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Formulation Development and Evaluation of Rosiglitazone Maleate Sustained Release Tablets using 3^2 Factorial Design

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Abstract: The main objective of present investigation is to formulate the sustained release tablet of Rosiglitazone Maleate using $\mathbf{3^2}$ factorial design. Rosiglitazone Maleate, an oral anti-diabetic agent. The SR tablets of Rosiglitazone Maleate were prepared employing different concentrations of HPMCK15M and Carboplol934P in different combinations as a rate retardants by Direct Compression technique using 3^2 factorial design. The quantity/ concentration of Polymers , HPMCK15M and Carboplol934P required to achieve the desired drug release was selected as independent variables, X_1 and X_2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) were selected as dependent variables. Totally nine formulations were designed and are evaluated for hardness, friability, thickness, % drug content, *In-vitro* drug release. From the Results it was concluded that all the formulation were found to be with in the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for $\mathbf{t_{10\%}, t_{50\%}, t_{75\%}, t_{90\%}}$. Validity of developed polynomial equations were verified by designing 2 check point formulations(C_1, C_2). According to SUPAC guidelines the formulation (F_5) containing combination of 25% HPMCK15M and 20% Carboplol934P, is the most similar formulation (similarity factor f_2=93.1376, dissimilarity factor f_1= 1.7642 & No significant difference, t= 0.06949) to marketed product (**AVANDIA**). The selected formulation (F_5) follows Higuchi's kinetics, and the mechanism of drug release was found to be Fickian Diffusion (n= 0.417).

Keywords: Rosiglitazone Maleate, $\mathbf{3^2}$Factorial Design, Sustained Release Tablet, HPMCK15M , Carbopol934P, SUPAC, Fickian Diffusion Mechanism, Zero order kinetics.

Introduction

Oral administration is the most convenient, widely used route for both conventional and novel drug delivery systems, and preferred route of drug delivery for systemic action. Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. There are many reasons for this, not the least of which would include acceptance by the patient and ease of administration . In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages[1]. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism as a result of which low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites[2].

Sustained release (SR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs[1].

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, the goal in the designing sustained / controlled drug delivery system is to reduce the dosing frequency or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery[3].

Sustained release dosage forms may be defined as any drug or dosage form modification that prolonged but not necessarily uniform release of drug. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from the dosage form. Zero-order release constitutes the drug release from the dosage form that is independent of the amount of drug in the delivery system (i. e., constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i. e., concentration dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery[4,5].

Sustained release tablet allowing a 2 fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a Prompt release dosage form[6,7]. Sustained release products provide advantage over Immediate release dosage form by optimising biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration[8,9].

Oral controlled drug delivery system represents one of the frontier areas of drug delivery system in order to fulfill the need for a long-term treatment with anti-HIV agents, anti-Diabetics(Oral Hypoglycaemics))[10]. Among the different controlled drug delivery (CDD) systems, matrix based controlled release tablet formulations are the most popularly preferred for its convenience to formulate a cost effective manufacturing technology in commercial scale. Development of oral controlled release matrix tablets containing water-soluble drug has always been a challenging because of dose dumping due to improper formulation resulting in plasma fluctuation and accumulation of toxic concentration of drug(Peak-Valley Concentration)[11]. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Over many years, numerous studies have been reported in the literature on the application of hydrophilic polymers in the development of controlled release matrix systems for various drugs [12,13,14].

Since the early 1950s, the application of polymeric materials for medical purposes is growing very fast. Polymers have been used in the medical field for a large extent [15]. Natural polymers remain attractive primarily because they are inexpensive, readily available, be capable of chemical modifications, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal stability and easy of compression [16]. This led to its application as excipient in hydrophilic drug delivery system. The various natural gums and mucilages have been examined as polymers for sustained drug release in the last few decades for example; guar gum, tragacanth gum, xanthan gum, pectin, alginates etc. In the development of a sustained release tablet dosage form. Availability of wide variety of polymer and frequent dosing interval helps the scientist to develop sustained release product. cellulose derivatives such as carboxymethyl cellulose (CMC), sodium carboxymethyl cellulose, hydroxyproyl cellulose (HPC), and hydroxypropyl methyl cellulose (HPMC) have been extensively studied as polymer in the controlled release tablet formulations[17]. These polymers are most preferred because of its cost effectiveness, broad regulatory acceptance, non-toxic and easy of compression. These dosage forms are available in extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. The future of sustained release products is promising in some area like chronopharmacokinetic system, targeted drug delivery system, mucoadhesive system, particulate system that provide high promise and acceptability.

Developing oral-sustained release formulations for highly water-soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets. Most of the researchers have worked on matrix tablets and multilayered matrix tablets. Among numerous approaches to oral SR formulation, matrix system of dosage form proves to be potential

because of its simplicity, ease of manufacturing, low cost, high level of reproducibility, stability, ease of scale up, and process validation [18].

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms[19].

The selection of the drug candidates for sustained release system needs consideration of several biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug molecule[20].

In the present study, a sustained release dosage form of Rosiglitazone Maleate has been developed that makes less frequent administering of drug.

Rosiglitazone is an antidiabetic agent belongs to the class of Thiazolidinediones, used in management of type-two diabetes mellitus. Rosiglitazone maleate has a half life of (3-4hr) and it reaches a peak plasma concentration after 1hrs and which is absorbed from gastrointestinal tract but solubility decreases with increasing pH in the physiologic range[21,22]. After 8 to 12 weeks of Rosiglitazone monotherapy, the dose may be doubled in case of insufficient response and this leads to higher incidence of dose dependent side effects. Such as gastro-intestinal disturbances, headache, altered blood lipids, oedema, hypoglycaemia**.** Further, adverse events of clinical significance which are reported frequently with conventional instant release dosage forms of the drug are oedema, anaemia and weight gain **.** Thus, there is a need to maintain Rosiglitazone at its steady state plasma concentration. Hence, the study was carried out to formulate and evaluate sustained release dosage form of Rosiglitazone Maleate as a model drug and had a aim that final batch formulation parameters should shows prolong drug release.

Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the in vivo environment.

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms[23,24,25,26].

Hence an attempt is made in this research work to formulate Sustained release (SR) Tablets of Rosiglitazone Maleate using HPMCK15M andCarbopol934P . Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The SR tablets formulation by direct compression method is most acceptable in large scale production.

A $\mathbf{3^2}$ full factorial design was employed to systematically study the drug release profile . A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of HPMCK15M and Carbopol 934P on the dependent variables, i.e. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (Time taken to release 10%,50%75%,90% respectively)

Materials and Methods

Materials used in this study were obtained from the different sources. Rosiglitazone Maleate was a gift sample from Aurobindo pharma Ltd, Hyderabad, India. HPMCK15M, Carbopol934P, Di Calcium Phosphate and Micro Crystalline Cellulose were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as Aerosil and magnesium stearate were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Rosiglitazone Maleate Sustained Release Tablets:

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses[27].

A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables HPMCK15M and Carbopol934P were used in formulation of Rosiglitazone Maleate sustained release (SR) Tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (HPMCK15M) at a concentration of 20%, 25%, 30%. three levels of factor X_2 (Carbopol934P) at a concentration of 15%, 20%, 25%.(% with respect to total tablet weight) was taken as the rationale for the design of the Rosiglitazone Maleate SR tablet formulation. Totally nine Rosiglitazone Maleate sustained release tablet formulations were prepared employing selected combinations of the two factors i.e X_1, X_2 as per 3^2 Factorial and evaluated to find out the significance of combined effects of X_1, X_2 to select the best combination and the concentration required to achieve the desired prolonged/ sustained release of drug from the dosage form.

Preparation of Rosiglitazone Maleate Sustained Release Tablets:

All ingredients were collected and weighed accurately. Sift Rosiglitazone Maleate with Microcrystalline Celulose and polymers through sieve no. 44# and then rinse with remaining excipients. Sift colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#. Pre-blend all ingredients (except lubricant- magnesium stearate) in blender for 15 minutes. Add magnesium stearate and then again blend for 5-6 minutes. Lubricated powder was compressed by using rotary tablet punching machine (RIMEK), Ahmedabad). Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Experimental Design:

Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of HPMCK15M was taken as X_1 and concentration of Carbopol934P was taken as X_2. Experimental design was given in the Table 1. Three levels for the Concentration of HPMCK15M were selected and coded as -1= 20%, 0=25%, +1=30%. Three levels for the Concentration of Carbopol934P were selected and coded as -1= 15%, 0=20%, +1=25%. Formulae for all the experimental batches were given in Table 2 [28,29].

Table 1: Experimental Design Layout

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1

Table 2: Formulae for the Preparation of Rosiglitazone Maleate Sustained Release Tablets as per Experimental Design

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Rosiglitazone Maleate	16	16	16	16	16	16	16	16	16
Microcrystalline Cellulose	30	30	30	30	30	30	30	30	30
HPMCK15M	120	120	120	100	100	100	80	80	80
Carbopol934P	100	80	60	100	80	60	100	80	60
Di Calcium Phosphate	127	147	167	147	167	187	167	187	207
Aerosil	2	2	2	2	2	2	2	2	2
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total Weight	400	400	400	400	400	400	400	400	400

Evaluation of Rosiglitazone Maleate Sustained Release Tablets:

Hardness[29]

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.

Friability[21]

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Content Uniformity[29]

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

Assay[22]

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N Hydrochloric acid, followed by stirring. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 318nm using 0.1 N Hydrochloric acid as blank.

Thickness [29]

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

In-vitro Dissolution Study:

The *In-vitro* dissolution study for the Rosiglitazone Maleate sustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 318 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

Kinetic modeling of drug release:

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release[30,31,32,33].

Results and Discussion:

Sustained release tablets of Rosiglitazone Maleate were prepared and optimized by 3^2 factorial design in order to select the best combination of different rate retarding agents, HPMCK15M, Carbopol934P and also to achieve the desired prolong/sustained release of drug from the dosage form. The two factorial parameters involved in the development of formulations are, quantity of HPMCK15M & Carbopol934P polymers as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 16 mg of Rosiglitazone Maleate were prepared as a sustained release tablet dosage form by Direct Compression technique as per the formulae given in Table 2.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness, mean diameter as per official methods and results are given in Table 3. The hardness of tablets was in the range of **5.17-5.50 Kg/cm^2.** Weight loss in the friability test was less than **0.67%**. Drug content of prepared tablets was within **acceptance range only**. Results for all Post-compression parameters were tabulated or shown in Table 3. *In-vitro* Dissolution studies were performed for prepared tables using 0.1 N HCl as a dissolution media at 50 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets are shown in Fig.1 and the dissolution parameters are given in Table 4. Cumulative % Drug release of Factorial Design Formulations F_1-F_9 at 12Hr were found to be in the range of **80.010-90.500 %**. From the result it reveals that the release rate was higher for formulations containing Low level of HPMCK 15M/ Carbopol934P compared with other Formulations containing Higher level, due to High concentration of polymer drug may have entrapped within a polymer matrix causing a decrease in rate of drug release. Therefore, required release of drug can be obtained by manipulating the composition of HPMCK15M and Carbopol934P.

Table 3: Post-Compression Parameters for the Formulations

S. No	Formulation Code	Hardness (kg/cm^2)	Diameter (mm)	Thickness (mm)	Friability (%)	Weight Variation	Drug Content
1	F_1	5.30	13.66	6.30	0.212	400.97	98.32
2	F_2	5.28	13.62	6.29	0.215	400.80	98.23
3	F_3	5.17	13.53	6.22	0 .217	399.93	97.88
4	F_4	5.20	12.98	6.16	0.225	400.067	97.44
5	F_5	5.37	12.90	6.12	0.667	400.617	97.36
6	F_6	5.40	12.87	6.10	0.258	400.217	97.00
7	F_7	5.50	11.47	5.80	0.175	400.817	96.40
8	F_8	5.40	12.86	6.08	0.208	400.45	96.65
9	F_9	5.50	12.20	5.93	0.080	400.033	96.04

Table 4: Regression Analysis Data of 3^2 Factorial Design Formulations of Rosiglitazone Maleate

S. No	Formulation Code	Kinetic Parameters											
		Zero Order			First Order			Higuchi			Korsmeyer-Peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	7.446	7.795	0.986	2.106	0.064	0.977	24.47	28.353	0.928	0.126	1.774	0.990
2	F_2	6.682	7.790	0.987	2.105	0.065	0.978	23.82	28.390	0.931	0.259	1.636	0.993
3	F_3	5.465	7.967	0.987	2.109	0.070	0.978	23.34	29.189	0.936	0.396	1.510	0.994
4	F_4	5.182	8.057	0.988	2.111	0.073	0.979	23.43	29.598	0.939	0.375	1.549	0.991
5	F_5	4.390	8.127	0.988	2.112	0.075	0.980	23.06	29.972	0.943	0.417	1.517	0.989
6	F_6	3.226	8.184	0.989	2.118	0.080	0.979	22.17	30.246	0.946	0.548	1.384	0.991
7	F_7	3.250	8.197	0.987	2.113	0.079	0.981	22.36	30.353	0.946	0.510	1.428	0.989
8	F_8	2.219	8.256	0.989	2.122	0.083	0.979	21.58	30.622	0.950	0.601	1.339	0.991
9	F_9	1.419	8.452	0.988	2.133	0.091	0.979	21.54	31.484	0.953	0.626	1.332	0.988
10	MP	3.762	8.155	0.988	2.113	0.077	0.980	22.63	30.133	0.945	0.474	1.461	0.990

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ due to formulation variables. Formulation F_5 containing 100 mg of HPMCK15M, 80 mg of Carbopol934P showed promising dissolution parameter (**$t_{10\%}$= 0.609 h, $t_{50\%}$ = 4.007 h, $t_{75\%}$ = 8.014 h, $t_{90\%}$ = 13.315 h**). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation[34].

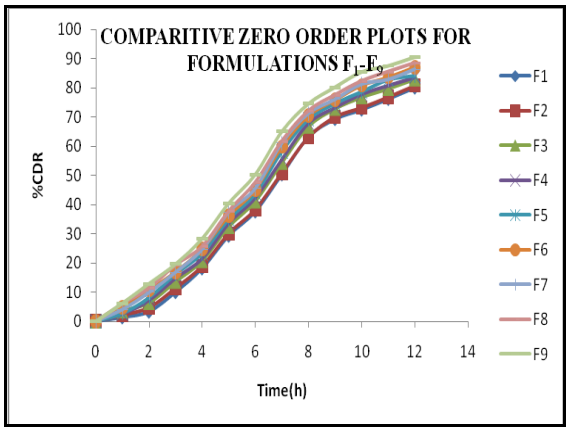

Fig.1 Comparative Zero Order Plots for F_1-F_9

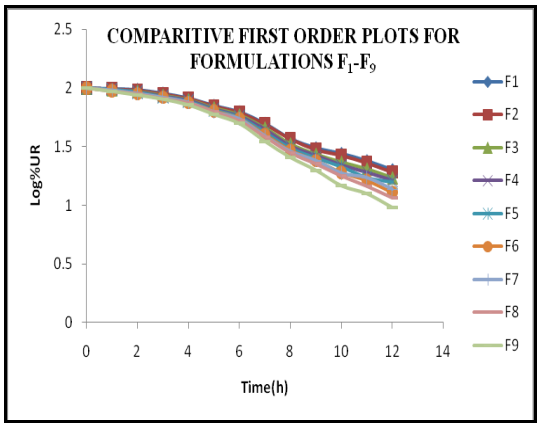

Fig.2 Comparative First Order Plots for F_1-F_9

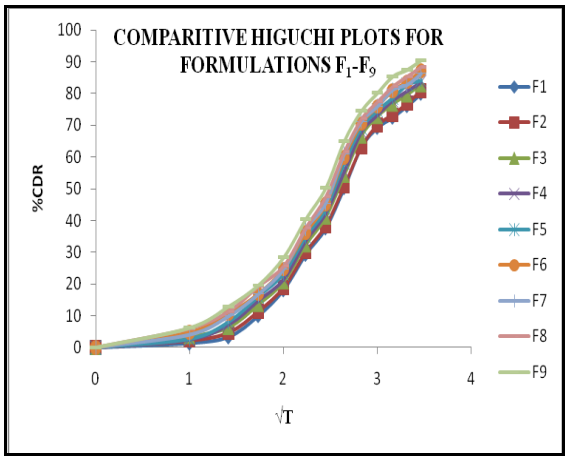

Fig.3 Comparative Higuchi Plots for F_1-F_9

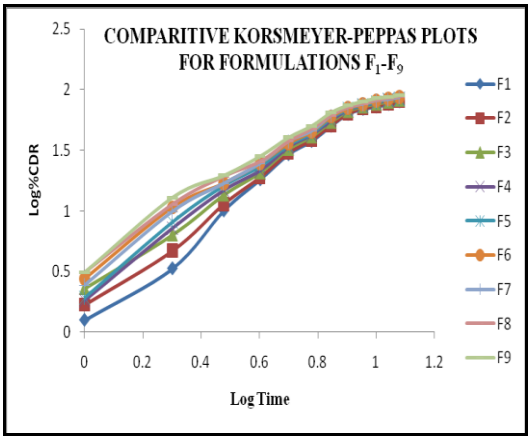

Fig.4 Comparative Korsmeyer-Peppas Plots for F_1-F_9

The *In -vitro* dissolution data of Rosiglitazone Maleate SR formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in fig.1,2,3,4. It was observed from the above that dissolution of all the tablets followed zero order kinetics with co-efficient of determination (R^2) values above 0.986. The values of r of factorial formulations for Higuchi's equation was found to be in the range of **0.928-0.953**, which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from **0.126- 0.626** that shows Fickian diffusion mechanism. Polynomial equations were derived for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis. The dissolution data (Kinetic parameters) of factorial formulations F_1 to F_9 are shown in Table 5.

Table 5: Dissolution Parameters of Rosiglitazone Maleate Sustained Release Tablets 3^2 Full Factorial Design Batches

S.No	Formulation Code	Kinetic Parameters			
		$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$)	$t_{90\%\ (h)}$
1	**F_1**	0.711	4.680	9.360	15.552
2	**F_2**	0.700	4.606	9.212	15.306
3	**F_3**	0.650	4.277	8.554	14.212
4	**F_4**	0.630	4.148	8.295	13.783
5	**F_5**	0.609	4.007	8.014	13.315
6	**F_6**	0.575	3.785	7.569	12.576
7	**F_7**	0.581	3.825	7.650	12.711
8	**F_8**	0.548	3.604	7.208	11.975
9	**F_9**	0.502	3.306	6.611	10.985
10	**MP**	0.594	3.906	7.813	12.981

Polynomial equation for 3^2 full factorial designs is given in Equation

$$\mathbf{Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1^2+b_{22} X_2^2\ldots}$$

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration(C_1, C_2).

The equations for $t_{10\%}$, $t_{50\%}$ $t_{75\%}$ and $t_{90\%}$ developed as follows,

$Y_1= 0.612+0.072X_1+0.0325X_2-0.005X_1X_2+0.01067\ X_1^2-0.01084X_2^2$ **(for $t_{10\%}$)**
$Y_2= 4.026+0.471X_1+0.214X_2-0.029\ X_1X_2+0.0696\ X_1^2-0.0688\ X_2^2$ **(for $t_{50\%}$)**
$Y_3= 8.053+0.943X_1+0.429X_2-0.058\ X_1X_2+0.140\ X_1^2-0.138\ X_2^2$ **(for $t_{75\%}$)**
$Y_4= 13.380+1.567X_1+0.712X_2-0.097\ X_1X_2+0.232\ X_1^2-0.229\ X_2^2$ **(for $t_{90\%}$)**

Table 6: Dissolution Parameters for Predicted and Observed Values for Check Point Formulations

Formulation Code	Predicted Value				Actual Observed Value			
	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$)	$t_{90\%\ (h)}$	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$)	$t_{90\%\ (h)}$
C_1	0.53	3.50	6.99	11.05	0.54	3.49	7.01	11.06
C_2	0.69	4.52	9.04	15.04	0.69	4.53	9.06	15.05

The positive sign for co-efficient of X_1 in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of HPMCK15M increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ value increases. In other words the data demonstrate that both X_1 (amount of HPMCK15M) and X_2 (amount of Carbopol934P) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$). From the results it can be concluded that, and increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The Dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarised in Table 6. The closeness of Predicted and Observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. The Contour Plots were presented to show the effects of X_1 and X_2 on $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$. The final best (Optimised) formulation (F_5) is compared with marketed product (**AVANDIA**)shows similarity factor (f_2) 93.1376, difference factor (f_1) 1.7642 (There is no significant difference in drug release because t_{cal} is<0.05).

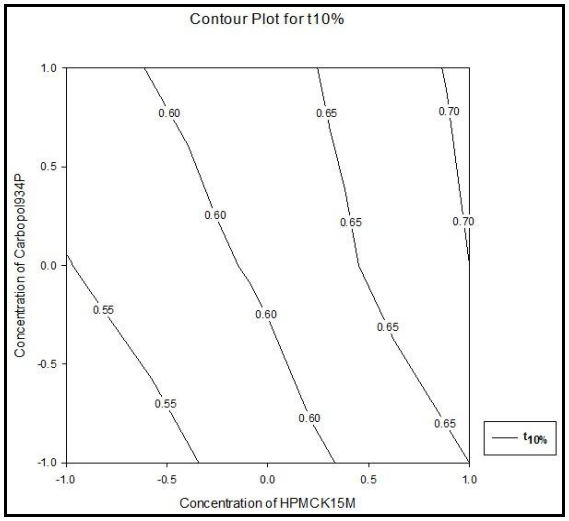

Fig.5 linear Contour Plot for $t_{10\%}$

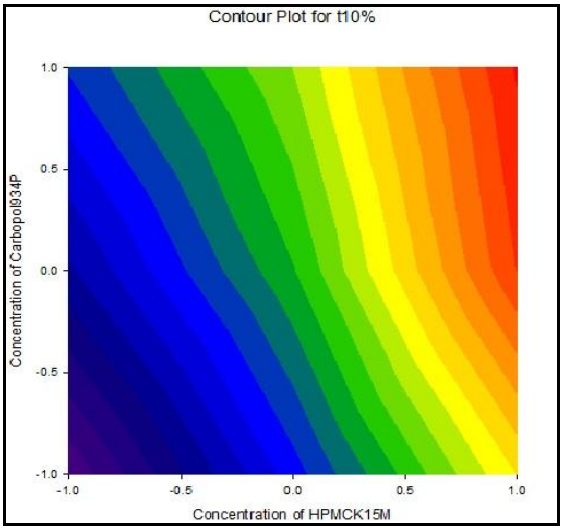

Fig.6 Contour Plot for $t_{10\%}$

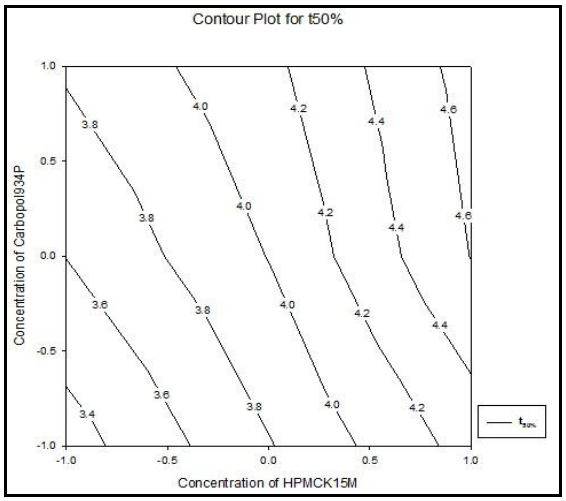

Fig.7 linear Contour Plot for $t_{50\%}$

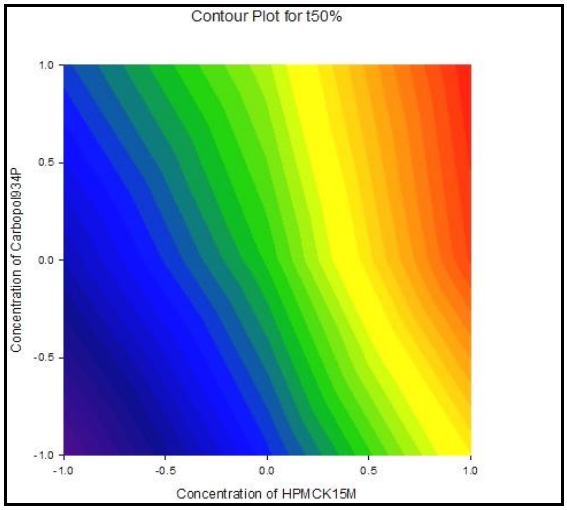

Fig.8 Contour Plot for $t_{50\%}$

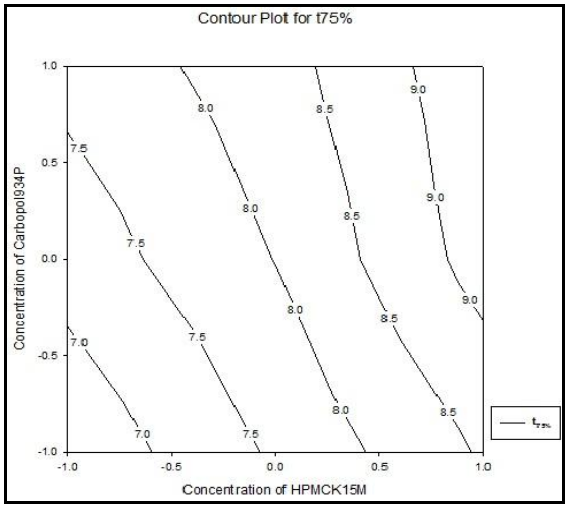

Fig.9 linear Contour Plot for $t_{75\%}$

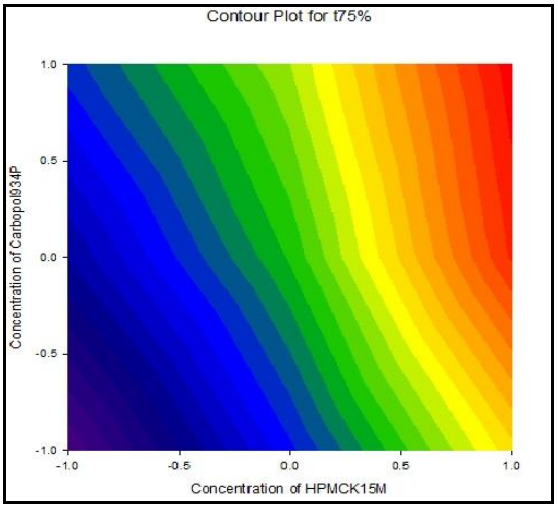

Fig.10 Contour Plot for $t_{75\%}$

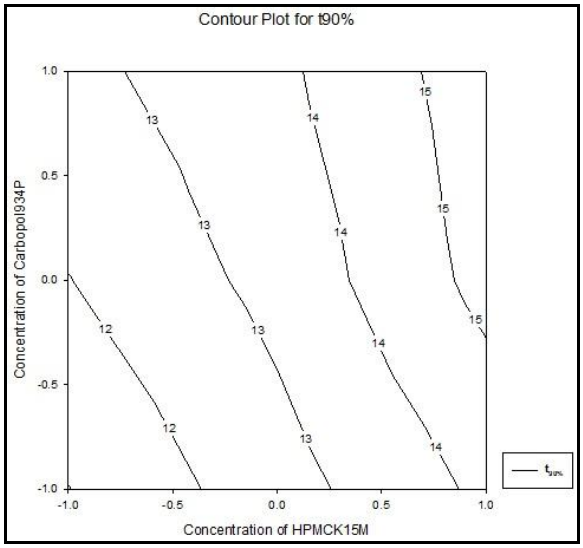

Fig.11 linear Contour Plot for $t_{90\%}$

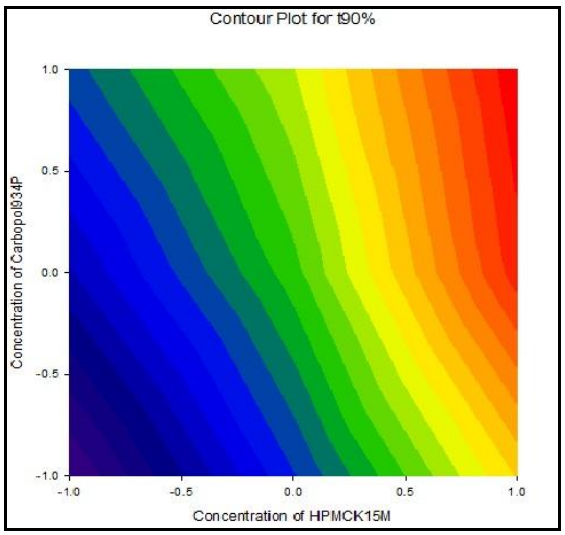

Fig.12 Contour Plot for $t_{90\%}$

Conclusion

The present research work envisages the applicability of rate retarding agents such as HPMCK15M and Carbopol934P in the design and development of sustained release tablet formulations of Rosiglitazone Maleate utilizing the 3^2 factorial design. From the results it was clearly understand that as the retardant concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Fickian Diffusion, Zero order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation **F_5** may be used once a day administration in the management of Type-II Diabetes mellitus.

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