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DESIGNING A SUSTAINED-RELEASE SOLID ORAL FORMULATION FOR OVERACTIVE BLADDER TREATMENT: A QUALITY BY DESIGN APPROACH

Neeraj Sharma[1], Daksh Bhatia[2], Sharda Shambhakar[1]*, Pavitra Solanki[3]

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ABSTRACT

Background: Mirabegron, a first-in-class β3-adrenergic agonist used for managing overactive bladder (OAB), is well-documented in the literature. However, its low oral permeability results in poor bioavailability, limiting patient compliance and tolerability. To address this, the present study focuses on developing a sustained-release (SR) tablet of mirabegron with enhanced oral effectiveness. In this research, mirabegron was combined with polyethylene oxide to improve permeability and formulated as an HPC-loaded SR tablet, promising improved bioavailability and anti-OAB efficacy. **Methods:** Tablet design and optimization were carried out using the Box-Behnken Design (Design Expert® 12 software) to refine formulation parameters. The study aimed to create a commercially viable SR tablet with improved intestinal permeability, bioavailability, and clinical acceptance. **Results:** The optimized formulation showed a 34.8% increase in bioavailability compared to the marketed tablet. In vivo pharmacokinetic studies demonstrated a 31.77% increase in plasma concentration over the marketed formulation. **Conclusion:** The developed formulation is safe and effective, offering improved therapeutic potential for treating overactive bladder. This work represents a significant advancement in OAB management and highlights the commercial viability of the emerging mirabegron SR tablet in meeting current therapeutic needs.

INTRODUCTION

Overactive bladder (OAB) is a prevalent and chronic condition affecting millions of people worldwide, characterized by urinary urgency, frequency, nocturia, and, in some cases, urge incontinence[1]. The background of OAB is rooted in the complex physiology of bladder control, which involves a delicate balance between the central nervous system, peripheral nerves, bladder muscles, and urethral function[2,3]. Historically, OAB was often underdiagnosed and undertreated due to the stigma associated with urinary symptoms and the misperception that it was a normal part of aging. However, increasing awareness and research over the past few decades have shed light on the condition's impact on quality of life, particularly in older adults.

[1]*Department of Pharmaceutics, Banasthali Vidyapith, P.O. Banasthali Vidyapith, Rajasthan-304022, India*
[2]*Department of Pharmacognosy, KIET School of Pharmacy, Ghaziabad, Uttar Prdaesh-201206, India*
[3]*Department of Pharmaceutics, Delhi Pharmaceutical Sciences and Research University, New Delhi-110017, India*

For Correspondence: **ssambhakar@yahoo.co.in**

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OAB management typically includes antimuscarinics or β3-adrenoceptor agonists like mirabegron, which relaxes the bladder's detrusor muscle to increase capacity and reduce urgency, frequency, & incontinence [4,5]. However, immediate-release forms require multiple daily doses, affecting adherence. Mirabegron's marketed tablet faces bioavailability issues due to low solubility or permeability, resulting in variable absorption and delayed onset, impacting symptom management. These challenges necessitate higher doses and affect therapeutic consistency, limiting mirabegron's effectiveness for patients needing quick symptom relief [6–8]. Current treatments for overactive bladder (OAB) face several limitations that hinder their effectiveness and patient adherence. Oral medications like mirabegron often suffer from low bioavailability due to poor absorption, leading to inconsistent therapeutic outcomes. Immediate-release formulations require frequent dosing, which can reduce convenience and compliance [9]. Additionally, antimuscarinic drugs commonly used for OAB are associated with side effects such as dry mouth, constipation, and cognitive issues, further discouraging long-term use. The delayed onset of action and variability in drug absorption due to individual differences or dietary factors also impact their reliability. Moreover, treatment options for patients who do not respond to standard therapies are limited, while advanced formulations can be costly and less accessible [3]. These challenges highlight the need for innovative approaches to improve drug delivery, efficacy, and patient experience. This study aims to develop pharmaceutically interchangeable SR matrix tablets to treat OAB effectively. The novelty behind this research includes the enhancement of permeability of mirabegron to enhance its bioavailability because it has low bioavailability due to its low permeability[10,11]. Polyethylene oxide (PEO) for permeability enhancement is used in this work, and HPC is utilised to sustain the tablet's release. This study addresses a critical need in treating OAB by focusing on developing SR matrix tablets that are pharmaceutically interchangeable, effective, and patient-friendly. The research outcomes are expected to contribute to advancing drug delivery technologies, ultimately leading to better patient outcomes in managing OAB and potentially other chronic conditions.

MATERIALS

Mirabegron (Drug) was purchased from TCI Chemicals (India) Pvt. Ltd. Polyethene oxide (PEO), PEG6000, and Hydroxypropyl Cellulose were used for binding and sustained release properties (Moly Chem, India). Magnesium stearate (CDH Fine Chemicals Delhi), Methanol HPLC grade, and Ethanol HPLC grade (Merck, Mumbai, India) were used throughout the research work. The chemicals used for this research work were analytical grade.

Methods

Preparation of Mirabegron tablet

Tablets were prepared by top-spray wet granulation [12–14]. The process begins by sifting polyethylene glycol, hydroxypropyl cellulose, and polyethylene oxide through a #24 sieve to ensure uniform particle size. Mirabegron is dissolved in methanol to create a clear granulating solution. The granulation is performed in a fluid bed processor at a controlled temperature of **40–45°C** to ensure efficient drying without degrading the active ingredient. The granules are dried to achieve a moisture content of **≤1%**, as excessive moisture can compromise the blend's compressibility and stability. After drying, the granules are sifted, with any large particles milled to a consistent size. The blending step is performed for **10 minutes at 12 RPM**, ensuring uniform distribution of all excipients. Finally, magnesium stearate is added for lubrication, and the blend is compressed into tablets. This detailed description ensures reproducibility and highlights critical process parameters impacting tablet quality.

Physicochemical characterization of Mirabegron and excipients compatibility

Analytical techniques like DSC, XRD and FTIR successfully characterised Mirabegron and its excipients.

Formulation development based on Box-Behnken Design (BBD)

After assessing various factors, only high-variability ones were considered for the final risk assessment. High-risk factors included concentrations of PEO, HPC, and magnesium stearate; medium-risk factors included temperature, mixing speed, and formulation time; and low-risk factors included equipment age and glass quality. Only high-risk factors were optimised using the Box-Behnken design [15,16].

Preformulation parameters

Once formulated according to guidelines, the quality of a tablet largely depends on the physicochemical properties of the blends. Numerous formulation and process variables involved in the mixing process can significantly influence the characteristics of

the resulting blends. Therefore, before formulation development, the blends underwent thorough preformulation testing and analysis [17,18].

Evaluation of post-compression parameters for prepared Tablets

Quality control tests were conducted on the compression-coated tablet, including weight variation, hardness, friability, and thickness [3,19,20].

HPLC method development (Chromatographic conditions)

Experiments used a Shimadzu HPLC with an Eclipse XDB C18 column and a mobile phase of 95:5 methanol-acetonitrile. Mirabegron absorbance was detected at 251 nm, with a pre-filtered and degassed mobile phase.[21–24].

Uniformity of content

The drug content uniformity of mirabegron tablets was evaluated according to the Indian Pharmacopoeia standards. Ten tablets were weighed, crushed, and dissolved in methanol to prepare serial dilutions. The content was then analysed at 251 nm using HPLC[25,26].

In-vitro drug release

The release study of the optimised mirabegron tablet, along with Mirakem and Myrbetriq tablets, was performed across different pH conditions (0.1N HCl at pH 1.2, pH 4.5, and pH 6.8) using USP apparatus-I at 37°C and 100 rpm. Samples were collected at specified intervals, filtered, diluted, and analysed at 251 nm. To evaluate the drug release mechanisms, the data were fitted into release behavior models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas [27–29].

Ex-vivo gut permeation analysis

The confocal microscopy method was employed to evaluate the depth of drug penetration in intestinal tissues. Tissue samples from the excised rat intestine were carefully cleaned with Kreb's Ringer phosphate buffer (KRPB) to remove debris and then sectioned into 6 cm sacs. After drug exposure during the permeation study, the tissues were thoroughly rinsed to eliminate unabsorbed drug from the surface. The prepared tissues were fixed in 4% paraformaldehyde for stabilisation and then mounted on microscope slides. Imaging was conducted using a confocal laser scanning microscope (model: LMI-U.K. Inverted + Mortic Microscope, EA100i) equipped with a fluorescence detector.

Imaging Parameters:

- **Excitation Wavelength:** 488 nm
- **Magnification:** 20x
- **Scanning Depth:** Up to 50 μm
- **Z-Stack Interval:** 1 μm

These settings were optimised to capture the fluorescence intensity of the drug molecules within the tissue, allowing for precise penetration depth measurement. Samples were collected over 2 hours at intervals, with medium replacement [30,31]. The cumulative amount of drug permeated through the sac was determined through HPLC, and the flux and apparent permeability coefficient of the Mirabegron matrix SR tablet and Myrbetriq tablet were determined by the following formula:

Flux (J) = Conc. ($\mu g.ml^{-1}$) x Dilution factor x Volume of medium (ml)/Permeation media (cm^2) x 100

Apparent permeability coefficient, $P\ (cm.min^{-1}) = J/C_0$

Where C_0 is the initial concentration in the donor compartment.

Pharmacokinetic study

The pharmacokinetic studies were carried out on three different groups, each consisting of 4 rats:

Group I: Myrbetriq® tablets (marketed tablet); oral (25 mg)

Group II: Mirabegron sustained-release matrix tablet (15.5 mg/kg; oral)

Group III: Mirakem tablet (15.5 mg/kg; oral)

The Myrbetriq® and Mirakem® tablets were purchased from the local market and administered orally. The developed mini-tablet formulation was administered orally, and blood samples were collected from the retro-orbital plexus at various time intervals (0, 0.5, 1, 2, 4, 8, and 12 hours) into EDTA-coated tubes (Bio-Plus, India). The plasma was promptly extracted by centrifuging the samples at 5000 rpm for 20 minutes at 4°C, after which the supernatant was collected for further LC analysis [5,7,32].

Histological analysis

Histological analysis of the rat bladder was performed by fixing the tissue in a solution of 4% paraformaldehyde and 10% EDTA (pH 7.4). The bladder was then embedded in paraffin, and transverse sections were prepared and mounted onto microscope slides. Microscopic examination used an LMI-U.K. Inverted + Mortic Microscope (EA100i) at 20x magnification[8,33–35].

Stability study

A stability study aims to show how a drug's or product's quality varies over time in response to environmental elements,

including light, humidity, and temperature. For the stability investigation, room temperature (30±2°C/65±5% RH) was used as the storage environment. The pills from the optimised formulation were kept for 30 days in plastic zip bags after being wrapped in aluminium foil. Following this time frame, the tablets' in vitro disintegration, hardness, friability, weight fluctuation, and moisture absorption were assessed[36–38].

Statistical Analysis

Every experiment was carried out three times. The mean ± SD is used to express the data in this publication. One-way analysis of variance (ANOVA) was used to determine the significance of the difference, and the data were only deemed significant when the p-value was less than 0.05 [39,40].

RESULTS AND DISCUSSION

Preparation of Mirabegron tablet

The top spray wet granulation method prepared the tablets according to the runs obtained after applying the Box-Behnken Design (Table 1). A total of 15 different runs were obtained, and they were prepared and evaluated for drug release, hardness, and Carr's index.

Table 1: No. of runs obtained for factors and responses

Runs	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
	A: Conc. of PEO (%)	B: Conc. of HPC (%)	C: Conc. of Mag. Stearate (%)	Drug Release (%)	Hardness (N)	Carr's Index (%)
1	30	12	1	90.4	91.2	20.1
2	30	11	1.5	88.2	90.7	15.5
3	30	11	0.5	88.4	90.1	19.1
4	40	12	0.5	93.2	97.5	18.4
5	30	13	0.5	92.8	95.7	18.5
6	20	12	1.5	86.3	89.1	15.4
7	40	11	1	91.4	91.9	19.6
8	20	13	1	88.1	89.4	19.7
9	40	12	1.5	92.3	91.5	15.8
10	30	12	1	90.4	90.3	20.1
11	20	12	0.5	88.2	89.4	18.7
12	30	12	1	90.5	90.3	20.1
13	30	13	1.5	92.7	94.3	16.5
14	40	13	1	95.1	93.7	18.9
15	20	11	1	87.3	85.9	18.5

Optimisation of mirabegron matrix sustained release tablet by DoE

Drug release (%) = + 90.35 + 2.76 (A) + 1.67 (B) – 0.3875 (C)

Hardness (N) = + 90.60 + 2.60 (A) + 1.81 (B) – 0.8875 (C) – 0.4250 (AB) – 1.42 (AC) – 0.5000 (BC) – 0.6000 (A^2) +0.2250 (B^2) + 1.87 (C^2)

Carr's Index (%) = + 20.10 + 0.00500 (A) + 0.1125 (B) – 1.44 (C) – 0.4750 (AB) + 0.1750 (AC) + 0.04000 (BC) – 0.6250 (A^2) – 0.3000 (B^2) – 2.40 (C^2)

Where "A" is the concentration of PEO, "B" is the concentration of HPC, and "C" is the concentration of Magnesium stearate

The selection of high-risk factors—polyethylene oxide (PEO), hydroxypropyl cellulose (HPC), and magnesium stearate—for optimisation was based on their significant impact on the formulation's critical quality attributes (CQAs), including drug release, tablet hardness, and flow properties.

Polyethylene Oxide (PEO): PEO was chosen due to its key role in enhancing intestinal permeability and modulating the sustained release of mirabegron. Its concentration directly influences the drug's release profile, as excessive PEO can result in slower release, while insufficient amounts may compromise sustained-release characteristics.

Hydroxypropyl Cellulose (HPC): HPC was included because it is a matrix-forming polymer that governs the tablet's integrity and release kinetics. Variations in HPC concentration significantly affect the tablet's sustained-release behavior and mechanical strength.

Magnesium Stearate: Magnesium stearate, a lubricant, was prioritised for its impact on blend uniformity and tablet compressibility. Improper amounts could lead to flowability issues during manufacturing and variability in tablet hardness.

Exclusion of Medium- and Low-Risk Factors

Factors such as mixing speed, granulation time, and equipment variability were categorised as medium- and low-risk based on preliminary experiments and risk assessment. These factors showed minimal influence on CQAs when varied within standard operational ranges. For instance:

- Mixing speed and granulation time were found to have negligible effects on drug release or hardness compared to polymer concentrations.
- Equipment variability (e.g., processor type, age) and environmental factors like temperature were controlled during manufacturing and did not significantly affect the outcomes

The optimisation process was streamlined by focusing on high-risk factors that demonstrated a statistically significant impact on CQAs, ensuring efficient and robust tablet design without unnecessary complexity.

Validation of Predicted and Experimental Outcomes for Drug Release, Hardness, and Carr's Index

The optimised formulation was validated by comparing the predicted values obtained from the Box-Behnken Design (BBD) model with the experimentally observed values for critical quality attributes (CQAs) such as drug release, hardness, and Carr's index.

Predicted and Experimental Data Comparison: The predicted values were generated using the BBD mathematical models for the selected high-risk factors (PEO, HPC, and magnesium stearate). These predictions were then validated by preparing the optimised formulation under the same conditions and measuring the CQAs.

Validation Observations:

- The experimental values closely matched the predicted values, with deviations of less than 1% for all parameters.
- This minimal deviation demonstrates the reliability and accuracy of the BBD optimisation model.

Model Correlation and Predictability

The correlation coefficient (R^2) values for the regression models of the CQAs were above 0.95, indicating a strong fit between the model and experimental data. These results confirm that the optimisation model accurately predicts the performance of the developed formulation, ensuring reproducibility and robustness in manufacturing. By validating the results through experimental confirmation, the study provides the credibility of the design approach and its practical applicability in achieving the desired formulation attributes.

Parameter	Predicted Value	Experimental Value	% Deviation
Drug Release (%)	90.35	90.42 ± 0.23	0.08%
Hardness (N)	90.60	90.73 ± 0.12	0.14%
Carr's Index (%)	20.10	20.22 ± 0.10	0.6%

3D Response surface plot analysis

The results indicate that the formulation after optimization leads to the development of the following parameters, which will lead to the desired outcomes. PEO at a concentration of 34.7 %, HPC at 11%, and magnesium stearate at 0.5 % was found to be the optimised tablet, which resulted in a drug release of 90.36%, hardness at 93.23%, and Carr's index at 21% (Figure 1).

Preformulation evaluation of final optimised blend for tablet

The final ratios of all the optimised excipients were obtained and examined for Hausner's ratio, bulk density, tapped density, and angle of repose following the optimisation of every process parameter. The angle of repose readings indicate the powder blend's good flow qualities. The optimised formula's bulk density of 0.398±0.032 (gm/cm3) indicates the powder has good flow characteristics. The optimised formula's tapped density of 0.562±0.015 suggests that the powder has good flow characteristics. According to the optimised recipe, Hausner's ratio indicates the powder's good flow qualities, below 1.20.

Post-compression evaluation of optimised mirabegron sustained release matrix tablet using DSC, XRD and FTIR

The DSC analysis of the optimised mirabegron matrix sustained-release tablet was performed and found that the mirabegron peak was diminished, suggesting the change in phase from crystalline to amorphous, resulting in increased solubility and permeation

(Figure 2a). The results of XRD are quite similar to the DSC as the XRD analysis of the optimised mirabegron matrix sustained release tablet was performed and found that the mirabegron peak was diminished, suggesting the change in phase from crystalline to amorphous, resulting in increased solubility and permeation (Figure 2b). The FTIR analysis of the optimised mirabegron matrix sustained-release tablet suggests similar absorption bands when compared with the mixture showing the presence of drug and excipients in the same physical state with that of the mix (Figure 2c).

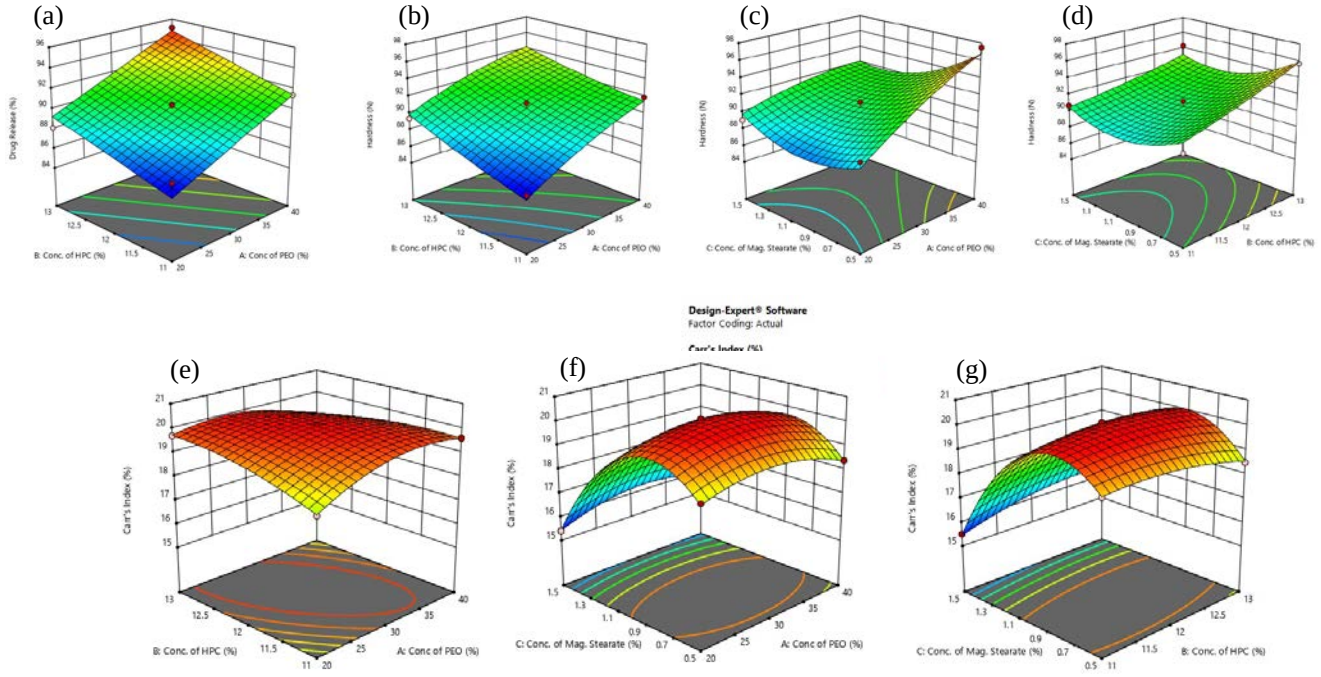

Figure 1: 3D Response Surface Plot Representing Optimization Outcomes (a) Effect of PEO concentration on drug release, (b) Influence of HPC and magnesium stearate on tablet hardness, (c) Combined effect of PEO and HPC on tablet hardness, (d) Effect of PEO concentration on Carr's index, (e-f) Combined effects of formulation factors on Carr's index.

In-vitro drug release

These results suggest that the drug is stable and released in a sustained manner (Table 2, Figure 3a). The Higuchi model (R^2 = 0.989) best fits the data, indicating diffusion-controlled drug release. The Korsmeyer-Peppas model further confirms non-Fickian diffusion as the predominant mechanism. These findings are well supported by previous reports [29,41].

Ex-vivo gut permeation analysis

The intestinal permeability of Myrbetriq and Mirabegron sustained release matrix tablets is shown in Figure 3b. Following two hours of study design, the flow was measured and found to be 1189.73 ± 95.67 (Myrbetriq tablet) and 2741.54 ± 142.16 (Mirabegron sustained release matrix tablet). The Mirabegron sustained release matrix tablet (86.31 ± 12.53) and Myrbetriq tablet (32.51 ± 11.64) were found to have the same apparent permeability coefficient. Comparing the Mirabegron sustained release tablet to the Myrbetriq tablet, the drug-matrix formation increased the permeability by nearly three times ($p < 0.001$). The presence of PEO, which greatly penetrates the intestinal mucosa and increases the oral bioavailability, was credited with the improved permeability of the Mirabegron sustained release tablet.

Depth permeation analysis by confocal microscopy

By using confocal microscopy, the depth of drug penetration was ascertained. The depth of drug penetration in the Myrbetriq tablet is only 10 µm–12 µm (Figure 3c), however the inclusion of PEO particles in the Mira matrix tablet obviously gives it an edge. The confocal results indicated that the Mirabegron sustained release matrix tablet had increased drug penetration, which is explained by the 19 µm depth (Figure 3c). These results imply that enhanced intestinal permeability, which results in higher oral bioavailability, is a definite benefit of the developed Mirabegron sustained release matrix tablet. This method provides visual confirmation of improved intestinal permeability achieved with the developed formulation.

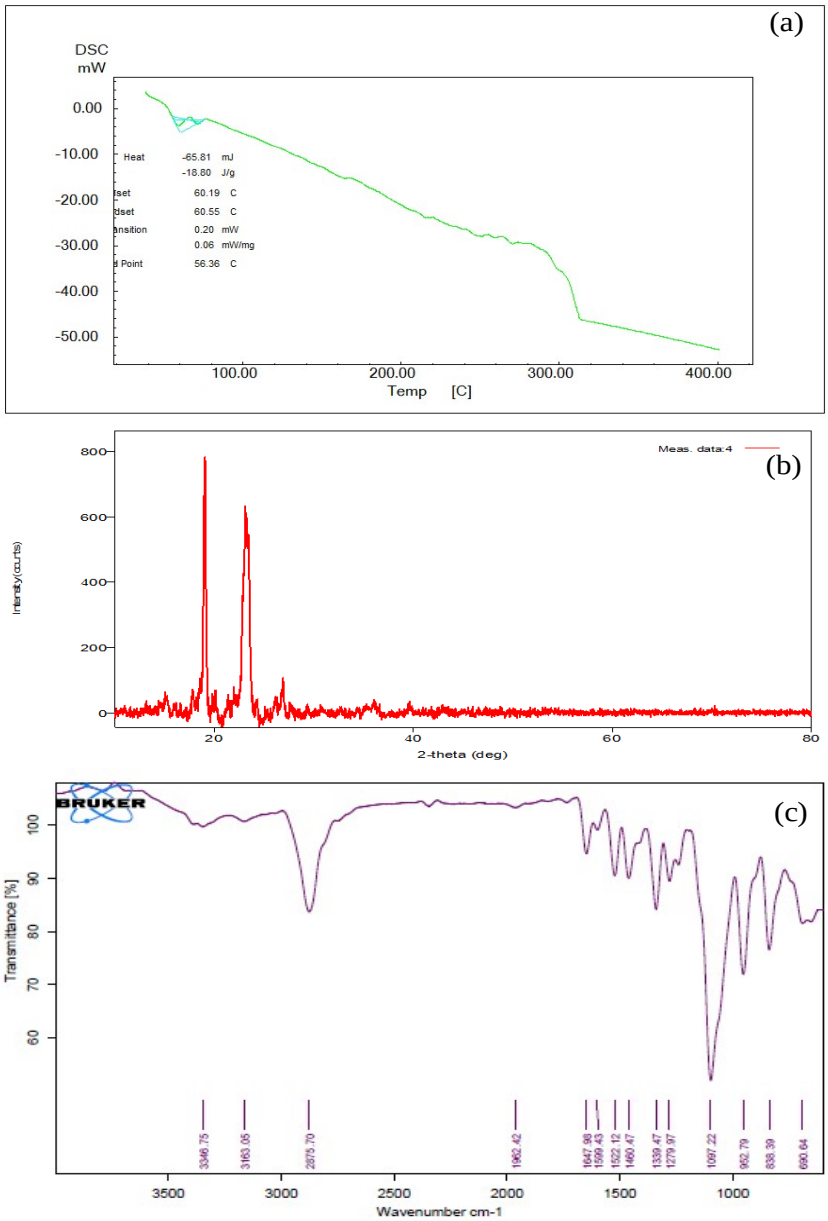

Figure 2: Characterization of the Optimized Mirabegron SR Matrix Tablet (a) Differential Scanning Calorimetry (DSC) analysis indicating the conversion of mirabegron from crystalline to amorphous form, (b) X-ray Diffraction (XRD) pattern showing diminished crystalline peaks, and (c) Fourier-transform infrared spectroscopy (FTIR) analysis confirming compatibility of the drug with excipients.

Table 2: Dissolution of tablets in phosphate buffer pH 6.8

Time (Hr.)	Mirabegron SR Tab CDR (%)	Myrbetriq Tab CDR (%)	Mirakem Tab CDR (%)
0	0	0	0
1	13.9±1.65	14.3±1.67	13.5±1.64
3	25.74±1.22	27.79±1.05	28.42±1.33
5	46.33±1.31	47.27±1.23	45.51±1.51
7	71.12±2.53	72.04±2.24	73.11±2.78
8.5	86.43±3.44	87.93±4.03	84.55±2.33
10	91.42±4.22	92.22±4.21	89.28±3.78
12	98.33±4.41	97.41±3.32	97.53±3.82

Uniformity of content

The drug content ranged from 97.56 ± 1.86% to 103.57 ± 2.19% and was very consistent among tablet forms. It was discovered that the maximum percentage of drug content for every formulation was 103.57 ± 2.19%. For every formulation, the minimum percentage of drug content was determined to be 97.56 ± 1.86%. It falls within the IP-specified range of ± 5%.

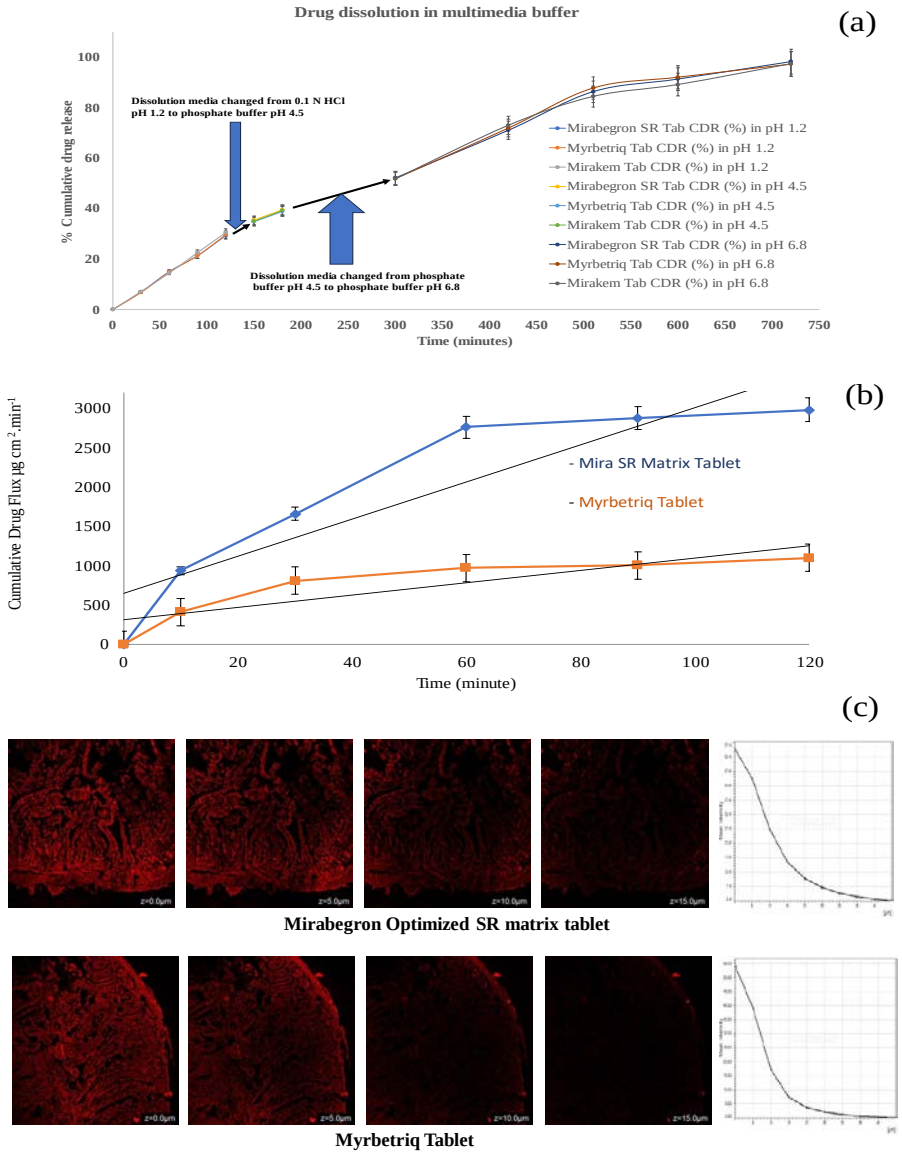

Figure 3: Evaluation of Drug Release, Permeability, and Depth Penetration (a) Cumulative percentage drug release of the Mirabegron SR tablet compared to Myrbetriq and Mirakem tablets across different pH media, (b) Cumulative drug flux of Mirabegron SR tablet and Myrbetriq tablet indicating enhanced permeability, (c) Depth penetration analysis using confocal microscopy showing increased drug penetration depth for the Mirabegron SR tablet (19 µm) compared to Myrbetriq tablet (10–12 µm)

Drug content determination by HPLC method

The HPLC chromatogram of the mirabegron was plotted against the area vs concentration from 10 to 100 ppm. The calibration plot was also plotted to represent the linearity of the developed HPLC method, and the correlation coefficient was found to be 0.9992

Pharmacokinetic study

The pharmacokinetic analysis showed that Mirabegron sustained-release matrix tablets achieved significantly higher plasma concentration (Cmax 1116.05 ± 121.27 µg/ml) compared to Myrbetriq® (Cmax 457.41 ± 73.29 µg/ml), with a statistically significant difference ($p < 0.01$). Peak concentration occurred at 2 hours for both formulations (Table 3). Additionally, the sustained-release tablet's AUC (4669.33 ± 417.65 µg.hr/ml) was significantly greater than that of Myrbetriq® (1933.47 ± 183.48 µg.hr/ml) ($p < 0.01$), enhancing relative bioavailability by 181.7%. These findings indicate the potential of the developed formulation to improve the bioavailability of low-absorption drugs (Figure 4).

Histopathology

Transverse sections of the bladder from the control group, disease-induced group (OAB), Mirakem tablet-treated group, Myrbetriq-treated group, and the mirabegron sustained-release matrix tablet-treated group were examined using H&E staining and observed under a microscope. The urothelium appeared thinner in the overactive bladder (OAB) group, and the muscle bundles were separated with condensed collagen. In the control group, the urothelium was normal, with well-organized muscle

bundles and layers and minimal interlacing collagen. The findings in the mirabegron suspension-treated group were similar to those in the Myrbetriq-treated group. In contrast, the mirabegron sustained-release matrix tablet-treated group showed nearly normal bladder physiology. In the OAB group, collagen densely interlaced the muscle bundles, with a collagen-to-smooth muscle ratio of 2, whereas the sham group exhibited normal collagen distribution between muscle bundles (Figure 5).

Table 3: Pharmacokinetic parameters determination

Parameters	Mirakem tablet (Oral)	Mira Sustained Release Matrix Tablet (Oral)	Myrbetriq® (Oral)
Dose (mg/kg)	25	15.5	15.5
$t_{1/2}$ (hr)	1.5	1.85	1.97
AUC $_{0\text{-}t}$ (µg.hr/ml)	992.84± 97.38	4669.33 ± 417.65	1933.47 ± 183.48
AUC $_{0\text{-infinity}}$ (µg.hr/ml)	997.35± 47.83	4738.39 ± 733.27	1965.44 ± 86.89
T_{max} (hr)	2	2	2
C_{max} (µg/ml)	247.41 ± 23.29	1116.05 ± 121.27	457.41 ± 47.59

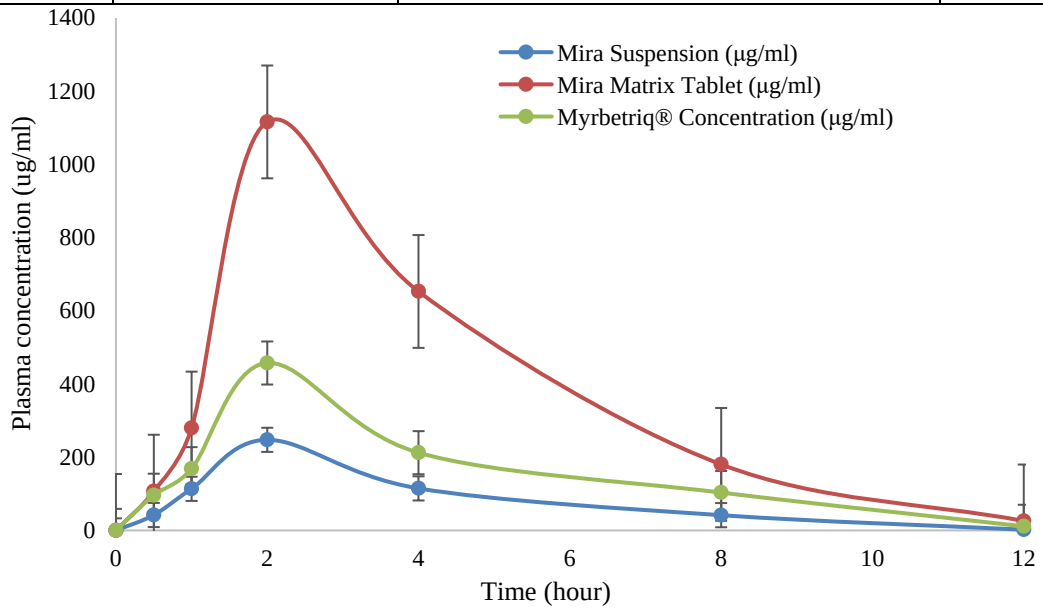

Figure 4: Pharmacokinetic Profile of Mirabegron Formulations

Plasma concentration-time curves comparing the Mirabegron SR matrix tablet, Myrbetriq marketed tablet, and Mirakem tablet, highlighting the higher Cmax and prolonged AUC of the SR formulation.

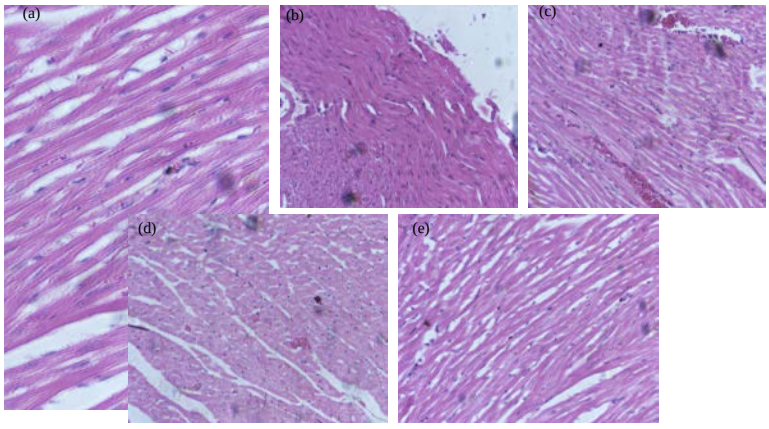

Figure 5: (a) Control group showing normal urothelium and collagen distribution, (b) Disease-induced group with thin urothelium and dense interlacing collagen, (c) Mirakem tablet-treated group with partially improved structure, (d) Myrbetriq-treated group showing moderate improvement, (e) Mirabegron SR matrix tablet-treated group exhibiting nearly normal urothelium and collagen distribution.

Urothelium Thickness

- In the overactive bladder (OAB) group, the urothelium appeared thin, reflecting disease pathology.
- The mirabegron sustained-release (SR) matrix tablet group showed almost normal bladder physiology, indicating significant improvement compared to the disease group.

Collagen Density

- In the OAB group, collagen was densely interlaced with muscle bundles, with a collagen-to-smooth muscle ratio 2.
- In the control group, collagen was normally distributed between muscle bundles.
- The mirabegron SR matrix tablet group exhibited near-normal collagen distribution, similar to the sham group, suggesting reduced fibrosis and restored bladder structure.

Stability study

The manufactured sustained-release tablet remained stable for one month at 30°C ± 2°C/65% ± 5% RH, according to ICH Q1A(R2) guidelines detailing the storage conditions and evaluation criteria, which are shown in Table 4. Tablet characteristics such as weight fluctuation, friability, hardness, and drug content showed no discernible variations. The results confirm that the optimised SR matrix tablets exhibit excellent physical and chemical stability under typical storage conditions. This stability ensures consistent therapeutic efficacy, patient safety, and suitability for commercial production. Future studies could extend the stability assessment to longer durations and varying environmental conditions to further validate shelf-life claims.

DISCUSSION

Clinical Impacts

The study's findings highlight significant improvements in the pharmacokinetics, bioavailability, and physiological outcomes associated with the developed Mirabegron sustained-release (SR) matrix tablet:

- Enhanced Bioavailability: The SR tablet demonstrated a 31.77% increase in plasma concentration and a nearly threefold improvement in intestinal permeability compared to marketed formulations (Myrbetriq). These improvements may improve symptom control for overactive bladder (OAB) patients, reducing urinary urgency, frequency, and incontinence.
- Prolonged Drug Action: The optimised formulation achieved sustained drug release for up to 12 hours, which could improve adherence by reducing dosing frequency, enhancing patient convenience, and ensuring consistent therapeutic effects.
- Restoration of Bladder Physiology: Histological analysis showed that the SR formulation restored bladder urothelium thickness and reduced fibrosis, potentially more effectively addressing the underlying pathology of OAB than existing treatments.

Table 4: Before and after batch stability study of mirabegron sustained release matrix tablet

Parameters	Optimised Mirabegron Sustained release matrix tablet (n=3)	
	Before stability	After stability
Weight variation (mg)	250.12±4.5	249.11±3.2
Hardness (N)	97.2±1.3	96.9±1.4
Friability (%)	0.88±0.1	0.89±0.2
Drug content (%)	99.27±1.5	99.01±1.3

Commercial application challenges

Despite the promising results, several challenges must be addressed before commercialising the developed SR tablet:

- Manufacturing Complexity: The advanced formulation, which uses polyethylene oxide (PEO) to enhance permeability, requires precise control over granulation, blending, and compression processes, potentially increasing production costs.
- Scalability: Transitioning from lab-scale to industrial-scale production could encounter challenges, such as achieving consistent granule size and uniform API distribution.
- Regulatory Approvals: The novel formulation will require rigorous regulatory evaluations to demonstrate safety, efficacy, and bioequivalence compared to existing treatments.
- Market Competition: Competing with established products like Myrbetriq and addressing cost-effectiveness will be critical for commercial success.
- Patient Access: Pricing strategies must consider affordability to ensure accessibility, particularly in resource-limited settings.

Future Research Directions

The findings open up multiple avenues for future research to enhance the therapeutic potential of the developed SR formulation:

- Clinical Trials: Conducting large-scale, randomised clinical trials in diverse patient populations is essential to validate the efficacy and safety of the SR tablet and determine its long-term effects.
- Formulation Optimization: Further research into alternative excipients or coating materials could reduce production costs or improve the formulation's robustness.
- Mechanistic Studies: Investigating the precise molecular mechanisms by which PEO enhances intestinal permeability could inform the development of other drugs with poor bioavailability.
- Broader Applications: Expanding the SR matrix technology to other therapeutic areas, particularly for drugs with similar bioavailability challenges, could diversify its applications.
- Patient-Centric Designs: Exploring the feasibility of flexible dosage forms, such as mini-tablets or dispersible formulations, could enhance usability for elderly or pediatric patients with OAB.

CONCLUSION

The findings from this study demonstrate that the developed Mirabegron sustained-release (SR) matrix tablet offers significant advancements in the treatment of overactive bladder (OAB). By addressing the limitations of existing formulations, such as low bioavailability and the need for frequent dosing, the optimised SR tablet achieved the following practical outcomes

1. **Enhanced Bioavailability and Permeability**: Using polyethylene oxide (PEO) in the formulation increased intestinal permeability, resulting in a nearly threefold improvement compared to the marketed Myrbetriq tablet. This enhancement directly translates into more efficient drug absorption and sustained therapeutic action.
2. **Improved Pharmacokinetics**: The SR formulation showed a 31.77% increase in plasma concentration and extended drug release over 12 hours, significantly reducing dosing frequency. This can improve patient compliance, convenience, and adherence to therapy.
3. **Restored Bladder Physiology**: Histological analysis revealed that the SR tablet-treated group exhibited nearly normal urothelium thickness and reduced collagen density, effectively mitigating OAB-induced bladder damage. These outcomes emphasise the formulation's potential for addressing underlying pathological changes rather than merely alleviating symptoms.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Neeraj Sharma and Sharda Shambhakar contributed to writing the draft of the manuscript. Daksh Bhatia and Sharda Shambhakar supervised the research work and reviewed the manuscript draft. Neeraj Sharma and Pavitra Solanki conducted the experimental work and collected the data. All the authors reviewed the final draft of manuscript.

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