ISSN 2347-3614

UNIQUE JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL SCIENCES

Available online: www.ujconline.net

Research Article

PREPARATION AND *IN-VITRO* EVALUATION OF ROSIGLITAZONE MALEATE MATRIX TRANSDERMAL SYSTEMS FOR DIABETES MELLITUS

Nagesh C[1*], Attimarad Sunil L[2], MM Shankaraih[3], Venkatesh JS[3], Kant Aman[4], Chandrashekhara S[5], Karigar Asif A[6]

[1]Professor and Head, Department of Pharmaceutics, Maratha Mandal's College of Pharmacy, Belgaum, Karnataka, India
[2]Lecturer, Department of Pharmaceutics, Maratha Mandal's College of Pharmacy, Belgaum, Karnataka, India
[3]Professor, Department of Pharmaceutics, S.C.S. College of Pharmacy, Harapanahalli, Karnataka, India
[4]PG Scholar, Department of Pharmaceutics, S.C.S. College of Pharmacy, Harapanahalli, Karnataka, India
[5]Associate Professor, Department of Pharmaceutics, Maratha Mandal's College of Pharmacy, Belgaum, Karnataka, India
[6]Professor and Head, Department of Pharmaceutical Analysis, Maratha Mandal's College of Pharmacy, Belgaum, Karnataka, India

Received 30-08-2015; Revised 28-09-2015; Accepted 27-10-2015

*Corresponding Author: **Dr. Nagesh C,**
M.Pharm, PhD, Professor and Head, Department of Pharmaceutics, Maratha Mandal's College of Pharmacy, Belgaum, Karnataka, India Mobile: 07899470762

ABSTRACT

The present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of rosiglitazone maleate using blends of two different polymeric combinations, hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose (EC) and Eudragit with HPMC. Physical parameter including moisture content, moisture uptake, flatness, tensile strength, percentage elongation were carried out to study the stability of the formulations and *in-vitro* diffusion of the experimental formulations were performed to determine the amount of rosiglitazone maleate present in the patches. Drug–excipient interaction studies were carried out using DSC and Fourier transform infrared (FTIR) spectroscopic technique. *In vitro* drug permeation study was conducted in a modified Franz's diffusion cell and the drug release kinetics was fit into zero order, first order, Higuchi and Pappas model. All the formulations were found to be suitable for formulating in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and polymers used. The formulations of HPMC: EC provided slower and more sustained release of drug than the HPMC: Eudragit formulations during *in-vitro* permeation studies and the formulation HPMC: EC (1:3) was found t o provide the slowest release of drug. Based on the above observations, it can be reasonably concluded that HPMC–EC polymers are better suited than HPMC–Eudragit polymers for the development of TDDS of rosiglitazone maleate.

Keywords: Rosiglitazone Maleate, Transdermal Patches, Eudragit, HPMC, Ethyl Cellulose, *In-Vitro* Skin Permeation Studies.

INTRODUCTION

Transdermal drug delivery (TDDS) represents the successful and innovative area of research in drug delivery, it is ideally suited for chronic diseases and known to enhance therapeutic efficacy, bioavailability and to avoid any adverse effects[1-2]. Transdermal drug delivery systems are the dosage forms which delivers the drugs across the skin to achieve systemic effects. The transdermal drug delivery systems has gained lot of interest during last decade as it offers many advantages over conventional drug delivery systems notably avoidance of first pass hepatic metabolism, patients compliance, reduction in gastric disturbances. The main aim of the transdermal product is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of drug in the skin. Transdermal patches control the delivery of drugs at controlled rates by employing an appropriate combination of hydrophilic and lipophilic polymers[3-6].

Diabetes mellitus is chronic metabolic disorder characterized by hyperglycemia, abnormal lipid protein metabolism along with specific long term complications affecting the retina, kidney and nervous systems. In the present study Rosiglitazone maleate an anti-diabetic drug in the thiazolidinedione class was selected as a model drug. Like other thiazolidinediones, the mechanism of action of Rosiglitazone is by activation of the intracellular receptor class of the peroxisome proliferators activated receptors (PPARs), specifically PPARγ. Rosiglitazone is a selective ligand of PPARγ, and has no PPARα-binding action. The half-life of rosiglitazone maleate is 3-4 h and it reaches a peak plasma concentration after 1 h. It is highly soluble in 0.1 mol/l HCl (11.803 mg/ml) and its solubility decreases with increasing pH over the physiological range[7-9]. By considering the above properties it was decided that rosiglitazone maleate was selected as suitable drug for the proposed study hence choosen as a model drug.

The system designs for transdermal patches include matrix, micro reservoir, reservoir, and adhesive and membrane–matrix hybrid. Matrix type transdermal patches remain among the most popular, as they are easy to manufacture.

The present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) containing rosiglitazone maleate as a model drug employing various ratios of hydroxyl propyl methyl cellulose (HPMC) and Eudragit as well as HPMC and EC. The aim was to compare the polymeric combinations in terms of *in vitro* permeation of the drug and to find out the best possible ratio of hydrophilic and lipophillic polymeric combination, which may be chosen for further studies.

MATERIALS AND METHODS

Materials

Rosiglitazone maleate and eudragit S100 was purchased from Yarrow chemicals pvt. ltd. Mumbai. Hydroxy propyl methyl cellulose (HPMC), ethyl cellulose, propylene glycol, dibutyl pthalate, methanol, chloroform of analytical grade was obtained from S.D. Fine chemicals Pvt. ltd, Mumbai, India.

A) Preoformulation studies of drug and excipients

Drug–excipient interaction study by IR spectrophotometer

The pure drug, rosiglitazone maleate and polymeric mixture of HPMC, EC, sodium alginate and, Eudragit were mixed separately with IR grade KBr in the ratio of 1:100 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000–400 cm^{-1} in Perkin Elmer 1600 series FT-IR instrument.

Differential scanning calorimetry (DSC)

DSC thermograms of pure drug (rosiglitazone maleate) and its physical mixture with polymers (HPMC, EC, Eudragit, sodium alginate) were carried out to investigate any possible interaction between the drug and the utilized polymers. The selected heating rate is from 121º C to 3000º C at an increase of 100º C per minute using Perkin Elmer 6 DSC[10, 11].

B) Preparation of transdermal patches containing Rosiglitazone

The matrix-type transdermal patches containing Rosiglitazone maleate were prepared by solvent casting technique using different ratios of EC, HPMC and Eudragit. The polymers in different ratios were dissolved in the respective solvents as shown in the Table 1. The drug was then added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Di-butyl phthalate and propylene glycol were used as plasticizers. The solution was poured on the glass mould having surface area of 16 cm^2. The glass moulds were kept on leveled surface and covered by inverted funnel to allow controlled evaporation of solvent at room temperature till a flexible film was formed. Dried films were carefully removed, checked for any imperfections and stored in desiccators until use. Then the patches were cut into 1x1 cm^2 patches. Drug incorporated for each 4x4 cm^2 patch was 12 mg.

C) Evaluation of transdermal patches containing Rosiglitazone: The following physical studies were conducted**.**

Physical appearance:

The physical appearance of the films was found out by examining the films opposite to a clear source of light for their transparency, color, clarity, flexibility and smoothness.

Uniformity of thickness:

Film thickness was measured by a digital screw gauge (Mitutoyo, Japan) at five different random points on the patch. The average of five observations was taken and standard deviation was calculated[12].

Weight variation:

The six patches of 1x1 cm^2 was cut and weighed on digital electronic balance for weight variation test. The test was done to check uniformity of weight and batch to batch variation[13].

Folding endurance:

The folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance[14].

Flatness:

A transdermal patch should possess a smooth surface and should not constrict with time. Flatness is determined by taking three longitudinal strips and cut from each patch at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length was determined. Flatness was measured by determining percent constriction, with zero percent constriction equivalent to 100% flatness[15]. % constriction was calculated using the formula, **Constriction (%)** = L_I - L_2/L_2 X 100 where, L_2 is final length of each strip and L_1 is initial length of each strip.

Tensile strength:

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength. The tensile strength of the patches was determined by using a tensile strength instrument. The sensitivity of the machine is 1mg to 500kg. It consists of two loaded cell grips. The lower one was fixed and upper one was movable. The test film of specific size (4×1cm^2) was fixed between these cells grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms[16]. Tensile strength was calculated using formula

Tensile strength (kg/cm^2) = Break force (kg)/ Cross sectional area of the sample (cm^2).

Percentage elongation:

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below formula[17].

Elongation at break (%) = Increase in length at break point (cm) / Original length (cm) X 100.

Estimation of drug content:

Drug content was determined by taking small pieces of patch of 1 cm^2 each (1 x 1 cm) were cut from different parts of the film. Each piece was taken in a separate stoppered conical flasks containing 1% acetic acid and made upto 100 ml with phosphate buffer pH 7.4. The mixture was stirred vigorously for 6 h using magnetic stirrer. The above solutions were filtered and suitable dilutions were made. Absorbance was measured using Shimadzu UV/VIS Spectrophotometer 1700 at a λ_{max} of 313 nm[18].

Estimation of percentage moisture loss:
The patch were weighed accurately and kept in a desiccators containing fused calcium chloride for at least 24 h or more until it showed a constant weight. The moisture content was calculated using following formula[19].
% moisture loss= Initial weight – Final weight / Initial weight Initial X 100.
Estimation of percent moisture absorbed:
The patch were weighed accurately and kept in desiccators at 40 C for 24 h. Then patch were 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 desiccators, respectively, at room temperature. Then the weights were measured periodically until shows constant weights. Percent moisture absorbed was calculated using the following formula[20],
% moisture absorbed= Final weight – Initial weight / Initial weight X 100
***In-vitro* diffusion study:**
In the present study *in-vitro* release of Rosiglitazone Maleate from various matrix systems was studied using Franz diffusion cell using cellophane membrane. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The receptor compartment was surrounded by a water jacket for maintaining the temperature at 37 ±1ºC and it was provided with sampling port. Diffusion media in the receptor compartment was stirred with magnetic needle. The diffusion medium used was phosphate buffer solution pH 7.4. The drug containing film with a support of a backing membrane was kept in the donor compartment and it was separated from the receptor compartment by standard membrane. The semi permeable membrane was previously soaked for 24 h in phosphate buffer (pH 7.4). The donor and receptor compartment hold together using clips of strong grip. The receptor compartment containing dissolution medium was maintained at 37 ±1ºC by circulating the water in outer jacket from organ bath. The diffusion medium was stirred with magnetic needle 2 mm in diameter and 6 mm in length operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the standard membrane. At each sampling time the solution in the receptor compartment was completely withdrawn and replaced with fresh phosphate buffer solution. The samples were filtered through Whatman filter paper. The concentration of the drug was determined by UV spectrophotometer at 313nm for the drug content[21,22].
Analysis of drug release data
To analyze the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from the diffusion studies was fitted into Zero order, First order, Higuchi matrix and Peppas model. By comparing the regression values obtained (R- value), the best fit model was selected[23,24].
Stability studies
All the transdermal patches were subjected to short term stability studies as per ICH guidelines. Patches were placed in a glass beaker lined with aluminum foil and kept in a humidity chamber maintained at 40 ± 2° C with a relative humidity of 75 ± 5% RH for 1 month.
Changes in the appearance, drug content, folding endurance and weight variation of the patches were investigated after storage. The data presented were the mean of three determinations. Percentage drug present in the patches was determined spectrophotometrically at 313 nm and reported in the Table 6. Further there is a need of accelerated stability testing of these dosage forms to determine their shelf life.
The patches were also observed for their appearance and texture. These properties did not change in all the patches during the period of study[25].

RESULTS AND DISCUSSION

Eleven formulations of RZM transdermal patches were prepared using various polymers such as HPMC, EUD S100 and EC in different ratios. The composition of all formulations was shown in Table 1. The prepared formulations were subjected to the following evaluation parameters.
A. Preoformulation studies of drug and excipients
Fourier Transform Infrared spectroscopy (FT-IR)
FT-IR studies were carried out for pure drug and physical mixture of pure drug with polymers (HPMC: EUD S100 and HPMC: EC). IR spectra were shown in Fig. 1-6.
The drug polymer interactions was ruled out, as there was no major shifts in the absorption bands (peaks) of Rosiglitazone maleate in presence of polymeric combination viz. HPMC: EUD S100 and HPMC: EC respectively.
Differential scanning calorimetry
As described in the methodology chapter the DSC study was carried out for pure drug and physical mixture of pure drug with polymer. DSC peaks were shown in the Fig. 7-9. The DSC thermograms for pure drug and its physical mixture (RZM + HPMC+EUD S100 and RZM +HPMC +EC polymer) were determined to understand any interaction between drug and polymer. It was observed from the above thermograms that there was no appearance of new peaks, no change in peak shape and its onset. The results indicated that there was no interaction between drug and the polymer.
B. Physical evaluation of transdermal patches
Physical appearance
The fabricated patches were found to be thin, white in color and visually smooth surfaced. The drug and polymer distribution was uniform.
Thickness
The thickness value of prepared films is shown in Table 2. The data of films thickness indicates that there was no much difference in thickness within formulation although these were selected randomly. The thickness value of the prepared films varied from 0.142± 0.06 to 0.166 ± 0.01 mm.
Weight variation
Drug loaded films were tested for uniformity of weight and the results of weight variation are given in Table 2. The weight variation was found to be in the range of 0.017 ± 1.2 to 0.021 ± 1.8. The weight variation value indicates that films were uniform in weight. As the concentration of HPMC decreases there was decrease in weight in formulation F1-F6. Similarly, as the concentration of EC increases there was

increase in weight in formulation F7-F11. This is an agreement in uniformity of weight of patches.

Folding Endurance

The values of folding endurance of all formulations are given in the Table 2. The folding endurance was found to be in the range of 126 ± 1 to 192 ± 2. Folding endurance values for HPMC: EUD S100 patches were more than 150 whereas HPMC: EC patches were more than 100. This data reveals that the patches have good mechanical strength along with flexibility.

Flatness

The flatness of the transdermal patches (Table 2) was found to be in the range of 99 ± 0.04 to 100 ± 0.1. All the patches showed almost hundred percent flatness, which indicates no amount of constriction of the formulated patches.

Tensile strength

The tensile strength of prepared patches was reported in Table 3. The tensile strength was found to be in the range of 0.386 ± 0.15 to 0.956 ± 0.19. The formulation F9 showed the best tensile strength. The tensile strength of HPMC: EUD S100 patches were lesser than HPMC: EC patches. This was due to more solubility of polymers.

Percentage Elongation

The % elongation values of all the patches were shown in Table 3. The % elongation was found to be in the range of 28.31 ± 0.13 to 42.42 ± 0.24. The formulation F9 showed minimum % elongation among all the other patches.

Estimation of Drug content

The percentage drug content in various formulations ranged from 78.85 ± 0.73 to 89.56 ± 0.62 % as given in the Table 2. It was observed from the drug content data that there was no significant difference in drug content uniformity.

Percentage moisture absorption

The formulation F9 showed lowest percent moisture absorption than other formulations. This might be because of the low water permeability of ethyl cellulose polymer. Low moisture uptake also protects the materials from microbial contamination and avoids bulkiness of the patches. The values for the moisture uptake have been given in the Table 3.

Percentage moisture loss

Moisture loss studies were conducted on all formulations and reported in Table 3. It was observed that the formulation F1 showed maximum amount of moisture loss because of more concentration of HPMC. Formulation F9 showed minimum percentage of moisture loss because of more concentration of hydrophobic polymer viz... EC.

***In-vitro* drug release studies**

In-vitro diffusion studies of RZM transdermal patches were carried out using cellophane membrane in phosphate buffer pH 7.4. The apparatus was designed with the objective of mimicking the conditions of skin activity to certain extent. The *in-vitro* diffusion study of RZM transdermal patch has shown increase in percentage release with increase in amount of HPMC polymer. The time required for 50% of drug release was found to be maximum for F1 (5 hrs). As increase in EUD S100 concentration with HPMC there was decrease in drug release, this may be due to more solubility of HPMC. Maximum drug release was obtained in patches where EC concentrations are less, but when the concentration of EC was increased has shown relatively retarded drug release as shown by formulation F9. When HPMC: EC formulations were compared against HPMC: Eudragit formulations in terms of drug release rate, it was observed that rate of drug release was much higher in the case of Eudragit containing polymer matrix. Eudragit (polymethyl methacrylate) is known to have larger cavity size in its polymeric network and thus, it may involve a faster mode of diffusion of rosiglitazone from the HPMC: Eudragit formulations as compared to the formulations of HPMC: EC combinations. The releases of drug from the formulations were shown in the Table no 4-5 and Fig no 10-11. When the average rate constants of these three formulations were compared, it was found that F9 (HPMC: EC, 1:3) had the slowest release rate of all the formulations studied. Based on the above observations, it can be reasonably concluded that HPMC–EC polymers are better suited over HPMC–EUD S100 polymers for the development of TDDS of RZM and the formulation F9 (HPMC: EC, 1:3) may be used for further pharmacokinetic and pharmacodynamics studies in suitable animal model.

Data analysis

- The curve fitting results of the release rate profile of the designed formulation shown in Table no 6. The data analysis gave an idea on the release rate profile and the mechanism of the drug release. All the RZM films follows 1st order kinetics.
- The data of the formulated films fit peppas equation, which indicates that the drug was released by initial swelling and follows super case II transport. The Higuchi's plot indicates the release of water soluble and lower soluble drug incorporated in solid matrices and found that drug particles disposed in a uniform matrices behaving as a diffusion media, dissolution from a planer system having a homogenous matrices and obeys Higuchi's equation.

Stability studies

- All the medicated patches were subjected to short term stability studies. Patches were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained 40 ± 2 ^{o}C with a relative humidity of 75 ± 5% RH for 3 month as per ICH guidelines. The results of stability studies are shown in the Table no. 7.
- Changes in the appearance, drug content, folding endurance and weight variation of the patches were investigated after storage. Percentage drug present in the patches was determined spectrophotometrically at 313 nm and reported in the Table 7. Further there is a need of accelerated stability testing of these dosage forms to determine their shelf life.

The patches were also observed for their appearance and texture. These properties did not change in all the patches during the period of study.

CONCLUSION

Rosiglitazone is an effective antidiabetic agent, and widely used to treat type-II diabetes. Rosiglitazone has a half life of 3-4 hrs and undergo first pass hepatic metabolism when administered orally. Hence in the present work efforts have

been made to prepare transdermal drug delivery systems using hydrophilic and hydrophobic polymers. Transdermal patches were prepared by solvent casting method using combination of HPMC, eud S100 and EC in various concentrations, propylene glycol and dibutyl phthalate were used as plasticizers. The films were subjected for various tests like uniformity of thickness, weight, folding endurance, flatness, tensile strength, percentage elongation, drug content, percentage moisture loss, percentage moisture absorbed and in-vitro diffusion studies. The results of thickness, weight variation and drug content of all the formulation were found to be uniform. The invitro release study confirms that combination of HPMC and eud S100 shows highest drug release as compared to formulations containing HPMC and EC. Based on the above observations, it can be reasonably concluded that HPMC–EC polymers are better suited over HPMC–Eudragit polymers for the development of TDDS of rosiglitazone and the formulation F9 (HPMC: EC, 1:3) may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

ACKNOWLEDGEMENT

Authors are thankful to the Principal and Management TMAE'S S C S college of Pharmacy, Harapanahalli and Maratha Mandal's College of Pharmacy, Belgaum for providing us suitable facility to conduct the work.

REFERENCES

1. Shakeel F, Baboota S, Ahuja A, Ali J, Shafiq S, J. Nanobiotechnol. 2008; 6: 213.
2. Shakeel F, S. Baboota, A. Ahuja, J. Ali, S. Shafiq, J. Drug Target 2008; 1(6): 733.
3. Keith AD Polymeric matrix consideration for transdermal devices, Drug Dev. Ind. Pharm. 1983; 9: 605–621.
4. Chien YW, Development of transdermal drug delivery system, Drug Dev. Ind. Pharm. 1987; 13: 589–651.
5. Misra AN, Transdermal drug delivery in: N.K. Jain (Ed.), Controlled and Novel Drug Delivery, Varghese Publication, New Delhi, 1988, pp. 100–129.
6. Walters KA, Transdermal drug delivery: system design and composition in: K. Swarbrick, J.C. Boylan (Eds.),, Encyclopedia of Pharmaceutial Technology, Marcel Dekker, New York, NY, 1999,pp. 306–320.
7. Reynolds JEF. Martindale-the extra Pharmacopoeia. Director of the Council of Royal Pharmaceutical Society of Great Britain, 2005; 34: 345.
8. McEvoy GK. AHFS Drug Information. Authority of the board of the American Society of the Health-System Pharmacists, 2004, 3055-3058.
9. Chapel Sky C, Thompson-culkin K, A. K. Miller, *et al*. Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insuffi ciency. J. Clin. Pharmacol., 2003; 43: 252-259.
10. James wells. Preformulation preparations. 2nd ed. Edinburgh(London): Churchill Livingston ; 2003.
11. Loganathan V, Senthikumar B, Reddy MVS, Sreekanth N, Ubaidulla U. Compatibility studies between sparfloxacin and tablet excipients through differential scanning calorimetry. Int J Pharm Excip 2003; 2(34):661-64.
12. Raghavendra K, Doddayya H, Marihar SC, Patil CC, Habbu PV. Comparative evaluation of polymeric films for transdermal application. The Eastern Pharmacist 2000; XLIII (513): 109-111.
13. Saxena M, Mutalik S, Reddy MS. Formulation and evaluation of Transdermal patches of metoclopramide hydrochloride. Ind drugs. 2006; 43(9):740-5.
14. Baichwal RW (1983) Advances in drug delivery systems. Bombay: MSR Foundation, pp 136- 47.
15. Sanap GS, Dama GY, Hande AS, Karpe SP, Nalawade SV, Kakade RS. Preparation Transdermal Mo-nolithic Systems of Indapamide by Solvent Casting Method and The Use of Vegetable Oils As Permeation Enhancer. Int J Green Pharmacy. 2008; 2(2): 129-33.
16. Samanta MK, Dube R, Suresh B. Transdermal drug delivery system of Haloperidol to overcome self induced extrapyramidal syndrome. Drug Dev Ind Pharm. 2003; 29(4): 405-415.
17. Lec ST, Yac SH, Kim SW, Berner B. One way membrane for transdermal drug delivery systems / system optimization. Int. J. Pharm. 1991; 77: 231-7.
18. Koteswar UN. Preparation and evaluation of captopril transdermal matrices. Indian Drugs 1992; 29:680-8.
19. Shinde AJ, Kevin C Garala, Harinath N More. Development and characterization of transdermal therapeutics system of tramadol hydrochloride. Asian J pharma. 2008; 2(4) :265-269.
20. Mukherjee B, Mahapatraa S, Guptab R, Patraa B, Tiwarib A, Arora P. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation European Journal of Pharmaceutics and Biopharmaceutics. 2005; 19: 475–483.
21. Udupa N, Pandey N, Praveen SH. Formulation and evaluation of Nimesulide transdermal drug delivery systems. Indian J Pharm Sci. 2000; 62:376-9.
22. Ghosal SK, Bhattacharya M, Mandal SC, In vitro release and permeation kinetics of pentazocaine from matrix dispersion type transdermal drug delivery systems. Drug Dev Ind Pharm 1994; 20:1933-41.
23. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur. J Pharm Sci., 2001; 13: 123–33.
24. Higuchi T.: J. Pharm. Sci.1963; 84: 1464.
25. ICH Q1A (R2), Stability testing guidelines: Stability testing of new drug substances and products. The European agency for the evaluation of medicinal products, 2003; CPMP/ICH/2736/99: 4-20.

Table 1: Formulation of Transdermal systems of Rosiglitazone

Formulation code	Polymer HPMC:EUDS100	Polymer HPMC:EC	Plasticizers	Solvents (1:1)
F1	4:0	–	PG (30%)	Methanol : Dichloromethane
F2	3:1	–	PG (30%)	Methanol : Dichloromethane
F3	1:1	–	PG (30%)	Methanol : Dichloromethane
F4	1:3	–	PG (30%)	Methanol : Dichloromethane
F5	2:3	–	PG (30%)	Methanol : Dichloromethane
F6	3:2	–	PG (30%)	Methanol : Dichloromethane
F7	–	3:1	DBP (30%)	Methanol : Chloroform
F8	–	1:1	DBP (30%)	Methanol : Chloroform
F9	–	1:3	DBP (30%)	Methanol : Chloroform
F10	–	2:3	DBP (30%)	Methanol : Chloroform
F11	–	3:2	DBP (30%)	Methanol : Chloroform

Table 2: Physical evaluation of Rosiglitazone maleate transdermal patches

Formulation code	**Weight Variation (mg)	**Mean Thickness (mm)	*Folding Endurane	*Flatness (%)	*Drug Content (%)
F1	0.0168 ±1.52	0.162±0.05	145 ± 2.13	100 ± 0.03	82.14±0.062
F2	0.0172 ±1.74	0.164±0.01	163 ±4.34	100 ± 0.02	81.42 ± 0.41
F3	0.0175 ±1.54	0.153±0.03	176 ±4.04	99 ± 0.06	89.56 ± 0.62
F4	0.0180 ±2.10	0.149±0.02	152 ± 1.20	100 ± 0.03	78.85 ± 0.73
F5	0.0176 ±1.32	0.144±0.08	192 ±2.54	100 ± 0.2	85.28 ± 0.15
F6	0.0170 ±2.27	0.166±0.01	159 ± 3.11	99± 0.04	83.29 ± 0.85
F7	0.0191 ±1.54	0.142±0.06	126 ± 1.44	100 ± 0.08	83.81 ± 0.27
F8	0.0197 ±1.76	0.161±0.12	140 ± 3.56	99 ± 0.06	86.91 ± 0.33
F9	0.0212 ±2.45	0.157±0.06	156 ± 6.33	100 ± 0.05	78.78 ± 0.59
F10	0.0204 ±2.02	0.148±0.02	149 ± 1.72	100 ± 0.1	81.94 ± 0.72
F11	0.0194 ±1.44	0.158±0.02	138 ± 5.14	100 ±0.01	89.15 ± 0.83

* → Average of five observations
** → Average of three observations

Table 3: Physical evaluation of Rosiglitazone maleate transdermal patches

Formulation Code	*Tensile Strength (kg/cm2)	*Elongation (%)	**Moisture Loss (%)	**Moisture Absorption (%)	
				75% NaCl	93% NH4HPO4
F1	0.386±0.15	42.42±0.24	7 ± 0.22	7.14 ± 0.48	11.30±0.19
F2	0.427±0.17	39.12±0.58	5.52 ±0.86	5.81± 0.16	8.13 ±0.26
F3	0.469±0.28	38.4 ± 0.11	3.55 ±0.21	3.42 ± 0.56	5.71 ± .063
F4	0.732±0.44	34.8 ±0.62	2.85 ±0.36	2.77 ± 0.62	5.11 ±0.41
F5	0.539±0.22	37.33±0.53	4.14 ±0.48	3.40 ± 0.36	6.47 ± 0.81
F6	0.673±0.34	35.65±0.56	3.65 ±0.63	4.11 ± 0.98	6.28 ± 0.75

F7	0.525 ± 0.3	37.18±0.75	4.37 ±0.45	4.18 ± 0.38	4.56 ± 0.17
F8	0.638±0.27	34.52±0.46	3.14 ±0.51	2.53 ± 0.62	3.30 ± 0.76
F9	0.956±0.19	28.31±0.13	2.41 ±0.42	2.35 ± 0.54	4.52 ± 0.43
F10	0.870±0.82	30.43 ±0.5	4.08 ±0.29	2.94 ± 0.31	3.92 ± 0.93
F11	0.592±0.16	36.88±0.71	3.19 ±0.45	3.60 ± 0.27	4.63 ± 0.45

* → Average of five observations
** → Average of three observations

Table 4: Percentage cumulative drug diffused from matrix system of formulation F1 – F6

Time (hrs)	% cumulative drug released					
	F1	F2	F3	F4	F5	F6
1	19.55	18.68	19.05	15.72	16.17	19.57
2	29.85	26.86	23.34	22.27	24.43	25.82
3	37.32	33.22	28.18	27.13	29.50	33.29
4	45.98	42.03	35.08	30.74	33.99	39.71
5	58.68	50.83	39.85	36.24	38.47	47.18
6	65.54	57.37	48.50	45.97	45.13	52.85
7	74.20	64.35	56.92	52.55	54.68	60.48
8	79.44	73.15	61.76	56.79	60.17	66.75
9	84.07	78.31	68.11	64.01	65.15	73.61
10	88.70	83.01	74.06	68.88	69.72	78.24
11	90.94	86.50	78.76	72.03	74.64	81.67
12	93.77	88.94	82.49	75.63	79.12	84.67

Table 5: Percentage cumulative drug diffused from matrix system of formulation F7 – F11

Time	% cumulative drug release				
	F7	F8	F9	F10	F11
1	18.56	16.48	14.17	16.80	17.34
2	26.82	24.07	21.15	21.51	25.06
3	34.65	32.03	29.74	30.71	33.27
4	41.29	39.19	35.66	38.52	40.10
5	50.4	47.14	40.98	44.79	48.86
6	56.95	52.27	45.52	50.82	54.46
7	63.49	59.21	50.23	57.48	61.78
8	68.48	64.56	56.76	62.53	66.60
9	75.39	69.92	60.25	67.35	71.17
10	78.46	74.06	66.01	72.58	76.58
11	82.15	77.34	69.67	74.81	79.87
12	85.53	80.76	72.21	77.64	82.38

Table 6: Comparative kinetic values of drug release from transdermal matrix Systems of formulation F1 – F11

Formulation code	Higuchi equation	Zero order equation	First order equation	Peppas equation	
	R^2	R^2	R^2	R^2	N
F1	0.990	0.956	0.990	0.994	0.664
F2	0.989	0.971	0.980	0.992	0.669
F3	0.971	0.984	0.983	0.967	0.652
F4	0.976	0.983	0.987	0.979	0.631
F5	0.971	0.986	0.973	0.976	0.657
F6	0.988	0.973	0.981	0.987	0.646
F7	0.994	0.964	0.990	0.995	0.643
F8	0.995	0.968	0.994	0.995	0.665
F9	0.993	0.976	0.991	0.998	0.671
F10	0.994	0.968	0.996	0.990	0.665
F11	0.992	0.965	0.994	0.996	0.657

Table 7: Percentage drug present in Rosiglitazone patches at 40 ºC/ 75 % RH for 3 months

Formulation Code	Time (months)			
	0 month	1 month	2 month	3 month
F1	82.14	81.57	80.34	79.09
F2	81.42	80.64	79.48	78.32
F3	89.56	88.62	87.29	86.58
F4	78.85	77.53	76.44	75.61
F5	85.28	84.35	83.59	82.15
F6	83.29	82.24	81.38	79.95
F7	83.81	82.93	81.29	80.16
F8	86.91	86.06	85.11	83.87
F9	78.78	77.61	76.52	75.33
F10	81.94	80.15	79.26	78.08
F11	89.15	87.71	86.42	85.90

*Each reading is an average of three determinations

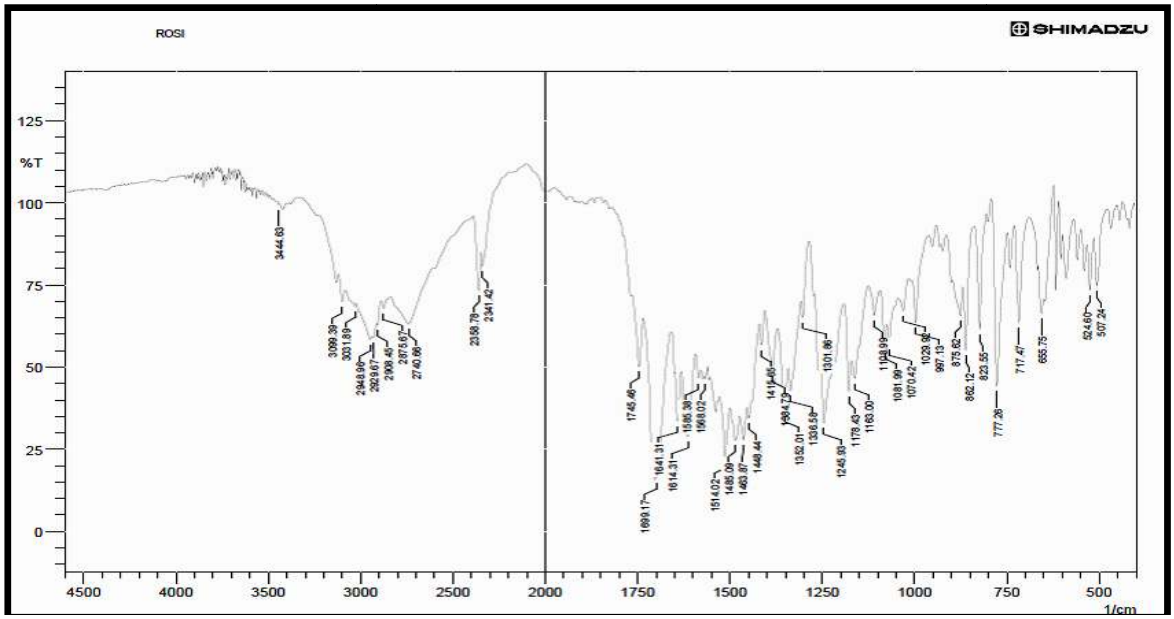

Fig. 1: FT-IR spectrum of pure Rosiglitazone

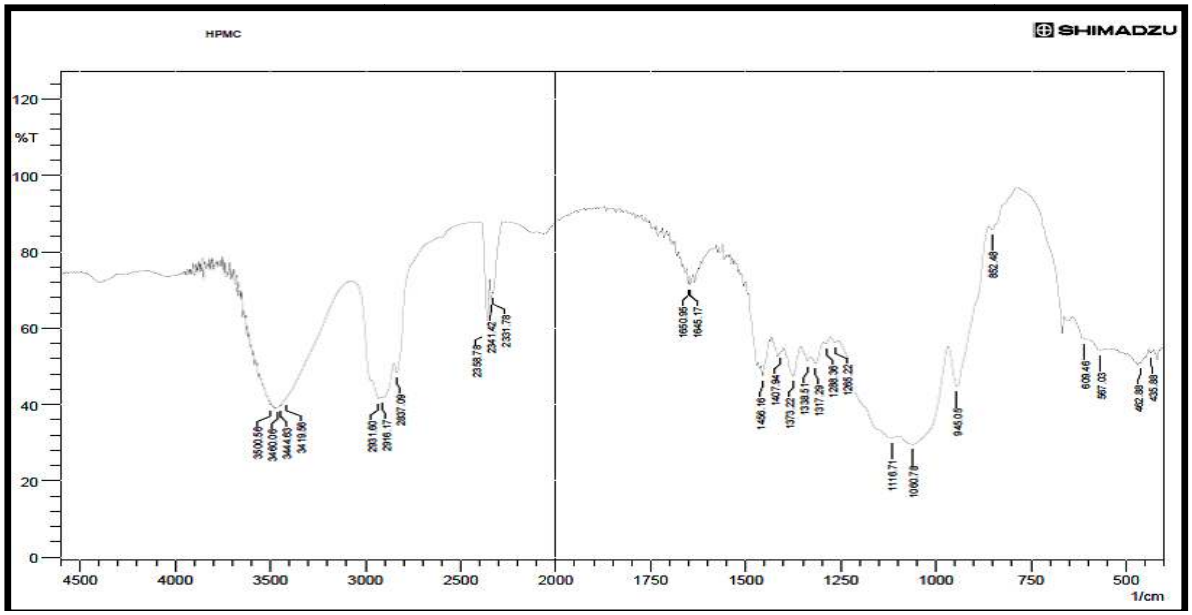

Fig. 2: FT-IR spectrum of pure Hydroxy propyl methyl cellulose

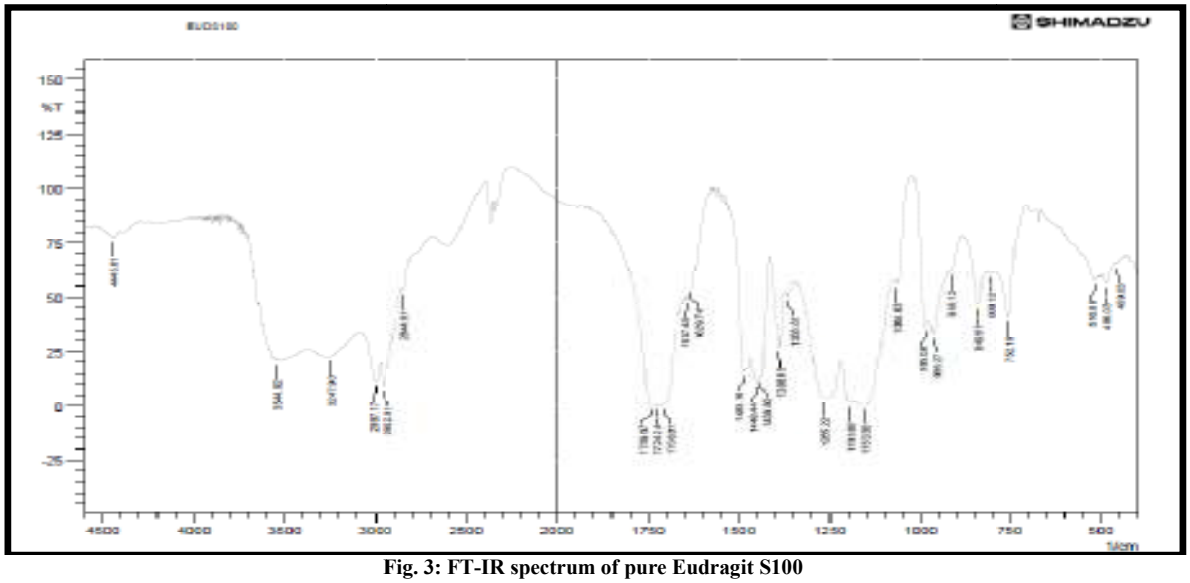

Fig. 3: FT-IR spectrum of pure Eudragit S100

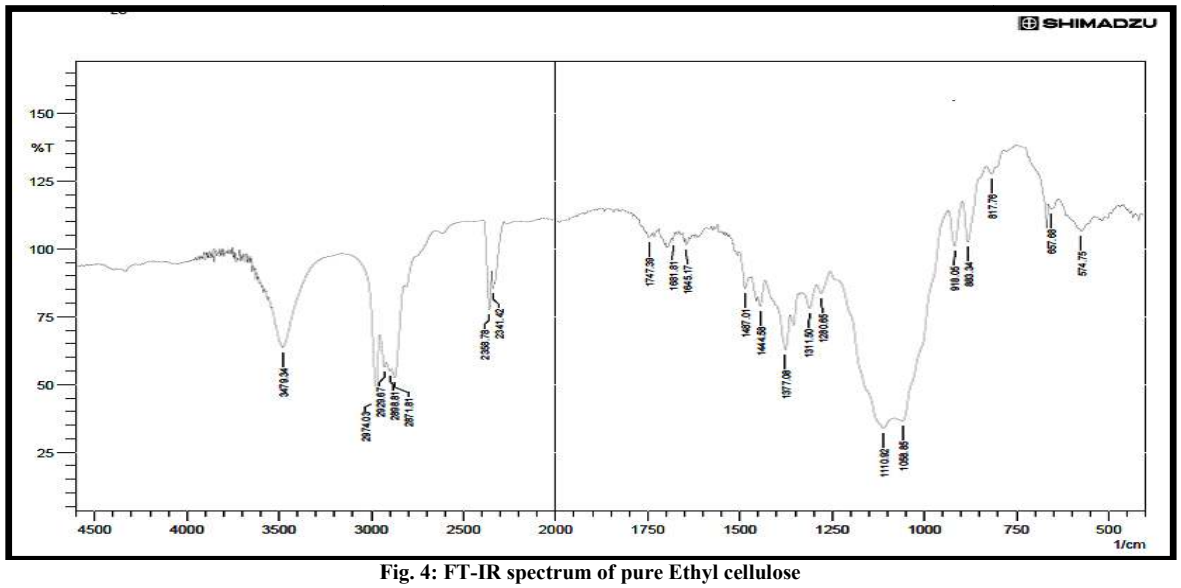

Fig. 4: FT-IR spectrum of pure Ethyl cellulose

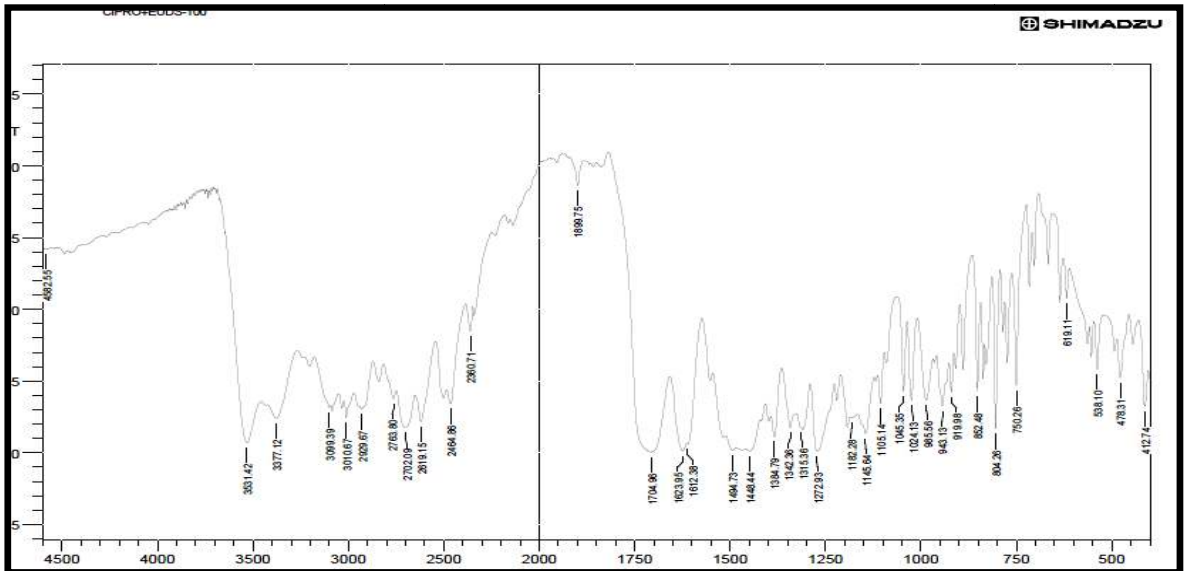

Fig. 5: FT-IR spectrum of physical mixture of Rosiglitazone, HPMC and EUD S100

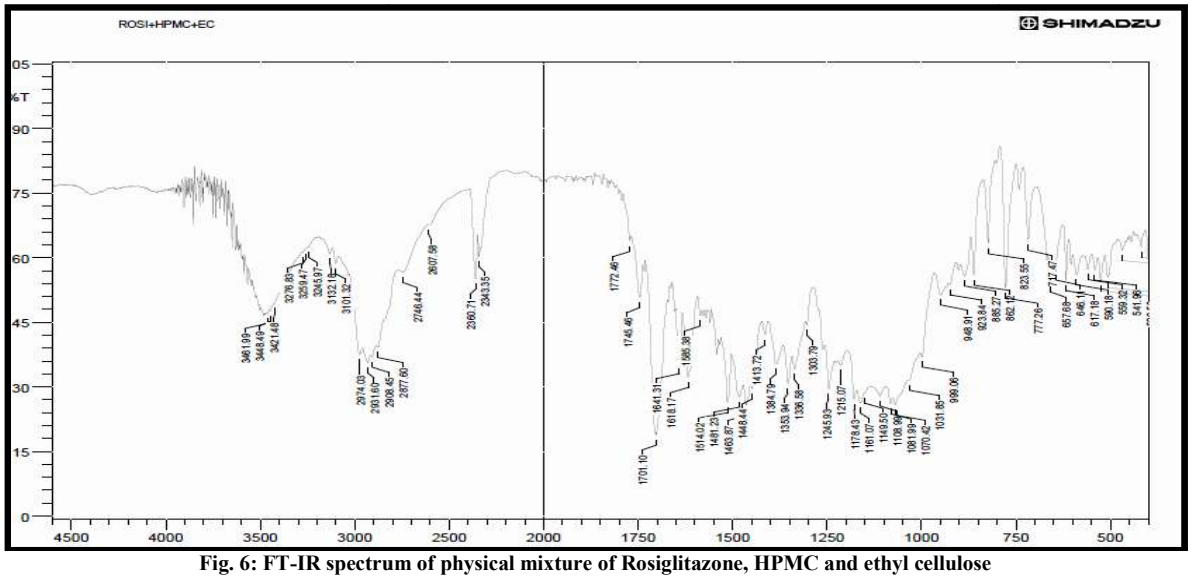

Fig. 6: FT-IR spectrum of physical mixture of Rosiglitazone, HPMC and ethyl cellulose

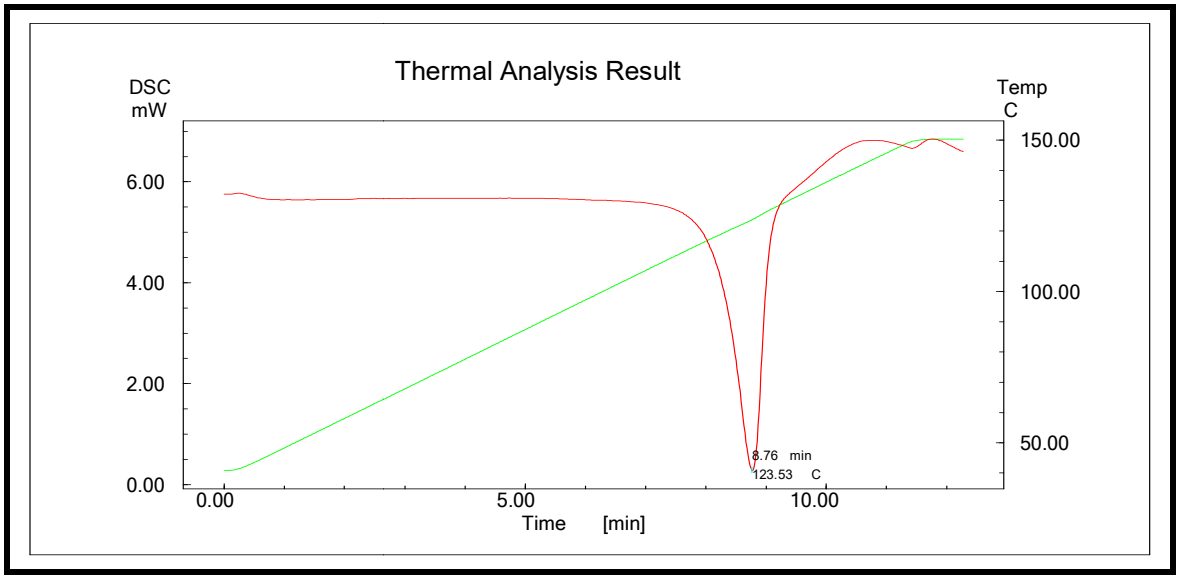

Fig. 7: Differential scanning calorimetry spectrum of pure Rosiglitazone

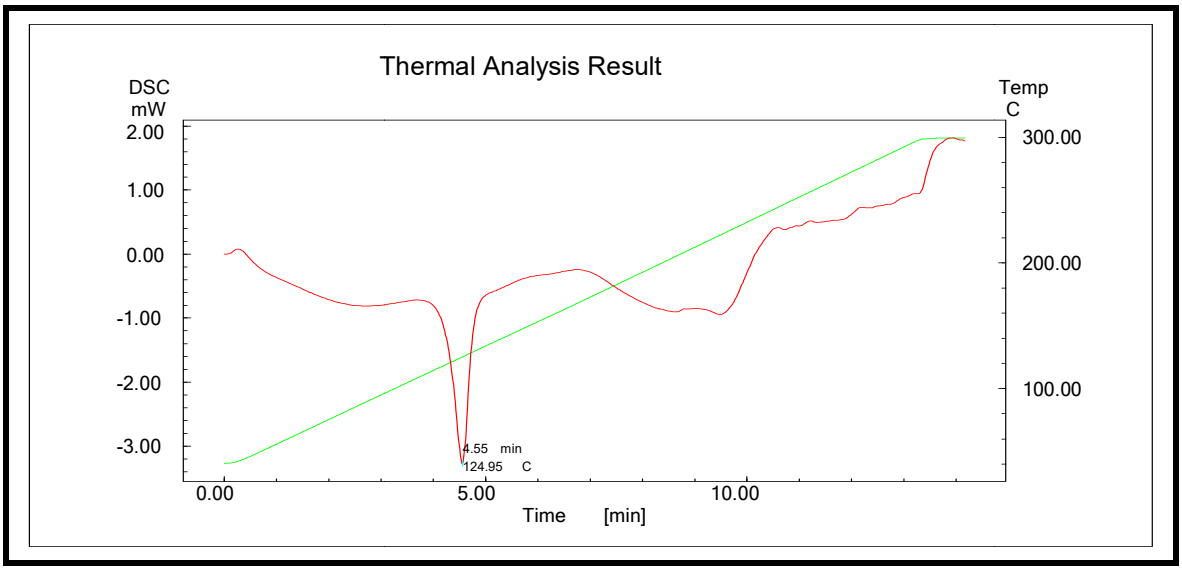

Fig. 8: Differential scanning calorimetry spectrum of physical mixture of Rosiglitazone, HPMC and EUD S100

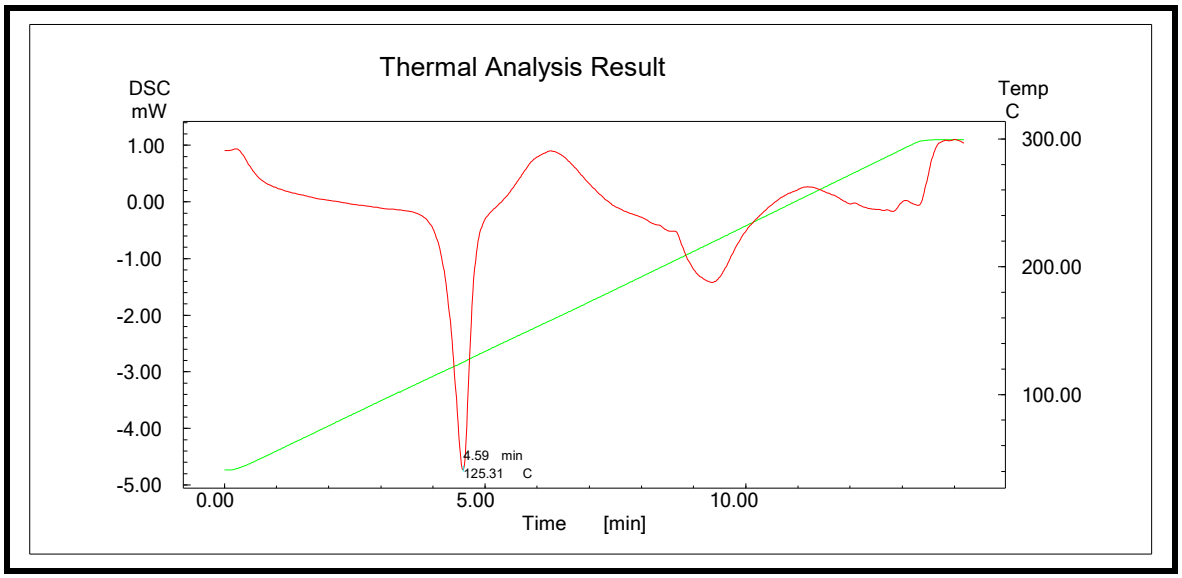

Fig. 9: Differential scanning calorimetry spectrum of physical mixture of Rosiglitazone, HPMC and Ethyl cellulose

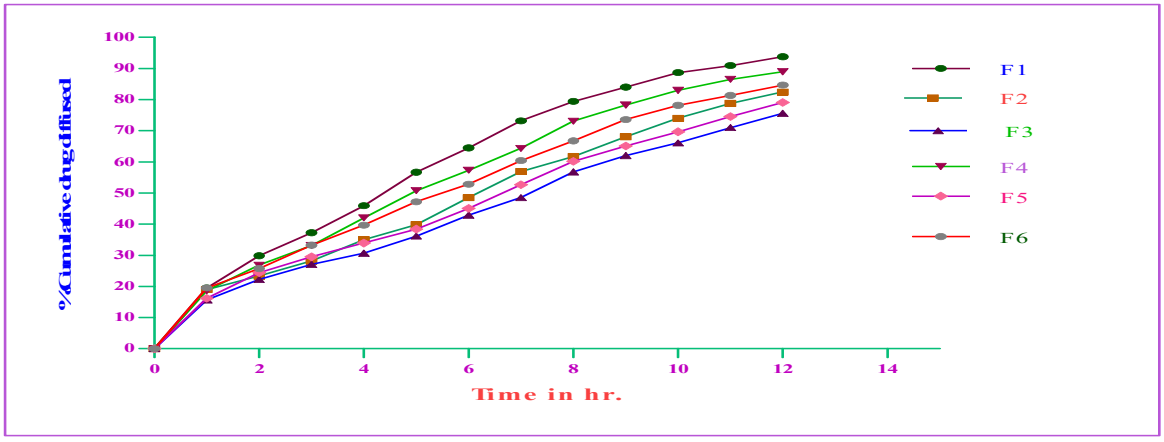

Fig. 10: Percentage cumulative drug diffused from formulation F1 –F6

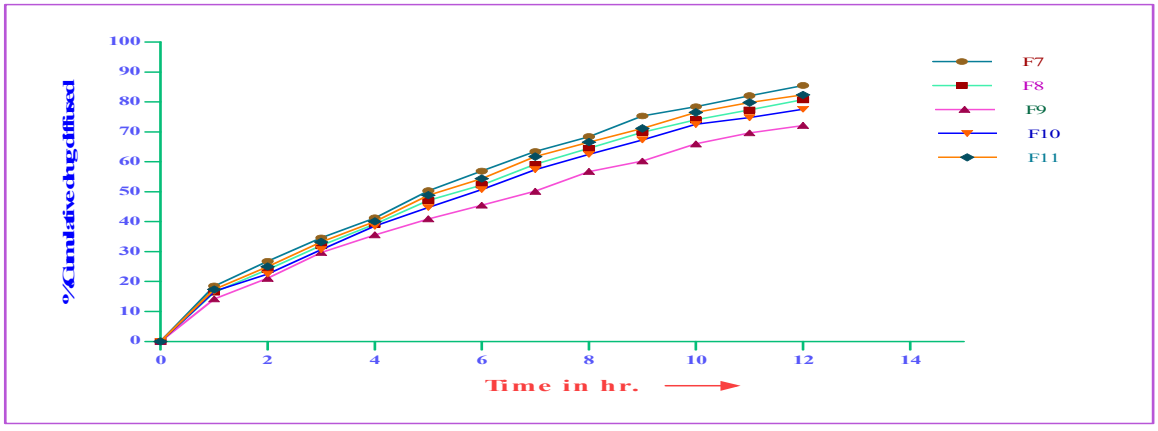

Fig. 11: Percentage cumulative drug diffused from formulation F7 – F11

Source of support: Nil, Conflict of interest: None Declared