Development and characterization of transdermal patch of modified form of Brexpiperazol

Abstract:

Aim: Brexpiprazole (BPZ) is a typical antipsychotic drug used for the treatment of schizophrenia and depression. It is classified under BCS class-II with low aqueous solubility and high intestinal permeability. In the present investigation, a solid dispersion of BPZ was prepared to improve the solubility. A transdermal patch was optimized using the central composite design to control the delivery of BPZ.

Place and Duration of Study: The formulation was prepared and characterized at K. B. Institute of Pharmaceutical Education and Research, Gandhinagar, Gujarat, India during January 2021 to September 2021.

Methodology: A solid dispersion of BPZ was prepared using PEG 6000.A transdermal patch of BPZ was prepared and optimized using central composite design. Independent variables were fixed as ratio of RLPO: RSPO=2:1 (X_1) and conc. of plasticizer (Triacetin) %W/W of polymer (X_2). Dependent variables were fixed as folding endurance% (Y1) and cumulative % drug release at 24, 48, 72 and 96 hrs respectively (Y2-Y5) for the optimization of transdermal patch of SD of BPZ. Optimized formulation was characterized fully for its safety and efficacy using *ex-vivo* permeation study, skin irritation study and stability study.

Result: The tensile strength of optimized patch was 2.1±0.045 Kg/cm^2. The thickness and hardness of patch was 0.0478±0.025 and 80.54±2.64gm/mm. The moisture content and moisture uptake values were 5.2%±0.36 and 6.21±0.24% respectively. Drug content was found to be 99.41±2.64%. The flux value obtained from BRX-SD-TP was 0.06 µg/cm^{2}h. The flux was very proximal to the desired flux value. Prepared formulation was non-irritant and stable.

Conclusion: From the findings it can be concluded that BRX-SD-TP was successfully developed for treatment of Schizophrenia.

Key Words: Brexpiprazole , Schizophrenia, Solid dispersion, Central composite design, Trasndermal Patch.

1. Introduction

Schizophrenia exhibits typical positive (hallucination, delusion, thought disorders) and negative (social withdrawal, lack of energy, emotion and motivation) symptoms affecting daily activities and inadvertently requires drug therapy.[1]

The treatment of schizophrenia remains challenging, as knowledge about its pathophysiology and sub grouping of this heterogeneous group of disorders is lacking.[2]

Currently, the treatment of schizophrenia and other psychotic disorders, such as bipolar disorder, is supported by the availability of a large number of antipsychotic drugs; however, their beneficial effects are sometimes hampered by the adverse effects, which can be different, based not only on patient characteristics but also on the medicinal product.[3,4]

Brexpiprazole (BRX) is an atypical antipsychotic that was approved by the US Food and Drug Administration in July 2015 for treatment of schizophrenia and as an adjunctive therapy to antidepressant medications for the treatment of major depressive disorder (MDD).1 While the mechanism of action for brexpiprazole is unknown, it is believed that the combination of partial agonist activity at the serotonin 5-hydroxytryptamine (HT)1A and dopamine D2 receptors and antagonist activity at serotonin 5-HT2A mediates its efficacy. Brexpiprazole also has some affinity for the dopamine D3 (Ki 1.1 nM), noradrenergic α1A (Ki 3.8 nM), histamine H1 (Ki 19 nM), and muscarinic M1 (67% inhibition at 10 μM) receptors. [5]

The clinical limitations of the commercially available oral and injectable dosage forms for the delivery of antipsychotic drugs may be potentially overcome by their administration via the transdermal route. The later allows minimization of the liver first-pass effect, to avoid gastrointestinal irritation and drug degradation while maintaining a steady plasma drug concentration that results in a reduction of dosing frequency and adverse effects. Moreover, it is a convenient, painless, non-invasive way to self administer drugs and improve adherence to therapy. These all cumulatively increase patient compliance and uniform drug plasma concentration through medication period. [6]

BRX is classified under BCS class-II drugs i.e. a drug with lower solubility and high permeability. Since BRX is a poorly water-soluble drug, it is highly desirable to obtain modified form with improved solubility. [7]

So, in the present study an attempt have been made to increase solubility of BRX using solid dispersion approach in first phase and to incorporate the modified form into transdermal

patch in second phase. The developed formulation was characterized by different technique to assess its stability and performance.

2. Methods

Quantification of BRX using RP HPLC

Quantification of BRX was done by RP HPLC using Acetonitrile and Methanol (60:40) as mobile phase and Inertsil-ODS C18 (250×4.6 mm packed col, 5µ) as column. The flow rate was kept at 1.0 ml/min and mobile phase was run for 8 min. The volume of injection was 20 µl and detection wavelength was 215 nm. [8]

Preparation of Solid dispersion of BRX (BRX-SD)

Solid dispersions of BRX (BRX-SDs) were prepared by solvent evaporation method. An appropriate amount of carriers (PEG 6000/PVP K30/HPBCD) was added to solution of BRX in 15mL blend of acetone and dichloromethane (1:1). The solution was stirred at 60 rpm and the solvent was evaporated under reduced pressure at 40°C in a rotary flash evaporator for 2 h. The obtained solid dispersions were subsequently stored in a vacuum oven at room temperature for 48 h to remove the residual solvent. The dried solid residue was pulverized and sieved through 250 µm sieve. The samples obtained were stored in desiccator until use. [9]

Physicochemical characterization:

The developed BRX SDs were evaluated for various physicochemical parameters including yield, drug content, particle size and various micromeritic properties. Its structural characterization was done by FTIR and DSC. FTIR was performed by Shimadzu IR Prestige 21spectrometer (Shimadzu Europa GmbH, Germany), with a horizontal Golden Gate MkII single-reflection ATR system (Specac, UK). DSC analyses were performed using a Shimadzu DSC-50 (Shimadzu Scientific Instruments, USA) differential scanning calorimeter.

Preparation of BRX-SD loaded transdermal patch (BRX-SD-TP)

The casting solutions were prepared by dissolving weighed quantities of polymers in a solvent mixture. The SD (equivalent to drug) and plasticizer were added to the various polymer solutions individually and mixed thoroughly to form a homogenous mixture. It was kept aside without any disturbances to remove the entrapped air if any. About 3 ml of

casting solutions were pipetted into glass petriplate and allowed to dry at room temperature for 24 hrs followed by oven at 40-45° for 30 minutes.[10]

Optimization of BRX-SD-TP using central composite design (CCD)

Application of CCD [11,12]

The detail layout of CCD formulation batches are summarized in Table 1. The applied design was validated by SEG and its standard error was found. Independent variables were fixed as ratio of RLPO: RSPO=2:1 (X_1) and conc. of plasticizer (Triacetin) %W/W of polymer (X_2). Dependent variables were fixed as folding endurance% (Y1) and cumulative % drug release at 24, 48, 72 and 96 hrs respectively (Y2-Y5).

Table 1. Layout of CCD batches

Batch	Coded values		Actual values	
	X_1	X_2	X_1	X_2
F1	-α	0	1.17157	10
F2	+ α	0	6.82843	10
F3	0	+ α	4	17.0711
F4	0	-α	4	2.92893
F5	-1	-1	2	5
F6	-1	+1	2	15
F7	+1	-1	6	5
F8	+1	+1	6	15
CP1	0.20	0.84	4.40	14.21
CP2	-0.655	0.07	2.69	11.70

Also to confirm the evolved model, different check point batches (CKP1 and CKP2) were formulated. % PE was also determined to assess the accuracy of evolved model. Detail ANOVA study was performed to under the significant and non significant impact of factors.

Percentage error (%PE) = [(Experimental value-Predicted value)/Experimental value]*100

Folding endurance

This test was carried out to check the efficiency of the plasticizer and the strength of the patch prepared using different polymers. The folding endurance is defined as the number of folds required to break any polymeric patch. The folding endurance was measured manually by repeatedly folding a small strip of the film (2×2 cm) at the same place until it broke. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance. Three patches of each type were taken for the test.

Surface pH

Patches were kept in contact with 0.5 ml of double distilled water for 1 h in glass tubes and were allowed to swell. A combined glass electrode was brought near the surface of patch and pH readings were taken after allowing an equilibration period of 1 min.

***Ex vivo* drug permeation**

Drug permeation study was carried out using the skin of male Wistar rats. The tissue was collected from local slaughter house. The skin samples were cut, removed, and washed with normal saline. The receptor compartment of the Franz diffusion cell was filled with 30 ml of phosphate buffered saline (pH 7.4). The BRX-SD-TP was applied over the skin of the rat in the donor compartment. The temperature of the assembly was constantly maintained at 37 ± 2 °C and the stirring rate controlled at 50 rpm. Samples (5 ml aliquots) were withdrawn at suitable time intervals and replaced with the same amount of medium to maintain the receptor phase volume to 30 ml. The samples were analyzed HPLC method. [13]

Stability study:

Stability study of BRX-SD-TP was carried out for 3 months, according to the ICH guidelines at room temperature and 40 ± 2 °C/75 ± 5% relative humidity (RH) using a stability chamber. The patch was evaluated for visual inspection, drug content, hardness, and moisture content and flux. [14]

Skin irritation study:

Dog skin was collected from local slaughter house and preserved in saline solution till further use. The skin was mounted on Franz diffusion cell and recipient compartment was filled by PBS 7.4. BRX-SD-TP was applied in donor receptor and after experiment histopathy study was performed. The study was also compared with normal control (distilled water) and positive control (IPA).

3. Result and Discussion

Quantification of BRX using RP HPLC

The drug showed linearity between 2 to 12 ppm concentration ranges. The drug run time was 8 min and RT was found at 3.90 min. The calibration curve and representative chromatogram of BRX is shown in Figure 1.

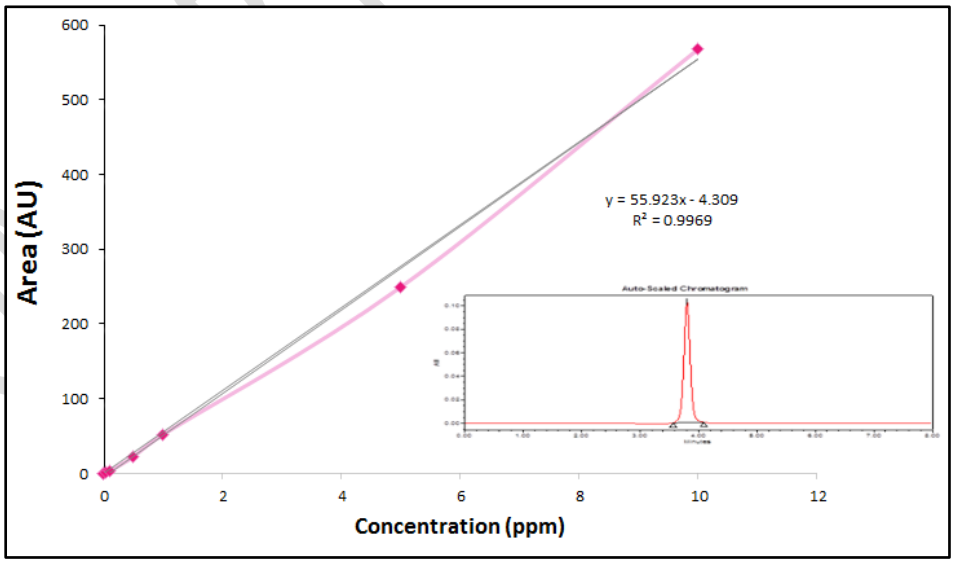

Figure 1. Calibration curve of BRX (HPLC)

Preparation of Solid dispersion of BRX (BRX-SD)

Different carriers were used to prepare solid dispersion of BRX. The increase in solubility of BRX due to different carriers is depicted in Table 2. Highest solubility was found in SD prepared with PEG 6000 at ratio of 1:2. So, PEG 6000 was selected further.

Table 2. Solubility of solid dispersion of BRX

Drug: Carrier	Ratio	Solubility (mg/ml)		
		Water	PBS 7.4	ABS 5.5
BP: PEG 6000	1:0	0.00415	0.00537	0.0434
	1:1	0.0082	0.0115	0.0634
	1:2	0.0124	0.0179	0.0951
	1:3	0.0104	0.0163	0.0897
BP:PVP K 30	1:0	0.00437	0.00627	0.049
	1:1	0.00754	0.00941	0.0602
	1:2	0.0103	0.0143	0.0864
	1:3	0.00984	0.0126	0.0822
BP: HPβCD	1:0	0.0047	0.00598	0.045
	1:1	0.00641	0.00748	0.0641
	1:2	0.00846	0.0122	0.0833
	1:3	0.00822	0.0105	0.0798

Optimization of BRX-SD-TP using central composite design (CCD)

Validation of CCD

Figure 3 shows standard error graph (SSG) of applied CCD. This graph represents over all standard error which is less than unity proving rationalized selection of CCD for given data set in formulation of BRX-SD-TP.

Application of CCD

The results of CCD batches are presented in Table 3. The results show that remarkable variation in data confirming sensitivity of selected in dependent variables (X1 and X2) on CQAs.

Table 3. Results of CQAs of CCD batches

Batch	X1	X2	Y1	Y2	Y3	Y4	Y5
C1	1.171573	10	24	34.19	59.15	86.12	96.89
C2	6.828427	10	28	26.89	51.08	75.005	91.55
C3	4	17.07107	36	38.55	59.18	87.89	98.99
C4	4	2.928932	19	30.18	52.18	78.16	93.15
C5	2	5	12	33.15	62.59	80.15	95.18
C6	2	15	30	34.15	62.56	85.89	99.16
C7	6	5	18	24.03	49.48	79.12	93.58
C8	6	15	31	30.98	59.88	76.48	92.01

The ANOVA analysis of selected dependent and independent variables is shown in Table 3. The significant and non-significant level of main, interaction and polynomial effect are denoted as ‘S’ and ‘NS’. Non-significant terms were omitted from full MLR equation and further reduced MLR equations were derived.

Table 4. ANOVA analysis of IVs and CQAs for BRX-SD-TP

CQAs	Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Y1	Model	398.7221	2	199.36	21.309	0.0036	Significant
	A	20.02449	1	20.024	2.1403	0.2033	
	B	378.6976	1	378.69	40.478	0.0014	
Y2	Model	121.7139	3	40.571	6.7524	0.0481	Significant
	A	63.92276	1	63.922	10.638	0.0310	
	B	48.94051	1	48.940	8.1453	0.0462	
	AB	8.850625	1	8.8506	1.4730	0.2916	
Y3	Model	171.0512	3	57.017	9.660	0.0264	Significant
	A	92.49838	1	92.498	15.672	0.0167	
	B	51.35655	1	51.356	8.7016	0.0420	

	AB	27.19623	1	27.196	4.6080	0.0984	
Y4	Model	138.6264	3	46.208	6.7012	0.0487	Significant
	A	85.53655	1	85.536	12.404	0.0244	
	B	35.53371	1	35.533	5.153	0.0857	
	AB	17.5561	1	17.556	2.546	0.1858	
Y5	Model	55.14808	3	18.382	9.2711	0.0284	Significant
	A	33.21899	1	33.218	16.753	0.0149	
	B	14.22846	1	14.228	7.1760	0.0553	
	AB	7.700625	1	7.7006	3.883	0.1201	

The detail ANOVA study reveals that the model best fits for all selected five responses (Y1-Y5). The MLR equations relating relation between CQAs and IVs are listed below.

Folding Endurance = +24.75 +1.58* A +6.88 * B

%CPR at 24h = +31.52-2.83 * A +2.47 * B +1.49 * A * B

%CPR at 48h = +57.01 -3.40 * A +2.53 * B+2.61 * A * B

%CPR at 76h = +81.10 -3.27 * A +2.11 * B -2.09 * A * B

%CPR at 96h = +95.06 -2.04 * A +1.33 * B -1.39 * A * B

Furthermore, the impact of independent variables (X1 and X2) on selected CQAs (Y1-Y5) was studied by contour plots. s. The contour plots (2D) for given responses are shown ion Figure 2.

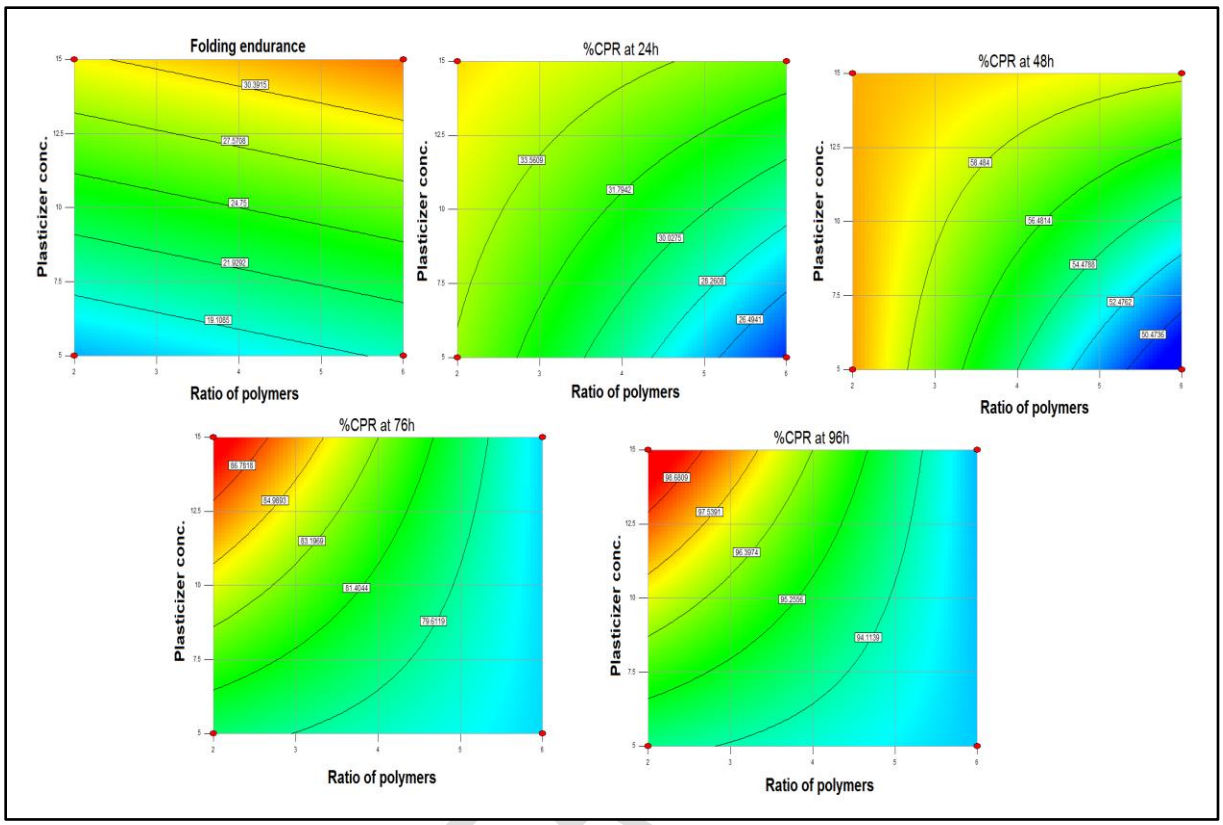

Figure 2. Contour plots of selected CQAs

Check point batches were defined from the yellow region of overlay plot (Figure 3) to find the validity of reduced MLR evolved models.

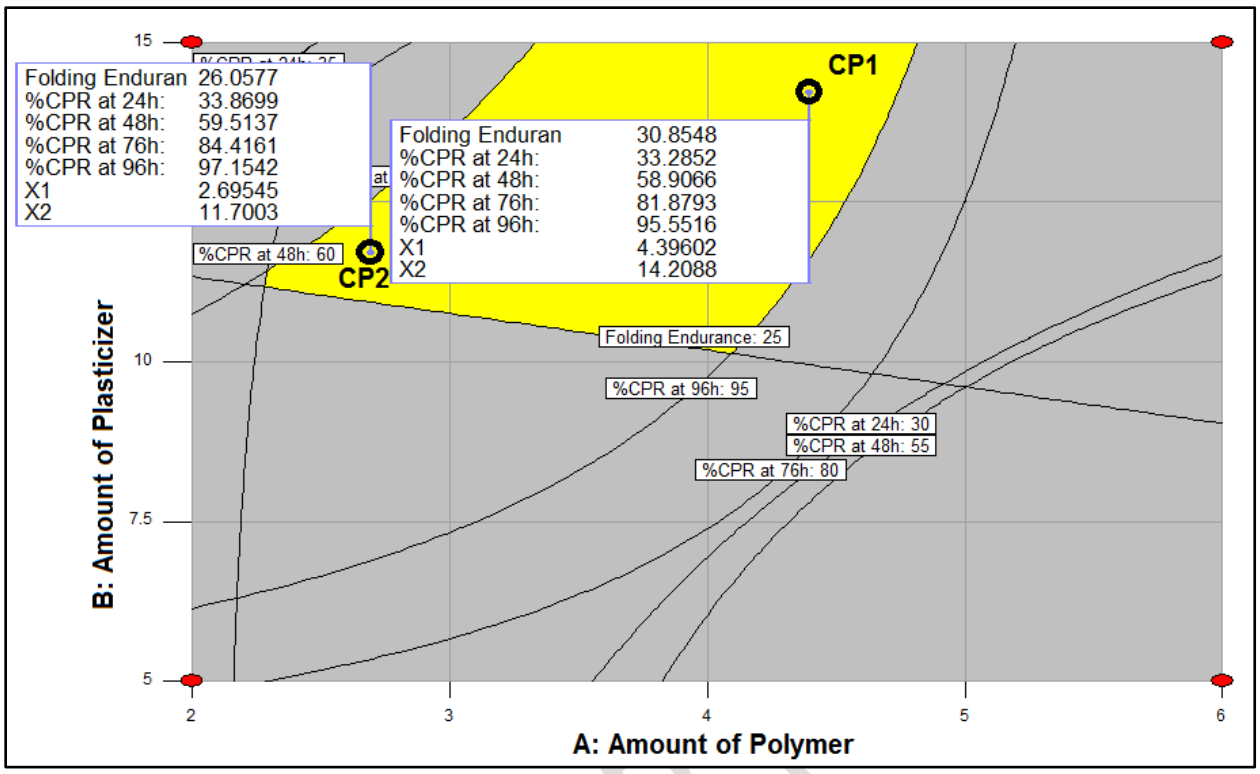

Figure 3. Derivation of Check point batch from overlay plot

% PE of check point batches were calculated and were found below 5% (Table 5), which proves the legitimacy of acquired models.

Table 5. %PE of check point batches

Check point batches	CQAs	Observed	Predicted	%PE
CP1	Y1	29.66	30.85	3.86
	Y2	31.84	33.28	4.33
	Y3	60.32	58.91	2.39
	Y4	78.42	81.88	4.23
	Y5	92.46	95.55	3.23
CP2	Y1	25.46	26.06	2.3
	Y2	32.56	33.87	3.87
	Y3	56.94	59.51	4.32
	Y4	82.45	84.42	2.33
	Y5	93.47	97.15	3.79

Characterization of BRX-SD-TP

Physicochemical parameters

The tensile strength of optimized patch was 2.1± 0.045 Kg/cm^2. The thickness and hardness of patch was 0.0478± 0.025 and 80.54± 2.64gm/mm. The moisture content and moisture uptake values were 5.2%± 0.36 and 6.21± 0.24% respectively. Drug content was found to be 99.41± 2.64%.

Ex vivo drug permeation study

There was a significant difference between cumulative % drug amount permeated from BRX-SD-TP and plain gel of BRX. The flux value obtained from BRX-SD-TP was 0.06 µg/cm^{2}h. The flux was very proximal to the desired flux value.

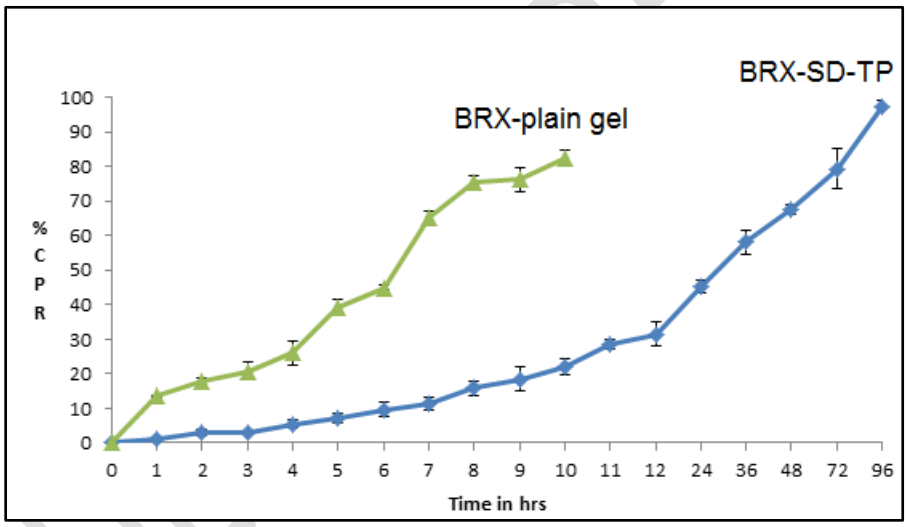

Figure 4. *Ex-vivo* drug permeation from BRX-SD-TP

Stability study

The results of stability study are shown in Table 6. Statistical test showed that there was no significant difference ($P > 0.05$) in quality attributing parameters existed between fresh and stored patches. This confirms stable characteristics of BRX after stipulated time period of stability study.

Table 6. Stability study data of BRX-SD-TP

Condition	Time	Hardness (gram/mm)	Moisture Content (%)	Drug content (mg/cm^2)	Flux (µg/cm^{2}h)	Sign of instability
RT	Initial	80.54±2.64	5.20%±0.36	99.41±2.64	0.060	No
	After 3 months	76.45±3.22	5.83%±0.44	99.98±3.14	0.058	No
40+ 2°C/ 75+5% RH	Initial	80.54±2.64	5.20%±0.36	99.41±2.64	0.06	No
	After 3 months	77.62±3.24	5.71%±0.56	99.87±2.05	0.056	No

Skin irritation study

Skin irritation of BRX-SD-TP must be studied as it would be staying in initiate contact with skin for longer time. Figure 5 shows histopathy images of BRX-SD-TP with IPA and control. Cell destruction is observed in IPA treated skin, whereas intact skin layers were found in both BRX-SD-TP and control. This reveals that developed formulation is safe to apply on skin for longer time.

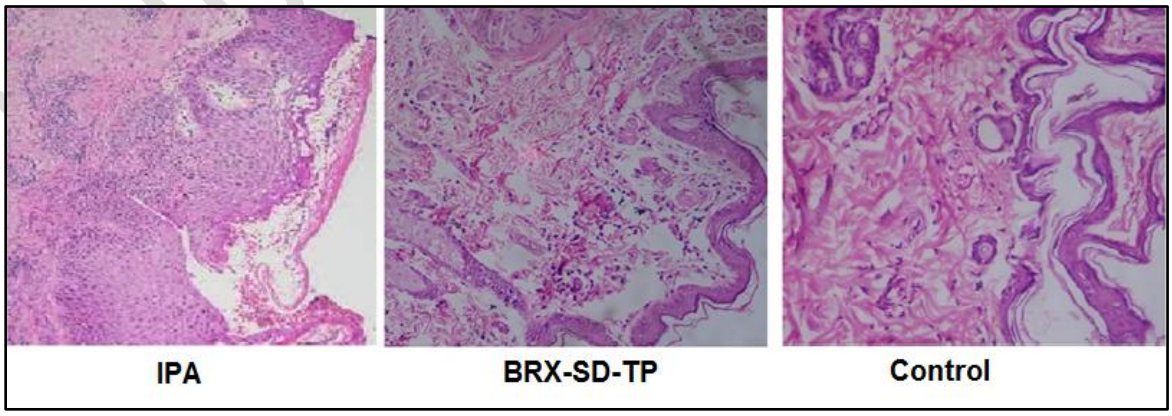

Figure 5. Comparative skin irritation study of formulation

4. Conclusion

From the findings it can be concluded that BRX-SD-TP was successfully developed for treatment of Schizophrenia. Solubility of BRX was significantly increased by approach of solid dispersion using PEG 6000 as a hydrophilic carrier. Employment of CCD have assisted for optimization of BRX-SD-TP and extracted coherent information of relation between IVs and selected CQAs. Developed formulation was found compatible with skin and results of short term stability study exhibited stable characteristics of BRX-SD-TP.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

5. References

1. Zajdel, Pawel, et al. "Quinoline-and isoquinoline-sulfonamide analogs of aripiprazole: novel antipsychotic agents." *Future medicinal chemistry* 6.1 (2014): 57-75.
2. Kane, John M., and Christoph U. Correll. "Past and present progress in the pharmacologic treatment of schizophrenia." *The Journal of clinical psychiatry* 71.9 (2010): 0-0.
3. Stroup, T. Scott, and Neil Gray. "Management of common adverse effects of antipsychotic medications." *World Psychiatry* 17.3 (2018): 341-356.
4. Krause, Marc, et al. "Antipsychotic drugs for elderly patients with schizophrenia: A systematic review and meta-analysis." *European Neuropsychopharmacology* 28.12 (2018): 1360-1370.
5. Diefenderfer, Lauren A., and Courtney Iuppa. "Brexpiprazole: A review of a new treatment option for schizophrenia and major depressive disorder." *Mental Health Clinician* 7.5 (2017): 207-212.

6. Prausnitz, Mark R., and Robert Langer. "Transdermal drug delivery." *Nature biotechnology* 26.11 (2008): 1261-1268.
7. Rama, Veeraswamy, et al. "Novel cocrystals of brexpiprazole with improved solubility." *Journal of Crystal Growth* 551 (2020): 125910.
8. Pulusu, V. S., K. C. Routhu, and S. S. B. Chikkaswamy. "Quantitative determination of brexpiprazole by RP-HPLC method." *Pharmaceutica Analytica Acta* 10.2 (2019): 610.
9. Kumar, Narendra, et al. "Development, characterization and solubility study of solid dispersion of terbinafine hydrochloride by solvent evaporation method." *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm* 2.3 (2014).
10. Kahali, Nancy, Jasmina Khanam, and Nondita Ghosh. "An attempt to enhance solubility of metoclopramide base by Solid dispersion strategy and its application on development of Transdermal device." *Brazilian Journal of Pharmaceutical Sciences* 57 (2021).
11. YU, Yang, et al. "Optimized Preparation of Drug in Adhesive Transdermal Patch by Central Composite Design/Response Surface Methodology [J]." *Chinese Journal of Experimental Traditional Medical Formulae* 9 (2007).
12. Woo, Fong Yen, et al. "Formulation optimization of galantamine hydrobromide loaded gel drug reservoirs in transdermal patch for Alzheimer's disease." *International journal of nanomedicine* 10 (2015): 3879.
13. Gannu, Ramesh, et al. "Development of nitrendipine transdermal patches: in vitro and ex vivo characterization." *Current Drug Delivery* 4.1 (2007): 69-76.
14. Parhi, Rabinarayan, and Suresh Padilam. "In vitro permeation and stability studies on developed drug-in-adhesive transdermal patch of simvastatin." *Bulletin of Faculty of Pharmacy, Cairo University* 56.1 (2018): 26-33.