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Research Article

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FORMULATION AND DEVELOPMENT OF BILAYER TABLET CONTAINING IRBESARTAN AND METFORMIN HYDROCHLORIDE FOR DIABETIC HYPERTENSIVE PATIENTS

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ABSTRACT

Background: Hypertension is a common complication of type II diabetes. The present research work aimed to develop bilayer tablets that would manage type II diabetes patients with hypertension. The prepared bilayer tablet has an immediate-release layer of anti-hypertensive irbesartan and a sustained-release (SR) layer of anti-diabetic metformin hydrochloride. The purpose of these bilayer tablets was to increase patient compliance by converting two separate monotherapy to single combination therapy. **Methodology**: Several ratios of polymers, including HPMC K100M, EC, Eudragit, and Guar gum, were employed to prolong the drug release for twelve hours. An immediate-release layer of irbesartan was prepared by spherical agglomeration. The physical properties, drug content, solubility profiles, release kinetics, and stability of prepared bilayer tablets were assessed. **Results and Discussion**: The examination of SR granules and bilayer tablets revealed outstanding packing qualities and excellent flow properties, with bulk and tapped densities ranging from 0.39-0.46 g/cm³ and 0.42-0.55 g/cm³, respectively. In vitro dissolution tests revealed that the immediate-release layer gave an initial burst of Irbesartan. Still, the sustained-release layer of metformin showed controlled drug release over 12 hours at greater polymer concentrations. According to stability testing, the bilayer tablets' physical properties, drug content, and dissolving profiles did not change significantly. **Conclusion**: The bilayer tablet combination of Irbesartan and Metformin exhibited desired physical features, controlled drug release, and stability. This formulation represents a viable treatment option for diabetic hypertensive patients, offering effective and consistent management of both disorders while improving patient compliance.

INTRODUCTION

The simultaneous development of type II diabetes mellitus and hypertension presents a significant clinical treatment challenge because of the combined risks of cardiovascular issues and the associated pathophysiological pathways [1]. Approximately 33% of individuals with diabetes also have hypertension,

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according to the International Diabetes Federation (IDF) and the American Diabetes Association (ADA) [2]. Among older adults in particular, this comorbidity is common. For example, according to data from the Centre for Disease Control and Prevention, almost half of persons with diabetes who are between the ages of 45 and 64 also have high blood pressure [3,4]. For those 65 years of age and above, this rate rises to more than 70% [4]. Reducing morbidity and mortality among affected patients necessitates efficient treatment of both illnesses. Traditional treatment methods frequently necessitate polypharmacy, in which multiple medications are given for different diseases. This polypharmacy may cause problems such as reduced patient compliance, higher medical expenses, and an increased risk of hazardous drug interactions [5]. Developing combined drug solutions is highly desirable, as it would simplify the treatment routine while retaining therapeutic efficacy, which is critical. Given this, creating bilayer tablets combining metformin hydrochloride and irbesartan seems like a creative and interesting tactic.

Irbesartan, an Angiotensin II receptor blocker (ARB), is commonly prescribed for managing hypertension [6]. Irbesartan blocks the action of angiotensin II, a potent vasoconstrictor, leading to vasodilation and subsequent reduction in blood pressure. This mechanism helps prevent cardiovascular complications associated with chronic hypertension. In contrast, metformin hydrochloride, the primary treatment for type II diabetes mellitus, reduces hepatic glucose production and enhances insulin sensitivity. By addressing these critical physiological aspects, metformin effectively lowers blood glucose levels and improves insulin action in diabetes management [7]. The integration of both medications into a bilayer tablet aims to provide comprehensive management of both hypertension and hyperglycemia, addressing both conditions simultaneously in a single treatment regimen.

The basis for their creation is the dual-release mechanism of bilayer tablets – an immediate-release layer for a rapid start of action and a sustained-release layer for a more prolonged therapeutic effect. Irbesartan, which is the immediate-release layer in this study, takes advantage of its requirement for quick antihypertensive effect, which is essential for preventing acute hypertension episodes [8]. To sustain glycaemic control effectively for prolonged periods, metformin hydrochloride is formulated with a sustained-release layer that allows for gradual and consistent drug release [9]. Reducing the tablet count enhances patient adherence and ensures a consistent therapeutic effect by reducing fluctuations in drug plasma concentrations that can lead to adverse impacts or suboptimal efficacy. The bilayer technology tailors drug delivery to match each drug's distinct pharmacokinetic and pharmacodynamic profiles, aligning with the principles of precision medicine.

This study aims to develop bilayer tablets incorporating irbesartan and metformin hydrochloride to improve the treatment of patients with hypertensive diabetes. By integrating the management of these interconnected conditions into a single dosage form, the objective is to enhance patient care and treatment effectiveness. By developing this innovative pharmaceutical formulation, the study seeks to address complex clinical needs, potentially yielding improved therapeutic outcomes and greater patient satisfaction.

MATERIALS AND METHODS

Materials

Irbesartan was sourced from CTX Lifescience Pvt. Ltd., India, and Metformin HCl was provided by Atompharma, India. Talc, EC, and PVP K30 were acquired from HiMedia Labs, Mumbai, India. HPMC was generously supplied by Colorcon Asia Pvt. Ltd., Goa, India, and Eudragit was gifted by Evonik, Mumbai, India. High-performance liquid chromatography (HPLC) grade acetonitrile and water were obtained from Merck Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade and procured from Merck Pvt. Ltd., Mumbai, India. Double-distilled water was employed throughout the study.

Methodology

Preparation of Bilayer tablets

A sustained release (SR) layer of Metformin HCl (MtHCl) was prepared using a wet granulation method using different polymers, as per Table 1. The pharmaceutical industry frequently uses wet granulation to prepare sustained-release tablets. This method aggregates powder particles with a granulating fluid to create more prominent, consistent granules. These granules improve the powder blend's flow characteristics and compressibility, creating premium tablets. In this situation, varying polymers can control the drug release profile and provide long-lasting therapeutic benefits. Polymers like Ethyl Cellulose (EC), Hydroxypropyl Methyl Cellulose (HPMC), especially HPMC K100M, and Eudragit RSPO are used in

different ratios to make sustained-release tablets using wet granulation [10,11]. These polymers were selected for their ability to create a matrix that regulates the release of the active pharmaceutical ingredient (API), thereby controlling its diffusion rate. The immediate-release layer of Irbesartan was prepared using directly compressible agglomerates [12], which had been optimized and documented in previous studies.

A rotary press with eight stations was employed to compress the blend after adding magnesium stearate as a lubricant. A 10-mm flat punch was used on an 8-station rotary tablet machine for the bilayer tablet compression process. Initially, the die cavity was carefully filled with SR MtHCl granules, followed by a gentle pre-compression to ensure uniform distribution and prevent intermixing with the subsequent layer. The pre-compressed SR layer was then overlaid with the immediate-release layer blend, and final compression was conducted at the optimal compression pressure determined in earlier investigations [13].

Table 1: Formulation of sustained release layer of Metformin Hydrochloride

Code	MtHCl	EC	ERSPO	HPMC K100M	PVP K30	MCC
F1	500	30	-	-	40	230
F2	500	30	100	-	40	130
F3	500	30	-	100	40	130
F4	500	30	-	-	40	130
F5	500	30	50	50	40	130
F6	500	30	50	-	40	130
F7	500	30	-	50	40	130
F8	500	30	100	100	40	30
F9	500	30	100	-	40	30
F10	500	30	-	100	40	30
F11	500	30	50	100	40	80
F12	500	30	100	50	40	80

EC: Ethyl Cellulose, ERSPO: Eudragit RSPO, HPMC K100M: Hydroxypropyl Methylcellulose K100M, PVP K30: Polyvinyl Pyrrolidone K30, MCC: Microcrystalline cellulose; *All quantity are in mg.

Evaluation of the tablets

The bilayer tablets were immediately evaluated post-development for hardness, weight variation, thickness, friability, and drug content [14]. The weight variation of 20 tablets was measured with an electronic balance. A Monsanto hardness tester was used to analyze tablet hardness in six samples. Friability tests were conducted in a friabilator at 25 rpm for four minutes. The tablet thickness was measured with a vernier caliper. The absorbance of samples and standards was measured with a UV/Visible spectrophotometer to quantify drug content.

In vitro drug release studies

The in vitro drug release study of bilayer tablets, designed with one immediate-release layer and one sustained-release layer, was conducted using a USP Type II paddle apparatus [15]. Each dissolution vessel was filled with 900mL of 0.1 N HCl (pH 1.2) and maintained at 37 ± 0.5°C. Tablets were accurately placed into the vessels, with paddles rotating at 100 rpm. Samples were collected at intervals of 5, 10, 20, 30, and 40 minutes for the immediate-release and SR layers; the dissolution medium was replaced with 900 mL of phosphate buffer (pH 6.8). Then samples were collected at 1, 2, 4, 6, 8, 10, and 12 hours for the sustained-release layer, replacing the withdrawn medium with fresh buffer to maintain sink conditions.

The samples were filtered to remove undissolved particles and analyzed using a UV/Visible spectrophotometer to determine drug concentration, referring to standard calibration curves. Data were plotted as cumulative percentage of drug release over time for both layers, providing insight into the release kinetics and confirming the formulation's therapeutic efficacy. All measurements were triplicated to ensure accuracy and reproducibility [16].

Stability Studies

Stability analysis of the improved bilayer tablets was conducted as per ICH recommendations. Every tablet was individually sealed in a blister pack and kept for six months under settings that were in line with accelerated stability testing: 40°C ± 2°C and 75°RH ± 5% relative humidity [17].

Samples were taken out of storage monthly and carefully analyzed for drug content, drug release in vitro, thickness, hardness, friability, and weight consistency. After that, a statistical analysis was performed on the gathered information. The stability study evaluates the formulation's resilience under accelerated settings to guarantee product quality and patient safety. This will provide important information about the formulation's shelf-life, effectiveness, and suitability for long-term storage.

RESULTS AND DISCUSSION

Evaluation of SR granules

The physical characteristics of the SR granules in different tablet formulations were assessed. According to the tapping method, the produced granules' bulk and tapped densities ranged from 0.39-0.46 g/cm^3 and 0.42-0.55 g/cm^3, respectively. This suggests good packing qualities [15]. Good flow property was indicated by Carr's index and Hausner's ratio, which ranged from 4.98% to 11.97% and 1.09 to 1.15, respectively. The angle of repose for granules ranged from 27.73° to 35.02°, indicating additional analysis of the flow parameters of the particles [15,18]. The value shows that the granules have good flow properties because of size and sphericity [19].

Physical properties of bilayer tablet

The bilayer tablet batches were all developed under the same conditions, ensuring consistency in the production process and minimizing manufacturing differences. After an extensive evaluation of each formulation, the findings indicated that weight variation, hardness, thickness, and friability were all within permissible limits as per official specifications, as shown in Table 2. Additionally, every batch satisfied the weight variation requirements (90 - 110%), which guarantees tablet dosage uniformity - a critical component of reliable therapeutic results. Measurements of thickness attested to the tablets' consistent size, which is crucial for ensuring appropriate packaging and consistent dosage. Furthermore, uniform thickness helps preserve the proper drug release profile, essential for sustained-release and immediate-release layers to have the desired therapeutic impact. The hardness test and percent friability results showed that the created bilayer tablets had good operating properties, indicative of careful production procedures and strict quality control measures. Furthermore, the consistency of physical attributes between batches shows that the manufacturing process is repeatable, which is crucial for large-scale production.

All batches had a percent friability of less than 1.0%, indicating their mechanical integrity and resistance to breaking or chipping during handling, packing, and transportation [20]. The tablets' hardness, crucial for their longevity and patient comfort, was meticulously regulated to ensure they weren't too soft to shatter or hard to prevent decomposition. Subsequent examination revealed that the tablets' physical characteristics, drug content, and release profiles did not significantly alter throughout the stability tests. This stability is essential for the tablets to remain safe and effective for their shelf life. The tablet formulation's robustness and promise for effective therapeutic management in hypertensive diabetic patients are supported by its constant manufacturing and thorough quality control.

Table 2: Post-compression parameters of bilayer tablet

Batch	Thickness (mm)	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug Content	
					IRB	MtHCl
F1	4.78 ± 0.010	1006.16 ± 1.50	7.50 ± 0.01	0.46 ± 0.015	99.26 ± 0.24	98.57 ± 0.61
F2	4.76 ± 0.005	1005.87 ± 5.97	7.26 ± 0.46	0.40 ± 0.089	98.24 ± 0.53	99.02 ± 0.32
F3	4.79 ± 0.015	1003.19 ± 6.39	7.33 ± 0.44	0.53 ± 0.103	98.35 ± 1.07	99.13 ± 0.48
F4	4.77 ± 0.005	1002.28 ± 7.17	6.83 ± 0.27	0.53 ± 0.012	99.27 ± 0.58	99.59 ± 0.82
F5	4.77 ± 0.005	1001.73 ± 0.37	7.41 ± 0.50	0.61 ± 0.084	98.81 ± 1.01	99.32 ± 0.23
F6	4.76 ± 0.005	1008.59 ± 7.92	7.05 ± 0.21	0.27 ± 0.050	98.54 ± 0.57	98.13 ± 0.42
F7	4.76 ± 0.005	1005.33 ± 6.44	6.79 ± 0.11	0.47 ± 0.089	99.68 ± 0.63	99.96 ± 0.23
F8	4.78 ± 0.011	1001.04 ± 1.06	7.04 ± 0.17	0.45 ± 0.272	99.21 ± 0.33	99.29 ± 0.51
F9	4.76 ± 0.011	998.71 ± 0.99	7.3 ± 0.05	0.27 ± 0.004	97.36 ± 0.49	98.58 ± 1.04
F10	4.77 ± 0.005	1003.33 ± 6.46	7.28 ± 0.45	0.61 ± 0.038	99.17 ± 0.82	98.27 ± 0.56
F11	4.76 ± 0.005	1006.41 ± 3.86	7.33 ± 0.42	0.26 ± 0.009	99.61 ± 1.04	99.43 ± 0.53
F12	4.76 ± 0.005	1004.70 ± 6.24	7.06 ± 0.09	0.34 ± 0.201	99.46 ± 0.43	98.95 ± 0.55

* All numbers are the mean of three observations ± SD

In Vitro Dissolution Study

In-vitro dissolution studies were conducted to assess the bilayer tablets' release properties properly. Dissolution investigations were performed using a USP Type II paddle device at 37 ± 0.5°C. Samples were obtained to calculate the rates of medication release at predefined intervals. Plotting the cumulative % drug release versus time allowed for examining the bilayer tablets' release profile, as illustrated in Figures 1 and

2. In vitro testing revealed that the immediate-release layer of the bilayer tablet caused an initial burst release of Irbesartan. A 12-hour experiment assessed the dissolving parameters of the sustained-release layer containing metformin HCl (MtHCl).

The polymer concentration was the primary factor regulating drug release from the sustained release layer. Formulation F1, which used only ethyl cellulose (EC) as a polymer, could release around 100% of MtHCl. Certain formulations did, however, indicate faster drug release before the 12-hour mark, possibly due to unsuitable polymers or a reduced polymer concentration [21,22]. Drug release was effectively delayed for up to 12 hours in tablets containing a higher concentration of the polymer blend Eudragit RSPO (ERSPO) and HPMC K100M. This implies that to achieve the desired sustained-release profile, the proper polymer blend and concentration are needed [23]. Further research revealed that the release kinetics may be adjusted by adjusting the polymer ratios, guaranteeing a more regulated and reliable drug delivery system. The results above highlight the significance of meticulous polymer selection and concentration modification in creating bilayer tablets to attain accurate therapeutic results.

Stability studies

The optimized tablets (F11) were subjected to an accelerated stability analysis in the current work, which was maintained for six months at 40 ± 2°C and 75 ± 5% relative humidity. Several assessment parameters were evaluated during the stability period, such as drug content, in vitro release profile, hardness, friability, and weight uniformity. The outcomes are listed in Table 3. The stability study results suggest the formulation's robustness under accelerated settings, which showed no significant changes in any measured parameters at the three- and six-month marks.

The accelerated stability data were analyzed using a basic linear regression (Figure 3). P-values for the slopes were 0.38 for metformin hydrochloride (MtHCl) and 0.44 for irbesartan (IRB). According to ICH Q1A (2003) criteria, these p-values are more significant than 0.25, indicating little to no change over time [24,25]. This attests to the bilayer tablets' stability, ensuring their medicinal effectiveness and structural integrity are preserved during storage [26]. These results support the bilayer tablet formulation's long-term stability and dependability, indicating that it is appropriate for clinical application.

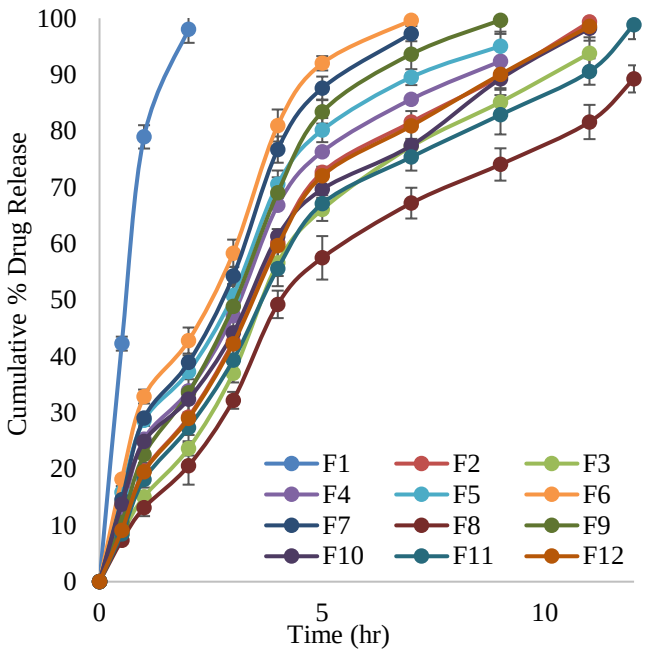


Figure 1: Dissolution profile of sustained release layer containing MtHCl

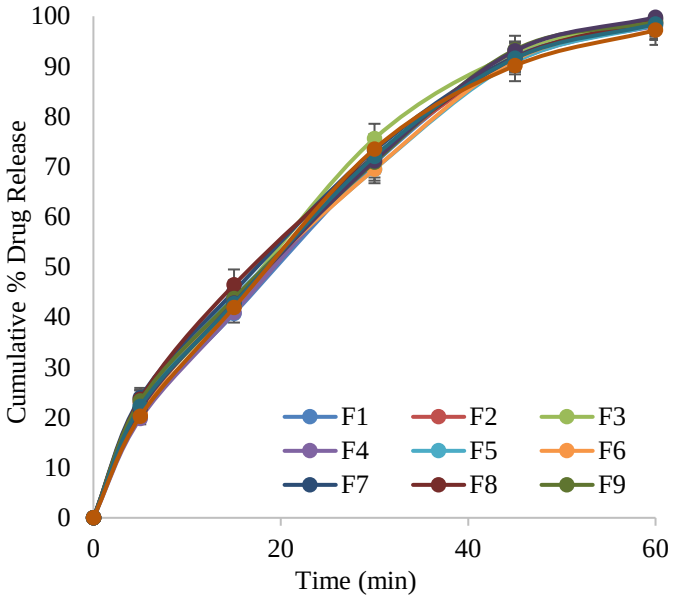


Figure 2: Dissolution profile of immediate release layer containing IRB

The Cp values for IRB and MtHCl were also >2.5, indicating little to no data variability [27]. They were 4.24 and 3.42, respectively. After calculating the CpK, it was discovered that there was either minimal or nonexistent data variability because the values obtained for IRB and MtHCl were > 2.5, at 2.91 and 3.57, respectively [28].

As seen in Figure 4, the stored tablets (F11) dissolving profile stayed the same as the samples that were examined very away

after manufacturing. It was discovered that there were no significant changes in the dissolution rates at different time intervals. With a *f*1 (dissimilarity factor) of 1.189 and a *f*2 (similarity factor) of 91.39, statistical analysis verified the similarity in the dissolution profiles of the immediate-release layer before (IRB) and after (IRBS) the stability period. Similar dissolving profiles for the sustained-release layer were also observed before (MtHCl) and after (MtHClS) the stability period, as indicated by *f*2 values of 87.06 and *f*1 values of 2.161. These findings show that the bilayer tablets' stability was successfully preserved during the storage time, guaranteeing steady drug release profiles and therapeutic effectiveness. The formulation's resilience against any deterioration or modification under the given storage conditions is further confirmed by the similarity factors (*f*2) being over 50 and the dissimilarity factors (*f*1) being below 15 [29,30].

Table 3: Results of evaluation parameters of F11 during stability periods

Parameters	Storage Periods		
	At initial time	3 Months	6 Months
Hardness, kg/cm^2	7.33 ± 0.42	6.84 ± 0.73	7.11 ± 0.31
Friability, %	0.26 ± 0.009	0.32 ± 0.008	0.31 ± 0.01
IRB content (%)	99.61 ± 1.04	98.85 ± 0.63	99.32 ± 0.54
MtHCl content (%)	99.43 ± 0.53	99.11 ± 1.17	99.27 ± 0.33

*All results are mean of three observations ± SD

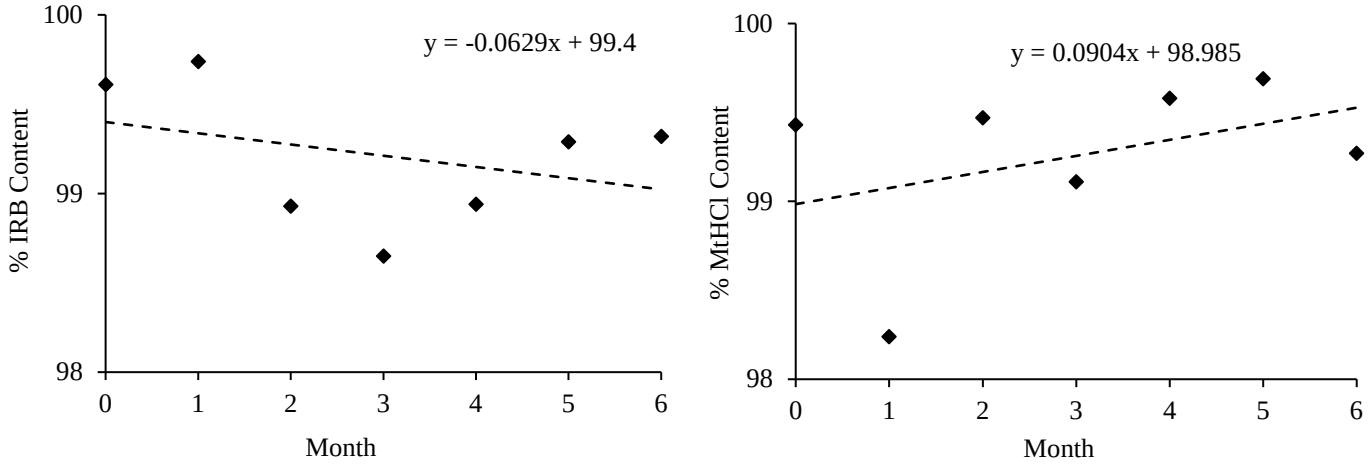
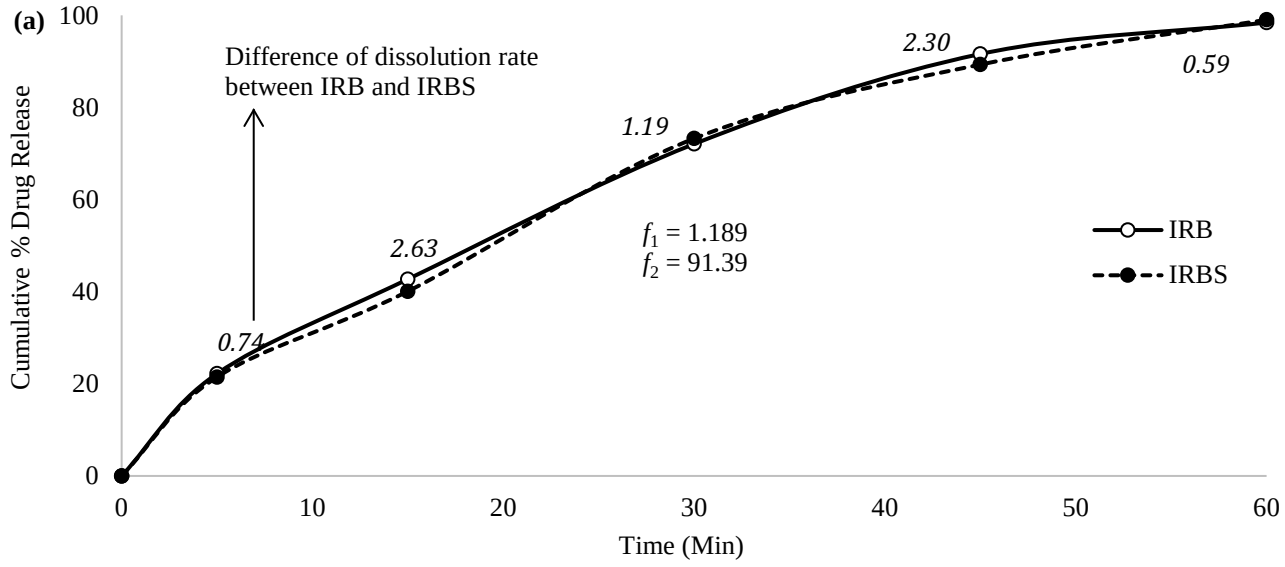


Figure 3: Statistical analysis for drug content of (a) IRB and (b) MtHCl



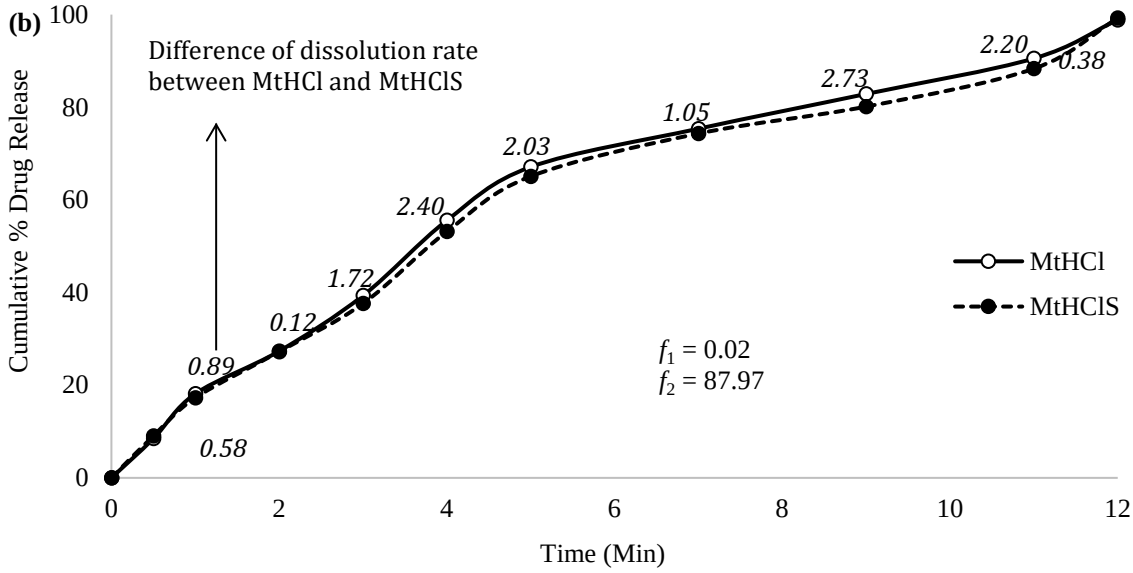


Figure 4: Dissolution profiles of (a) the immediate release layer of optimized tablets and (b) the sustained release layer of optimized tablets before and after stability testing periods

For combination drugs where the timing of drug release might significantly impact clinical results, maintaining the integrity of both the immediate-release and sustained-release layers is essential. The sustained-release layer, for example, maintains therapeutic levels over an extended period, enhancing patient compliance and overall therapy efficacy, while the immediate-release layer acts quickly. The outcomes also highlight how well the selected excipients and production techniques preserve the bilayer tablets' functional characteristics over time. These results further strengthen the bilayer tablet design's adaptability for long-term use, which makes it a dependable choice for treating chronic illnesses, including type II diabetes and hypertension. Rigid stability testing is crucial to the development of pharmaceuticals because it ensures stability and constant performance over time, which is necessary for regulatory approval and commercial acceptance. The stability of the optimized tablets was proved by the dissolving profile of the stored tablets, which confirmed the absence of drug interactions. The tablet formulation demonstrated stability at accelerated circumstances (40°C ± 2°C and 75% ± 5% RH). The study also found constant disintegration behavior throughout time. The bilayer tablet's capacity to prevent interactions between Irbesartan and Metformin HCl is critical to maintaining the drug's efficacy and safety. The tablets' capacity to preserve their physical integrity, drug content, and release profiles throughout storage demonstrated the formulation's robustness [31]. These findings emphasize the need for stability studies to ensure that the medicinal value of bilayer tablets remains intact over their shelf life.

CONCLUSION

To improve patient compliance, the study created bilayer tablets containing metformin hydrochloride (SR layer) and irbesartan (IR layer) to treat hypertension in individuals with type II diabetes. Because of their weak flow characteristics, the granules showed good precompression flowability when granulated using wet methods. The tablets satisfied every requirement for weight consistency, hardness, thickness, diameter, and friability. Formulation F11, comprising EC (30 mg), HPMC K100M (100 mg), and Eudragit RSPO (50 mg), was found to be the best for sustained release during in vitro dissolving testing. The efficacy and dependability of the formulation were validated by stability studies, which showed that the tablets remained stable with no appreciable changes in their physical attributes, drug content, or dissolution profile.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

V. D. Gorde contributed to the conceptualization of the research, supervision of the overall project, and final approval of the

manuscript. Contributed to the experimental design, data analysis, and interpretation of results. Punit R. Rachh was the primary researcher involved in the formulation and experimental development of the bilayer tablet and performed laboratory work, data collection, and analysis of the physical and chemical properties of the formulation. Someshwar Mankar assisted in optimizing the formulation process and conducting stability studies. He also contributed to writing the experimental section and results in the manuscript. Saurin Amin contributed to the literature review and played a significant role in the initial drafting of the manuscript. Participated in analyzing the efficacy of the bilayer tablet in diabetic hypertensive models. Prasad L. Gorde was involved in data compilation and statistical analysis and provided input on the interpretation of pharmacokinetic and pharmacodynamic studies. Assisted in manuscript revisions and critical feedback.

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