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Der Pharmacia Lettre, 2015, 7 (3):141-148
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Development and evaluation of aceclofenac transdermal patches with different permeation enhancers

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ABSTRACT

This research work was an attempt to formulate and evaluate matrix-type transdermal therapeutic system containing Aceclofenac with different permeation enhancers (in different 3 ratios) by the solvent evaporation technique and explores the effect of permeation enhancers on the in vitro permeability of aceclofenac across excised goat skin. Matrix transdermal patches were prepared by using hydroxyl propyl methyl cellulose (HPMC) by incorporating dibutyl phthalate incorporated as plasticizer and oleic acid, peppermint oil and iso-propyl myristrate (IPM) as permeation enhancers in different 3 ratios 2%, 4% and 6% v/v in whole formula. Permeation studies were performed using modified Franz diffusion cell. All the patches were uniform with respect to physiochemical evaluation. The in-vitro permeation study indicate that formulation ATP-3(6% v/v oleic acid) showed maximum release of 74.513% in 12 hrs emerging to be ideal formulation. The developed transdermal patches increase the efficacy of Aceclofenac for the therapy of arthritis and other pain.

Key words: Aceclofenac, TDDS, Arthritis, permeation enhancers, skin, NSAIDs, *in-vitro* permeation study etc

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INTRODUCTION

Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery, and also provides controlled release of the drug for extended period of the time. [(1)] Drug delivery through the skin to achieve a systemic effect without producing any fluctuations in plasma concentration of the drug. Continuous oral medication affected all organ, damage kidney and most hazardous action of NSAID class drug is produce ulcer specially in case of arthritis patient continuously pain persist. [(2)] Transdermal drug delivery system has been accepted as potential non-invasive route of drug administration, with advantages of prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy.[(3)]

The Transdermal Patche use on the largest organ of the body in terms of both weight and surface area. Skin is the outermost tissue of the human body. It has an area of approximately 16, 000 cm^2 for an adult and represents about 8% of the body weight. [(4)] The skin basically consists of three anatomical layers epidermis, dermis, subcutaneous. The Stratum corneum (SC), viable epidermis and dermis offer barriers to penetrating molecules. For a drug penetrating across the skin the greatest resistance is met in the SC. [(5)]

Rheumatoid arthritis is a chronic progressive disease associated with systemic inflammation. The disease directly affects physical function and mobility and results in substantial short-term and long-term morbidity. Furthermore, individuals with rheumatoid arthritis have a substantially shorter life expectancy than does the general population. Deaths from cardiovascular disease, infection, and cancer are increased among individuals with rheumatoid arthritis.[6] Rheumatology and dermatology requires the use of guidelines for drug toxicity monitoring, as adverse effects can be significant in some patients.[7]

NSAIDs are amongst the most widely used of all therapeutic agents. They are frequently prescribed for the long-term treatment of rheumatic musculoskeletal complaints. The major drawback of anti-inflammatory drug use is the occurrence of gastrointestinal side effects.[8] mechanism behind the activity(MOA) of Aceclofenac(ACH) is based on the inhibition of COX enzyme which involved in the production of prostaglandin synthesis.[9-10] The common method to improve drug permeation through the skin is to use penetration enhancers. Penetration enhancers can change the structure of skin lipids and alter the skin barrier function. [11]

The aim of this study is to develop transdermal patches of Aceclofenac using different permeation enhancers and to carry out in vitro diffusion behavior of prepared patches.

MATERIALS AND METHODS

Aceclofenac pure drug was obtained from Cadila pharmaceuticals, Ahmedabad Gujarat India, as a gift sample. The drug is soluble in Phosphate buffer pH 7.4 and freely soluble in acetone, ethyl alcohol, chloroform, ether. It is white, odorless, fine granular powder. Stored in air tight container protected from light at room temperature not exceeding 30^0c. The usual dose of Aceclofenac is 100 mg twice a day by oral route. Aceclofenac is readily absorbed from the gastrointestinal tract, peak plasma concentration occur about 4h after a dose, 99% bound to plasma protein.

Hydroxypropyl methylcellulose (HPMC) is a tasteless, white to slightly off white, fibrous or granular powder, soluble in cold water, forming a viscous colloidal solution. HPMC is a widely used as an excipient in oral and topical Pharmaceutical formulations. It is also used extensively in cosmetics and food products. Oleic acid, Peppermint oil, IPM use as permeation enhancer. Di butyl phthalate (DBT) Used as plasticizer. Soluble in water alcohol, ether used as an additive and used as a ectoparasiticide. All this additives obtained from Central drug store, MP, India.

Physiochemical Compatibility Investigation of Drug and Polymer:
The infrared (IR) spectra were recorded using a Fourier transform-infrared (FTIR Bruker, Japan) pallatization was done by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm–1. The spectra obtained for ACF, polymers, and physical mixtures of ACF with HPMC were compared. [12] Determination of λ_{max} of Aceclofenac in Phosphate buffer solution of pH 7.4 with the help of double beam UV-Visible spectrophotometer. It was observed to be **273** nm.

Table 1 Formulation of Aceclofenac Transdermal Patches

Batch no	Drug ACH (mg)	Polymer HPMC (mg)	Oleic acid (%)	Iso propyl myristate (%)	Peppermint oil (%)	Dibutyl Phthalate (%)	Methanol (ml)
ATP-1	150	250	2	-	-	15	19.5
ATP-2	150	250	4	-	-	15	20
ATP-3	150	250	6	-	-	15	20.5
ATP-4	150	250	-	2	-	15	19.5
ATP-5	150	250	-	4	-	15	20
ATP-6	150	250	-	6	-	15	20.5
ATP-7	150	250	-	-	2	15	19.5
ATP-8	150	250	-	-	4	15	20
ATP-9	150	250	-	-	6	15	20.5

Fabrication of Transdermal Patche:
Transdermal Patches containing ACF were prepared by using solvent evaporation technique with three different permeation enhancer's Oleic acid, Iso propyl myristate, and Peppermint oil in 2%, 4%, and 6% *v/v* ratio in different formulations. DBP 15 % (*v/v* of dry polymer composition) was used as a plasticizer. [13] DBP was added into the

homogeneous dispersion under slow stirring with a magnetic stirrer. Methanol was used as a solvent system, the solution casted in flat base Petri dish. After complete evaporation of solvent system and dry appearance of Patch it was removed from Petri dish. The films were stored (called as desiccator) for further studies. [14] Various compositions of different formulations are represented in Table 1.

Evaluation of Transdermal Patches

Physical evaluation

- **Thickness:** The thicknesses of the prepared Patches were measured in 3 different points by using a vernier caliper and determined the average thickness.
- **Physical appearance:** All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.[15]
- **Drug content determination:** An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of PBS in which drug is soluble and then the solution is placed in magnetic stirrer continuously for 24 h. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated by uv spectrophotometer in 10, 20, 30, 40, 50 µg/ml(dilutions).[16]
- **Weight Variation:** The Patches were subjected to mass variation by individually weighing randomly selected Patches.
- **Moisture lost:** The prepared films were weighed individually and kept in a desiccator. Containing calcium chloride at room temperature for 24 h. The films were weighed again after a specified interval. Percent moisture content is calculated by-[17]

% Moisture content = [Initial weight – Final weight / Initial weight] ×100

- **Moisture gain:** The accurately weighed films were kept in desiccators at room temperature for 24 hours, containing saturated solution of potassium chloride in order to maintain 80-90% RH. After 24 hours the films were taken out and weighed again. Percentage moisture uptake was calculated by-[18]

% moisture uptake = [Final weight- Initial weight/ initial weight] ×100

- **Folding Endurance:** 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. **[19]**
- **Tensile strength:** Tensile strength can be measured by the % elongation. In this evaluation parameter firstly cut a certain square shaped membrane, in these case, chosen about 3x3 cm length and 3 cm breadth, two different ends of this square shaped part of membrane attach with the help of clip, one end of the clip to be fixed, another end of clip attach with the point note down the weight, till the breaking point. At its breaking point note down the weight. [20]
- **Flatness:** 3 strips (longitudinal) were cut out from the prepared medicated film 1 from the middle center and 2 from the either side the lengths of each strip were measured. Then variation in the length due to the non-uniformity in flatness was measured by- %constriction=L1-L2/L2x100, L1=initial length of each strip, L2=final length of each strip [21]

Table 2 Evaluation parameter of transdermal patches

Formulation	Thickness (mm) ±SD	Weight variation (mg)	Elongation (%)	Moisture Gain (%)	Moisture lost (%)	Tensile Strength (kg cm^{-2})	Flatness %
ATP-1	0.19± 0.02	245± 1.89	2.99± 1.07	2.82 ±0.03	1.20 ± 2.18	19.19 ± 1.43	98±0.057
ATP-2	0.19±0.02	246± 2.4	2.32± 2.63	2.62±0.06	1.10 ± 1.69	18.85 ± 1.40	98±0.115
ATP-3	0.20±0.01	250± 1.88	2.78± 7.80	2.26±0.03	1.46 ± 2.80	19.79 ± 1.10	99±0.023
ATP-4	0.18± 0.02	246±2.3	2.95± 9.30	1.78±0.018	1.30 ± 1.72	15.64 ± 0.80	97.3±0.016
ATP-5	0.18± 0.03	248±1.6	2.59± 5.78	2.93±0.02	1.56 ± 2.80	19.10 ± 1.30	95.2±0.038
ATP-6	0.19±0.03	248±2.2	2.61± 4.23	3.23±0.021	1.36 ± 0.78	19.00 ± 0.81	98±0.024
ATP-7	0.18±0.02	242±1.21	2.58± 5.54	2.78±0.06	1.42 ± 1.29	18.19 ± 1.32	95.1±0.114
ATP-8	0.18± 0.03	247±2.46	2.53± 9.30	3.18±0.032	1.28 ± 2.68	19.88 ± 0.16	96.1±0.112
ATP-9	0.19 ± 0.02	250±2.31	2.86± 1.90	2.23±0.08	1.36 ± 1.89	19.71 ± 1.07	98.3±0.12

**ATP=Aceclofenac transdermal patche*

***In-Vitro* Permeation across Goat Abdominal Skin:**

Preparation of Goat Skin:

The abdominal skin of excised hairless goat skin was separated along the epidermal junction and it was kept in water bath, in maintained temperature 60^{o} for 50s the heat treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution for smoothing.

Skin Permeation Study:

Skin permeation study through Franz diffusion cell:

The cell is composed of two compartments: donor and receptor. The receptor compartment has a capacity of 30ml volume and effective surface area of 3x3 cm^2. The diffusion buffer is continuously stirred by a magnetic bar. The samples were taken from Franz diffusion cell for calculation percentage cumulative drug release for 12 hours. An important study of percentage drug release was performed in Franz diffusion cell which is filled with phosphate buffer saline solution pH 7.4 samples were taken from Franz diffusion cell replaced with same volume of fresh saline phosphate buffer to maintain the sink condition and observed the absorbance at the time interval of 15 min, 30 min, to 1 to 12 hours at 273 nm by spectrophotometrically. [22]

Table No. 3. % Cumulative Release of Drug through Skin

Time (hr.)	%CR ATP-1	%CR ATP-2	%CR ATP-3	%CR ATP-4	%CR ATP-5	%CR ATP-6	%CR ATP-7	%CR ATP-8	%CR ATP-9
0	0	0	0	0	0	0	0	0	0
1	13.193	14.702	13.018	9.352	11.439	13.158	10.737	11.088	11.544
2	21.486	22.554	21.802	13.639	17.644	20.316	17.074	17.817	18.488
4	30.213	33.368	34.159	20.404	22.794	30.619	20.779	21.341	19.905
6	36.410	40.557	41.239	23.105	31.987	39.851	28.098	32.390	35.677
8	38.852	53.782	54.404	26.611	42.425	53.416	37.933	41.938	41.593
10	52.252	63.322	64.292	30.766	56.127	63.893	47.919	53.004	53.053
12	59.992	70.186	74.513	36.144	67.131	74.065	60.277	61.253	61.916

RESULTS AND DISCUSSION

Investigation of compatibility of drug and polymer: drug –excipients play important role with respect to release of drug from patches here used FTIR technique to study interactions between drug and excipients. Figure 1.FTIR of pure drug Aceclofenac. Figure 2. Shows the physical compatibility between drug and polymer. Figure 1. Pure Aceclofenac showed major peaks at 3316.1, 2970.6, 1770.02, 1717.90, 1580.7, 1504.6, 1444.5, 1344.9, 1289.9, 1145.6, 1053.3, 751.9, 663.6 cm^{-1}.

From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. (Figure 1, 2)

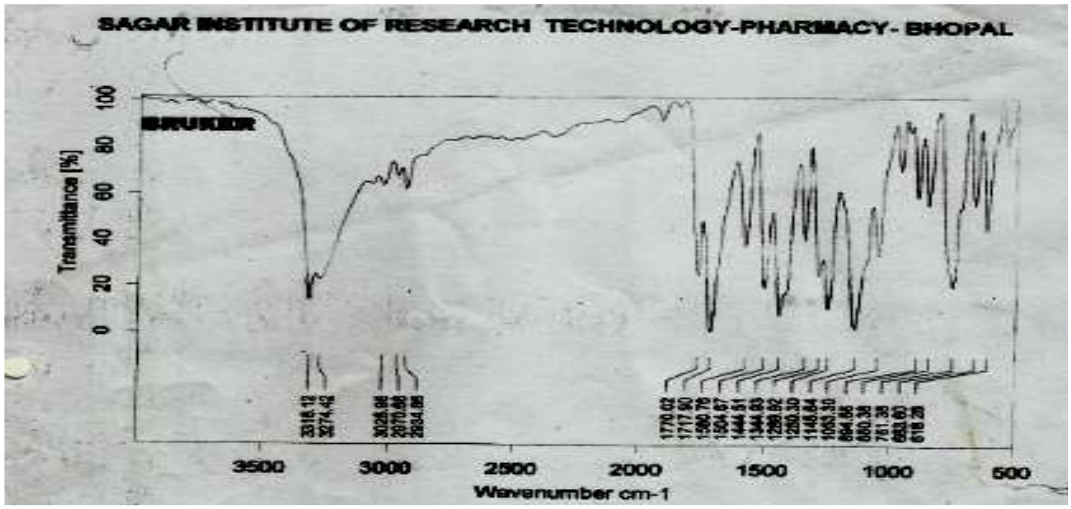

Figure 1. FTIR spectra of Aceclofenac

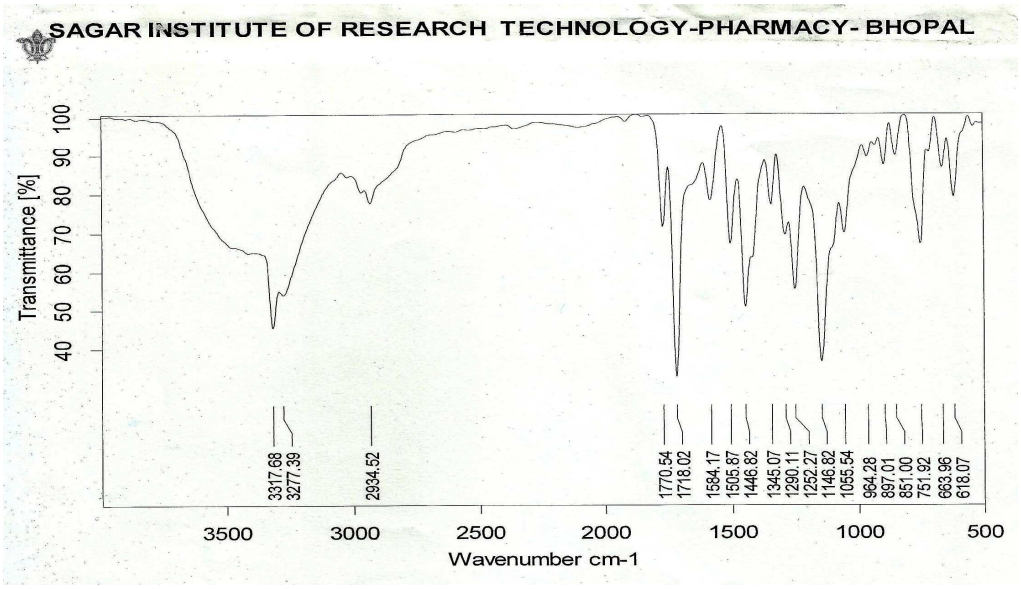

Figure 2. FTIR spectra of mixture of Aceclofenac and HPMC

Physiochemical Evolutions of films:

The results of the physiochemical evolution of Patches are shown in table 2. The thickness of patches range between 0.18 to 0.20 ± 0.01 mm which indicated that they are uniform in thickness. The weights ranging between 242±1.21 to 250± 1.88 mg this shows that different patches were relatively similar weight. Flatness is good ranging approx 99%. Folding endurance test results shows that the films would not break and would maintain their integrity when applied. Moisture gain studies indicated that the concentration of permeation enhancers added was not produce any effect on moisture gain. The moisture loss of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage.

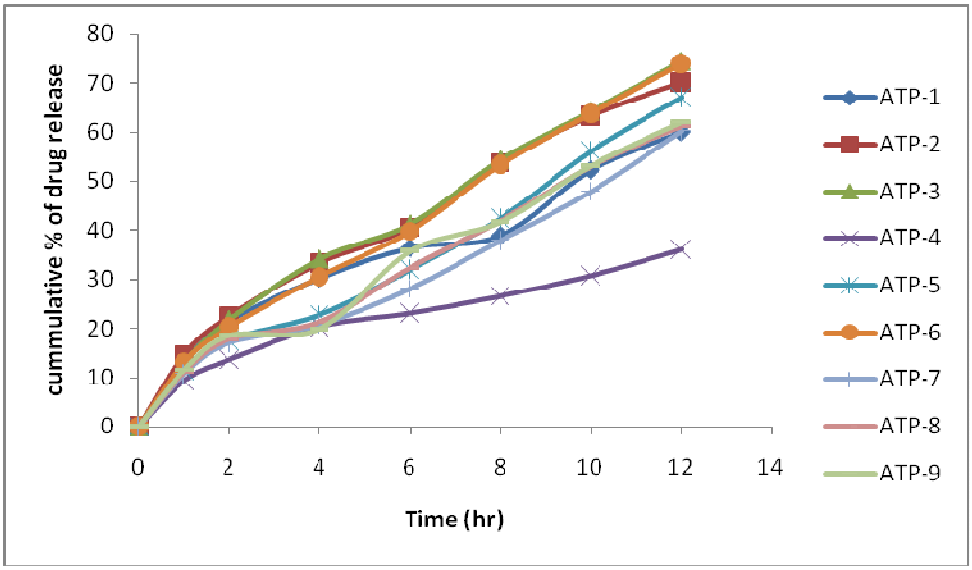

Figure 3. Drug Release Profile

***In-vitro* skin permeation:**

In the present study different permeation enhancers was used to prepare patches. In order to overcome the barrier properties of skin, penetration enhancers were employed in this study. To enhance the permeation of drug were used chemical enhancers. [23] These chemical substance temporarily diminishing the barrier of the skin and knows as

accelerants or sorption promoters can enhance drug flux Oleic acid is one of the earliest and most widely studied penetration enhancers. [24] The mechanism of oleic acid probably operates by penetrating into lipid structure with polar end close to the lipid polar heads because of its bent structure; it then disrupts and increases the fluidity of the lipid region. [25] The result of skin permeation study shown on Figure 3.

Permeability increases in Formulation (ATP-3) exhibited greatest 74.513 % of drug release value, while formulation (ATP-4) exhibited lowest 36.144 % drug release values in 12 hours. The cumulative amount of drug released from Patches is ordered as ATP-3 > ATP-6 > ATP-2 > ATP-5 > ATP-9 > ATP-8> ATP-7> ATP-1> ATP-4.The formulations ATP-3 achieved a high cumulative amount of drug permeation at the end of 12 hours. The permeability of Aceclofenac with oleic acid (6%) was found highest in our study.

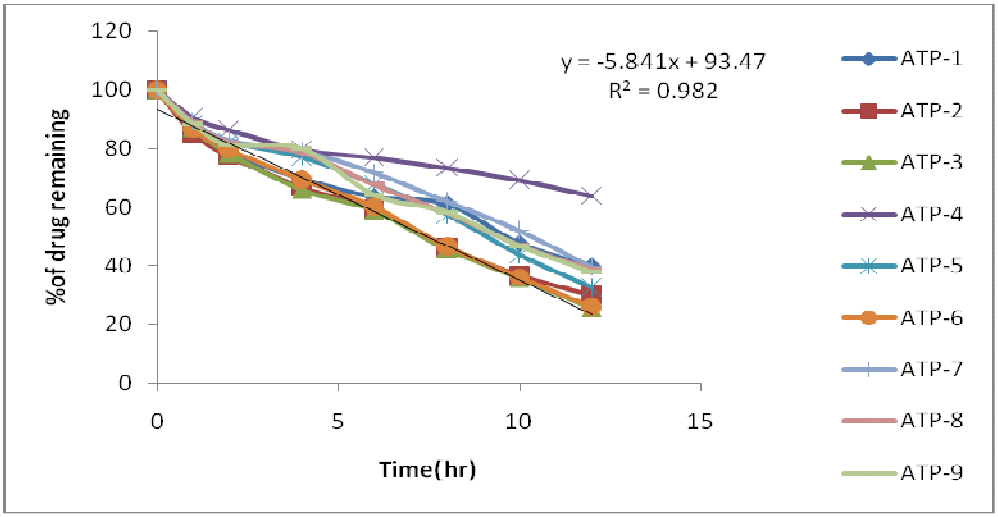

Figure 4- First Order Release Study of Aceclofenac Transdermal Patch

Table 4. Release Kinetic Modeling of Drug Release

Formulations	Zero Order	First order	Higuchi Equation
	R^2	R^2	R^2
ATP-1	0.960	0.937	0.980
ATP-2	0.937	0.988	0.971
ATP-3	0.988	0.981	0.962
ATP-4	0.961	0.965	0.972
ATP-5	0.965	0.975	0.961
ATP-6	0.975	0.989	0.946
ATP-7	0.989	0.985	0.941
ATP-8	0.985	0.982	0.962
ATP-9	0.982	0.965	0.951

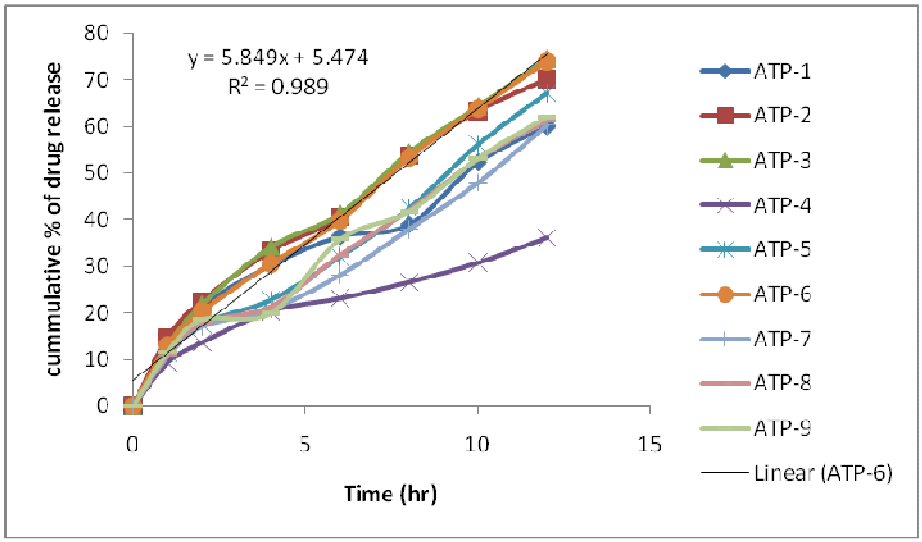

Figure 5- Zero Order Release Study of Aceclofenac Transdermal Patch

In vitro release profile is a tool that predicts in advance how the drug will behave in vivo. Thus, we can eliminate the risk of hazards of drugs because of direct experimentation in the living system. In vitro skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs. [26]

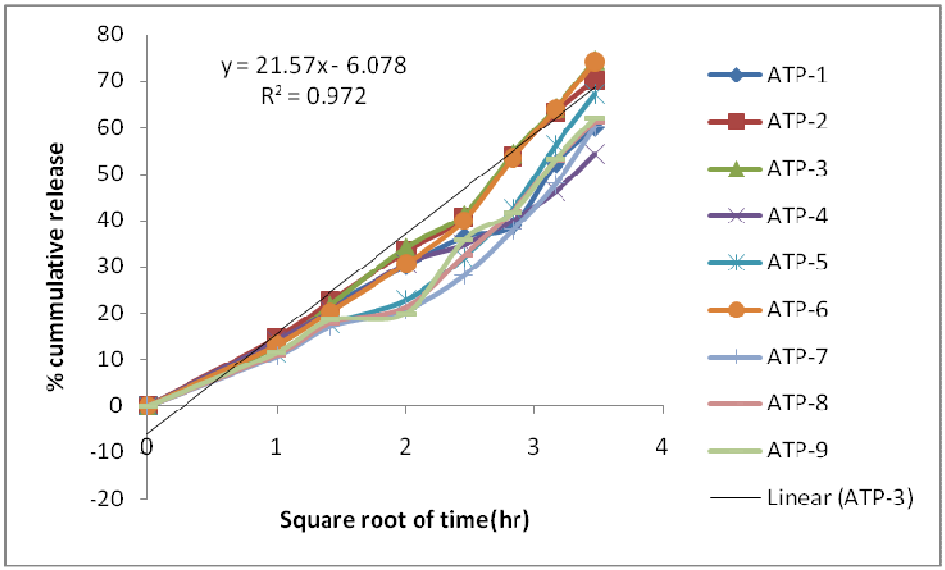

Figure 6 - Higuchi Equation of Aceclofenac Transdermal Patch

CONCLUSION

All the patches indicategood physiochemical propertylike thickness, flatness, wieght variation, folding endurance, moisture gain, moisture loss, drug release from patches,of Aceclofenac follows Frist order, kinetics. Effect of enhancers like oleic acid, peppermint oil, Ipm, has been checked by on In-vitro permeation of drug and was found to be effective. These studies indicated that as the concentration of penetration enhancer increased drug permeation was increased. This result revealed that the problems of Aceclofenac on oral administration like dissolution rate limited absorption of drug, gastric side effects, ulcer and bleeding can be overcome by applying Aceclofenac topically in the form of transdermal patch.

Acknowledgement
The authors are thankful to the Management, Cadila Pharmaceuticals Ahemdabad for gift samples of Aceclofenac and Sagar Institute of Research and Technology Science-Pharmacy for providing necessary facilities to carry out this work.

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