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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF DICLOFENAC SODIUM

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ABSTRACT

Objective: The main objective of this work is to fabricate Diclofenac Sodium transdermal patch to avoid first pass metabolism and to overcome the problems associated with its biological short half-life and fluctuations in plasma concentration upon oral administration. **Method:** The patch were prepared using Solvent Casting Method, using Methyl cellulose as polymer, Dibutyl phthalate as permeation enhancer and Ethanol: distilled water as solvent. The physical evaluation of the prepared patch include organoleptic observation, moisture uptake, moisture loss, content uniformity test, stability studies, swelling index, folding endurance. The drug release was determined using Franz diffusion cells in phosphate buffer (pH 7.4). **Result:** The result of physiochemical parameters of the transdermal patch were found satisfactory. Formula F2 produce best result among all patchs with smooth transparent texture and maximum folding endurance with minimum moisture loss and moisture uptake. The patch weight, thickness were found to be uniform. The drug content in F2 was 98%. Stability study indicates that drug remain stable for six months. **Conclusion:** This work is further aimed to analyse, concentration of drug reaching in the body and to study its effect.

KEYWORDS: Diclofenac Sodium, Transdermal patch and conventional dosage Form

1. INTRODUCTION

Since last decade, TDDS acquired a lot of interest due over the conventional dosage forms and oral controlled release delivery, specifically for the avoidance of hepatic first pass

effect.[1] Optimization of drug release through the skin directly into the systemic circulation and parallel minimize the retention and metabolism of the drug in the skin is the major goal of transdermal products.[2]

Administration of drugs in the conventional dosage forms as compare to the controlled or sustain release form usually results in large scale fluctuations in plasma drug concentrations leading to unwanted toxicity or poor effectiveness along with limitations such as repetitive dosing at certain time interval and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system.[3] The successful development of transdermal therapeutic system mainly depends on choice of drug, which should be non-irritant, non-toxic and must cross the various skin layer to produce the desired therapeutic effect at specific period of time. Drugs which produce these effects in small amounts with molecular weight range of 100-800 Da are ideal candidates for TDDS.[4]

Transdermal patches were developed in the 1970's and the first transdermal system, Transderm Scop (ciba, now Novartis) was approved by Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel, particularly by sea.[5] A Transdermal patch is a medicament adhesive patch which when applied to the skin utilizes passive diffusion of drug at controlled rate through the skin and into the blood stream.[6]

NSAIDs (Non-steroidal anti-inflammatory drugs) are mostly used for the preparation of transdermal patches for the treatment of inflammation or pain. The NSAIDs patches are safer and convenient to use than its oral dosage form. NSAIDs tablets for rheumatism leads to various side effects like internal stomach bleeding, increased acidity, ulcers can be avoided by using transdermal patches of NSAIDs.[7] On the other hand, the analgesic patch of NSAIDs can be used on the site of sprain or strain. These patch when applied on the skin in form of transdermal patch, without reaching higher plasma drug concentrations the drug penetrate the various layer of skin in sufficient amount to exert local therapeutic effect. Hence NSAIDs transdermal patches offers advantages of painless drug delivery, is easy to apply, provides faster and longer relief, and have no or few gastrointestinal side effects from the drug itself. That's the reason now a days patients are advised to take the NSAIDs patch over the other route because of its minimal side effects related to systemic toxicity and GIT irritation.[8]

Mainly, nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs, which are prescribed in both acute and chronic condition of rheumatoid arthritis, osteoarthritis, dysmenorrhea treatment because of their analgesic, antipyretic and anti-inflammatory effect. Diclofenac (2-[2-(2,6 dichlorophenyl amino) phenyl]acetic acid) is one of the most likely and commercially successful drug in the family of NSAIDs. The main mechanism of action of diclofenac is to inhibit the activity of cyclooxygenase (COX) by interdicting the prostaglandin (PG) synthesis thereby controlling the synthesis of thromboxanes and prostaglandins. The cyclooxygenase is an enzyme released during pain and inflammation whereas, thromboxanes and prostaglandins are mediators of vasoconstriction and inflammation.[9-11] The drug undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation. Its biological half-life is also very short, it is considered as a suitable candidate to formulate it into a sustained release matrix type transdermal patch system.[12]

The Diclofenac sodium also possesses the ideal characteristics such as poor bioavailability, short biological half-life and smaller dose etc., to be formulated in to a transdermal patch. Main added advantage of transdermal patches as it maintain constant and prolonged drug level, and dose frequency is reduced, self-administration, quick onset of action and easy termination of medication leads to provide higher level of patient compliance.[13,14]

Diclofenac was chosen as a model drug for present study as it possess near ideal characteristic, that the drug must have in formulation to develop different transdermal matrix films with different ratios of hydrophilic and hydrophilic –lipophilic combination containing the drug and to perform the physicochemical and in-vitro, in-vivo evaluation along with study of the prepared films.[15]

Diclofenac is efficiently and rapidly absorbed after conventional oral, rectal or intramuscular administration.[16,17] After intramuscular administration peak plasma concentrations are attained after 10 to 15 minutes. With the enteric-coated formulation peak concentration are reached after 1.5 to 2.5 hours, and this is delayed by food to 2.5 to 12 hours. After a single 50mg dose of this formulation, mean peak plasma concentration of unchanged diclofenac is 0.7 to 1.5 mg/L.[18-21] Like other NSAIDs, diclofenac is highly (>9.5%) protein bound. The mean total volume of distribution is 0.12 to 0.17 L/kg and that of the central compartment is 0.04 L/kg. The drug efficiently penetrates inflamed synovial fluid where high concentrations

are maintained compared with plasma concentrations. Diclofenac and its metabolites cross the placenta in animals, and small amount may be found in the breast milk of women.[22-26]

In healthy volunteers, mean plasma clearance of diclofenac is 16 L/h, and the mean elimination half-life of the terminal phase is 1.1 to 1.8 hours. The mean elimination half-life after a radiolabelled dose is about 30 hours for the tracer.[27-32] The initial dosage of conventional or enteric-coated Tablets of diclofenac is 150mg daily in 2 or 3 divided doses with meals, and in most patients therapeutic control can be maintained on 100mg daily.[33-35] A sustained release formulation can be administered once daily, and suppositories can be administered once or twice daily. Intramuscular diclofenac 75mg can be given for the urgent relief of acute pain such as renal or biliary colic. A further dose may be administered after 30 minutes if necessary, but as with oral administration the daily dosage should not exceed 150mg.[36-42]

2. MATERIAL AND METHOD

2.1 Material

All the chemicals used in this research were of standard analytical or pharmaceutical grade. Diclofenac Sodium was a gift sample obtained from pharmaceutical industry. Formulation of patch include- active ingredient, backing agent, plasticizer, penetration enhancer and solvent used are shown in **Table1.**

Table 1: Ingredients Table of Diclofenac Sodium Patch.

S. No.	INGREDIENTS	ACTIVITY
1.	Diclofenac Sodium (mg)	Active ingredient (Drug)
2.	Methyl Cellulose (mg)	Backing agent
3.	PG, PEG-400 (ml)	Plasticizer
4.	Dibutyl Phthalate (ml)	Penetration enhancer
5.	Distilled water: Ethanol (ml)	Solvent

2.2 Preparation of Patch by Solvent Casting Method

Transdermal patches were fabricated using methyl cellulose as a polymers containing diclofenac sodium by solvent casting method[43] shown in **Figure 1**. According to the formula methyl cellulose were accurately weighed and dissolved in mixture of ethanol: water (1:2) used as a solvent. The drug was then dispersed in the polymeric solution and plasticizer of dibutyl phthalate was added with continuous stirring using a magnetic stirrer to obtain homogeneous mixture. Lastly, the bottom of petridish were covered with aluminium foil and the resulting solution was poured into levelled mercury surface in a petridish covered with a

funnel in inverted position. The solvent was allowed to evaporate and left undisturbed at room temperature for the next 24 hour. The patch was obtained intact by slowly lifting from the Petri dish and transdermal patches were cut into radius of $2cm^2$.[44-46] Ingredients to be used are shown in **Table 2**.

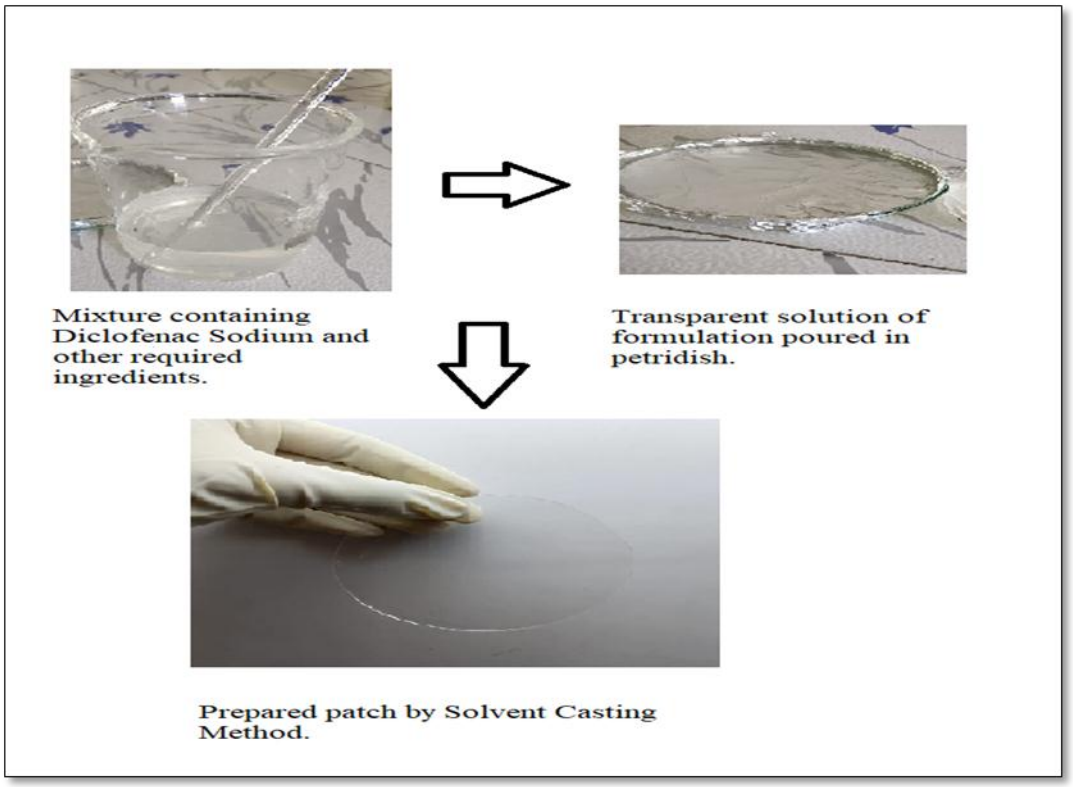

Figure 1: Preparation of Transdermal Patch by Solvent Casting Method.

Table 2: **Composition of Diclofenac Sodium Transdermal Patch in Different Ratio.**

S. No.	INGREDIENTS	F1	F2	F3	F4
1.	Diclofenac Sodium (mg)	25	25	25	25
2.	Methyl Cellulose(mg)	300	300	400	400
3.	PEG-400	-	-	1.2	1.2
4.	PG (ml)	1.2	1.2	-	-
5.	Dibutyl Phthalate	1.2	1.2	1.2	1.2
6.	Ethanol: Distilled water	1:2	1:2	1:2	1:2

3. Evaluation and Characterization of Medicated Patch

After getting the best formula based on accurate diclofenac sodium, it was further studied for its physical, mechanical and permeability of the drug. Physical and mechanical properties of medicated transdermal patch such as thickness, surface pH, content uniformity, folding endurance, moisture loss, moisture uptake, weight uniformity, and stability studies. Also medicated patch were evaluated for drug content, in-vitro drug release.

3.1 Physical Appearance

All the transdermal film were organoleptically inspected and all over elegance for colour, transparency, shape, texture of the surface, homogeneity of thickness, film formation (no collapse or shrinkage)upon drying.[47]

3.2 Thickness of Patch

The thickness of the drug loaded patch is determined by screw gauge and micrometer at different point and average of readings were calculated.[48]

3.3 Uniformity of Weight

Weight variation is determined by weighing 5 randomly selected patches and calculating the average weight. The individual weight should not digress significantly from the average weight.[49]

3.4 Folding Endurance

This test is performed to determine the elasticity and fragility of transdermal patches.[50] The test was conducted by folding the patch at the same point n number of times till the patch is broken. The number of folds is considered to be the value of resistance to folding.[51]

3.5 Surface pH

Each film was allowed to swell by adding 0.5mL of distilled water on the film surface for 1hr at room temperature. Then, pH was noted by bringing the electrode into contact to the surface of the film and allowing it to equilibrate for 1 min.[52]

3.6 Swelling Index

The film were weighed (W_F) immersed in a beaker containing 25mL phosphate buffer pH 7.4.The beaker were kept at 25℃ using thermo stated water bath. At specific intervals up to 2 hour, the swollen film were weighed (W_S) after removal of excess surface water by light blotting with a filter paper. The experiment was discontinued when the film begin to dissolve.[53] The swelling index was calculated by.

Swelling index $= \frac{W_S - W_F}{W_F} \times 100$

Where, W_F = weight of the dried polymer film.

W_S = weight after swelling.

3.7 Moisture Uptake

The films were placed in a desiccator containing activated silica gel for 24 hr. Then, they were weighed (W_D) and then transfer to another desiccator containing saturated sodium chloride (75%). The films were weighed daily until they showed constant weight (W_U).[54] The percentage of moisture uptake was calculated by.

Moisture uptake capacity% $= \frac{W_{U-W_D}}{W_D} \times 100$

3.8 Moisture Loss

The film were weighed (W_F), kept in a desiccator containing silica gel at 25℃ and weighed daily until they showed constant weight (W_D).[55] The percentage moisture loss was calculated by.

Moisture loss % $= \frac{W_{F-W_D}}{W_D} \times 100$

3.9 Content Uniformity Test

Randomly patches are selected and content in each patch is determined individually. If 9 out of 10 patches have content between 85% to115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches passes the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches passes the test.[56, 57]

3.10 Drug Content

A specified area of patch is to be dissolved in phosphate buffer solution (pH 7.4). The content was allowed to dissolve in solution. Then the solution is to be filtered through a filter medium and absorbance were measured with the help of UV at wavelength 320nm. Each value represents average of three different samples.[58-60]

3.11 Stability Study

The developed transdermal patch were sealed in polyethylene coated aluminium foils and kept at 40±0.5℃ and 75±5%RH for 6 months. The samples are withdrawn at different interval of 0, 30, 60, 90 and 180 days and analysed suitably for the drug content and any physical changes brought about on storage.[61-64]

3.12 In-Vitro Drug Diffusion Study

The in-vitro release study was performed using a modified Franz diffusion cell is the most common technique for measuring dermal absorption.[65-69] In this research drug diffusion were studied with the help of goat skin. After hair were shaven using razor, without damaging skin. The skin membranes were first hydrated for 30 minutes in the buffer solution (pH 7.4) at room temperature to remove extraneous debris or blood vessels.[70] The donor portion contains a transdermal patch of diclofenac sodium. The donor and receptor compartment separator membrane is the goat skin. The membrane is placed between the donor compartment and the receptor compartment with the dermis side facing the receptor compartment of the diffusion cell. The receptor compartment of the diffusion cell was filled with phosphate buffer (pH 7.4). The whole assembly was fixed on a magnetic stirrer with constantly and continuous stirred using magnetic bead and temperature was maintained at 32℃. The sample were withdrawn at different time interval and analysed for drug content spectophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal to maintain sink condition.[71-73]

4. RESULT AND DISCUSSION

4.1 Standard Graph of Diclofenac Sodium

The lambda max of the Diclofenac sodium was found to be 320nm. After the determination of lambda max the calibration curve and absorption are to be evaluated by the UV spectroscopy. The results of the absorption and concentration were given below in the **Table 3**. Standard graph of diclofenac sodium are shown in **Figure 2**.

Table 3: Concentration and Absorption of Diclofenac Sodium.

S. No.	Concentration(µg/ml)	Absorption
1.	2	0.160
2.	4	0.310
3.	6	0.463
4.	8	0.623
5.	10	0.790
6.	12	0.925

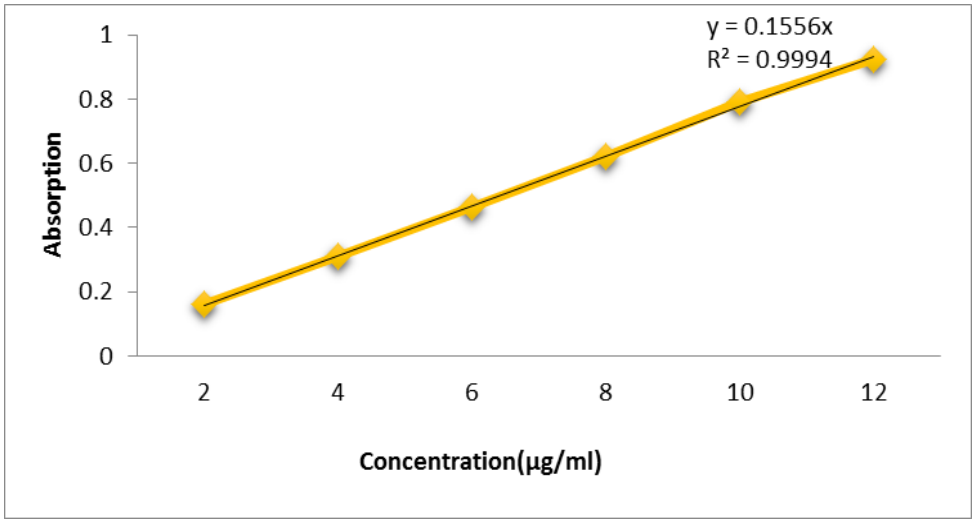

Figure 2: Standard Graph of Diclofenac Sodium.

4.2 Result of Evaluation Studies

4.2.1 Physical Appearance

The patch was visually inspected for colour, surface texture, shape. **Figure 3** and **Table 4.** Helps to explain the physical appearance of patch. Transdermal patch cut in $2cm^2$.

Table 4: Physical Appearance of Patch.

S. No.	Physical appearance	Result
1.	Color	Transparent
2.	Surface texture	Smooth
3.	Shape	Round

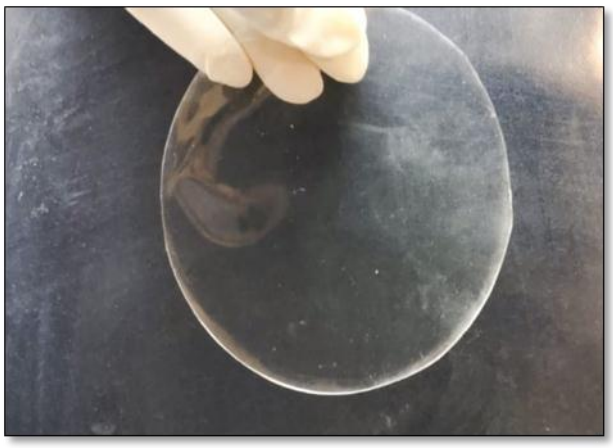

Figure 3: Transdermal Patch.

4.2.2 Thickness of Patch

The thickness of the prepared patch was measured by Vernier Caliper. The mean thickness was measured at different point of the film were given in **Table 5.**

Table 5: Determination of Thickness of Patch.

S. No.	Sample	Thickness (mm)
1.	F1	0.295±0.012
2.	**F2**	**0.245±0.09**
3.	F3	0.259±0.011
4.	F4	0.254±0.016

The thickness of patch was determined. It was found that F2 (0.2452mm) show less thickness whereas F1 (0.295mm) shows more thickness.

4.2.3 Uniformity of Weight

The quantified area of 2cm^2 radius is to be cut at different parts of the patch and weigh in digital balance. The average weight calculated from individual weight are shown in **Table 6.**

Table 6: Determination of Uniformity of Weight.

S. No.	Sample	Weight variation (mg)
1.	F1	590±0.025
2.	**F2**	**598±0.016**
3.	F3	593±0.017
4.	F4	587±0.026

Uniformity of weight was measured. It was found that F2 (598mg) shows more weight whereas F4 (587mg) shows less weight.

4.2.4 Folding Endurance

The folding endurance of the Patches are given below in the **Table 7.**

Table 7: Determination of Folding Endurance.

S. No.	Sample	Folding Endurance
1.	F1	26±8
2.	**F2**	**30±7**
3.	F3	27±4
4.	F4	27±5

Folding endurance of prepared transdermal patches were noted. It was found that more folding endurance value is seen in F2 (30) and less folding endurance value in F4 (27).

4.2.5 Surface pH

Surface pH of F1 to F4 were determined. The results were tabulated in **Table 8.**

Table 8: Determination of Surface pH.

S. No.	Sample	pH
1.	F1	6.6±1
2.	**F2**	**6.8±1**
3.	F3	5.9±2
4.	F4	6.3±1

Surface pH was determined and found to be that F2 (6.8) has more pH as compare to other samples.

4.2.6 Swelling Index

The swelling index at different time interval are given in **Table 9** and **Table 10.**

Table 9: Determination of Swelling Index after 1 hour.

S. No.	Sample	Swelling index (%)
1.	F1	1.86±0.046
2.	**F2**	**2.85±0.032**
3.	F3	2.33±0.049
4.	F4	1.75±0.043

Table 10: Determination of Swelling Index after 2 hour.

S. No.	Sample	Swelling Index (%)
1.	F1	2.97±0.083
2.	**F2**	**2.23±0.107**
3.	F3	3.54±0.053
4.	F4	2.96±0.056

Swelling index after completion of 2 hour was found that F3 has more percentage of swelling index in couple of hour and also film gets erode firstly as compare to other formulated patches.

4.2.7 Moisture Uptake

Moisture uptake of prepared transdermal patch F1 to F4 were determined. The results were tabulated in Table 11.

Table 11: Determination of Moisture Uptake.

S. No.	Sample	Moisture uptake
1.	F1	2.98%
2.	**F2**	**2.11%**
3.	F3	2.75%
4.	F4	2.56%

Moisture contents in various formulated patch were determined. It shows that F1 (2.98%) has more moisture content and F2 (2.11%) shows less moisture content.

4.2.8 Moisture Loss

Moisture loss of prepared transdermal patch F1 to F4 were determined. The results are tabulated in **Table 12.**

Table 12: Determination of Moisture Loss.

S. No	Sample	Moisture Loss
1.	F1	0.82%
2.	**F2**	**0.79%**
3.	F3	0.98%
4.	F4	0.95%

Moisture loss were determined and found that F3 (0.98%) shows more moisture loss and F2 (0.79%) shows less loss in moisture.

4.2.9 Content Uniformity Test

The Content uniformity of the samples are given below in the **Table 13.**

Table 13: Determination of Content Uniformity Test.

S. No	Sample	Content Uniformity
1	F1	96.4%
2	**F2**	**98%**
3	F3	95.0%
4.	F4	97%

4.2.10. Drug Content

Drug content determination of F1 to F4 formulations were measured spectrophotometrically at 284 nm. The drug content is calculated and results are tabulated in **Table 14.**

Table 14: Determination of Drug Content.

S. No	Sample	Drug content
1.	F1	91%
2.	**F2**	**98%**
3.	F3	97%
4.	F4	94%

Drug content were determined. It shows that F2 with (98%) drug content and F1 (91%) shows less drug content.

4.2.11. Stability Studies

The Stability of the various formulations at different period of time and in different temperature are tabulated below in the **Table.15- 18**.

Table 15: Stability data after 7 days.

S. No.	Sample	Temperature ℃		
		2-4℃	20-25℃	35-40℃
1.	F1	Stable	Stable	Stable
2.	**F2**	**Stable**	**Stable**	**Stable**
3.	F3	Stable	Unstable	Stable
4.	F4	Stable	Stable	Unstable

Table 16: Stability data after 14 days.

S. No.	Sample	Temperature ℃		
		2-4℃	20-25℃	35-40℃
1.	F1	Stable	Stable	Unstable
2.	**F2**	**Stable**	**Stable**	**Stable**
3.	F3	Stable	Unstable	Unstable
4.	F4	Stable	Unstable	Stable

Table 17: Stability data after 21 days.

S. No.	Sample	Temperature ℃		
		2-4℃	20-25℃	35-40℃
1.	F1	Stable	Stable	Unstable
2.	**F2**	**Stable**	**Stable**	**Stable**
3.	F3	Unstable	Unstable	Unstable
4.	F4	Stable	Unstable	Unstable

Table 18: Stability data after 28 days.

S. No.	Sample	Temperature ℃		
		2-4℃	20-25℃	35-40℃
1.	F1	Stable	Stable	Unstable
2.	**F2**	**Stable**	**Stable**	**Stable**
3.	F3	Stable	Unstable	Unstable
4.	F4	Unstable	Unstable	Unstable

4.2.12 In-Vitro Drug Diffusion Study

In-vitro drug diffusion studies are performed Franz diffusion cell. **Figure 4.** Shows the working process of Franz diffusion cell. Sample are withdrawn at different time interval shown in **Table 19.** And analysed spectrophotometrically at 320 nm against blank**. Figure 5.** Shows graphical representation of In-vitro study.

Figure 4: Working of Franz Diffusion Cell.

Table 19: Drug absorption range determined spectrophotometrically.

Absorption Range				
Time in minutes	**F1**	**F2**	**F3**	**F4**
05min.	0.110	**0.119**	0.105	0.157
10min.	0.201	**0.239**	0.215	0.208
15min.	0.371	**0.371**	0.308	0.367
20min.	0.458	**0.481**	0.399	0.467
25min.	0.458	**0.615**	0.399	0.547
30min.	0.458	**0.730**	0.399	0.632

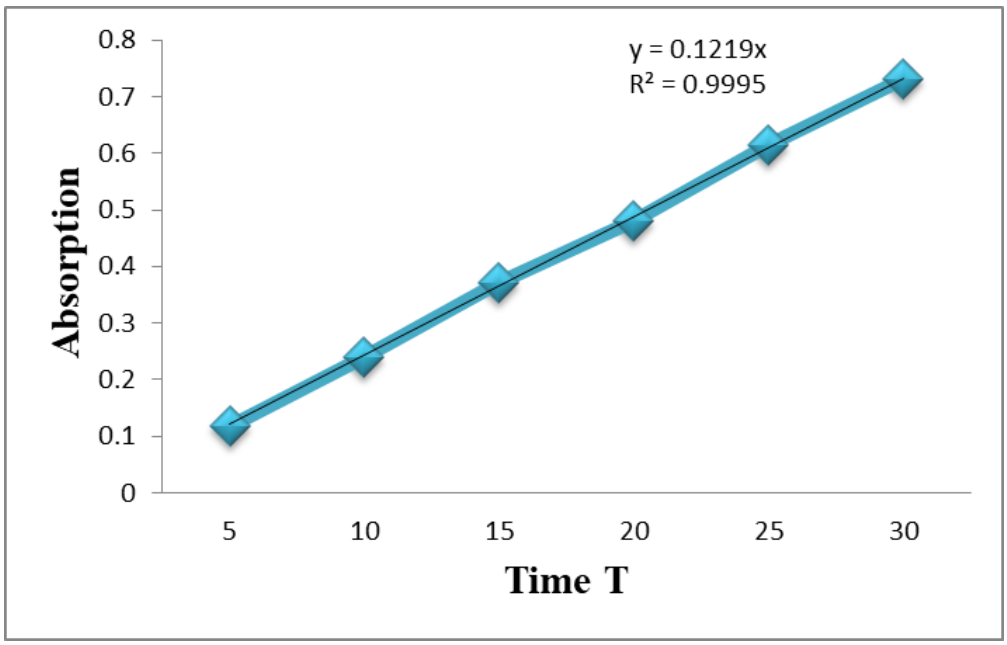

Figure 5: Graphical representation data of drug absorption by the Franz diffusion cell.

5. CONCLUSION

Transdermal application is one of the most promising method over the conventional form. Patch of Diclofenac sodium was successfully prepared with different polymers by solvent casting method. The present studies were helped in understanding the effect of formulation process variables especially the concentration of different polymers on the drug release profile. This study is further aimed to perform in-vivo studies for the concentration of Diclofenac sodium reaching into the skin and to study its effect, which will help to avoid the first pass metabolism and to make novel transdermal dosage form.

Evaluation parameters like physical appearance, uniformity of weight, thickness, folding endurance, moisture content, drug content and diffusion study of formulations F1-F4 were found to be acceptable. The evaluation studies shows that the patch formulation F2 having less thickness, high folding endurance, less moisture content, and have finest uniformity of weight characteristic as compared to other formulations. Parallel it also consumes more drug content than other formulations.

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