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## FORMULATION AND CHARACTERIZATION OF CLOZAPINE ADHESIVE PATCHES USING VARIOUS PRESSURE SENSITIVE ADHESIVES AND PERMEATION ENHANCERS

Milan B. Agrawal\* and Mayur M. Patel

Department of Pharmaceutics, Institute of Pharmacy, Nirma University, SG Highway, Chharodi, Ahmedabad - 382481, Gujarat, India.

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Pressure sensitive adhesives,  
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### Correspondence to Author:

**Milan B. Agrawal**

Research Scholar,  
Department of Pharmaceutics,  
Institute of Pharmacy, Nirma  
University, SG Highway, Chharodi,  
Ahmedabad - 382481, Gujarat, India.

**E-mail:** milanagrwal99@gmail.com

**ABSTRACT:** The present research work was intended to develop and characterize the transdermal adhesive patch of clozapine using different types of acrylate, polyisobutylene and silicon adhesives. Various permeation enhancers such as 1, 8 – cineole, D-limonene, Azone, IPM and Oleic acid were also evaluated to achieve desired permeation rate and hence to attain the improved bioavailability as compared to oral formulation. Formulation prepared were evaluated for physicochemical characterization, FTIR, DSC, permeability enhancement potential by *ex-vivo*, and stability studies. The results of the optimized formulation showed peel strength of  $411 \pm 3.56$  cN/cm, flux of  $109.59 \pm 1.59$  ( $\mu\text{g}/\text{h}/\text{cm}^2$ ) and % drug content of  $99.53 \pm 0.42\%$  which was stable up to six months in accelerated condition. The results of the study revealed that the developed transdermal patch of clozapine can be a promising alternative which provides effective management of schizophrenia in terms of improved patient compliance and bioavailability which in turn reduces the dosage frequency and hurdles associated with the caretakers and doctors.

**INTRODUCTION:** Schizophrenia is characterized by disintegration of thought processes and of emotional responsiveness. It is a severe form of mental illness affecting about 21 million people worldwide<sup>1, 2</sup>. Clozapine is taken twice daily, orally, in the form of tablet. However, when taken by oral route, it undergoes extensive first pass metabolism and oral bioavailability of clozapine is reported to be less than 27%<sup>3</sup>. Clozapine is extensively metabolized by hepatic microsomal enzymes (CYP1A2 and CYP3A4) and forms N-demethyl and N-oxide metabolites.

These makes delivery of clozapine, a challenging task for the efficacious therapy of nervous disorders such as schizophrenia, where prolonged drug delivery is essential for the people who may need assistance to receive medication by oral or by parenteral route. The topical drug delivery provides various benefits as compared to traditional dosage forms *viz.* improved compliance of patients on long-lasting therapy, maintaining a prolonged and constant plasma level of drug (thereby diminishing the side effects associated with the oral route), bypassing biotransformation, reducing inter and intra-patient variability and making it possible to put an end to drug therapy whenever needed<sup>4</sup>.

### MATERIALS AND METHODS:

**Materials:** Clozapine was given as a gift sample by Piramal Enterprises Ltd. India. Different grades of pressure-sensitive adhesives (PSA), release liners and backing membranes were procured from

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Henkel Corporation and 3M Healthcare. Isopropyl myristate (IPM) was purchased through Triveni Interchem Pvt. Ltd., Vapi, India. D-limonene and oleic acid were purchased from A.B. Enterprises, Mumbai, India. 1, 8-Cineole was purchased from Sanket Enterprises, Mumbai, India. Other reagents and chemicals used in the research were procured from reliable and standard sources.

#### Formulation of Transdermal Patches: 5, 6

Transdermal patches of clozapine were prepared by the solvent casting technique. Clozapine was dissolved in a concentration of 20% w/w along with pressure-sensitive adhesive (DT-387-2510) in a solvent system of ethyl acetate. In addition to this oleic acid (12.5% w/w of dry polymer weight) as permeation enhancer was added to the above solution. To prepare homogeneous dispersion, the mixture was continuously stirred for 30 min and poured on a release liner (Scotch pack 1022, 3M, USA). The patch was kept at room temperature for 10 minutes and then dried in oven at 50 °C for 5 min and laminated with backing membrane (Scotchpack 9723, 3M, USA).

#### Evaluation of Transdermal Patches:

**Physical Characterization:** The prepared transdermal patches (4.41 cm<sup>2</sup>) were evaluated for weight variation by digital electronic balance (Mettler Toledo, Ohio, USA). The thickness of the patch was measured by using a digital vernier calliper (Mitutoyo, Japan) at random points<sup>7</sup>. Peel strength was determined by loyd universal testing machine (LRX+) (Testometric, Rochdale, United Kingdom)<sup>8, 9</sup>. Drug content was quantified by dissolving the patch of size 4.41 cm<sup>2</sup> in 100 mL of methanol, which was then analyzed spectrophotometrically at a wavelength of 259 nm<sup>10</sup>.

**Ex-vivo Permeation Study:** The *ex-vivo* permeation studies were carried out in vertical Franz diffusion cell using Wistar rat skin (Approval no. ROFEL/IAEC/2018/3) after detaching the adhering fat and hair. The formulation was fixed on the skin in such a way that the drug matrix was facing the donor side. Phosphate buffer (pH 7.4) was used as receptor fluid maintained at a temperature of 32 ± 0.5 °C along with the agitation speed of 50 rpm. At different time intervals, the samples were withdrawn and exchanged with equal amounts of fresh media. Aliquots were analyzed

spectrophotometrically at a wavelength of 259 nm<sup>11</sup>. The drug permeated per cm of the patch was given as per the following equation and plotted against time and the flux was calculated as drug permeated per cm<sup>2</sup> per hour<sup>12</sup>.

$$Q_n = \frac{C_n \times V_0 + \sum_{i=1}^{n-1} C_i \times V_i}{S} \dots(1)$$

Where C<sub>n</sub> is the receiver solution concentration of drug, C<sub>i</sub> is the i<sup>th</sup> sample drug concentration, V<sub>0</sub> and V<sub>i</sub> are the receptor medium volume and sample volume, respectively, while S is the effective area of diffusion<sup>13</sup>.

**Interaction Studies:** The interaction studies were performed for finalized batch by doing comparison of the clozapine, PSAs, and a mixture of clozapine and PSAs based on FTIR (Jasco 1800, Tokyo, Japan) and DSC (Shimadzu 60A, Kyoto, Japan) studies<sup>14</sup>.

**Stability Study:** The accelerated stability testing study of the optimized transdermal patch was performed for 6 months, according to the ICH guidelines<sup>15</sup>. Adequate replicates of the optimized patch were composed and stability study was carried out at temperatures of 40 ± 2 °C and 75 ± 5% Rh for six months. Samples were withdrawn at an interval of 1, 3 and 6 months and drug content, flux, and peel strength analyzed for the stability samples and results were compared with freshly prepared patches<sup>16</sup>.

## RESULTS AND DISCUSSION:

**Selection of Pressure Sensitive Adhesives:** Based on the type and different physicochemical properties polyisobutylene, silicon and acrylate adhesives are selected for the study. Acrylate adhesives used for the study were based on functional groups, crosslinkers, vinyl acetate and viscosity of PSA **Table 1**.

The target skin permeation rate for Clozapine was calculated using the following equation<sup>17</sup>

$$J = (Cl \times C_p \times W)/A \dots(2)$$

Here, J corresponds to the flux (µg/h/cm<sup>2</sup>), A is the patch surface area (4.41 cm<sup>2</sup>), C<sub>p</sub> corresponds to the plasma concentration (100 µg/L), Cl is the rate of clearance (0.072 L/h/kg) and W is the weight of the patient (considered as 60 Kg)<sup>18</sup>.

The theoretically required flux for Clozapine as calculated from the above equation was found  $97.95 \mu\text{g}/\text{h}/\text{cm}^2$  which considered as  $\sim 100 \mu\text{g}/\text{h}/\text{cm}^2$ . The permeation rate is necessary for attaining the adequate plasma concentrations of the drug. Initially, for the screening of PSA, batches were prepared with 15% drug loading. This factor was kept constant to assess the impact of adhesive on drug permeation.

It was depicted from the results **Table 2** that flux for DT-87-6908 (polyisobutylene) and Bio-PSA 7-4302 (silicon) was found to be  $16.84 \pm 1.34 \mu\text{g}/\text{h}/\text{cm}^2$  and  $13.56 \pm 2.71 \mu\text{g}/\text{h}/\text{cm}^2$  respectively while for DT-87-9301 and DT-87-4098 (acrylate) it was found to be  $20.42 \pm 3.42 \mu\text{g}/\text{h}/\text{cm}^2$  and  $28.13 \pm 1.67 \mu\text{g}/\text{h}/\text{cm}^2$  respectively.

**TABLE 1: SELECTION OF PSA BASED ON THEIR PHYSICO-CHEMICAL PROPERTIES**

PSA	Type of PSA	Contains Vinyl Acetate	Functional Group	Cross-linkers	Viscosity mPa.s
DT-87-6908	Polyisobutylene	No	None	n/a	6000
Bio-PSA 7-4302	Silicone	No	None	n/a	9250
DT-87-9301	Acrylate	No	None	n/a	9500
DT-87-4098	Acrylate	Yes	None	n/a	6500
DT-387-2287	Acrylate	Yes	-OH	No	18000
DT-387-2516	Acrylate	Yes	-OH	Yes	4350
DT-387-2510	Acrylate	No	-OH	No	4250
DT-387-2353	Acrylate	No	-COOH	No	8000
DT-387-2852	Acrylate	No	-COOH	Yes	2500
DT-387-2052	Acrylate	Yes	-COOH	Yes	2750

Here all above mentioned PSAs having no functional groups attribute that acrylate adhesives are having higher flux than polyisobutylene and silicon adhesives.

Flux for DT-387-2287, DT-387-2516 and DT-387-2510 was found to be  $31.65 \pm 0.23 \mu\text{g}/\text{h}/\text{cm}^2$ ,  $34.91 \pm 1.37 \mu\text{g}/\text{h}/\text{cm}^2$  and  $44.13 \pm 1.08 \mu\text{g}/\text{h}/\text{cm}^2$  respectively **Fig. 1**. Here above mentioned, three acrylates are consisting of -OH (hydroxyl) functional group where flux for DT-387-2287 was found least in this -OH functional group category. This was attributed to its highest viscosity of 18000 mPa.s while in the case of DT-387-2516 and DT-387-2510 former was slightly lesser due to the presence of cross-linkers while the same is absent in case of DT-387-2510.

Now in case of DT-387-2353, DT-387-2852 and DT-387-2052 acrylate adhesives with -COOH (Carboxyl acid) functional group the flux was found to be  $8.16 \pm 2.19 \mu\text{g}/\text{h}/\text{cm}^2$ ,  $10.31 \pm 1.46 \mu\text{g}/\text{h}/\text{cm}^2$  and  $11.26 \pm 1.11 \mu\text{g}/\text{h}/\text{cm}^2$  respectively. Hence the flux found highest with -OH functional group was might be due to its characteristic of reducing the drug-tissue binding by occupying hydrogen bonding sites and giving the solvating effect of alpha-keratinin within corneocytes which leads to the marginal increase in lipid fluidity and hence the drug permeability.

So, it improves the solubility of the drug within stratum corneum and resulting in increased drug partition into the skin.

**TABLE 2: PHYSICO-CHEMICAL CHARACTERIZATION OF CLOZAPINE TRANSDERMAL PATCH**

PSA	Weight (mg)	Thickness (mm)	% Drug Content	Peel Strength (cN/cm)	Flux ( $\mu\text{g}/\text{h}/\text{cm}^2$ )
DT-87-6908	165.9±1.27	0.12±0.02	99.16±0.74	578±4.38	16.84±1.34
Bio-PSA 7-4302	168.1±1.35	0.09±0.01	98.02±0.56	610±4.67	13.56±2.71
DT-87-9301	164.7±1.19	0.10±0.01	99.29±1.21	465±3.19	20.42±3.42
DT-87-4098	162.1±1.52	0.11±0.02	97.67±0.63	493±4.28	28.13±1.67
DT-387-2287	165.3±1.43	0.09±0.01	99.41±0.82	718±5.16	31.65±0.23
DT-387-2516	166.8±1.05	0.10±0.01	98.13±0.67	562±3.43	34.91±1.37
DT-387-2510	164.9±1.46	0.10±0.01	99.03±0.89	584±3.17	44.13±1.08
DT-387-2353	168.2±1.38	0.11±0.02	97.38±0.61	632±4.58	8.16±2.19
DT-387-2852	165.5±1.62	0.12±0.02	98.61±0.46	607±3.79	10.31±1.46
DT-387-2052	163.3±1.13	0.10±0.01	96.49±0.57	598±3.06	11.26±1.11

(mean ± SD, n=3)

According to literature peel strength, less than 300 cN cm<sup>-1</sup> leads to poor adhesion, as shown in results peel strength was found greater than the mentioned criteria for all the adhesives. So, based on the result and discussion DT-387-2510 was selected for further studies.

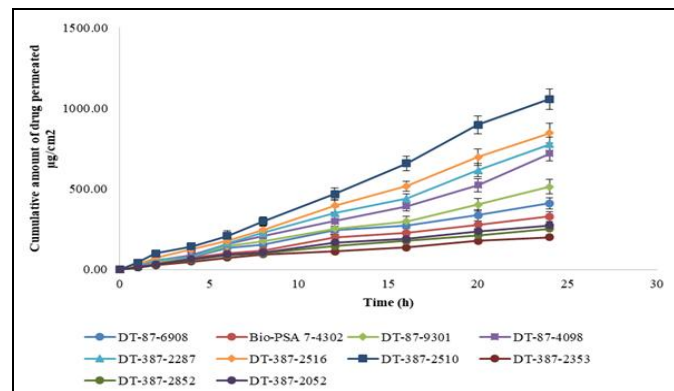


FIG. 1: EFFECT OF DIFFERENT PSA ON EX-VIVO SKIN PERMEATION

TABLE 3: CHARACTERIZATION OF CLOZAPINE TRANSDERMAL PATCH WITH DIFFERENT DRUG LOADING

Formulation	Drug loading (%)	Flux ( $\mu\text{g}/\text{h}/\text{cm}^2$ )	Weight (mg)	Thickness (mm)	Peel Strength cN/cm
A1	10	35.30±0.79	248.6±1.51	0.11±0.02	667±5.38
A2	15	44.13±1.23	164.9±1.26	0.10±0.01	584±4.98
A3	20	53.74±1.41	125.4±1.02	0.10±0.01	529±4.54
A4	25	56.11±1.97	102.7±1.05	0.09±0.01	443±4.43

(mean ± SD, n=3)

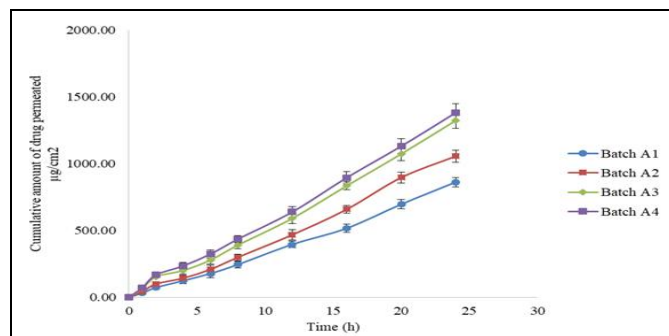


FIG. 2: EFFECT OF DRUG LOADING ON EX-VIVO SKIN PERMEATION

**Effect of Permeation Enhancer Type:** Batches B1 to B5 were prepared by using 1, 8 – cineole, D-limonene, azone, IPM, and oleic acid respectively at a concentration of 10% w/w (of dry weight polymer) to achieve the target flux. The flux values of clozapine ( $\mu\text{g}/\text{h}/\text{cm}^2$ ) in the presence of the

**Optimization of Drug Loading:** To determine the optimum concentration of clozapine, different batches A1 to A4 prepared with drug loading in a range of 10% - 30% to check its impact on skin permeation. It was depicted from the results that **Table 3** as the concentration of drug increases from 10% to 20% skin permeation increases from  $35.30 \pm 0.79 \mu\text{g}/\text{h}/\text{cm}^2$  to  $53.74 \pm 1.41 \mu\text{g}/\text{h}/\text{cm}^2$ . This was the effect due to the higher concentration gradient of the drug which may create reservoirs in the skin and from where permeate the drug. Flux was comparable for batches A3 and A4 **Fig. 2** which were due to the saturation of the skin beyond the threshold concentration of the drug. Hence, 20% drug loading was found to be optimum. As shown in the results, it can also be inferred that as the drug concentration increases PSA concentration decreases and hence the peel strength of the patch also decreases.

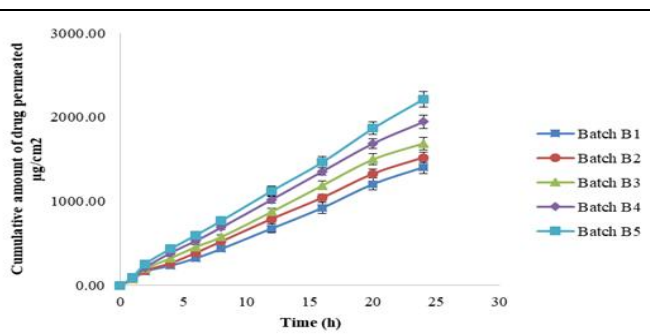


FIG. 3: EFFECT OF DIFFERENT PERMEATION ENHANCERS ON EX-VIVO SKIN PERMEATION

enhancers investigated and found to be highest for oleic acid *viz.*  $90.84 \pm 1.48 \mu\text{g}/\text{h}/\text{cm}^2$  (batch B5) and lowest for 1,8-cineole *viz.*  $58.33 \pm 1.21 \mu\text{g}/\text{h}/\text{cm}^2$  (batch B1) **Table 4**. Permeation profiles are shown in **Fig. 3**.

TABLE 4: DETAILS OF DIFFERENT PERMEATION ENHANCERS USED FOR THE STUDY (mean ± SD, n=3)

Formulation	Penetration Enhancers	Conc. Used (%)	Flux ( $\mu\text{g}/\text{h}/\text{cm}^2$ )	Enhancement Ratio	Peel Strength cN/cm
B1	1,8-cineole	10	58.33±1.21	1.08	492±4.16
B2	D-limonene	10	63.21±0.92	1.17	487±3.24
B3	Azone	10	71.37±1.34	1.32	464±3.27
B4	Isopropyl Myristate	10	81.51±1.05	1.52	437±3.32
B5	Oleic acid	10	90.84±1.48	1.69	452±3.49



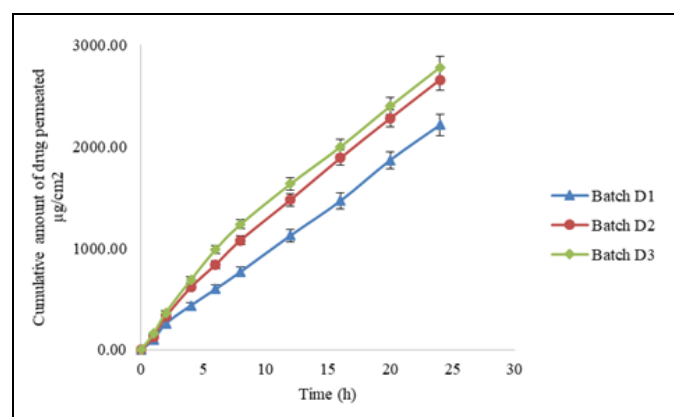
The values of flux in the presence of permeation enhancers were found in following decreasing order: Oleic acid > IPM > Azone > D-limonene > 1, 8 Cineole. The above results were ascribed to the lipophilic character of the permeation enhancers<sup>19</sup>. Oleic acid is a lipophilic fatty acid<sup>20</sup> with the log P value of 7.7<sup>21</sup>. Hence, OA promotes the partitioning of clozapine into the acceptor phase. Moreover, OA acts by disrupting the lipid bilayer and hence increase the drug flux while IPM fluidizes the stratum corneum lipids and thereby enhancing flux<sup>17</sup>. IPM Log p-value is 7.17<sup>22</sup> while for azone log p-value is 6.2<sup>23</sup>. Azones are non-interactive with the proteins; they get directly partitioned into the bilayer of lipid and by disrupting it they make the lipid layer more flexible 5,1,8-cineole disrupts the bilipid structure of subcutaneous layer<sup>24</sup> while D-limonene extracts the lipid from subcutaneous layer and thereby enhance the penetration<sup>25</sup>. It was reported that the terpenes with higher polarity are more potent enhancers for hydrophilic drugs whereas non-polar terpenes are better enhancers for lipophilic drugs<sup>26</sup>. log p-value of 1,8-cineole was found to be 2.82 ±

0.25. On the contrary, D-limonene is a non-polar (hydrocarbon) terpene with a log p-value of  $4.58 \pm 0.23$ <sup>27</sup>. So, based on the above findings OA was selected as the best suitable permeation enhancer for further studies and its effect on flux evaluated at different concentrations.

**Effect of Permeation Enhancer Concentration:** Permeation enhancer concentration plays a very important role in the permeation of the drug. Batches D1 to D3 were formulated by differing amounts of OA in range of 10%, 15% and 20% (of dry polymer weight) respectively. The flux value of clozapine ( $\mu\text{g}/\text{h}/\text{cm}^2$ ) for batch D1 was found to be  $90.84 \pm 1.48 \mu\text{g}/\text{h}/\text{cm}^2$  while for batches D2 and D3 was found to be  $109.59 \pm 1.59 \mu\text{g}/\text{h}/\text{cm}^2$  and  $113.69 \pm 1.74 \mu\text{g}/\text{h}/\text{cm}^2$  respectively **Table 5**. The rate of permeation of the drug increased with increasing the concentration of OA, reaching a maximum of 20% **Fig. 4**. Permeation rate obtained with 15% and 20% concentration of OA was comparable and no noteworthy difference was found<sup>28</sup>. Hence formulation D2 was evaluated for further characterization.

**TABLE 5: IMPACT OF CONCENTRATION OF OLEIC ACID** (mean ± SD, n=3)

Formulation	Penetration Enhancers	Conc. Used (%)	Flux ( $\mu\text{g}/\text{h}/\text{cm}^2$ )	Enhancement Ratio	Peel Strength cN/cm
D1	Oleic acid	10	90.84±1.07	1.69	452±3.21
D2	Oleic acid	15	109.59±1.59	2.04	411±3.56
D3	Oleic acid	20	113.69±1.74	2.11	376±3.13



**FIG. 4: EFFECT OF CONCENTRATION OF PERMEATION ENHANCERS ON EX-VIVO SKIN PERMEATION**

### Interaction Studies:

**FTIR Studies:** The FTIR spectra of pure clozapine demonstrated characteristic peaks at  $3296.71 \text{ cm}^{-1}$  (N-H stretching),  $2969.84 \text{ cm}^{-1}$  (C-H stretching),  $1551.45 \text{ cm}^{-1}$  (C=N stretching),  $1456.56 \text{ cm}^{-1}$  (Aromatic C=C Stretching),  $822.49 \text{ cm}^{-1}$  (C-Cl

stretching). Peaks of the FTIR spectra for physical mixture were detected at the same position as that of the drugs<sup>29</sup>.

In IR spectrum of Clozapine **Fig. 5**, the absorption at  $3296.71 \text{ cm}^{-1}$  was assigned to the stretching vibration of N-H group which was red-shifted to the wave number of  $3292.25 \text{ cm}^{-1}$  and  $3291.16 \text{ cm}^{-1}$  for clozapine physical mixture and clozapine formulation<sup>30</sup> and hence that red shift was attributed as a criterion for intermolecular hydrogen bonding<sup>31</sup>.

**DSC Studies:** The thermogram of pure clozapine exerted a sharp endothermic peak at  $188.59 \text{ }^\circ\text{C}$ , corresponding to the melting point of clozapine **Fig. 6**. The major peak of clozapine disappeared from the DSC thermogram of optimized formulation, which was due to the homogenous dispersion of the drug in the PSA matrix<sup>32</sup>.

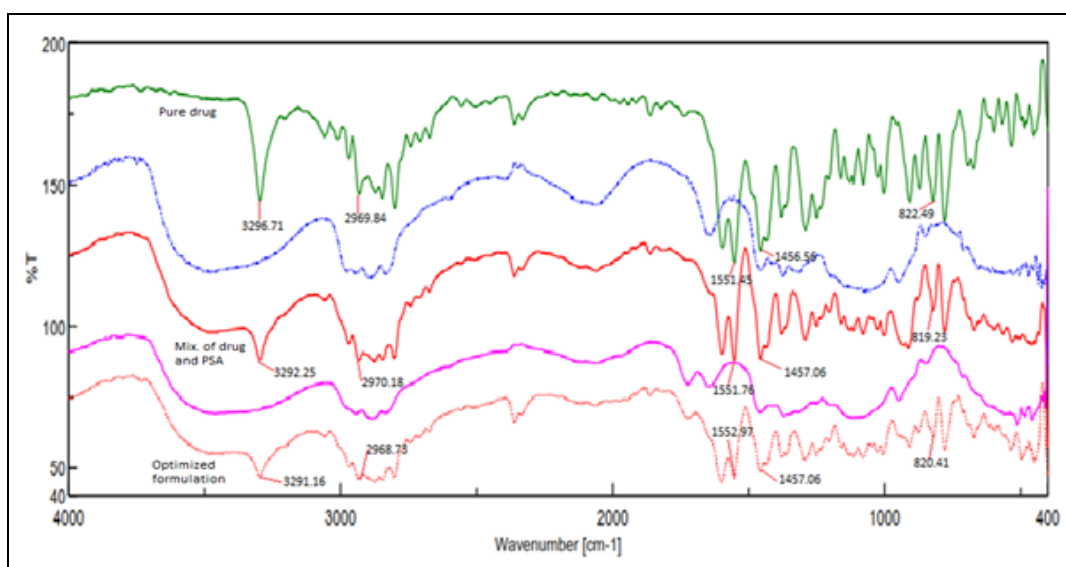


FIG. 5: FTIR SPECTRA OF PURE DRUG, PSA, PHYSICAL MIXTURE, BLANK PATCH AND DRUG LOADED PATCH

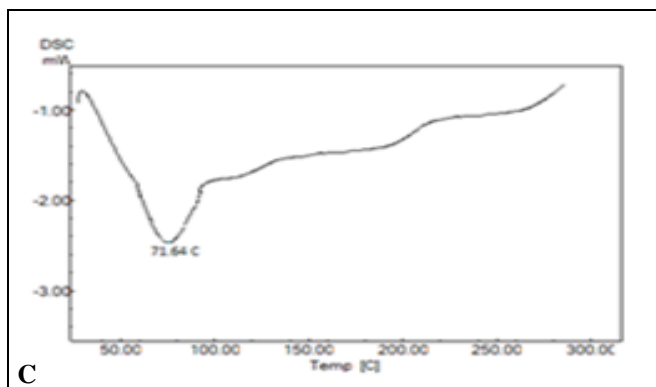
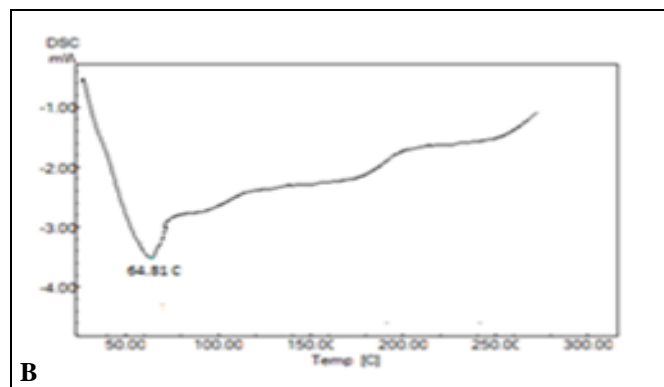
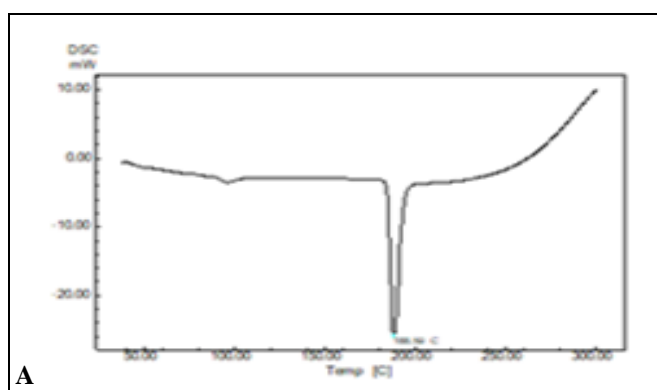


FIG. 6: DSC CURVE FOR (A) PURE DRUG, (B) PHYSICAL MIXTURE OF DRUG AND PSA AND (C) CLOZAPINE TRANSDERMAL PATCH

**Stability Study:** This is necessary for the evaluation of transdermal patches during the storage. The results revealed no changes in the physical appearance of the formulation after six months. The % drug content was found to be  $98.76 \pm 0.37\%$  after six months, while peel strength and flux were found  $405 \pm 3.15$  cN/cm and  $104.89 \pm 1.43$   $\mu\text{g}/\text{h}/\text{cm}^2$  respectively. The above results were insignificant ( $p > 0.05$ ) when compared with the results of fresh patches **Table 6**. From the above

findings, it was inferred that there was no drug crystallization observed even after six months.

TABLE 6: STABILITY STUDY FOR CLOZAPINE PATCH IN ACCELERATED CONDITION (mean  $\pm$  SD, n=3)

Time Point	Drug content (%)	Peel strength (cN/cm)	Flux ( $\mu\text{g}/\text{h}/\text{cm}^2$ )
Initial	$99.53 \pm 0.42$	$411 \pm 3.56$	$109.59 \pm 1.59$
1 Month	$99.38 \pm 0.56$	$417 \pm 4.67$	$104.54 \pm 1.67$
3 Month	$99.41 \pm 0.29$	$413 \pm 3.82$	$105.32 \pm 1.08$
6 Month	$98.76 \pm 0.37$	$405 \pm 3.15$	$104.89 \pm 1.43$

**CONCLUSION:** Clozapine transdermal patch was formulated using pressure sensitive adhesives along with permeation enhancers to provide the sustained release of the drug with better permeation rate and hence the bioavailability as compared to the marketed formulation. Hence, the developed clozapine PSA patch proves to be a better alternative to conventional dosage forms and can be utilized in schizophrenics with improved patient compliance with reduced dosage frequency.

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