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FORMULATION AND EVALUATION OF DICLOFENAC SODIUM TRANSDERMAL PATCHES

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ABSTRACT

The objective of the present study was to develop *Diclofenac Sodium* Transdermal patches to bypass first pass metabolism and overcome all the problem of conventional dosage forms. A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. The release rate from TDS can be tailored by varying polymer composition. The patches containing 2% diclofenac di-ethanolamine DFD were prepared using Eudragit E100 and poly vinyl pyrrolidone (PVP) as the adhesive polymer by the solvent evaporation technique. The effects of different pressure-sensitive adhesive and various permeation enhancers (Tween-80, propylene glycol, azone, N-methyl-2-pyrrolidone, menthol) on the *vitro* percutaneous absorption of diclofenac across rat skin were evaluated using a 2-chamber diffusion cell system. Diclofenac is a NSAID agent used for the treatment of rheumatoid arthritis, osteoarthritis and relief the pain of varying origin treatment. Evaluation parameters like physical appearance, uniformity of weight, thickness, folding endurance, moisture content, drug content, dissolution study and diffusion study are all carried out. The results show that patches of diclofenac sodium obtained by the solvent evaporation method had acceptable physicochemical characteristics and satisfactory % drug release.

KEYWORDS: Diclofenac, polymers, matrix system, adhesives, permeation enhancer, diffusion cell system, polyvinylpyrrolidone (PVP), ethyl cellulose and solvent evaporation technique.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs, which are used in both acute and chronic symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and dysmenorrhea treatment because of their analgesic, antipyretic and anti-inflammatory roles. Diclofenac(2-[2-(2,6 dichlorophenyl amino) phenyl]acetic acid) is one of the most prospective and commercially successful drug in the family of NSAIDs. The main mechanism of action is to inhibit the activity of cyclooxygenase (COX) by interdicting the prostaglandin (PG) synthesis.[29]

It undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation. Its biological half-life is also very short.[22] Thus, the drug has reasonably been chosen to develop a transdermal formulation to increase patient compliance.[19] The patches containing 2% diclofenac diethanolamine DFD were prepared using Eudragit E100 and polyvinylpyrrolidone (PVP) as the adhesive polymer by the solvent evaporation technique. The release rate from TDS can be tailored by varying polymer composition.[15]

To study the effect of plasticizers such as dibutyl phthalate and propylene glycol by using Keshary- Chein diffusion cell. The placebo and medicated films were evaluated for physicochemical properties and also medicated films were evaluated for area variation, drug content and percent cumulative drug release. The patches were tested for their potential to cause skin irritation/ sensitization in healthy human volunteer.[9] Placebo films were studied for flexibility, clarity, elasticity and ease of removal of films from the molds and also for thickness uniformity, percentage flatness, moisture uptake test, tensile strength, modulus of elasticity and percentage elongation at break.[15] The aim of the present work was to prepare transdermal patches of diclofenac and to study their therapeutic effect and stability over conventional dosage form.[22]

MATERIALS AND METHODS

Diclofenac sodium and poly vinyl pyrrolidone were purchased from Yarrow chem. Products, Mumbai, India. Ethyl cellulose and dibutyl phthalate were obtained as gift samples from Qualigens fine chemicals, Mumbai, India. Ethanol and chloroform were purchased from Jiangsu huaxi laboratory, China. All other chemicals used were of analytical grade.

PREFORMULATION STUDIES

DRUG EXCIPIENTS COMPATABILITY STUDIES:

Fourier –transform infrared (FT-IR) spectra was obtained using an FT-IR spectrometer (shimadzu 8400S, Japan). The sample (diclofenac sodium and excepients) were previously grounded and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powder at a pressure of 5 tons for 5 min in hydraulic press. Forty scans were prepared at a resolution of 4cm-1, from 4000 to 400 cm-1.

PREPARATION OF PATCHES

Films were prepared by the film casting method of specially designed glass molds with the plastic transparent sheet. According to the formula ethyl cellulose and poly vinyl pyrrolidone were accurately weighed and dissolved in chloroform: ethanol mixture used as solvent. The drug was then dispersed in the polymeric solution and plasticizer of dibutyl phthalate was added. The solution was stirred to attain semisolid like consistency and mounted on a glass substrate the rate of evaporation was controlled by placed an inverted funnel at room temperature for a day. The formed films were separated formulation of diclofenac patches.

Table 1: Composition of Diclofenac Sodium Transdermal Patches.

Patch Code	Ethyl Cellulose (Mg)	Poly Vinyl Pyrrolidone (Mg)	Diclofenac Sodium (Mg)	Ethanol (Ml)	Chloroform (Ml)	Di Butyl Phthalate (Ml)
P1	400	0.0	100	2.0	18	0.4
P2	400	50	100	2.0	18	0.4
P3	400	100	100	2.0	18	0.4
P4	400	150	100	2.0	18	0.4
P5	0.0	400	100	2.0	18	0.4
P6	50	400	100	2.0	18	0.4
P7	100	400	100	2.0	18	0.4
P8	150	400	100	2.0	18	0.4

EVALUATION OF PATCHES

The composition and concentration of the transdermal films has a considerable influence on the physical, mechanical properties as well as the permeability of the drugs. Physical and mechanical properties of blank and medicated transdermal films such as thickness uniformity, percent flatness, moisture uptake, tensile strength and percent elongation at break and modules of elasticity were studied. Also medicated films were evaluated for area, drug content and *in-vitro* drug release.

1-Physical appearance

All the transdermal films were visually inspected for color, clarity, flexibility and smoothness.

2-Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

3-Thickness of patch

The thickness of transdermal film is determined by screw gauge or micrometer at different point.

4-Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

5-Moisture content

To check the physical stability of the film in high humidity conditions, accurately weighed films were placed in a dessicator containing saturated solution of aluminum chloride (79.5% RH) for three days. The films were re-weighed and the percentage moisture absorption was calculated using the formula.[10,18]

$$\text{Moisture content} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

6-Drug content

An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 hours shaken manually. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution by appropriate dilution is estimated spectrophotometrically.

7-*In-vitro* drug dissolution study

The paddle method (USP apparatus I) can be employed for the assessment of the release of drug from the prepared patches. Dry films of known thickness is to be cut into definite

shapes, weighed and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500 ml dissolution medium or phosphate buffer (pH7.4) and the apparatus was calibrated to 32.50c±20c. The paddle was then set at distance of 2.5cm from the glass plate and operated at a speed of 50 rpm. Samples (5ml aliquots) can be withdrawn at appropriate time intervals up to12 hours and analyzed by UV spectrophotometer. The experiment is to be performed in triplicate and mean value calculated.

8-*In-vitro* drug diffusion studies

These studies are performed using a modified Franz diffusion cell[19] with a receptor compartment capacity of 50 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1 cm2 and placed over an adhesive tap and fixed to the cellophane membrane and attached to glass tube by the aid of rubber bands. The drug releasing membrane and the receptor compartment of the diffusion cell were filled with phosphate buffer pH 7.4. The temperature was maintained at 32ºC. The samples of 3ml were withdrawn at time interval of 10, 20, 30, 60, 120, 180 and 720 minutes, analyzed for drug content spectrophotometrically at λmax 270 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal.

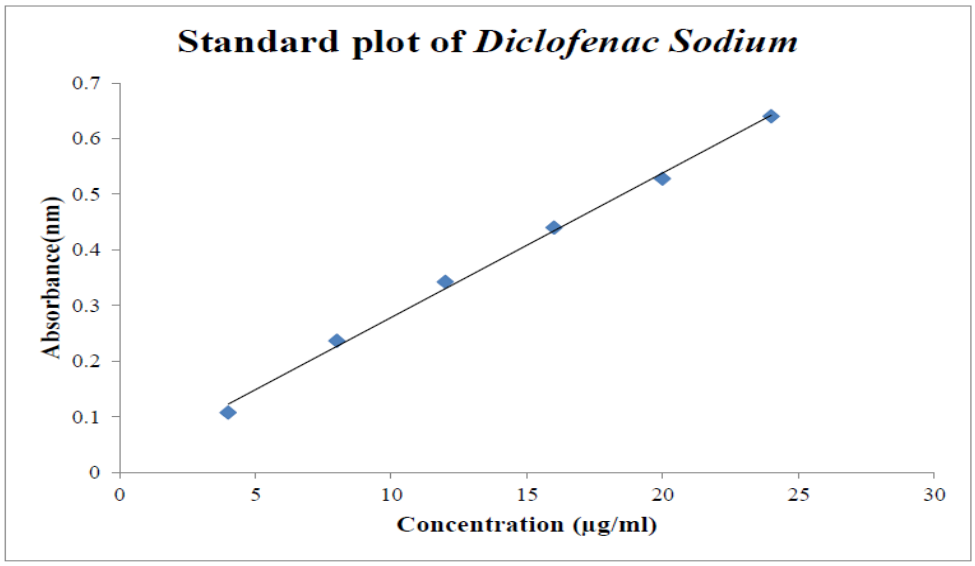
RESULTS AND DISCUSSION

STANDARD PLOT OF DICLOFENAC SODIUM

Standard plot of diclofenac sodium in phosphate buffer pH 7.4 was obtained as follows:-

Table 2: Standard plot for Diclofenac Sodium.

SL.NO	CONCENTRATION (µg/ml)	ABSORBANCE (nm)
1	4	0.108±0.005
2	8	0.237±0.007
3	12	0.343±0.011
4	16	0.440±0.006
5	20	0.528±0.013
6	24	0.640±0.009



Graph 1: Standard plot for Diclofenac Sodium.

FT-IR SPECTROSCOPIC STUDY

The possible interaction between the drug and excipients was studied by FT-IR spectroscopy.

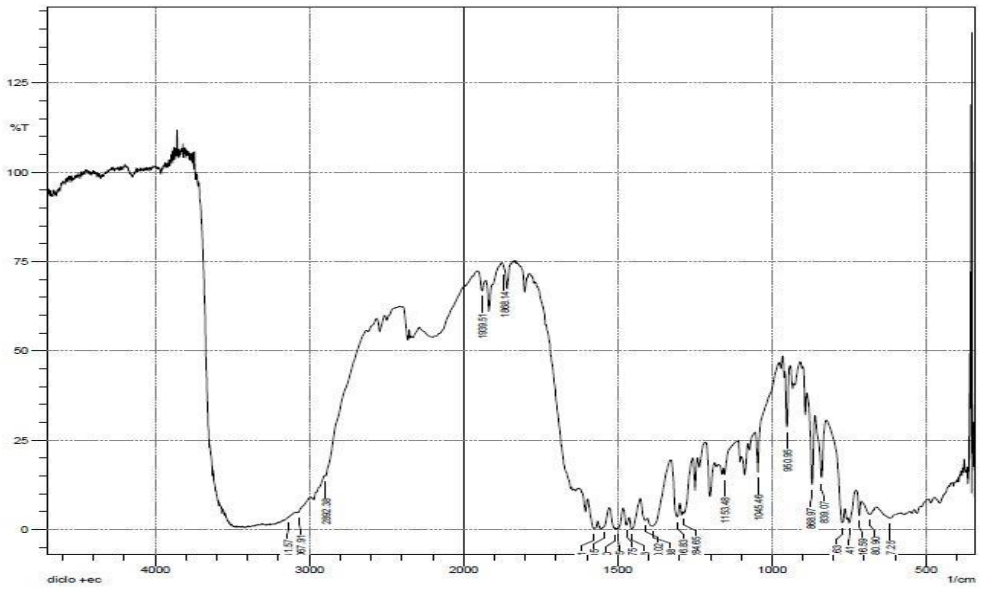


Figure 1: FT-IR spectra of diclofenac sodium.

Resolution: 4 [1/cm] **No. of Scans:** 30

Comment: Diclofenac sodium **Apodization:** Happ-Genzel.

Table 3: FT-IR spectra of diclofenac sodium.

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	586.36	80.9	5.182	599.86	565.14	2.618	0.389
2	765.74	43.922	23.693	781.17	759.95	4.676	1.301
3	864.11	73.81	15.818	881.47	856.39	1.867	0.76
4	916.19	84.116	8.422	927.76	906.54	1.071	0.357
5	939.33	87.654	2.317	943.19	933.55	0.467	0.039
6	1041.56	85.773	7.614	1055.06	1012.63	1.625	0.414
7	1089.78	81.263	4.844	1095.57	1076.28	1.308	0.185
8	1153.43	77.246	13.138	1168.86	1112.93	3.169	0.914
9	1195.87	77.431	12.294	1215.15	1168.86	3.184	0.995
10	1274.95	63.645	14.396	1288.45	1255.66	4.402	1.015
11	1381.03	28.54	41.614	1396.46	1327.03	14.355	5.996
12	1450.47	26.977	25.455	1458.18	1421.54	11.076	2.963
13	1504.48	28.524	43.654	1527.62	1483.26	13.329	6.99
14	1558.48	22.88	23.373	1564.27	1529.55	9.792	1.757
15	1577.77	7.896	35.303	1597.06	1566.2	21.351	10.304
16	2958.8	84.56	0.706	2962.66	2920.23	2.481	-0.078
17	3064.89	79.937	2.289	3074.53	3043.67	2.638	0.099
18	3251.98	73.567	12.657	3387	3124.68	24.517	7.643

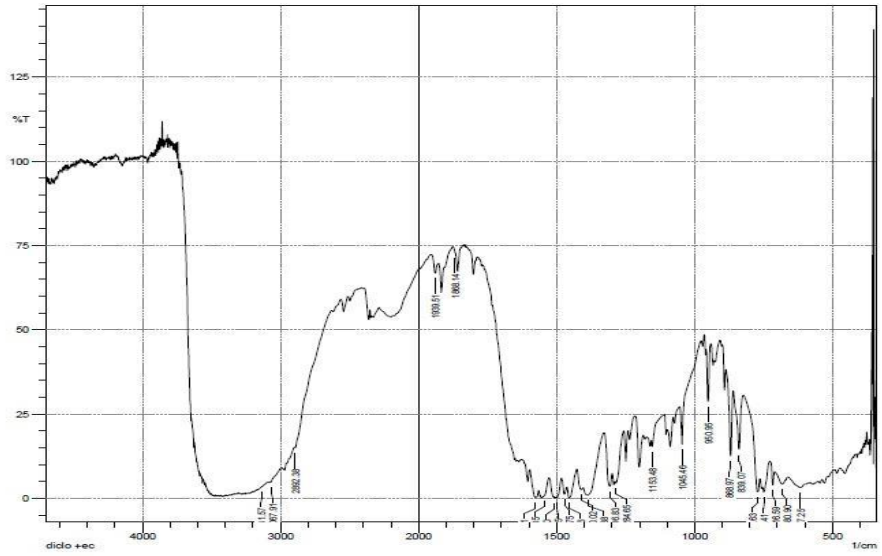


Figure 2: FT-IR spectra of diclofenac sodium and excipients.

Resolution: 2 [1/cm]a **No. of Scans :** 30

Comment : Diclo + excepients **Apodization :** Happ-Genzel.

Table 4: FT-IR spectra of diclofenac sodium and excipients.

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	617.25	3.18	0.85	629.79	599.89	43.08	1.5
2	680.9	4.24	1.94	709.83	670.29	49.68	3
3	716.59	3.89	5.25	727.19	709.83	19.62	1.75
4	748.41	1.82	3.01	753.23	728.16	32.59	2.64
5	769.63	1.95	6.42	822.68	763.84	50.67	5.32
6	839.07	14.18	17.02	860.29	822.68	23.18	4.19
7	868.97	12.47	21.56	887.29	860.29	16.03	3.73
8	950.95	28.73	16.3	957.7	941.3	7.01	1.35
9	1045.46	16.07	13.36	1054.14	976.02	36.37	1.7
10	1153.48	15.38	2.36	1156.37	1110.08	30.59	0.28
11	1284.65	4.48	2	1287.54	1256.68	30.5	1.07
12	1306.83	3.52	7.17	1327.08	1299.11	31.46	5.6
13	1386.88	0.91	5.88	1403.27	1328.05	99.35	17.97
14	1410.02	2.57	2.12	1425.46	1404.24	30.15	2.82
15	1452.46	0.19	4.67	1462.11	1426.42	60.2	15.37
16	1471.75	1.2	3.5	1481.39	1463.07	29.26	4.57
17	1498.75	0.28	0.7	1500.68	1482.36	33.46	1.3
18	1508.4	0.03	0.71	1525.76	1507.43	35.49	3.08
19	1545.05	0.71	0.27	1546.01	1526.72	30.48	0.15
20	1575.91	0.24	1.56	1596.16	1572.05	43.2	2.94
21	1868.14	72.94	0.25	1874.89	1867.17	1.01	-0.01
22	1939.51	66.83	4.17	1953.01	1926.97	4.13	0.27
23	2892.38	15	0.97	2897.21	2631.02	119.32	0.14
24	3067.91	4.81	0.18	3069.84	3002.33	78.92	0.11
25	3131.57	3.5	0.14	3133.5	3116.14	24.62	0.06

EVALUATION STUDIES

1-PHYSICAL APPEARANCE

The patches were visually inspected for colour, clarity, flexibility, thickness and smoothness.

Table 5: Physical Appearance of Patches.

SL.NO	PATCH CODE	COLOUR	CLARITY	FLEXIBILITY	SMOOTHENESS
1.	P1	Colourless	Clear	Flexible	Smooth
2.	P2	Colourless	Clear	Flexible	Smooth
3.	P3	Colourless	Clear	Flexible	Smooth
4.	P4	Colourless	Clear	Flexible	smooth
5.	P5	Colourless	Clear	Flexible	Smooth
6.	P6	Colourless	Clear	Flexible	Smooth
7.	P7	Colourless	Clear	Flexible	Smooth
8	P8	Colourless	Clear	Flexible	Smooth

2-UNIFORMITY OF WEIGHT

A specified area of patch is to be cut at different parts of the patch and weigh in digital balance. The average weight is calculated from individual weights.

Table 6: Determination of Uniformity of Weight.

SL.NO	PATCH CODE	MEAN WEIGHT (gm)
1.	P1	0.625±0.008
2.	P2	0.720±0.037
3.	P3	0.600±0.025
4.	P4	0.58±0.023
5.	P5	0.615±0.018
6.	P6	0.670±0.013
7.	P7	0.680±0.025
8.	P8	0.694±0.016

The uniformity of weight was determined. The patch P2(0.720 gm) shows more weight and patch P4(0.58 gm) shows less weight.

3-THICKNESS OF PATCHES

The thickness of patches was determined by using screw gauge. The mean thickness was measured at different points of the film.

Table 7: Determination Of Thickness Of Patch.

SL.NO	PATCH CODE	MEAN THICKNESS (mm)
1.	P1	0.5±0.012
2.	P2	0.73±0.015
3.	P3	0.63±0.030
4.	P4	0.58±0.011
5.	P5	0.52±0.017
6.	P6	0.62±0.09
7.	P7	0.66±0.013
8.	P8	0.61±0.021

The thickness of formulated patches was tabulated. It was found that P1 (0.5 mm) shows less thickness and P2 (0.73 mm) shows more thickness.

4-FOLDING ENDURANCE

Folding endurance of patches P1 to P8 were determined. The results were tabulated as follows.

Table 8: Determination of Folding Endurance.

SL.NO	PATCH CODE	FOLDING ENDURANCE
1.	P1	85±15
2.	P2	80±10
3.	P3	70±8
4.	P4	75±9
5.	P5	75±18
6.	P6	72±13
7.	P7	76±12
8.	P8	77±5

Folding endurance of prepared transdermal patches were noted. It was found that more folding endurance value is seen in P1 (85) and less folding endurance value in P2 (70).

5-MOISTURE CONTENT

The moisture content of prepared transdermal patches P1 to P8 were determined. The results were tabulated as follows.

Table 9: Determination of Moisture Content.

SL.NO	PATCH CODE	PERCENTAGE MOISTURE CONTENT (%)
1.	P1	2.11±0.36
2.	P2	3.23±0.55
3.	P3	3.98±0.95
4.	P4	2.18±0.7
5.	P5	2.17±0.46
6.	P6	2.23±0.45
7.	P7	3.08±0.45
8.	P8	3.18±0.17

Moisture content of patches were determined and the patch P3 (3.98%) shows more moisture content and P1 (2.11%) shows less moisture content.

6-DRUG CONTENT DETERMINATION

Drug content determination of P1 to P8 formulations were measured spectrophotometrically at 270 nm. The drug content is calculated and it was found to be as follows.

Table 10: Determination of Drug Content.

SI.NO	PATCH CODE	PERCENTAGE DRUG CONTENT (%)
1.	P1	80.7±0.046
2.	P2	79.0±0.042
3.	P3	76.5±0.054
4.	P4	78.1±0.037
5.	P5	77.7±0.036
6.	P6	76.0±0.012
7.	P7	75.5±0.014
8.	P8	78.1±0.013

Drug content of each formulations were tabulated the patch P1(80.7%) shows more drug content and P7(75.5%) shows less drug content.

7-In-vitro DISSOLUTION STUDY

The drug release of transdermal patch varies with respect to polymer. The release of drug from its dosage form plays an important role in determining the therapeutic effect of the medication.

Table 11: *In-vitro* Dissolution Study.

SL. NO	TIME IN MINS	PERCENTAGE CUMULATIVE RELEASE (%)							
		P1	P2	P3	P4	P5	P6	P7	P8
1.	10	11.7± 0.5	9.9± 1.7	8.9± 0.5	0.74± 0.02	10.2± 0.1	8.4± 1.3	6.8± 0.5	0.74± 0.02
2.	20	24.4± 0.8	21.99± 1.1	12.9± 1.4	1.94±0 .1	22.9± 0.6	20.4± 1	10.8± 1.1	2.14± 0.6
3.	30	37.7± 0.9	34.6± 0.9	17.2± 1.8	4.34± 0.3	36.2± 0.3	32.1± 0.2	15.1± 1.6	3.30± 0.3
4.	60	49.1± 1.2	48.5± 2.3	23.7± 2.3	8.04± 1.3	47.6± 1	47.0± 1.7	21.5± 2.0	6.01± 1.1
5.	120	63.0± 0.7	63.0± 1.5	36± 1.3	14.84± 1.6	62.5± 0.1	62.5± 1.0	34± 1.0	12.6± 0.6
6.	720	81.9± 2.3	79.7± 2.4	53± 2.1	26.54± 2.1	80.4± 2.0	78.2± 1.1	51.9± 1.6	24.3± 1.1

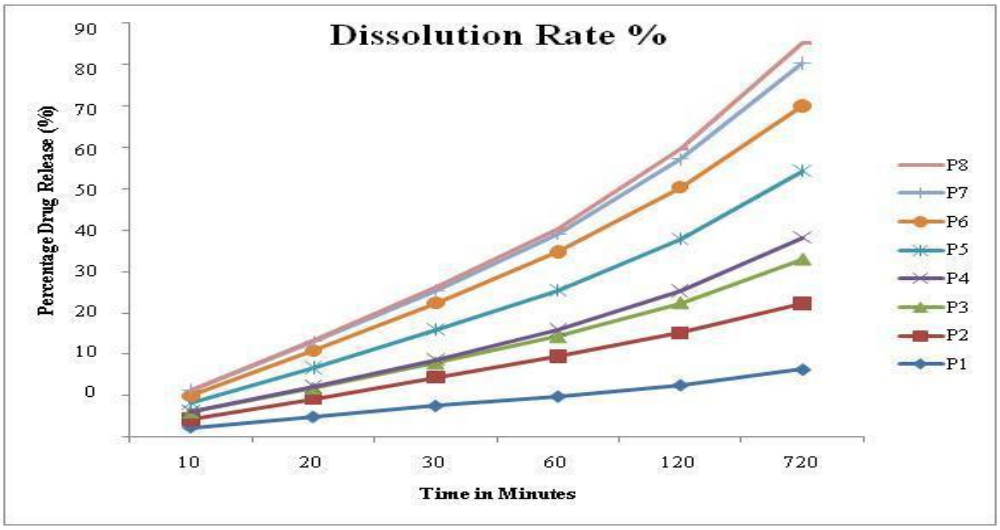


Figure 3: *In-vitro* Dissolution Study.

Among the four dissolutions the maximum in-vitro drug release was found in case of formulation no 1(81.9%) observed on a period of 720 minutes while the minimum *in-vitro* drug release is observed in case of formulation no.4 (26.54%).

In-vitro DRUG DIFFUSION STUDY

The studies are performed using a modified Franz diffusion cell with a receptor compartment capacity of 25ml. The patch was mounted on the cellophane membrane between donor and receptor compartment. Samples were withdrawn at specified time intervals and analyzed for drug content spectrophotometrically at λmax 270nm against blank. Result was tabulated.

Table 12: *In-vitro* Drug Diffusion Study.

SL. NO	TIME IN MINS	PERCENTAGE DRUG DIFFUSED (%)							
		P1	P2	P3	P4	P5	P6	P7	P8
1.	10	3.72± 0.2	3.10± 0.3	2.48± 0.1	0.31± 0.01	2.22± 0.7	2.6± 0.3	2.2± 0.1	0.31± 0.01
2.	20	8.68± 0.9	6.51± 0.8	5.58± 0.8	0.93± 0.5	7.1± 0.9	5.4± 0.8	4.58± 0.8	0.89± 0.4
3.	30	15.19±1 .7	12.09± 0.9	10.85± 0.7	2.17± 0.7	13.1± 1	10.5± 0.9	8.85± 0.7	3.02± 0.2
4.	60	23.87±1 .3	18.6± 0.3	16.74± 0.8	6.51± 0.5	22.3± 2	16.4± 0.3	15.4± 0.8	5.4± 0.3
5.	120	35.03±2 .2	27.28± 1.2	24.49± 1.3	12.4± 0.9	33.5± 1.4	26.2± 1.2	23.29± 1	13.2± 1.9
6.	720	48.05±1 .2	37.2± 1.5	33.48± 2.3	19.84± 1.5	46.5± 2	35.8± 1.5	32.5± 1.3	17.9± 2

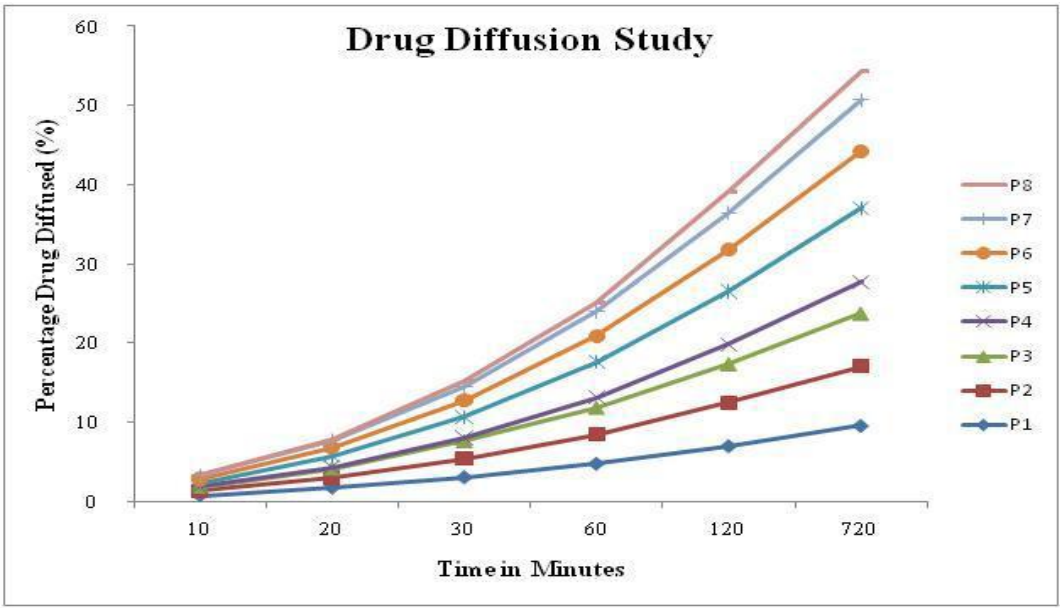


Figure 4: *In-vitro* Drug Diffusion Study.

CONCLUSION

The Transdermal drug delivery system is one of the most promising methods for drug application. The transdermal patch of diclofenac sodium with ethyl cellulose and poly vinyl pyrrolidine was prepared. Eight Patches were prepared and their physical, dissolution and diffusion properties were evaluated.

Evaluation parameters like physical appearance, uniformity of weight, thickness, folding endurance, moisture content, drug content, dissolution study and diffusion study of formulations P1-P8 were found to be satisfactory. The evaluation studies shows that the patch formulation P1 having less thickness, high folding endurance, less moisture content, and have optimum uniformity of weight characteristic as compared to other formulations. At same time they also have more drug content than other formulations.

The formulation P1also has pronounced effect when compared to other formulations. This can be confirmed by further *in-vitro* dissolution study and *in-vitro* drug diffusion study and the results obtained confirmed that there was an increased dissolution and diffusion rate when compared to other patches.

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