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Research Article

FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF ROSIGLITAZONE MALEATE

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ABSTRACT

The aim of the present study was to prepare and evaluate matrix type transdermal patches of Rosiglitazone Maleate by using Ethylcellulose and Eudragit as polymers at different combinations to minimize adverse effects associated with oral administration. Transdermal patches of Rosiglitazone Maleate were prepared by solvent evaporation method by varying the blend ratios of Ethylcellulose and Eudragit. The drug polymer interaction studies were carried out by FT-IR studies. The prepared patches were evaluated for their thickness, weight variation, folding endurance, percentage moisture absorption, percentage moisture loss and drug content. *In vitro* drug release was determined by using Franz diffusion cell in phosphate buffer (pH5.4). The release data was studied for various kinetic parameters to understand the mechanism of drug release from the developed formulations. IR studies revealed that the drug, polymer and excipients were compatible with each other. Thin, flexible, smooth and uniform films were obtained with Eudragit and ethyle cellulose using dibutyl phthalate as plasticizer. Thickness, weights and drug contents of all the formulations remained almost uniform with low SD values. The formulations E6, E7 formulated by incorporating 1% span 80 and tween 80. E5 showed good release of drug than another formulations. Formulation E5 was prepared by combination of ethyl cellulose and Eudragit in the ratio of 1 :(1:5) the release rate of drug is 99.95 in 24hrs. Studies have shown promising results and there is a scope for further pharmacokinetic evaluation.

Keywords: Rosiglitazone Maleate, ethyl cellulose, Eudragit, span 80, tween 80.

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 anti hyperglycemic class drugs.[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 cm2 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] Diabetes is a chronic progressive disease associated with systemic disorder. The disease directly affects physical function and mobility and results in

substantial short-term and long-term morbidity. Furthermore, individuals with Diabetes have a substantially shorter life expectancy than does the general population.

Deaths from cardiovascular disease, infection, and cancer are increased among individuals with Diabetis.[6] Diabetes and dermatology requires the use of guidelines for drug toxicity monitoring, as adverse effects can be significant in some patients.[7] anti hyperglycemic are amongst the most widely used therapeutic agents. They are generally prescribed for the long term treatment of diabetes.[8]

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.[9]

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

MATERIALS AND METHODS

Rosiglitazone pure drug was obtained from Lee PharmaPvt Ltd , Hydrabad, A.P , 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 120c. The usual dose of Rosiglitazone is 8 mg twice a day by oral route.

99.8% bound to plasma protein. Ethylcellulose is a tasteless, free-flowing, white to light tan colored powder, soluble in organic solvents, forming a viscous colloidal solution. EC, Eudragit are a widely used polymers in oral and topical Pharmaceutical formulations. It is also used extensively in cosmetics products. Tweens 80, Span 80, 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 HCOP chemical store,

Physiochemical Compatibility Investigation of Drug and Polymer

The infrared (IR) spectra were recorded using a Fourier transform-infrared (FTIR Bruker, Japan).

The spectra obtained for Pure drug, polymers, and physical mixtures ofdrug and polymer were compared.[10-12]

Determination of λmax of **Rosiglitazone** in Phosphate buffer solution of pH 5.4 with the help of double beam UVVisiblespectrophotometer. It was observed to be **229**nm.

Fabrication of Transdermal Patche

Transdermal Patches containing Rosiglitazone were prepared by using solvent evaporation technique with different polymers and permeation enhancer's in different ratios.

Methanol and chloroform 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.[13, 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]

Table 1: Formulation of Rosiglitazone Transdermal Patches

Sl No	Ingredients	E_1 (1:4)	E_2 (1:5)	E_3 (1:6)	HE_4 (1: (1:4)	HES_5 (1:(1:5)	HET_6 (1:(1:5)	HE_7 (1:(1:5)
1	Drug(mg)	8	8	8	8	8	8	8
2	Ethylcellulose (mg)	32	40	48	32	40	40	40
3	Eudragit (mg)	-	-	-	8	8	8	8
4	Dibutyl phthalate (%)	3ml	3ml	3ml	3ml	3ml	3ml	3ml
5	Tween-80(%)	-	-	-	-	-	1ml	-
6	Span-80(%	-	-	-	-	-	-	1ml

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 2x2 cm length and 2 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 eachstrip[21]

***In-Vitro* Permeation Study through Franz diffusion cell**
The cell is composed of two compartments: donor and receptor. The receptor compartment has a capacity of 10ml volume and effective surface area of 2x2 cm2. 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 24 hours. An important study of percentage drug release was performed in Franz diffusion cell which is filled with phosphate buffer saline solution pH 5.4 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, 30min, to 1 to 24 hours at 229 nm by spectrophotometrically.[22]

Table 2: % Cumulative Release of Drug through membrane

Sl No	Time (hrs)	Cumulative % of drug release						
		E-1	E-2	E-3	E-4	E-5	E-6	E-7
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.5	22.37±0.90	17.50±0.80	15.62±1.00	16.19±0.80	18.90±0.60	17.46±0.75	17.86±1.10
3	1	30.76±0.42	22.40±0.75	20.00±0.65	21.38±0.55	23.10±1.10	23.10±1.10	22.31±0.80
4	2	36.94±0.55	31.23±0.65	27.85±0.58	31.30±0.48	27.92±0.34	34.63±1.25	36.42±0.70
5	4	46.12±1.10	49.09±0.90	31.58±0.48	39.61±0.55	38.00±0.54	48.65±1.20	51.76±0.90
6	6	50.40±0.66	56.25±0.54	39.89±1.20	52.93±0.65	55.17±0.45	58.86±1.00	60.76±1.15
7	8	68.67±1.00	75.44±0.49	46.29±1.30	58.54±0.48	56.00±0.65	62.13±0.95	65.76±1.30
8	10	80.94±0.49	86.51±1.40	63.88±0.60	67.30±0.35	65.94±0.45	72.63±0.70	71.00±0.95
9	12	97.19±0.65	91.09±0.90	67.00±0.45	76.70±0.90	79.19±1.25	79.67±0.85	83.47±0.75
10	16		98.61±0.80	73.57±0.84	77.02±1.15	85.55±0.46	84.34±1.10	89.03±1.00
11	20			78.94±0.76	83.57±1.20	92.64±0.57	91.66±1.15	95.00±0.90
12	24			87.46±0.65	91.23±1.10	99.95±0.53	99.04±0.85	98.72±1.10

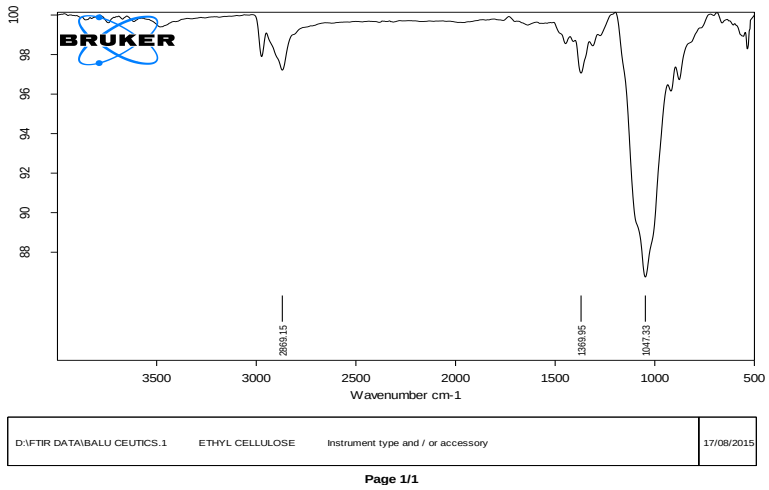

Fig. 1: FT-IR spectrum of Ethyl cellulose

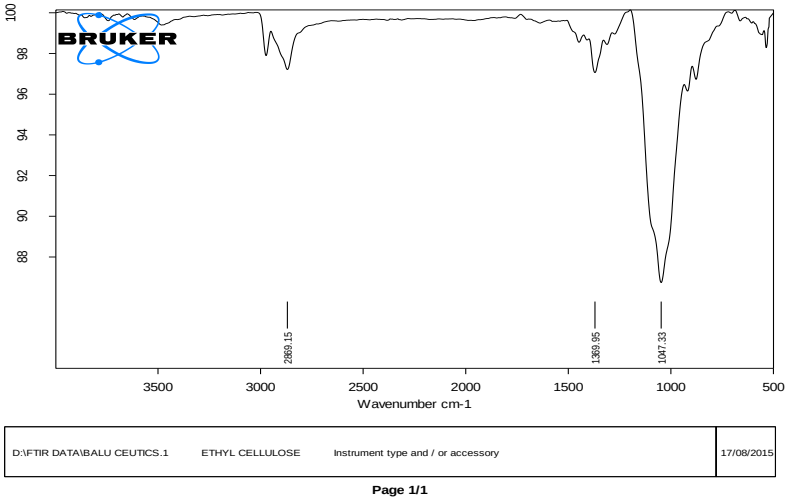

Fig. 2: FT-IR spectrum of Ethyl cellulose + Drug

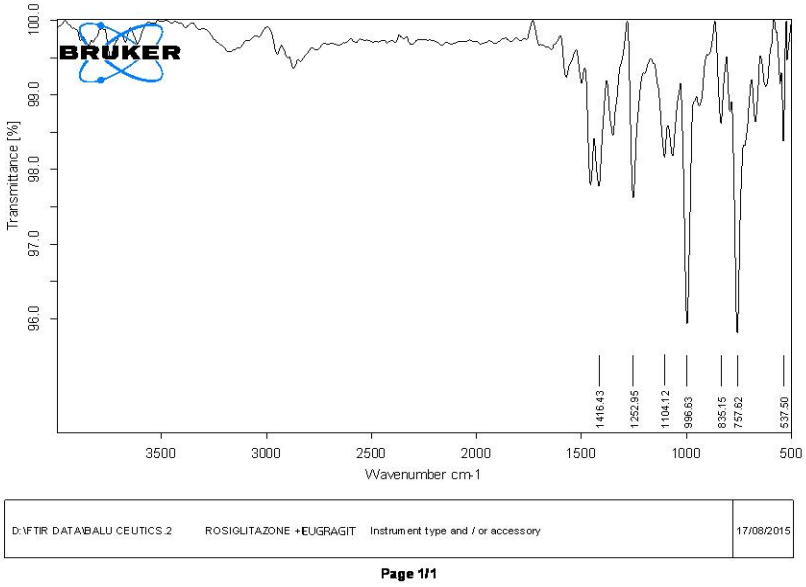

Fig. 3: FT-IR spectrum of Drug + Eudragit

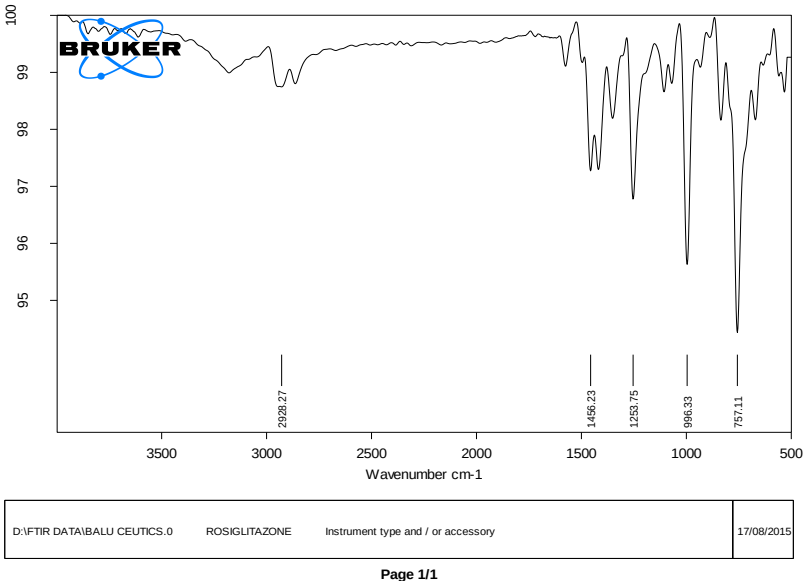

Fig. 4: FT-IR spectrum of pure drug

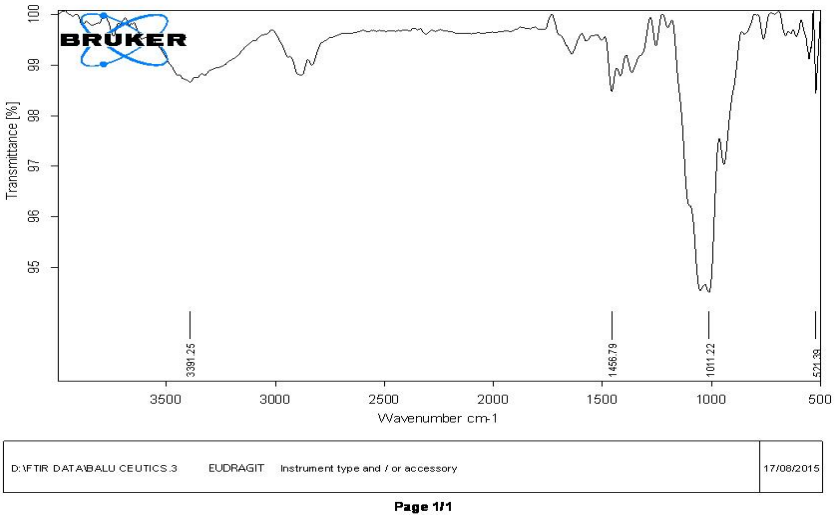

Fig. 5: FT-IR spectrum of Eudragit

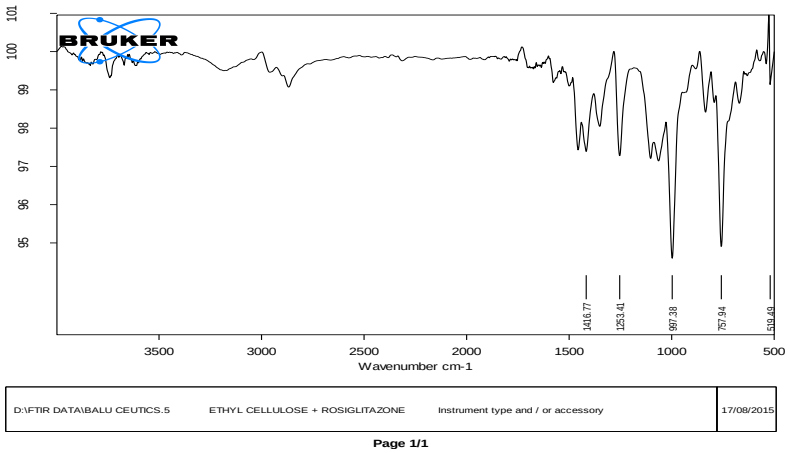

Fig. 6: FT-IR spectrum of Ethyl cellulose +Eudragit+ Drug

Physicochemical evaluation

Table 04 and 05 shows the physicochemical evaluation like the thickness ,folding endurance , percentage moisture absorbed ,percentage moisture lost ,Drug content uniformity.

Thickness of the patch

The thickness of the various patch ranged from 0.025±0.85 to 0.036±0.70 mm

Folding endurance

The folding endurance value ranged from 98±1.0 to 188±1.7 times.

Percentage of moisture absorbed

From the various formulation evaluated the percentage of moisture absorbed was in the range of 1.95±1.10to 2.95±1.35%.

Percentage of moisture loss

The various formulation evaluated the percentage of moisture lost was in the
Range 1.05±0.90to 1.50±1.30%.

Drug content uniformity

The percentage of drug content was uniform in the various evaluated transdermal patch .All the patches were evaluated five times to confirm the uniformity and was found to be nearly same in all the transdermal patch.

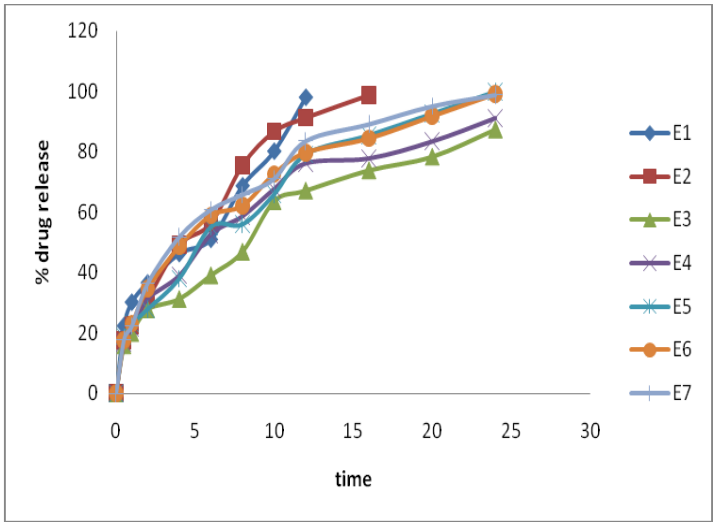

Fig. 7

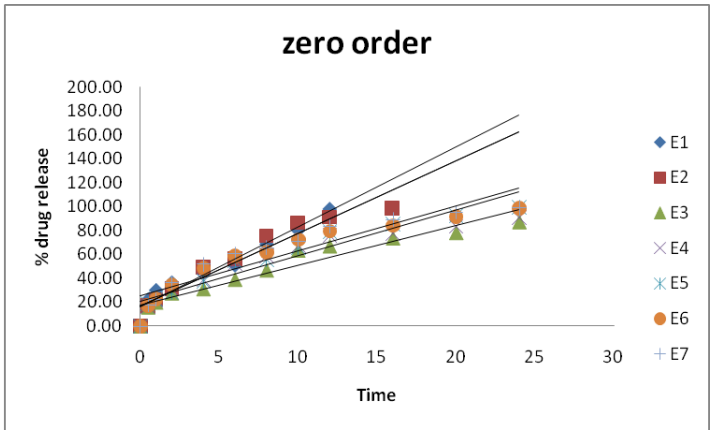

Fig. 8

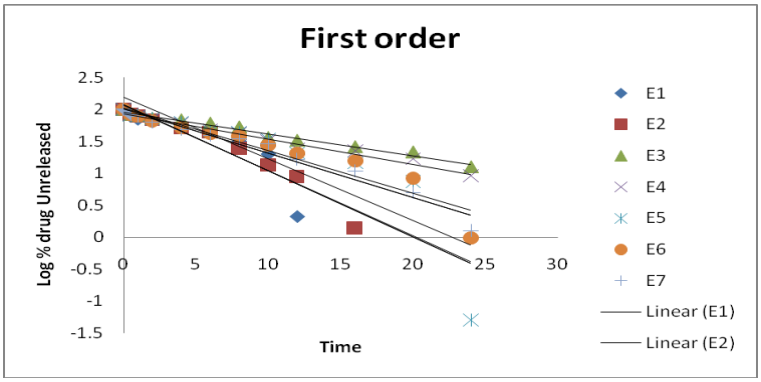

Fig. 9

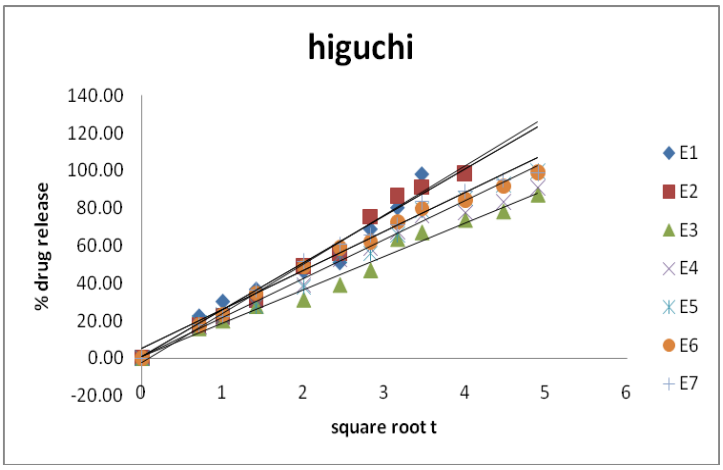

Fig. 10

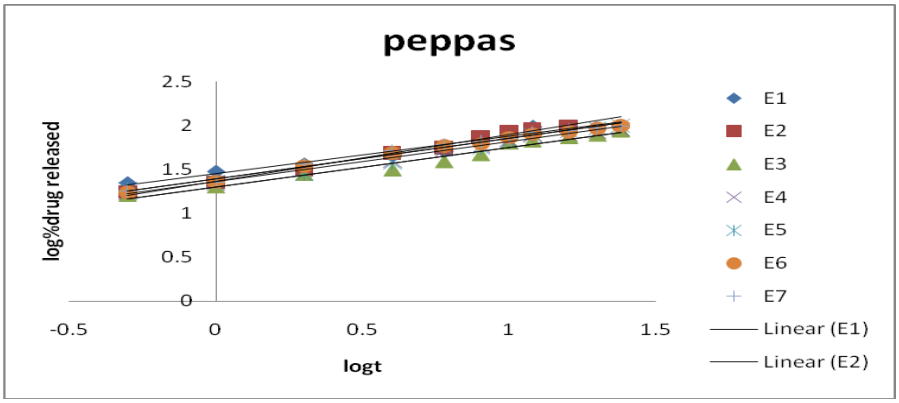

Fig. 11: Drug Release Profile

Table 3: Cumulative Percentage And Kinetic Value Obtained From Formulation E-1 To E-7

Formulations	Zero order	First order	Higuchi	pepas	n value
E1	0.9426	0.7638	0.8341	0.9512	0.426
E2	0.9263	0.9405	0.9286	0.9897	0.535
E3	0.9143	0.9733	0.8812	0.9679	0.451
E4	0.8725	0.9702	0.9499	0.9918	0.458
E5	0.9201	0.9814	0.9040	0.9772	0.458
E6	0.8682	0.9898	0.9706	0.9941	0.462
E7	0.8690	0.9855	0.9698	0.9893	0.471

SUMMARY AND CONCLUSION

- ✓ The aim of this investigation was to develop and evaluate matrix type transdermal patches for ROSIGLITAZONE with the polymers of Ethyl cellulose and Eudragit using different concentrations, di-butyl pthalate is used as plasticizer and also to evaluate the effect of Tween 80 ,Span 80 as permeation enhancers
- ✓ Formulation E1 to E3 was prepared by using ethyl cellulose alone in the ratio of 1:4, 1:5, 1:6, the release rate of drug is 97.19 , 98.61, 87.46 in 12, 16, 24hrs respectively.
- ✓ Formulation E4 and E5 was prepared by combination of ethyl cellulose and Eudragit in the ratio of 1 :(1:4) and 1 :(1:5) the release rate of drug is 91.23 and 99.95 in 24hrs respectively.
- ✓ Formulation E6 was prepared by the ratio of 1 :(1:5) with 1ml of span 80 the release rate of drug is 99.04 in 24hrs.
- ✓ Formulation E7 was prepared by the ratio of 1 :(1:5) with 1ml of tween 80 the release rate of drug is 98.72 in 24hrs.
- ✓ All the formulated patches evaluated for thickness, moisture absorbance, moisture loss, drug content. The obtained values give the satisfied result.
- ✓ The diffusion studies was carried out, from all the formulations E5 formulation is considered as the best formulation, the span, and tween was not much effect on release rate of drug.
- ✓ Based on R2 values the optimized formulation follows 1st order kinetics and peppas model and non- fickian diffusion mechanism.
- ✓ The fabricated transdermal patch was suitable for further In vivo studies based on the studies the requirement of dose can be adjusted by optimizing the patch size.

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