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Formulation Development and Evaluation Of Freely Water-Soluble Mirabegron -Loaded Controlled Release Matrix Tablets

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ABSTRACT
Formulation of controlled release matrix tablets of Mirabegron (MB) was done using direct compression method. Hydroxypropyl methylcellulose (HPMC K15M, HPMC K100M CR) was used as a release retardant, as was polyethylene oxide (PEO), ethyl cellulose (EC), and Kollidon-SR in the formulations. Diluents included microcrystalline cellulose (MCC) and lactose. Magnesium stearate (MS) 1% and talc 2 % were used as lubricants. Isopropyl alcohol (IPA) was utilised as a binder to dissolve the polyvinyl pyrrolidone (PVP-K90) at a 5% w/v concentration. Thirty different tablet formulations were designed with constant amount of MB in each tablet formulation (25 mg). The dissolution studies of CR matrix formulations were carried out in acidic buffer (pH 1.2) and phosphate buffer (pH 6.8). The Fourier decomposition Infrared spectroscopy indicated that there were no interactions between the medication and the polymers or the excipients. The manufactured controlled release tablets were tested for hardness, weight fluctuation, thickness, friability, drug content homogeneity, and in vitro dissolvability. Mirabegron extended-release tablets with a controlled release mechanism might be developed. HPMC K100M and Ethyl cellulose were used to generate the best formulation (F23) (1:1). F23 was deemed an optimum formulation since these tablets did not exhibit burst release and prolonged the release for 12 hours with a release pattern that was almost identical to that of the theoretical release profile.
Keywords: *Mirabegron, Controlled release, Matrixtablets, Freely water soluble*

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INTRODUCTION

Overactive bladder (frequency-urgency syndrome) is the commonest bladder problem in late life, affecting up to 41% of over-75-year-old individuals, and the elderly experience more severe disease. When talking about the overactive bladder (OAB), a question that comes into mind is what conditions are associated with the development of this physiopathologic state of the bladder. It has been observed that OAB is manifested during the following conditions: ageing, diabetes mellitus (DM), bladder outlet obstruction (BOO), spinal cord injury (SCI), stroke and brain injury, Parkinson's disease (PD), multiple sclerosis (MS), interstitial cystitis (IC), and stress and depression. For many years, antimuscarinic drugs have been the first-line pharmacological treatment for urgency, frequency, and urge incontinence, all symptoms of the disorder termed overactive bladder. Antimuscarinic treatment is not always effective and is associated with side-effects that limit its clinical use [1-4].

Mirabegron is a novel, once-daily, orally active, first-in-class, potent β_3-adrenoceptor agonist recently approved by Food and Drug Administration for overactive bladder therapy. Phase II studies and four large-scale phase III multinational randomized, controlled trials have supported the efficacy and tolerability of mirabegron in the clinical trial setting of patients with overactive bladder for up to 12 weeks of therapy and in the long term (12 months). The reported incidence and severity of treatment-emergent and serious adverse effects were similar to antimuscarinics, but with a more than threefold lower incidence of dry mouth compared with tolterodine [5-7].

Over the past several decades, controlled-release technology has rapidly emerged as a drug delivery system that offers novel approaches for the delivery of bioactive compounds into systemic circulation at a predetermined rate, which significantly improves drug bioavailability and clinical outcomes with decreased toxicity. Sustained-release (SR) dose forms are designed in such a way that the rate of drug release from the tablet matrix occurs in a controlled manner over an extended period of time maintaining a constant plasma drug level thus improving patient compliance and effective clinical outcomes [8]. The

development of sustained drug delivery systems is a challenging task in terms of providing a constant drug release profile retaining the dosage form in the stomach or upper small intestine until all the drug is completely released in the desired time. An ideal oral drug delivery system will steadily release a measurable and reproducible amount of drug over an extended period of time [9-10].

The aim of the current work was an attempt to develop SR matrix tablets of Mirabegron for improved patient compliance and better therapeutic effects of various polymers with different polymeric compositions. Various physical tests were performed for the formulated tablets such as weight variation, and thickness, hardness, and friability tests. The tablets were evaluated for uniformity of active ingredients by performing a pharmaceutical assay. The release of the model drug from the developed matrix tablets was performed in phosphate buffer of pH 6.8. The mechanism of drug release was studied by subjecting drug release data to various kinetic models.

MATERIAL AND METHODS

Materials

Mirabegron(MB) was kindly gifted by Glenmark pharmaceuticals (India) Limited. Hydroxypropyl methylcellulose (HPMC K15M, HPMC K100M CR) and ethylcellulose were purchased from Merck Limited (India). Kollidon® SR was provided by Sigma aldrich (India). Microcrystalline cellulose and lactose was procured from S.D Fine Chem Ltd (India). Magnesium stearate, Isopropyl alcohol, polyvinyl pyrrolidone and Talc was purchased from the Sigma aldrich, India. All other materials used were analytical grades.

Methods

Preparation of extended release matrix tablet formulations

Matrix tablets formulations of MG were designed and formulated using Hydroxypropyl methylcellulose (HPMC K15M, HPMC K100M CR), ethylcellulose and Kollidon® SR by direct compression technique. The amount of MG in each tablet formulation was kept constant (25 mg), as available in the market, whereas quantity of different viscosity grades and types of polymers ranges from 20 to 40%. Accurately weighed quantities of drug and excipients were passed through mesh 20 screen for size uniformity. The mixture was transferred in a polybag to mix thoroughly by adding talc (2%) as lubricant and magnesium stearate (1%) as glidant. MCC was used as diluent in all formulations. Final blend was compressed using single punch machine. To investigate the influence of concentration and viscosity grades of polymers on release of Mirabegron controlled release matrix tablet, all formulations were evaluated for in-vitro release. The compositions of Mirabegron-controlled release formulations are listed in table 1.

Table 1: The compositions of Mirabegron-controlled release formulations

Matrix Tablets Containing HPMC K15M*								
F.Code	**MG (mg)**	**HPMC K15M (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F1	25	12.5	72.9	6	qs	1.2	2.4	120
F2	25	12.5	60.4	6	qs	1.2	2.4	120
F3	25	12.5	47.9	6	qs	1.2	2.4	120
F4	25	12.5	35.4	6	qs	1.2	2.4	120
Matrix Tablets Containing Polyethylene Oxide								
F.Code	**MG (mg)**	**PEO (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F5	25	12.5	72.9	6	qs	1.2	2.4	120
F6	25	25	60.4	6	qs	1.2	2.4	120
F7	25	37.5	47.9	6	qs	1.2	2.4	120
F8	25	50	35.4	6	qs	1.2	2.4	120
Matrix Tablets Containing HPMC K100M CR*								
F.Code	**MG (mg)**	**HPMC K100M CR (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F9	25	12.5	72.9	6	qs	1.2	2.4	120
F10	25	25	60.4	6	qs	1.2	2.4	120
F11	25	37.5	47.9	6	qs	1.2	2.4	120
F12	25	50	35.4	6	qs	1.2	2.4	120
Matrix Tablets Containing Ethylcellulose*								
F.Code	**MG (mg)**	**EC (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F13	25	12.5	72.9	6	qs	1.2	2.4	120
F14	25	25	60.4	6	qs	1.2	2.4	120

F15	25	37.5	47.9	6	qs	1.2	2.4	120
F16	25	50	35.4	6	qs	1.2	2.4	120
Matrix Tablets Containing Kolliodon-SR*								
F.Code	**MG(mg)**	**Kolliodon-SR (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F17	25	12.5	72.9	6	qs	1.2	2.4	120
F18	25	25	60.4	6	qs	1.2	2.4	120
F19	25	37.5	47.9	6	qs	1.2	2.4	120
F20	25	50	35.4	6	qs	1.2	2.4	120
Matrix Tablets Containing HPMC K100M and EC								
F.Code	**MG(mg)**	**HPMC K100M (mg)**	**EC (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F21	25	40	10	35.4	6	qs	1.2	2.4	120
F22	25	30	20	35.4	6	qs	1.2	2.4	120
F23	25	25	25	35.4	6	qs	1.2	2.4	120
F24	25	20	30	35.4	6	qs	1.2	2.4	120
F25	25	10	40	35.4	6	qs	1.2	2.4	120
Matrix Tablets Containing HPMC K100M and HPMC K15M*									
F.Code	**MG (mg)**	**HPMC K100M (mg)**	**HPMC K15M (mg)**	**MCC (mg)**	**PVPK90 (mg)**	**IPA (mL)**	**MS (mg)**	**Talc (mg)**	**Total (mg)**
F21	25	40	10	35.4	6	qs	1.2	2.4	120
F22	25	30	20	35.4	6	qs	1.2	2.4	120
F23	25	25	25	35.4	6	qs	1.2	2.4	120
F24	25	20	30	35.4	6	qs	1.2	2.4	120
F25	25	10	40	35.4	6	qs	1.2	2.4	120

Characterization

Micrometric properties of powders Powder flow plays an important role in the manufacturing of a fine tablet. The flow properties of the powder blends were evaluated by determining the bulk density, tapped density, and angle of repose.

Bulk density

To measure the bulk density, a pre-sieved powder blend was carefully poured into a dry graduated cylinder without compaction and the weight and volume were measured. The unit of bulk density is g/mL and is given by

Db = M V0

Where M represents the mass of powder and V0 represents the bulk volume of the powder.

Tapped density

Tapped density was calculated by pouring a known mass of powder blend in a graduated cylinder placed on a mechanical tapping apparatus. The compact volume of the powder after tapping was measured. Tapped density is also expressed as g/ mL and is given by

Dt = M Vt

Where M represents the mass of powder and Vt is the tapped volume of the powder.

Angle of Repose

Angle of repose The funnel method was adopted to measure the angle of repose. The powder was allowed to drop from the funnel to form a cone to a maximum height. The diameter of the heap (D) and height of the heap (h) was measured and the angle of repose (θ), which was calculated using the following formula:

tan θ = h/r

where h = height of the powder heap

r = radius of the powder heap

θ = angle of repose

Hardness or crushing strength of tablets

The hardness test represents the structural integrity and the point at which the tablet breaks during storage, transportation, and handling before use. Moreover, the hardness of the tablet also affects the disintegration time. The hardness was measured using a digital hardness tester.

Compressibility Index (Carr's Index)

Carr‟s index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable.

CI = (TD-BD) x 100/TD

where, TD is the tapped density and BD is the bulk density.

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index **[**11-12].

Hausener's Ratio = Tapped density/Bulk Density

Evaluation of Matrix Tablets

General appearance

The general appearance of the Tablets from each formulation batch was observed. The general appearance parameters are Shape and Colour was evaluated visually.

Uniformity of Weight

Twenty Tablets were randomly selected and weighed individually. The average weight was also measured. The percentage deviation of Tablets was calculated and compared with standard specifications.

Weight Variation Test

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = (WA–WI) x 100/ WA

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% friability was calculated as follows

% Friability = (W1 – W2) x 100/W1

Where, W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

Disintegration test for Mirabegron matrix Tablets

One tablet each was placed in each of the six tubes of the basket. The assembly was suspended in Phosphate buffer pH-6.8 maintained at a temperature of 37^0C + 0.5^0C and the apparatus was operated. The time taken for complete disintegration of all tablets was noted.

Drug Content (Assay)

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 20 tested tablets lies within the range of 90% to 110% of the standard amount.

Weigh and transfer 20 tablets to a 100 mL volumetric flask, add about 50 mL of diluent, shake on mechanical shaker for 60 minutes at 200 rpm. Further sonicate for 15 minutes with intermediate shaking to disintegrate the tablets completely. Cool to room temperature and dilute with diluent to volume and mix well. Allow undissolved particles to settle. Filter the clear supernatant solution through 0.45µ Prefilter + PTFE Syringe filter, discard first 2-3 mL filtrate.

Pipette out 4 mL of clear filtrate in 100 mL volumetric flask, dilute with diluent to volume and mix.

In -Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 6, USP type II dissolution apparatus (Paddle method) at 50 rpm in 900 mL of pH 6.8 phosphate buffer solution1,2,3,4,6,8,10,12 Hours.Maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 251 nm.

Details of dissolution test:

Apparatus	:	USP II (Paddle)
Dissolution Medium	:	pH 6.8 phosphate buffer
Medium volume	:	900 mL
Temperature	:	37.0 ± 0.5ºC
Speed	:	50 rpm
Time Point	:	1,2,3,4,6,8,10,12Hours.
Wavelength	:	251 nm

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm-1.

Stability study

Optimized batch of Mirabegron tablets (F23) were kept for a short term stability study in high density polyethylene sealed cover at 40 ± 2 ºC / 75 ± 5% RH as per ICH Guidelines. Samples were withdrawn for six and twelve weeks of storage and evaluated for appearance, drug content and in vitro dissolution [13-15].

RESULT AND DISCUSSION

The granules for matrix tablets were characterized with respect to angle ofrepose, bulk density, tapped density, Carr's index, and drug content (Table 2). Angle of repose was less than 35° and Carr's index values were less than 21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content was more than 90 % for all the granules of different formulations.

Table 2: Physical Properties of Precompression Blend

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	29.05	0.276	0.322	14.28	1.16
F2	26.24	0.308	0.364	15.38	1.18
F3	25.49	0.214	0.251	14.74	1.17
F4	26.97	0.341	0.388	12.11	1.13
F5	26.56	0.422	0.506	16.60	1.19
F6	27.33	0.475	0.566	16.07	1.1
F7	29.25	0.324	0.376	13.82	1.16
F8	28.75	0.481	0.572	15.90	1.18
F9	32.27	0.320	0.397	19.39	1.24
F10	25.38	0.524	0.599	12.52	1.14
F11	25.49	0.494	0.566	12.72	1.14
F12	33.65	0.521	0.629	17.17	1.20
F13	26.27	0.487	0.561	13.19	1.15
F14	33.21	0.518	0.627	17.38	1.21
F15	27.88	0.544	0.643	15.39	1.18
F16	30.45	0.386	0.473	18.39	1.22
F17	27.34	0.510	0.591	13.70	1.15
F18	26.43	0.375	0.442	15.15	1.17
F19	28.77	0.533	0.617	13.61	1.15
F20	19.29	0.434	0.497	12.67	1.14
F21	21.25	0.520	0.582	10.65	1.11
F22	26.43	0.412	0.483	14.69	1.17
F23	28.73	0.362	0.428	15.42	1.18
F24	24.77	0.488	0.537	9.12	1.10
F25	28.47	0.498	0.582	14.43	1.16
F26	26.42	0.439	0.521	15.73	1.18
F27	32.51	0.539	0.652	17.33	1.20
F28	28.19	0.559	0.649	13.94	1.16
F29	33.17	0.482	0.589	18.16	1.22
F30	29.58	0.331	0.393	15.77	1.18

Evaluation of matrix tablets:

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 118.4 and 122.3 mg. The hardness of the tablets ranged from 5.08 to 6.16 kg/cm2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.88 to 3.40 mm. All the formulations satisfied the content of the drug as they contained 90 to 103 % of Mirabegron and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 3: Physical Evaluation of Matrix Tablets

Formulations	Hardness (kg/cm2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	5.58±0.40	3.14±0.80	118.6±0.41	0.43	99.12±2.47
F2	4.25±0.57	3.08±0.66	120.6±1.14	0.54	100.24±1.25
F3	4.91±0.80	3.24±0.52	120.8±1.48	0.64	102.55±2.31
F4	5.66±0.55	3.20±0.20	118.8±1.64	0.12	101.22±0.88
F5	5.50±0.31	3.37±0.25	120.4±0.54	0.39	95.28±0.80
F6	4.41±0.60	3.32±0.89	119.0±0.43	0.37	95.35±1.14
F7	4.08±0.30	3.33±0.25	119.2±0.83	0.58	99.53±1.87
F8	5.00±0.44	3.38±0.73	120.5±0.80	0.77	96.34±2.18
F9	5.50 ±0.44	3.22±0.17	119.8±1.48	0.36	98.25±1.37
F10	5.08±0.37	2.98±0.88	122.1±0.93	0.48	97.35±0.43
F11	4.25±0.57	3.24±0.71	119.9±0.67	0.64	93.28±1.99
F12	4.33±0.50	3.06±0.46	119.2±0.83	0.27	94.57±1.22
F13	5.00±0.31	3.00±0.68	121.2±0.83	0.42	91.29±0.98
F14	5.58±0.37	2.93±0.83	119.8±0.19	0.69	95.39±2.06
F15	5.41±0.70	3.11±0.36	121.2±0.97	0.15	98.88±0.88
F16	5.41±0.69	2.95±0.75	122.3±0.84	0.86	100.68±1.39
F17	5.66±0.65	3.33±0.59	119.8±0.38	0.37	98.90±2.31
F18	4.58±0.57	2.98±0.38	122.2±0.92	0.29	90.35±2.09
F19	6.16±0.70	3.32±0.65	122.9±0.90	0.59	97.66±2.04
F20	5.08±0.37	3.26±0.43	120.2±0.76	0.35	100.44±1.21
F21	4.75±0.77	3.25±0.37	122.0±1.22	0.53	99.54±2.15
F22	5.30±0.47	3.31±0.56	120.1±1.82	0.38	102.87±0.97
F23	5.75±0.57	3.36±0.74	121.3±0.97	0.51	97.43±2.11
F24	4.66±0.35	3.15±0.71	121.5±0.96	0.28	102.82±1.55
F25	5.08±0.86	3.15±0.56	118.4±1.04	0.71	93.78±1.56
F26	5.16±0.65	3.35±0.50	120.6±1.48	0.47	99.21±2.07
F27	5.16±0.75	3.20±0.44	121.4±1.09	0.42	96.27±1.88
F28	5.25±0.97	3.30±0.27	120.5±1.01	0.33	90.76±2.54
F29	5.25±0.67	3.11±0.55	120.7±0.65	0.66	92.55±1.56
F30	5.25±0.57	3.31±0.44	120.9±0.99	0.21	91.99±2.81

***In-Vitro* Drug Release Studies**

The different concentrations of different polymers showed different release patterns. From the release data of different formulations, it was observed that the release rate of most of the formulation were more than 80% to 90% in 10 hours study period [Figures1]. An efficient extended release formulation of Mirabegroncould be designed as controlled release tablets. The optimised formulation (F23) was developed by using HPMC K100M and Ethyl cellulose (1:1). The results of dissolution studies indicated that formulation F-23, the most successful of the study, exhibited drug release pattern very close to theoretical release profile. The designed matrix tablets F-23 of Mirabegron, which release 26% respectively of drug in the first hour and extend the release upto 12 hours, can overcome the disadvantages associated with conventional tablets formulation of Mirabegrontablets. By observing the release data it may be concluded that the release rate of drug from matrix formulations largely depends upon type of polymer and its amount.

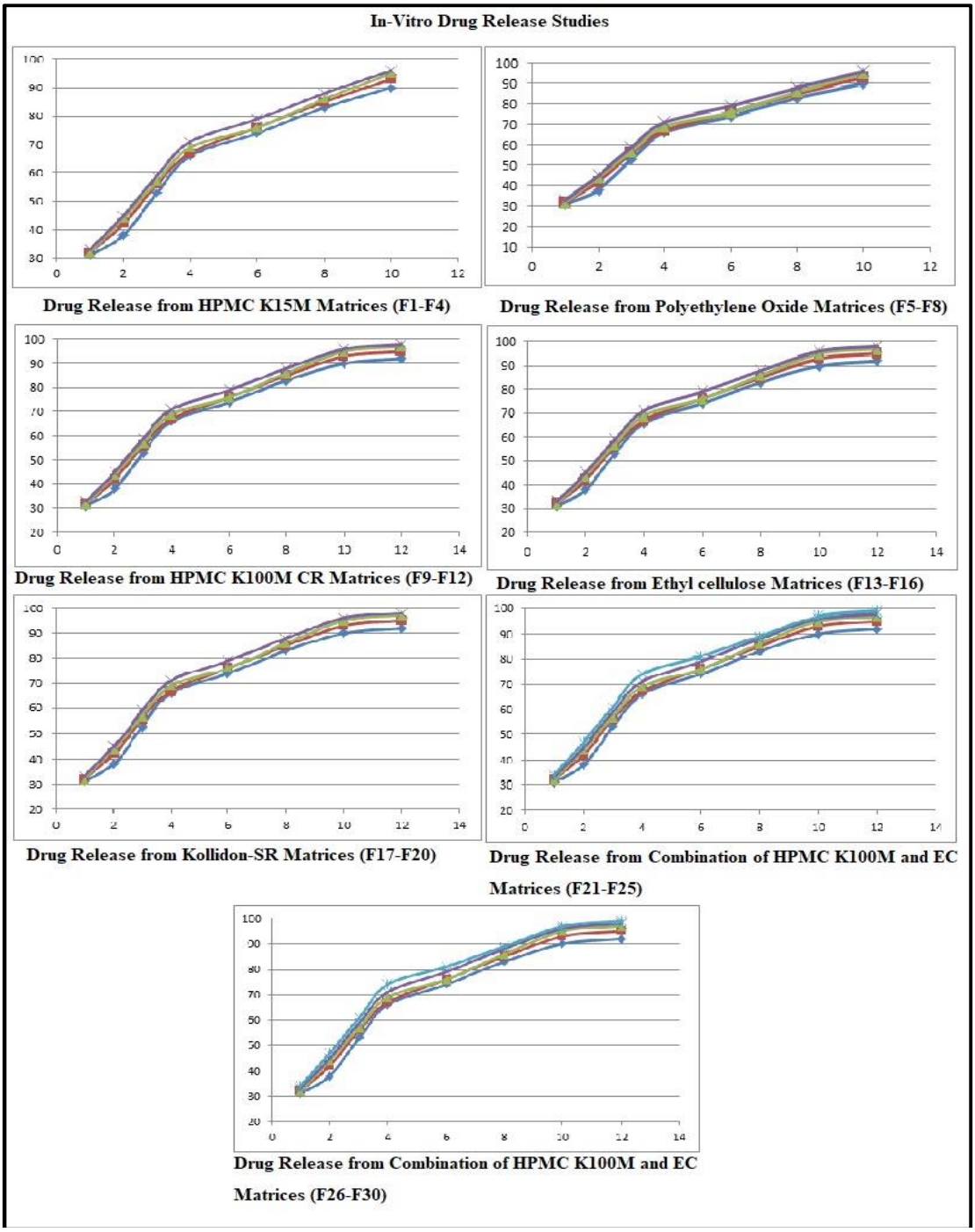

Figure 1: In- vitro drug release studies of different Formulations

FTIR Studies

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and other excipients.

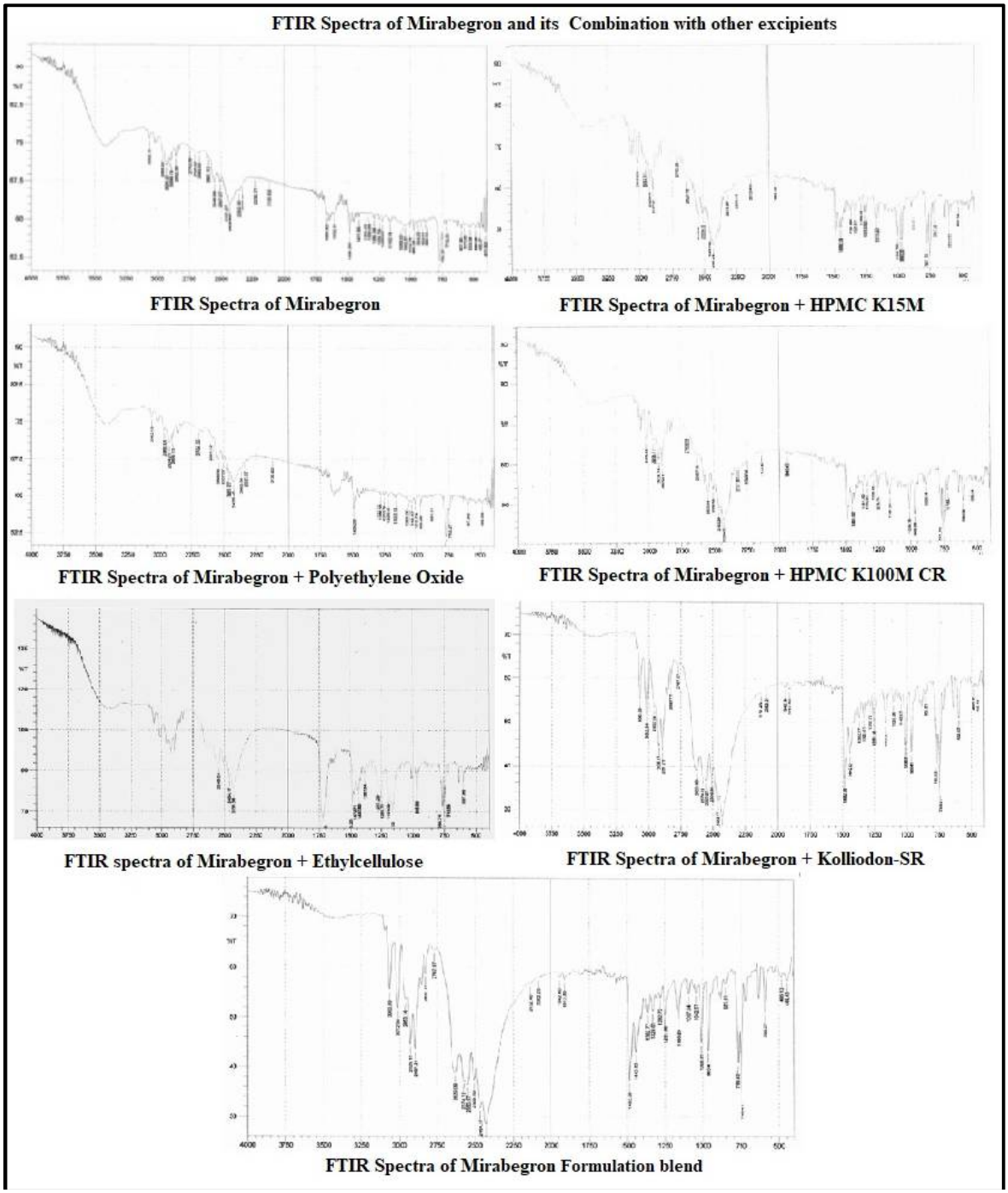

Figure 2: FTIR spectra of mirabegron and its combination with other excipients

Stability study

Stability studies of optimized formulations were analyzed for 12 weeks by evaluating its hardness, swelling index and release study. It is seen that in all three batches, there is no any significance difference in hardness, swelling index and in-vitro release study till 12 week stability study. It reveals that all three formulations (F-23) are stable.

CONCLUSION

In this study, the observations show that the Mirabegron matrix tablets extend the release rate of drug for a prolong period of time for least 12 hrs. Stability studies were performed in accordance to ICH guidelines and no change in physical appearance and no appreciable drug loss were observed. This indicates that the formulation complies with the stability tests. Thus, the polymer will surely serve as a novel and effective drug release retardant with better patient compliance.

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CONFLICT OF INTEREST
No conflict of interest was declared by the authors.

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