Material and Method: Captopril used as active moiety for transdermal systems. Captopril was obtained as a free sample from torrent pharma, Dipropylene glycol and oleyl alcohol was taken from croda. Bio PSA AC7-4202 silicone pressure sensitive adhesive was obtained from dow corning and Duro-tak®87-4287 acrylate pressure sensitive adhesive was obtained from national starch. Other excipients were used, colloidal silicone dioxide, tween-80, povidone K-12 and dehydrated alcohol. Matrix type of captopril transdermal system with combination of silicone and acrylate adhesive was prepared. Different concentration of captopril (5-15% w/w), di propylene glycol, oleyl alcohol (2.5-7.5% w/w) was used to get the desired delivery and different drying conditions (25-500C temperature, 20-40 min residence time) was used to get the desired volatile content.
Results: Captopril was delivered from 1.38-1.51 mg/day and 69.07-75.57 mcg/cm2/hr. 12% w/w of captopril and 7-9% w/w of dipropylene glycol concentration were required to get the desired delivery of captopril. 300C for 30 min was required to get the desired level of DPG to get drug delivery and residual solvent to get the desired adhesion.
Conclusion: Captopril and DPG concentration is responsible for drug delivery and drying condition is responsible to get the desired adhesion of the transdermal system. Further preclinical investigations are essential before to use of transdermal as an alternative with longer duration of action, improved bioavailability and patient convenience.
Keywords: Transdermal system, Captopril, Release liner, backing film, penetration enhancers, matrix stiffener, semi-solid suspension.

INTRODUCTION

In recent year, USFDA and EMA accentuate to submit the ANDA or NDA based on quality by design (QBD) concept. In concern to USFDA and EMA, captopril transdermal formulation is developed based on QBD. DOE and PAT are the main tools for QBD. As per critics, quality of the product can't be achieved by testing; quality can be achieved by understanding. As per recent ICH guideline for pharmaceutical development, ICH emphasis on the product should be design by quality by design concepts. Design of experiment is well known tool in pharmaceutical industry to qualitative and quantitative estimation of ingredients drug product development and process development. DOE can consider the all potential factors that affect the process add product development and evaluate easy, fastest, systematically and simultaneously. By using DOE, You can evaluate effect of the different factors on response. Also identify the criticality of the factor on response. Optimized formulation can easily predict with the help of DOE. Process analytical technique (PAT) is also used in pharmaceutical

industry to evaluate the process of manufacturing. PAT is used during real time quality investigation of the product. Our conventional method is to evaluate the effect of physical and chemical parameter like, viscosity, pH, temperature and pressure, while PAT mainly considered the Raman, near IR and IR type of physicochemical properties of the process.

Captopril, an orally active inhibitor of an angiotensin-converting enzyme (ACE) has been widely used for the treatment of hypertension and congestive heart failure. As per physicochemical properties and other problem related to the oral dosage form, Transdermal formulation is the suitable formulation for captopril.

Thus, the objective of this present research investigation was to develop a transdermal system to deliver the captopril at predetermine controlled rate as well as to evaluate the pre formulation and formulation variables which affect in-vitro characteristics of the transdermal system of captopril. A semisolid suspension type of transdermal drug delivery system of captopril was developed and investigated due to its higher delivery with minimum patch area and as low as possible drug concentration. Acrylate and silicone type of pressure sensitive adhesive was used to develop the semi-solid suspension type of transdermal system.

Dipropylene glycol and oleyl alcohol were used as the permeation enhancer and fluoropolymer coted polyester (PET) release liner and polyethylene (PE) and PET backing film to protect the transmission of captopril with penetration enhancers.

As an initial development study after pre formulation, the effect of three formulation factors (drug concentration and two penetration enhancer concentration,) and two manufacturing factors (Drying time and drying temperature) was considered on the release of the drug from patch and permeation properties of captopril from transdermal patches, peel, tack, shear for adhesion study and for residual solvent remain in patch. After completion of the initial optimization, an attempt was made to obtain an optimized formulation by design of experiments so as to achieve a desired release (100% in 24 h) and permeation flux (1.488 mg/h) of captopril from the patch over a 24 hr patch application period. Compared with conventional type of dosage form optimization technic experimental design method give many advantages like lower number of total experiment, better understanding of effect of individual experiment and also identify the individual effect on individual excipients. Based on experimental design it will be easy to evaluate the effect of individual process step and individual excipients on quality of the product.

After selection of different excipients for captopril transdermal formulation, we need to optimize the different concentration of captopril, penetration enhancer. As per the thermodynamic first law of diffusion, penetration of diffusion from matrix is directly related to the concentration of the active in formulation. Penetration enhancers are work to improve the penetration of the active from matrix. Parameters for penetration enhancer and drug concentration are established by using design of experiment study using a 2-level 3 factor (23) design with DOE software. DOE is used in development of pharmaceutical products. DOE has the many of the objectives.

MATERIA AND METHO:

MATERIAL:

Captopril was obtained as a free sample from torrent pharma, Dipropylene glycol and oleyl alcohol was taken from croda. Bio PSA AC7-4202silicone pressure sensitive adhesive was obtained from dow corning and Duro-tak®87-4287 acrylate pressure sensitive adhesive was obtained from national starch. Other excipients were used, colloidal silicone dioxide, povidone K-12 and dehydrated alcohol.

SELECTION OF BACKING FILM AND RELEASE LINER:

Based on history of their use in transdermal products and others physical characteristics, translucent polyethylene backing film, Scotchpak™ 9732 (Translucent Polyethylene Monolayer Film) was selected for further evaluation. Scotchpak™ 9732 is printable, flexible and has very low moisture vapor transmission rate (MVTR). Silicone and fluoropolymer coated polyester release liners are present in many other approved transdermal systems. Selected liner should be easy to remove/ peel-off from adhesive matrix. Silicone coated release liner is not suitable when we use silicone polymer as a pressure sensitive adhesive. Fluoropolymer coated polyester liner Scotchpak™ 1020 is used as release liner.

FABRICATION OF CAPTOPRIL TRANSDERMAL SYSTEMS:

Excipients were selected based on pre-formulation studies. Penetration enhancer was selected based on solubility and

compatibility, pressure sensitive adhesive selected based on physicochemical properties and solubility and compatibility study. After proper mixing of all the excipients, blend of captopril was coated on release liner and laminate with backing film. Solvent casting method was used to prepare the semisolid suspension type of transdermal drug delivery system. Two polymer BIO-PSA AC7-4202 (Silicone Adhesive) and Duro-Tak® 87-4287 (Acrylic Adhesive 4287) was mix properly with Tween-80. Captopril was solubilized in ethanol under mixing in a SS container until to get the clear solution. Povidone was added to uniform dispersion and mix to ethanol gets the clear solution of povidone. Dipropylene glycol, oleyl alcohol and colloidal silicone dioxide was added and mix. The drug solution was added slowly to the adhesive mixture. The blend was analyzed for Captopril assay, viscosity and % non-volatiles. Blend was spread over the selected release liner on particular thickness by coating knife in single zone coater and put into the oven over at particular or predetermine temperature for predetermine time for removal of the organic solvent. During removal of the solvent, some of the critical penetration enhancer is also loss. So during drying of the laminate, solvent as well as volatile penetration enhancer is also optimizing to get the desired level of solvent and penetration enhancers and finally to get the predetermine drug delivery.

STATISTICAL OPTIMIZATION OF THE FORMULATION VARIABLES USING EXPERIMENTAL DESIGN APPROACH

Factorial design: The Regular Two-Level Factorial Design, Full two-level factorial designs may be run for up to 9 factors. These designs permit estimation of all main effects and all interaction effects (except those confounded with blocks). Design-Expert offers a wide variety of fractional factorial designs. Design-Expert calculates detailed information about the alias structure. This evaluation should be inspected to ensure the selected design can cleanly estimate the interactions of interest. A 2-level 5 factor (25) design of experiments was performed on coating and drying conditions with responses to optimize. Captopril blend was metered on release liner on predetermining thickness and put into oven for predetermine time, hence drying temperature and time considered as a factors. The drying process for captopril transdermal system is designed to remove ethyl acetate present in Duro-tak® 4287 and Bio-PSA® 4202 polymers and the ethanol used as processing aid for blending to soluble the captopril. During drying process volatile penetration enhancer is loss and after drying process remain penetration enhancers in the patch improve the delivery of the drug, hence dipropylene glycol and oleyl alcohol considered as factors. The factors studied to elicit major effects on the responses were concentration of Dipropylene glycol, skin flux delivery, peel, tack, shear, ethanol and ethyl acetate in final formulation.

RESULTS AND DISCUSSION

The response results given in table were individually analyzed using analysis of variance (ANOVA) to differentiate significant and non-significant responses that can affect coating and drying process. The 2-level 5 factor model having one center point is significant for di-propylene glycol and oleyl alcohol content (Y1 and Y2) and significant for Drug release skin flux, peel, tack, shear, ethanol and ethyl acetate (Y3, Y4, Y5, Y6, Y7 and Y8). Oleyl alcohol is only non-significant factor in this study and non-significant parameters are not discussed further. Results of ANOVA is mention in below table. Only significant factors are considered further.

1. Dipropylene glycol content:

Different drying condition, temperature and residence time is given the significant contribution for concentration of di-propylene glycol content.

Figure1: Pareto Chart of Effect on DPG

Dipropylene glycol were loss during drying condition and it is responsible for the delivery of the drug. Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model.

Figure 2: Response surface of Effect on DPG

The Analysis of Variance (ANOVA) results are presented in table 8. The Model F-value of 63.46 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. Figure 1 shows the pareto chart which illustrates the significance of the three parameters on drug delivery. Factor D and E drying condition associated with the highest negatove effect on DPG concentration in final formulation. As per response surface graph, concentration of DPG in blend gives positive effect and Drying condition gives negative

Table 1: Factor and responses for 2-level 5 factor (2^5) DOE study of drying process (102, 103)

	Drying condition factors	Two Levels		
		-1	**0**	**+1**
A	Captopril Concentration	5.00	10.00	15.00
B	Dipropylene glycol concentration	2.50	5.00	7.50
C	Oleyl alcohol concentration	2.50	5.00	7.50
D	Drying Temperature	25.00	37.50	50.00
E	Drying Time	20.00	30.00	40.00

	Responses	**Critical**	**Justification**	**Acceptable range**
Y1	Captopril contents(% of LC)	No	No change during process	95.0-105.0
Y2	Dipropylene Glycol (% of LC)	Yes	Volatile and change during process	90.0-110.0
Y3	Oleyl alcohol (% of LC)	No	No change during process	90.0-110.0
Y4	Drug delivery, skin flux	Yes	Depend on level of enhancers and API	1.40-1.60 mg/hr
Y5	Peel (g/mm)	Yes	Depend on level of enhancers and solvents	Near about 30
Y6	Tack (g/mm^2)	Yes		Near about 25
Y7	Shear (min)	Yes		Near about 75
Y8	Ethanol (PPM)	Yes	Depend on process	<1000
Y9	Ethyl Acetate (PPM)	Yes	Depend on process	<500

Once you finalized factor and response and add in to 2 level 5 factorial design in DOE software with two center points it will provide you total 33 experiments as per below table after that you need to perform the experiment and add the response result into software.

Table 2: Factor for 2-level 5 factor design of DOE study from 1 to 11

Factors		**Run**										
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Captopril	**%dry w/w**	5	5	5	5	5	5	5	5	5	5	5
DPG		2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	7.5	7.5	7.5
OA		2.5	2.5	2.5	2.5	7.5	7.5	7.5	7.5	2.5	2.5	2.5
TEM	**Deg C**	25	25	50	50	25	25	50	50	25	25	50
TIME	**MIN**	20	40	20	40	20	40	20	40	20	40	20

Table 3: Factor for 2-level 5 factor design of DOE study from 12 to 22

Factors		**Run**										
		12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Captopril	**%dry w/w**	5	5	5	5	5	10	15	15	15	15	15
DPG		7.5	7.5	7.5	7.5	7.5	5	2.5	2.5	2.5	2.5	2.5
OA		2.5	7.5	7.5	7.5	7.5	5	2.5	2.5	2.5	2.5	7.5
TEM	**Deg C**	50	25	25	50	50	37.5	25	25	50	50	25
TIME	**MIN**	40	20	40	20	40	30	20	40	20	40	20

Table 4: Factor for 2-level 5 factor design of DOE study from 22 to 33

Factors		**Run**										
		23	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**
Captopril	**%dry w/w**	15	15	15	15	15	15	15	15	15	15	15
DPG		2.5	2.5	2.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
OA		7.5	7.5	7.5	2.5	2.5	2.5	2.5	7.5	7.5	7.5	7.5
TEM	**Deg C**	25	50	50	25	25	50	50	25	25	50	50
TIME	**MIN**	40	20	40	20	40	20	40	20	40	20	40

Table 5: Responses and results for 2-level 5 factor design of DOE study from 1 to 11

Responses	RESPONSES/RESULTS										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
DPG, %LC	102	94.6	88	82	99	94	86	82.5	99.8	93.9	87.8
Skin flux, mcg/cm²/hr	51.5	41.5	36	33	61	53	43	38	65.5	58	51
Peel, g/mm	35.2	32	30	27	38	35	33	29.5	38.1	34.9	33.12
Tack, g/mm²	30	26.8	25	21	33	30	28	24.3	32.9	29.7	27.92
Shear, min	84.8	75.8	71	61	93	84	79	68.8	93	84	79
Ethanol, ppm	35.2	32	30	27	38	35	33	29.5	38.1	34.88	33.1
E. Acetate, ppm	30	26.8	25	21	33	30	28	24.3	32.9	29.68	27.9

Table 6: Responses and results for 2-level 5 factor design of DOE study from 11 to 22

Responses	RESPONSES/RESULTS										
	12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
DPG, %LC	84	101	95.3	89.2	85.4	99.8	104	98.4	91.5	85.3	98.1
Skin flux, mcg/cm²/hr	43	67	61	51.5	42	66	64	54	45.5	39.5	67.5
Peel, g/mm	29.6	37	33.8	32.1	28.5	31.2	32.8	29.6	27.1	24.3	34.9
Tack, g/mm²	24.4	31.8	28.6	26.9	23.3	25.6	27.6	24.4	21.9	19.2	29.7
Shear, min	69	90	81	76	66	76.1	78.1	69.1	62.1	54.1	83.9
Ethanol, ppm	29.6	37	33.8	32.1	28.5	31.2	32.8	29.6	27.1	24.3	34.9
E. Acetate, ppm	24.4	31.8	28.6	26.9	23.3	25.6	27.6	24.4	21.9	19.1	29.7

Table 7: Responses and results for 2-level 5 factor design of DOE study from 22 to 33

Responses	RESPONSES/RESULTS										
	23	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**
DPG, %LC	92.9	86	79.8	99.4	94.2	87	81.1	102	96.3	89.4	83.2
Skin flux, mcg/cm²/hr	60	51.5	46	82.5	74.5	66	60	83.5	76	69.5	59
Peel, g/mm	31.7	29.2	26.4	36.9	33.7	31	28.4	35.9	32.8	30.3	27.5
Tack, g/mm²	26.5	24	21.2	31.7	28.5	26	23.2	30.7	27.6	25.1	22.3
Shear, min	74.9	67.9	59.9	89.6	80.6	74	65.6	87	78	71	63
Ethanol, ppm	31.7	29.2	26.4	36.9	33.7	32	28.4	35.9	32.8	30.3	27.5
E. Acetate, ppm	26.5	24	21.2	31.7	28.5	26	23.2	30.7	27.6	25.1	22.3

Table 8: Results of Analysis of Variance for selected factorial model:

Model	**Sum of squares**	**degrees of freedom**	**Mean square**	**F value**	**P Value**	
DPG	1476.12	6	246.02	63.46	<0.0001	Significant
Flux	2.21	7	0.32	336.65	<0.0001	Significant
Peel	399.57	7	57.08	997.44	<0.0001	Significant
Tack	399.57	7	57.08	997.44	<0.0001	Significant
Shear	3157.8	6	526.3	246.76	<0.0001	Significant
Ethanol	56664	3	18880	286.08	<0.0001	Significant
Ethayl Acetate	14160	3	47199.7	286.08	<0.0001	Significant

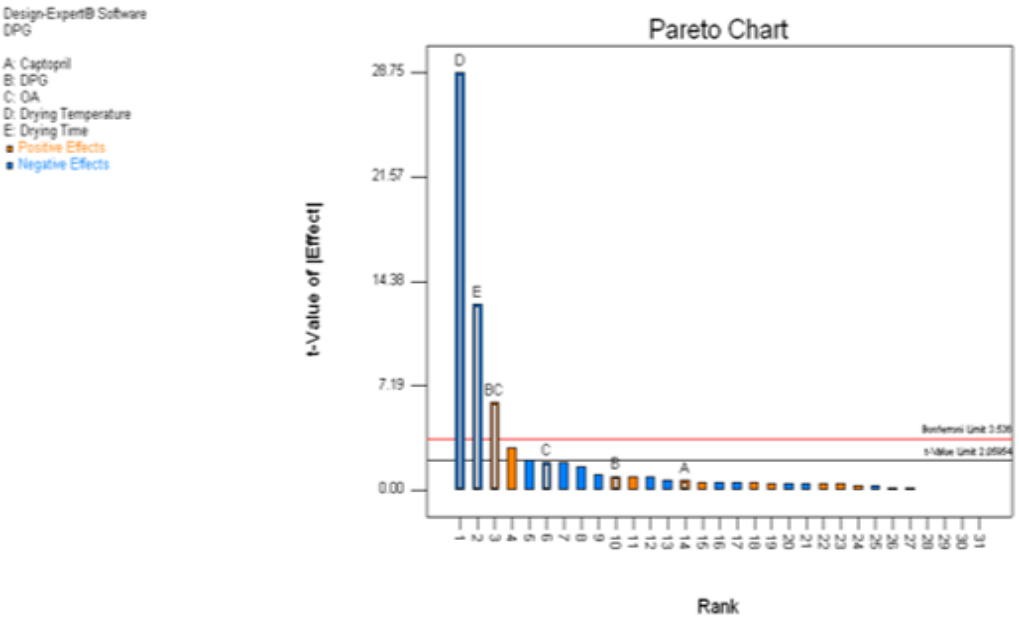

Figure1: Pareto Chart of Effect on DPG

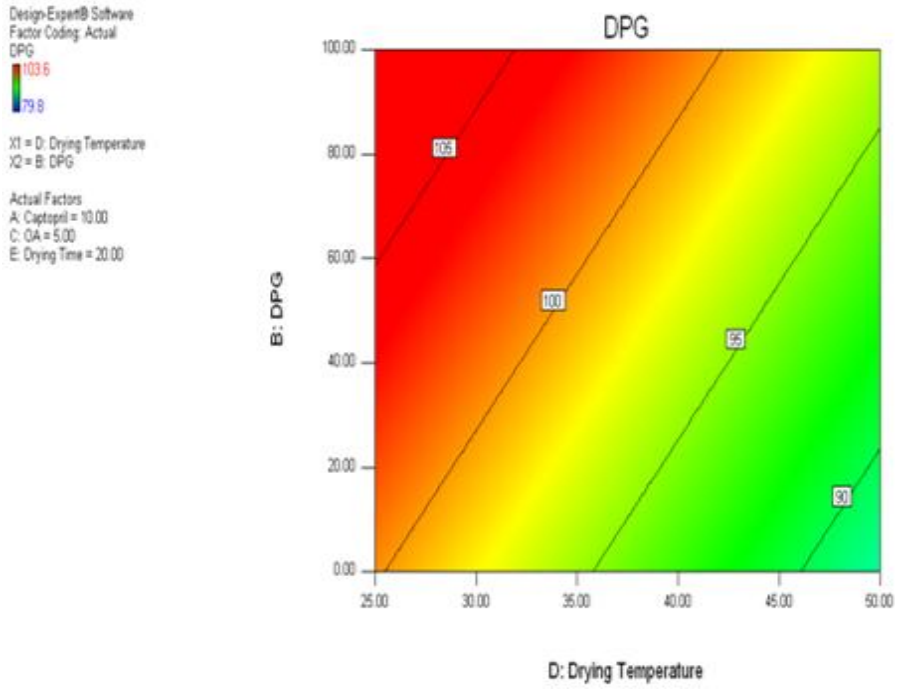

Figure 2: Response surface of Effect on DPG

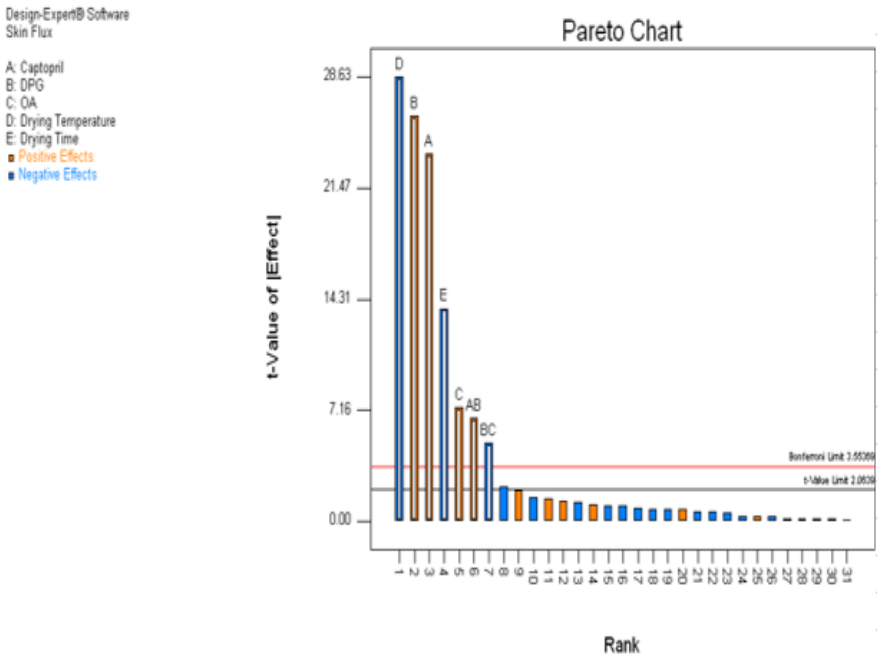

Figure 3. Pareto Chart of Effect Analysis for skin flux

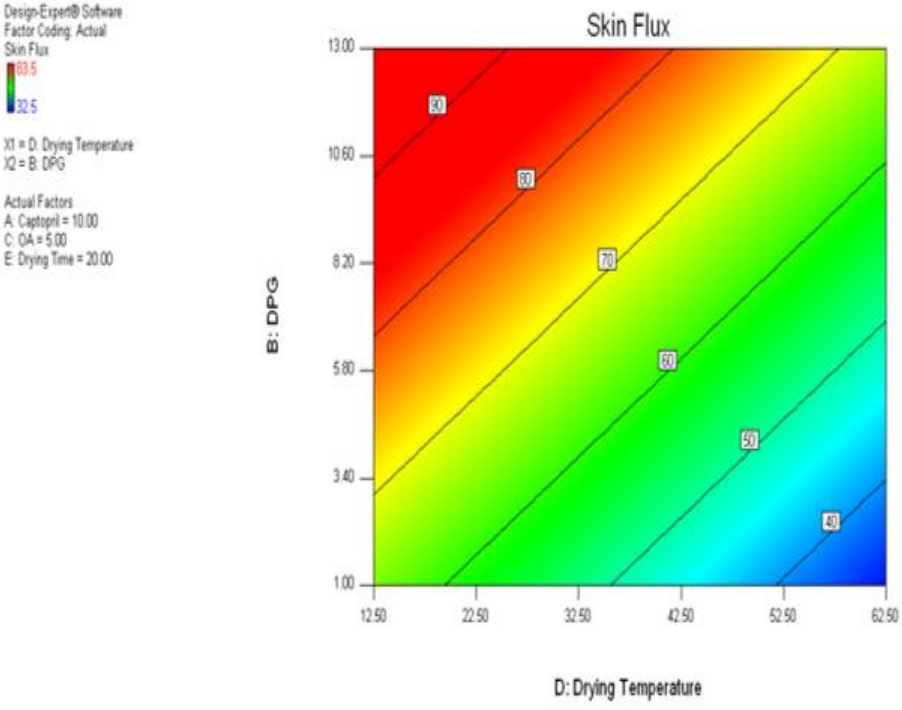

Figure 4. Response surface of Effect Analysis for skin flux

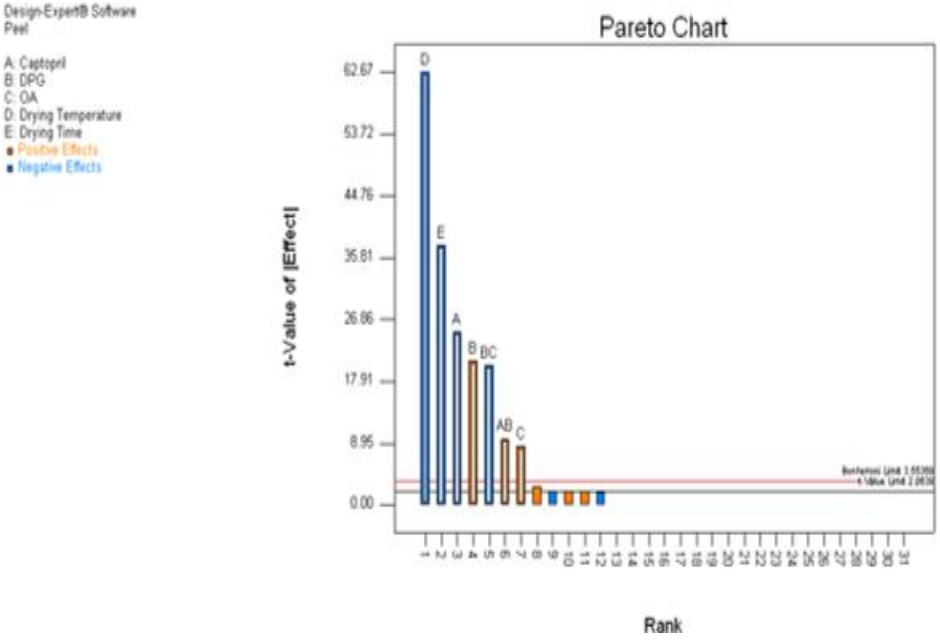

Figure 5: Pareto Chart of Effect Analysis for peel

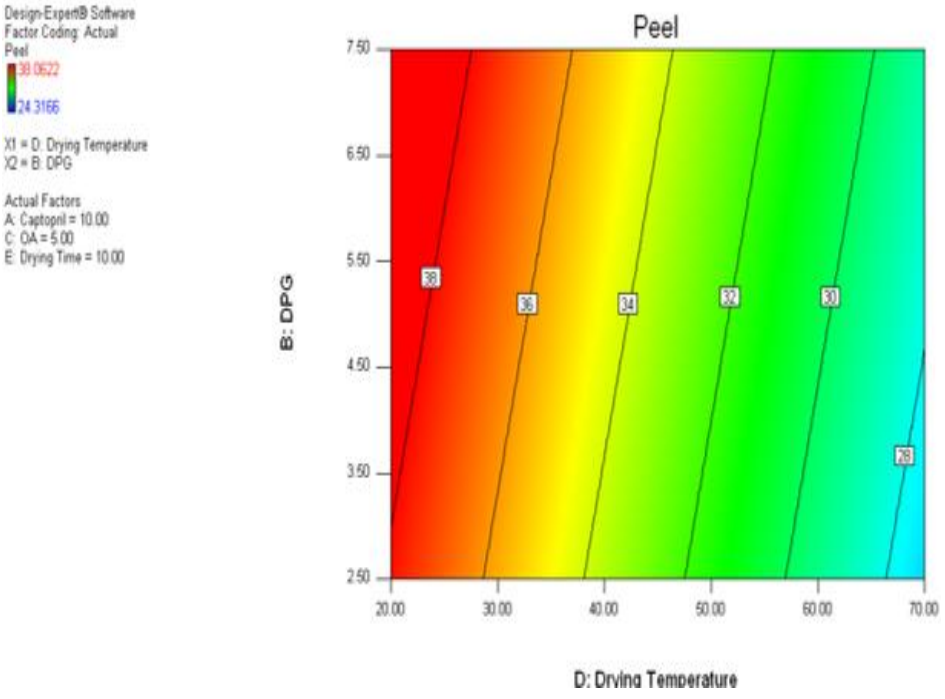

Table 6: Response surface of Effect Analysis for peel

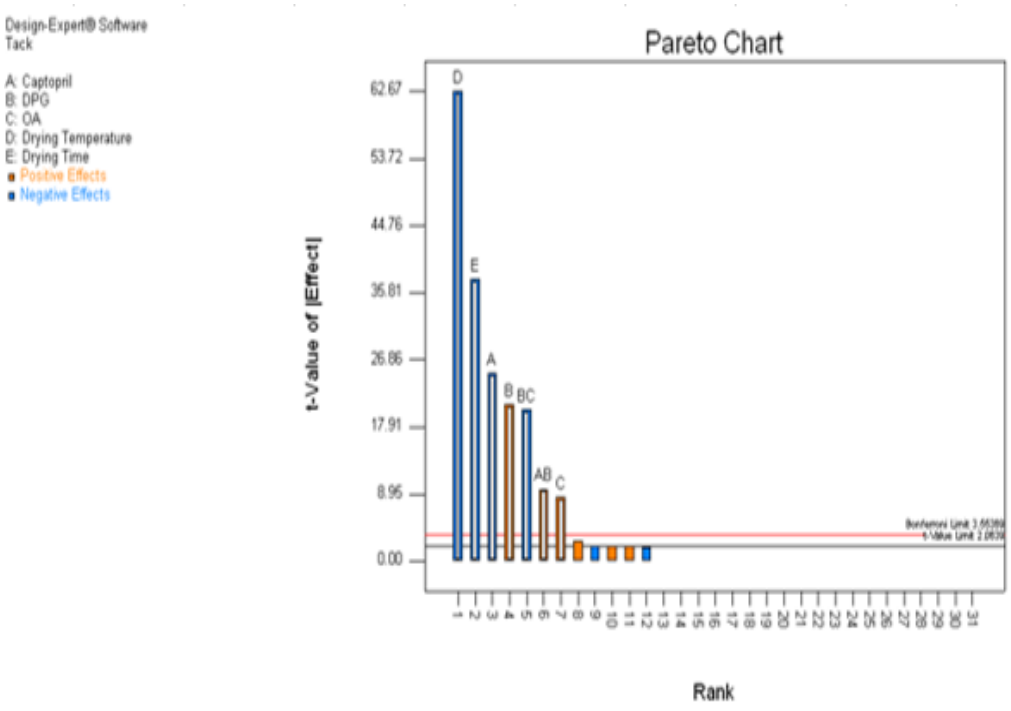

Figure 7: Pareto Chart of Effect Analysis for Tack

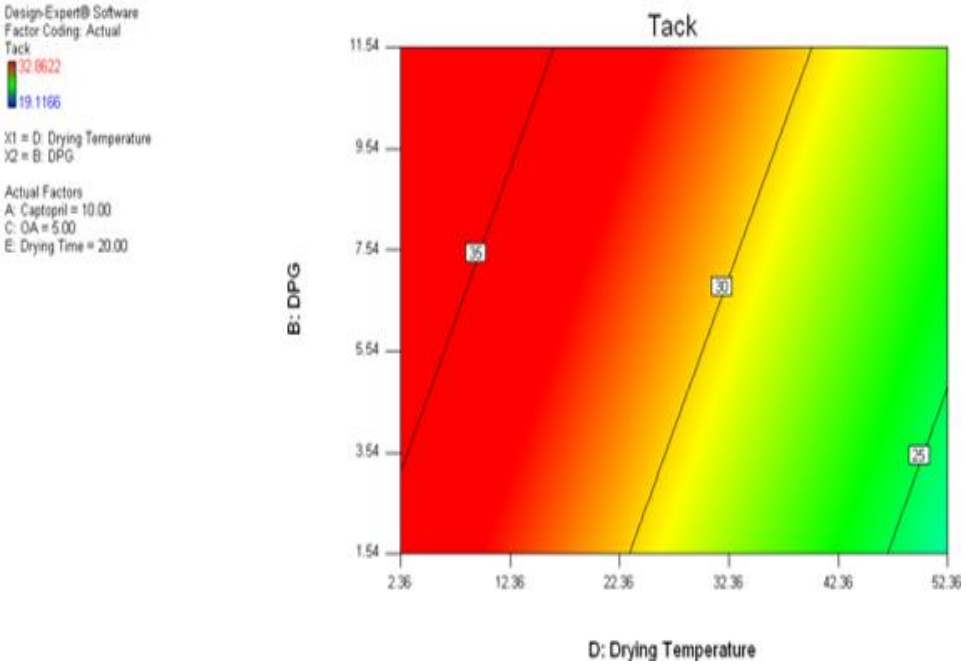

Figure 8: Response surface of Effect Analysis for Tack

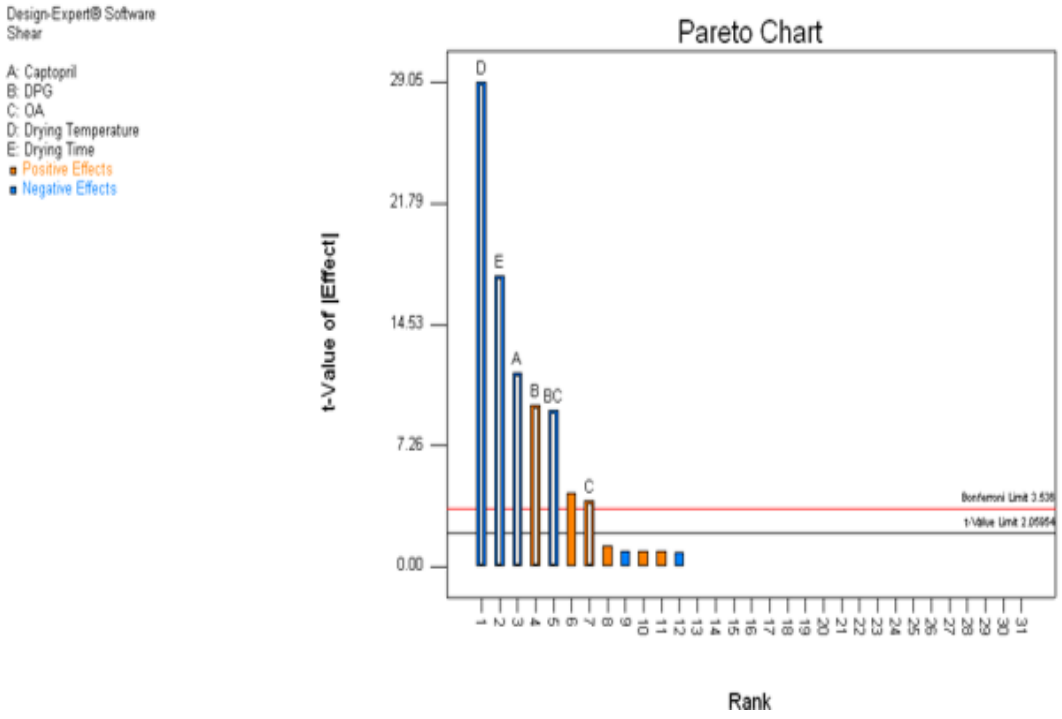

Figure 9: Pareto Chart of Effect Analysis for shear

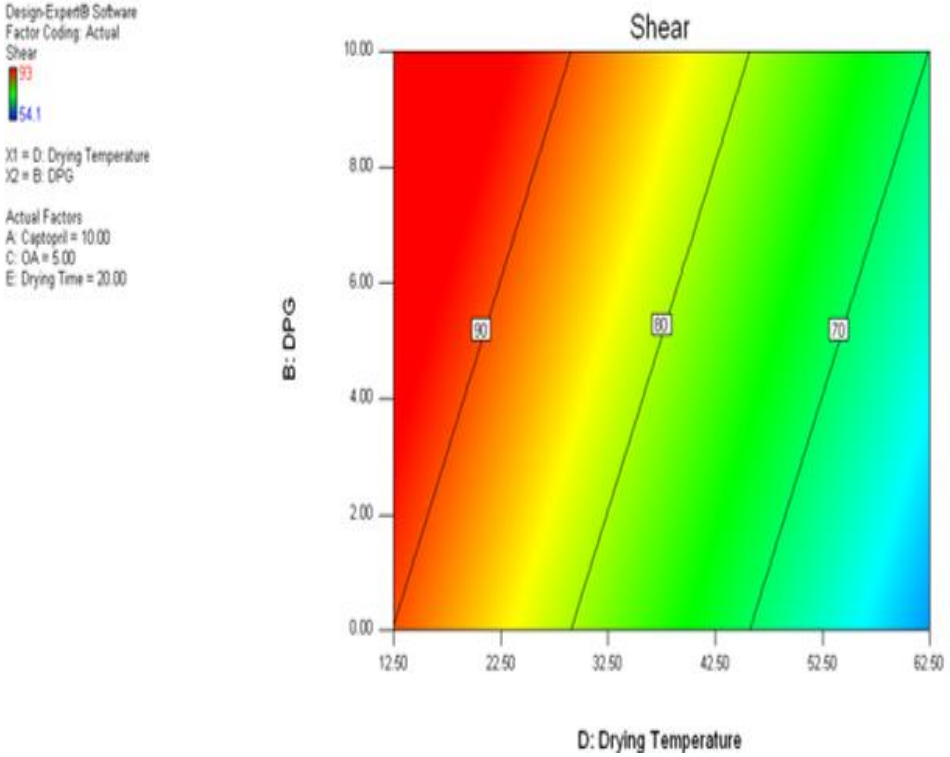

Figure 10: Response surface of Effect Analysis for shear

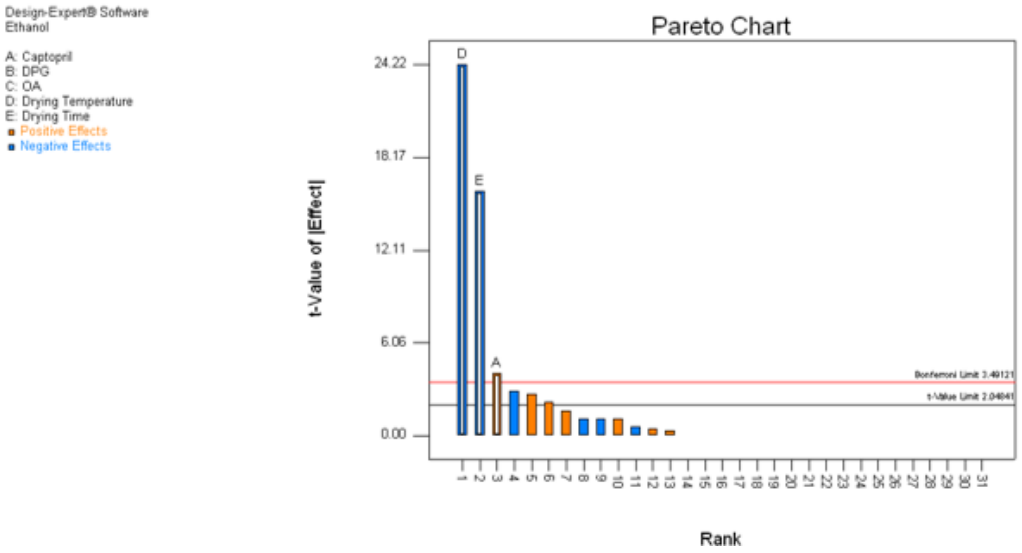

Figure 11: Pareto Chart of Effect Analysis for ethanol

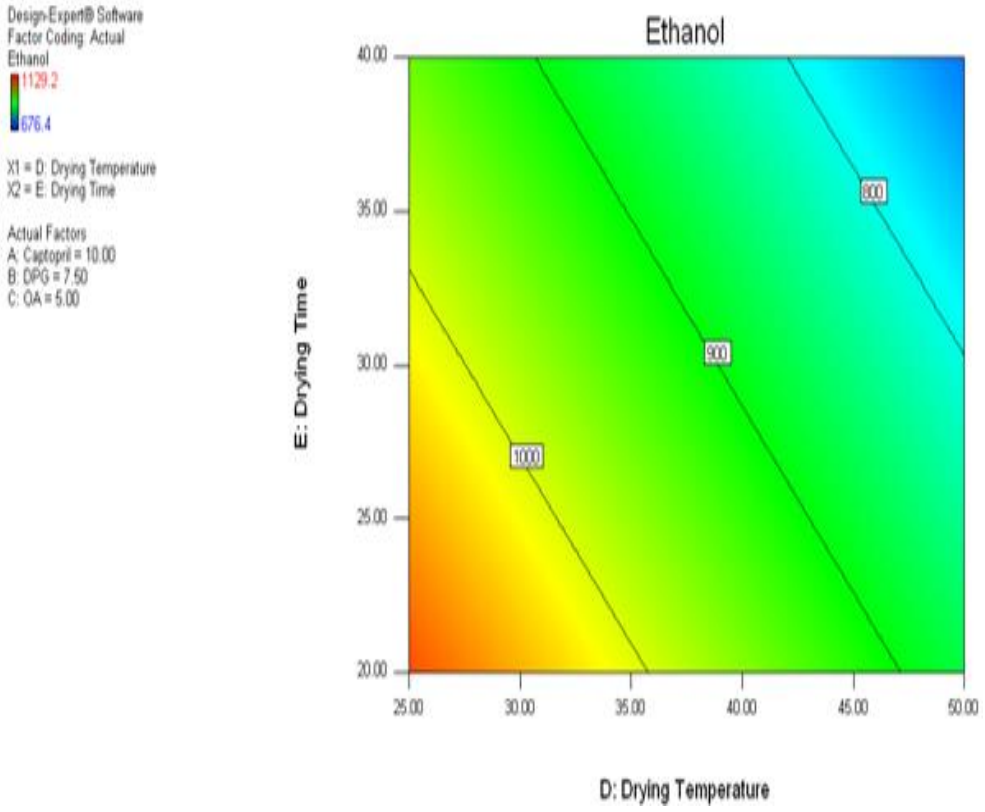

Figure 12: Response surface of Effect Analysis for ethanol

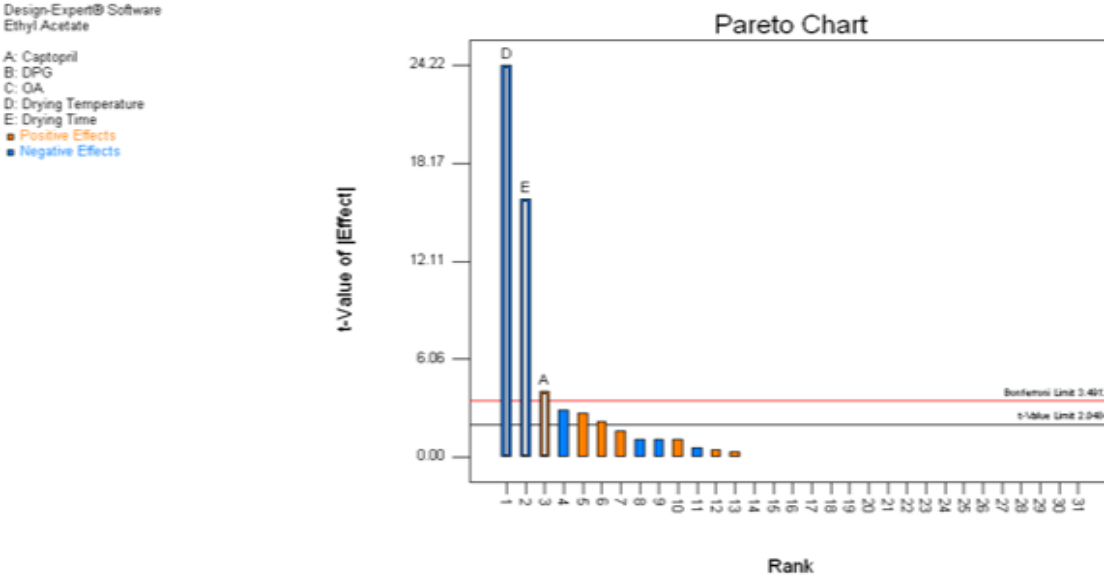

Figure 13: Pareto Chart of Effect Analysis for ethyl acetate

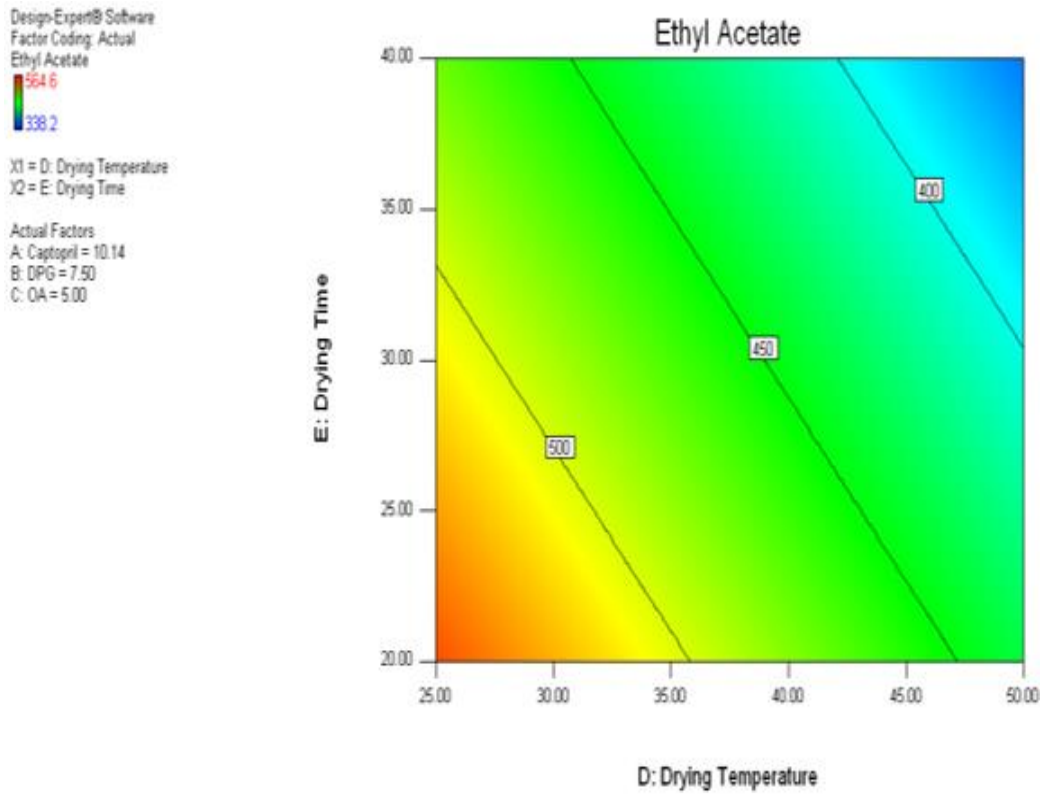

Figure 14: Response surface of Effect Analysis for ethyl acetate

effect on DPG content per patch.

2. Skin flux drug delivery:

Different concentration of captopril and penetration enhancers' effect are analyzed on skin flux.

Figure 3: Pareto Chart of Effect Analysis for skin flux

Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in table 8. The Model F-value of 338.65 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case initial three factors are the significant model terms compared with with other parameters.

Figure 4: Response surface of Effect Analysis for skin flux

Figure 3/4 shows the pareto chart and response surface which illustrates the significance of the all five parameters on skin flux. Drying condition gives negative effect and concentration of DPG and captopril gives positive effect. Response surface displays the effect of DPG concentration and drying temperature on skin flux. Skin flux is increased with increase the DPG concentration and decrease the drying temperature. DPG gave the positive effect and drying temperature gave the negative effect on skin flux.

3. Peel adhesion property:

Initially, at different concentration of captopril and penetration enhancers was performed for drug release and in-vitro adhesion study. Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model.

Figure 5: Pareto Chart of Effect Analysis for peel

The Analysis of Variance (ANOVA) results are presented in table 8. The Model F-value of 997.44 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case A is significant model terms.

Table 6: Response surface of Effect Analysis for peel

Figure 5/6 shows the pareto chart and response surface which illustrates the significance of the parameters on peel. Factor D gives maximum negative effect on peel and factor B gives positive effect on peeel. As per response surface, drying conditions and captopril concentration gives negative affect and DPG concentration gives positive effect on peel adhesion.

4. Tack adhesion value:

Initially, at different concentration of captopril and penetration enhancers was performed for drug release and in-vitro adhesion study.

Figure 7: Pareto Chart of Effect Analysis for Tack

Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in table 8. The Model F-value of 997.44 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case D is significant model terms.

Figure 8: Response surface of Effect Analysis for Tack

Figure 7/8 shows the pareto chart and response surface which illustrates the significance of the three parameters on shear. Factor D gives maximum negative effect with A and E on tack and factor B gives positive effect on tack. Increase the tack properties with increase the concentration of DPG and decrease the drying temperature.

5. Shear adhesion value:

Initially, at different concentration of captopril and penetration enhancers was performed for drug release, solvent and in-vitro adhesion study.

Figure 9: Pareto Chart of Effect Analysis for shear

Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in table 8. The Model F-value of 246.76 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case D is significant model terms.

Figure 10: Response surface of Effect Analysis for shear

Figure 9/10 shows the pareto chart and response surface which illustrates the significance of the three parameters on shear. Factor D, E and A gives maximum negative effect on shear and factor B, and C gives positive effect on shear. Increase the shear properties with decrease the concentration of DPG and decrease the drying temperature.

6. Ethanol residual solvent:

Initially, at different concentration of captopril and penetration enhancers was performed for drug release, solvents and in-vitro adhesion study.

Figure 11: Pareto Chart of Effect Analysis for ethanol

Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in table 8.

Figure 12: Response surface of Effect Analysis for ethanol

The Model F-value of 286.08 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case D is significant model terms. Figure 11/12 shows the pareto chart which illustrates the significance of the three parameters on shear. Factor A gives maximum positive effect on ethanol and factor D and E gives negative effect on ethanol. Increase the ethanol content with decrease the drying temperature and drying time.

***7*. Ethyl acetate residual solvent:**

Initially, at different concentration of captopril and penetration enhancers was performed for drug release, solvents and in-vitro adhesion study.

Figure 13: Pareto Chart of Effect Analysis for ethyl acetate

Since replications were included in the DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in table 8.

Figure 14: Response surface of Effect Analysis for ethyl acetate

The Model F-value of 286.08 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.050 indicate model terms are significant. In this case D is significant model terms. Figure 13/147 shows the pareto chart and response surface which illustrates the significance of the three parameters on shear. Factor D and E gives maximum negative effect on ethyl acetate and factor A gives positive effect on ethyl acetate.

IN SUMMARY, ALL THE VARIABLES:

Concentration of DPG, captopril, and residence time and temperature had a significant impact on drug delivery, peel, tack, shear and DPG content in patch of the dried matrix. However, as anticipated, the effect analysis also shows that the other factors like Oleyl alcohol concentration do not have a significant effect on captopril content per patch. After evaluating the effect of all the factors on response as per the design expert, we have to anticipate our goal with higher and lower limit of our all factors and responses. After finalization of acceptable upper and lower range for factor and response we need to give weightage of all individual response and factors as well as importance of all response and factors. In factors, captopril is in range of 8-12% with optimum importance, penetration enhancers DPG and OA is in range of 5-9% and 2-4%, drying condition is in range of 25-500C drying temperature and 20-40 min drying time. In responses, DPG is in 90-110% of label claim and 1.4-1.6 ratio of skin flux, 20-40 g/mm peel force, 20-40 g/mm2 tack force and 60-90 min shear, 750-1000ppm ethanol and 250-500ppm ethyl acetate level. For importance, only skin flux give highest 5, any other factors considered 3. Based on these responses, the Design-Expert® software defined a series of possible combinations of process parameters that are predicted to provide a high quality matrix and closeness of fit to the criteria for each solution as shown in table 9. In figure 15, the closeness of fit to desirable matrix is indicated in color with red to reddish orange indicating a good fit to the criteria; while yellow-green-blue indicate progressively poorer comparisons to the desired criteria without identifying which parameters deviate from the desired level.

The design space described that captopril concentration and DPG concentration is the critical parameter and that is in between 8-12% captopril and 7-9% DPG in dry matrix. Oleyl alcohol concentration is proposed 1-4% in dry matrix. After design of experiment evaluation, responses of DOE was well within range, e.g. DPG above 90%, human cadaver skin flux ratio within 1.4-1.5mcg/hr. peel between 33-36g/mm, tack within 29-30g/mm2, shear in 80-90min and residual solvents like ethanol below 1000ppm and ethyl acetate below 500ppm.

Figure 16: Design Space for Zone 2 at 500C Red Indicates Higher Desirability and overlay plot

The overlay plot shown in Figure 16 was used to identify an appropriate design space for each factor that would ensure that the targets for all quality attributes are met

concurrently. Factor C, OA concentration was selected as a constant at 3.0% w/w in dry form and also drying time and drying temperature remain constant at 30 as a factor D and E.

Other main factor captopril concentration and DPG content per patch was variable to get the desired design space to get the good drug delivery form the skin. In design space with green color, we got the desired delivery of skin flux with other adhesion parameter and DPG content per patch. In gray zone, one or more response may be failed to meet the desired criteria; other two parameters like captopril and DPG content per patch were important and variable for design space.

CONCLUSION:

Drug delivery from the skin through the transdermal system is the critical parameter for development. Captopril and DPG concentration in the patch is the main factor that effect on delivery. DPG concentration in patch is also effected by the drying parameter, time and temperature so for the delivery of captopril from patch, captopril and DPG concentration and drying time and temperature is the critical parameters. Captopril and DPG concentration in patch gives the positive effect and drying temperature and time give the negative effect on delivery. Oleic acid concentration is not much impact on the drug delivery and adhesion properties of the patch. Captopril concentration is between 8-12% w/w and dipropylene glycol concentration is between 7-9% w/w required to get the desired delivery of captopril from skin in the range of 1.4-1.5 mcg/hr. Higher concentration of dipropylene glycol and oleic acid should be evaluate in wear study after finalization from in-vitro adhesion study.

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