RESEARCH ARTICLE

Formulation and *In-vitro* Evaluation of Bilayer Tablet of Olmesartan Medoxomil for Biphasic Drug Release

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ABSTRACT

Objective: The current study aimed to optimize the bioavailability and absorption of olmesartan in the lower gastrointestinal tract by creating a bilayer tablet for biphasic drug release.

Methods: Microcrystalline cellulose was combined and direct compression the requirement for an early response to address an undesirable defect or condition. In the current instance, 5 mg of olmesartan must be released immediately, and the remaining 10 mg of olmesartan must be released gradually to maintain the therapeutic concentration. In order to adjust the release pattern of the olmesartan sustained release tablet in accordance with the needs of therapy and IP guidelines.

Result: The best cumulative drug release was demonstrated by formulation. All formulations for immediate release support the first-order kinetics. As a result, all three formulations were chosen for additional research. Dissolution rate for long-term release Cumulative drug release from the SR1 to SR3 formulations using HPMC K15M and gum acacia was up to 24 hours. Utilizing HPMC K15M and guar gum, the formulations SR1, SR2, and SR3 demonstrated cumulative drug releases of 72.66, 69.19, and 92.66%, respectively. The best cumulative release of the drug was demonstrated by formulations SR1, SR2, and SR3. Consequently, everyone was chosen for additional research. The cumulative drug release for the IR1-SR1, IR2-SR2, and IR3-SR3 bilayer tablet formulations was 95.24, 90.15, and 91.09%. Up to 12 hours of cumulative drug release from the formulation was observed. As a result, it was determined that IR1-SR1 was the best formulation out of all of them due to its strong correlation between the total cumulative percentage of medication releases and time, which was 95.24% up to 12 hours.

Keywords: Olmesartan, Sustained release, Immediate release, Hypertension.

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INTRODUCTION

Design and development of oral olmesartan tablets for sustained and immediate release are the focus of this research to relieve high blood pressure. The preferred medicine delivery method is oral administration. It is because this method has many benefits, including easy dosing, patient compliance, and formulation versatility. Because of the brief stomach retention time, oral medication absorption is frequently restricted.[1] Humans have a stomach retention period of 3 to 4 hours. The short GI transit time, uncertain gastric emptying rate, and the fact that some medications have an absorption barrier in the stomach and duodenum are some of the issues with the oral route. Olmesartan's bilayer tablet effect was consistently stronger than its matrix tablet effect.[2] Using instant release dose, the medication can be released from the therapeutically effective level quickly The therapeutically effective concentration can be retained for a longer period of time with sustained release dosage form than with standard dose form. The incidence of local and systemic side effects can be decreased with a sustained release dose form.[3] When multiple medications have varied release profiles, bilayer tablets are preferred. A non-peptide angiotensin II receptor antagonist called olmesartan

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medoxomil is used to treat mild to moderate hypertension. This medication has a very low oral bioavailability of just approximately 26%, is mildly basic, and is lipophilic.[4] Bilayer tablets can be used to segregate two incompatible substances, release two medications sequentially in combination, and create sustained-release tablets where the first layer is an immediate-release starting dose and the second layer is a maintenance dose.[6,7] Rapidly delivering instant medication levels is the goal of immediate-release drug delivery devices. Immediate-release drug delivery is preferred for medications with lengthy biological half-lives, high bioavailability, lesser clearance, and shorter elimination half-lives. However, the primary requirement for an immediate-release dosage form is a drug's poor solubility and the requirement for an early response to address an undesirable defect or condition.[8] In the current instance, 5 mg of olmesartan must be released immediately, and the remaining 10 mg of olmesartan must be released gradually to maintain the therapeutic concentration. In order to adjust the release pattern of the olmesartan sustained release tablet in accordance with the needs of therapy and IP guidelines, biphasic release with varying ratios of super disintegrant in the immediate release layer and rate retarding polymer in the sustained release layer was prepared. One layer of the bilayer tablet was made with super disintegrant for instant drug release, and the second layer was made with a different polymer in a different ratio for sustained release. For chronic hypertension patients, patient compliance is higher when the medication is administered in a sustained-release dosage form as opposed to traditional tablets and an instant-release dosage form.

MATERIALS AND METHODS

Material

Materials for the study were gathered from a variety of sources. A free sample of olmesartan medoxomil was provided by Uni Medico Lab. in Dehradun, India. We purchased HPMC k4m, Xanthan gum, MCC, and lactose from Loba Chem. Pvt. Ltd. in Mumbai. Other excipients were purchased from S.D. Fine Chem. Ltd. in Mumbai, such magnesium stearate and talc.

Method

Procedure for immediate release layer of tablet

The formula shown in Table 1 was used to create immediate-release tablets. Microcrystalline cellulose was combined and the direct compression method was used. Each component was precisely weighed before being put through a sieve with a mesh size of # 80. Talc was added after the medication and polymer had been well combined for 15 minutes using a mortar and pestle. These components were properly combined before the powder mixture was run using sieve size # 44, Sifted via filter number 44 with the diluent immediately compressible lactose was microcrystalline cellulose. Disintegrants sodium starch glycolate and sifted medication were combined completely. The diluent immediately compressible lactose was microcrystalline cellulose. Disintegrants sodium starch glycolate and sifted medication were combined completely. The resulting powder mixture was assessed for a number of factors, including powder properties and LoD. Then, add magnesium stearate as lubricant, this mixture was compressed.

Procedure for sustained release layer of tablet

The Direct Compression process was used to create the olmesartan medoxomil sustained-release Tablets. Table 2 displays the chemical composition of each tablet. All ingredients needed for the formulation were gathered, precisely weighed, and put through sieve no. 40. They were thoroughly blended for 10 to 15 minutes in a plastic bag or triturate. Magnesium stearate was mixed to the powder mixture, which was then combined again for 4–5 minutes. The mixture was then compressed using a rotary tablet compressor. Both official standards and unofficial tests were used to evaluate tablets. The containers used to package the tablets were airtight and moisture-proof.

Formation of bilayer tablet

Compressed the tablet using 9 mm round punches at a gentle compression force (2–3 kg/cm^2). Since the sustained release layer has a white hue and the immediate release layer of the bilayer tablet has a pink color, the layers were distinguished based on color. Different formulations were compressed to achieve the required drug release from the SR layer and IR layer.

Evaluation of Powder Blend

Partical size distribution

Vibration sieve equipment were used to measure the particle size distribution. The coarsest sieve of a sieve stack made up of six sieves with progressively smaller apertures was loaded with powder, and the stack as a whole was mechanically vibrated. The particles are thought to be kept on the sieve mesh after 10 minutes.[10]

Active-excipient interaction study

The medication, polymer, and other formulation constituents were identified by employing FTIR and IR spectroscopy. The spectra were obtained by using the KBr discs technique. Various powder properties were performed.

Evaluation studies for tablet

The thickness, hardness, friability, weight variation, disintegration time, medication content, and *in-vitro* dissolution studies were all analyzed for each tablet.[15-18]

Dimensional analysis

Using a vernier calliper, the tablets› diameter and thickness were measured. Average values were computed using 20 tablets from each batch.

RESULT AND DISCUSSION

The bilayer tablet of Olmesartan for biphasic drug release were prepared successfully.

Precompression parameters of the immediate release layer of the tablet

The angle of repose, bulk density, tapped density, Hausner's ratio (HR), and the Olmesartan rapid-release layer compressibility

Table 1: Formula of sustained release

Formulation Code	*SR1*	*SR2*	*SR3*
Ingredients (g)			
Olmesartan	0.4	0.4	0.4
Lactose	3.4	3.4	3.4
Carbopol	0.8	1.2	0.4
HPMCK 15	0.8	0.4	1.2
Xanthan	0.8	0.8	0.8
Guar Gum	0.8	0.8	0.8
Acecia	0.8	0.8	0.8
Mg. Stearate	0.12	0.12	0.12
Talc	0.08	0.08	0.08

Combination of Sustained release layer

Table 2: Formula of immediate release

Formulation Code	*IR1*	*IR2*	*IR3*
Ingredients (g)			
Olmesartan	0.2	0.2	0.2
Lactose	1.2	1.2	1.2
MCC	1.2	1.6	0.8
SSG	1.2	0.8	1.6
Ferric Oxid Red	0.04	0.04	0.04
Mg	0.08	0.08	0.08
Talc	0.08	0.08	0.08

Combination of Immediate release layer

Table 3: Powder flow properties of immediate release

Code	*Parameter*				
	Bulk density(g/cm^3)	*Tapped density (g/cm^3)*	*Hausner's ratio*	*Compressibility index (%)*	*Angle of repose*
IR1	0.571 ± 0.02	0.591 ± 0.01	1.03 ± 0.02	3.50 ± 0.05	0.536 ± 0.19
IR2	0.578 ± 0.02	0.595 ± 0.03	1.02 ± 0.02	2.94 ± 0.013	0.613 ± 0.16
IR3	0.572 ± 0.01	0.607 ± 0.01	1.06 ± 0.01	6.11 ± 0.11	0.7 ± 0.09

Micromeritic properties of precompression immediate release layer (IR)

index were all assessed. The bulk density was discovered to be between 0.571 to 0.578 g/cm^3. The density when tapped ranged from 0.591 to 0.595g/cm^3. Angles of repose ranged between 0.536 to 0.71. The compressibility index fell between 2.94 to 6.11%. The HR fell between the 1.02 to 1.06 range depicted in Table 3.

Precompression parameters of sustained release layer of the bilayer tablet

The wet granulation process was used to create the Olmesartan sustained release layer, and the powder's angle of repose, bulk density, tapped density, HR, and carr's index were all measured. The bulk density found to be between 0.47 to 0.445 g/cm^3. The density when tapped ranged from 0.593 to 0.682 g/cm^3. Angles of repose ranged between 0.688 to 0.21. The compressibility index fell between 45.70 to 53.25%. The HR was within the range of 1.45 to 1.53, as shown in Table 4.

Compatibility study

The drug and excipients were confirmed by the FTIR spectrum analysis, which revealed that none of the distinctive peaks of active drug and excipients changed.

Post-compression parameters of the bilayer tablet

The hardness, friability, weight, and thickness of the olmesartan sustained release layer post compression parameter were assessed. Each formulation's tablet had hardness in the range of 6 to 10 kg/cm^2. Friability ranged from 0.55 to 0.62%.

Figure 1: Sustained release

Figure 2: Immediate release

Table 4: Powder flow properties of sustained release

Code	*Parameter*				
	Bulk density(g/cm^3)	*Tapped density (g/cm^3)*	*Hausner's ratio*	*Compressibility index (%)*	*Angle of repose*
SR1	0.431 ± 0.02	0.652 ± 0.01	1.51 ± 0.02	51.27 ± 0.05	0.821 ± 0.19
SR2	0.407 ± 0.02	0.593 ± 0.03	1.45 ± 0.02	45.70 ± 0.013	0.714 ± 0.16
SR3	0.445 ± 0.01	0.682 ± 0.01	1.53 ± 0.01	53.25 ± 0.11	0.688 ± 0.09

Micromeritic properties of precompression sustained release layer (SR)

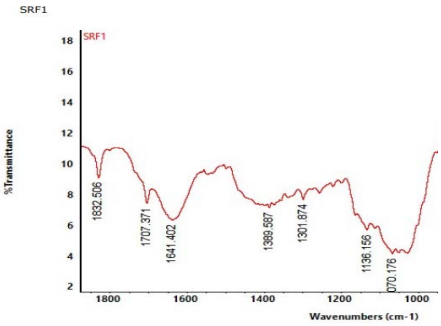

Figure 3: FTIR SRF1formulation

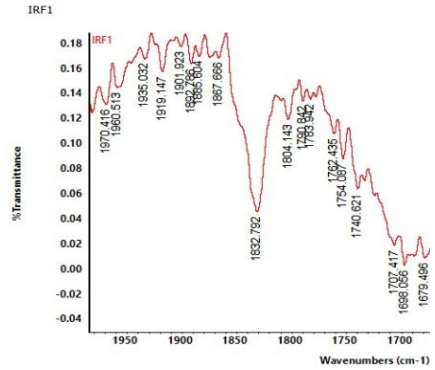

Figure 4: FTIR IRF1 formulation

The range of weights for each formulation's tablet ranged from 0.291 to 0.312 mg, although each tablet stayed within the Indian Pharmacopoeia's weight restrictions. All of the tablets had consistent weights and a small standard variation. All of the pills were found to be between 4 mm in thickness.

The range of all tablets' drug content was discovered to be between 92.34 and 97.34%. Evaluations of floating experiments and swelling indices for sustained release were made. The swelling index of each formulation's tablet was discovered to be between 123.41 and 155.70%. The floating lag time was discovered to be between. min. and. min. All tablets' floating times were discovered. The yield percentage was discovered in the 81 to 91% parameter range reported in Table 5.

In-vitro drug release study

For the *in-vitro* study, the USP Dissolution Apparatus II (Paddle) was employed. A dissolution profile for IR1's immediate release was discovered in comparison to IR2 and IR3. The drug released 84% in 30 minutes using the IR2 formulation. It uses 5% weight-for-weight sodium starch glycolate. In 30 minutes, 95% of the drug was released using the IR1 formulation, and the regression coefficient (r2) value was 0.996. A comparative in vitro drug release pattern of immediate release layers is used with 5%w/w crospovidone.[19] As a result, all three formulations were chosen for additional research.

Dissolution rate for long-term release Cumulative drug release from the SR1 to SR3 formulations using HPMC K15M and gum acacia was up to 24 hours. Utilizing HPMC K15M and guar gum, the formulations SR1, SR2, and SR3 demonstrated cumulative drug releases of 72.66, 69.19, and 92.66%, respectively. These are sustained-release formulations SR1, SR2, and SR3.

The cumulative drug release for the IR1-SR1, IR2-SR2, and IR3-SR3 bilayer tablet formulations was 95.24, 90.15, and 91.09%, as shown in Table 5 and Figure 1. Up to 12 hours of cumulative drug release from the formulation was observed. As a result, it was determined that IR1-SR1 was the best formulation out of all of them due to its strong correlation the final cumulative percentage of drug releases and time, which was 95.24% up to 12 hours.

Kinetic release

All formulations' immediate release layer release profiles were compared to the zero-order, or first-order, model. Regression analysis of the data was performed using statistical MS-Excel algorithms.

The first-order model was used to analyze the data, and the results are displayed in the IR1 to IR3 values. The regression coefficient value (r2) for the IR1 formulation was 0.996. Because first-order release profiles' regression coefficient values are close to 1 compared to zero-order release profiles, the findings suggested that release characteristics follow first-order drug release.

The values for the zero-order, first-order, Higuchi model, and Korsmeyers-Peppas models were used to compare the release profiles of a sustained release layer for all formulations. In comparison to other formulations, the cumulative percentage of drug release F1 was larger.

In Table 6, the values for the Higuchi model, the Korsmeyers-Peppas model, the zero-order model, and the first-order model were used to compare the release profiles of a sustained release layer for all formulations. According to Table 10's Figures 2 and 3, the cumulative percentage drug release for formulation SR1 was larger than that of other formulations, and the regression coefficient value (r2) 0.966, 0.984, 2, and 3, as well as 0.966, 0.984, and 0.946 for the regression coefficient value (r2). Additionally, these formulations support a 'n' value between 0.44 and 0.59 and have larger cumulative drug percentages release. These three formulations were chosen for additional study after the evaluation of the aforementioned parameters Figure 4.

Table 5: Pre compression parameter

Formulation code	*Hardness (kg/cm^2)*	*Friability (%w/w)*	*Weight variation (mg)*	*Thickness (mm)*	*Drug content (%)*	*Swelling index (%)*	*Percentage yield (%)*
F1	6 -9	0.55	0.291	4	95.20	142.43	91
F2	7-10	0.62	0.312	4	97.10	123.41	84
F3	8-10	0.61	0.295	4	92.34	155.70	81

Evaluation of Olmesartan tablets

Table 6: The cumulative percentage drug release for different formulations

SI.NO	*Time (min)*	*Cumulative percentage drug release (IR1-SR1)*	*Cumulative percentage drug release (IR2-SR2)*	*Cumulative percentage drug release (IR3-SR3)*
1	30	30.21	28.77	26.22
2	60	45.21	47.33	43.65
3	90	55.57	55.66	54.62
4	120	59.77	62.88	60.21
5	150	68.33	70.43	62.11
6	180	72.66	78.56	66.74
7	210	76.88	82.85	72.45
8	240	82.88	85.78	77.62
9	480	88.91	88.91	88.91
10	720	95.12	91.12	90.23

In-vitro drug release data of bilayer formulations

CONCLUSION

Olmesartan's bilayer tablet effect was consistently stronger than its matrix tablet effect. Both the instant release and the sustained release are contained in the bilayer tablet composition. A controlled-release hydrophilic matrix is the second layer. It aims to sustain a useful plasma concentration of the medication in the blood for a long time. This helps to reduce the frequency of dosing, improve the efficacy of the drug, and increase patient compliance. The first layer is designed to obtain the immediate release of the drug, with the goal of reaching a therapeutic effect of the drug. Therefore, an effort was made to create a bilayer tablet of antihypertensive medication to diagnose and treat chronic diseases.

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