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FORMULATION AND EVALUATION OF REPAGLINIDE PATCHES FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increases the bioavailability. Repaglinide is an Anti-Diabetic drug with a shorter half-life (1 hr), low bioavailability (56 %) undergoes extensive first pass metabolism are required to maintain the therapeutic level it has chosen as transdermal drug delivery system. The present study was to formulate and evaluate transdermal drug delivery system of Repaglinide using polymers such as HPMC & Eudragit RLPO by solvent casting technique. The prepared formulations were evaluated for different physicochemical characteristics like Weight Variation, Folding Endurance, Flatness, pH of patches, % Moisture Content, % Moisture uptake, % Elongation, % Drug Content & % Drug Release. The drug release characteristics of the formulation were studied *in-vitro* by using artificial semi-permeable membrane. The *in-vitro* drug release plot has shown that the drug release followed zero order kinetics & Higuchi model, which was evidenced from the regression values. Based on the drug release and physicochemical values obtained from the formulation F_2 is considered as an optimized formulation which shows higher percentage of drug release (98.20±0.27 % at 14 hour) with diffusion mediated mechanism.

KEYWORDS: **Repaglinide, Transdermal Patches, Transdermal Drug Delivery, Solvent Evaporation Technique & Anti- Diabetic Patches**

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INTRODUCTION

The advantages of transdermal drug delivery system (TDDS) include the control of drug release, prolongation of steady-state plasma concentration with much less peak-and-trough variation, improving the safety and patient convenience.[1] Intensive research has showed that transdermal route is a potential mode of delivery of lipophillic drugs in the systemic circulation . Matrix based transdermal formulations have been developed for a number of drugs such as Nitroglycerine and Ephedrine. [2] Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged illness and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance.[3] Repaglinide, a carbamoylmethyl benzoic acid derivative, is the first of a new class of oral antidiabetic agents designed to normalise postprandial glucose excursions in patients with Type 2 Diabetes Mellitus. Like the Sulphonylureas, Repaglinide acts by stimulating release of insulin from the β-cells of the pancreas. Repaglinide is rapidly and completely absorbed, with maximum plasma concentrations (Cmax) occurring aproximatly within an hour after oral administration.It possesses low oral bioavailability (56%) due to hepatic first pass metabolism after oral administration and has a short biological half life of 1h which makes frequent dosing 0.5 to 4 mg in 3 to 4 times in a day necessary to maintain the drug within the therapeutic blood levels for long periods. It has melting point of 130-131^0 C, short half life (1 hr), Mol. wt. 452.58[4] and lipophilicity log P value 3.97 [5]. Hence, Repaglinide is an ideal drug candidate for transdermal drug delivery. The purpose of the present work was to develop transdermal formulation of Repaglinide which increases the patient compliance and also sustain the release of drug to improve the bioavailability by using Eudragit RLPO & HPMC as polymer.

MATERIALS & METHODS

MATERIALS

Repaglinide was obtained as a gift sample from USV Limited(Khed, Ratnagiri, Maharashtra, India), HPMC K100M from Colorcon Asia Pvt. Ltd., (Goa, India). Eudragit RLPO(ERLPO) from Evonik India Pvt. Ltd(Mumbai, India), Propylene Glycol & Polyethylene Glycol(PEG)-400 from Nulife Pharmaceutical, (Pune, India), Double Distilled water was used throughout the study & all other chemicals and solvents were analytical reagent grade and purchased from commercial suppliers. The results obtained were analyzed for various pharmacokinetic parameters using pk functions of Microsoft excel.

METHODS

Drug–Polymer Interaction Studies

To search the possible interaction between Repaglinide and polymeric materials of the patches, infrared (IR) spectra of pure substances and their formulation (F_2) were recorded using IR Spectrophotometer (FTIR-4100 JASCO- Japan) by KBr pellet method. [6, 7]

Preparation of Transdermal Patches

Repaglinide loaded transdermal patches containing different ratios of HPMC K100M and Eudragit RLPO were prepared by solvent casting method. The requisite ratios of polymers were weighed and were allowed to swell for 6 h in Methanol–Dichloromethane (1:1) solvent mixture. Plasticizer such as PEG-400 & Permeation enhancer such as Propylene glycol was incorporated at 20% w/w of polymer dry weight. Calculated amount of Repaglinide was mixed with homogenous polymer solution and poured into aluminum foil wrapped glass ring as mold (28.26 cm^2). A funnel was placed over the mould in inverted position to control the rate of evaporation. The casting solvent mixture was allowed to evaporate overnight at room temperature. The dried patches were cut into required size (3.14 cm^2) and wrapped in aluminum foil. Then, these Patches were kept in desiccator containing saturated solution of $CaCl_2$ as desiccant, at room temperature prior to use.[8-9]

Experimental Design

A response surface type Central Composite Design was employed using Design-Expert Software (Version 7.0.0 Stat-Ease Inc., Minneapolis, USA). Independent factors are HPMC K100M (X1) and Eudragit RLPO (X2) concentrations at three levels.[10-11] Weight Variation, Folding Endurance, Flatness, pH of patches, % Moisture Content, % Moisture uptake, % Elongation, % Drug Content & % Drug Release after 14 hours were kept as dependent variables.[10-11] The different formulations of Repaglinide Transdermal Patches is as shown in Table-1.

Table 1

Different formulation batches are as follows

Code	Drug	Polymer		Plasticizers	Enhancers	Name of Solvents	Quantity
	Repaglinide	HPMC K100M	ERLPO	PEG-400	Propylene Glycol	DCM: Methanol	
F_1	90.00 mg	250.00 mg	600.00 mg	20 % w/w	20 % w/w	1:1	15 ml
F_2	90.00 mg	200.00 mg	237.87 mg	20 % w/w	20 % w/w	1:1	15 ml
F_3	90.00 mg	250.00 mg	300.00 mg	20 % w/w	20 % w/w	1:1	15 ml
F_4	90.00 mg	150.00 mg	300.00 mg	20 % w/w	20 % w/w	1:1	15 ml
F_5	90.00 mg	150.00 mg	600.00 mg	20 % w/w	20 % w/w	1:1	15 ml
F_6	90.00 mg	129.29 mg	450.00 mg	20 % w/w	20 % w/w	1:1	15 ml
F_7	90.00 mg	200.00 mg	662.13 mg	20 % w/w	20 % w/w	1:1	15 ml
F_8	90.00 mg	270.71 mg	450.00 mg	20 % w/w	20 % w/w	1:1	15 ml
F_9	90.00 mg	200.00 mg	450.00 mg	20 % w/w	20 % w/w	1:1	15 ml

Note: 3.14 CM^2 Patch Contains 10 mg Repaglinide. DCM: Dichloromethane

Evaluation of Transdermal Patches

Weight Variation

Prepared patches were cut into 3.14 cm^2 pieces and weight of each patch was determined by using digital balance. The average weight of each patch and standard deviations were calculated.[12-13]

Folding Endurance

A strip of Patch of specific surface area (2 cm^2) was cut and folded repeatedly at one place till it broke. The number of times the patch was folded before breaking at the same place represented folding endurance.[14-15]

Flatness

Longitudinal strips were cut out from the prepared patch, the length of each strip was measured, and then variation in the length due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips, and a 0% constriction was considered to be 100% flatness.[16-17]

$$\text{Constriction (\%)} = L_1 - L_2 / L_1 \times 100$$

Where, L_1 = Initial length of each strips and L_2 = Final length of each strips.

Surface pH

For the determination of surface pH three patches of each formulation were allowed to swell for 2 hrs in a petri dish containing 5 ml of phosphate buffer pH 7.4.[18] The surface pH was measured by pH paper placed on the surface of patches and allowed to equilibrate for 1 min. The average of the three readings was recorded.[19]

Percentage of Moisture Content

The prepared patches were weighed and kept in desiccator containing activated silica at room temperature for 24 h**.** The individual patches were weighed on every alternate day until a constant weight was achieved. The percentage of moisture content was calculated by determining the difference between initial and final weight with respect to final weight.[20-22]

$$\text{Moisture Content (\%)} = W_1 - W_2 / W_2 \times 100$$

Where, W_1 = Initial weight of each patch and W_2 = Final weight of each patch.

Moisture Uptake

Repaglinide Transdermal patches were weighed and placed in desiccators containing a saturated solution of sodium chloride at 74% relative humidity (RH). After first week, the patches were taken out and weighed. The percentage of Water Absorptive Capacity (Moisture Uptake) was calculated as the difference between the final and initial weight with respect to the initial weight.[23-24]

$$\text{Moisture Uptake (\%)} = W_2 - W_1 / W_1 \times 100$$

Where, W_1 = Initial weight of each patch and W_2 = Final weight of each patch

Percentage of Elongation

Elongation of the Patches was determined by Texture Analyzer (Brookfield-CT3-10KG). Rectangular strips of 40mm × 30mm were fixed in such a way that the length of patch between the jaws. The percentage elongation was determined by noting the length just before the break point and substituted in the following Equation.[25-26]

$$\text{Elongation (\%)} = L_1 - L_2 / L_2 \times 100$$

Where, L_1 = Final length of each strips and L_2 = Initial length of each strips.

Determination of Drug Content

Formulated drug-loaded Patches were evaluated for uniformity of drug content. Strips of 3.14 cm^2 from each formulation were randomly selected and transferred into a100 ml volumetric flask containing pH 7.4 phosphate buffer and Methanol. The flask was stirred for 4 h on magnetic stirrer.[27] a blank was similarly prepared using a drug-free Patch. The obtained solutions were filtered through a 0.45 µm membrane. The drug content was then determined after proper dilution by UV spectrophotometer at 246 nm (JASCO V-630, Japan).[28]

In Vitro Drug Release Study

Drug release studies were performed with freshly prepared patches in Franz diffusion cells with volume of 27 ml and a diffusion area of 4.90 cm^2. The receptor compartment contained pH 7.4 Phosphate Buffer at 37 ^{0}C (corresponding to 32 ^{0}C at the release interface) and was stirred at 50 rpm with a magnetic stirrer. Circular patches (diameter: 2.00 cm, patch thickness: approximately 0.25 mm to 0.27 mm) were centrally attached to circular piece of cellulose acetate membrane with a diameter of 2.5 cm. The cellulose acetate membrane was mounted between the donor and receptor compartment of the diffusion cell. The 1 ml samples were withdrawn at different time intervals and an equal amount of phosphate buffer, pH 7.4 was replaced each time. Absorbance of the samples were measured spectrophotometrically at 246 nm taking phosphate buffer solution, pH 7.4, as blank The experiment was performed in triplicates and the mean values were calculated.[29-32]

RESULT AND DISCUSSION

Drug–Polymer Interaction Studies

The incompatibility between the Drug and Excipients were studied by FTIR spectroscopy. The spectral data of pure Repaglinide, HPMC, ERLPO and Repaglinide Transdermal Patch (F_2) are presented in Fig.01-04. The results indicate that there was no chemical incompatibility between drug and excipients used in formulation.

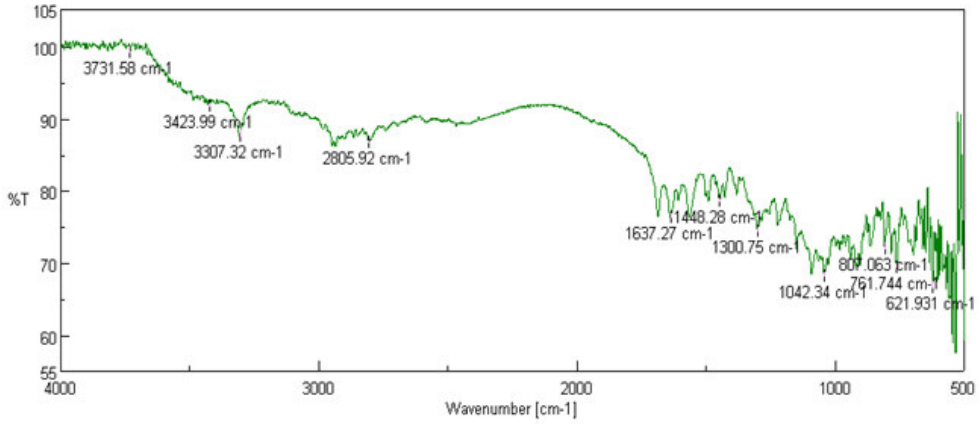

Figure 1
FTIR spectra of Repaglinide

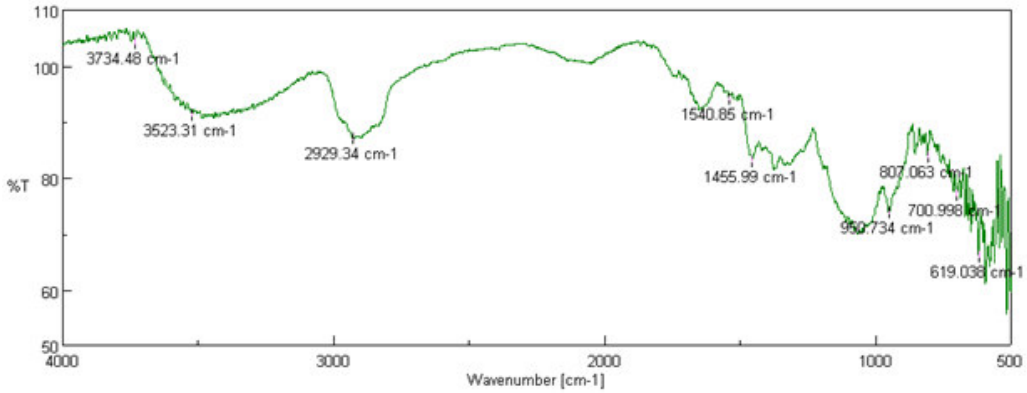

Figure 2
FTIR spectra of HPMC K100M

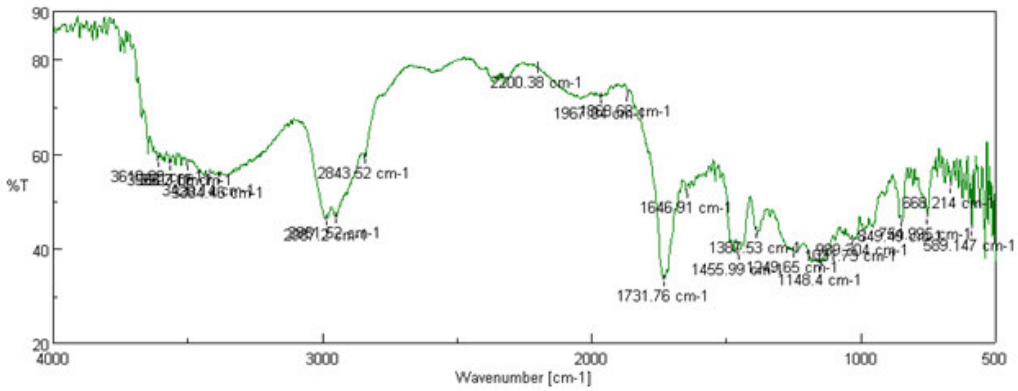

Figure 3
FTIR spectra of Eudragit RLPO

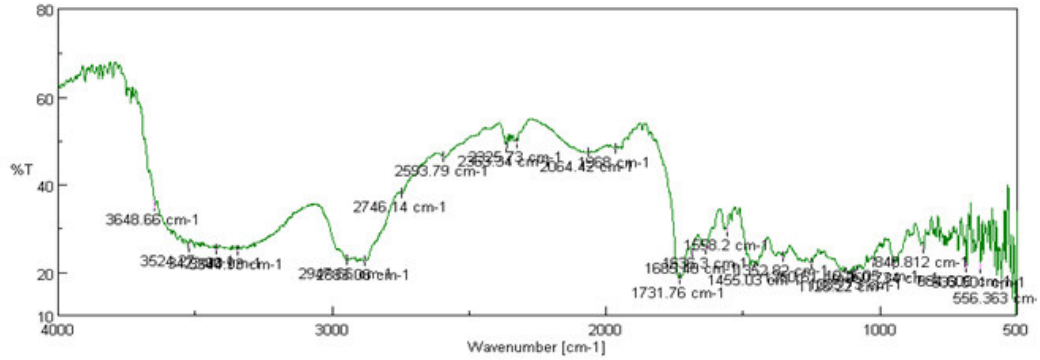

Figure 4
FTIR spectra of Repaglinide Transdermal Patch (F_2)

Weight Variation

The weight of patches ranged between 102 ± 0.577 mg and 115 ± 1.528 mg, which is found relatively similar with different batches of formulations. A slight variation in the weights of patches was observed within the formulation of same batch which is indicated by the low standard deviation values. The average weight of the Patches increased with increased concentration of the polymers used in producing the Patches as shown in Table 2.[33]

Folding Endurance

The values of folding endurance were found to vary from 285 ± 4.509 to 325 ± 5.132 which indicates good strength and elasticity. The folding endurance test results (Table2) showed that the Patches prepared from all formulations which shows that transdermal patches were more flexible and durable. These results demonstrated the sturdiness of the patches in maintaining their integrity with general skin folding when applied.

Table 2
Physicochemical Properties of Repaglinide Transdermal Patches*

Formulation	Weight Variation(mg)	Folding Endurance	Flatness (%)	Surface pH	MC (%)	MU (%)	Elongation (%)	Drug Content (%)
F_1	114±1.000	322±6.658	99.16±1.44	6.33±0.57	6.99±0.15	12.95±0.21	60.74±3.39	99.07±0.18
F_2	102±0.577	285±4.509	99.08±1.37	5.66±0.57	5.09±0.07	8.35±0.50	31.85±3.39	98.94±0.28
F_3	109±1.000	301±5.568	100.08±0.14	5.96±0.05	6.50±0.12	11.75±0.50	37.77±2.22	98.50±0.18
F_4	105±1.000	294±4.000	99.91±0.14	6.33±0.57	4.47±0.06	7.29±0.15	42.96±3.39	98.75±0.57
F_5	113±0.577	321±3.606	99.08±1.37	6.33±0.57	4.70±0.17	7.71±0.12	57.03±3.39	99.19±0.38
F_6	108±1.000	306±4.726	100.00±0.00	6.00±1.00	4.18±0.21	6.53±0.34	54.07±1.28	98.32±0.18
F_7	115±1.000	325±5.132	100.08±0.14	5.66±0.57	6.28±0.25	10.57±0.51	62.96±3.39	98.01±0.28
F_8	112±0.577	316±6.000	100.00±0.00	5.33±0.57	7.262±0.23	14.54±0.22	48.88±4.44	98.44±0.60
F_9	111±1.528	313±5.686	99.91±0.14	5.66±0.57	5.62±0.24	9.28±0.16	52.59±3.39	99.13±0.28

***All values are expressed as mean ± SD (n = 3). MC: Moisture content & MU: Moisture uptake**

Flatness

Flatness (%) of the patch formulations were found satisfactory, which ranged between 99.08 ± 1.37 and 100.08 ± 0.14 % (Table 2. The results of the flatness study showed that the formulation Patches have a negligible change in the length, indicating a near 100% flatness. The patches from all tested formulations appeared to have a smooth, flat surface that could be maintained when the patch is applied to the skin without any visible signs of constriction.[16, 34]

Surface pH

For a dermatological preparation to be safe and nonirritant its pH must be between 4 and 7.[35]Surface pH was mainly done to know whether the patch is acidic or basic. Irritation will persist if the Patch is more acidic or basic. Surface pH of the transdermal patches was in between 5.33±0.57 and 6.33±0.57 (Table 2) which match to the pH of the skin, infers that the patch is nonirritant & desirable property.[36]

Moisture Content & Moisture uptake

Moisture content and moisture uptake studies provide information regarding stability of the formulation.[37]The % moisture content in the patches ranged from 4.18±0.21 to 7.262±0.23. The % moisture uptake in the formulations was in the range of 6.53±0.34 to 14.54±0.22 (Table2). The results revealed that the moisture content and moisture uptake were found to increase with increasing concentration of hydrophilic polymer (HPMC).[38]The low level of moisture content in the formulation helps them to remain stable and from being a completely dried and brittle Patches and low moisture uptake protects the material from microbial contamination and bulkiness of the patches.[39]

Percentage of Elongation

Percentage Elongation at break of the formulations prepared from combination HPMC K100M & ERLPO at different ratios which ranged between 31.85±3.39 % to 62.96±3.39 % (Table 2). The prepared patches were also found to be strong enough & provide good mechanical properties. It was also observed that the percentage elongation at break values increased with increasing concentration of ERLPO polymer.[14, 25, 40]

Drug Content

The drug content (%) in all prepared formulations varied between the range 98.01±0.28 % to 99.19±0.38 %. Uniformity of drug distribution throughout the patch was proved by the low value of SD (Table 2). This indicates the uniform reproducible drug release from the patch.[28]

In Vitro Drug Release

The *in vitro* drug release pattern of Repaglinide from formulated transdermal patches is shown in Fig. : 04-08. All these transdermal patches slowly released the drug, incorporated and sustained over a period of 14 h. The drug release from transdermal patches varied with respect to the polymer composition and nature. An increase in drug release from the transdermal patches was found with increasing concentration of polymers that are more hydrophilic in nature.[41-42] Among all formulations, the maximum *in vitro* drug release (98.20±0.27 %) over a period of 14 h was observed in the case of formulation No. F_2, while the minimum i*n vitro* drug release (74.05±0.66 %) was found in the case of formulation No. F_7 which shows that the concentration of Eudragit RLPO increases and decreases the drug release. The *in vitro* drug release was more sustained for the Repaglinide transdermal patches which were composed with high proportion of ERLPO. In order to predict and correlate the release behavior of Repaglinide from different patches, it is necessary to fit into a suitable kinetic model. The *in vitro* Repaglinide release data from transdermal patches were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Koresmeyer–Peppas. The results of curve fitting into these models (Figure: 04-08) indicates the drug release behavior from these patches of Repaglinide (Table3). When the release rate of Repaglinide and their respective correlation coefficients were compared, it was found to followed zero-order kinetic (R^2=0.996 to 0.999) and Higuchi models (R^2=0.9996 to 0.999) (Table3). In order to understand the mechanism of drug release, *in vitro* release data were treated to kinetic models and linearity was observed with respect to zero-order kinetic & Higuchi equation. As indicated by higher values R^2, the drug release from all the formulations follows Zero-order drug release and Higuchi model with sustained release diffusion mediated mechanism

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Table 3
***In Vitro* drug Release of Repaglinide Transdermal Patches**

Formulation	% Drug Release after 14 hrs*	R^2			
		Zero Order	First Order	Higuchi	Peppas
F_1	78.05±0.19	0.997	0.938	0.997	0.762
F_2	98.20±0.27	0.999	0.801	0.999	0.743
F_3	95.67±0.31	0.996	0.841	0.996	0.764
F_4	93.48±0.88	0.998	0.876	0.998	0.761
F_5	81.28±0.77	0.999	0.940	0.999	0.766
F_6	85.24±0.56	0.999	0.935	0.999	0.756
F_7	74.05±0.66	0.999	0.964	0.999	0.766
F_8	90.87±0.44	0.999	0.900	0.999	0.752
F_9	87.26±0.69	0.999	0.927	0.999	0.750

***All values are expressed as mean ± SD (n = 3).**

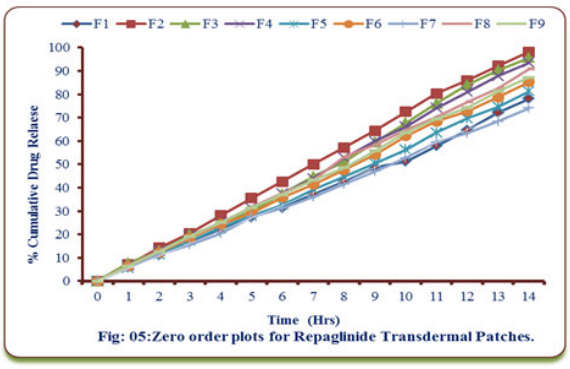

Figure 5
Zero order plots for Prepared Repaglinide Transdermal Patches(F_1-F_9)

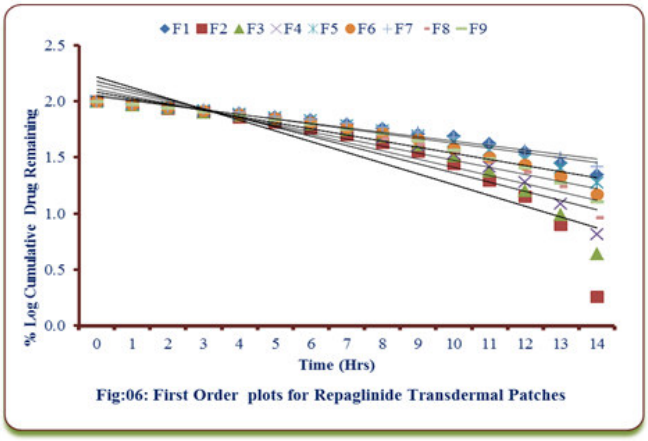

Figure 6
First order plots for Prepared Repaglinide Transdermal Patches (F_1-F_9)

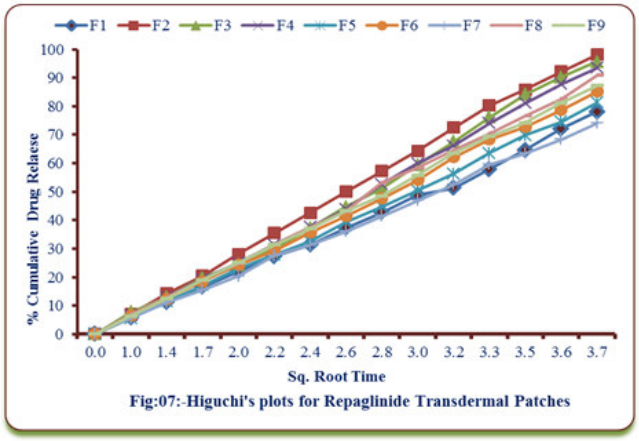

Figure 7
Higuchi's plots for Prepared Repaglinide Transdermal Patches (F_1-F_9)

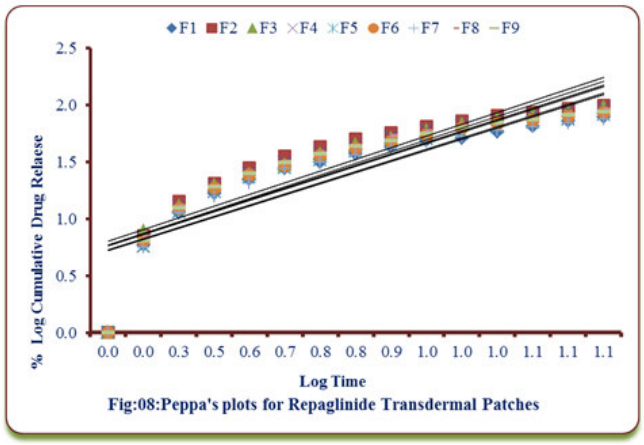

Figure 8
Korsmeyer- Peppa's Plots for Prepared Repaglinide Transdermal Patches (F_1-F_9)

CONCLUSION

Transdermal patches of Repaglinide using polymers like HPMC and ERLPO in various proportions and combinations showed satisfactory physicochemical characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated Repaglinide transdermal patches. From the present investigation, it can be concluded that such transdermal patches of Repaglinide may provide sustained transdermal delivery for prolonged periods in the therapy of Diabetics, which can be a good way to bypass the extensive hepatic first-pass metabolism & HPMC and ERLPO of moderate level useful for preparation of sustained release matrix transdermal patch formulation. Further, from the above finding it can be concluded that formulation F_2 is the best formulation which is substantiated by its higher in *vitro* drug release.

CONFLICT OF INTEREST

Conflict of interest declared none.

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