IJPSR (2020), Volume 11, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 December 2019; received in revised form, 13 February 2020; accepted, 18 February 2020; published 01 December 2020

DESIGN SPACE EVALUATION OF FORMULATION AND PROCESS VARIABLES OF REPAGLINIDE TRANSDERMAL THERAPEUTIC SYSTEM

Dhavalkumar Pethani * [1] and Shailesh Prajapati [2]

Department of Pharmaceutical Sciences [1], Hemchandracharya North Gujarat University, Patan - 384265, Gujarat, India.
Kalol Institute of Pharmacy [2], Gandhinagar - 382721, Gujarat, India.

Keywords:

Repaglinide, Quality by design, Transdermal, patch, Critical quality attributes, Design space

Correspondence to Author:
Dhavalkumar Pethani

Ph.D. Student,
Department of Pharmaceutical Sciences, Hemchandracharya North Gujarat University, Patan - 384265, Gujarat, India.

E-mail: dcpethani@gmail.com

ABSTRACT: Repaglinide, a blood-glucose-lowering drug, has low oral bioavailability (56 %) due to first-pass metabolism and shorter half-life (~1 hour) lead to frequent dosing to control blood glucose level. Repaglinide Transdermal Therapeutic System (TTS) was prepared to provide continuous drug delivery for a prolonged period of time. Factors affecting critical quality attributes (CQA) of Repaglinide TTS are optimization of drug load in the adhesive matrix, selection of design, selection of permeation enhancer, matrix thickness, optimization adhesive characteristics, and optimization of delivery rate for a prolonged period of the time. In this research, the impact of critical material attributes (CMA), for example, the concentration of API and permeation enhancers, were studied on CQA like drug delivery and adhesive performance of the product using optimal full factorial design. Moreover, critical process parameters (CPP) were identified using the response surface method, and the impact of identified CPP (drying temperature) on CQA (residual solvents) was evaluated. The results of the design of the experiments study indicate a significant impact of API and permeation enhancer concentration on drug delivery along with mixed impacts on adhesion characteristics. A statistical model was determined based on the relationship between CMA, CPP, and CQA for predictability of the results in design space, and further, this model was validated based on % prediction error. The skin flux results show that Repaglinide TTS can provide the sustain drug delivery over the time period of 72 h.

INTRODUCTION: Repaglinide (RP) is an oral antidiabetic drug of the meglitinide category. Mechanism of action of Repaglinide is blocking of potassium channel (ATP-dependent) of beta cells of the pancreas to inhibit insulin secretion and thereby lower blood glucose level.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(12).6198-06

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(12).6198-06

The reported oral bioavailability of RP is 56% [1] due to extensive hepatic first-pass metabolism. Plasma concentrations of RP fall rapidly, reaching pre-dose concentrations within 4 or 5 h after oral administration of 2 mg Rg [2].

RP has a very shorter half-life of about 1 h, and therefore, a multi-dose regimen per day generally preferred. RP is available in oral dosage forms on the market. Considering the physicochemical characteristic of RP supports the development of the transdermal therapeutic system (TTS). The skin permeability of RP through human skin was reported in several papers [3].

The objective of this work was to evaluate the impact of formulation and process variables on the development in transdermal drug delivery containing RP. The investigational study was conducted in two stages to optimize the formulation design. The former dealt with study of skin permeation enhancers (SPEs) and drug load in an adhesive matrix to improve the RP permeability through human skin using factorial design. This study appears of interest since limited works on transdermal research performed for RP [4, 5, 6].

Transdermal patches usually contain the drug-containing adhesive blend, which is coated onto polyester film as a solution from which the solvent is then removed using appropriate drying process. In this event, knowledge, and control of the levels of residual solvents is important quality attributes [7]. Ideally, residual solvents of TTS are adequately low so that they do not pose a safety concern nor impact the functional and performance properties of the TTS [8]. Higher levels of the residual solvents may lead to skin irritation. Therefore, it is desirable to minimize the amount of residual solvents in the patch as much as possible. Thus, in the latter stage of the development, process development was performed using a response surface method to minimize residual solvents in the formulation.

In the transdermal manufacturing process, a critical process that may affect the CQAs (residual solvents) of the product is the drying process. Drying parameters like drying temperature, blower speed, and residence time in a drying oven may affect the level of the residual solvent in the drug product.

MATERIALS AND METHODS:

Materials: The drug Repaglinide base was obtained as a gift sample from Zydus Cadila, Ahmedabad, India. Pressure-sensitive adhesive (PSA) Durotak® 87-900A and Durotak® 87-2516 were obtained as a gift sample from Henkel (Drogenbos, Belgium). Human Cadaver skin samples were obtained from Science Care Inc. (Philadelphia, USA). Isopropyl Palmitate was supplied by Signet chemical corporation privet limited. (Mumbai, India). Oleic acid was obtained from the Croda Chemicals (India) private limited (Mumbai, India). Scotchpak™ 9733, CoTran™ 9720, Scotchpak™ 9744 and Scotchpak™ 1109 were obtained from 3M India Limited (Mumbai, India). Other chemicals, solvents, and reagents were of analytical grade.

Optimal Full Factorial Design: In repaglinide TTS, drug concentration and permeation enhancer concentration were varied using the design of experiments to understand the individual and interactive effects of each formulation component. Varying amount of each component was compensated using polymer, *i.e.,* Durotak 87-2516, to derive the final dry matrix weight. Optimal full factorial design was used to study the effect of drug and permeation enhancer concentration on drug delivery and *in-vitro* adhesion characteristics of the final formulation. Three continuous independent formulation variables were selected for the design: AI concentration (X1), propylene glycol concentration (X2), and oleic acid concentration (X3). Each independent variable was investigated at lower and higher levels in the formulation. The full factorial design is presented in **Table 1**.

The effect of formulation variables on the skin flux of RP and *in-vitro* adhesion properties (peel and shear) were investigated. The results were evaluated using design expert® software, including the main effects and the interaction terms. For each response variable, a multiple regression model fitted the data ($p<0.05$). The insignificant terms were eliminated by the forward elimination process to adjust the model. Design expert® software (Stat-Ease, Inc., USA) was used to analyze the data.

Box-Behnken Design: Box-Behnken design is well-known for process optimization study [9, 10]. Box-Behnken design is a response surface methodology to evaluate the impact of different process variables on the specific response. This tool analyses and evaluate the data based on a statistical calculation to understand the relationship between studied variables and responses. Three continuous independent process variables were selected for the design: Drying Temperature (°C) (X1), Blower Speed (X2), and Residence time (X3). Each independent variable was investigated at lower and higher levels during the process. The design is presented in **Table 2**. The effect of process variables on the residual solvents in the formulation (peel and shear) were investigated. The results were

evaluated using design expert® software, including the main effects and the interaction terms.

Repaglinide TTS Preparation: The adhesive blend was prepared by mixing the ingredients into the adhesive polymer in order to obtain formulation samples with the composition reported in **Table 1.** These blends were cast at a specified doctor knife gap of Mathis coater (Mathis, Switzerland) onto Scotchpak 9744 (release liner) and dried in an oven at 60 °C for 20 min. The dried adhesive matrix film then laminated with Scotchpak 1109 (backing film) at lamination pressure of 3.0 bar using laminator (LL-100, ChemInstruments, Fairfield, Ohio).

TABLE 1: DESIGN RUN AND ANALYTICAL RESULTS FOR FORMULATION VARIABLES

Run	Repaglinide (%w/w)	Propylene glycol (%w/w)	Oleic acid (%w/w)	Durotak 87-2516 (%w/w)	Tack (gm/19.6 mm^2)	Shear (Min)	Flux (µg/cm^2/hr)
1	5	7	5	78	752	83	5.06
2	5	7	1	82	714	115	3.98
3	10	3	1	82	594	183	4.34
4	10	7	1	78	642	156	5.42
5	10	7	5	74	689	123	7.34
6	5	3	5	82	684	126	4.12
7	5	3	1	86	604	157	3.31
8	5	3	1	86	594	149	3.46
9	5	7	1	82	697	124	4.09
10	10	3	5	78	638	164	6.39
11	10	7	5	74	701	136	7.19
12	10	3	1	82	578	171	4.21
13	10	3	5	78	647	176	6.14
14	5	7	5	78	734	94	5.11
15	10	7	1	78	659	168	5.61

TABLE 2: DESIGN RUN AND ANALYTICAL RESULTS FOR PROCESS VARIABLES

Run	Drying Temperature (˚C)	Blower speed (RPM)	Residence time (Min)	Ethyl acetate (ppm)	n-Heptane (ppm)
1	65	1500	30	254	1249
2	65	1100	20	309	1658
3	50	700	20	759	3159
4	50	1500	20	623	2687
5	65	1500	10	352	1892
6	80	700	20	145	759
7	80	1100	30	95	328
8	80	1500	20	129	549
9	50	1100	30	559	2406
10	65	700	30	359	1589
11	80	1100	10	206	1194
12	65	700	10	319	2166
13	50	1100	10	749	3687
14	65	1100	20	287	1594
15	65	1100	20	298	1610

Repaglinide Assay by HPLC Method: The patch matrix was dissolved in a mixture of methanol and pH 4.5 phosphate buffer (7:3). Dilute with additional diluent (a mixture of methanol and pH 4.5 phosphate buffer) to achieve a concentration of about 80 mcg/ml. Sonicate the sample for 20 minutes and filter a portion of the solution. The system consisted of a Shimadzu LC-20AT low-pressure gradient solvent delivery module and a 245 nm diode array detector. A thermo-fisher synchronize C-18 column with 4.0 mm × 60 mm contain 5 µm particle size was used for the elution. A mobile phase, a mixture of methanol and pH 2.5 phosphate buffers (7:3) was delivered at a flow rate of 1.0 ml/min. the column temperature is maintained at 40 °C.

Tack Test: Adhesive property of the transdermal patch matrix can be represented by tack value. The test sample should be stored in a conditioning

chamber at controlled room temperature for 24 h before the test. Remove the release liner of the test specimen and place the test sample in such a way that the adhesive matrix side is facing upward side on the platform of the universal testing machine. Operate the instrument probe at a speed of 305 mm/min to touch the surface of the test specimen. After a dwell time of 2 ± 0.01 sec, separate the probe of the instrument at the same speed of 305 mm/minute. Record the force required to separate the probe from the adhesive matrix. Average of five measurements shall be reported as tack value.

Shear Test: Shear adhesion indicates the cohesive property of the transdermal patch adhesive matrix [11, 12]. Low cohesion in the patch may result in the formation of adhesive strings beyond the perimeter of the patch (cold flow) during stability and in-use condition on the skin, or adhesive residues transferred to packaging material [13]. To perform a shear test, cut the sample in size of 1-inch width and 2-inch length. After removing the release liner of the test specimen, apply on the stainless steel plate to cover an area of about 1 × 1 inch. Load the test panel, sample, and shear clip into the appropriate panel holder. Attached 200 gm standard weight at the free end of the test specimen and record time to fall down the weight. Record the average shear of five measurements.

***Ex-vivo* Skin Permeation Method:** Human cadaver skin samples were heat separated by immersing in the water at 45 °C to 60 °C for 60 sec and separate the stratum corneum from the dermis using blunt forceps [14, 15]. *Ex-vivo* skin permeation was performed in a modified Franz diffusion cell (cell capacity of 10 ml, the surface area was about 2 cm^2) using human cadaver skin samples. Cut the transdermal patch using 3 cm^2 circular die tools. After removing the release liner, the patch was placed on top of the appropriate skin sample and ensured for proper adhesion of the patch. The patch was applied to the receptor compartment and slightly overlapped the edges of the cell opening. The donor compartment was placed on the top and clamped each cell. The receptor compartment was filled with phosphate-buffered pH of 7.4. The entire assembly was magnetically stirred and maintained at a temperature of 32.0 + 0.5 °C for 72 h. The experiment was triplicated, and the mean result recorded. At predetermined time points, samples were withdrawn by complete decantation from the receptor compartment using a dropper and refill the cells with fresh media at defined withdrawal time points.

The samples were analyzed to detect drug concentration transport through the skin. At the end of the permeation experiment, all the skin samples were visually inspected for any visible damage or abnormalities. REPA permeated in μg/cm^2 at each time points were calculated and a graph of cumulative permeation (μg/cm^2) *vs.* Time (hrs.) was plotted. The slope of the graph for each time point was calculated from the linear regression curve obtained from the graph of Cumulative permeation and reported Skin flux (μg/cm^2/hr) [16].

RESULTS AND DISCUSSION:

Design Space Model for Formulation Variables: Results of the various responsibilities of the formulation design study are provided in **Table 1**. These responses, *i.e.,* tack, shear, and skin flux, were analyzed using design expert software for its main effects and interaction effects on the formulation characteristics. Design space evaluation of the formulation was performed to study the impact of concentration of critical components, *i.e.,* API and permeation enhancers of the formulation on critical quality attributes of the transdermal patches, i.e., drug delivery and *in-vitro* adhesion properties. Data shows that there is a significant impact of each factor on the product CQA.

Response Analysis: Tack: Based on the evaluation of half-normal plot, Pareto chart, and interaction plots, the significant factors affecting the tack of transdermal patches were determined, and these plots are provided in **Fig. 1**. Pareto chart clearly shows that Factor B, C, and A crosses the Bonferroni limit, and therefore, these factors significantly affect the tack performance of the product. Factor B and C (*i.e.,* PG and oleic acid concentration) have positive effects on tack, meaning that as the concentration of these components increase, tack value increases, whereas repaglinide concentration has a negative impact on the tack. According to the ANOVA summary, F value of 54.06 implies that the model is significant. There is only a 0.01 % chance that a 'Model F-value' this large could occur due to noise. The R-

squared summary indicates that "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable, and 20.888 indicates an adequate signal. This model can be used to navigate the design space. The interaction plot of factors BC shows that at average repaglinide concentration, tack value increases with increasing concentration of PG and oleic acid. In contrast, the interaction plot of factors AB indicates that at average oleic acid concentration, tack value decreases even if the increase in PG concentration.

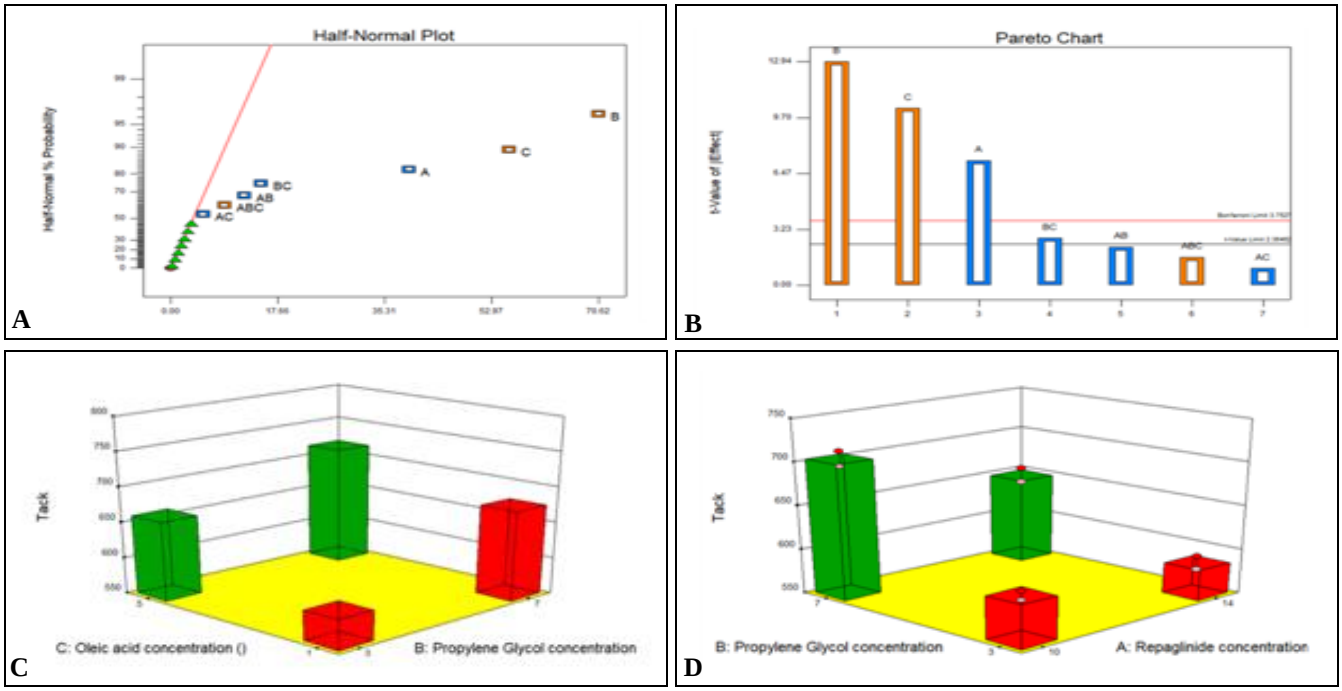

FIG. 1: RESPONSE ANALYSIS-TACK: (A) HALF NORMAL PLOT; (B) PARETO CHART; (C) INTERACTION PLOT OF FACTOR B AND C; (D) INTERACTION PLOT OF FACTOR A AND B.

Response Analysis: Shear: Based on the evaluation of half-normal plot, Pareto chart, and interaction plots, the significant factors affecting the tack of transdermal patches were determined, and these plots are provided in **Fig. 2**.

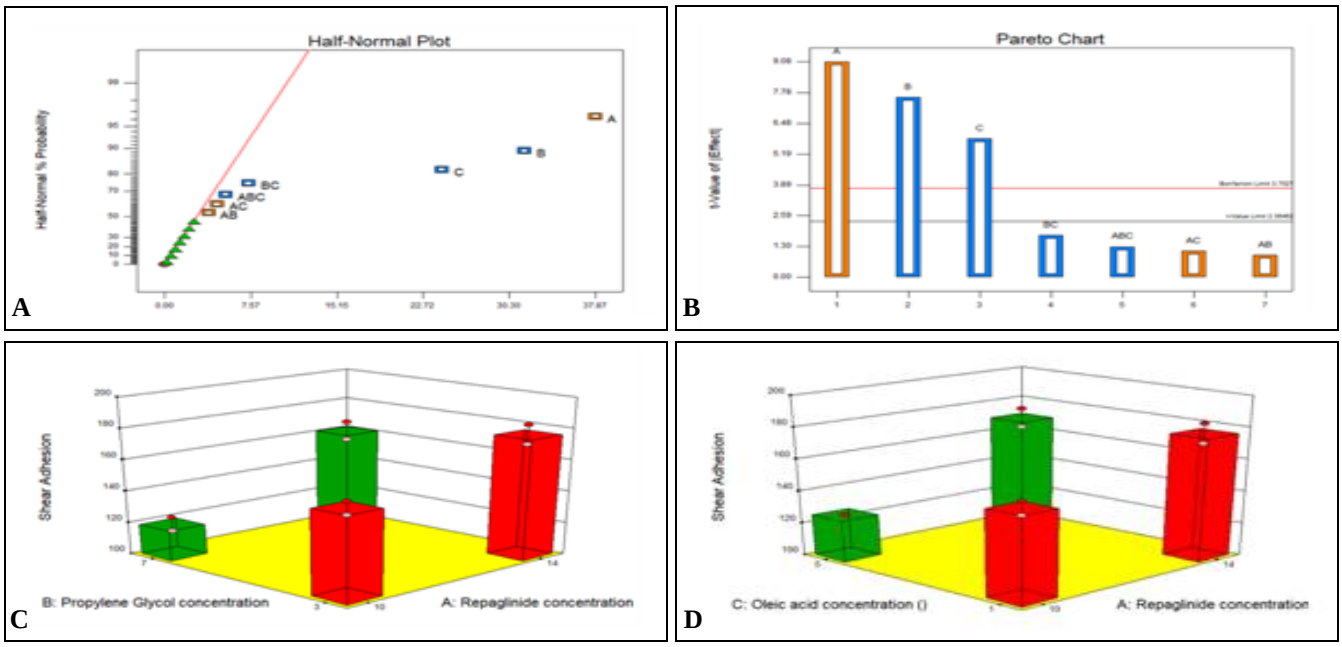

FIG. 2: RESPONSE ANALYSIS-SHEAR: (A) HALF NORMAL PLOT; (B) PARETO CHART; (C) INTERACTION PLOT OF FACTOR A AND B; (D) INTERACTION PLOT OF FACTOR A AND C

Pareto chart clearly shows that Factor A, B, and C crosses the Bonferroni limit, and therefore, these factors significantly affect the cohesive strengths (shear value) of the product. Factor A (*i.e.*, repaglinide concentration) has positive effects on the shear, meaning that as the concentration of this component increase, the shear value increases while, in contrast, PG and oleic acid concentration have a negative impact on the shear. According to the ANOVA summary, the F value of 28.52 implies that the model is significant. There is only a 0.01 % chance that a 'Model F-value' this large could occur due to noise. The R-squared summary indicates that "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable, and 15.3999 indicates an adequate signal. This model can be used to navigate the design space. The interaction plot of factors AB shows that at average oleic acid concentration, the sheer value increases with increasing concentration of Repaglinide and PG. In contrast, the interaction plot of factors AC indicates that at average PG concentration, shear value decreases even if an increase in oleic acid concentration.

Response Analysis: Average Flux Rate: Pareto chart clearly demonstrates that Factor A, B, C, and interaction term AC crosses the Bonferroni limit, and therefore, these factors significantly affect the average skin flux rate of the product. All these factors have positive effects on the average skin flux rate of the drug, meaning that as the concentration of this component increase, average skin flux rate increase. According to the ANOVA summary, F value of 261.23 implies that the model is significant. There is only a 0.01% chance that a 'Model F-value' this large could occur due to noise. The R-squared summary indicates that "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable, and 47.507 indicates an adequate signal. This model can be used to navigate the design space. Interaction plot of factors AC and factors AB clearly evident that synergistic effects on the flux rate of repaglinide as an increase in the concentration of oleic acid and propylene glycol. The impact of oleic acid concentration is higher on the skin flux rate of repaglinide when compared to propylene glycol.

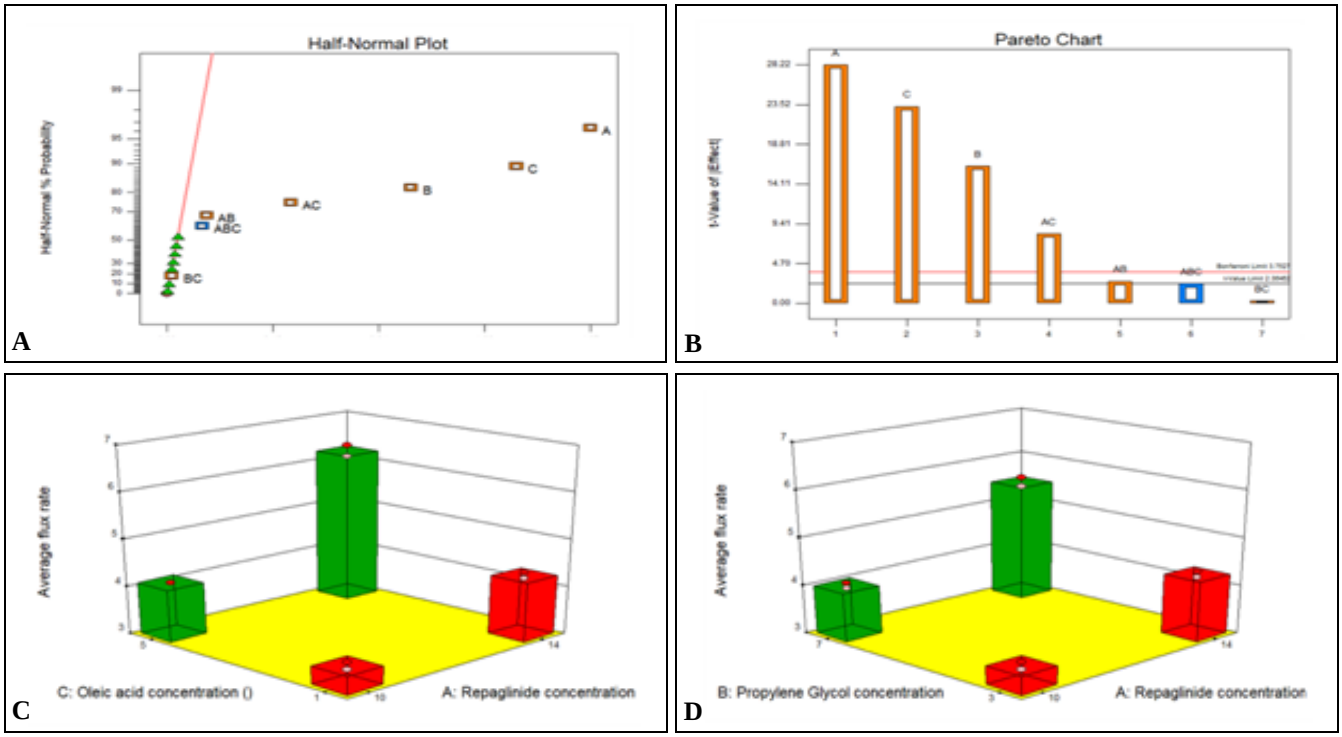

FIG. 3: RESPONSE ANALYSIS-SKIN FLUX: (A) HALF NORMAL PLOT; (B) PARETO CHART; (C) INTERACTION PLOT OF FACTOR A AND C; (D) INTERACTION PLOT OF FACTOR A AND B

Design Space Model for Process Variables: Design space study of the manufacturing process was performed to understand the impact of critical process parameters like drying temperature, blower speed, and residence time on critical quality attributes of the transdermal patches *i.e.*, residual

solvents content. Data shows that there is a significant negative impact of drying temperature on the product CQA, and the other two factors (blower speed and residence time do not have a significant impact on the residual solvent content of the drug product.

Response Analysis: Ethyl acetate: According to ANOVA summary, F value of 35.96 implies that the model is significant. There is only a 0.05 % chance that a 'Model F-value' this large could occur due to noise. The R-squared summary indicates that "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable, and 17.342 indicates an adequate signal. This model can be used to navigate the design space. The normal probability plot indicates that all the residuals follow a normal distribution, wherein all points follow a straight line; indicates that all residuals are normal.

Contour plot and surface plot for ethyl acetate showing the effect of temperature and blower speed at fixed residence time is presented in **Fig. 5**. According to the data of the plot, there is a significant negative impact of the drying temperature on ethyl acetate content of the drug product. For example, as temperature increase from 50 °C to 74 °C, ethyl acetate content in the drug product reduced from 700 ppm to 200 ppm. Moreover, **Fig. 4** also evident that blower speed and residence time do not have any significant impact on the ethyl acetate content of the drug product.

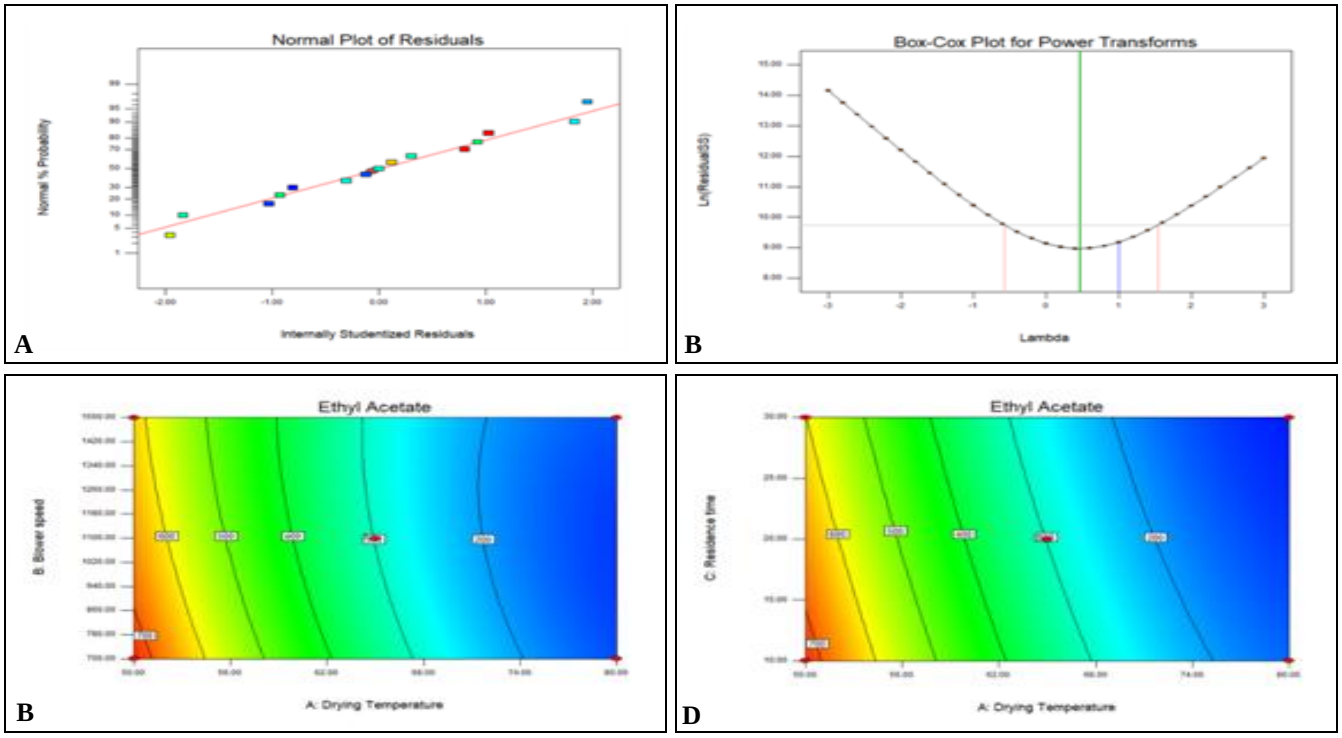

FIG. 4: RESPONSE ANALYSIS-ETHYL ACETATE: (A) NORMAL PLOT OF RESIDUALS; (B) BOX-COX PLOT; (C) CONTOUR PLOT OF FACTOR A AND B; (D) CONTOUR PLOT OF FACTOR A AND C

Response Analysis: n-Heptane: According to ANOVA summary, F value of 205.14 implies that model is significant. There is only a 0.05 % chance that a 'Model F-value' this large could occur due to noise. R-squared summary indicates that "Adeq Precision" measures the signal to noise ratio.

A ratio greater than 4 is desirable, and 43.380 indicates an adequate signal. This model can be used to navigate the design space. The normal probability plot **Fig. 5** indicates that all the residuals follow a normal distribution, wherein all points follow a straight line; indicates that all residuals are normal.

Box cox plot **Fig. 5** provides a guideline for selecting the correct power law transformation. A recommended transformation is listed, based on the best lambda value, which is found at the minimum point of the curve generated by the natural log of the sum of squares of the residuals. If the 95% confidence interval around this lambda includes 1

then the software does not recommend a specific transformation. For n-Heptane, the recommended transformation is a square root. Therefore, transformation done for square root and data analyzed.

Contour plot and surface plot for n-heptane showing the effect of temperature and blower speed at fixed residence time is presented in **Fig. 5**. According to the data of the plot, there is a significant negative impact of the drying temperature on the n-heptane content of the drug product. For example, as temperature increase from 50 °C to 74 °C, n-heptane content in the drug product reduced from approximately 3000 ppm to 1000 ppm.

Moreover, blower speed and residence time do not have any significant impact on the n-heptane content of the drug product.

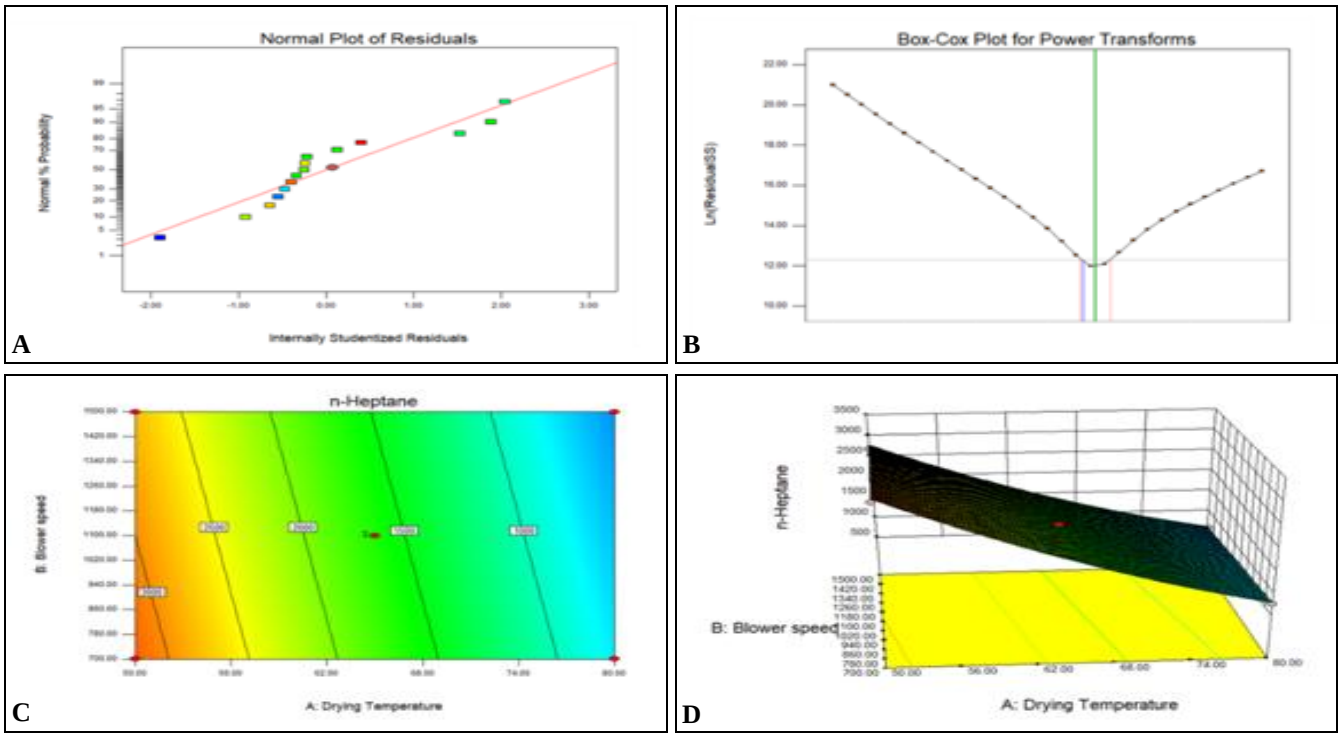

FIG. 5: RESPONSE ANALYSIS- N-HEPTANE (A) NORMAL PLOT OF RESIDUALS; (B) BOX-COX PLOT; (C) CONTOUR PLOT OF FACTOR A AND B; (D) 3D CONTOUR PLOT OF FACTOR A AND B

CONCLUSION: Based on the design space study and considering the impact of various factors, the highest flux rate (7.34 mcg/cm^2/hr) was observed for the formulation containing 6% of repaglinide, 7% of propylene glycol and 5% of oleic acid. This flux rate and cumulative permeation are very close to target delivery of about 2 mg repaglinide per day for an extended period of 72 h. The concentration of RP, propylene glycol and oleic acid have significant ($p<0.05$) on drug delivery through the skin.

Design space study of the manufacturing process was performed to understand the impact of critical process parameters like drying temperature, blower speed, and residence time on critical quality attributes of the transdermal patches *i.e.*, residual solvents content. Data shows that there is a significant negative impact of drying temperature on the product CQA, and the other two factors (blower speed and residence time do not have a significant impact on the residual solvent content of the drug product. It is always desirable to have minimum residual solvents in the transdermal drug product, and mostly compliance criteria shall be determined based on ICH guidance or USP chapter 463. These model can be suitable to navigate the design space to derive the process parameters which provides the acceptable response.

ACKNOWLEDGEMENT: Authors would like to acknowledge Zydus Cadila (Ahmedabad, India) for providing repaglinide and Zydus Technologies Ltd. (Ahmedabad, India) for providing pressure-sensitive adhesives as generous gift samples.

Authors appreciate the support of department of pharmaceutics, Kalol Institute of Pharmacy (Gujarat, India), for their support during this work.

CONFLICTS OF INTEREST: Authors report no conflict of interest.

REFERENCES:

1. El-Maghraby GM, Osman MA, Abd-Elrahman HE and Elsisi AE: Self emulsifying Liquisolid tablets for enhanced oral bioavailability of repaglinide: *In-vitro* and *in-vivo* evaluation. Journal of Applied Pharmaceutical Science 2014; 4(09): 012-021.
2. Liang-Chen W, Fu-Sheng F, Yan-Ping G, Guang Y and Chun-Lin L: Characteristics of repaglinide and its mechanism of action on insulin secretion in patients with newly diagnosed type-2 diabetes mellitus. Medicine 2018; 97: 38.
3. Shinde UA, Modani SH and Singh KH: Design and development of repaglinide microemulsion gel for transdermal delivery. AAPS PharmSciTech 2018; 19(1): 315-25.
4. Zaman M, Khalid U, Khan NUH, Sultana K, Hanif M and Aftab K: Polymeric transdermal drug delivery system of ramipril and repaglinide: *in-vitro* and *ex-vivo* evaluation. EC Pharmacology and Toxicology 2017; 4(1): 20-32.
5. Sahu M, Bhowmick M and Rathi J: Preformulation screening of repaglinide for transdermal anti-diabetic therapy. Journal of Drug Delivery & Therapeutics 2017; 7(4): 103-09.
6. Reddy RPS, Bose PSC, Sruthi V and Saritha D: Investigation of Kondagogu gum to develop transdermal film of repaglinide. Asian J Pharm Clin Res 2018: 11(4): 440-45.
7. Goswami T and Audett J: Chemistry, manufacturing and controls in passive transdermal drug delivery systems. Therapeutic Delivery 2015: 6(9).
8. Buskirk GAV: Passive transdermal systems white paper incorporating current chemistry, Manufacturing and Controls (CMC) Development Principles. PharmSciTech AAPS 2012; 13(1): 218-30.
9. Sharma D, Maheshwari D, Philip G, Rana R, Bhatia S, Singh M, Gabrani R, Sharma SK, Ali J, Sharma RK and Dang S: Formulation and optimization of polymeric nanoparticles forintranasal delivery of lorazepam using box-behnken design: *in-vitro* and *in-vivo* evaluation. BioMed Research International 2014; 14.
10. Dahaghin Z, Mousavi HZ and Sajjadi SM: A novel magnetic ion imprinted polymer as a selective magnetic solid phase for separation of trace lead(II) ions from agricultural products, and optimization using a Box–Behnken design. Food Chemistry 2017; 237: 275-81.
11. Satas D: Handbook of Pressure Sensitive Adhesive Technology. 3rd ed. Satas & Associates; 1999.
12. Cilurzo F, Gennari CGM and Minghetti P: Adhesive properties: A critical issue in transdermal patch development. Expert Opinion on Drug Delivery 2012; 9(1): 33-45.
13. Wokovich AM, Prodduturi S, Doub WH, Hussain AS and Buhse LF: Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eur J Pharm Biopharm 2006; 64: 1-8.
14. Eman A, Yousef SA, Pastore MN, Telaprolu K, Mohammed YH, Namjoshi S, Grice JE and Roberts MS: Skin models for the testing of transdermal drugs. Clin Pharmacol 2016; 8: 163-76.
15. Zhang Q, Murawsky M, LaCount T, Hao J, Kasting GB, Newman B, Ghosh P, Raney SG and Li SK: Characterization of temperature profiles in skin and transdermal delivery system when exposed to temperature gradients *in-vivo* and *in-vitro*. Pharm Res. 2017; 34(7): 1491-04.
16. Akram MR, Ahmad M, Abrar A, Sarfraz RM and Mahmood A: Formulation design and development of matrix diffusion controlled transdermal drug delivery of glimepiride. Drug Des Devel Ther. 2018; 12: 349-64.

How to cite this article:
Pethani D and Prajapati S: Design space evaluation of formulation and process variables of repaglinide transdermal therapeutic system. Int J Pharm Sci & Res 2020; 11(12): 6198-06. doi: 10.13040/IJPSR.0975-8232.11(12).6198-06.