Journal of Advanced Pharmaceutical Sciences and Natural Products

DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLETS OF MIRABEGRON FOR THE TREATMENT OF OVERACTIVE BLADDER

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ABSTRACT

Conventional immediate-release medication formulations used to treat OAB frequently call for frequent dosing, which can result in inconsistent plasma drug levels and poor patient compliance. In order to provide longer therapeutic activity and better patient adherence, the current study focuses on developing and evaluating sustained release (SR) matrix tablets containing the β3-adrenergic receptor agonist mirabegron. Hydrophilic polymers including polyethylene oxide (PEO) and hydroxypropyl cellulose (HPC) were used in the formulation of Mirabegron SR matrix tablets utilizing a top-spray granulation technique. By taking into account important factors including polymer concentrations and lubricant levels, the formulation was adjusted using Box-Behnken Design (BBD). To guarantee the powder blend had appropriate flow characteristics, pre-compression parameters such bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose were assessed. Hardness, friability, weight fluctuation, and drug content homogeneity were all assessed after compression. To replicate gastrointestinal circumstances, in vitro drug release investigations were conducted in various pH mediums. Following appropriate kinetic models, the improved formulation showed prolonged, regulated, and sustained drug release. DSC, FTIR, and XRD compatibility tests verified that there were no notable drug–excipient interactions, demonstrating the formulation's stability. The findings showed that polymer concentration is a key factor in regulating drug release behavior. Therefore, by increasing therapeutic efficacy, lowering dosage frequency, and boosting patient compliance, the new sustained release matrix tablets of mirabegron present a viable strategy for the efficient control of overactive bladder.

Keywords: Overactive bladder; Sustained release; Matrix tablets; Polyethylene oxide (PEO); Box–Behnken Design; Drug release kinetics; Controlled drug delivery.

1. Introduction

This ailment is characterized by an uncontrolled need for urination, where frequency of urination is generally increased with or without urinary incontinence and nocturia. It causes poor sleep and interferes with the normal daily schedules and may also lead to anxiety and depression[1]. The distribution of dry and wet Overactive Bladder in females was 7.6% and 9.3% respectively. It was 13.6% and 2.6% in males[2].

Overactive Bladder occurs due to fragile hip diaphragm, injury to nerve fibers, UTI, excise weight, and postmenopausal condition. The bladder contracts leading to a strong desire to urinate, although bladder is not completely filled[3]. OAB occurs due to any abnormality in the patho-physiology of urination, which a complex network between the brain, neurons, and bladder muscles. Any event in this complex network that impairs functioning of associated neurons, bladder muscles, emptying, and storage of bladder is expressed as OAB symptoms (e.g. urgency, frequency, and nocturia)[4]. Oxybutynin chloride is non- selective antagonist of muscarinic receptor and has numerous adverse effects like blurry eye-vision, dryness of mouth, constipation moreover sometimes decline in cognition, so patient discontinuation rate are very high. Solifenacin succinate, Darifenacin, Fesoterodine fumarate is M2 and M3 selective antimuscarinic drugs. Matrix tablets are oral tablets in which the polymers form a network like structure within which API is thoroughly distributed. The API release from the matrix takes place either through diffusion, erosion or by both. The matrix can be of different types, including water-repellant type, lipid matrix, hydrophilic matrix, and biodegradable matrix. The aim of the study was to prepare and evaluate sustained release tablets of Mirabegron for the treatment of overactive bladder.

2. Material & methods

Table 1: List of materials

S.No.	Materials	Brandname/ Grade	Category	Manufacturer
1.	Mirabegron	-	API	Megafine Pharma (P)Ltd.,India
2	Polyethylene oxide	Sentry POLYOXWSR N60K LEO	Controlled release polymer	Dow Chemicals(P) Ltd., India
3	Polyethylene glycol	POLYGLYKO L-6000 PF	Diluent/ Controlled Release polymer	Clariant,India

4	Hydroxypropyl cellulose	KLUCEL-EXF	Binder	Ashland,USA
5	Butylated hydroxytoluene	Butylated hydroxytoluene	Antioxidant	Finar,India
6	Magnesium stearate	Magnesium stearate	Lubricant	Nitika Pharmaceuticals Ltd., India
7	Opadrywhite	Opadrywhite	Film forming agent	Colorcon,India
8	HPMC2910/ Hypromellose (USP, PhEur,JP)	6cP	Polymer	
9	Titanium dioxide	-	Opaquant extender	
10	PEG6000	MW6000	Polymer	

2.1 Methods

2.1.1 Physicochemical characterization

The mirabegron was visually analyzed for its color and appearance.

2.1.2 Melting point

In a fine capillary (previously sealed at bottom) small amount of mirabegron was filled and kept inside the digital melting point apparatus. The experiment was performed in triplicate[5].

2.1.3 Solubility analysis

Shake flask method was used to determine the aqueous solubility of mirabegron. A surplus amount of mirabegron was added to distilled water (10 mL) and kept in a mechanical shaker overnight to achieve the equilibrium. After 24h, the filtered solution (through 0.45µm syringe filter) was analyzed for the amount of drug using a UV spectrophotometer[6].

2.1.4 Preparation of calibration curve by UV spectrophotometer

A solution of 1000 µg/mL (Stock A) was prepared by dissolving 10 mg of mirabegronin methanol (10mL), which upon subsequent dilution nf 1 mLto 10mLusing methanol gave a solution of 100 µg/mL (Stock B). Then scanning of Stock B solution was performed in the range of 200-400 nm by UV spectrophotometer to give the λmax. Then different dilutions ranging from 2-10 µg/mLwere prepared from stockB and their absorbance was measured at the λmax obtained[5].

2.1.5 Compatibility studies

It was performed between mirabegron, PEO and HPC by three different analytical techniques, including DSC, FTIR, and XRD.

2.1.6 Differential scanning calorimetry (DSC)

Approximately 5mg of Mirabegron, PEO, HPC, and their physical mixture were weighed individually and placed inside the aluminium crucible separately. After sealing, the crucible was kept in the DSC instrument (Phoenix, 204 F1). Duringanalysis, flowrate of heatwas10 °C/min, nitrogengaswas50mL/min, and temperature range used was 30°C to 200°C.The thermogram of the mirabegron between temperature vs heat flow were obtained and was compared to look for any interactions.

2.1.7 X-ray diffraction (XRD)

The XRD spectra of the mirabegron, HPC, PEO and their physical mixture was obtained by the X-ray diffraction instrument and was compared[7].

2.1.8 Fourier transform infra-red spectroscopy (FTIR)

The FTIR spectra of Mirabegron, PEO, HPC, and their physical mixture were obtained by FTIR spectrophotometer (Shimadzu), in the region of 400- 4000 cm-1. Then the spectra were compared to analyze for the presence of any drug-excipient interactions.

2.1.9 Pre-compression parameter analysis

Numerous independent variables related to formulation and processes like mixing, drying rate etc. could significantly influence the properties of the resulting blends. Hence, prior to formulation development, the blends underwent thorough preformulation testing and analysis[8].

Bulk Density

For bulk density analysis, a clean and dry graduated measuring cylinder was used, typically of 100 mL capacity. A pre-weighed amount (m) of the powder was filled inthe cylinder and allowed to settle after 3 gentle taps.

Tapped density

The sample kept on the bulk density apparatus (during bulk density determination) was allowed to tap 500 times. The tapped density was calculated by the formula given. During tablet compression, the powder's tapped density play a crucial role in die filling and packing of materials.

Carr's/Compressibility index

The compressibility index of the powder blend indicates about the type of flow.

Hausner's ratio

The Hausner's factor also gives information about the nature of powder flow.

Angle of repose(Θ)

Flow property is also indicated by the 'angle of repose' and it was determined by the funnel method. Almost 10g of the powder blend was taken and was poured through the funnel (clamped through a burette stand),in such a way that a heap was formed.

2.1.10 Formulation development based on Box-Behnken Design (BBD)

After assessing various factors, only high-variability ones were considered for final risk

assessment. High-risk factors included concentrations of PEO, HPC, and magnesium stearate; medium-risk included temperature, mixing speed, and formulation time; low- risk included equipment age and glass quality. Only high-risk factors were optimized using Box-Behnken design[9].

2.1.11 Preparation of mirabegron tablet

Tablets were prepared by top-spray granulation method. The process began by sifting polyethylene glycol, hydroxyl propyl cellulose, and polyethylene oxide through a #24 sieve to ensure uniform particle size. Mirabegron was dissolved in methanol to create a clear granulating solution. The granulation was performed in a fluidized bed processor at a controlled temperature of 40–45°C to ensure efficient drying without degrading the active ingredient. The granules were dried to achieve the moisture content of ≤1%, as excessive moisture may lead to altered compressibility and stability. After drying, the granules were sifted; along with any large particles milled to a consistent size. The blending step was carried out for 10 min at 12 rpm, ensuring uniform distribution of drug and the excipients.

2.1.11 Optimization of mirabegron tablets by Box-Behnken Design

The Design Expert software (version 13) was used to apply Box-Behnken Design (BBD) for the formulation optimization of 'Mirabegron sustained release tablets'. The concentration of Polyethylene oxide (PEO), Hydroxypropyl cellulose (HPC) and Magnesium stearate was taken as independent variables, at three different concentrations[10].

Table 2: Variables and their levels in the formulation optimization of Mirabegron SR tablet

Variables	Level		
Independent	**low**	**medium**	**high**
PEO	20	30	40
HPC	11	12	13
Mg stearate	0.5	1.0	1.5
Dependent variables (Response)			
Drug release(%)			
Hardness(N)			
Carr's Index			

By applying BBD, a total of 15 different runs were obtained. All the trial batches of 15 runs were prepared and evaluated for drug release, hardness, and Carr's index.

Table 3: Runs generated by Box-Behnken Design

Runs	Factor1	Factor2	Factor3
	A:Conc.ofPEO (%)	B:Conc.ofHPC (%)	C: Conc. Of Mg. Stearate (%)
1	30	12	1
2	30	11	1.5
3	30	11	0.5
4	40	12	0.5
5	30	13	0.5
6	**20**	**12**	**1.5**
7	40	11	1
8	20	13	1
9	40	12	1.5
10	30	12	1
11	20	12	0.5
12	30	12	1
13	30	13	1.5
14	40	13	1
15	20	11	1

2.1.12 Release study

The in-vitro release study of the optimized Mirabegron sustained release tablets along with the Mirakem and Myrbetriq tablets, was performed in multi-media, i.e., 0.1N HCl (pH 1.2, for 1-2h); Phosphate buffer, pH 4.5 (for next 1h), and pH 6.8 (3h onwards). It was performed using the USP dissolution apparatus (Type I) at 37°C and 100 rpm. The samples were collected at specified time intervals, filtered, diluted, and analyzed at 251 nm. The graph was plotted between time (min) vs % Cumulative drug released[5].

2.1.13 Weight Variation

the weight variation of random 20 tablets were taken and then calculate their average weight of it and then compared the weight of individual tablets with the average weight[6].

2.1.14 Hardness

we took random 5 tablets and measured by the help of Pfizer Hardness tester and then the mean (n=3) and standard deviation of all the tablets were obtained.

2.1.15 Friability

Pre-weighed 20 tablets and placed them in the Roche Friabilator apparatus and then the apparatus for 100 revolutions at 25 rpm. The tablets were considered for acceptance when they losses less than 1.0 % of their weight.

2.1.16 Drug content

Ten tablets were weighed, crushed, and dissolved in methanol to prepare serial dilutions. The content was then analyzed at 251 nm using HPLC.

3. Result and discussion

3.1 Physicochemical characterization

3.2 General appearance

The mirabegron was off-white colored and crystalline in nature.

3.3 Melting point

The melting point of mirabegron was determined by a digital melting point apparatus and was found to be 144.25±0.02 °C**.**

3.4 Solubility studies

The solubility of mirabegron in distilled water was determined by the Shake flask method and was found to be 0.071±0.514 mg/mL (i.e., poorly soluble in water), which is in agreement to the reported value of 0.082mg/mL.

3.5 Preparation of calibration curve by UV spectrophotometer

When the mirabegron solution was scanned by UV spectrophotometer, the λ max was obtained at 251 nm. The high r^2value (0.993) indicated the high correlation between the variables.

3.6 DSC analysis

The DSC thermogram of pure mirabegron exhibited a sharpe endothermic peak at around 144.25°C, corresponding to its melting point. This indicated the crystalline nature of mirabegron. The presence of a distinct transition confirmed the purity and thermal stability of the drug in its unprocessed form. The DSC curve of PEO showed a characteristic endothermic peak around 63°C, corresponding to its melting point. The thermogram confirmed that PEO existed in a semi-crystalline state, as indicated by the moderate heat flow transition. No additional degradation peaks were observed in this temperature range, suggesting its thermal stability under normal processing conditions. The DSC thermogram of HPC displayed abroad endothermic peak at around 343°C to 350°C, indicating its thermal decomposition rather than melting. This behavior was typical of polymeric excipients like HPC, which degrade upon heating rather than undergoing a sharp melting transition. The results suggested that HPC has good thermal stability up to this temperature. The DSC thermogram of the physical mixture exhibited multiple transitions.

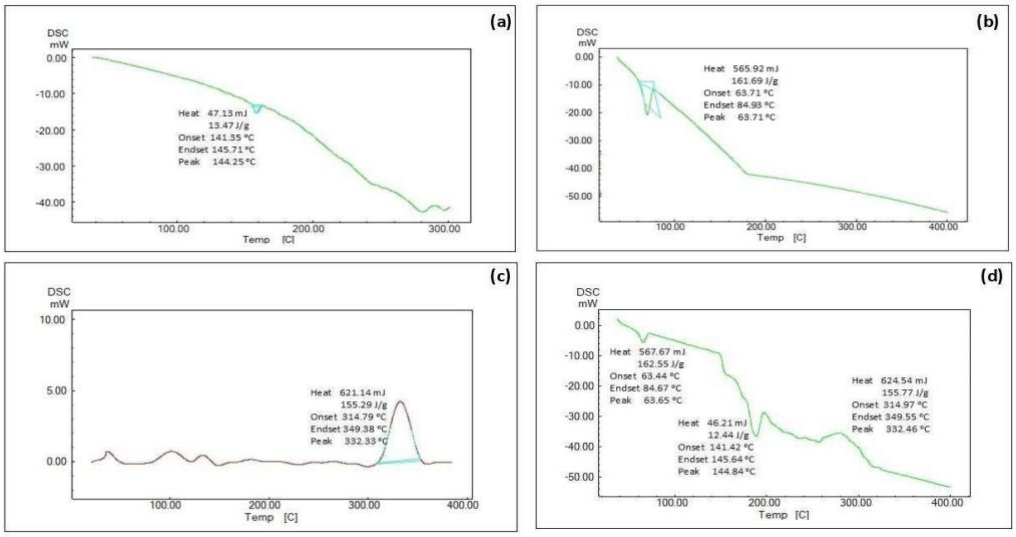

Fig. 1: DSC analysis of (a) pure mirabegron drug (b) PEO (c) HPC and (d) Physical mixture indicating compatibility

3.7 FTIR spectroscopy

Mirabegron (Pure Drug)

The FTIR spectrum of pure mirabegron shows characteristic absorption bands at specific wave numbers:

N-H stretching (~3300cm^{-1}) indicating amine groups.

C=O stretching (~1670cm^{-1}) associated with carbonyl functional groups.

C-N and C-H bending vibrations (~1200–1500 cm^{-1}) confirming the presence of aromatic and aliphatic components. These peaks confirm the structural integrity of mirabegron in its pure form.

Polyethylene Oxide (PEO)

Strong C-O-C stretching (~1100cm^{-1}) due to ether linkages.

Broad O-H stretching (~3400cm^{-1}) indicating hydrogen bonding. These peaks confirm its polymeric structure.

Hydroxy propyl cellulose (HPC)

O-H stretching (~3400cm^{-1}) indicating hydroxyl groups.

C-O-C stretching (~1050cm^{-1}) from ether bonds.

Broad peaks due to its amorphous nature, characteristic of cellulose derivatives.

Physical mixture (Mirabegron+PEO+HPC)

FTIR analysis confirms that mirabegron, PEO, and HPC retain their individual chemical structures in the physical mixture. The absence of significant peak shifts or new functional groups suggests good compatibility.

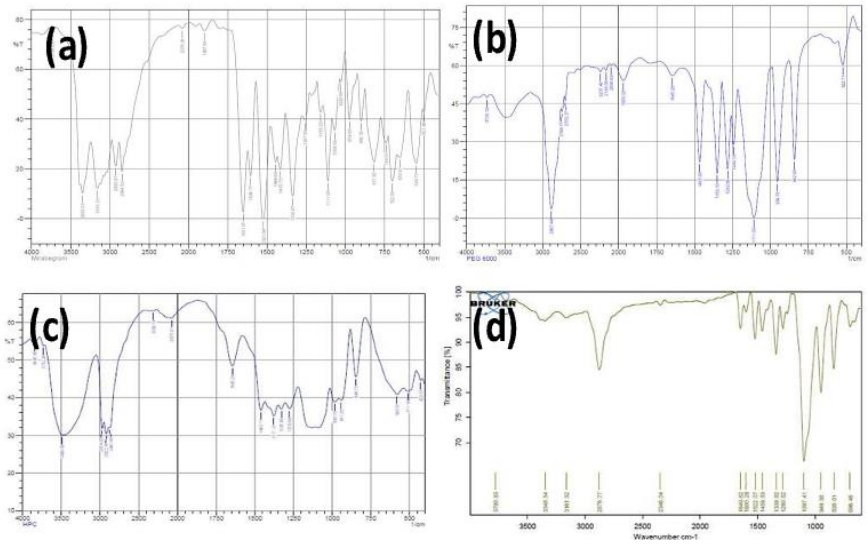

Fig. 2: FTIR spectra of (a) pure mirabegron drug (b) PEO (c) HPC and (d) Physical mixture indicating compatibility

3.8 X-ray diffraction analysis

The XRD pattern of pure mirabegron exhibit sharp and intense diffraction peaks, particularly in the 2θ range of 10°–30°, indicating its highly crystalline nature.

3.9 Pre-compression parameters of the optimized tablet blend

The values of pre-compression parameters are given are presented in Table 4. The values of Carr's index (29.1814 ± 0.15), Hausner's ratio (1.412 ± 0.07) and angle of repose (30.72º ± 1.30) for mirabegron indicated that it has moderate to poor flow properties. The good flow qualities of the optimized powder blends

Table 4: Pre-compression parameters

S. no.	Parameters	Mirabegron *(pure drug)*	Optimized tablet blend *(obtained after DOE)*
1.	Bulk density	0.39±0.03	0.44±0.34
2.	Tapped density	0.56±0.01	0.52±0.12
3.	Carr's index (CI)	29.1814±0.15(poor)	15.38±0.06(excellent)
4.	Hausner's ratio (HR)	1.412±0.07(moderate)	1.18±1.30(good)
5.	Angle of repose (θ)	30.72º±1.30 (moderate)	27.72º±1.05(good)

3.10 Appearance

The surface of the prepared tablets was regular and also uniform in size, tablets were off white in colour.

3.11 Friability

The % friability of the prepared tablets was found to be less than 1% in line with pharmacopoeial standards.

3.12 In-vitro drug release study

The results of *in-vitro* drug release are as follows:

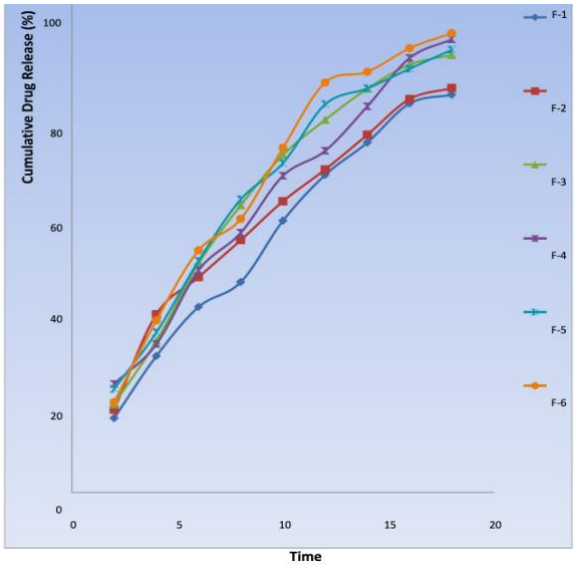

Fig. 5: Cumulative % Drug release of Sustained Release Tablets

Conclusion

The current study focused on developing and evaluating sustained release (SR) matrix tablets containing the β3-adrenergic receptor agonist mirabegron. Hydrophilic polymers including polyethylene oxide (PEO) and hydroxypropyl cellulose (HPC) were used in the formulation. By taking into account important factors including polymer concentrations and lubricant levels, the formulation was adjusted using Box-Behnken Design (BBD). Following appropriate kinetic models, the improved formulation showed prolonged, regulated, and sustained drug release. DSC, FTIR, and XRD compatibility tests verified that there were no notable drug–excipient interactions, demonstrating the formulation's stability. The findings showed that polymer concentration is a key factor in regulating drug release behavior. Therefore, by increasing therapeutic efficacy, lowering dosage frequency, and boosting patient compliance, the new sustained release matrix tablets of mirabegron present a viable strategy for the efficient control of overactive bladder.

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