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Design and Development of Metoprolol Succinate Dual-Phase Extended-Release Tablets

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ABSTRACT

This study presents comprehensive preformulation, precompression, and postcompression evaluations for the development of dual-phase extended-release tablets of Metoprolol Succinate (MTS). Preformulation studies confirmed the identity and purity of MTS through organoleptic assessment, melting point analysis, and FTIR spectroscopy, which validated the presence of characteristic functional groups and demonstrated compatibility with key excipients including MCC PH101, HPMC K4M, PVP K30, sodium stearyl fumarate, and colloidal silicon dioxide. UV spectrophotometric analysis established a λmax of 240 nm, and calibration curves in 0.1 N HCl and phosphate buffer pH 6.8 exhibited excellent linearity ($R^2 \approx 0.99$). Solubility studies revealed high solubility in water, 0.1 N HCl, and methanol, with moderate solubility in PBS pH 6.8, indicating favorable dissolution across physiological pH conditions. Precompression studies of immediate-release (IR1–IR3) and sustained-release (F1–F6) blends demonstrated acceptable flow and compressibility, with all formulations exhibiting suitable micromeritic properties for direct compression. Postcompression evaluations confirmed compliance with pharmacopoeial standards, as tablets exhibited adequate hardness, friability below 1%, acceptable weight variation, uniform thickness, and drug content ranging from 98.23% to 99.52%. In vitro dissolution studies showed that drug release was strongly influenced by polymer viscosity, with HPMC K4M–based formulations (F1–F3) providing more sustained release than Eudragit L100–based formulations (F4–F6). Among the formulations, F3 (containing 20 mg HPMC K4M) demonstrated the most controlled release over 12 hours. Stability studies of F3 confirmed no significant changes in tablet quality under accelerated conditions (40 ± 2°C/75 ± 5% RH) for three months. Overall, the findings support the successful development of a stable and effective dual-phase extended-release tablet of Metoprolol Succinate suitable for sustained therapeutic action.

Keywords: *Metoprolol Succinate; Preformulation Studies; Dual-Phase Extended-Release Tablets; FTIR Compatibility; In Vitro Drug Release; HPMC K4M*

1. INTRODUCTION

Drug delivery research aims to design formulations that achieve therapeutic needs associated with specific pathological conditions [1-2]. Extended-release drug delivery systems have gained significant importance due to their ability to maintain consistent plasma drug concentrations, improve bioavailability, decrease dosing frequency, and minimize adverse effects [3]. Metoprolol succinate, a β1-selective adrenergic blocker used in the management of hypertension, angina, and heart failure, is characterized by a short biological half-life (3–7 hours) and moderate oral bioavailability (~50%). Conventional immediate-release (IR) formulations often result in plasma concentration fluctuations requiring multiple daily doses [4-5]

These fluctuations may compromise therapeutic efficacy, produce dose-related side effects, and negatively impact patient compliance. Targeting drug release to the upper gastrointestinal tract (duodenum and jejunum), where metoprolol absorption is optimal, may enhance its bioavailability [6]. A dual-phase extended-release (ER) formulation, integrating an IR component with a hydrophilic matrix-based ER component, offers the advantage of a rapid onset followed by prolonged, controlled release [7-10]

Dual-phase extended-release tablets of metoprolol succinate will maintain therapeutic blood levels for 24 hours, reduce plasma concentration variability, and improve patient adherence compared to IR formulations [11]. Targeting absorption in the upper gastrointestinal tract will enhance oral bioavailability beyond the reported 50%. Metoprolol succinate was selected due to its therapeutic relevance, pharmacokinetic limitations (short half-life and low bioavailability), site-specific absorption, and suitability for modification into ER formulations [12-15]. Its established safety profile further permits structural modifications to improve therapeutic outcomes without compromising tolerability.

2. MATERIALS AND METHODS

Materials

The materials used in the formulation of the dual-phase extended-release tablets included Metoprolol Succinate (MTS) obtained from IPCA Laboratories Ltd., Ratlam; Eudragit L100, hydroxypropyl methylcellulose K4M, and microcrystalline cellulose procured from S.D. Fine Chemicals, Mumbai; PVP K30 sourced from LOBA Ltd.; and sodium CMC, sodium stearyl fumarate, and colloidal silicon dioxide A200, all obtained from Qualigen, Mumbai.

Preformulation Studies

Melting Point

Melting point of drug was measured by melting point apparatus. A small quantity of drug powder was placed into a capillary tube. The capillary tube is inserted into the heating block, and the heating is continued until melting is completed. The temperature range at which powder started to melt to complete melting was observed [16-17].

Determination of λmax and Calibration Curve

A 1 mg/mL stock solution was prepared in 0.1 N HCl. Serial dilutions (5–50 µg/mL) were analyzed using a UV spectrophotometer at 200-400 nm. The λmax was determined to be 240 nm, and a standard calibration curve was constructed [18-20].

FTIR Spectroscopy

FTIR spectrum of MTS was determined in a FTIR spectroscope (Perkin Elmer-Spectrum RX-I FTIR Spectrophotometer, USA) using KBr pellet. The peaks obtained were analyzed to confirm the structure of Metoprolol Succinate [21-22].

Solubility Studies

Drug solubility was examined in various solvents by shaking 0.5 g of drug in each solvent and observing solubilization behavior [23].

Drug–Excipient Compatibility

Drug and excipients were mixed in various ratios and stored at refrigerated, room-temperature, and accelerated stability conditions (40°C ± 2°C / 75% RH). FTIR spectra were analyzed for any chemical interaction [24-26].

Precompression Characterization of Granules

The flow properties of the prepared granules were evaluated using multiple precompression parameters. The angle of repose was determined by the funnel method. Bulk density was measured by transferring a weighed quantity of metoprolol succinate granules into a 50 mL measuring cylinder without tapping [27]. Tapped density was determined by subjecting the granule-containing cylinders to 500 taps using a USP-compliant tapped density tester. Compressibility was assessed through Carr's Compressibility Index, providing an estimate of the powder's packing ability. Additionally, the Hausner ratio, an indicator of interparticle friction, was calculated as the ratio of tapped density to bulk density. Collectively, these parameters were used to characterize the flow behaviour and suitability of the granules for tablet compression [28-30].

Formulation of Dual-Phase Extended-Release Tablets

Extended-Release Layer

The extended-release (ER) layer was prepared using a wet granulation process. The formulation consisted of MTS, microcrystalline cellulose PH101, hydroxypropyl methylcellulose K4M, and Eudragit L100, which were blended uniformly in a high-shear granulator. An aqueous solution of polyvinylpyrrolidone (PVP) K30 was used as the granulating binder and added incrementally to form a consistent wet mass [31-32]. The wet granules were dried using fluid bed drying, followed by sieving to ensure uniform particle size distribution. The dried granules were then blended with colloidal silicon dioxide (Aerosil® 200, 1.00%) and sodium stearyl fumarate (5.00%) to enhance flowability and compressibility, yielding the final blend for the extended-release granules (Table 1).

Table 1: Composition of Metoprolol Succinate extended release layer

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Metoprolol Succinate	75	75	75	75	75	75

MCC PH101	50	45	40	50	45	40
HPMC K4M	10	15	20	-	-	-
Eudragit L100	-	-	-	10	15	20
PVP K30	5	5	5	5	5	5
Sodium stearyl fumarate	5	5	5	5	5	5
Colloidal silicon dioxide A200	5	5	5	5	5	5
Total Tablet weight	150	150	150	150	150	150

Immediate-Release Layer

The immediate-release (IR) component was similarly prepared by wet granulation, using MTS and MCC PH101 as the core ingredients. Granulation was carried out with an aqueous solution of PVP K30 as the binding agent. After granulation, the wet mass was dried in a fluid bed dryer and sieved to produce uniform granules. To the dried granules, sodium carboxymethyl starch was added as a superdisintegrant, along with colloidal silicon dioxide A200 and sodium stearyl fumarate as glidant and lubricant, respectively, to obtain the final immediate-release granule blend (Table 2) [33-34].

Table 2: Composition of Metoprolol Succinate Immediate release layer

Ingredients (mg)	Formulation code		
	IR1	IR 2	IR3
Metoprolol Succinate	25	25	25
MCC PH101	60	55	50
PVP K30	5	5	5
Sodium CMC	5	10	15
Sodium stearyl fumarate	3	3	3
Colloidal silicon dioxide A200	2	2	2
Total Tablet weight	100	100	100

Dual-Phase Extended-Release Tablets Compression

The Dual-Phase Extended-Release Tablets was manufactured using a Rimek mini press tablet press. The extended-release layer, equivalent to 75 mg of MTS, was first filled and lightly compressed. Subsequently, the immediate-release layer, equivalent to 25 mg of MTS (F2), was layered and compressed to form the bilayer hydrophilic matrix core tablet [35-36].

Film Coating

The compressed bilayer core tablet was coated with manual film coating method, where film applied at a 2.00% weight gain, to provide mechanical integrity, protection from environmental moisture, and improved swallowability. The film-forming material, cellulose acetate as the film-forming agent, (6.00 %) and PGE6000 (1.50 %), were dissolved in a mixture of acetone–water (86.00 %-6.50 %) to form a coating solution (Table 3). The core tablets were then coated with the coating solution, resulting in the final product as hydrogel matrix-based extended-release bilayer tablet of MTS [37-40].

Table 3: Composition of coating solution

Ingredients	Quantity (mg)
Cellulose acetate	6mg
PEG6000	1.5mg
Acetone	86ml
Distilled water	6.5ml qs

Evaluation of Prepared Tablets

Tablet evaluation parameters included hardness, friability, thickness, weight variation, and drug content to ensure the mechanical integrity and quality of the formulation. Hardness, assessed using a Monsanto hardness tester, measured the tablet's ability to withstand mechanical stress during handling and storage. Friability, determined with a Roche Friabilator, evaluated the tendency of tablets to chip or crumble, calculated as the percentage weight loss after tumbling. Tablet thickness was measured using a digital vernier caliper to ensure uniformity, while weight variation was assessed by weighing twenty randomly selected tablets to confirm consistency in dosage. Drug content was evaluated by dissolving a powdered sample in 0.1 N HCl, filtering, diluting, and measuring absorbance at 240 nm against a calibration curve to determine the percentage of metoprolol succinate present in the tablets [41-43].

In Vitro Dissolution Studies of Metoprolol Succinate Dual-Phase Extended-Release Tablets

Dissolution rate studies of Dual-Phase Extended-Release Tablets of MTS was performed under gastric conditions. This test was performed using the USP dissolution apparatus type II at 50 rpm. A Bilayered tablet containing 100 mg of MTS was placed in the dissolution vessel containing 900mL of 0.1N HCl maintained at 37±0.5ºC for initial 2hrs and then completely replaced with PBS pH6.8 for remaining period of drug release. At pre-decided time intervals, samples from the dissolution medium were withdrawn, filtered, and concentrations of Metoprolol were determined spectrophotometrically at λmax 240nm [44-45].

Stability Study

The studies were conducted on best selected formulation on the basis of dissolution studies and as per ICH guidelines which recommend a temperature of 40±2^{0}C, a relative humidity of 75±5% and period of 3 months for accelerated stability studies. The sampling time was kept at 1, 2 and 3 months. The studies were performed using stability chamber (Thermo Lab, Mumbai). Changes in the appearance and drug content of the stored raft forming tablets were investigated during the period and after 3 month [46].

3. RESULTS AND DISCUSSION

Preformulation studies

Preformulation studies were conducted to confirm the identity, purity, and suitability of Metoprolol Succinate for developing dual-phase extended-release tablets. The organoleptic evaluation revealed that the drug sample matched official IP standards, exhibiting a white crystalline, odorless solid, confirming its authenticity. The melting point determination further supported drug purity, with the observed melting range of 133-135°C closely aligning with the standard value of 134–138°C, indicating absence of significant impurities.

FTIR spectroscopy provided structural confirmation through characteristic peaks corresponding to hydroxyl, aliphatic C–H, carbonyl, aromatic, ether, and amine functional groups, all consistent with the known structure of Metoprolol Succinate. Compatibility studies using FTIR analysis of drug–excipient mixtures showed no major shifts or disappearance of characteristic peaks, confirming the absence of chemical interactions between MTS and excipients such as MCC PH101, HPMC K4M, PVP K30, sodium stearyl fumarate, and colloidal silicon dioxide, thereby validating their suitability in the formulation.

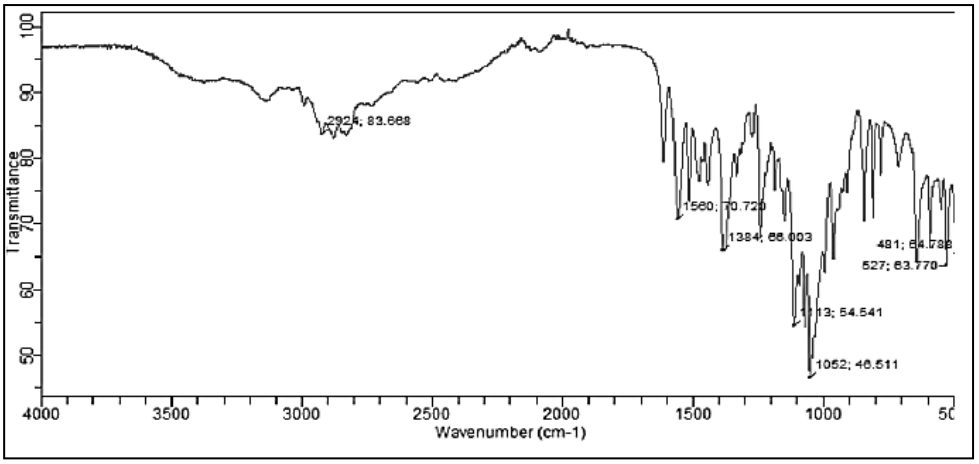

Figure 1: FTIR analysis of drug–excipient mixtures

UV spectrophotometric analysis established the λmax at 240 nm, and calibration curves prepared in both 0.1 N HCl and pH 6.8 phosphate buffer demonstrated excellent linearity ($R^2 \approx 0.99$), supporting their reliability for quantitative drug estimation (Table 4-5 and Figure 2-3).

Table 4: Absorbance data of Metoprolol succinate in distilled water for preparation of calibration curve, at 240 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.172
3	20	0.354
4	30	0.538
5	40	0.712
6	50	0.935

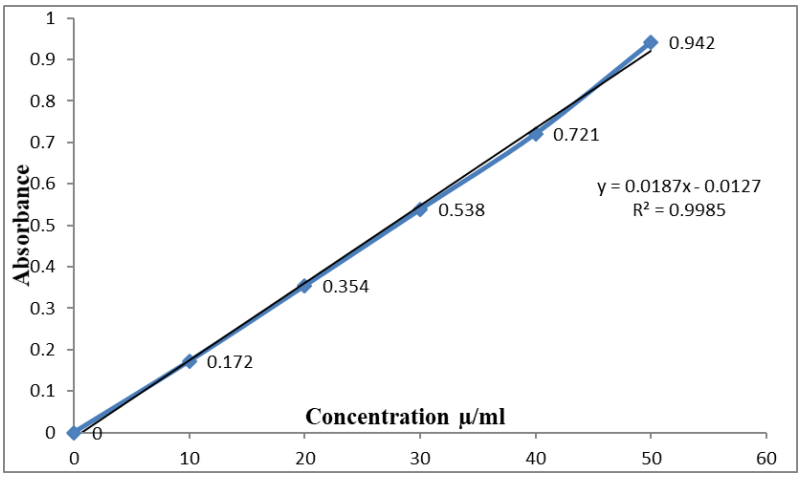

Figure 2: Calibration curve of Metoprolol succinate in 0.1N HCl

Table 5: Absorbance data of Metoprolol succinate in phosphate buffer pH-6.8 for preparation of calibration curve at 240 nm

S.No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.146
3	20	0.360
4	30	0.536
5	40	0.703
6	50	0.876

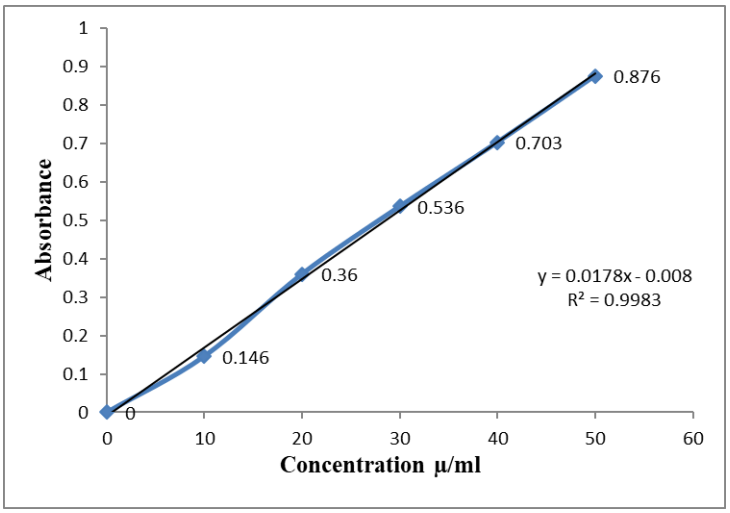

Figure 3: Calibration curve of Metoprolol succinate in pH 6.8

Solubility studies revealed that MTS is freely soluble in water, 0.1 N HCl, and methanol, and soluble in PBS pH 6.8, indicating good dissolution behavior in both gastric and intestinal environments (Table 6).

Table 6: Solubility of MTS in different solvents

Solvents	Solubility
Distilled Water	Freely soluble
PBS pH6.8	Soluble
0.1 N HCl	Freely soluble
Methanol	Soluble

Precompression Characterization

The precompression characterization of the powder blends for both the fast-release (IR1–IR3) and sustained-release (F1–F6) layers of Metoprolol Succinate was carried out to ensure suitability for compression and to predict the performance of granules during tablet manufacturing. For the fast-release blends, variations in the amounts of MCC PH101 and Sodium CMC influenced the flow characteristics, while other excipients were kept constant (Table 7). These results confirm that the fast-release granules possessed adequate flow and compressibility for successful layer formation.

Table 7: Precompression parameters of the Metoprolol Succinate fast-release layer

Parameter	IR1	IR2	IR3
Bulk Density (g/cm³)	0.36	0.40	0.45
Tapped Density (g/cm³)	0.45	0.50	0.56
Angle of Repose (°)	25.5°	27.4°	29.6°
Compressibility Index (%)	8.69	15.00	30.35
Hausner's Ratio	1.09	1.18	1.43

For the sustained-release formulations (F1–F6), the inclusion of different concentrations of HPMC K4M and Eudragit L100 influenced the micromeritic properties of the granules. All blends demonstrated acceptable bulk and tapped densities, indicating efficient particle packing and suitable compressibility. The angles of repose across formulations suggested good flow properties, which were further supported by moderate compressibility index and Hausner ratio values. The presence of MCC PH101 and colloidal silicon dioxide contributed positively to flow, while PVP K30 and sodium stearyl fumarate enhanced granule cohesion and lubrication (Table 8). Overall, the precompression results revealed that all powder blends, for both the immediate- and sustained-release layers, exhibited satisfactory flow and compressibility characteristics, supporting their suitability for bilayer tablet manufacturing.

Table 8: Precompression Parameters of Metoprolol Succinate Sustained-Release Layer Formulations

Parameter	F1	F2	F3	F4	F5	F6
Bulk Density (g/cm³)	0.38	0.40	0.42	0.39	0.41	0.43
Tapped Density (g/cm³)	0.47	0.49	0.52	0.48	0.50	0.54
Angle of Repose (°)	26.2°	27.1°	28.5°	25.9°	27.8°	29.3°
Compressibility Index (%)	19.14	18.36	19.23	18.75	18.00	20.37
Hausner's Ratio	1.24	1.22	1.24	1.23	1.22	1.26

Post-compression Evaluation

The dual-phase extended-release tablets of Metoprolol Succinate were evaluated for key quality parameters to ensure their suitability for sustained-release application. All formulations exhibited hardness values below 5 kg/cm². Friability values were below 1%, confirming good mechanical strength and resistance to surface abrasion. Weight variation for all formulations complied with IP limits, remaining within ±5%, indicating uniform die filling and consistent content distribution. Tablet thickness ranged from 3.0 to 3.9 mm, ensuring good physical uniformity and structural integrity. Drug content analysis showed values between 98.23 ± 1.24% and 99 ± 2.08%, confirming accurate and uniform incorporation of Metoprolol Succinate within the tablets. Overall, the evaluation results demonstrated that all formulations met the essential pharmaceutical quality requirements for extended-release tablet systems (Table 9).

Table 9: Post Compression Parameters of MTS Dual-Phase Extended-Release Tablets

Formula code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	(%) Drug content
F1	6.9±0.4	3.0±0.4	299.41±0.32	0.20±0.17	98.23±1.24
F2	6.3±0.2	3.1±0.1	295.09±0.57	0.12±0.15	99.52±2.08
F3	6.4±0.4	3.6±0.2	300.57±0.26	0.29±0.14	99.12±1.62

F4	6.4±0.5	3.4±0.3	296.86±0.39	0.35±0.12	98.48±2.66
F5	6.9±0.3	3.7±0.2	298.73±0.23	0.30±0.16	98.26±0.88
F6	6.2±0.3	3.8±0.3	302.72±0.47	0.42±0.13	99.10±2.12

In Vitro Drug Release Study from Dual-Phase Extended-Release Tablets

The *in vitro* drug release of the extended-release formulations F1 to F6 was evaluated using a USP Type II dissolution apparatus in 900 mL of 0.1N HCl for 2hrs followed by PBS pH 6.8 at 37 ± 0.5°C with a paddle speed of 50 rpm (Table 10 and Figure 4). Drug release was measured over a 12-hour period. Formulations F1 to F3 used HPMC K4M, a high-viscosity hydrophilic polymer, while F4 to F6 used Eudragit L100, a lower-viscosity grade.

The drug release from the extended-release formulations was primarily controlled by the type and concentration of HPMC polymers used. F1–F3 (HPMC K4M-based) demonstrated slower drug release due to higher viscosity of HPMC K4M. As the concentration increased from 10 mg (F1) to 20 mg (F3), the release rate decreased, indicating more effective gel barrier formation and slower diffusion of drug. F4–F6 (Eudragit L100-based) released the drug more quickly than corresponding K4M formulations. Although Eudragit L100 also forms a gel matrix, its lower viscosity results in a thinner, less resistant gel barrier, permitting faster drug diffusion. At equal concentrations, K4M-based formulations consistently released the drug more slowly than K100LV-based formulations, confirming that polymer viscosity plays a critical role in controlling release. F3 (20 mg K4M) showed the most controlled and sustained release profiles and hence selected as best formulation.

Table 10: Cumulative % Drug Release of Metoprolol Succinate from F1 to F6

Time (hr)	Cumulative % Release					
	F1	F2	F3	F4	F5	F6
0	0.0	0.0	0.0	0.0	0.0	0.0
1	18.2 ± 1.4	15.1 ± 1.6	12.7 ± 1.3	25.6 ± 1.8	21.4 ± 1.7	18.1 ± 1.5
2	30.9 ± 1.5	26.2 ± 1.2	21.6 ± 1.4	42.8 ± 2.0	37.5 ± 1.9	33.4 ± 1.6
4	54.7 ± 1.7	47.9 ± 1.5	41.3 ± 1.6	68.3 ± 1.8	61.7 ± 2.0	57.2 ± 1.7
6	72.5 ± 1.8	66.3 ± 1.6	58.4 ± 1.5	86.1 ± 1.9	78.3 ± 2.1	72.6 ± 1.8
8	85.6 ± 1.6	78.4 ± 1.7	70.9 ± 1.6	94.3 ± 1.6	89.5 ± 1.8	83.8 ± 1.9
10	93.4 ± 1.4	88.1 ± 1.6	80.6 ± 1.7	98.7 ± 1.4	95.4 ± 1.6	90.1 ± 1.7
12	97.2 ± 1.2	93.5 ± 1.5	89.2 ± 1.6	99.5 ± 1.2	97.3 ± 1.4	94.2 ± 1.6

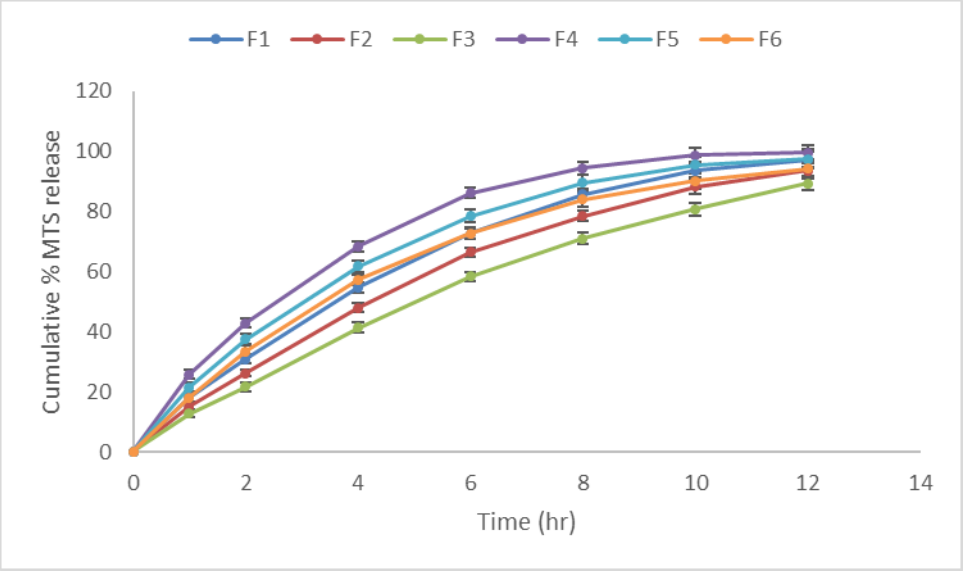

Figure 4: Cumulative % Drug Release of Metoprolol Succinate from F1 to F6

Stability Study

Stability studies were conducted to assess the changes in the quality of MTS dual-phase extended-release tablets during storage. The stability of formulation F3 was monitored for a period of 3 months. The results indicated that the content, of the tablets showed no significant changes at a temperature of 40±2°C with a relative humidity of 75%±5%. The dual-phase extended-release tablets of MTS demonstrate good stability.

4. CONCLUSION

In conclusion, this study presents a promising dual-phase extended-release tablet system that enables once-daily dosing of MTS, potentially improving treatment adherence and patient convenience. However, to advance the clinical applicability of extended-release dosage forms, further formulation optimization is necessary—particularly to enhance drug bioavailability under fasting conditions and prolong gastrointestinal residence time. Future strategies could include the development of gastric floating dual-phase tablets, which would help retain the dosage form in the upper GI tract for longer periods, thereby maximizing absorption.

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