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FORMULATION AND IN-VITRO EVALUATION OF MIRABEGRON EXTENDED-RELEASE TABLETS USING HPMC

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Abstract

The current investigation centered on the development and in vitro assessment of extended release (ER) tablets of Mirabegron utilizing Hydroxypropyl Methylcellulose (HPMC) as the polymer for controlling release. Mirabegron, which acts as a β3-adrenergic receptor agonist, is prescribed for the management of overactive bladder syndrome. The objective was to develop an extended release formulation that ensures prolonged drug release, improved patient compliance, and consistent plasma drug levels.

Nine formulations (F1–F9) were prepared using various grades and concentrations of HPMC (K4M, K100M, and K100LV) and evaluated for pre-compression, post-compression, and in vitro drug release parameters. Fourier Transform Infrared (FTIR) analysis confirmed the absence of interactions between Mirabegron and excipients, ensuring formulation stability. The pre-compression evaluations confirmed favourable flow properties with a Carr's Index range of 18.33–24.50% and an angle of repose between 25.17° and 29.68°. Analyses conducted after compression showed that all formulations complied with the pharmacopeial criteria for weight uniformity, hardness, friability, and thickness.

Drug release profiles revealed significant variations, with formulation F9 showing optimal sustained release characteristics, achieving 92.88% drug release over 7 hours with zero-order kinetics.

This study highlights the potential of hydrophilic matrix systems in achieving controlled drug release. The findings pave the way for developing effective extended release formulations, offering therapeutic benefits such as reduced dosing frequency, enhanced treatment adherence, and improved management of chronic conditions like overactive bladder syndrome. Future studies should focus on in vivo evaluations and scale-up for commercial production.

Keywords: Mirabegron, Extended Release, HPMC, Wet Granulation

INTRODUCTION

1. EXTENDED-RELEASE TABLETS

One kind of modified-release dosage form called an extended release (ER) tablet is made to release the active pharmaceutical ingredient (API) gradually over an extended period of time.[1] Extended release pills guarantee maintained drug levels in the circulation, lowering dosage frequency and enhancing patient adherence in contrast to immediate-release tablets, which release the medication rapidly.[2]

1.1 Need of Extended-Release Tablets

Maintaining medication plasma concentrations within the ideal therapeutic window is the major objective of extended-release systems in order to increase effectiveness and reduce volatility. This strategy is especially helpful for long-term illnesses where stable medication levels are essential for efficient disease management, such as diabetes, hypertension, pain management, and neurological disorders.[3]

1.2 Drug Release Mechanism of Extended Release Tablets

The controlled release of medications in extended-release tablets is regulated by many mechanisms:

a. Controlled by Diffusion

In reservoir systems, the medication is encased in a semi-permeable membrane, and diffusion over the barrier causes release. In Matrix Systems diffusion happens through the matrix material as the drug is distributed within a polymer matrix.

b. Systems with Dissolution Control

To manage the release rate, the medicine is either coated with a layer that dissolves gradually or contained within a slowly dissolving carrier.

c. Systems Under Osmotic Control

This system manages the dispensing of medications through an osmotic pressure difference. The drug is administered at a controlled rate via a laser-created opening in a semi-permeable barrier that surrounds a core filled with the medication and osmotic materials.

d. Resins that exchange ions

When the gastrointestinal tract's pH changes, the medication that is bound to ion-exchange resins is released.

e. Systems of Erosion and Swelling

When the tablet's polymers come into contact with stomach contents, they expand and create a gel barrier that controls medication distribution. The matrix slowly breaks down in erosion-based devices, enabling continuous drug release.

1.3 Development and manufacturing of extended-release tablets

Pharmaceutical Formulation Techniques: Matrix Tablets

Matrix tablets represent a promising method for developing extended-release drug therapies since they provide the most cost-effective option for sustained and controlled release solid dosage forms. These tablets can be described as "oral solid dosage forms where the drug or active ingredient is uniformly distributed within either hydrophilic or hydrophobic matrices that act as agents to slow down the release rate."

These systems provide medication continuously through processes governed by dissolution and diffusion. In stomach, the matrix tablet slowly erodes due to acidic environment. However, in the higher pH environment of the upper small intestine, the tablet quickly breaks down into smaller coated pieces that gradually release the medication. There are two separate mechanisms for release: one is zero-order erosion that results in a reducing surface area, while the other is the dissolution of the coated fragments; however, the overall release pattern of the tablet, which consists of these two mechanisms occurring sequentially, tends to be almost linear for the majority of the dosage. This allows for the maintenance of blood concentrations of the active pharmaceutical ingredient within a narrow range, ensuring that levels stay above the minimum effective threshold while remaining below the toxic level.
This kind of sustained-release tablet has demonstrated its effectiveness as a dependable sustained-release formulation with a precise release profile. [4]

1.4 Hydrophilic tablets with a matrix

Currently, hydrophilic matrix systems stand out as one of the most fascinating methods for drug delivery. Due to their affordability, wide regulatory acceptance, and adaptability in attaining specific drug release profiles, they are commonly used to control the rate at which pharmaceuticals are released. One definition of hydrophilic matrix tablets is "homogeneous dispersion of drug molecules inside the skeleton of hydrophilic polymers, such as sodium alginate, cellulose derivatives, polyethylene oxide, Carbopol, or xanthan gum, among others, that swells upon coming into touch with water. Controlled release systems that swell are referred to as these systems.
Alongside diffusion and swelling, the dissolution of polymers plays a crucial role in influencing the rate of drug delivery. While for certain polymers, either swelling or dissolution might be the primary factors, the kinetics of drug release usually arises from a combination of both processes.
It is possible that the observed release rate is the zero-order release. Compression method is adopted to create the majority of commercial hydrophilic matrices. As a result, the fundamental steps required to make the matrices—such as combining and compressing the

ingredients—are the same as those required to prepare regular tablets. In the production of matrix tablets, granulation before mixing and coating are complimentary processes that are frequently employed. Additional excipients are typically included as diluents, lubricants, and anti-adhesives in addition to the medication and the release-limiting polymer. There are two major categories of polymers that are utilized to create hydrophilic matrices.
A. Cellulose derivatives include sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC) 25, 100, 4000, and 15000 cPs, and methylcellulose 400 and 4000 cPs.
B. Natural or semi-synthetic non-cellulose polymers, such as agar-agar, carbo gum, alginates, olasses, mannose and galactose polysaccharides, chitosan, and modified starches.[5]

1.5 Hydrophobic matrix tablets

The method involves compressing the medication into a tablet by mixing it with an inert or hydrophobic polymer, allowing for an extended release from an oral dosage form. The dissolved drug infiltrates a series of pathways created among the compacted polymer particles, resulting in a prolonged release.
Despite the usage of insoluble polymers, this is the only technique in which regulated drug release may be achieved without the use of polymers. The primary components used in the hydrophobic matrix which control the drug release rate are not soluble in water. The phase of liquid infiltration into the matrix dictates the rate in these formulations.
Diffusion serves as one potential method for the discharge of medication in these types of tablets. Particular matrix tablets lose their effect in presence of water and digestive fluids. During the medication release process, the insoluble component of the formulation aids in maintaining the physical structure of the hydrophobic matrix. To manage the release of the medication, it may be essential to incorporate soluble components such as lactose into the formulation. As a result, the mechanism for release entails the movement of the active ingredient from the matrix system through diffusion, and the Higuchi equation, which details release kinetics as a function of the square root of time, can be used to characterize these release properties. [6]

2 Overactive Bladder

Overactive bladder syndrome (OAB) is defined by an elevated need to urinate more often during the day or night, which may or may not be accompanied by urinary incontinence.[7] This syndrome exerts a substantial impact on the quality of life for affected individuals, necessitating a comprehensive understanding of its underlying mechanisms and effective management strategies.[7]

2.1 Pathophysiology of Overactive Bladder Syndrome

Different elements may play a role in overactive bladder (OAB), and the primary cause can differ from person to person. The beginnings of OAB are still under investigation and are not well comprehended. Nevertheless, four theories have been proposed to elucidate the basic mechanisms of OAB. [8]

1. The neurogenic hypothesis proposes that a reduction in inhibitory neural signals, along with

a rise in afferent signals from the bladder, triggers the voiding reflex. [9]

2. The myogenic theory indicates that the detrusor muscle shows an increased responsiveness to cholinergic stimulation, which leads to an upsurge in spontaneous activity. [10]
3. The theory of the autonomous bladder suggests that changes or intensifications in phasic activity are triggered by muscarinic stimulation.[11]
4. The afferent signaling hypothesis: during bladder filling, unprompted contractions lead to heightened afferent signals, which consequently enhance the perception of bladder fullness. [12]

2.2 Non-Pharmacological Treatment

The primary treatment recommended is behavioral therapy, as it carries no risks and has demonstrated effectiveness in numerous instances. Patients are encouraged to implement lifestyle changes: shedding excess weight, limiting fluid consumption, eliminating coffee, spices, acidic beverages, and alcohol, quitting smoking, managing bowel health and preventing constipation, increasing physical activity, and enhancing overall well-being. All of these changes have been shown to yield positive outcomes.[7]

2.3 Pharmacological Treatment

The initial category of pharmacological agents includes antimuscarinic medications (anticholinergic), which facilitate some relaxation of the detrusor muscle. Through years of usage and clinical research, these medications have proven to be safe, generally well tolerated, and effective, resulting in substantial improvement in symptoms and an enhanced quality of life. The most commonly used antimuscarinics are oxybutynin, tolterodine, fesoterodine, trospium, propiverine, and solifenacin. [7]

The second category of medications utilized is β3-agonists. Research has indicated that of the three β adrenoceptors found in the bladder, β3 is the most prominent and plays a key role in promoting detrusor relaxation during the bladder filling phase. Mirabegron has been the sole β3-agonist on the market since 2013, and studies have shown favorable results for symptoms of overactive bladder (OAB). In addition, this agonist is generally well received by patients. Mirabegron is classified as a second-line treatment option. Its effectiveness is similar to that of antimuscarinics, but it presents fewer side effects, particularly concerning the occurrence of dry mouth.[12]

The objective of the research is to develop Mirabegron extended-release tablets utilizing a wet granulation method with HPMC and to conduct in-vitro assessment, as well as to compare the release profiles of the formulated tablets with those of a commercial sample.

3. MATERIALS AND METHODOLOGY

The formulation of Mirabegron extended release tablets included Mirabegron, HPMC K4M, HPMC K100M, HPMC K100LV, Microcrystalline Cellulose, Lactose, Magnesium Stearate, and Talc. All the raw materials were generously provided by Vega Pharmaceuticals Pvt. Ltd. All reagents and solvents utilized for the analysis were of suitable Analytical Grade.

3.1 EVALUATION OF PRECOMPRESSION PARAMETERS

Pre-formulation studies are investigation of physical and chemical nature of drug. Physical identification of mirabegron was carried out in terms of color, texture, taste and odour.

The FTIR spectra of pure drug and formulation blend were studies using FTIR. The spectra were obtained by AGILENT FTIR Cary 630. The samples were directly placed on crystal and spectra were recoded.

The formulation blends were evaluated for Angle of Repose, Bulk Density, Tapped Density and Carr's Index using standard methods.

3.2 FORMULATION DEVELOPMENT

Mirabegron extended-release tablets were formulated by wet granulation approach. Mirabegron, HPMC, Lactose monohydrate and MCC were sifted from sieve # 60. Purified Talc and Magnesium Stearate were sifted from sieve # 80. Povidone K-30 was dissolved in Isopropyl Alcohol. Rapid Mixer Granulator was used and the intragranular dry materials were mixed for 15 minutes. Wet granulation was carried out and wet mass was then dried at Fluidized Bed Dryer at 60°C until moisture content of dried granules was at (2 ± 0.5 %) w/w. Dried granules were sifted from mesh # 20 and mixed with extragranular materials (HPMC, MCC) in Rapid Mixer Granulator. Magnesium Stearate and Purified Talc was added and lubrication was carried out for 90 seconds.

Lubricated granules were then compressed in CIP Lab Press 10 Station using D-tooling, 6.50 mm round, standard biconcave, plain punch. Tablets were then evaluated for various parameters.

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

Table 1: Value of Angle of Repose [13]

arr's Index	**Flow Character**
10	Excellent
-15	Good
-20	Fair
-25	Passable
-31	Poor
-37	Very Poor
38	Very Very Poor

Table 2: Value of Carr's Index [13]

Formulation of Mirabegron extended-release tablets

S. No.	Material	Grade	mg/ tablets								
			F1	F2	F3	F4	F5	F6	F7	F8	F9
Intragranular											
1	Mirabegron	IH	25	25	25	25	25	25	25	25	25
2	HPMC K 4M	IP	16.5	19.25	22	-	-	-	-	-	-
3	HPMC K 100 M	IP	-	-	-	16.5	19.25	22	-	-	-
4	HPMC K 100 LV	IP	-	-	-	-	-	-	16.5	19.25	25
5	MCC PH 102	IP	21.875	19.125	16.375	21.875	19.125	16.375	21.875	19.125	16.375
6	Lactose Monohydrate	IP	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Granulating Solution											
7	PVP K 30	IP	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
8	Isopropyl Alcohol*	IP	QS	QS	QS	QS	QS	QS	QS	QS	QS
Extragranular / Dry Mixing											
9	HPMC K 4M	IP	16.5	19.25	22	-	-	-	-	-	-
10	HPMC K 100 M	IP	-	-	-	16.5	19.25	22	-	-	-
11	HPMC K 100 LV	IP	-	-	-	-	-	-	16.5	19.25	25
12	MCC PH 102	IP	21.875	19.125	16.375	21.875	19.125	16.375	21.875	19.125	16.375
Lubrication											
13	Magnesium Stearate	IP	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
14	Purified Talc	IP	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Total Core Weight			110	110	110	110	110	110	110	110	110

Table 3: Composition of Mirabegron extended release tablets

3.3 EVALUATION OF PRE-COMPRESSION PARAMETERS OF MIRABEGRON EXTENDED-RELEASE TABLETS

3.3.1 PHYSICAL PARAMETERS OF TABLETS

Formulated tablets were tested for weight variation as per pharmacopoeia. Percentage deviation was calculated. The Hardness, Average Thickness and Average Diameter of tablets were examined. The Roche friabilator was utilized to evaluate friability by adhering to the outlined procedure.

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

Table 4: Indian Pharmacopeia specifications for tablet weight variation

3.3.2 DISSOLUTION TEST / IN-VITRO DRUG RELEASE STUDY

In-vitro drug release of formulated Mirabegron extended release tablets were determined by High Performance Liquid Chromatography using the method as described in Analytical Profile of Mirabegron extended release tablets published by National Medicines Laboratory, Government of Nepal. [14] Following Conditions and procedure were followed to study the in-vitro drug release of all formulated tablets.

Dissolution Apparatus: USP I
Dissolution Medium: 900 ml of Phosphate Buffer pH 6.8
Speed: 100 RPM
Sampling Time: 1, 3, 5, 7, 8.5, 10 and 12 hours. [15]

Procedure: The dissolution parameters outlined earlier were adhered to for the experiment. Upon reaching the designated time intervals during the dissolution test, 15.0 ml of the sample solution was taken, and fresh dissolution medium was added after each sample withdrawal. The solution was filtered using a 0.45 µm nylon filter, and the filtrate was collected in an HPLC vial after discarding the initial 2 ml. Chromatographic system as described in Assay was used. The reference and test solution were injected. The percentage release of Mirabegron for each sampling time was calculated.

3.3.3 Drug Content (Assay by HPLC): [39]

Drug content of tablets was analysed by HPLC method using following outlined conditions.

Chromatographic conditions:

Column:	4.6 mm × 250 mm; 5 µ (packing- C18)
Column temperature:	45ºC
Detector:	UV

Flow rate: 1.0 ml per minute
Wavelength: 250 nm
Injection volume: 10 µl

System suitability: In the chromatogram obtained with the standard solution, the % RSD value of the area of principal peak for 5 replicate injections should not be more than 2.0%, tailing factor for principal peak should not be more than 2.0 and the column efficiency for principal peak should not be less than 2000 theoretical plates.

The standard solution and test solutions were injected. % Drug content of Mirabegron was calculated in Mirabegron extended release tablets using the given formula.

3.3.4 APPLICATION OF RELEASE RATES KINETICS AND CALCULATION OF SIMILARITY FACTOR (F2)

In order to analyze the kinetics of drug release from the dosage form, the gathered data from formulation were utilized in zero-order, first-order, Higuchi, and Korsmeyer-Peppas release models.

The dissolution profiles of the product or products can be analyzed under different testing conditions (like media pH) by employing either model-independent or model-dependent methods.

A widely accepted method for evaluating dissolution profiles is the model-independent similarity factor (f2) approach. The f2 parameter is expressed by the equation.

$$F2 = 50 \text{ X Log } \{[1 + (1/n) \Sigma t=1 \text{ n } (Rt - Tt)^2] - 0.5 \text{ X } 100\}$$

In this equation, Tt and Rt are the average dissolution values of the test and reference products at a specific time point (t), respectively, while n represents the number of time points utilized for comparing the average dissolutions.

Dissolution profiles of Market Sample and Test product were performed in a single media of Ph 6.8 Phosphate buffer. The percentage cumulative drug release was calculated for recommended sampling time points and as from the above equation, f2 value between market sample and formulated samples were calculated.

4. RESULTS AND DISCUSSION

4.1 Physical Identification was carried out for drug sample. The result of physical identification of Mirabegron drug are reported in table 5.

S.No.	Property	Observation
1.	General description	Off white crystalline powder
2.	Odour	Odourless
3.	Taste	Bitter
4.	Melting point	142.66 ºC
5.	Solubility	Soluble in DMSO, N,N-Dimethylformamide, Insoluble in water

Table 5: Physical Identification of Mirabegron

4.2 FTIR Spectroscopy

Mirabegron was scanned in FTIR and the resulting spectra was compared with Reference spectra in Library. Qualitative analysis showed 97% match confirming that the drug is Mirabegron.

Formulation blend of Mirabegron mixed with HPMC K4M, HPMC K100 M, HPMC K00 LV was scanned for its transmittance and compared with pure IR spectra of Mirabegron. All principal peak of Mirabegron was found intact, which indicated that there is no any interaction amongst drug and excipients used.

Qualitative analysis of Mirabegron with Reference

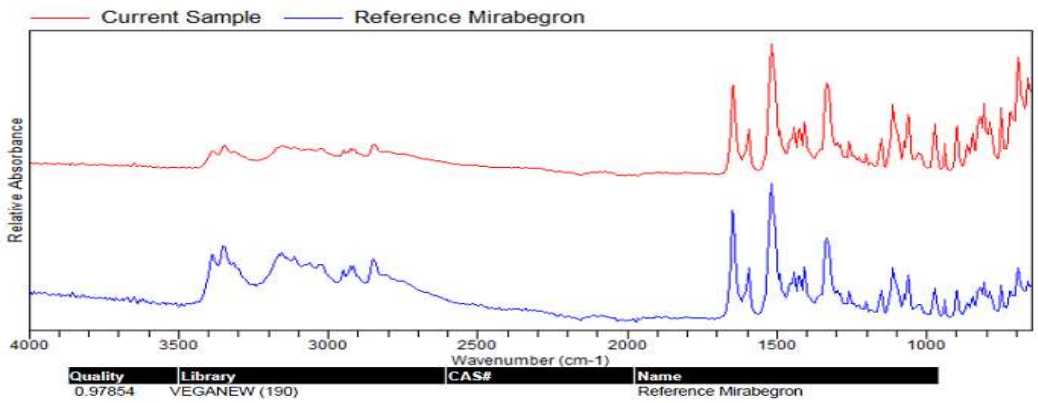


Figure 1: Qualitative analysis of Test sample (Mirabegron) with Reference Spectra

IR Spectra of Pure Mirabegron

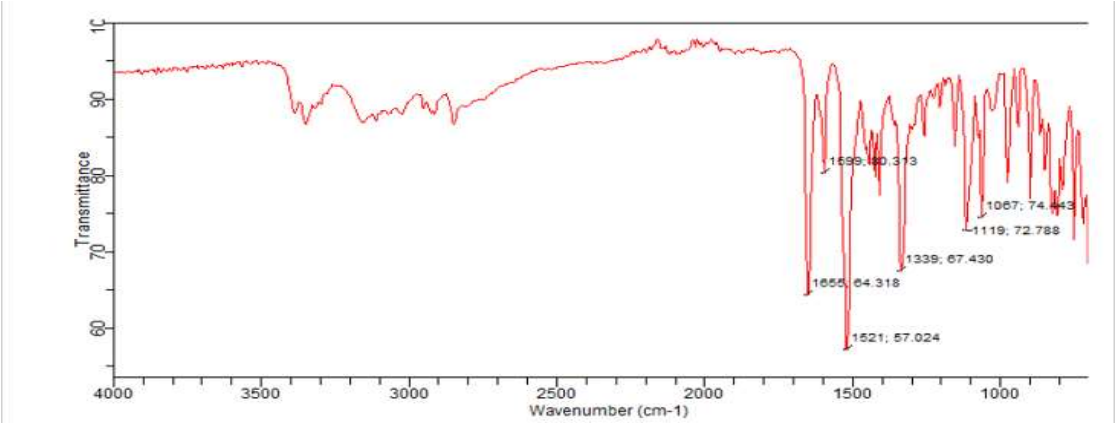


Figure 2: IR Spectra of Pure Mirabegron

IR Spectra of Mirabegron with HPMC K 4 M and its formulated blend

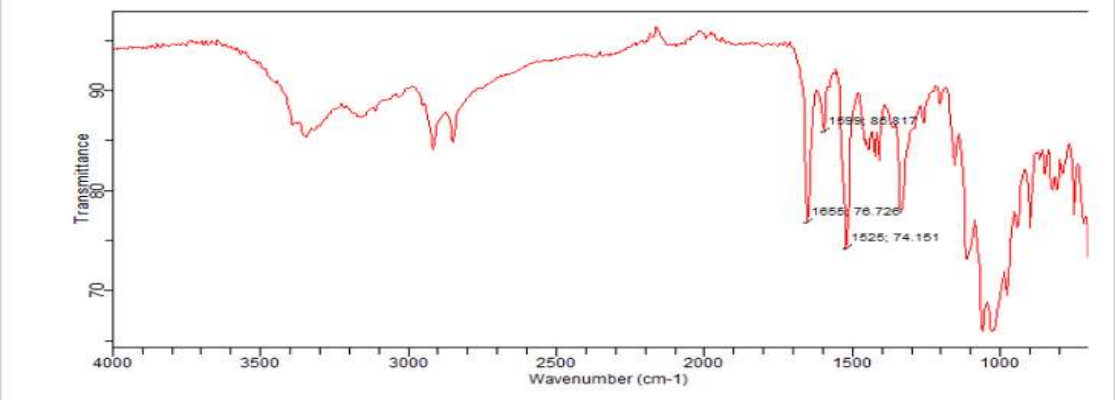


Figure 3: IR Spectra of Mirabegron with HPMC K 4 M

IR Spectra of Mirabegron with HPMC K 100 M and its formulated blend

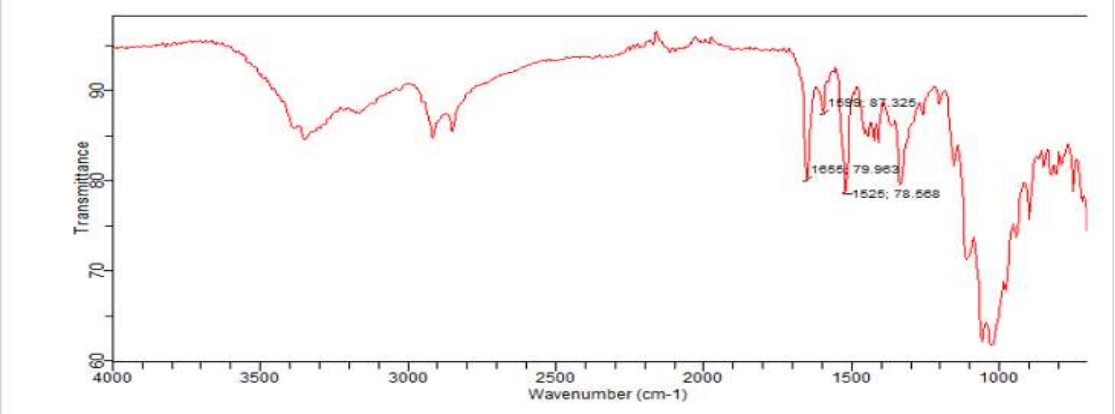


Figure 4: IR Spectra of Mirabegron with HPMC K 100 M

IR Spectra of Mirabegron with HPMC K 100 LV and its formulated blend

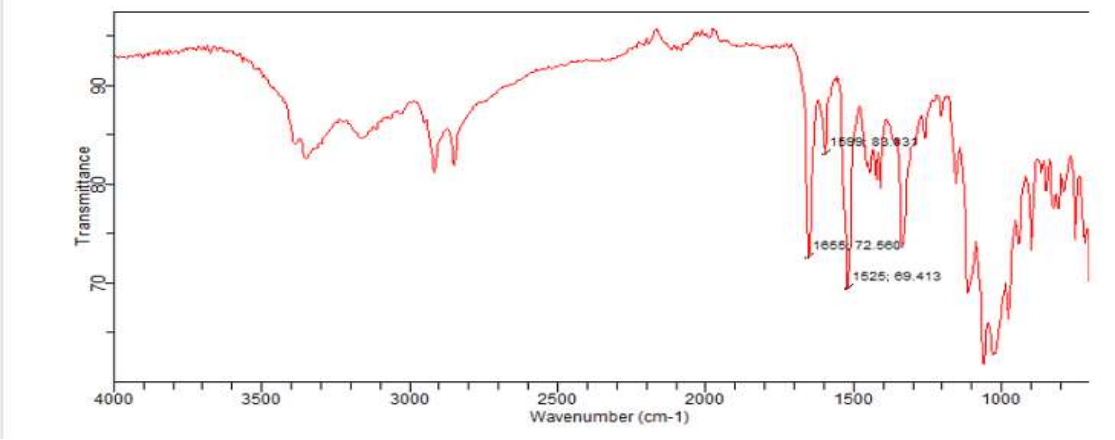


Figure 5: IR Spectra of Mirabegron with HPMC K 100 LV

4.3 Evaluation of Pre Compression Parameters

The pre-compression parameters were assessed for all the blended formulations. The angle of repose, bulk density, tapped density, and Carr's Index were determined for nine different formulations. The angle of repose for all formulations ranged from 25.17° to 29.68°. Bulk

density for 9 formulations was observed between 0.378 g/ml to 0.423 g/ml. Tapped density for 9 formulations were observed between 0.490 g/ml to 0.520 g/ml. The compressibility of powders in nine different formulations was examined, and Carr's Index was determined. It was found to be between 18.33 to 24.50. The results of pre-compression parameter showed that all formulation blend showed excellent flow property with fair to passable powder characteristics. All results are tabulated in Table 6.

4.4 Evaluation of Post Compression Parameters

Samples from each batch of tablets underwent a weight variation test, where the differences in weight and percentage deviation were determined for each tablet. The average weight of the tablets falls between approximately 108.40 and 111.40 mg**,** with the acceptable limit being ±7.5% for tablets weighing between 80 and 250 mg. The outcomes of the test indicated that the tablet weights complied with the requirements set by the pharmacopoeia. Hardness of tablets for all formulated batches were checked and found to be between 4.40 kgf to 8.66 kgf. Average thickness was measured for all formulated batches and was found to be between 3.30 and 3.43 mm, which showed consistent thickness. Friability was calculated for all formulated batches and was found to between 0.01% to 0.09%. The friability measurements fall well within the acceptable range, indicating the strong mechanical properties of the tablets that were formulated. The drug content (Assay) of all formulation was determined by using HPLC. The drug content was found to be between 97.07% and 101.48%. All batches complied with given acceptable limit of not less than 90% and not more than 110% of the stated amount of Mirabegron. It indicated a very uniform distribution of drug content. The results of post-compression parameters are tabulated in Table 7.

Formulations	Angle of Repose	Bulk Density (g / ml)	Tapped Density (g / ml)	Carr's Index
F1	26.17	0.396	0.510	22.22
F2	26.10	0.378	0.500	24.24
F3	28.37	0.385	0.510	24.50
F4	29.68	0.386	0.502	23.10
F5	28.21	0.378	0.490	22.85
F6	25.70	0.384	0.490	21.53
F7	25.22	0.423	0.520	18.64
F8	25.17	0.416	0.510	18.33
F9	26.56	0.395	0.490	19.33

Table 6: Pre-Compression Parameters of Formulated Batches F1 – F9

Formulations	Weight Variation (mg)	Hardness (kgf)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	110.95	6.77	3.35	0.04	100.43
F2	111.00	7.62	3.32	0.02	97.07
F3	108.40	4.40	3.43	0.09	101.22

F4	108.85	8.66	3.30	0.01	98.88
F5	109.10	7.56	3.32	0.02	100.32
F6	111.40	6.24	3.42	0.04	101.48
F7	109.35	7.83	3.34	0.01	99.90
F8	109.70	7.21	3.32	0.01	98.88
F9	108.75	6.50	3.40	0.04	98.49

Table 7: Post Compression Parameters of Formulated Batches4.5 In-vitro Drug Release Study

An in-vitro study on drug release was conducted for all formulations. The cumulative percentage drug release was calculated for each batch. Formulations using HPMC K 100 M (F6) showed the least drug release with 47.50% at 12 hours for F6. The viscosity and concentration of polymer had a direct effect on release of drug. As the concentration of polymer increased along with viscosity, greater was the drug release retardation. All formulations using HPMC K 100 LV showed optimum drug release with 90% and above at 7 hours.

Amongst all, F9 showed the best drug release and so, it was chosen for application of release rate kinetics and calculation of similarity Factor with Market Sample. The % drug release for formulations F1 -F9 are shown in Table 8, 9 and 10.

Time	**Cumulative percentage drug release (%)**		
(hour)	**F1**	**F2**	**F3**
0	0	0	0
1	27.28	23.93	7.16
3	57.65	41.28	20.45
5	76.85	50.80	33.48
7	82.92	64.09	45.69
8.5	84.55	70.72	53.28
10	85.75	74.92	60.18
12	86.30	82.46	67.72

Table 8: Dissolution profile of Mirabegron extended release tablets prepared with HPMC K 4M

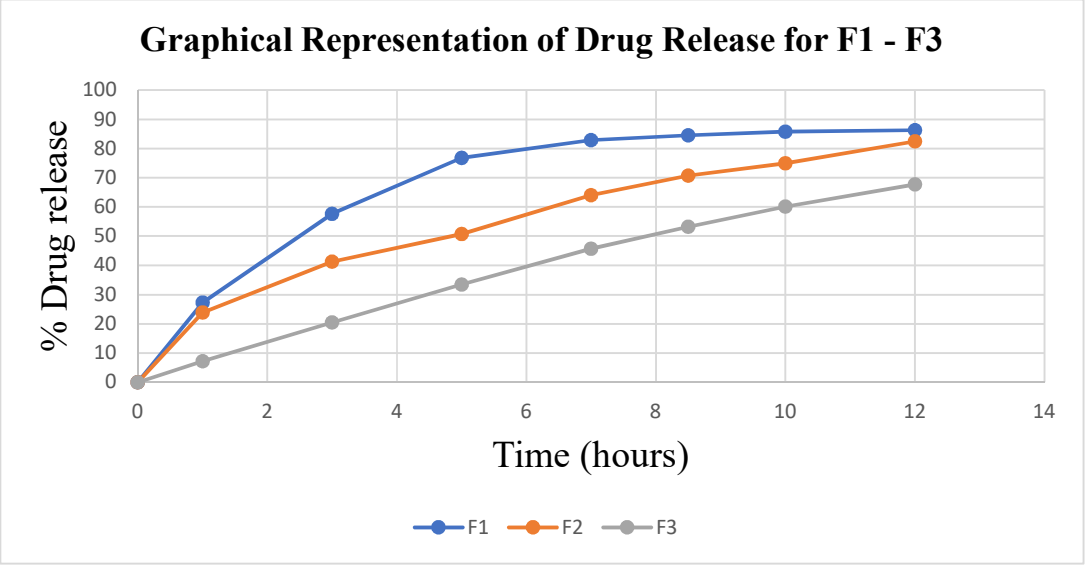


Figure 6: Graphical Representation of Cumulative Drug Release for F1 – F3

Time (hour)	**Cumulative percentage drug release (%)**		
	F4	**F5**	**F6**
0	0	0	0
1	9.86	5.42	4.41
3	21.7	16.00	14.29
5	33.41	26.72	22.85
7	43.81	37.15	31.62
8.5	51.11	43.71	37.49
10	57.00	50.40	42.68
12	64.01	57.94	47.50

Table 9: Dissolution profile of Mirabegron extended release tablets prepared with HPMC K 100M

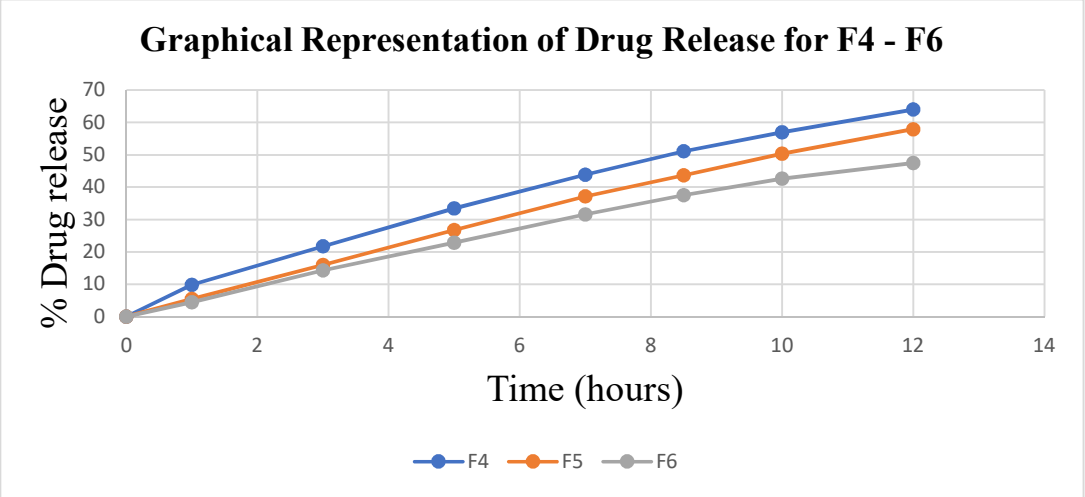


Figure 7: Graphical Representation of Cumulative Drug Release for F4 – F6

Time (hour)	**Cumulative percentage drug release (%)**		
	F7	**F8**	**F9**
0	0	0	0
1	9.30	6.34	5.51
3	44.76	41.76	33.70
5	80.14	79.39	67.14
7	96.63	98.70	92.88
8.5	97.12	99.29	94.29
10	96.99	99.82	94.05
12	96.33	98.71	93.46

Table 10: Dissolution profile of Mirabegron extended release tablets prepared with HPMC K 100 LV

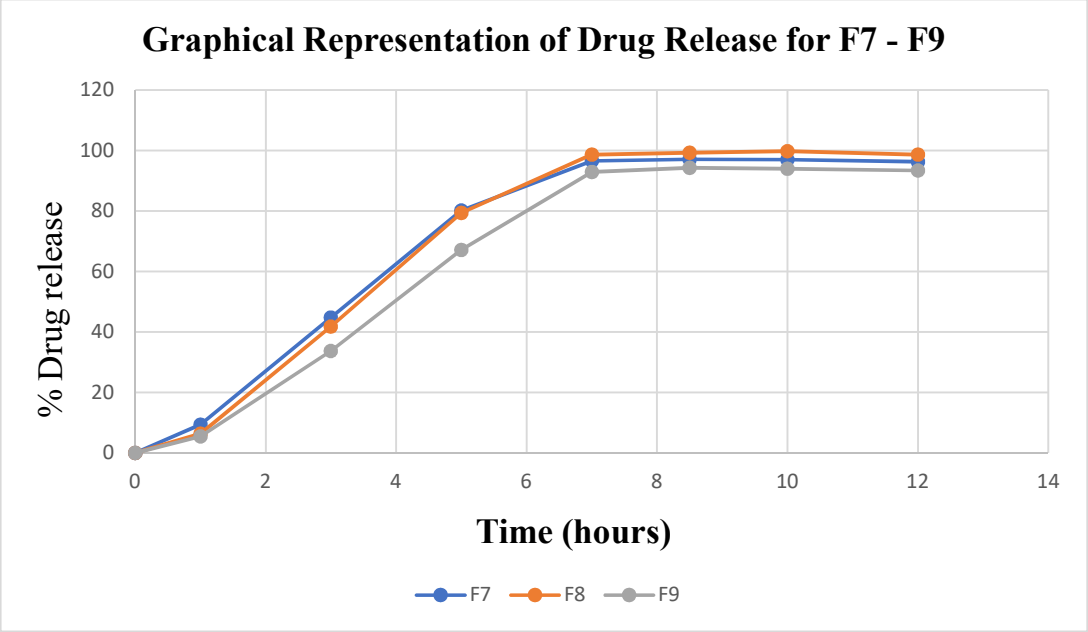


Figure 8: Graphical Representation of Cumulative Drug Release for F7 – F9

4.6 Application of Release Rate Kinetics and Calculation of Similarity Factor (F2)

Formulation F9 demonstrated the most favorable drug release profile, therefore it was chosen to assess the characteristics of drug release from the dosage form. More than 90% of drug was released at 7 hour time interval showing asymptote condition. Thus, data of time interval and drug release up to 7 hours were only taken into consideration for mathematical calculation for release rate kinetics. The results of curve fitting for the release rate profile of the developed formulations provided insights into the drug release mechanism. According to the data analysis, the drug release was determined to follow zero-order kinetics, with the mechanism most accurately described by zero-order, as the plots demonstrated the greatest linearity. The diffusion constant 'n' was 0.671 which indicated that the drug release was controlled by more than one process.

The similarity factor (f2) for the dissolution profile of formulation F-9 was determined by comparing it to the marketed sample. Similarity factor (F2) value was found to be 73.07, which is within acceptable limit. The result indicated that the dissolution profiles of the Test and Reference were comparable.

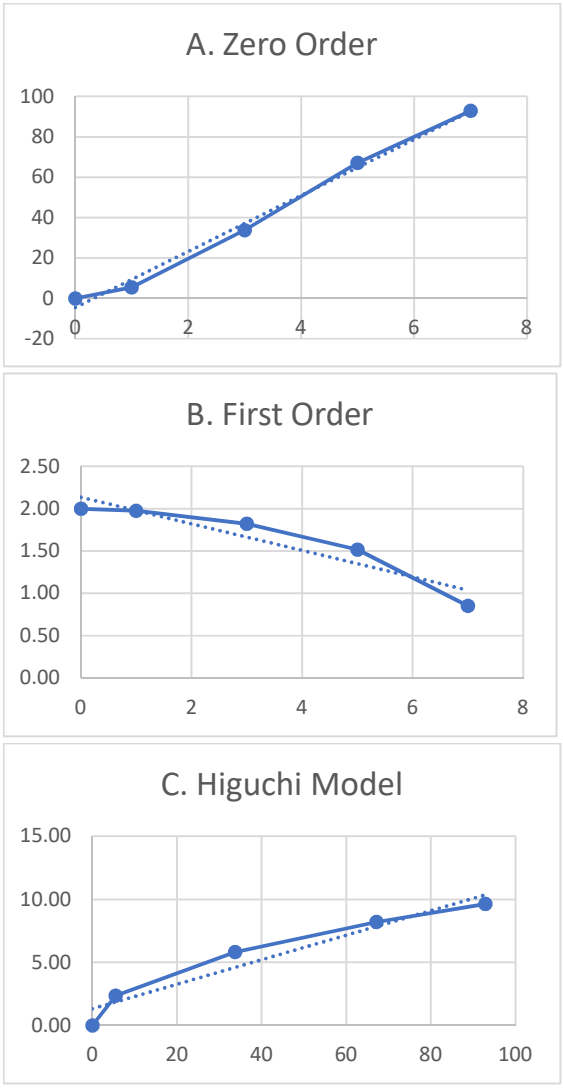
Formulation	Zero Order Kinetics		First Order Kinetics		Higuchi's Kinetics		Korsmeyer-Peppas	
	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
F9	13.87	0.99	-0.156	0.88	0.097	0.93	0.671	0.99

Table 11: Release Rate Kinetics for F9

Time	**Cumulative % Drug Release**

(hour)	F9	Marketed Formulation
1	5.51	6.81
3	33.70	33.41
5	67.14	66.87
7	92.88	95.11
8.5	94.29	101.21

Table 12: Similarity Factor Calculation between F9 and Market Sample



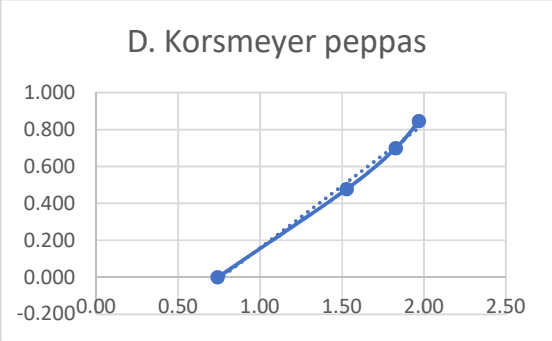


Figure 9: Release rate kinetics for F9: A. Zero order Kinetics, B. First order kinetics, C. Higuchi Model, D. Korsmeyer peppas model

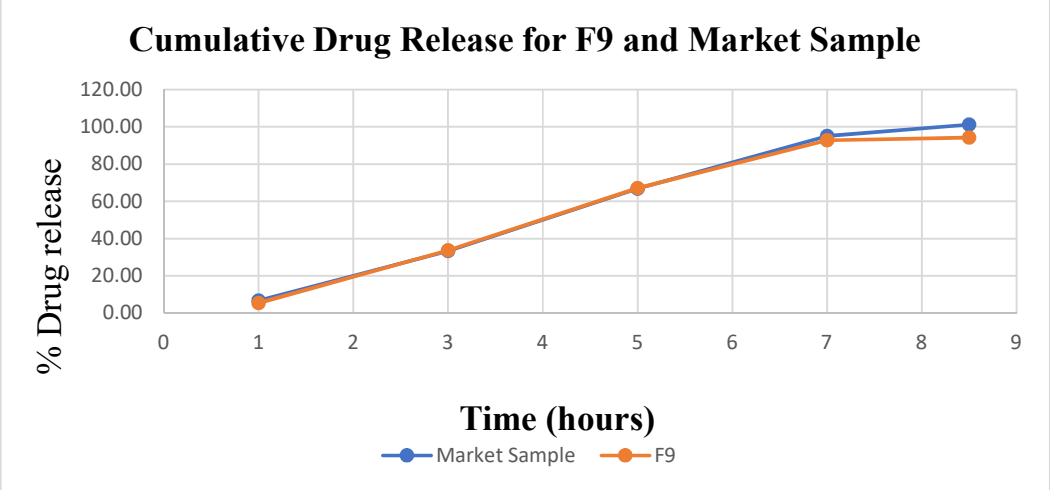


Figure 10: Graphical Representation of Cumulative Drug Release for F9 and Market Sample

5. SUMMARY AND CONCLUSION

The development and assessment of Mirabegron extended release (ER) tablets utilizing different grades of Hydroxypropyl Methylcellulose (HPMC) as the release-controlling polymer were the main objectives of the study. The goal was to create extended release tablets with predictable release kinetics and ultimately better therapeutic effectiveness and better patient compliance. As the main matrix-forming agent, HPMC showed that it could control the kinetics of release. 9 formulations were formulated using various grades and concentration of HPMC. The formulation mixture underwent several pre-formulation assessments, and the flow characteristics were positive, suggesting that the powder blend exhibits favorable flow properties. The formulations created with HPMC K 100 LV successfully slowed drug release for as long as 7 hours. Of all the formulations, the F9 formulation exhibited the most favorable release rate. Additionally, F9 underwent release kinetics analysis, which indicated that the formulation adhered to zero-order kinetics. The

formulation, F9, presents a promising option for reducing dosing frequency and maintaining consistent plasma concentrations, which is critical for improving patient adherence and minimizing side effects.

Challenges and Future Directions

Although the study effectively addressed important formulation design and evaluation aspects, future research should concentrate on the following areas:

• Verifying bioequivalence and therapeutic efficacy through in vivo studies.
• Examining the wet granulation method's scalability for commercial production.
• Examining the impact of gastrointestinal variability on drug release in a range of patient populations.

This study advances sustained-release drug delivery systems and lays the groundwork for future innovations in pharmaceutical formulations.

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