ORIGINAL ARICLE

Development and Evaluation of Gastroretentive Floating Bilayer Tablets Containing Ivabradine hydrochloride and Trimetazidine dihydrochloride

Sagar S. Jadhav, Atul A. Phatak

Department of Pharmaceutics, PES Modern College of Pharmacy, Pune, Maharashtra, India

Abstract

Introduction: Unlike conventional angina treatment medicines, newer antianginals such as Ivabradine hydrochloride and Trimetazidine dihydrochloride displayed therapeutic potential without negative effects. However, IBH and TMZ both have shorter half-life and require multiple dosing. Literature study revealed that bilayer tablet of combination is not available. Hence, the objective of present research was to formulate and evaluate bilayer floating gastroretentive tablets with IBH immediate and TMZ floating release layer. **Materials and Methods:** Simple direct compression method and floating technique was employed. IBH and TMZ layer developed separately. IBH layer prepared using Avicel-112, Klucel EXF ultra, and Vivasol/Crosscarmelose sodium while TMZ layer developed using Kollidon SR, Benecel K 200 M, and Sodium bicarbonate. Best trials combined for the preparation of bilayer tablet. Tablets evaluated for pre-compression and post-compression parameters, floating time, floating lag time (FLT), total floating time swelling index, and matrix integrity. **Results:** Melting point, differential scanning calorimetry, and ultraviolet absorbance confirmed the identity and purity of drug. Fourier transform infrared spectrum of active pharmaceutical ingredient and drug mixture with excipients demonstrated the compatibility. IR layer trial I-4 showed passable flow with 3 s of disintegration time in distilled water and 100% drug release within 5 min. Floating layer trial T-8 showed fair flow characteristic, 15 s FLT, >24 h of total floating time and controlled the drug release more than 12 h without burst effect. **Discussion:** Preformulation study result revealed that the both the drug are pure form and compatible. For immediate release layer, Vivasol (Crosscarmelose) showed best disintegration and combination HPMC K200 M and Kollidon SR polymer with sodium carbonate provided controlled release with low FLT and high total floating time. **Conclusion:** Based on research findings, it can be concluded that bilayer gastroretentive tablets successfully formulated with IBH as IR layer and TMZ as floating layer. Combination of polymer needed for drug release control with tablet floatability. Hydrophilic polymer Benecel K200 M forms matrix channel which entrap sodium bicarbonate bubbles and tablet become buyant while Kollidon SR and stearic acid contributes in retardation of drug release.

Key words: Ivabradine hydrochloride, Trimetazidine dihydrochloride, Gastroretentive Bilayer tablets, Floating, Angina

INTRODUCTION

Ischemic heart diseases (IHDs) are most common and prominent cause of death worldwide.[1] It affects public health and quality of life which at last burdened on public health as well as global economy.[2] Chronic stable angina is common manifestation of IHDs that affect 58% of patients with coronary artery diseases (CAD).[3] Angina pectoris first described by Wiliam Heberden in 1968 and explained angina as smothering sensation or tightness across the front of chest which transfer to left arm or both the arm as well as jaw or back.[4] When angina symptoms continue for more than 2 months without change in severity, character, or triggering circumstances, then it is regarded as chronic and stable angina.[4] According to ESC guidelines, pharmacological therapy for angina classified as first-line

Address for correspondence:
Sagar S. Jadhav, Department of Pharmaceutics, PES Modern College of Pharmacy, Pune, Maharashtra, India.
Phone: +919975100096.
E-mail: sagarsjadhav1@gmail.com

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drug (beta-blockers, calcium channel blockers, and short-acting nitrates) and second-line drug (Long-acting nitrate, ivabradine, nicorandil, ranolazine, and trimetazidine). This classification of ESC interrogated as there is no evidence or data about dominance of one class over the other.[5,6] First-line drug discovered earlier, and hence, they are choice of physician. However, second-line drug discovered recently, gone through stringent testing protocol and have more evidence-based data compared to first-line traditional drug.[7] Second-line or newer antianginals prescribed when first-line agent shows more side-effects or develop intolerance and remain symptomatic, contraindicated in certain cases of diabetes, and chronic obstructive pulmonary disease (COPD) patients.[5,6] Combination therapy with additive or synergistic effect may give better result to control angina symptoms; however, tailored based therapy considering individual patient profile will give beneficial results.[8] Ideal angina therapy involves tailored approach according to individual patient profile and pathophysiology, hemodynamic profile, adverse effects, potential drug interaction, and comorbidities.[9] Hence, the objective of current research was to develop bilayer floating tablets consisting combination of IBH as immediate release layer and TMZ as floating extended release layer.[10] Very less work available on application of IBH combined with TMZ in CAD patients after PCI, that is, percutaneous coronary intervention. Combination showed effective role of anti-inflammatory and antioxidant damage also improves intradermal functions.[11]

IBH is first pure selective and specific heart rate lowering agent. It was approved by US Food and Drug Administration in April 2015 and in 2012 by EMA.[12,13] It is alone clinically approved if current inhibitor also known as pacemaker current or funny current.[14] IBH has proven effectiveness in patients with comorbidities such as asthma, COPD, diabetes mellitus, and peripheral vascular diseases.[15] It reduces heart rate in dose dependent manner without affecting on myocardial inotropic function, coronary vasomotor tone, or systematic vascular resistance.[16] Ivabradine is small molecule with 468.6 g/mol molecular weight, high solubility (50 mg/mL), and 3.17 partition coefficients but it has low oral bioavailability (40%) due to its extensive first pass metabolism. Due to shorter elimination half-life (2 h), it is prescribed in BID dose and 2.5–7.5 mg strength.[17] It is well tolerated in HF patients.[10]

TMZ is clinically effective antianginal agent used in prophylaxis and management of angina pectoris. Unlike first-line drug such as beta-blockers, calcium channel blockers, and long-acting nitrates, TMZ shows antischemic effect without hemodynamic changes and protects heart from deleterious consequences of ischemia. It is BSC class I drug with high solubility and permeability but it has shorter half-life about 6 h. Its dosing frequency is TID if dose is 20 mg and BID if dose is 35 mg and OD if dose is 80 mg to ensure relatively constant plasma level.[18-20] TMZ widely used in Europe and Asia, which selectively inhibits long chain 3-ketoacyl-co-enzyme A thiolase, enzyme responsible to catalysis in terminal step of fatty acid β-oxidation thereby shifting cardiac energy metabolism from fatty acid oxidation to glucose oxidation.[21]

Unique mechanisms of TMZ separate it from other antianginals. It is recommended by ESC as add on therapy with other antianginal drug.[22] It is devoid of negative inotropic, chronotropic, or vasodilatory properties also known as metabolic modulator.[23]

After thorough literature, it was found that dosage forms for combination of IBH and TMZ not available in market. Therefore, both the drug selected for further study and effective angina treatment.

MATERIALS AND METHODS

Materials

Ivabradine hydrochloride was procured from Kores (India) Limited, Raigad. Trimetazidine dihydrochloride was obtained as gift sample from Intelliscend, Mumbai. Avicel PH-102 and Avicel PH-112 were generously provided as gift samples by Signet Excipients Pvt. Ltd. Colloidal silicon dioxide by Madhu Silica Pvt. Ltd. Gujarat, Neelicert FD&C blue by Neelikon Food Dyes And Chemicals Ltd, Explotab and Vivasol by Rettenmaier India (JRS) Pvt. Ltd., Benecel K100 M Pharm XR, Benecel K200M Pharm CR, Polyplasdone XL, Klucel EXF Ultra Pharm by Ashland, Maharashtra., Kollidon SR by BASF, Navi Mumbai. All were used as ingredients for the formulation development. All other excipients and chemicals used for research were analytical grade.

Methods

Drug authentication

Color

Small quantity approximately 10–15 mg of IBH and TMZ were taken on butter paper and observed in well-illuminated place.

Melting point of drug

Melting points of IBH and TMZ were determined by glass capillary method. The programmable melting point apparatus was used. Drug filled capillaries with one-end sealed and thermometer were placed in the Veego melting point apparatus. Readings were recorded in triplicate.

Determination of absorbance (λ-max)

Stock solution of IBH and TMZ standard prepared by accurately weighing and transferring 10 mg of both the drug in 100 mL of 0.1N HCl separately and the total volume was brought to 100 mL with 0.1N HCl, respectively, to obtain stock solution. This stock solution further used to prepare

various working solutions. Working solutions of both the drug scanned in ultraviolet (UV) Spectrophotometer (Shimadzu) at 200–400 nm range to determine the maximum absorbance (λ max) using 0.1N HCl as blank.[24]

Fourier transform infrared (FTIR) spectra of IBH, TMZ, and mixture

IR absorption spectra of IBH, TMZ, and tablet blends were recorded using FTIR spectrophotometer (FTIR-Shimadzu) wherein 1–2 mg of drug sample and excipients were used. The spectra of drug individual and combination with excipients were recorded by scanning in range of 4000–400 cm^{-1}. IR spectra of drug and mixture of drug with excipients compared to identify any interaction or compatibility.

Differential scanning calorimetry (DSC)

The DSC analysis of IBH and TMZ were carried out using DSC (Mettler Toledo, USA). Sample of drug was accurately weighed and put into aluminium pan, sealed and the DSC thermograms of both active pharmaceutical ingredient (API) recorded at a heating rate of 10°C/min.

Development of IBH IR layer tablets

All IR layer batches were taken by direct compression approach. Procedure is given below. All ingredients were weighed as per formula given in Table 1. Small quantity of fines of Avicel were collected through 100# (150 µ) sieve and mixed with color. All remaining material, API, super disintegrant, and Klucel sifted through 40# (425 µ) sieve. This mixture was mixed manually for 5 min in polybag. Moreover, lubrication was carried out by sifting magnesium stearate from 60# (250 µ) sieve for 3 min.

Single-layered tablets were compressed (Rotary tableting machine Cip D 8-Lab Press) using simple direct compression method with round 10.00 mm standard concave punch plane on both the sides.

Formulation of TMZ floating layer tablets

All ingredients weighed as per mentioned in formula displayed in Table 2 and sifted through #40 (425 µ) sieve except stearic acid which was passed through 60# (250 µ). Drug and stearic acid first mixed for 3 min then remaining all sifted materials mixed for 5 min. Lubrication was performed for 2 min using stearic acid by separate sifting through 60# sieve and then added into pre-lubricated granules.

Moreover, single-layered tablets were compressed using simple direct compression approach with 10 mm, round, plane on both sides, and standard concave punches.

Development of bilayer tablets

Based on the results of flow properties, disintegration time of immediate release tablets, dissolution and floating study of gastro retentive tablets, immediate release trial I-4, and gastroretentive release trial T-8 were selected for further compression into bilayer tablets, as shown in Table 3. Simple direct compression method was employed for the preparation of bilayer tablet. Tablets were compressed using 10 mm standard concave punch plane on both the sides. Required quantity of T-8 floating layer blend weighed and poured into die cavity and compressed with very low compression force which was pre compression force. Then, second layer of immediate release weighed accurately and poured on top of the first layer. Compression force increased by rotating the knob (main compression or final compression force) such that both the layers would compressed into single bilayer tablet and to get the desired hardness without layer separation.

Evaluation of blend and tablets

Powder flow characteristics

Physical properties for both IR and floating layer blend such as bulk density, tapped density, Hausner ratio, and Carr's compressibility index were carried out on Electrolab tap density tester (USP). All readings were taken in triplicate and average calculated.[25]

Table 1: Composition of IBH immediate release blend

S. No	Ingredients	I-1	I-2	I-3	I-4	I-5	I-6
	mg/tab						
1	Ivabradine HCl				5		
2	Avicel PH 102	137	137	137	-	-	-
3	Avicel PH 112				137	137	137
4	Vivasol	5	-	-	5	-	-
5	Explotab	-	5	-	-	5	-
6	Polyplasdone XL	-	-	5	-	-	5
7	Klucel ultra pharm	2	2	2	2	2	2
8	FD&C Blue	0.5	0.5	0.5	0.5	0.5	0.5
	Lubrication						
7	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)		150	150	150	150	150	150

Table 2: Composition of TMZ floating layer blend

S. No.	Ingredients	T-1	T-2	T-3	T-4	T-5	T-6	T-7	T-8
	mg/tab								
1	TMZ					35			
2	Steric acid	0	0	0	0	0	0	3.5	3.5
3	Benecel K15 M CR	124	124	124	95	95	73	-	-
4	Benecel K100 M CR	-	-	-	-	-	-	64	-
5	Benecel K200 M	-	-	-	-	-	-	-	64
6	Kollidon SR	-	-	-	-	-	125	154.5	154.5
7	Guar gum	29	-	-	29	29	-	-	-
8	Xanthan gum	-	29	-	-	-	-	0	-
9	Carnauba wax	-	-	29	-	-	-	-	-
10	Carbopol 974P	-	-	-	29	-	-		-
11	Sodium CMC	-	-	-	-	29	-	-	-
12	Ashacel	25	25	25	25	25		-	-
13	Sodium bicarbonate	65	65	65	65	65	45	40	40
14	Colloidal Silicon dioxide	1	1	1	1	1	1.5	1.5	1.5
					Lubrication				
15	Stearic acid	2	2	2	2	2	1.5	1.5	1.5
Total weight (mg)		281	281	281	281	281	281	300	300

Table 3: Composition of best formulae for bilayer tablets

S. No.	Composition of bilayer tablets				
	Floating gastroretentive layer	mg/tablet	% w/w	Immediate release layer	mg/tablet or % w/w
1	TMZ	35.0	11.67	Ivabradine HCl	5.00
2	Steric acid	3.5	1.17	Avicel PH 112	89.50
3	Benecel K200 M	64.0	21.33	Cabosil	0.25
4	Kollidon SR	154.5	51.50	Vivasol	2.75
5	Sodium bicarbonate	40.0	13.33	Klucel ultra pharm	1.50
6	Colloidal Silicon dioxide	1.5	0.50	Color	0.75
			Lubrication		
7	Stearic acid	1.5	0.50	Magnesium Stearate	0.25
		300	100		100.00
Weight of bilayer tablet (mg)				400	

Bulk density (ρ_{bulk}) = Weight of test sample in g, (W)/unsettled apparent volume (V_0)

Tapped density (ρ_{tapped}) = Weight of test sample in g, (W)/final tapped volume (V_f)

$$\text{Compressibility Index (\%)} = 100 \times [(\rho_{tapped} - \rho_{bulk})/\rho_{tapped}]$$

$$\text{Hausner Ratio} = (\rho_{tapped}/\rho_{bulk})$$

Post-compression parameters

All the compressed tablets were evaluated for appearance, weight, thickness, diameter, hardness, friability test of bilayer tablets, DT of immediate release layer and floating time, floating lag time (FLT), swelling index (SI), and dissolution testing of floating layer.

Appearance

Single layered and bilayer tablets were observed visually to check for physical appearance.

Weight of individual layers and bilayer tablets

Weight of individual layer and bilayer tablets were checked using analytical weighing balance (Shimadzu AUX 220). Average and SD were calculated for all trials.

Tablet dimensions

Diameter and thickness of individual layers and bilayer tablets were measured in triplicate with Digital Vernier caliper (Aerospace).

Tablet hardness or crushing strength

Tablet hardness was measured with the help of Rolex hardness tester (Monsanto type). Hardness determined by holding tablet between jaw and nozzle, rotate the screw knob till the tablet breaks. Tablet hardness indicates strength of tablet which prevents it from breaking or damage during packaging and transportation. Readings were recorded in triplicates (Measuring unit Kilogram per square centimeter).

Friability test

Electrolab EF-2 friabilator (USP) was used for the determination of tablet friability. Bilayer tablets correspond to 6.5 g taken and weighed, noted as (w_1), and then placed in friabilator which rotates at 25 rpm. After 100 revolutions means after 4 min, final weight (w_2) was measured by de-dusting. % Friability was calculated using below formula,

$$\text{Friability (\%)} = \frac{\left(\text{Weight of tablet before test, } w_1\right) - \left(\text{Weight of tablet after test, } w_2\right)}{\left(\text{Weight of tablet before test, } w_1\right)} \text{ x } 100$$

FLT and total floating time

Glass beaker containing 100 mL of 0.1N hydrochloric acid taken and maintained at 37 ± 2°C. Tablet was dropped into the beaker and measured the time required for tablet to come at the top surface of solvent again after dropping was determined as FLT. Moreover, the total time for which tablet remains at the top surface of solvent or buoyant was determined as total floating time or total buoyancy time.[26]

%SI

Glass Petri dish containing 20 mL of 0.1 N hydrochloric acid taken and maintain at 37 ± 5°C. Initial tablet weight recorded and dropped in Petri dish. Tablet was removed after regular time interval, excess solvent taken off by tissue paper. Moreover, tablet reweighed using analytical weighing balance. SI was calculated using below mentioned formula,[27]

$$\text{SI } (\%) = \frac{(\text{Weight of the tablet at interval} - \text{Weight of tablet before immersion})}{(\text{Weight of tablet before immersion})} \times 100$$

Disintegration time (For IR layer)

DT of immediate release layer determined using Electrolab disintegration tester ED-2L (USP), consisting of 6 glass tubes. Disintegration test started by placing one tablet in each tube and the basket arch positioned in a 1 L beaker of water at 37°C ± 2°C.

In vitro dissolution study

Dissolution test performed using 0.1 N HCl as dissolution medium, USP II, that is, paddle type apparatus at 50 rpm speed and 37 ±0.5°C temperature. Absorbance of withdrawn aliquot samples at predetermined time intervals was analyzed with suitable dilutions if necessary, using UV Spectrophotometer (Shimadzu) at 231 nm and 286 nm for TMZ and IBH, respectively, with 0.1 N HCl as blank. Moreover, percentage drug released from tablet plotted against time.[27]

Matrix integrity

Tablet intactness (holding the mechanical shape) was checked throughout the *in vitro*-dissolution test and recorded the observations.[26]

RESULTS

The aim of this research work was to formulate and evaluate bilayer tablets containing IBH as immediate release and TMZ in floating layer. IBH has low half-life (2 h) with BID dosing frequency and TMZ has TID dosing frequency with 6 h of elimination half-life. Therefore to reduce the dosing frequency, effective treatment and to improve patient compliance by adherence to therapy two drugs were combined in single bilayer tablet. IBH incorporated in IR layer so as to provide immediate action and TMZ added in floating extended release layer to achieve extended release.

Drug identification

The melting points of IBH and TMZ are represented in Table 4. Drug was identified and purity confirmed by comparing the average of replicate readings with reported values in literature.

UV spectroscopic absorbance

Maximum absorbance wavelength determined using UV visible spectroscopic method. Moreover, λ max of IBH and TMZ were found to be 286.60 and 231.40, respectively. Absorbance spectrums of both the drug displayed in Figure 1.

Drug-excipient compatibility study

FTIR spectrum of API as such and mixture showed in Figures 2 and 3. IR spectra of API and mixture of API with excipients did not display any significant shift in peaks which mean devoid of any interaction, with compatibility between API and excipients during the compression process.

Table 4: Melting point of drug

Drug name	IBH	TMZ
Appearance	**White crystalline powder**	**White crystalline powder slightly hygroscopic**
Melting point (°C) (n=3)±SD		
Reported	191–196	231–235
Observed	194.3±1.1	232±1

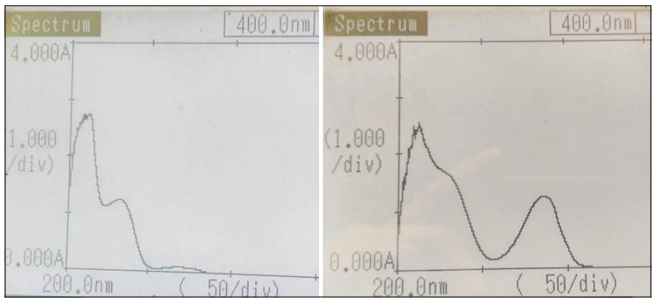

Figure 1: Absorbance spectrum of TMZ and IBH

DSC Thermogram of Drug

DSC study was performed to determine melting characteristics of drug. DSC of IBH and TMZ showed in Figure 4.

Endothermic peak observed at 194.87°C and 239.17°C for IBH and TMZ, respectively. Endothermic peak signifies the melting point of the API and it is related to purity of drug.

Powder flow characteristics of blends

Powder flow properties were determined and results depicted in Table 5. All Trial-1 to Trial-5 had poor flow characteristics whereas Trial-6, Trial-7, and Trial-8 showed passable, good, and fair flow properties, respectively.

Post compression parameters

Physical parameters of average weight, thickness, diameter, hardness of immediate, and floating release tablets after compression are displayed in Table 6.

DT of immediate release tablets

Tablets of all the trials had very low DT in range of 4–10 s; however, trial-4 exhibited very low DT among all the trials without palpable mass in sieve.

FLT of TMZ tablets

Batches T-6, T-7, and T-8 composed of Kollidon SR had low FLT in range of 8–15 s, whereas trial number T1 to T-5 without Kollidon SR had high FLT in range of 28–34 s. Higher FLT could result in gastric clearance due to peristaltic movement and housekeeping waves in stomach.

Total floating time

Trials T-1 to T-5 floating tablets showed more than 15 h of total floating time while trial T-6 to T-8 had more than 24 h of total floating time in 0.1 N HCl.

SI (%)

Floating layer tablets containing Benecel displayed high swelling compared to tablets with combination of Kollidon SR and Benecel. % SI portrayed in Table 7.

Matrix integrity

All the tablets remained intact and maintained the shape throughout the *in vitro* dissolution study in 0.1 N HCl medium.

Dissolution study

T-1 to T-5 released drug within 12 h whereas T-6, T-7, and T-8 controlled the drug release more than 12 h, which showed in Figure 5. IR trial-1–6 released 100% drug quickly in <5 min.

All graph indicated that there was no burst release from floating layer tablets.

Post-compression parameters of bilayer tablets displayed in Table 8.

DISCUSSION

Preliminary trials were executed using combination of HPMC K15MCR and natural polymers such as guar gum, xanthan gum, and carnauba wax with sodium bicarbonate as effervescent agent, T-1 to T-5 floating tablets were formulated successfully but drug release controlled up to 12 h. Hence, for further retardation, the drug release natural polymers were replaced by synthetic polymer Kollidon SR in T-6. It was observed that combination of HPMC and Kollidon SR

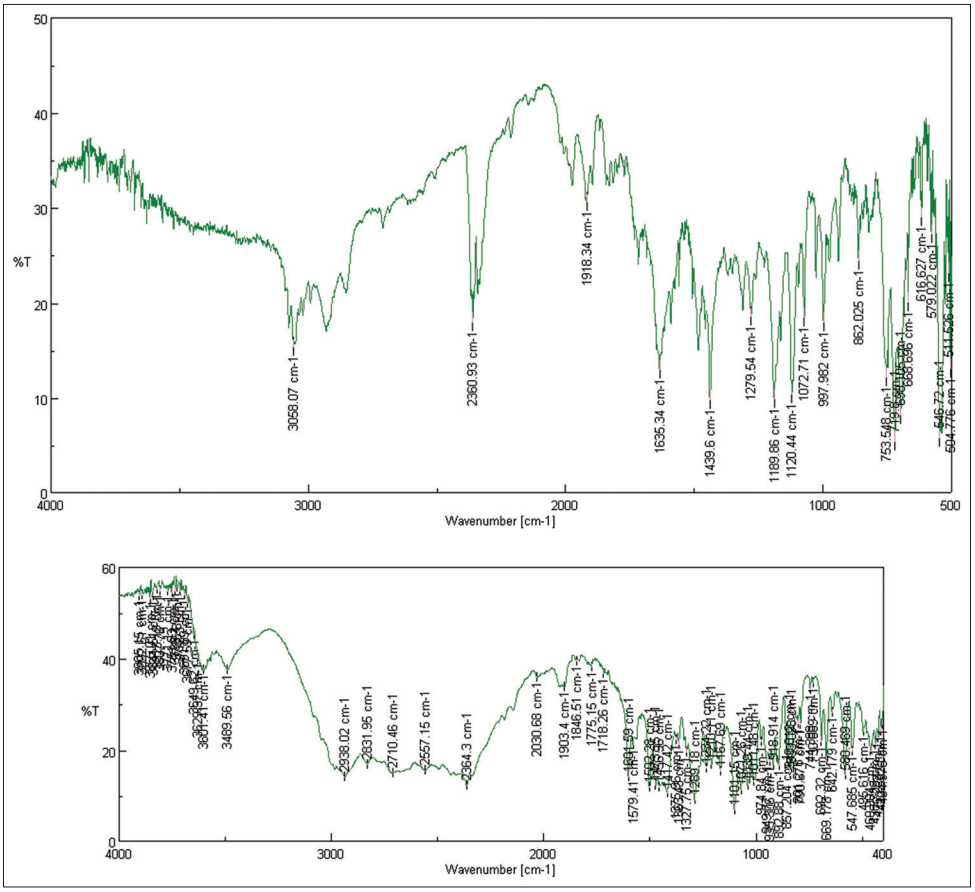

Figure 2: Fourier transform infrared spectra of TMZ as such active pharmaceutical ingredient and its tablet blend

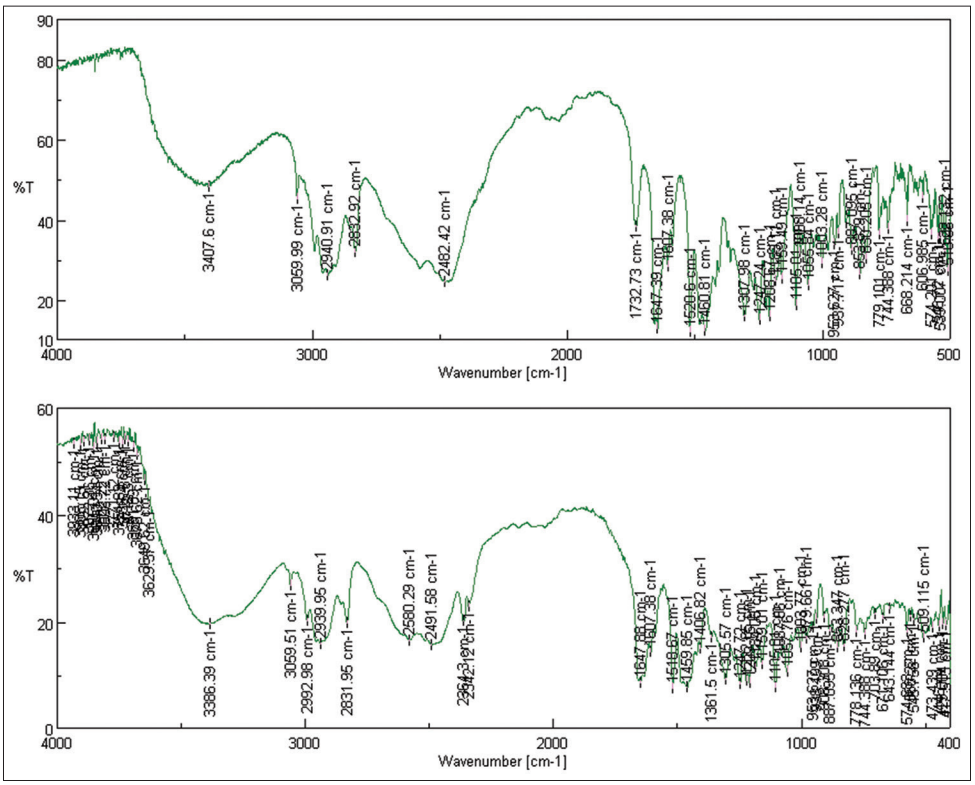

Figure 3: Fourier transform infrared spectra of IBH as such and its immediate release blend

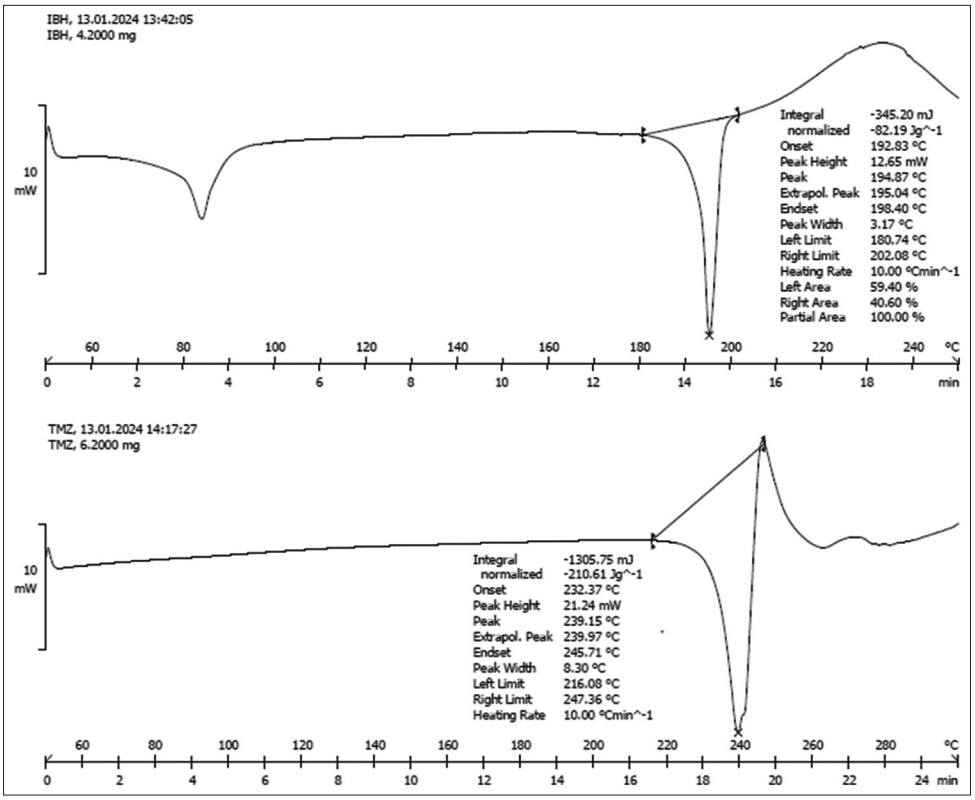

Figure 4: Differential scanning calorimetry thermogram of IBH and TMZ

Table 5: Powder flow properties of floating and IR layer blends

Parameters / Trial no.	Bulk density (g/mL)±SD (*n*=3)	Tapped density (g/mL)±SD (*n*=3)	Carr's compressibility index (%)±SD (*n*=3)	Hausner ratio±SD (*n*=3)	Flow[25]
Trimetazidine floating layer blend					
T-1	0.424±0.00	0.651±0.01	34.862±1.20	1.536±0.03	Very poor
T-2	0.439±0.01	0.636±0.02	31.001±1.16	1.425±0.02	Poor
T-3	0.446±0.00	0.648±0.01	31.136±0.91	1.447±0.02	Poor
T-4	0.454±0.00	0.631±0.01	28.047±0.94	1.390±0.02	Poor
T-5	0.441±0.00	0.616±0.01	28.404±0.29	1.397±0.00	Poor
T-6	0.385±0.01	0.514±0.01	25.124±0.58	1.336±0.01	Passable
T-7	0.407±0.01	0.478±0.01	15.635±1.66	1.186±0.02	Good
T-8	0.403±0.00	0.493±0.01	18.283±1.67	1.224±0.03	Fair
Ivabradine hydrochloride immediate release layer blend					
I-1	0.377±0.00	0.503±0.01	25.117±1.52	1.336±0.03	Passable
I-2	0.393±0.00	0.525±0.01	25.132±1.58	1.336±0.03	Passable
I-3	0.370±0.00	0.497±0.01	25.615±0.76	1.344±0.01	Passable
I-4	0.385±0.01	0.507±0.01	24.098±0.60	1.318±0.01	Passable
I-5	0.387±0.00	0.514±0.01	24.736±1.36	1.329±0.02	Passable
I-6	0.371±0.00	0.484±0.01	23.266±0.780	1.303±0.01	Passable

SD: Standard deviation

controlled the drug release more than 12 h without dose dumping or burst release. Kollidon SR exhibits low density therefore reduced FLT as well as total floating time and ultimately reduced quantity of effervescent material sodium bicarbonate. In addition, it also showed good flow which contributed to improve the flow properties when combine with other polymers. To further control drug release Benecel K15 MCR was replaced with Benecel K200 MCR as high

Table 6: Physical parameters of tablets

Parameters / Trial no.	Weight±SD (in mg) *n*=10	Thickness±SD (in mm) *n*=10	Diameter±SD (in mm) *n*=5	Hardness±SD (kg/cm²) *n*=5
Trimetazidine floating layer tablets				
T-1	280.0±1.15	3.99±0.01	10.01±0.01	4.8±0.4
T-2	281.2±0.79	3.86±0.02	10.01±0.01	4.6±0.2
T-3	279.9±1.10	3.80±0.01	10.00±0.01	5.0±0.2
T-4	280.4±1.84	3.96±0.02	10.01±0.01	5.0±0.3
T-5	280.4±1.07	3.98±0.01	10.00±0.02	5.1±0.5
T-6	280.7±1.25	4.52±0.02	10.02±0.01	6.4±0.4
T-7	298.2±1.48	4.35±0.02	10.01±0.01	10.7±0.5
T-8	299.0±1.41	4.50±0.03	10.01±0.01	9.5±0.5
Ivabradine immediate release layer tablets				
I-1	149.7±1.06	2.91±0.02	10.02±0.01	4.6±0.3
I-2	149.7±1.25	2.90±0.02	10.02±0.01	4.6±0.2
I-3	148.7±1.25	2.90±0.02	10.01±0.01	4.8±0.4
I-4	149.4±0.97	2.93±0.02	10.01±0.01	4.8±0.1
I-5	149.0±0.94	2.90±0.02	10.02±0.01	4.5±0.3
I-6	149.1±0.99	2.94±0.02	10.02±0.01	4.8±0.1

SD: Standard deviation

Table 7: Swelling index of floating layer tablets

%Swelling Index±standard deviation (*n*=3)				
Trial no.	Time in h			
	1	2	3	4
T-1	46.7±1.1	68.1±1.2	82.5±1.0	101.1±1.5
T-2	48.8±4.0	79.9±2.3	99.0±2.0	114.4±1.3
T-3	47.5±1.0	81.1±0.1	102.9±3.0	119.2±2.4
T-4	49.9±2.4	56.4±2.4	87.7±4.8	102.0±3.3
T-5	48.2±1.3	87.9±2.0	96.0±1.4	105.0±2.0
T-6	33.8±0.7	52.2±0.9	62.1±1.6	65.3±0.6
T-7	28.8±1.1	48.4±1.6	61.4±1.9	67.9±2.2
T-8	33.0±0.9	54.0±0.9	65.2±2.6	69.3±3.3

Table 8: Parameters of bilayer tablets

Parameters	Results
Image of bilayer tablets	
Appearance	Uncoated bilayer tablets with two distinct layers, circular in shape, blue immediate release layer, and white floating layer
Thickness (mm)	6.15±0.05
Diameter (mm)	10.01±0.02
Hardness (Kg/cm²)	12.2±3
Friability (%)	0.12±0.2
Disintegration time (seconds)	3±1
Floating lag time (seconds)	15±3
Total floating time (h)	>24 h
Dissolution time	Immediate release had 100% drug release within 5 min while floating release controlled the drug release more than 12 h.

viscosity grade polymer and quantity of second polymer, Kollidon SR was increased.

Immediate release layer developed using three different superdisntiegrants, namely, Vivasol, Explotab, and polyplasdone XL. Klucel ultrapharm selected as binder, I-4 trial showed promising results such as DT, it was 4–6 s without palpable mass on mesh, flow properties of blend, and compressibility. Therefore, trial I-4 was selected for further IR layer for bilayer tablet compression.

Bilayer gastroretentive tablets were successfully formulated by floating approach using simple direct compression method. Combining Kollidon SR as polymer not only reduced the drug release but also eliminated the burst effect of high-soluble drug, also improved compressibility, flow properties, reduced FLT, and increased total floating time. Stearic acid mixing with API further contributed synergistically in release retardation.

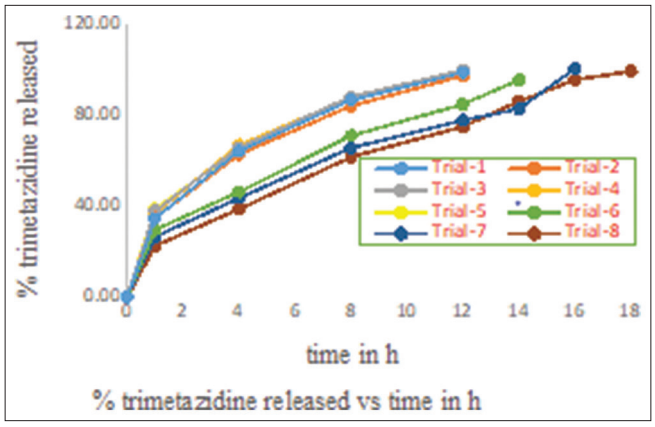

Figure 5: % TMZ drug release from floating layer tablets

CONCLUSION

It can be concluded from current research work, that bilayer gastroretentive floating tablet is promising dosage form to deliver two highly water soluble short half-life drug so as to reduce multiple dosing frequency and effective treatment of angina with better patient compliance.

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