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Development and *In Vitro* Evaluation of Metoprolol Tartrate Formulation for Improved Therapeutic Efficacy

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Abstract

Hypertension is a major complication often associated with diabetes mellitus, significantly increasing the risk of cardiomyopathy, stroke, hyperlipidemia, ischemic cerebrovascular disease, and peripheral vascular disease. These complications contribute substantially to morbidity and mortality, especially among middle-aged and older individuals. Metoprolol tartrate, a beta-blocker, is widely used for the management of hypertension and prevention of cardiac complications in diabetic patients. The objective of this research was to develop a sustained-release (SR) formulation of metoprolol tartrate for once-daily administration to improve therapeutic efficacy and patient compliance. Sustained-release tablet formulations (F1 to F7) were prepared using release-retarding agents such as HPMC K100 and Eudragit RSPO. The granules for the SR tablets were evaluated for their flow properties to ensure uniformity and reproducibility during the manufacturing process. The formulated SR tablets were subjected to various evaluations, including weight variation, hardness, thickness, swelling index, and in vitro drug release studies. The optimized formulation (F7) demonstrated a controlled and sustained drug release for 12 hours, ensuring a consistent therapeutic effect. The results indicate that the developed sustained-release formulation of metoprolol tartrate offers an effective once-daily treatment option for hypertension. This novel formulation has the potential to enhance patient compliance, improve treatment outcomes, and significantly contribute to the management of hypertension and associated cardiovascular risks.

Keywords: Hypertension, Metoprolol Tartrate, Hyperlipidemia, Cardiomyopathy

1. Introduction

Hypertension and cardiovascular disorders are among the leading causes of morbidity and mortality worldwide[1]. Their increasing prevalence underscores the need for effective management strategies and novel therapeutic approaches[2]. Hypertension, or high blood pressure, is a long-term medical condition that poses a significant global health challenge[3]. It is characterized by chronically elevated blood pressure levels, where the force exerted by blood against the walls of arteries remains higher than normal over an extended period[4]. Blood pressure is measured in millimeters of mercury (mmHg) and expressed as two values: systolic blood pressure (SBP) and diastolic blood pressure (DBP). Clinically, hypertension is diagnosed when SBP is consistently ≥140 mmHg or DBP is ≥90 mmHg across multiple readings. These thresholds are based on guidelines provided by the American College of Cardiology (ACC) and the European Society of Cardiology (ESC)[5].

Often called the "silent killer," hypertension may develop asymptomatically, meaning most individuals are unaware of their condition until complications arise[6]. It remains one of the most prevalent risk factors for cardiovascular diseases (CVDs), contributing substantially to heart attacks, strokes, heart failure, and kidney diseases. Globally, an estimated 1.28 billion adults aged 30–79 years suffer from hypertension, according to the World Health Organization (WHO)[7]. However, only one in five individuals with hypertension has it adequately controlled, underscoring the urgency of early diagnosis and effective management.

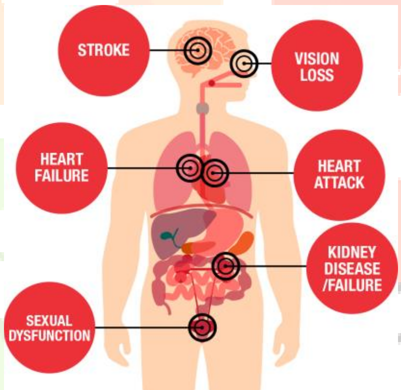

Figure 1: Health Threats Associated with Hypertension

Metoprolol is a selective beta-1 blocker commonly employed as the succinate and tartrate derivatives depending if the formulation is designed to be of immediate release or extended release[8]. The possibility of the generation of these formulations comes from the lower systemic bioavailability of the succinate derivative[9]. To this date, it is one of the preferred beta-blockers in general clinical guidelines and it is widely prescribed in the Netherlands, New Zealand, and the US[10]. Metoprolol was developed since 1969 by US Pharmaceutical Holdings I and FDA approved in 1978. Metoprolol is a beta-1-adrenergic receptor inhibitor specific to cardiac cells with negligible effect on beta-2 receptors[11]. This inhibition decreases cardiac output by producing negative chronotropic and inotropic effects without presenting activity towards membrane stabilization nor intrinsic sympathomimetics[12-14].

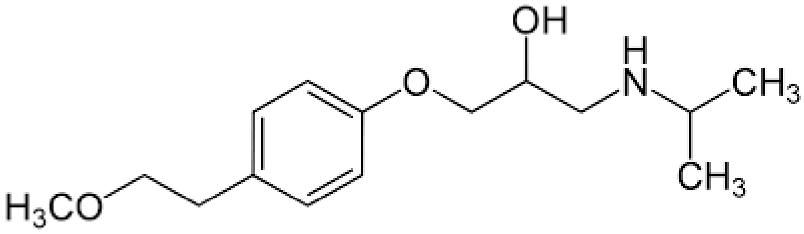

Figure 2: Chemical Structure of Metoprolol Tartarate

2. Methodology

Metoprolol tartrate and hydroxypropyl methylcellulose (HPMC K100M) were obtained from SD Fine Chem Ltd., Mumbai and Biocon biopharmaceutical company, India respectively. Eudragit RSPO was obtained from nice chemicals private limited, Cochin, India. All other excipients were of analytical research grade and used as received.

S.No.	NAME OF INGREDIENTS	COMPANY NAME AND GRADE
1	Metoprolol tartrate	SD Fine Chem Ltd., Mumbai
2	HPMC K100M	Biocon biopharmaceutical company, India
3	Eudragit RL-100	Nice chemicals private limited

Table 1: List of Chemicals

S.No.	EQUIPMENTS	MANUFACTURER
1.	UV Visible Spectro Photometer1800	Shimadzu, Japan
2.	Weighing balance	India
3.	Dissolution apparatus	Labindia disso 2000
4.	Hot air oven	TECHNICO, Thana East Maharashtra
5.	Magnetic Stirrer	REMI motors Ltd.
6.	Mechanical shaker	REMI motors Ltd.
7.	Disintegration apparatus	Labindia disso 2000

Table 2: List of equipment's

2.1 Formulation of Metoprolol Tartrate Granules:

Metoprolol tartrate, a commonly prescribed medication for hypertension management, was combined with release-retarding agents such as HPMC K100 and Eudragit RSPO, along with other excipients detailed in Table 3. The formulation process involved geometrically mixing the ingredients in a blender and passing them through a sieve #44 to ensure uniformity of the mixture. PVP K-30, a binder, was then added to the dry mix to create a cohesive mass. This mass underwent further processing, passing through sieves #10 and #22 to form granules of desired size. The granules were subsequently dried in a tray drier at 60°C to remove excess moisture. To facilitate tablet formation, the dried granules were lubricated with magnesium stearate. Finally, the granules were compressed using round flat plain upper and lower punches to produce tablets with consistent weight and drug content. This meticulously controlled process ensures the uniform distribution of active ingredients and excipients, ultimately contributing to the quality and efficacy of the final product.

Batch No.	Metoprolol Tartrate	Hpmc K100	Eudragit Rspo	Pvpk-30	Lactose	Magnesium Stearate
F1	10	20	-	10	5	5
F2	10	-	20	10	5	5
F3	10	10	10	10	5	5
F4	10	15	5	10	5	5
F5	10	17	3	10	5	5
F6	10	3	17	10	5	5
F7	10	5	15	10	5	5

Table 3 Formulation of Metoprolol tartrate granules with different polymers in (mg)

2.2 Preformulation Study

2.2.1 Bulk Density

Bulk density is the ratio of the mass by volume of an untapped powder sample. The bulk density is measured in g/ml. The bulk density depend on upon both the density of the powder particles and on the arrangement of the powder particles. The bulk density influence preparation, storage of the sample. The mathematical representation given below.

Bulk density = weight of the drug/Bulk volume

2.2.2 Tapped Density

In tapped density the bulk powder mechanically tapped in a graduated cylinder until the change in volume is observed. Here the tapped density is calculated as mass divided by the final volume of the powder.

Tapped density = weight of the granules/tapped volume

2.2.3 Angle of Repose

It gives an idea of flowability of a powder or a bulk solid. There are some factor which responsible for the flowability of powders such as particle size, size distribution, shape, surface area etc. Flowability of the powder depend on the different environment and can be changed easily. The angle of repose was calculated by the following formula.

$$\theta = \tan^{-1} h/r$$

2.2.4 Compressibility index (or) Carr's index (i)

It is one of the most important parameter to characterize the nature of powders and granules. Compressibility is an important measure that can be obtained from bulk and tapped densities. It is calculated by using the following formula and expressed in terms of %.

Carr's index (%) = (Tapped density - Bulk density/ Tapped density) x 100

2.2.5 Hausner's Ratio

It is an important character to determine the flow property of powder and granules. This can be calculated by the following formula.

Hausner's ratio = Tapped density / Bulk density

2.2.6 Drug-Polymer Interaction Studies By FT-IR

Infrared radiation can be worked in two different ways, either the radiation is absorbed by the sample or it can passed through the sample. FT-IR results represent the molecular absorption and transmission of the sample which gives a fingerprint image of the sample. So for different samples it carry unique spectra and gives the blue print of the sample. This characterization is very useful for analysis of number of samples. In FTIR analysis sample has been analysed in the wave number between 4000-400 cm-1.KBr pallets is prepared for the FTIR analysis. KBr is added with the sample and finally pallet has been formed and submitted to the FTIR analysis. Potassium bromide (KBr) is the commonest alkali halide used in the pellets due to its high transparency. FT-IR analysis can be used for the identification of unknown materials, determination of quality and compatibility of the sample in a mixture. FTIR absorption spectra of pure drug, all the polymers used and the combination of drug and polymers were taken to confirm the identity of the drug and to detect the interaction of the drug with the excipients.

2.3 Calibration Curve By Uv Spectrophotometer

The absorbance maxima (λ max) of Metoprolol tartrate was determined by using double beam UV spectrophotometer, Shimadzu (UV2001) Corp., Japan. An accurately weighed 100 mg of Metoprolol tartrate is dissolved in pH 6.8 Phosphate buffer and make up the volume up to 100 mL in a volumetric flask (Stock solution: I, mg/mL). From this 10 mL of solution were pipette out and make up the volume up to 100 mL (Stock solution: II, 100 µg/mL). The aliquots were prepared whose concentration ranging from 2-12 µg/mL and the absorbance were measured at 222 nm by using UV spectrophotometer, against blank solution shown in figure 3 and in Table 4.

Concentration in µg/mL	Absorbance at 222 nm
0	0
2	0.145
4	0.318
6	0.51
8	0.64
10	0.81
12	0.98

Table 4 : Calibration curve data of Metoprolol tartrate

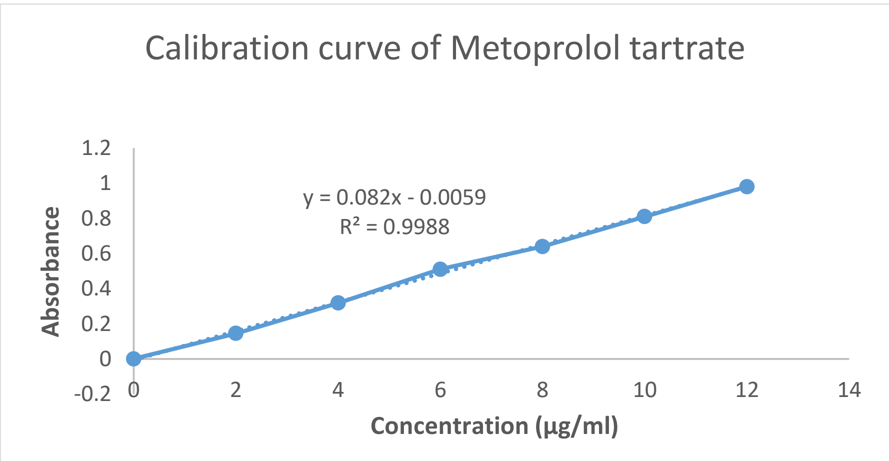

Figure 3: Calibration curve of Metoprolol tartrate

3. Results and Discussion

3.1 Pre-Compression Study

Bulk density and tapped density are crucial parameters that depend on the nature and size of a compound. These properties may vary due to factors such as crystallization, milling, or formulation processes. They offer valuable insights into the size of the final dosage form and affect compression and flow properties post-production. The pre-compression results of metoprolol tartrate are detailed in Table 5, demonstrating excellent flow properties and compliance with specified limits.

S. No.	Pre-Compression Parameters	Metoprolol tartrate
1	Bulk density (g/mL)	0.24 ± 0.91
2	Tap density (g/mL)	0.25 ± 0.25
3	Angle of repose (0)	22.84 ± 0.41
4	Carr’s index	9.83 ±0.61
5	Hausner’s ratio	1.03 ± 0.14

Table 5 : Pre-Compression data for Metoprolol tartrate API

3.2 Drug Polymers Physical Compatibility Studies

Metoprolol tartrate and polymers (HPMC K100M, Eudragit RSPO) mixtures were consider for the pre-compatibility study. FTIR absorption spectra of pure drug, with all the polymers used and the combination of drug and polymers were taken to confirm the identity of the drug and to detect the interaction of the drug with the excipients.

3.3 Drug Compatibility Study Using FT-IR

The FTIR spectrum of drug (Metoprolol tartrate), individual polymers (HPMC K100 and Eudragit RSPO) and different composition of drug - polymers has shown in Figure 6.1 to 6.5. Obtained result reveals that there is no shifting or change in spectra of pure API when it is in combined with pure polymers. This proves that individual polymers and their different weight ratios are compatible with the drug metoprolol tartrate.

3.4 Flow Properties

The prepared granules of all the 7 formulation are taken to study the flow properties. The flow properties of each formulation such as bulk density, tapped density, angle of repose, compressibility index and Hausner’s ratio are determined and flow properties of all the 7 formulation are found to be satisfactory.

3.5 Post-Compression Parameters

The physicochemical properties of metoprolol tartrate sustained release tablets (Formulation F1-F7) were comprehensively evaluated to understand their impact on the drug release pattern. These properties, listed in Tables 6.3, is crucial determinants of the tablets' performance and efficacy. Parameters such as weight variation, hardness, thickness, friability, disintegration time, and dissolution rate were assessed to ensure the tablets' quality and consistency. Weight variation reflects the uniformity of drug content among tablets within the same batch, while hardness measures the tablets' mechanical strength and resistance to breakage.

Thickness assessment ensures uniformity in tablet size, which affects dosing accuracy and patient compliance. Friability testing evaluates the tablets' resistance to mechanical stress and abrasion during handling and transportation. Disintegration time assesses the tablets' ability to break down into smaller particles for drug dissolution and absorption, while dissolution rate determines the rate at which the active ingredients are released and become available for systemic circulation. These physicochemical properties collectively influence the tablets' drug release kinetics, bioavailability, and therapeutic efficacy, thereby playing a vital role in ensuring safe and effective treatment for patients.

3.6 *in-vitro* Drug Release

The dissolution test for the tablets was conducted following the guidelines outlined in the United States Pharmacopeia (USP). The test was performed using USP apparatus II, commonly known as the paddle apparatus, which provides a controlled environment for dissolution testing. Initially, 900 mL of 0.1 N hydrochloric acid (HCl) was used as the dissolution medium, simulating the acidic environment of the stomach. The paddle was rotated at a speed of 50 revolutions per minute (RPM) for the first hour to ensure uniform mixing and dissolution of the tablets. After the initial hour, the 0.1 N HCl was replaced with phosphate buffer solution at pH 6.8 to mimic the conditions of the small intestine, where drug absorption predominantly occurs. The dissolution test was continued for a total duration of 12 hours, with the paddle rotating continuously throughout the test period.

During the dissolution test, samples were collected at specified time intervals to assess the release of metoprolol tartrate sustained release tablets. For the sustained-release layer containing metoprolol tartrate, samples were collected at 0, 2, 4, 6, 8, 10, and 12 hours to monitor the prolonged release of the drug over the entire test duration.

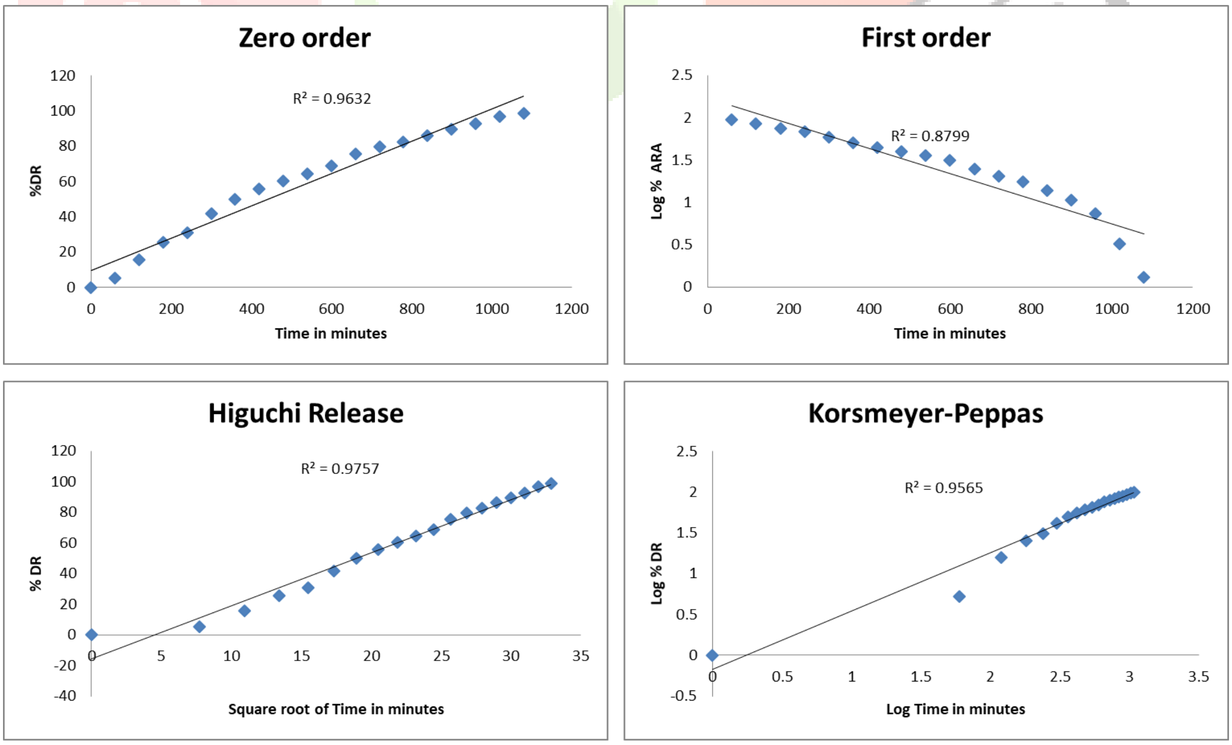

Figure 4. Release kinetics of metoprolol tartrate formulation

4. Conclusion

The study highlights the importance of polymer selection and ratio optimization in achieving a desired drug release profile. The high-viscosity grade of HPMC K100 proved effective in forming a robust gel matrix, while the hydrophobic Eudragit RSPO provided the necessary resistance to ensure sustained drug release over an extended period. The combination of these polymers addresses the challenges associated with the short half-life of metoprolol tartrate, reducing dosing frequency and improving patient compliance. Formulation F7, with a higher concentration of Eudragit RSPO, emerged as the most effective in sustaining the release of metoprolol tartrate, achieving 98.78% release at 12 hours. This highlights the potential of hydrophilic-hydrophobic polymer blends in controlling the release of highly water-soluble drugs and optimizing therapeutic outcomes.

The study underscores the significance of polymer science in drug delivery, providing a foundation for further research and development in sustained-release systems for water-soluble drugs.

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