FORMULATION AND CHARACTERIZATION OF TRANSDERMAL FILMS OF TORASEMIDE

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ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique by using 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of Torasemide. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate. All prepared formulations indicated good physical stability. *In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best *in-vitro* skin permeation through rat skin (Wistar albino rat) as compared to all other formulations. The results followed the release profile of Aceclofenac followed mixed zero-order and first-order kinetics in different formulation. However, the release profile of the optimized formulation F4 (r2 = 0.9935 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. These results indicate that the formulation containing the F4 [CAP: PVP (6:1)] has shown optimum release in   concentration independent manner.

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Introduction

Transdermal delivery of drugs is a novel drug delivery system and this system breaks many barriers in drug therapy like need of assistance, intermediate dosing and uncomfortable administration1. The transdermal route of administration is recognized as one of the potential route for local and systemic delivery of drugs, it also provides a controlled release of medicament into patients2. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance3. Torsemide is a loop diuretic and chemically known as 3-pyridine sulfonamide N-[[(1-methylethyl) amino]-carbonyl]-4-[(3-methylphenyl) amino]4. It acts by inhibiting the Na +/ K +/ 2Cl – carrier system in the lumen of the thick ascending portion of the loop of Henle, resulting in the decrease in reabsorption of sodium and chloride. The aims of the present study were to prepare transdermal patches of Torasemide using various polymers; and to study the in-vitro diffusion behavior of prepared transdermal patch formulations in the presence. The purpose was to provide the delivery of the drug at a controlled rate across intact skin.

Materials and Methods

Torasemide was received as a gift samples from Lincoln Pharmaceuticals, Ahmedabad, India. Poly vinyl pyrrolidine, HPMC, Poly ethylene Glycol were generous gift from Colorcon Asia Pvt. Ltd (Mumbai, India) and Maan Pharmaceuticals Ltd. (Ahmedabad, India), respectively. Other materials used in the analytical grade. Double-distilled water was used throughout the study.

FORMULATION

Trial batch formulations for preparation of free films: 5-12. In trial formulation: A EC: PVP 3:2, 2:3, 4:1 and 1:4 are used in combination with three solvent (Plasticizer-PEG 400), which are given in table no.5102. In trial formulation: B EC: PVP 3:2, 2:3, 4:1 and 1:4 are used in combination with three solvent (Dibutyl phthalate), which are given in table no.6103. In trial formulation: C HPMC: PVP 3:2, 2:3, 4:1 and 1:4 are used in combination with three solvent (Plasticizer-PEG 400), which are given in table no.7104. In trial formulation: D HPMC: PVP 3:2, 2:3, 4:1 and 1:4 are used in combination with three solvent (Plasticizer- Dibutyl phthalate), which are given in table no.8105. In trial formulation: E EC: HPMC 3:2, 2:3, 4:1 and 1:4 are used in combination with three solvent (Plasticizer-PEG 400) which are given in table no. 9.106.In trial formulation: F Hydroxyethylcellulose are used in different combination solvent (Plasticizer-PEG 400) which are given in table no. 1-6.

Table no.1: TRIAL FORMULATIONS: A

Ingredients	Formulation Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (EC)	3%	3%	3%	2%	2%	2%	4%	4%	4%
Polyvinyl pyrrrolidone (PVP)	2%	2%	2%	3%	3%	3%	1%	1%	1%
Chloroform	q.s	-	-	q.s	-	-	q.s	-	-
Methanol	-	q.s.	-	-	q.s	-	-	q.s	-
Ethanol	-	-	q.s.	-	-	q.s	-	-	q.s
Polyethylene glycol 400	30%	30%	30%	30%	30%	30%	30%	30%	30%

Table no 2: TRIAL FORMULATIONS: B

Ingredients	Formulation Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (EC)	3%	3%	3%	2%	2%	2%	4%	4%	4%
Polyvinyl pyrrrolidone (PVP)	2%	2%	2%	3%	3%	3%	1%	1%	1%
Chloroform	q.s	-	-	q.s	-	-	q.s	-	-
Methanol	-	q.s.	-	-	q.s	-	-	q.s	-
Ethanol	-	-	q.s.	-	-	q.s	-	-	q.s
Dibutyl phthalate	30%	30%	30%	30%	30%	30%	30%	30%	30%

Table no 3: TRIAL FORMULATIONS: C

Ingredients	Formulation Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydroxypropylmethylcellulose	3%	3%	3%	2%	2%	2%	4%	4%	4%
Polyvinyl pyrrrolidone (PVP)	2%	2%	2%	3%	3%	3%	1%	1%	1%
Chloroform	q.s	-	-	q.s	-	-	q.s	-	-
Methanol	-	q.s.	-	-	q.s	-	-	q.s	-
Ethanol	-	-	q.s.	-	-	q.s	-	-	q.s
Polyethylene glycol 400	30 %	30 %	30 %	30 %	30 %	30 %	30 %	30 %	30 %

Table no.4: TRIAL FORMULATIONS: D

Ingredients	Formulation Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydroxypropylmethylcellulose	3%	3%	3%	2%	2%	2%	4%	4%	4%
Polyvinyl pyrrrolidone (PVP)	2%	2%	2%	3%	3%	3%	1%	1%	1%
Chloroform	q.s	-	-	q.s	-	-	q.s	-	-
Methanol	-	q.s.	-	-	q.s	-	-	q.s	-
Ethanol	-	-	q.s.	-	-	q.s	-	-	q.s
Dibutyl pthalate	30%	30%	30%	30%	30%	30%	30%	30%	30 %

Table no 5: TRIAL FORMULATIONS:

Ingredients	Formulation Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydroxypropylmethylcellulose	3%	3%	3%	2%	2%	2%	4%	4%	4%
Ethyl cellulose	2%	2%	2%	3%	3%	3%	1%	1%	1%
Chloroform	q.s	-	-	q.s	-	-	q.s	-	-
Methanol	-	q.s.	-	-	q.s	-	-	q.s	-
Ethanol	-	-	q.s.	-	-	q.s	-	-	q.s
Polyethylene glycol 400	30%	30%	30%	30%	30%	30%	30%	30%	30%

Table no.6: TRIAL FORMULATIONS: F1-F6

Sr. No.	Formulation Code	Hydroxyethylcellulose (g)	PEG 400 (g)
1	F1	0.5	0.150 (30%)
2	F2	0.75	0.150 (30%)
3	F3	1	0.150 (30%)
4	F4	1.5	0.150 (30%)
5	F5	2.5	0.150 (30%)
6	F6	3.5	0.150 (30%)

PREPARATION OF MEDICATED FILMS

The solubility of polymer should match with solubility of drug so as to prepare the transparent medicated films. The solubility of polymers was checked. Hydroxyethylcellulose was soluble in cold water, water: dichloromethane, water: methanol and water: alcohol, water: ethanol. The solubility of Torasemide was checked in above-mentioned solvents. Considering solubility of drug and polymer, the solvent system of water: methanol was chosen.

The TDDS was prepared by film casting technique The TDDS was composed of different concentration of hydroxyethyl cellulose (table 1-6), along with drug; torasemide (2.5% w/w), 30% w/w plasticizer; polyethylene glycol-400 (based on polymer weight). All ingredients were dissolved in mixture of water: methanol (20:80) solvent system on magnetic stirrer. Ultrasonicator removed the air bubbles generated in the process.

The homogenous mixture was poured into plastic moulds. The solvent was allowed to evaporate at controlled rate by placing an inverted funnel over the plastic moulds. The control of evaporation is necessary for uniform drying of films. The drying was carried out at room temperature for duration of 24 hours. After 24 hours the dry films was removed from plastic moulds and stored in desiccators until used.

EVALUATIONS OF FILMS

Thickness
The thickness of films was measured by digital Vernier caliper with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation (Figure:2).

Weight variation test
Weight variation test was done by weighing each of five films individually. The average of film was taken as weight of films. The three disks of 3.14 cm2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.

Percent flatness
The percent flatness was measured by cutting the film into three strips from canter of the film. The strips were cut so that each should have 4cm length and 0.5cm breadth. Each strip was put on the clean surface without applying any additional pressure and measured its length to nearest centimeter by digital Vernier caliper.

Moisture content
The film was weighed and kept in a desiccator containing calcium chloride at 40° C in a drier for at least 24 hr or more until it showed a constant weight and was reported in terms of percentage (by weight) moisture content. The results are found in Table .10 and Figure:2.

Moisture uptake
The films casted in plastic moulds were used for moisture uptake studies. A weighed film kept in glass chamber at 40° c For 24 h was taken out and exposed to two different relative humidity of 75%(saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) in two different glass chamber, respectively, at room temperature. Then the weights were measured periodically.(Table:11,Figure:3,4)

Tensile Strength
The tensile strength was determined by the apparatus designed as shown in fig 1.The instrument was designed such that it had horizontal glass platform with scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The glass platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 4cm length and 0.5cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The strips were marked with ink 2cm apart and 1cm from each end. Each strip was fit in clips in such a way that the markings would be just visible. The rate of change of stress was kept constant with the increment of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation (Table:12).

Drug content
The patch of area 3.14cm2 was cut and dissolved in methanol and the remaining volume was made up with methanol to 100ml in 100ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10ml. The absorbance of the solution was taken at 288 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.
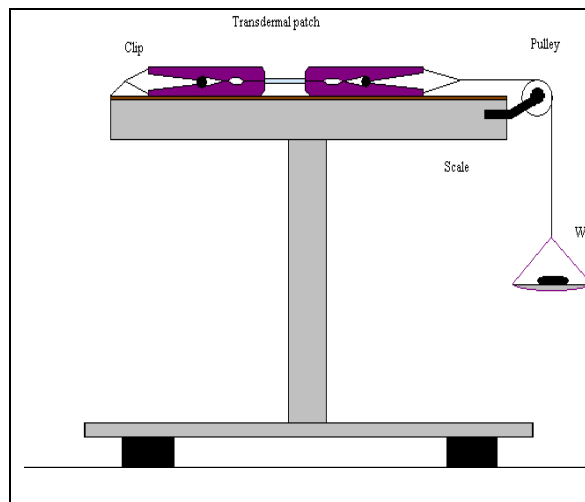

Fig. 1: Tensile strength measuring apparatus

Area variation
The films were cut by using cutter. The change in area would change the drug content of the patch. The error in cutting was checked by measuring the area of the films. Three disks, same disks used for weight variation tests, were taken for accurate measurement of area of films. Taking accurate dimensions of films using Vernier caliper did the measurement of area. The calculated area was compared with the actual area.

Folding endurance
The folding endurance was measured manually for the prepared films. A strip (4*3 cm) cut evenly and repeatedly folded at the same place till it broke .The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

In vitro performance [17]
In vitro dissolution studies
The drug dissolution studies were carried to see drug release from matrix type of patch of drug. The studies were performed using US Pharmacopoeia paddle-type dissolution apparatus. The transdermal patch was cut with area of $3.14cm^2$ and by using double side

adhesive tape; the patch was pressed on the tape for one minute so that it could be firmly stick to the disk. Then, in temperature maintained dissolution apparatus, Air bubbles, if any, were removed and the test was carried out at 50 rpm. The dissolution medium used was 900ml saline phosphate buffer pH 7.4 containing 20% PEG v/v polyethylene glycol. The temperature was maintained at 37± 2°C. Samples were collected hourly for 12 hours and analyzed at 285 nm. Dissolution without medicated patch was carried out in duplicate keeping remaining setup same, to ensure any interference due to the disk assembly or adhesive tape. Then, dissolutions of patches were carried out in duplicates.

In vitro permeation studies [18,19]
**Preparation of skin**
The abdominal skin of albino mice weighing 25-30 g used. Hairs on the abdominal area were removed using depilatory agent for 10 min about 12 h before sacrifice and allowed to dry. With the help of wet cotton the hairs were scrubbed and Mice were sacrificed by cervical dislocation. Abdominal skin was excised. The skin was kept in normal saline solution in refrigerator until skin was used for diffusion study. Prior to use, the skin was allowed to

equilibrate with room temperature. Then skin was mounted between donor and receptor compartment of cell. The skin was clamped in such a way that the dermal side will be in contact with receptor medium.

Diffusion cell [20]
The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. In vitro studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. mice abdominal skin. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin was used to stir the receptor solution using magnetic stirrer. The mice abdominal skin was placed on receptor compartment and both compartments held tight by clamps.

Fig. 2: Franz diffusion cell for permeation studies
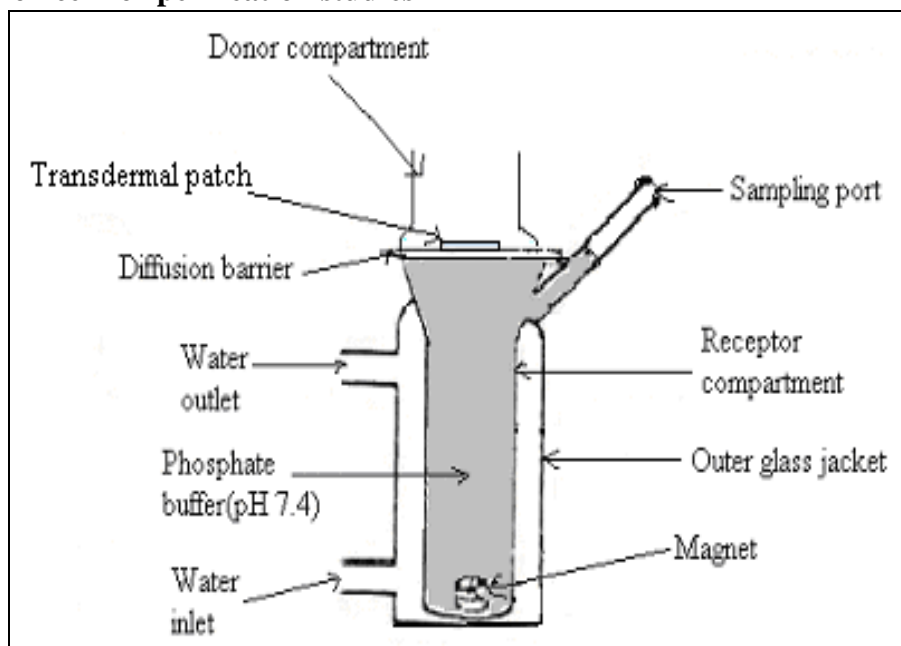
Selection of receptor medium

Saline Phosphate buffer pH 7.4 containing 20% v/v polyethylene glycol was used as receptor compartment of a modified Franz diffusion cell. The selection of receptor fluid is an important criterion in the in vitro skin permeation studies. Biphasic characteristics of the receptor fluid are desirable as the diffusion of drug molecules is through both aqueous and non-aqueous heterogeneous media. PEG-400 and normal saline are commonly chosen to provide the biphasic characteristics to the receptor fluid. Moreover, PEG-400 is a non-interacting fluid for the receptor media.

Method:

The volume of diffusion cell was 16 ml and stirred with bent stainless steel pin. The temperature was maintained at $37 \pm 1°C$ with the help of hot plate. The diffusion was carried out for 12 hours and 1 ml sample was withdrawn at an interval of 1 hour. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 285 nm.

Analysis of permeation data[21, 22]

The flux (mcg/cm2.h) of torasemide was calculated from the plot of the cumulative amount of torasemide was calculated from the slope of the plot of the cumulative amount of torasemide permeated per square centimeter of skin membrane at steady-state permeability coefficient (kp) of the drug through excised skin was calculated.

Skin irritation test [23]

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The skin irritation test was performed on six healthy rabbits weighing between 1.3 to 1.5 kg. Adhesive tape USP was used as control film. Drug free polymeric film was used as control. The dorsal surface of rabbits was cleared well and the hair was removed by a depilatory preparation .The skin was cleared with rectified spirit. The transdermal patches containing drug were placed over the skin with the help of adhesive tape. The films and the patches were removed after 24 h and the skin was examined for erythema for 7 days .The entire experimental protocol involving laboratory animal approved by the IAEC. The results are shown in Table no: 19 and Figure: 7-11.

EVALUATION OF FILMS

Film appearance
The film formed is transparent and uniform.
Thickness
Table. 7: Thickness Uniformity

Formulation	Thickness (mm)
F1	0.122 ± 0.0083
F2	0.156 ± 0.0054
F3	0.184 ± 0.0054
F4	0.216 ± 0.0083
F5	0.238 ± 0.0050
F6	0.251 ± 0.0089

The thickness of the patches (with varying ratios of HEC) varied from 0.122 to 0.251 mm .The low values for standard deviation indicates physical uniformity of the patches.

Table.8: Weight variation

Formulation	Weight variation (mg)
F1	90±0.707
F2	93± 1.14
F3	98±. 0.707
F4	104±0.547
F5	112±0.726
F6	125±0.547

Table. 9: Percent Flatness

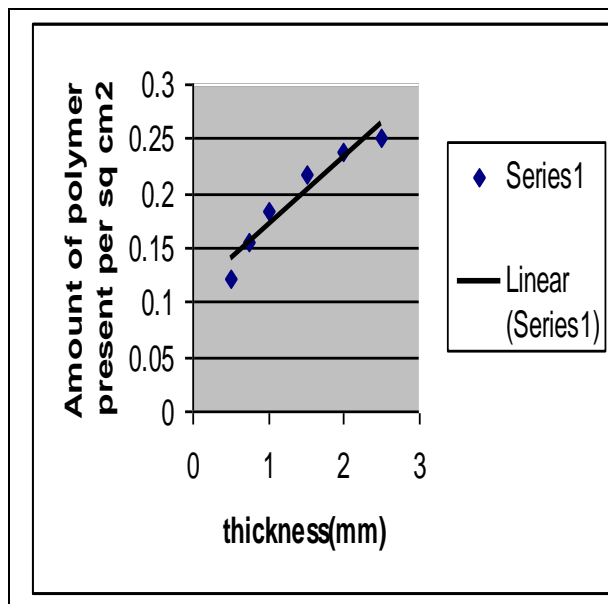| F1	F2	F3	F3	F4	F6
100	100	100	100	100	100

Fig: 2:Relationship between amount of polymer present per sq cm2 and thickness

Weight variation

The weights ranged of formulation between 90.24mg to 125 .68 mg
The physicochemical studies like moisture content, moisture uptake, flatness etc.provide information regarding the stability of the formulations. (Table 10,11,&12)

Moisture content

The percentage moisture content of the patches was calculated from the weight difference relative to the final weight. The moisture content in the formulations was found to increase with the increasing concentration of hydrophilic polymer HEC. (Table 10)

Table 10: Moisture content

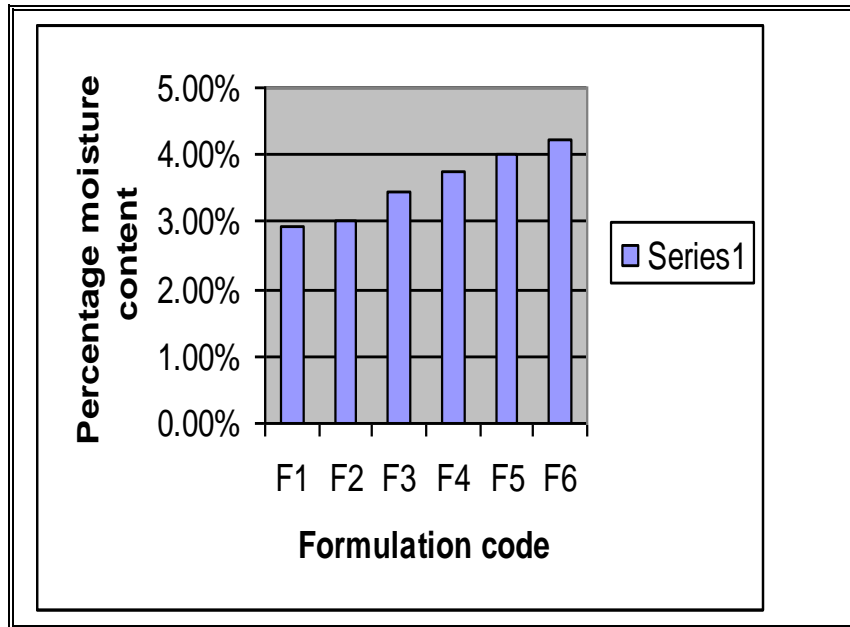| Formulation	Moisture content
F1	2.95%
F2	3.01%
F3	3.45%
F4	3.77%
F5	4.01%
F6	4.22%

Fig: 3: Percentage moisture content from torasemide containing different matrix films prepared by using different conc. of HEC
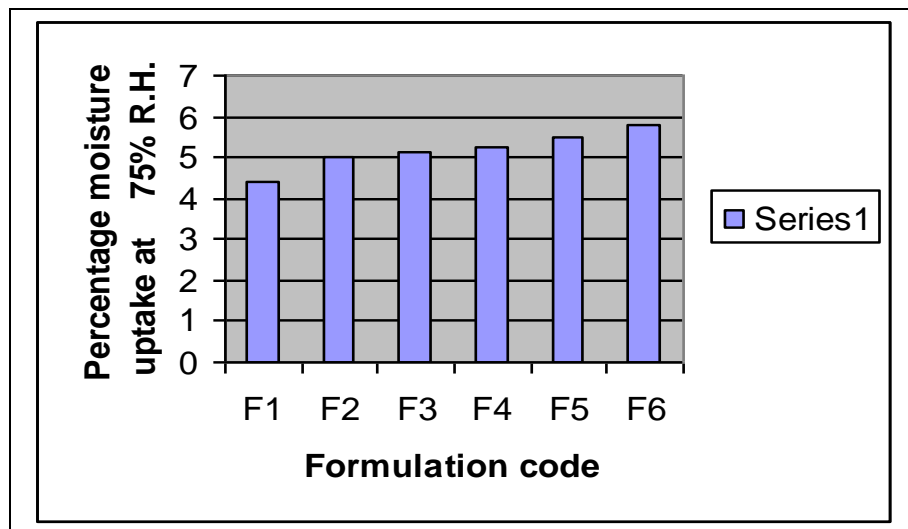

Fig: 4: Percentage moisture uptakes by different Matrix films prepared by using different conc. HEC at 75% R.H.
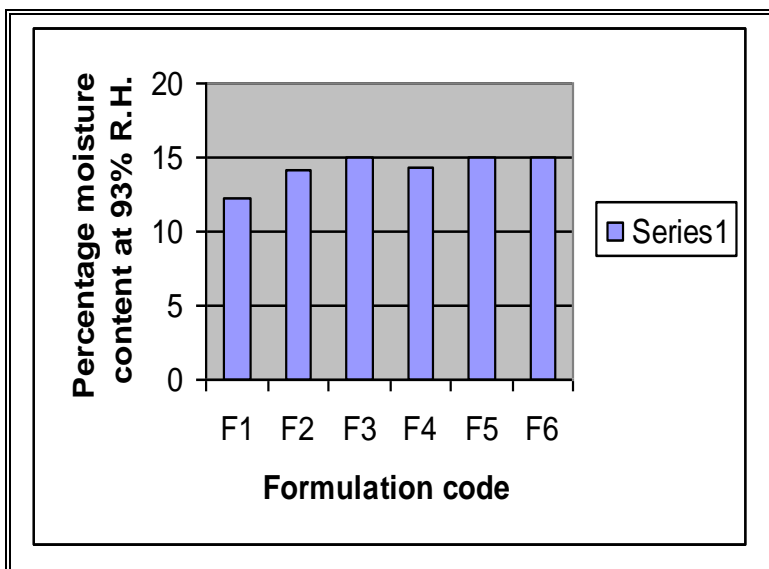
Fig:4 Percentage moisture uptakes by different matrix films prepared by using different conc. HEC at 93% R.H.

Moisture uptake
The water absorption capacity was found to increase with increase in concentration of hydrophilic polymer HEC with increase RH.

Table. 11: Moisture uptake

Relative humidity	Moisture uptake % w/w					
	F1	F2	F3	F4	F5	F6
75% RH	4.38	4.98	5.13	5.23	5.5	5.77
93 % RH	12.32	14.08	14.95	14.23	14.98	15.01

Tensile strength
  Table No.12 Tensile strength

Formulation	Tensile strength
F1	$9.33 \times 106 \pm 0.2486$
F2	$9.69 \times 106 \pm 0.1289$
F3	$9.54 \times 106 \pm 0.5048$
F4	$9.33 \times 106 \pm 0.2486$
F5	$9.29 \times 106 \pm 0.6094$
F6	$9.77 \times 106 \pm 0.2664$

Modulus of elasticity

Table No.13 Modulus of elasticity

Formulation	Modulus of elasticity
F1	$9.33 \times 106 \pm 0.2486$
F2	$9.74 \times 106 \pm 0.1779$
F3	$9.77 \times 106 \pm 0.5048$
F4	$9.33 \times 106 \pm 0.2486$
F5	$7.65 \times 106 \pm 0.3239$
F6	$7.85 \times 106 \pm 0.2154$

Percent elongation

Table No.14 Percent elongation

Formulation	Percent elongation
F1	100
F2	101.6
F3	100
F4	100
F5	111.3
F6	118

The tensile strength increased whereas percentage elongation decreased with increase in conc. of HEC. The tensile strength results obtained in formulations indicates the risk of film cracking. But, no sign of cracking in of patches was observed, which might be attributed to the addition of plasticizer PEG-400 (30% w/w of polymer weight). Addition of PEG-400 resulted in formation of smooth films.

Table 15: Drug content

Formulation	Drug content
F1	93.2%
F2	93.5%
F3	94.2%
F4	96.1%
F5	95.3%
F6	97.5%

Drug content

Further as shown in Table 28, the drug content analysis of the prepared formulations that the process used to prepare the patches in the investigation is capable of giving uniform drug content and minimum batch variability. The drug content of the transdermal systems was found to be uniform among various batches and ranged between 93.2% to 97.5% (Table no.15) This demonstrates homogenous distribution of the drug.

**Folding endurance**

Table 16: Folding endurance

Formulation	Folding endurance
F1	18±1.9
F2	26 ± 2.1
F3	28 ±1.4
F4	39 ± 3.6
F5	58 ±3.0
.F6	88 ±3.2

The folding endurance was measured manually, films were folded 88 times maximum in Formulation F6 and if the film shows any cracks it was taken as end point. The folding endurance was better in F6 formulation and shown in table no :16.

In vitro performance study
In vitro dissolution studies

Fig: 5 Comparative dissolution study of formulations F1, F2, F3, F4, F5& F6
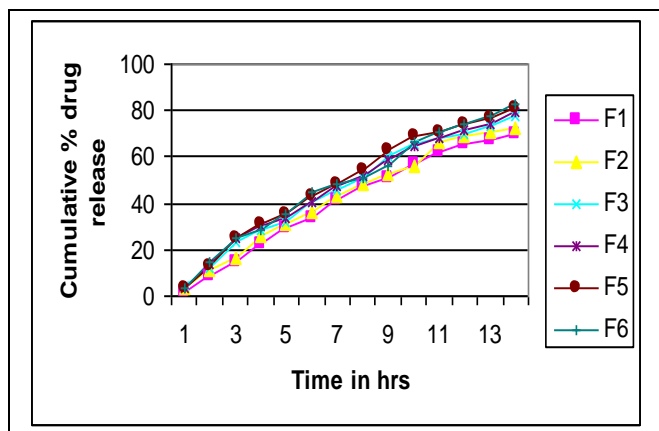
In vitro dissolution studies were carried out for the different formulations using USP disso using normal saline and PEG –400 as dissolution fluid at 37 0C to determine drug content in the patches.
The medicated films showed drug dissolution study in % cumulative release. The relationship can be established as, F6 >F5 > F4>F3>F2>F1   . It can

be said that increasing concentration of polymer increased cumulative drug release. Thus, by varying amount of polymer in film, percent release can be varied as per our rationale. Drug-polymer affinity can be major factor that control release of drug from formulation. Maximum percentage of drug release (i.e.82.92%) was observed with formulation F6 and the minimum (i.e. 70.14%) was found with formulation F1.It is well acknowledged that the addition of hydrophilic component to an insoluble film former tends to enhance its release rate constants. This phenomenon may be due to dissolution of the aq. fraction of the film which leads to formation of pores & decrease of mean diffusion path length of drug molecules to be released into dissolution medium.The compartative results are reported in figure no:5.
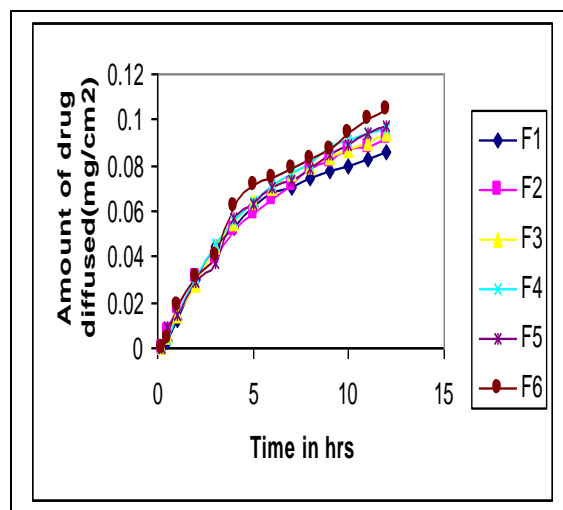In vitro permeation studies.

Fig: 6 In vitro release profiles of torasemide from TDDS formulations F1, F2, F3, F4, F5, F6

Release of drug from transdermal patches is controlled by the chemical properties of drug and delivery form as well as the physiological and physicochemical properties of the biological membrane. Matrix or monolithic transdermal drug delivery devices are used when the rate of drug permeation through the stratum corneum is the rate-limiting step for the drug absorption. The drug release matrix system is rapid initially and falls as the matrix is depleted of drug. Rate controlling factors include, for example drug concentration in matrix, chemical nature of matrix material, and device geometry.Fig.6

shows the cumulative amount of torasemide permeated through mice abdominal skin, into a receptor solution, as a function of time from the various patches. Films of hydrophilic polymer with different concentrations were studied. Formulation F6 showed highest cumulative release. Increasing the proportion of HEC concentration increases the cumulative release; this increased release rate may be due to highly hydrophilic nature of HEC, which has very less interactions with drug. Due to its high hydrophilicity it absorbs water and swells resulting in the more release of drug from the films.

Analysis of permeation data

The important data obtained from permeation experiments serve as the permeation profile that is used to calculate flux value. The permeability and flux values for each formulations according linear regression and summarized in Table.no.17,18.

Table: 17:Permeability Characteristics and flux value

Formulation	Flux (mg cm2 h-1)	Permeability (cm2 h-1)
F1	0.0255±0.0011	0.010±0.0006
F2	0.0317 ± 0.0018	0.015± 0.007
F3	0.0455± 0.0041	0.021±0.0016
F4	0.0493± 0.028	0.028±0.001
F5	0.0548±0.032	0.032±0.0023
F6	0.0623±0.014	0.037± 0.028

The enhancement of skin flux with increase of drug concentrations may be due to accumulation of a greater amount of drug on the skin surface. The improvement in skin flux with the increase of HEC concentration. The enhancement in drug solubility provides increased thermodynamic activity, which facilitates the skin permeation of drug. The other possible mechanism of the increased permeation with increasing HEC content in film is its co-enhancing property in aqueous vehicle system.

Data analysis

Table: 18. Estimated values of n and k by regression of log (Mt/M) on log (t)

Formulation	n	k	R2
F1	0.7210	0.245	0.9326
F2	0.7684	0.1993	0.9658
F3	0.5933	0.3056	0.8917
F4	0.7619	0.0296	0.9742
F5	0.7719	0.0635	0.9854
F6	0.7801	0.0738	0.9901

Kinetic treatment to in-vitro release data.

In order to characterize drug release profiles, zero order kinetics and matrix kinetics (Higuchi's equation) were calculated from the slope of the released amount versus time (t) or released amount versus square root of time

(t1/2) (Table No.19) Different kinetic equations were applied to interpret the release rate of Torasemide from formulations F1, F2, F3, F4, F5, F6.The coefficient determined graphically are shown in Table.no.19

Table No: 19 Kinetic treatment to in vitro release data (R2) of Formulations F1, F2, F3, F4, F5, F6

Formulation	Zero order	First order	Higuchi
F1	0.9207	0.7165	0.9790
F2	0.9686	0.7714	0.9871
F3	0.8670	0.6579	0.9468
F4	0.9478	0.8045	0.9763
F5	0.9841	0.8250	0.9864
F6	0.9901	0.8331	0.9913

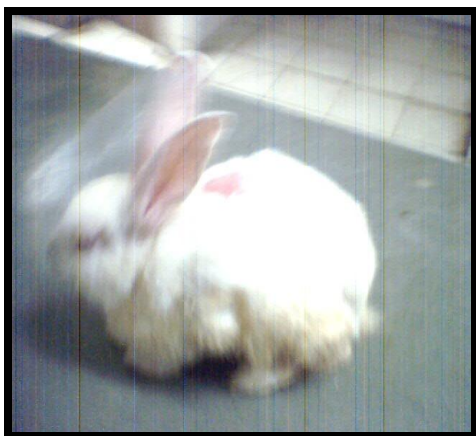**Skin irritation test**

Fig No:7 Transdermal patch applied to Rabbit

Photographs of Rabbit skin treated with transdermal patch

Fig no: 8 Intact after 24 hrs
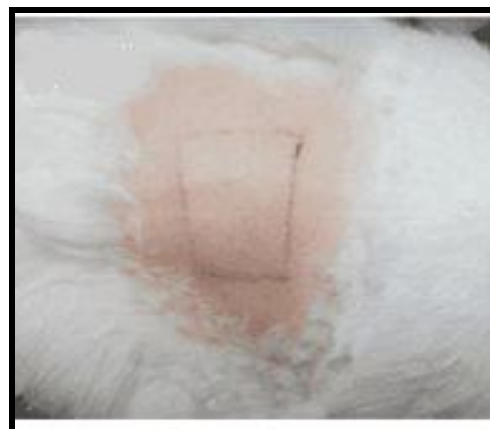

Fig no. 9 Abraded after 24 hrs

Fig no.10 Intact after 72 hrs

Fig no.11 Abraded after 72 hrs
Table: 20 Skin irritation test

Day	Control	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0.5	0	0
2	0	0	0	0	0.5	0	0
3	0	0	0	0	0.5	0	0
4	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0

The visual score was 0 (none) on both the erythema and the edema scale. There was no sign of skin irritation. Hence, the developed transdermal formulations are free of skin irritation.

CONCLUSION

The formulation F4 [CAP: PVP (6:1)] has shown optimum release in   concentration independent manner. Higuchi's plot for the formulation revealed that the predominant mechanism of   drug release is diffusion. Good correlation is observed between in-vitro and ex-vivo profile, which reveals the ability of the formulation to reproduce the in-vitro release pattern   through various biological membranes. Primary skin irritation studies revealed that the formulation F4 has no erythema and oedema.The formulation F4 has achieved the object of extended release, reduced frequency of administration and thus may improve the patient compliance. As an extension of this work pharmacokinetic studies, in-vivo studies on higher animals and controlled clinical studies on human beings can be carried out in future.

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