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Development of Bilayer Tablet Formulation for Co-Delivery of Metformin Hydrochloride & Metoprolol Tartrate for Enhanced Therapeutic Impact

Srikrishna.T[1*], S. Nivedhitha[2], Y. Namrutha[3]

[1,3] Department of Pharmaceutics, Swathi College of Pharmacy, Venkatachalam (M & P) SPSR Nellore District – 524320 A.P., India.

[2] Department of Pharmacognosy, Swathi College of Pharmacy, Venkatachalam (M & P) SPSR Nellore District – 524320 A.P., India.

Corresponding Author E-Mail: srikrishna.nlr@gmail.com

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KEYWORDS

Metformin, Metoprolol Tartrate, Bilayer Tablet, Crosspovidone and Sodium Starch Glycolate

ABSTRACT:

Introduction: Diabetes mellitus often accompanies serious complications like hypertension, heart issues, and stroke, particularly affecting older adults. Metformin hydrochloride is the standard medication for type 2 diabetes, Metoprolol tartrate is commonly used to manage hypertension in diabetic individuals. The need arises for a comprehensive treatment approach to address these complications effectively.

Objectives: Aim was to develop a bilayer tablet formulation capable of releasing metformin gradually and metoprolol immediately, facilitating once-daily dosing. This formulation would target both diabetes and hypertension concurrently, potentially offering improved therapeutic benefits compared to conventional treatments.

Methods: To achieve objectives, we meticulously formulated various bilayer tablet formulations (F1 to F7), employing specific release-retarding agents for sustained metformin release and super disintegrants for immediate metoprolol release. These formulations subjected to rigorous testing, evaluating their flow properties and various tests such as weight variation, hardness, thickness, swelling index, and in vitro drug release.

Results: The bilayer tablets containing metformin and metoprolol showed rapid release of the drugs within just 40 minutes. While Formulations F1 and F2 used different super disintegrants, Cross povidone and sodium starch glycolate (SSG) respectively, Formulations F3 to F7 experimented with varying ratios of these super disintegrants. Among these, Formulation F7 stood out as the most effective for sustaining the release of metformin hydrochloride, while the composition of super disintegrants in the metoprolol layer also led to optimal immediate-release outcomes.

Conclusions: The developed bilayer tablet formulation shows promise in offering enhanced therapeutic efficacy compared to traditional dosage forms. These results underscore the importance of carefully selecting polymer combinations and adjusting super disintegrant ratios to fine-tune drug release patterns and enhance formulation performance. By simplifying the dosing regimen to once daily and addressing both diabetes and hypertension simultaneously, has the potential to improve patient compliance and treatment.

1. Introduction

Diabetes and Hypertension are the most common coexisting disorders which may be fatal. Here, combination therapy is favourable which may confer the treatment of both the disorders simultaneously. Metoprolol tartrate is a cardio selective beta-blocker used in the management of hypertension, angina pectoris, and heart failure. Metformin hydrochloride is an orally administered biguanide and the first-line choice for the management of type 2 diabetes.

Multilayer tablets represent a sophisticated drug delivery system wherein multiple layers of different drugs or formulations are compressed into a single tablet [1-4]. This innovative dosage form allows for the simultaneous or sequential release of multiple drugs, each tailored to meet specific therapeutic needs.

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Multilayer tablets offer several advantages over conventional dosage forms, including enhanced efficacy, improved patient compliance, and reduced dosing frequency. This comprehensive discussion will delve into the concept of multilayer tablets, exploring their design, formulation, evaluation, and applications in modern pharmaceuticals. Designing multilayer tablets involves careful consideration of several key factors to ensure optimal performance and efficacy [5, 6]. Multilayer tablets allow for the simultaneous or sequential delivery of multiple drugs, making them ideal for combination therapy regimens targeting complex diseases or conditions that require multiple medications. Multilayer tablets allow for the simultaneous or sequential delivery of multiple drugs, making them ideal for combination therapy regimens targeting complex diseases or conditions that require multiple medications [7,8]

Release-retarding agents are indispensable components in the formulation of sustained-release (SR) [9-12] formulations, especially in bilayer tablets, where precise control over drug release kinetics is paramount. Hydroxypropyl Methylcellulose [13] (HPMC) K100 and Eudragit S100 stand out as key polymers owing to their remarkable film-forming properties and their capacity to establish a robust matrix for controlled drug release.Crosspovidone and Sodium Starch Glycolate (SSG) are two widely utilized super disintegrants, renowned for their exceptional ability to promote rapid tablet disintegration and dissolution [14]. Bilayer tablets containing Metoprolol Tartrate, the inclusion of these super disintegrants is crucial for ensuring prompt drug release and therapeutic efficacy.

In combination Metoprolol with Metformin or as a standalone treatment, several formulations of bilayer tablets and other formulations [15–20], containing pharmacologically active ingredients, have been investigated using analytical techniques [21, 22]. This study aims to develop Metoprolol with Metformin with controlled drug release by utilizing a blend of polymers are commonly employed in extended-release formulations. By carefully adjusting the ratios of these polymers, the kinetics of drug release are optimized to maximize medication efficacy. Bilayer tablets offer a promising solution for optimizing drug delivery, especially in cases where combination therapy is necessary. By addressing the limitations of single-layer formulations, these tablets contribute to improved patient outcomes and better disease management.

2. Methods

Metformin HCl and hydroxypropyl methylcellulose (HPMC K100M) were obtained from Biocon biopharmaceutical company, India. Eudragit RSPOwas obtained from nice chemicals private limited, Cochin, India. All other excipients were of analytical research grade and used as received.

Formulation of Metformin HCl Granules

Metformin hydrochloride, a commonly prescribed medication for diabetes management, was combined with release-retarding agents such as HPMC K100 and Eudragit RSPO, along with other excipients. 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 16×32-inch 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.

Table 1: Formulation of Metformin HCl granules with different polymers in (mg)

BATCH NO.	METFORMIN	HPMC K100	EUDRAGIT RSPO	PVPK-30	LACTOSE	MAGNESIUM STEARATE
F1	500	200	-	40	50	10
F2	500	-	200	40	50	10
F3	500	100	100	40	50	10
F4	500	150	50	40	50	10
F5	500	170	30	40	50	10

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F6	500	30	170	40	50	10
F7	500	50	150	40	50	10

Formulation of Metoprolol Tartrate Granules

Metoprolol tartrate, was combined with super disintegrants such as sodium starch glycolate and crosspovidone, along with other excipients. Aspartame, a sweetening agent, was incorporated into the formulation to mask the bitter taste of the drug, enhancing patient acceptability. Initially, the ingredients were geometrically mixed to ensure uniform distribution. Subsequently, a wet granulation technique was employed, similar to the process used for the sustained-release granules. This involved the gradual addition of a binding agent to the mixed ingredients to form cohesive granules. The granules were then dried to remove excess moisture and ensure stability. Obtained granulation, lubricants were added and blended thoroughly. The lubricated granules were then manually fed into the die over the SR layer of the bilayer tablet. This step ensures proper layering of the immediate-release granules over the sustained-release layer, facilitating the desired drug release profile. Finally, the granules were compressed using 16×32-inch round flat plain upper and lower punches to form tablets of consistent weight and drug content.

Table 2: Formulation of Metoprolol Tartrate containing granules (mg)

Batch No.	Drug (mg)	CP (mg)	SSG (mg)	Lactose (mg)	MS (mg)	Aspartame (mg)	Total weight (mg)
F1	10	5	-	70	5	10	100
F2	10	-	5	70	5	10	100
F3	10	3	2	70	5	10	100
F4	10	1	4	70	5	10	100
F5	10	2.5	2.5	70	5	10	100
F6	10	2	3	70	5	10	100
F7	10	4	1	70	5	10	100

Pre-formulation Study

The prepared granules of all the 7 formulations 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 formulations are found to be satisfactory.

Drug-Polymer Interaction Studies by FTIR

In FTIR analysis sample has been analyzed in the wave number between 4000-400 cm-1KBr pellets is prepared for the FTIR analysis. 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.

Method Development by UV Spectrophotometer

Calibration Curve of Metformin Hcl

Metformin has been subjected to preformulation study using different concentrations (2, 4, 6, 8, 10,12µg/ml) of metformin standard solutions. The absorbance was measured at 232nm by UV-Visible spectrophotometer. A standard plot of absorbance vs. concentration was drawn at both the pH (pH-6.8).

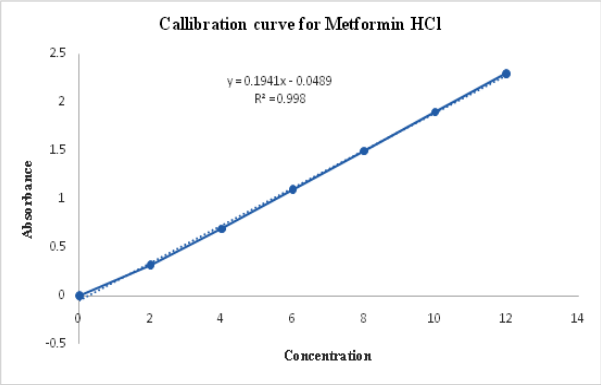

Fig 1: Calibration curve of Metformin HCl at pH 6.8

The absorbance maxima (λ max) of Metoprolol tartrate were determined by using double beam UV spectrophotometer, Shimadzu (UV2001) Corp., Japan. An accurately weighed 100 mg of Metoprolol tartrate 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

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prepared whose concentration ranging from 2-20 µg/mL and the absorbance were measured at 222 nm by using UV spectrophotometer, against blank solution.

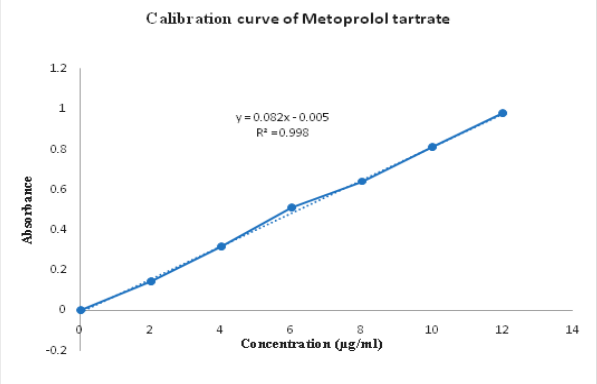

Fig 2: Calibration curve of Metoprolol Tartrate at pH 6.8

3. Results

Pre-Compression Study

The pre-compression results of metformin HCl, demonstrating excellent flow properties and compliance with specified limits.

Table 3: Pre-Compression data for Metformin HCl API

S. No.	Pre-Compression Parameters	Metformin HCl
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

Drug Compatibility study using FTIR

The FTIR spectrum of drug (Metformin hydrochloride and metoprolol tartrate), individual polymers (HPMC K100, Eudragit RSPO, super disintegrants like crosspovidone and sodium starch glycolate) and different composition of drug - polymers 0. 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,super disintegrantsand their different weight ratios are compatible with the drug metformin hydrochloride and

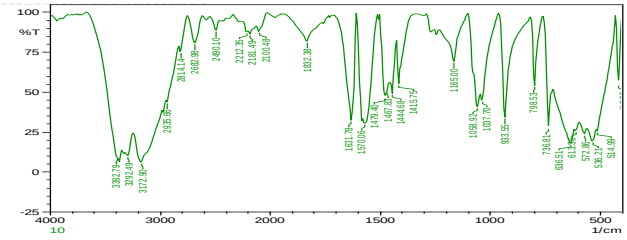

Fig 3: FTIR spectrum of Metformin HCl

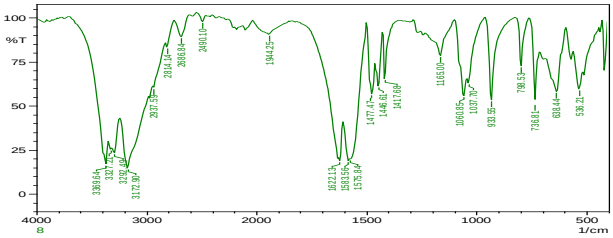

Fig 4: FTIR spectrum of HPMC K100M

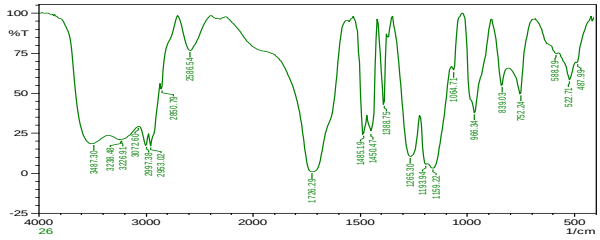

Fig 5: FTIR spectrum of Eudragit RSPO

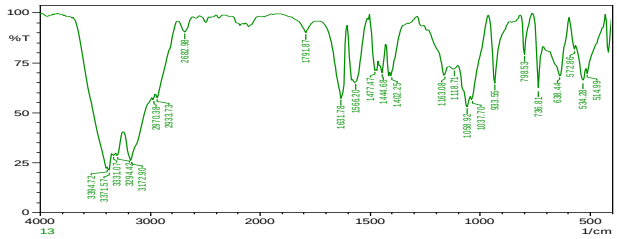

Fig 6: FTIR spectrum of Metformin HCl and HPMC K100M

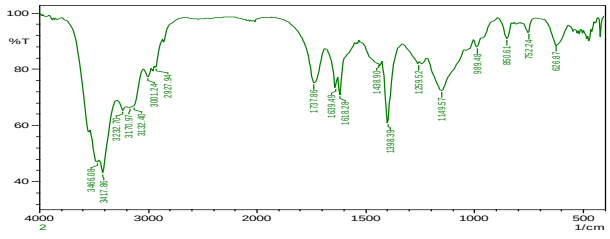

Fig 7: FTIR spectrum of Metformin HCl and Eudragit RSPO

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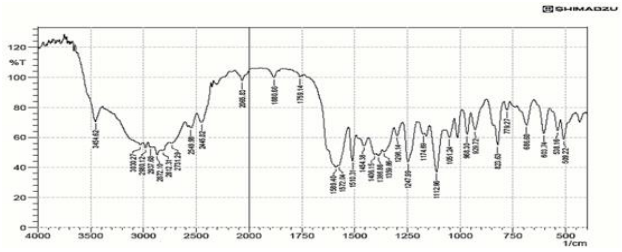

Fig 8: FTIR spectra of Metoprolol Tartrate

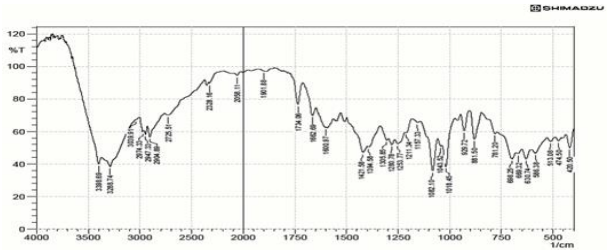

Fig 9: FTIR spectra of Crospovidone

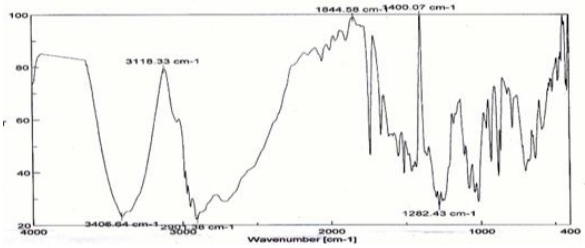

Fig 10: FTIR spectra of sodium starch glycolate

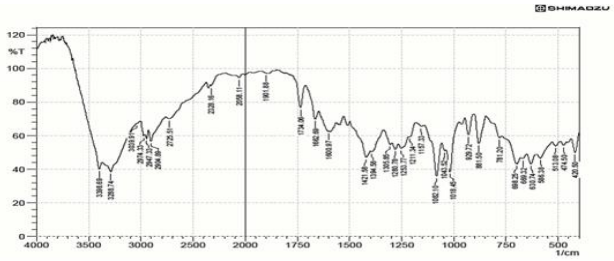

Fig 11: FTIR spectra of Metoprolol Tartrate and Crospovidone

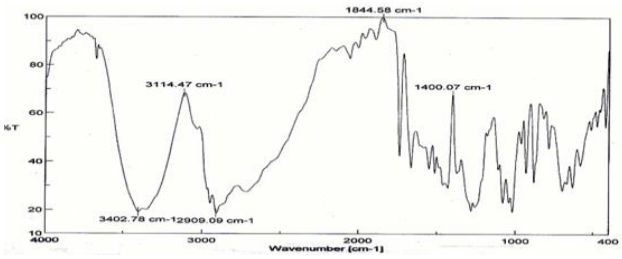

Fig 12: FTIR spectra of Metoprolol Tartrate and Sodium starch glycolate

Pre-Compression Parameters

Table 4: Pre-compression parameters for Metformin HCl SR granules

Formulation	Bulk density g/cm3	Tapped density g/cm3	Hausner's ratio	Carr's index %	Angle of repose(θ)
F1	0.3954±0.0180	0.4254±0.0014	1.12±0.02	10.42±0.02	26.42±1.46
F2	0.3752±0.0200	0.4564±0.0010	1.10±0.01	12.42±0.02	28.22±1.04
F3	0.3920±0.0152	0.4987±0.0024	1.14±0.02	10.22±0.02	30.42±1.00
F4	0.4022±0.0224	0.4579±0.0044	1.12±0.02	11.32±0.02	28.66±1.60
F5	0.3910±0.0102	0.4296±0.0004	1.12±0.01	12.22±0.02	26.88±1.44
F6	0.3526±0.0080	0.4359±0.0094	1.12±0.02	11.34±0.02	30.42±1.62
F7	0.3562±0.0222	0.4654±0.0074	1.10±0.01	10.54±0.02	26.42±1.96

Table 5:Pre-compression parameters for Metoprolol Tartrate IR granules

Formulation	Bulk density g/cm3	Tapped density g/cm3	Hausner's ratio	Carr's index %	Angle of repose(θ)
F1	0.4256±0.0202	0.5362±0.0434	1.44±0.02	11.22±0.02	30.12±1.04
F2	0.4734±0.0226	0.5724±0.0346	1.40±0.02	12.32±0.02	30.42±1.04
F3	0.4240±0.0134	0.5272±0.0254	1.34±0.02	12.42±0.02	29.12±1.42
F4	0.4278±0.0224	0.5279±0.0435	1.42±0.02	12.62±0.02	29.56±1.42
F5	0.46760±0.0342	0.5320±0.0483	1.62±0.02	12.42±0.02	26.28±1.46
F6	0.4346±0.0460	0.5089±0.0534	1.42±0.02	11.44±0.02	31.22±1.48
F7	0.4212±0.0272	0.5203±0.0537	1.62±0.02	11.34±0.02	28.28±1.64

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Table 6: Post-compression parameters for SR and IR Bilayer tablet

Formulation	Tablet Weight variation (mg)	Tablet Hardness (kg/cm^2)	Tablet Thickness (mm)	Tablet Friability (%)	Drug content (%)
F1	900.42±2.01	6.71±0.08	5.98±1.06	0.51±0.23	98.31±0.16
F2	901.14±1.31	6.31±0.05	5.08±0.13	0.43±0.13	97.03±0.54
F3	902.62±1.76	6.57±1.1	4.93±0.37	0.59±0.75	98.63±0.05
F4	899.08±0.61	5.93±1.52	4.81±1.09	0.65±0.32	97.93±0.76
F5	900.81±0.31	5.87±1.81	5.78±0.83	0.55±0.62	98.76±0.81
F6	902.83±1.74	6.73±0.63	5.19±1.76	0.57±0.13	99.81±0.32
F7	903.74±1.51	6.06±0.53	5.76±0.53	0.61±0.23	97.11±0.42

In-Vitro Drug Release

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 immediate-release layer of the tablets. After the initial hour, the 0.1 N HCl was replaced with phosphate buffer solution at pH 6.8. 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 both metoprolol tartrate and metformin hydrochloride from their respective layers in the bilayer tablets. For the immediate-release layer containing metoprolol tartrate, samples were collected at 0.5, 10, 15, 20, 30, and 45 minutes to capture the early stages of drug release. Meanwhile, for the sustained-release layer containing metformin hydrochloride, 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. The collected samples were then analyzed using a UV spectrophotometer to determine the concentration of each drug in the dissolution medium. Metoprolol tartrate was quantified at a wavelength of 222 nm, while metformin hydrochloride was quantified at a wavelength of 232 nm, as specified in the drug monographs. By measuring the absorbance of the samples at these specific wavelengths, the concentration of each drug in the dissolution medium could be determined accurately.

Table 7: In-vitro dissolution profile (%) for Metoprolol Tartrate IR formulation F1-F7

Formulation	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min
F1	34.38	53.31	79.91	99.29	-	-	-	-
F2	18.12	34.77	50.82	66.12	79.17	87.21	96.87	99.89
F3	57.68	68.35	81.39	93.12	99.91	-	-	-
F4	15.13	28.11	43.18	57.22	71.52	85.51	99.38	
F5	34.71	67.21	99.81	-	-	-	-	-
F6	18.71	37.71	56.22	75.18	91.33	100.11	-	-
F7	20.71	39.71	59.22	77.18	94.33	100.19	-	-

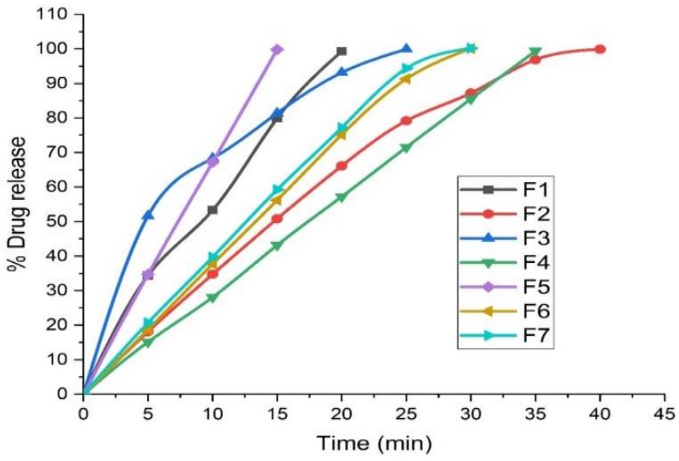

Fig 13: In-vitro drug release of Metoprolol Tartrate IR Formulations F1-F7

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Table 8: In-vitro dissolution profile (%) for Metformin hydrochloride SR Formulation F1-F7

Formulation	1h	2h	3h	4h	5h	6h	7h	8h	9h	10h	11h	12h
F1	17.58	33.80	47.98	64.37	79.10	89.68	99.35	-	-	-	-	-
F2	11.85	19.46	29.28	40.96	51.44	64.91	77.78	88.47	88.53	88.83	-	-
F3	29.35	44.22	58.87	64.91	72.39	79.78	84.11	92.19	96.35	99.28	-	-
F4	13.31	26.76	40.22	53.11	66.28	79.71	86.31	94.22	99.91			-
F5	12.55	23.11	37.32	48.36	61.51	74.33	87.55	99.18				
F6	9.96	17.40	24.03	34.13	45.94	56.26	68.7	78.39	89.17	92.81		
F7	19.62	33.90	48.84	55.83	60.81	64.96	68.82	73.71	79.52	85.22	92.11	98.78

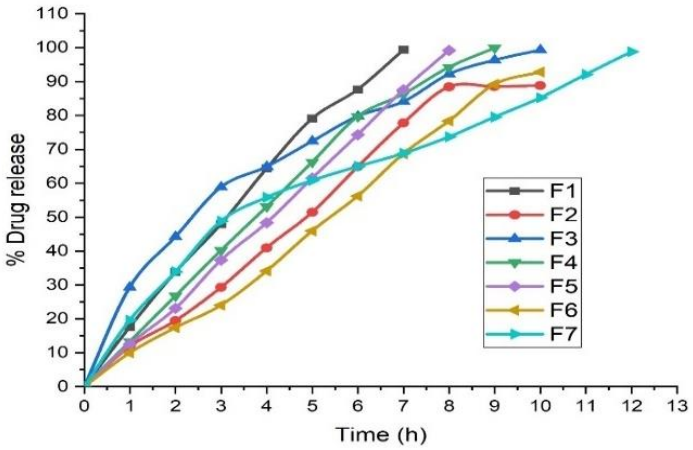

Fig 14: In-vitro dissolution profile of Metformin hydrochloride SR Formulations F1-F7

4. Discussion

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 metformin HCl are detailed in Table 3, demonstrating excellent flow properties and compliance with specified limits.

Drug Polymers Physical Compatibility Studies

The FTIR spectrum of drug (Metformin hydrochloride and Metoprolol Tartrate), individual polymers (HPMC K100, Eudragit RSPO, super disintegrants like Crospovidone and sodium starch glycolate) and different composition of drug - polymers has shown in Figure 3 to 12. 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, super disintegrants and their different weight ratios are compatible with the drug Metformin hydrochloride and Metoprolol Tartrate.

Flow Properties

The prepared granules of all the 7 formulations 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 formulations are found to be satisfactory. The values were shown in Table 4 and Table 5.

Post-Compression Parameters

The physicochemical properties of Metformin hydrochloride and Metoprolol Tartrate Bilayer tablets (Formulation F1-F7) were comprehensively evaluated to understand their impact on the drug release pattern. These properties, listed in Tables 6, are 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

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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.

In-Vitro Drug Release

During the dissolution test, samples were collected at specified time intervals to assess the release of both Metoprolol Tartrate and Metformin hydrochloride from their respective layers in the Bilayer tablets. For the immediate-release layer containing Metoprolol Tartrate, samples were collected at 0.5, 10, 15, 20, 30, and 45 minutes to capture the early stages of drug release. Meanwhile, for the sustained-release layer containing Metformin hydrochloride, 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. The collected samples were then analyzed using a UV spectrophotometer to determine the concentration of each drug in the dissolution medium. Metoprolol Tartrate was quantified at a wavelength of 222 nm, while Metformin hydrochloride was quantified at a wavelength of 232 nm, as specified in the drug monographs. By measuring the absorbance of the samples at these specific wavelengths, the concentration of each drug in the dissolution medium could be determined accurately represent in Table 7 and Table 8 and % drug release have shown in figure 13 and figure 14.

5. Conclusion

The incorporation of hydrophobic polymer Eudragit RSPO into a hydrophilic polymer solution containing HPMC K100 presents an effective strategy to modulate the release rate of Metformin, a highly water-soluble drug. HPMC K100, known for its high viscosity grade, and Eudragit RSPO were individually utilized in Formulations F1 and F2, respectively. Subsequent formulations (F3 to F7) employed varying ratios of HPMC K100 and Eudragit RSPO. Notably, Formulation F1, comprising solely of HPMC K100, exhibited sustained metformin release up to 99.35% at 7 hours, while Formulation F2 with Eudragit RSPO demonstrated 88% drug release at 8 hours. Formulations F3 to F7, incorporating different ratios of HPMC K100 and Eudragit RSPO, showcased enhanced control over Metformin release, achieving percentages ranging from 92.81% to 99.91% over varying time intervals. This underscores the potential of high-viscosity polymers, particularly when combined with hydrophobic counterparts, to act as effective barriers for controlling the release of highly water-soluble drugs like Metformin.

Similarly, Bilayer tablets containing Metoprolol Tartrate and super disintegrants demonstrated rapid drug release profiles within 40 minutes. Formulations F1 and F2 employed individual super disintegrants, namely Crospovidone and sodium starch glycolate (SSG), respectively. In contrast, Formulations F3 to F7 utilized different ratios of Crospovidone and SSG. Notably, Formulation F1 exhibited Metoprolol Tartrate release of 99.29% at 20 minutes, while Formulation F2 achieved 99.89% drug release at 40 minutes. Formulations F3 to F7, incorporating combinations of the two super disintegrants, showcased superior immediate release (IR) profiles, achieving percentages ranging from 99.38% to 100% over varying time intervals. Notably, Formulation F7 emerged as the optimal formulation for sustained Metformin hydrochloride release, while the composition of super disintegrants in the Metoprolol Bilayer tablet also yielded the best IR results. These findings highlight the significance of polymer combinations and super disintegrant ratios in modulating drug release profiles and optimizing formulation efficacy.

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