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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF MIRABEGRON EXTENDED RELEASE TABLETS

V. Suresh Kumar*, P. Munija, A. Tejaswini
Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad, India
**Corresponding author: munijapharma@gmail.com*
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ABSTRACT
IN the present study extended-release tablets of Mirabegron were successfully prepared by using various polymers like HPMC K 100M, carbopol 940, and xanthan gum by "direct compression method. Based on the pre-formulation studies for drug excipients, compatibility was observed and there were no compatibility problems with the excipients used in the study. Evaluation parameters like weight variations friability, hardness, thickness, and drug content were found to be within the limits. Among all the developed formulations F7 was selected as the best formulation, [XR (OR) ER] formulations have the longer period of time when compared with other formulations. The drug in zero order model based on the pharmacokinetics, extended-release formulation suitable for drug concentration at steady state, is determined by elimination half-life & dosing interval. The drug with short half-lives with a clear relationship between the concentration & response indicate decreasing toxicity by slowing drug absorption therapeutic compounds with short half-lives. These are excellent candidates for extended-release preparation because these can decrease dose frequency.

Keywords: Mirabegron, HPMC K 100M, carbopol 940 and xanthan gum, extended release tablets, direct compression method.

1. INTRODUCTION
The aim of the study was to formulate and *in vitro* evaluation of Mirabegron extended-release tablets by using different polymers such as HPMCK100M, CARBOPOL940, and XANTHAN GUM. Extended-release formulations [1-4] are the slow release drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 to 12 hours), drugs are metabolized before absorption either in the lumen (or) the tissues of the intestine, can show decreased bioavailability from the extended releasing system. These oral formulations are low-risk dose dumping, flexibility, of blending to attain difference release pattern as well as reproducible and short gastric residence time. Transfer of drug from one compartment to other if follows zero-order kinetic process then such drugs are a poor candidate for oral ER delivery system, it should be of first-order kinetics [5].
The drug Mirabegron (Myrbetriq) is taken once daily and is orally active. Mirabegron is a potent and selective agonist for beta-3 adrenegic receptors, which plays an important role once beta-3 receptors are activated, the detrusor smooth muscle relaxes, to allow for a larger bladder capacity, mirabegron indicated for the treatment of overactive bladder (OAB) with symptoms of urinary frequency, urgency, urge urinary incontinence. Thus biopharmaceutical classification of Mirabegron is class-ll, the molecular weight of the drug is 396.506gm/mole (Mol. formula C_{21} H_{24} N_4O_2S).
The category of the drug is an adrenergic. The product is formulated as prolonged-release film-coated tablets which are developed as a hydrophilic gel-forming matrix formulation designed for continuous drug release through the GI tract. The proposed posology is 50mg once daily with or without food. The recommended dose of Mirabegron is 25mg orally once.

2. MATERIAL AND METHODS
Mirabegron, HPMCK100M, Carbopol 940, Xanthan gum, Lactose, Magnesium stearate, and Talc were used for formulation. All the formulations were prepared by the direct compression method. The compositions of

different formulations are given in table 1, the tablets were prepared as per the procedure given below and the aim is to prolong the release of mirabegron. The total weight of the tablet was considered 200mg.

2.1. Preparation of Mirabegron Extended-release tablets

Mirabegron and all ingredients were individually passed through sieve no. 60. All the ingredients were mixed thoroughly by triturating up to 15min and the powder mixture was lubricated with talc. The tablets were prepared by using the direct compression method [6-8].

2.2. Drug - excipient compatibility studies

2.2.1. Fourier Transform Infrared (FTIR) Spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR GERMANY (Alpha T). The solid powder sample was directly placed on a yellow crystal which was made up of Zn Se. The spectra were recorded over the wave number of 4000cm^{-1} to 400cm^{-1}.

Table 1: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mirabegron	50	50	50	50	50	50	50	50	50
HPMC K100M	25	50	75	-	-	-	-	-	-
Carbopol 940	-	-	-	25	50	75	-	-	-
Xanthan gum	-	-	-	-	-	-	25	50	75
Lactose	118	93	68	118	93	68	118	93	68
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200

All the quantities were in mg.

2.3. Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia [9].

2.3.1. Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan\theta = h / r \quad \tan\theta = \text{Angle of repose}$$

h = Height of the cone, r = Radius of the cone base

Table 2: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2.3.2. Bulk density

Density is defined as weight per unit volume. Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape, and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blends. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was

carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:
Bulk Density = M / Vo
Where M = weight of the sample, Vo = apparent volume of powder

2.3.3. Tapped density

After carrying out the procedure as given in the measurement of bulk density, the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until the difference between succeeding measurements is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

2.3.4. Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it measures the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.
For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:
Carr's Index = [(tap - b)/tap] × 100
Where b = Bulk Density, Tap = Tapped Density

Table 3: Carr's index value (as per USP)

Carr's index	Properties
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair to Passable
2 - 35	Poor
33 - 38	Very Poor
>40	Very Very Poor

2.4. Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug contents [10].

2.4.1. Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.
% Deviation = (Individual weight - Average weight / Average weight) × 100

Table 4: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

2.4.2. Hardness

The hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion, or breakage under conditions of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using a Monsanto hardness tester and the average is calculated and presented with deviation.

2.4.3. Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

2.4.4. Friability

It is measured by the mechanical strength of tablets.

Roche friabilator was used to determine the friability by following the procedure. Pre-weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of the test, the tablets were reweighed, loss in the weight of the tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2)/W] × 100

Where W1 = Initial weight of three tablets, W2 = Weight of the three tablets after testing

In vitro drug release studies

Dissolution parameters:

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl, p H 6.8 Phosphate buffer

RPM -- 50

Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature -- 37°C + 0.5°C

A 900ml 0f 0.1 HCl was placed in a vessel and the USP apparatus -II (Paddle Method) was assembled. The medium was allowed to equilibrate to a temp of 37°C + 0.5°C. Tablet was placed in the vessel and the apparatus was operated for 2 hours then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals 5 ml of sample was withdrawn, filtered, and again 5ml media was replaced. Suitable dilutions were done with media and analyzed spectrophotometrically at the required wavelength using UV-spectrophotometer.

2.5. Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release models [11-14].

3. RESULTS AND DISCUSSION

3.1. Drug excipients compatibility studies

3.1.1. Fourier Transform-Infrared Spectroscopy

No change in the peaks of the graph is seen which indicates no interaction of drug and excipients.

3.2. Pre formulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.382±0.032 to 0.536±0.05 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.462±0.015 to 0.593±0.03 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 17 which show that the powder has good flow properties. All the formulations have shown the hausner ratio; below 1.20, indicating the powder has good flow properties.

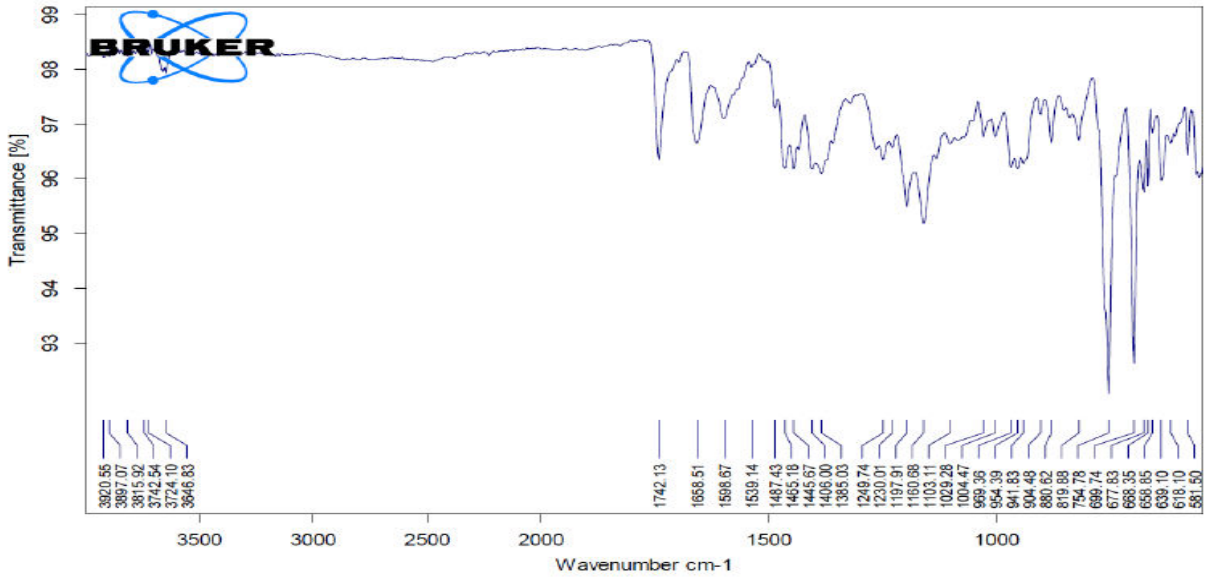

Fig. 1: FT-TR Spectrum of Mirabegron pure drug

Fig. 2: FT-IR Spectrum of Optimised Formulation

Table 5: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	27.22±1.31	0.410±0.069	0.496±0.020	17.33±0.320	1.20±0.013
F2	28.35±1.64	0.382±0.032	0.462±0.015	17.31±0.208	1.20±0.015
F3	28.23±1.6	0.405±0.05	0.470±0.032	13.82±0.198	1.16±0.016
F4	29°76′±0.02	0.536±0.05	0.593±0.03	15.96±0.01	1.18±0.02
F5	26°49′±0.01	0.492±0.06	0.542±0.04	9.22±0.06	1.1±0.02
F6	28°63′±0.02	0.521±0.03	0.596±0.02	12.5±0.03	1.14±0.03
F7	27°09′±0.03	0.528±0.02	0.586±0.06	9.89±0.04	1.1±0.02
F8	27°01′±0.02	0.498±0.03	0.549±0.02	9.22±0.02	1.1±0.06
F9	26°14′±0.03	0.477±0.04	0.542±0.02	11.99±0.01	1.13±0.02

3.3. Evaluation of post compression parameters for prepared Tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

3.3.1. Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 6. The average weight of the tablet is approximately in range of 196.4to 200.0mg, so the permissible limit is ±7.5% (>250 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

3.3.2. Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data were shown in Table 6. The results showed that the hardness of the tablets is in range of 4.1 to 6.2 kg/cm^2, which was within IP limits

3.3.3. Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table 6. The result showed that thickness of the tablet is raging from 3.12 to 3.82mm.

3.3.4. Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 6. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets

Table 6: Post compression parameters for tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	198.3	6.2	0.19	3.15	97.25
F2	199.5	4.9	0.27	3.65	99.34
F3	197.6	5.1	0.10	3.42	96.14
F4	200.0	5.3	0.64	3.12	97.61
F5	198.9	4.8	0.57	3.82	99.32
F6	196.4	5.3	0.33	3.61	97.38
F7	197.2	5.2	0.46	3.72	99.46
F8	198.3	4.1	0.52	3.22	98.11
F9	199.2	4.8	0.39	3.69	97.42

3.3.5. Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 97.25-99.46 %. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

3.3.6. In Vitro Drug Release Studies

From the dissolution data it was evident that the formulations prepared with HPMC K100M as polymer retarded the drug release up to desired time period i.e., 12 hours. Formulations prepared with Carbopol 940 retarded the drug release in the concentration of 74 mg (F6 Formulation) showed required release pattern (i.e., retarded the drug release up to 12 hours and showed maximum of 98.22 % in 12 hours with good retardation. The Formulation Containing Xanthan gum in 25 Mg concentration showed good retarding nature with required drug release in 12 hours i.e. 99.29%.

From the above results it was evident that the formulation F7 is best formulation with desired drug release pattern extended up to 12 hours.

3.3.7. Release Rate Kinetics to Dissolution date [1, 2]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

From the above graphs it was evident that the formulation F7 was followed Zero order release kinetics.

Table 7: Dissolution data of Mirabegron tablets prepared with HPMC K100M

Time (hr)	Cumulative percent drug dissolved		
	F1	F2	F3
0	0	0	0
0.5	12.42	8.17	6.92
1	17.89	19.61	13.03
2	21.47	23.78	19.62
3	35.13	35.23	27.47
4	43.56	39.97	36.89
5	51.21	47.62	43.56
6	58.94	53.19	49.84
7	67.73	62.31	57.47
8	75.26	69.86	65.35
9	79.98	76.92	68.13
10	83.29	83.27	72.58
11	92.42	90.63	76.21
12	96.16	93.79	82.18

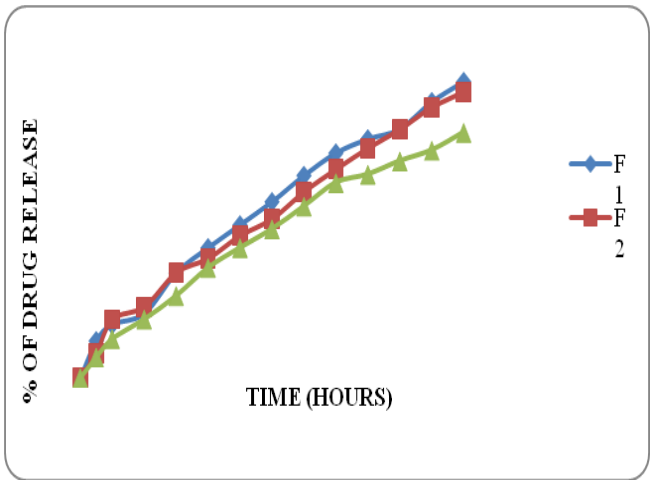

Fig. 3: Dissolution profile of Mirabegron (F1, F2, F3 formulations).

Table 8: Dissolution Data of Mirabegron Tablets Prepared With Carbopol 940

Time (hr)	Cumulative percent drug dissolved		
	F4	F5	F6
0	0	0	0
0.5	8.22	10.50	18.93
1	13.96	15.93	22.64
2	18.32	21.16	29.82
3	26.15	27.68	38.63
4	32.67	35.52	47.72
5	38.31	42.83	52.48
6	49.97	53.97	60.37
7	56.42	61.25	69.16
8	64.23	68.31	76.53
9	70.85	73.58	80.72
10	75.96	82.31	88.19
11	81.36	86.96	91.54
12	87.24	90.18	96.23

Table 9: Dissolution data of Mirabegron tablets prepared With Xanthan gum

TIME (hr)	Cumulative percent drug dissolved		
	F7	F8	F9
0	0	0	0
0.5	15.27	19.24	11.15
1	21.31	25.98	17.94
2	26.49	29.72	21.67
3	34.27	32.72	25.56
4	48.86	38.13	34.40
5	52.34	42.90	37.58
6	63.15	56.88	41.10
7	72.97	59.34	52.67
8	76.68	64.51	57.25
9	83.56	76.56	65.32
10	90.52	78.49	74.15
11	93.31	80.20	80.52
12	99.29	85.15	90.19

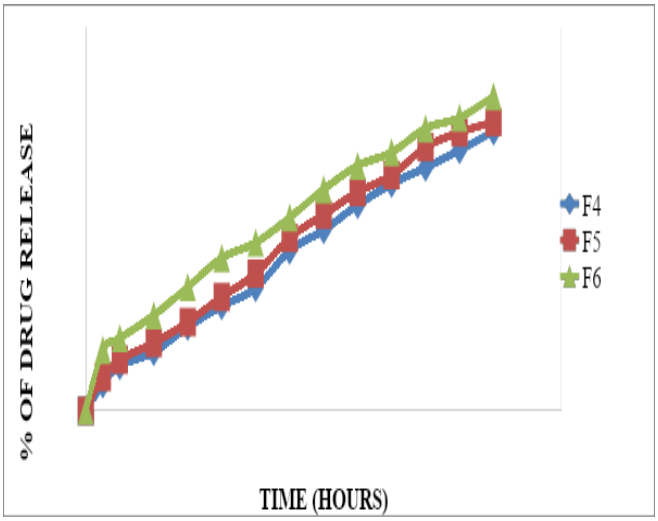

Fig. 4: Dissolution profile of Mirabegron (F5, F6, F7, F8 formulations)

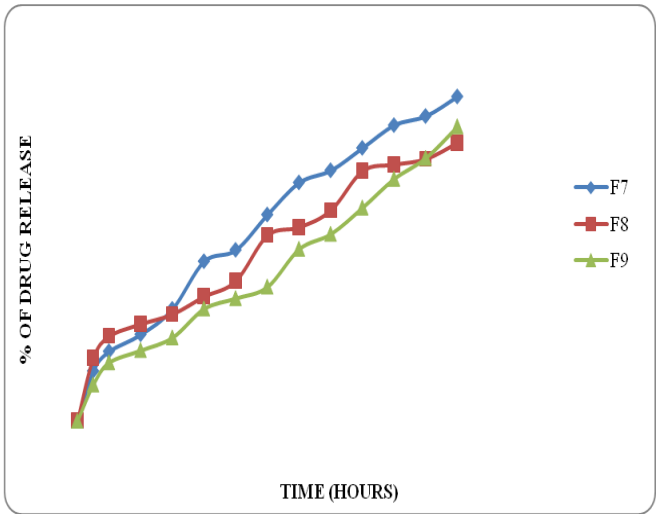

Fig. 5: Dissolution profile of Mirabegron (F9, F10, F11, F12 formulations).

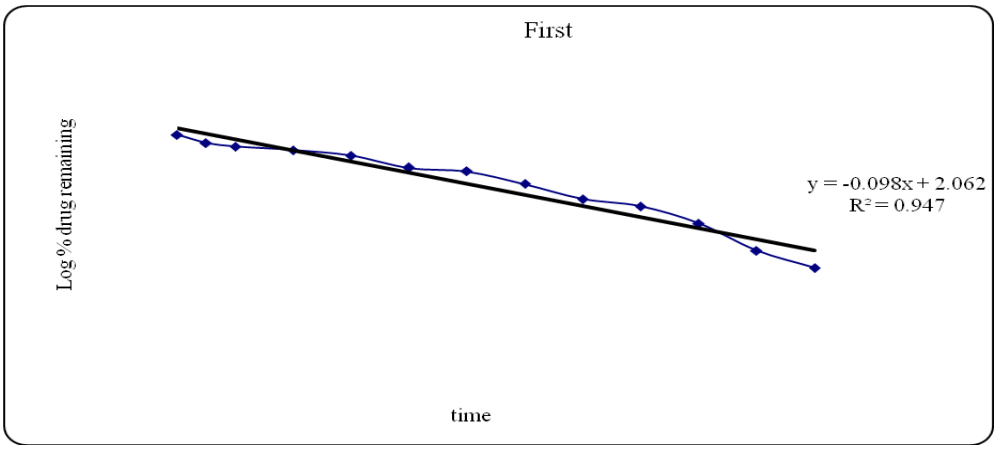

Fig. 6: Zero order release kinetics graph

Table 10: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
15.27	0.5	0.707	1.184	-0.301	1.928	30.540	0.0655	-0.816	84.73	4.642	4.392	0.249
21.31	1	1.000	1.329	0.000	1.896	21.310	0.0469	-0.671	78.69	4.642	4.285	0.356
26.49	2	1.414	1.423	0.301	1.866	13.245	0.0378	-0.577	73.51	4.642	4.189	0.453
34.27	3	1.732	1.535	0.477	1.818	11.423	0.0292	-0.465	65.73	4.642	4.036	0.606
48.86	4	2.000	1.689	0.602	1.709	12.215	0.0205	-0.311	51.14	4.642	3.712	0.930
52.34	5	2.236	1.719	0.699	1.678	10.468	0.0191	-0.281	47.66	4.642	3.626	1.016
63.15	6	2.449	1.800	0.778	1.566	10.525	0.0158	-0.200	36.85	4.642	3.328	1.314
72.97	7	2.646	1.863	0.845	1.432	10.424	0.0137	-0.137	27.03	4.642	3.001	1.640
76.68	8	2.828	1.885	0.903	1.368	9.585	0.0130	-0.115	23.32	4.642	2.857	1.785
83.56	9	3.000	1.922	0.954	1.216	9.284	0.0120	-0.078	16.44	4.642	2.543	2.099
90.52	10	3.162	1.957	1.000	0.977	9.052	0.0110	-0.043	9.48	4.642	2.116	2.525
93.31	11	3.317	1.970	1.041	0.825	8.483	0.0107	-0.030	6.69	4.642	1.8g84	2.757
99.29	12	3.464	1.997	1.079	-0.149	8.274	0.0101	-0.003	0.71	4.642	0.892	3.749

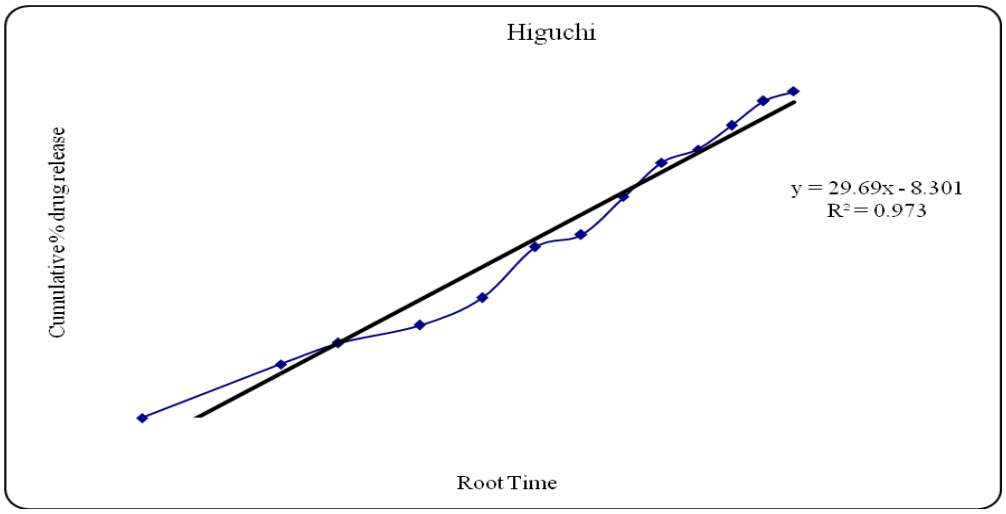

Fig. 7: Higuchi release kinetics graph

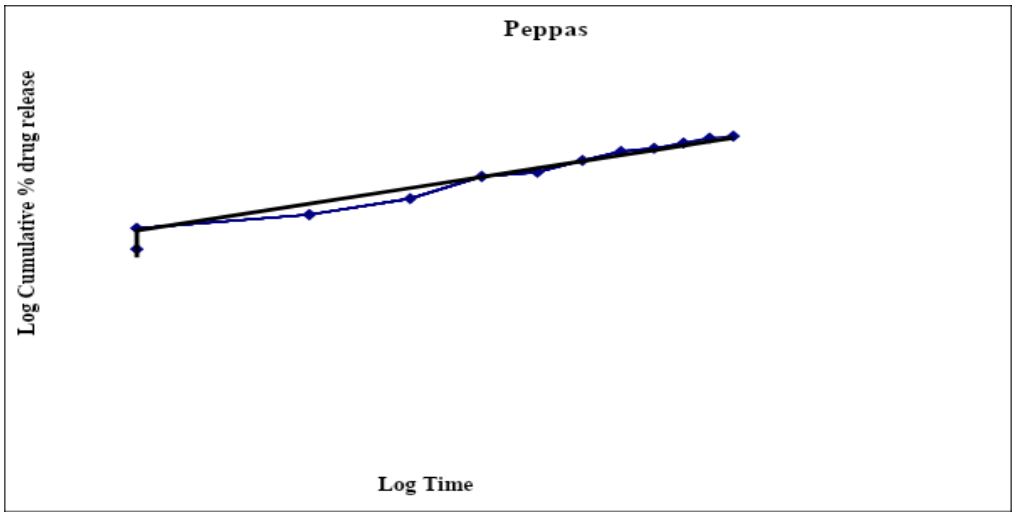

Fig. 8: Kars mayerpeppas graph

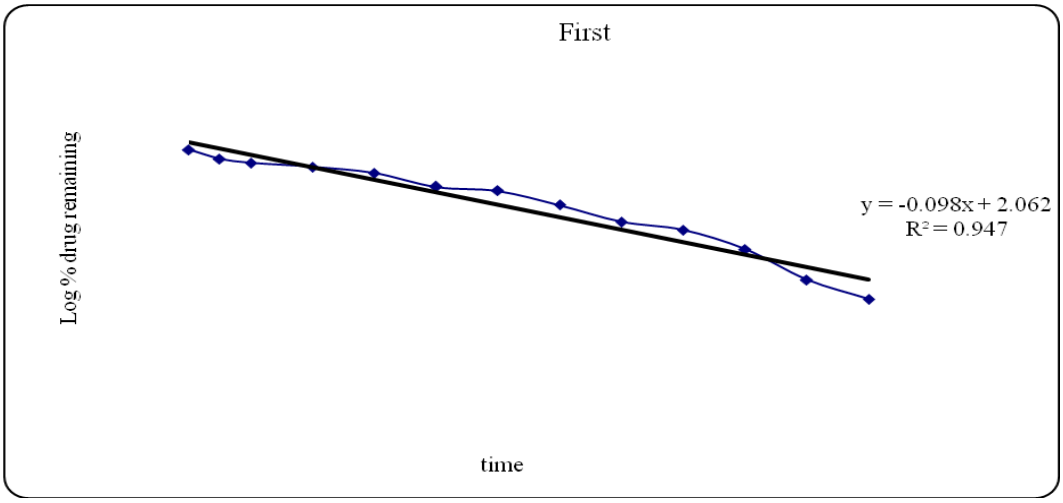

Fig. 9: First order release kinetics graph

4. CONCLUSION

In the present research work the extended release matrix formulation of Mirabegron by using various polymers were prepared. The formulation was developed by using various polymers such as HPMC K100M, Carbopol 940 and Xanthan gum. The formulation blend was subjected to various pre formulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among the formulations prepared by using HPMC K 100 M were able retard drug releases up to 12 hours. Formulations prepared with Carbopol 940 retarded the drug release up to 12 hrs. Among all formulation, direct compression tablets showed maximum drug release. Among all formulations, F7 formulation was considered as optimised formulation. It showed 99.29 % drug release at 12hrs. The optimised formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Zero order release kinetics of drug release.

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Conflict of interest

The authors declare that there is no conflict of interest

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