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ORIGINAL ARTICLE

FORMULATION AND EVALUATION OF HYDROGEL TRANSDERMAL PATCH OF A SELECTED NSAID

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ANU ABRAHAM[1], DR. SR. DAISY P A[2], BOBY JOHNS GEORGE[3], NOBY THOMAS[4], PRAVEEN RAJ[5]

Corresponding Author: [1]Department of Pharmaceutics, St. Joseph's College of Pharmacy, Cherthala, Kerala, India. E- Mail: anubaiju2010@gmail.com
Co-Authors: [2]HOD, Department of Pharmaceutics, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.
[3, 4, 5]Faculty, Department of Pharmaceutics, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.

Abstract

Background and Objectives: *Transdermal drug delivery system overcomes the difficulties associated with oral drug delivery and improves therapeutic efficacy and safety of drugs, as it is site-specific due to temporal placement of dosage form on the body that reduces both size and number of doses.* ***Methods:*** *In the present study effort was taken to formulate and evaluate Hydrogel based Transdermal patch of a selected NSAID. Nine formulations of matrix type hydrogel transdermal patches of Aceclofenac were prepared.* ***Results:*** *The pre formulation results obtained for all formulations were satisfactory. The drug- excipients compatibility study was also performed using FTIR and the results established that, there is no significant compatibility in drug and excipients. The physico –chemical properties such as physical appearance, thickness, weight variation, tensile strength, surface pH, swellability, water vapour transmission rate, percentage moisture uptake and folding endurance were evaluated.* ***Conclusion:*** *The in-vitro drug permeation studies of the prepared patches were conducted and finally the optimized formulation was selected.*

Keywords: *Aceclofenac, Poly Vinyl Alcohol, Chitosan, solvent casting method, swellability, In-vitro drug permeation study.*

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INTRODUCTION

Most commonly the drugs[1] are given by oral route because of ease of administration but have significant draw backs like low bioavailability due to first pass hepatic metabolism and tendency to produce rapid blood levels that lead to a need for frequent dosing, which can be inconvenient and costly. To overcome these difficulties transdermal drug delivery system has been developed, which improves therapeutic efficacy and safety of drugs, as it is site-specific due to temporal placement of dosage form on the body that reduces both size and number of doses. Transdermal patches deliver the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

Transdermal therapeutic systems[2] are defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug(s) through the skin at controlled rate to the systemic circulation.

Polymer hydrogels[3] are a still new, rapidly developing group of materials, gaining wide applications in many fields, especially pharmacy, medicine and agriculture. The term hydrogel describes three dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water. It is a permanent or chemical gel stabilized by covalently cross-linked networks. These chemical hydrogels may be prepared either by cross-linking water soluble polymers or by converting hydrophobic polymers in to hydrophilic polymers that are then cross-linked to form a network. Hydrogels can be formulated in a variety of physical forms including slabs, micro particles, nanoparticles, coatings, patches and films.

The characteristic[4] of a successful hydrogel-based transdermal drug delivery patch include painless adhesion to the human body, stability of form and composition, purity, reproducibility, compatibility with active ingredients and high water content. Furthermore because of their high water content, swollen hydrogels can provide a better feeling for the skin in comparison to conventional ointments and patches.

Transdermal drug delivery of NSAIDs[5] is feasible in recent years. The system appears to minimize gastrointestinal side effects and hepatic first pass effect. Furthermore the controlled and sustained release of the active ingredients may be achieved with an enhanced patient compliance. Transdermal delivery of NSAIDs is suitable in case of long term treatment.

Aceclofenac[6] is a non-steroidal anti-inflammatory prodrug with a short biological half- life of 4 hours and has the adverse effects commonly encountered with the NSAIDS, on oral administration. It is a relatively new drug rather a prodrug of diclofenac and is available in the treatment of arthritis as a conventional dosage form.
In the present study attempt is made to develop and optimize a novel hydrogel based transdermal patch[7] using the polymers like PVA and chitosan for the transdermal delivery of Aceclofenac, thereby enhancing the bioavailability of selected drug.

Materials and methods

Materials:

Aceclofenac was obtained from Complimentary sample from Ipca Labs, Mumbai. Poly vinyl alcohol obtained from S. D. Fine chemical, Mumbai. Chitosan obtained from Central Institute of Fisheries Technology, Cochin. Maleic anhydride obtained from Chemdey's corporation, Haripur, Rajkot. Poly ethylene glycol obtained from Loba chemie, Mumbai, India. Acetic acid obtained from Nice chemicals Pvt. Ltd, Cochin. All the other laboratory chemicals used in the study were of analytical reagent grade.

Preformulation study:

Preformulation studies[8] should focus those physico-chemical properties of the new

compound that could affect drug preformulation and development of an efficacious dosage form.

Objectives of the preformulation study are therefore,

- Establish physico-chemical parameters of a new drug entity.
- To determine its kinetics and stability
- To establish its compatibility with common excipients

Following were done,

- Organoleptic properties
- Melting point
- Partition coefficient determination[9]
- Solubility determination[10]

Compatibility of the study:

Infra- red spectroscopy:

Infra-red spectroscopy[11] can be used to investigate and predict any possible physicochemical interactions between different components in a formulation and therefore, it can be applied to the selection of suitable, chemically compatible excipients. The aim of the present study was to find out the possible interaction[12] between the selected polymer chitosan and the drug and also to identify the compatibility between the drug and the polymer.

Standardization of Aceclofenac:

Preparation of phosphate buffer P^H 7.4

Dissolve[13] 2.38 g of disodium hydrogen phosphate, 0.19 g of potassium di hydrogen phosphate and 8 g of sodium chloride in sufficient water and make up to 1000ml. adjust the P^H necessary.

Preparation of standard solution

100 mg drug[14] was dissolved in 10 ml methanol and make up to 100 ml with pH 7.4 phosphate buffer. From this 10 ml was withdrawn and makeup to 100 ml with phosphate buffer to get working standard solution. Aliquots 1ml, 2ml, 3ml, 4ml, 5ml, were pipetted out and made up to 50ml with the same buffer solution and absorbance[14] was measured at 273 nm.

Preparation of transdermal patches:

Nine different combinations[15] of matrix type transdermal patches composed of different concentrations of PVA, chitosan and drug were prepared by solvent evaporation method. PVA were accurately weighed and dissolved in 10ml of hot water. Chitosan in 1.5% acetic acid was added to the different formulations and blended well (Table1). Maleic anhydride solution was added drop wise. Then the entire mixture was stirred well for 30 min. Polyethylene glycol was used as plasticizer. The resultant uniform solution was cast on the cylindrical mould, and dried at room temperature for 24hrs. An inverted funnel was placed over the Petridish to prevent fast evaporation of the solvent. After 24hrs, the dried patches were taken out and stored in desiccators for further studies.

Evaluation of transdermal patches:

Physical appearance

All the transdermal films[16] were visually inspected for colour, clarity, flexibility and smoothness.

Thickness

Patch thickness[17] was measured using micrometer screw gauge at three different places of each patch and the mean value was calculated and reported.

Weight uniformity

The films[18] of different batches were dried at 60◦ C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights.

Tensile strength

In order to determine the elongation[19] as a tensile strength, the polymeric patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The

elongation i.e. the distance travelled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg cm^2.

Swellability

The patches[20] of 2.5 cm^2 was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

Folding endurance

Folding endurance[21] of the patches was determined by repeatedly folding one patch at the same place till it either breaks or develops visible cracks on folding number of times manually, which was considered satisfactory to reveal good patch properties. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. The number of times the films could be folded at the same place without breaking gives the value of folding endurance.

Surface pH

The patches[22] were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1h in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 min.

Water Vapour Transmission (WVT)

Glass vials[23] of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 3, 6, 12, 18, 24 hrs.

Percentage moisture uptake

The weighed films[24] were kept in a desiccator at room temperature for 24 hours and then exposed to 84% RH using a saturated solution of potassium chloride. The films were weighed repeatedly until they showed a constant weight.

Drug entrapment efficiency

The transdermal patches[25] were tested for the content uniformity. A film of size 4 $cm^2$was cut and placed in a 100ml volumetric flask. 100ml of a pH 7.4 buffer was added. The contents were stirred in a magnetic stirrer for 24 hrs. After 24hrs, measured out or pipetted out 1ml from this and made volume up to 50 ml by addition of pH 7.4 buffer. The absorbance of the solution was measured against the corresponding blank solution at 273nm.

***In-vitro* skin permeation studies**

The *In-vitro* skin[26] permeation studies were carried out using dorsal section of full thickness skin from albino rats whose hair had been removed on the previous day using electric clipper. The transdermal patches were firmly pressed on the centre of the rat skin once adhesion to the skin surface had been confirmed; the skin was quickly mounted on the diffusion tube which acted as a donor compartment. 50 ml of phosphate buffer pH 7.4 as a diffusion medium was taken in the beaker which acted as the receptor compartment to maintain the sink condition. The donor compartment was kept in contact with receptor compartment and receptor compartment was stirred magnetically during the study. Sample 1ml[27] was withdrawn and replaced with 1ml of fresh phosphate buffer pH 7.4 at different time intervals. The samples were analysed using UV spectrophotometer at 273 nm to estimate aceclofenac.

Mechanism of release study

To understand[28] the mechanism of release of Aceclofenac from the patches the drug release of optimized drug loaded patches were studied. A graph was plotted with percentage release Vs √time. If linearity is

observed, the release mechanism is by Higuchi's diffusion.

Stability study of optimized formulation

Stability study[29] was carried out for optimized patch formulation at 40±2^{0}c and 75 ± 2% RH humidity chamber. After 15 days and 1 month samples were withdrawn and evaluated[30] for physicochemical properties and *in-vitro* diffusion study.

Combination 1	Ingredients					
	PVA	Chitosan	Drug	Maleic anhydride	PEG	Water
C_1	-	2%	50	1.5%	2%	10 ml
C_2	0.5	2%	50	1.5%	2%	10 ml
C_3	1	2%	50	1.5%	2%	10 ml
C_4	1.5	2%	50	1.5%	2%	10 ml
C_5	2	2%	50	1.5%	2%	10 ml
C_6	2.5	2%	50	1.5%	2%	10 ml
C_7	3	2%	50	1.5%	2%	10 ml
C_8	3.5	2%	50	1.5%	2%	10 ml
C_9	4	2%	50	1.5%	2%	10 ml

Table 1. Formulation code for hydrogel patches of combination 1

RESULTS AND DISCUSSION

Preformulation of the study:

The pre formulation results obtained for all formulations were satisfactory. Solubility studies were conducted in buffer solutions of pH 7.4. This was conducted to determine appropriate solvent for diffusion. Since in pH 7.4 buffer, solubility of the drug is moderate and the amount is quantifiable in UV range, pH 7.4 buffer was selected as vehicle for further *in-vitro* diffusion studies.

Calibration curve of aceclofenac:

Calibration curve of Aceclofenac in phosphate buffer is pH 7.4.

Compatibility of studies:

In order to investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies were carried out. IR spectrum for pure drug and physical mixture of drug-polymers were obtained and analysed for principle peaks. Drug - excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. 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.

Optimizing the formula for fabrication of transdermal patch:

Combinations from C1 –C9 were fabricated using varying concentrations of PVA and fixed concentration of chitosan (2%) by solvent casting method. Maleic anhydride concentration (1.5%w/v) and PEG (2%) as taken as constant.

Organoleptic properties	Description	Crystalline
	Odour	Odourless
	Colour	Colourless
	Taste	Bitter
Melting point range		150 -155^{0}c
Solubility		practically insoluble in water, freely soluble in acetone, sparingly soluble in pH 7.4 buffer, soluble in alcohol and methanol
Partition coefficient		5.20

Table 2. Preformulation parameters

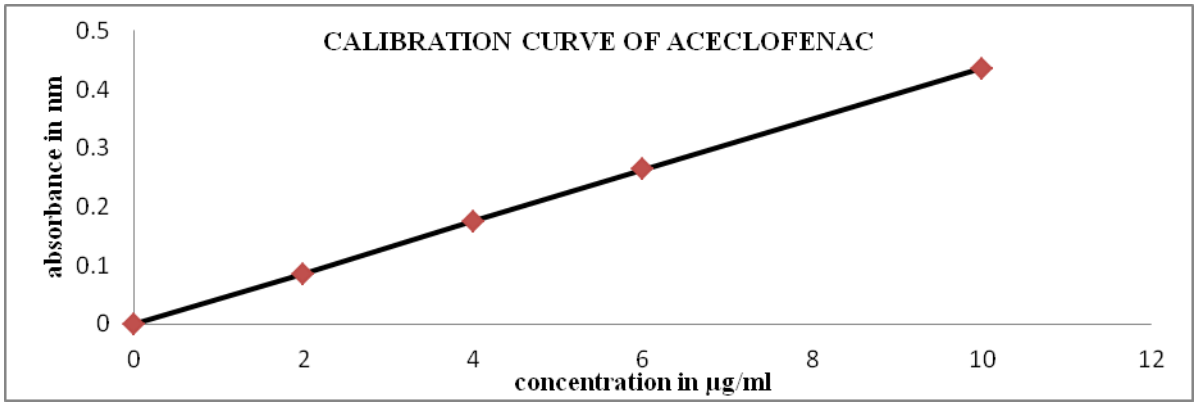

Fig 1. Calibration curve of aceclofenac

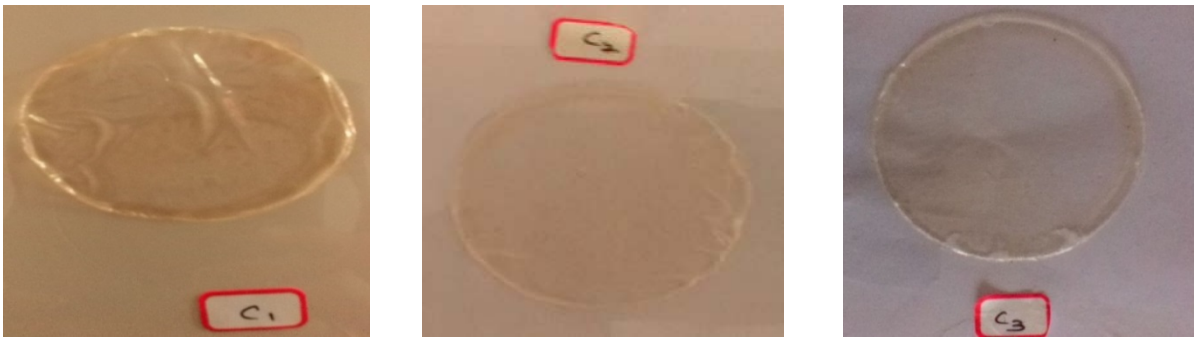

Fig.2a. Prepared patches

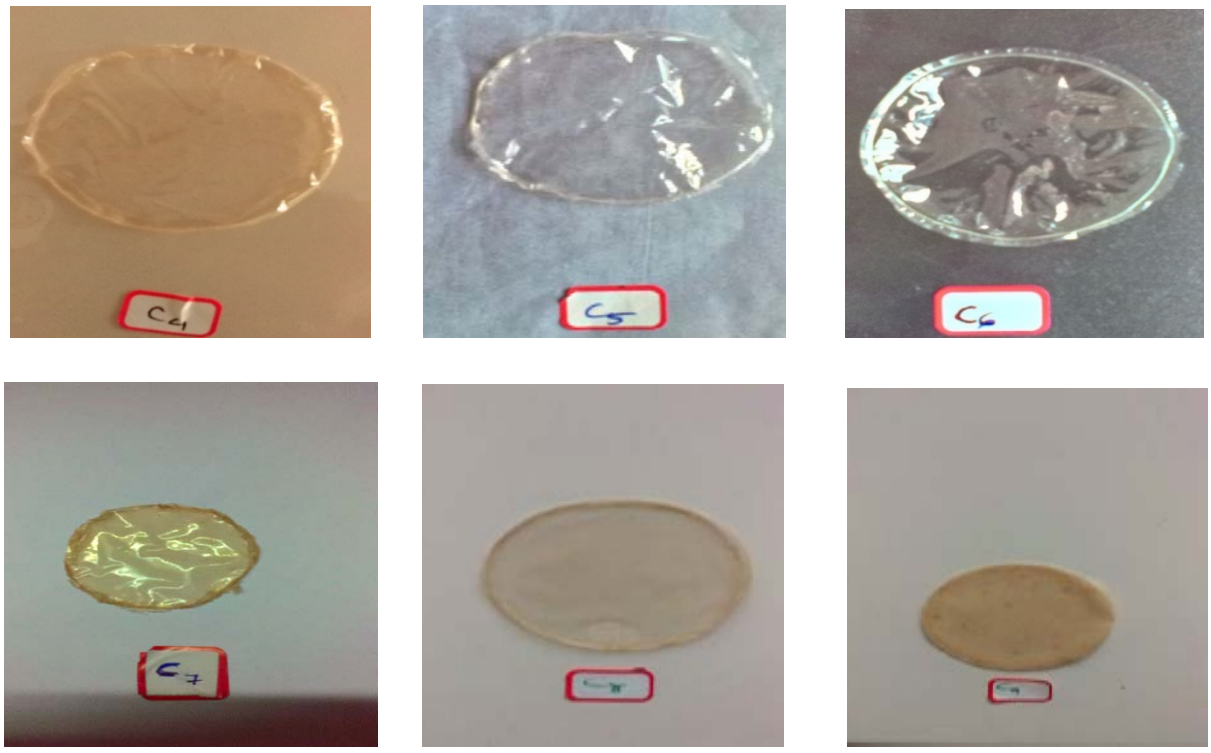

Fig.2b. Prepared patches

Evaluation of prepared patches

Prepared patches of combination $C_1 – C_9$ were subjected to physical evaluation visually and the data shown in table 3.from the physical evaluation data the better appearance and texture showed by the combinations C_6, C_7 and C_8. The prepared hydrogel transdermal patches of aceclofenac were subjected to physico-chemical evaluation such as thickness and the results were shown in table 4. The data indicates that all combinations ($C_1 – C_9$) measured thickness with minimum standard deviation values. The thickness varied from 0.24 – 0.37 mm. The minimum standard deviation values assured that the process used for preparing the drug delivery system is capable of giving reproducible results.

The weight of combinations C_1-C_9 ranges between 103 – 203 mg. The deviation in the weight was within the limits as it confirming by the minimum standard deviation values. It was observed that the variation in weight in different combination which may be due to the variation in polymeric content

The folding endurance of combinations $C_1 – C_9$ was measured manually and data were shown in the table 4. It measures the ability of patch to withstand rupture. It was found that the values in the range of 93 – 236. The values of combination C_6, C_7 and C_8 were found to satisfactory. The results indicate that the patches would not break and would maintain their integrity with general skin folding when used.

The tensile strength of combinations was measured using the tensiometer which fabricated locally. The results shown in the table indicate that the tensile strength was found to be varying with the nature of polymers. Chitosan reduces the tensile strength, combination C_1 shows lowest value as it contains 2% chitosan only. Combination C_8 shows maximum tensile strength of 1.549 kg/cm^2.

Water vapour transmission study was conducted for combination $C_1 – C_9$ and the data were shown in the table 4. The result of water vapour transmission study reviled that

all the formulation are permeable to water vapour.

The percentage moisture absorption studies were conducted for combinations C_1 – C_9 and the results were shown in table 5. The results indicated that the increase in PVA content increases the percentage moisture absorption. This may be due to the hydrophilicity of PVA. The surface pH of all the combinations was in the range 7.0 – 7-3 and hence no skin irritation expected.

The swellability of combinations C_1- C_9 were measured and the data shown in the table 5. The swellability of C_1 is 12.902 % which is lower than other combinations. This indicates that the swelling behaviour is greatly influenced by the PVA content. This is because PVA is a water soluble polymer and blending of PVA with Chitosan tends to increase the water uptake due to the increasing of hydrophilic groups. PVA chains entangled with the chitosan chains leading to the formation of hydrogel network.

The percentage of drug content of combinations C_1 – C_9 varied between 61.59 %– 93.61 % and it indicated that the combinations C_6, C_7 and C_8 had good drug containing capability.

***In-vitro* drug permeation study**

The permeation of drug from the dosage form plays important role in transdermal drug delivery and in determining the therapeutic effect of the medication. Upon application of patch, the releases from the dosage form to the skin, diffuses through the layers of skin and is transported away by the blood. *The in-vitro* permeation of the drug from patch to the blood was studied at 37 $\pm$ 0.5^0C using phosphate buffer pH 7.4 as release medium.

Release of the drug from prepared hydrogel transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the polymer matrix.
The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains.

The results indicates the cumulative percent of drug permeated from formulations C_1,C_2, C_3,C_4, C_5, C_6, C_7, C_8, C_9 were 50.36 %, 66.69 % ,67.15 %, 73.44 %, 76.17 %, 77.33 %, 83.95 %, 94.33 %, 66.35 % respectively after 6 hrs. The increase of release with increase of PVA content in the patch may be due to the leaching of PVA and pore formation. This leads to an increase in the external film area exposed to the solvent, increased internal porosity and decreased the tortuosity. Also PVA has anti-nucleating effect that converts crystalline drug into high energy amorphous state with improved solubility. The enhancement in solubility of drug increases thermodynamic activity that facilitates permeation of drug across the skin. The rapid leaching of hydrophilic fraction of polymers resulted in the formation of pores and thus leads to the decrease of mean diffusional path length of drug molecules to permeate in dissolution medium.

As combination C_8 shows maximum release it was selected as optimized combination for hydrogel transdermal patch of Aceclofenac.

Kinetics of drug release

The formulation C_8 was selected as best formulation. The drug release data of combinationC_8 was plotted in accordance with Higuchi model. A graph was plotted with % release Vs √time. Linearity is observed, the release mechanism is by Higuchi's diffusion

Ideally, controlled drug delivery systems should deliver the drug at a controlled rate over a desired duration. Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion
The R^2 value of combination C8 was 0.926 which was more close to unity. This indicates that the drug release from the combination occurs via diffusion process.

Combination code	Colour	Clarity	Appearance
C_1	colourless	Transparent	Thin, Smooth
C_2	colourless	Transparent	Thin, Smooth
C_3	colourless	Transparent	Thin, Rough
C_4	colourless	Transparent	Smooth
C_5	colourless	Transparent	Smooth
C_6	colourless	Transparent	Smooth
C_7	colourless	Transparent	Smooth
C_8	colourless	Transparent	Smooth
C_9	colourless	Opaque	Thick, Rough

Table 3. Physical appearance

Combination code	Thickness (mm)	Weight uniformity (mg)	Folding endurance	Tensile strength (kg/cm^2)	WVTR ($gm/hr./cm^2$)
C_1	0.24 ± .008	103 ± 6.84	93 ± 5.249	0.719 ± 007	$1.99*10^{-3}$
C_2	0.27 ±. 016	125 ± 3.29	103 ± 3.741	0.809 ±.018	$2.03*10^{-3}$
C_3	0.28 ± .037	134 ± 4.32	126 ± 2.624	0.810 ±.007	$2.09*10^{-3}$
C_4	0.31 ± .024	159 ± 7.11	194 ± 0.816	0.889 ± .013	$2.36*10^{-3}$
C_5	0.32 ± .004	160 ± 7.61	186 ± 4.027	0.998 ± .020	$2.59*10^{-3}$
C_6	0.32 ± .004	161 ± 2.65	205 ± 3.771	1.056 ± 004	$2.75*10^{-3}$
C_7	0.33 ± .018	173 ± 1.41	230 ± 2.357	1.211 ± .012	3.04810^{-3}
C_8	0.35 ± .016	191 ± 1.69	236 ± 1.247	1.549 ± .006	$3.20*10^{-3}$
C_9	0.37 ± .004	203 ± 1.24	106 ±3.559	1.107 ± .007	$3.56*10^{-3}$

Table 4. Physico-chemical properties such as t, weight uniformity, folding endurance, tensile strength, WVTR

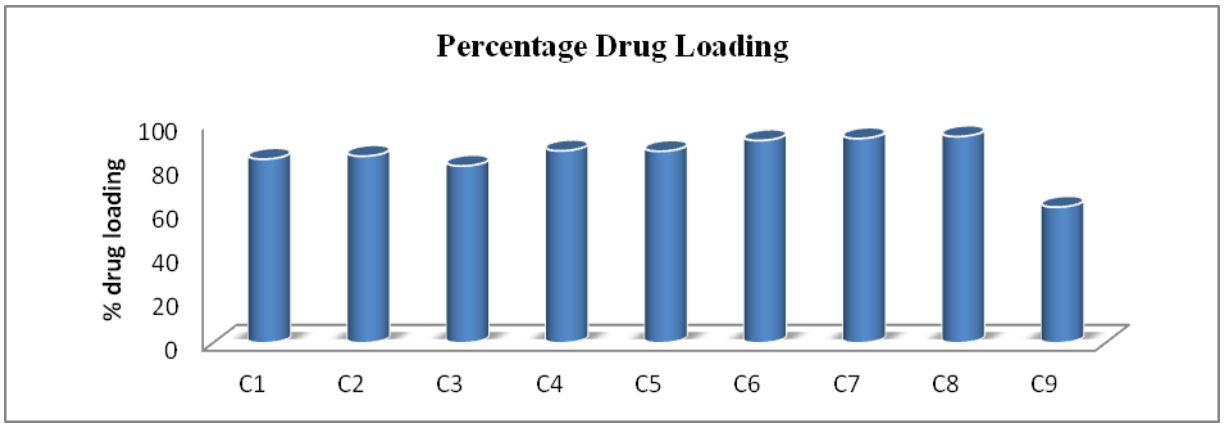

Fig.3. Percentage drug loading of formulations c_1-c_9

Combination code	PMA (%)	Surface P^H	Swellability (%)	% Drug loading
C_1	1.080 ±.113	7.0 ±.091	12.902 + .412	83.37
C_2	1.634 ±.075	7.2 ± .162	20. 623 + .013	84.69
C_3	1.974 ± .182	7.2 ± .081	20.846 + .096	80.25
C_4	2.45 + .071	7.0 ± .094	21.143 + .517	87.14
C_5	3.184 ± .192	7.3 ± .141	23.753 + .136	86.93
C_6	3.945 ± .181	7.2 ± .081	22.482 + .247	91.82
C_7	4.133 ± .134	7.0 ± .094	23.124 + .168	92.71
C_8	4.919 ± .286	7.2 ± .047	24.445 + .054	93.61
C_9	5.796 ± .414	7.1 ± .141	25.933 + .159	61.59

Table 5. Physico-chemical properties such as PMA, surface pH, swellability, drug loading

Combination code	Absorbance at 6^{th} hrs	Cumulative drug release at 6^{th} hrs	Cumulative % released at 6^{th} hrs
C_1	0.743	20.98	50.36
C_2	0.782	28.22	66.69
C_3	0.953	26.93	67.15
C_4	1.131	31.99	73.44
C_5	1.170	33.08	76.17
C_6	1.255	35.48	77.33
C_7	1.375	38.89	83.95
C_8	1.562	44.12	94.33
C_9	0.723	20.41	66.35

Table 6. In-vitro drug release profile

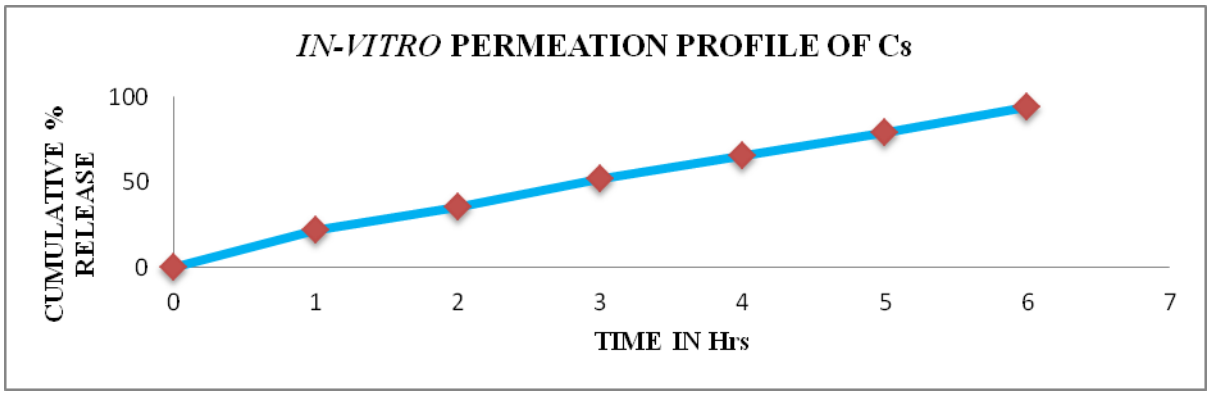

Fig.5. *In-vitro* permeation profile of formulation c8

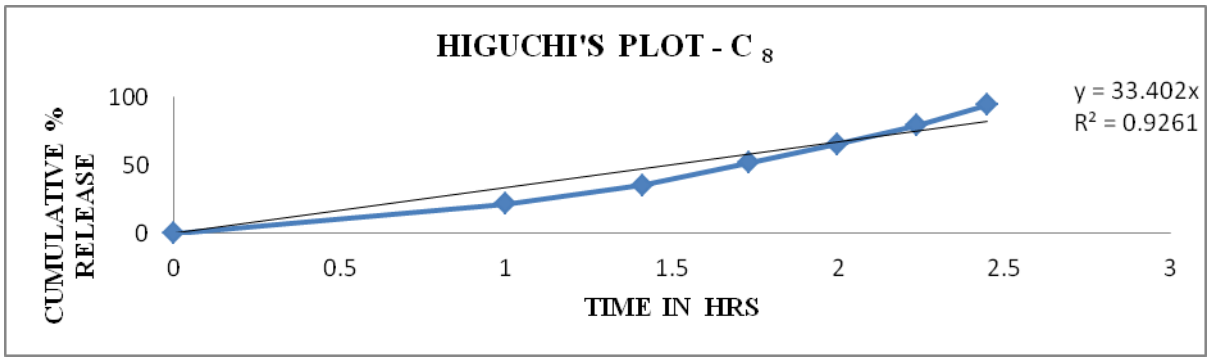

Fig.6. Higuchi's plot for combination c8

Physico-chemical parameter	**After 15 days at 40 ± 2^{0}c & 75% RH**	**After 30 days 40 ± 2^{0}c & 75% RH**
Physical appearance	Smooth and flexible	Smooth and flexible
Thickness	0.34 mm	0.34 mm
Tensile strength	1.542 kg/cm^2	1.541 kg/cm^2
Weight uniformity	191 mg	191 mg
Folding endurance	233	233
WVTR	3.21 * 10^{-3} gm/hr/cm^2	3.21 * 10^{-3} gm/hr/cm^2
PMA	4.919 %	4.919 %
Surface pH	7.1	7.1
Swellability	24.251%	24.451%
Drug entrapment efficiency	93.42 %	93.42%

Table 7. Stability data of physico-chemical properties

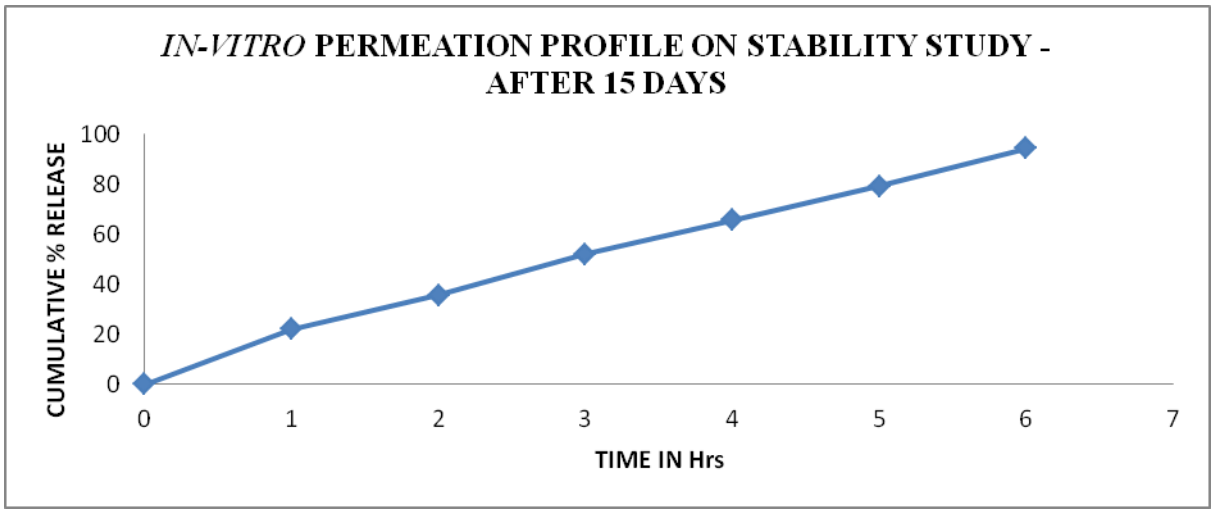

Fig. 7: In-vitro permeation profile on stability study –after 15 days

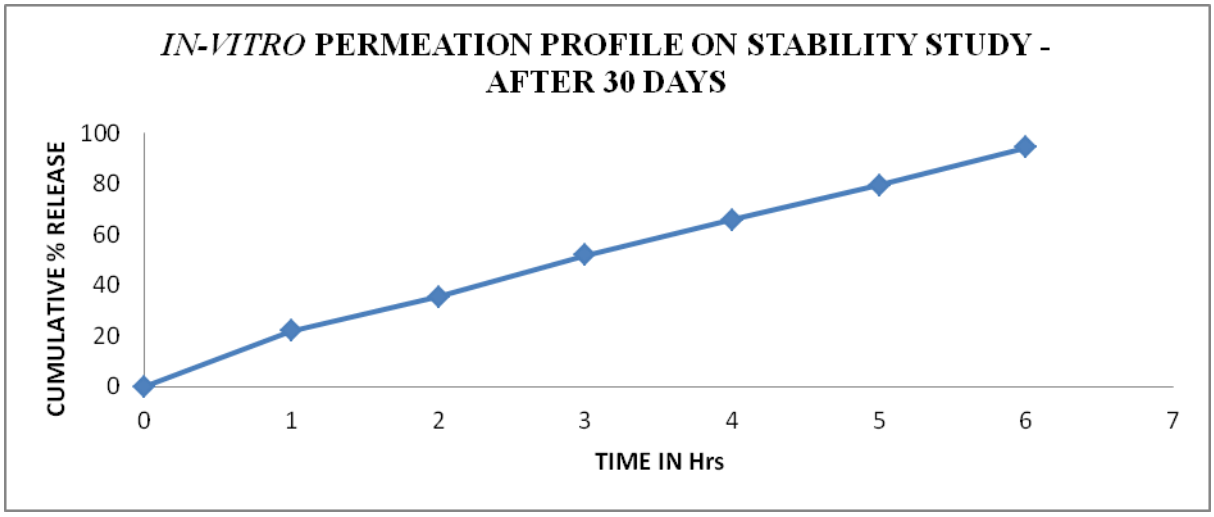

FIG.8. *In-vitro* permeation profile on stability study –after 30 days

Stability data:

In order to determine the change in physico-chemical parameters and *in-vitro* release profile on storage, stability study was carried out at 40±2^{0}c and 75 ± 2% RH for 30 days. Sampling time was 15 days and 30 days. The physico-chemical parameter of the optimized formulation was not significantly changed on storage. The *in-vitro* release profiles shown on figure 7 and 8. The results indicate that the formulation was stable on the required storage condition.

CONCLUSION

The *in-vitro* drug permeation studies of the prepared patches were conducted and finally the optimized formulation was selected.

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