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Research Article

DEVELOPMENT AND EVALUATION OF MUCOADHESIVE BILAYER GASTRORETENTIVE TABLETS OF TRIMETAZIDINE DIHYDROCHLORIDE AND IVABRADINE HYDROCHLORIDE

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ABSTRACT

Objective: The objective of the present investigation was to combine ivabradine hydrochloride (IBH) and trimetazidine dihydrochloride (TMZ) in bilayer mucoadhesive gastroretentive tablets for effective treatment of angina, reduce multiple dosing, and to discover best alternative to conventional drug with lesser adverse effects.

Methods: Bilayer gastro retentive tablets formulated using simple direct compression method and mucoadhesive approach wherein IBH incorporated in immediate release (IR) while TMZ as mucoadhesive layer. Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and melting point and ultraviolet (UV) spectroscopy performed to evaluate compatibility and purity of active pharmaceutical ingredient (API). IBH IR layer prepared using Avicel-112, Vivasol, Klucel and TMZ mucoadhesive layer developed using Benecel K200M, Kollidon SR, Xanthan gum, and stearic acid. Bilayer tablets prepared with simple direct compression and evaluated for physical parameters, *in vitro* dissolution, mucoadhesive strength, % swelling index, stability study for 6 months, and *in vivo* study conducted in New Zealand white rabbits using barium sulfate in TMZ tablets.

Results: DSC, FTIR, UV spectroscopy, and melting point confirmed the purity of both the API and their compatibility. IBH IR layer quickly disintegrated within 5 s and released complete drug. TMZ mucoadhesive layer controlled release up to 12 h with 51.15 N mucoadhesive strength. Tablet remained unchanged after 6 months stability study at 40°C–75% temperature-RH condition. Furthermore, X-ray imaging study for 24 h confirmed that TMZ tablet retained in rabbit stomach for more than 12 h.

Conclusion: Based on stability study, results and *in vivo* testing it was concluded that IBH and TMZ mucoadhesive bilayer tablets successfully developed using simple direct compression. Further optimization required to control the drug release and to increase gastric retention time.

Keywords: Mucoadhesive, Bilayer tablets, Immediate release, Gastroretentive, Ivabradine hydrochloride, Trimetazidine dihydrochloride.

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INTRODUCTION

Oral route is the most common, convenient and attractive due to its several advantages such as easy manufacturing, patient compliance, ease of administration, cost effectiveness, large scale manufacturing, and flexibility to develop immediate, sustained, and controllable delivery [1,2]. Serious drawbacks of conventional oral drug delivery such as large fluctuation in drug availability observed due to physiological factors such as variations in pH, high enzymatic activity, and fast gastric emptying [3]. This fast transit from GI tract causes incomplete drug absorption and poor effectiveness therefore frequent drug administration required to maintain therapeutic level [4,5]. To overcome these limitations, gastroretentive drug delivery system (GRDDS) plays crucial role. GRDDS increases gastric retention time, improves absorption, and reduces fluctuations that ultimately resulted in better effectiveness with less adverse effects [6]. Suitable drug candidates for GRDDS possesses characteristics such as shorter half-life (e.g. ranitidine) [7], degrade in colonic pH (e.g. ranitidine), local action in stomach (e.g. Metronidazole) [8], low solubility at higher intestinal pH (e.g., Furosemide and diazepam), or drug with narrow absorption window (e.g. riboflavin) [9,10]. GRDDS can be developed using several approaches that include super porous hydrogel, bio/mucoadhesive, raft forming, magnetic, ion-exchange, expandable, and low- and high-density system [11]. Bioadhesive GRDDS dosage adhere to gastric epithelial cells or mucous and extends the gastric retention by increasing intimacy and duration of contact [12]. "Mucoadhesion can be defined as a state in which two components of which one is of biological origin are held together for extended periods of time by the help of interfacial forces" [13] Polymers such as chitosan, sodium alginate, sodium CMC, xanthan gum, chitosan, hyaluronic acid, pectin, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, and polyacrylic acid have mucoadhesive nature; therefore, these ingredients are most commonly used in formulation of mucoadhesive tables [6,14,15]. Combination of polymer such as HPMC and xanthan gum prevents burst effect with drug release in controlled fashion [16].

Ischemic heart disease (IHD) is leading cause of death globally. Chronic stable angina is most common and prevalent symptomatic clinical manifestation of IHD. Term "Angina" is derived from Latin verb "angere" means to strangle. It is chest discomfort of cardiac origin [17]. "Angina" first defined by William Heberden in 1768 [18]. Stable angina result due to imbalance between oxygen supply and demand myocardial cells [19]. According to European society of cardiology (ESC) guidelines, pharmacological treatment for symptomatic relief of angina mainly divided into two group as first-line (beta blockers [BB's], short acting nitrates and calcium channel blockers [CCB's]) and second-line agents (ivabradine, nicorandil, ranolazine, long acting nitrates, and trimetazidine). Second-line drug prescribed when patient contraindicated to first choice or do not tolerate or remain symptomatic [20,21]. Neither first-line nor second-line drug are superior for angina but effective therapy focuses on individual, tailored approach, and considering comorbidities of patient [22]. This patient centered treatment guide also called as Diamond approach [23]. In past few years, this classification is questioned due to more evidence based data to support newer or second choice drugs. Pharmacological treatment have two main goals first to alleviate symptoms and

improve the quality of life and second to improve prognosis, prevent cardiovascular events such as myocardial infraction and cardiovascular death. To control the symptoms, effectively combination of two or more drug with synergistic or additive effect is needed [20,24]. Fixed dose combination combines two or more drug in single formulation for patient convenience, reduce dosing, cost saving, and treatment of elder patient with comorbidities [25]. Ivabradine is first selective I*f* channel inhibitor lowers heart rate without negative inotropic or lusitropic effect [26,27]. IBH has elimination half-life of 2 h with 40% oral bioavailability and dose ranges from 2.5 to 7.5 mg twice daily. IBH can be combined with BB's, CCB's, nitrates, nicorandil, trimetazidine, or ranolazine but not recommended with verapamil or diltiazem [28]. IBH is mainly considered when patient contraindicated or not able to tolerate BB's in presence of asthma or severe chronic obstructive airway disease [29]. Trimetazidine dihydrochloride (TMZ) is first known 3-ketoacyl coenzyme A thiolase inhibitor that shift cardiac energy metabolism from fatty acid oxidation to glucose oxidation [30]. TMZ lowers angina symptoms without affecting hemodynamic parameters. ESC recommended TMZ as add on therapy with other anti-anginal drug [31]. Its half-life is around 6 h; therefore, dose of TMZ is 20 mg thrice daily as immediate release (IR) tablets and modified release tablet 35 mg Twice a day (BID). [32] Hence to overcome challenges like frequent dosing, shorter half-life, effective treatment, reduce adverse effect, and best alternative to traditional first-line therapy, the objective of present study was to develop successful and marketable bilayer gastroretentive tablets with combination of ivabradine hydrochloride (IBH) as IR layer and TMZ in mucoadhesive layer alternative to conventional angina treatment.

METHODS

Materials

IBH obtained as gift sample from Lupin, Ltd. Sikkim, TMZ received from Sharon, Biomedicine Ltd. Maharashtra, Avicel-112 was gift sample from Signet Excipients Pvt. Ltd., Colloidal Silicon Dioxide from Madhu Silica, Neelicert FD&C Yellow-5 color obtained from Neelikon Food Dyes and Chemicals Ltd., Roha, Maharashtra., Vivasol received from Rettenmaier India Pvt. Ltd.(JRS) Maharashtra, Klucel EXF Ultra Pharm, Benecel K200 M Pharm CR, Benecel K100 M Pharm XR received from Ashland, Maharashtra. Sodium CMC from Pioma Chemicals, Mumbai, and Kollidon SR received from BASF, Navi Mumbai. Guar Gum was obtained from Neelkanth Finechem, Rajasthan. Carbopol 974 P received from Lubrizol. Xanthan gum from Anmol Chemicals, Mumbai. Magnesium stearate from SD Fine Chemicals. Goat mucosa was obtained from local slaughter center, Nigdi, Pune.

Methods

Fourier-transform infrared (FTIR) spectroscopy

Drug, excipient, and mixture with finely powdered KBr (Potassium Bromide) taken in one cavity and large amount of KBr in other cavity were subjected to FTIR scan (JASCO FT/IR-4100) in 400–4000 cm^{-1}. Generated IR spectra compared and interpreted to identify any possible interaction and compatibility [33].

Differential scanning calorimetry (DSC)

DSC analysis was carried out using DSC equipment (Mettler Toledo, USA/DSC-1). 3–7 mg of solid sample or mixture was used for test with heating rate of 10°C/min in temperature range of 50–250°C. DSC thermogram of all samples was recorded and interpreted based on obtained graphs [33].

Visual appearance of active pharmaceutical ingredient (API)

15–20 mg of IBH and TMZ taken on butter paper separately and observed in well-illuminated place to check color and crystalline nature.

Melting point

Melting point was determined using melting point apparatus (Veego). Both the drug IBH and TMZ both were filled separately in sealed capillary at one end. Drug filled capillaries kept in two different slots. Stirrer of apparatus started using stirrer knob and heating with heating knob and continuously observed the transition of solid phase into liquid state with magnifying glass. Reading was noted in triplicate to take the average.

Ultraviolet (UV) spectroscopy

Both API IBH and TMZ weighed separately and transferred into 100 mL of flask. Approximately 50–60 mL of 0.1 N HCl (Hydrochloric Acid) added into flask, agitated till API disappear and remaining volume was made with 0.1 N HCl. From this solution required, quantity was pipetted and transferred to 10 mL flask and volume was made with 0.1N HCl. This solution was scanned in UV range 200–400 nm on UV-Visible spectrophotometer (Jasco V-630). This solution was scanned in UV range 200–400 nm on UV-Visible Spectrophotometer (Jasco V-630) using 0.1 N HCl as blank solvent.

Preparation of mucoadhesive layer

All ingredients weighed accurately as per formula of each trial given in Table 1. First API mixed with stearic acid for 3 min then remaining all the ingredients were passed through 40# (425 microns) sieve and mixed for 5 min manually and lubricated for 2 min using stearic acid, which was previously passed through 60# sieve (250 microns). Initially, single layer tablets were compressed using 10 mm, round plane standard concave punches so as to check the compressibility and other challenges related to direct compression process.

Preparation of IR layer

IR blend prepared by accurately weighing ingredients as per the formula given in Table 2. First Avicel-112 passed through 100#

Table 1: Composition of mucoadhesive layer trials

Serial number	Trial ingredients	TM-1 (mg/tablet)	TM-2 (mg/tablet)	TM-3 (mg/tablet)	TM-4 (mg/tablet)	TM-5 (mg/tablet)	TM-6 (mg/tablet)
1	TMZ	35					
2	Stearic acid	3.5	3.5	3.5	3.5	3.5	3.5
2	Kollidon SR	50	60	60	60	60	60
3	Benecel K15 M	87.5	-	-	-	-	-
4	Benecel K200 M	-	77.5	77.5	77.5	77.5	77.5
5	Guar gum	50			50		
6	Sodium CMC		50				
7	Xanthan gum			50			
8	Sodium alginate					50	
9	Carbopol 974 P						50
10	Colloidal silicon dioxide Lubrication	2.5	2.5	2.5	2.5	2.5	2.5
11	Stearic acid	1.5	1.5	1.5	1.5	1.5	1.5
Total		230	230	230	230	230	230

This table showed composition of all the trials carried out using different polymers to develop TMZ mucoadhesive tablets. Sr. No: Serial number, TM: Trimetazidine mucoadhesive trial, mg: milligram, Sodium, CMC: Sodium carboxy methyl cellulose

Table 2: Composition of IBH-1 immediate release layer trials

Serial number	Trial number ingredients	IBH-1, mg/tablet	IBH-2, mg/ tablet	IBH-3, mg/tablet
1	IBH	5	5	5
2	Avicel-112	134	134	134
3	Vivasol	4.6	-	-
4	Explotab	-	4.6	-
5	Polyplasdone XL	-	-	4.6
6	FD&C yellow 5	1	1	1
7	Klucel	2	2	2
8	Colloidal silicon dioxide	1.7	1.7	1.7
	Lubrication			
9	Magnesium stearate	1.7	1.7	1.7
Total		150	150	150

Table 2: displayed composition for Ivabradine IBH layer trials taken using different superdisintegrants. IBH-1: Ivabradine hydrochloride trial-1

(150 microns) sieve and fines were collected. Collected fines mixed with color FD&C Yellow 5. All remaining ingredients passed through 40# (425 microns) sieve except magnesium stearate passed through 60# sieve (250 microns). Single layer tablets were compressed using 10 mm round plane standard concave punches.

Precompression study

Tap density tester (Electrolab USP) was used for assessing the flow parameters both IR and mucoadhesive release blend. Flow properties such as bulk density, tapped density, Carr's Index, and Hausner ratio calculated using below formulae, 3 times and average value measured.

Bulk Density (g/mL)=Weight of test sample/Initial volume

Tapped density (g/mL)=Weight of test sample/Final Volume

Carr's index=Tapped density/Bulk density

Hausner ratio=100 × [Tapped density-Bulk density]/Tapped density

Compression of bilayer tablets of IBH and TMZ

Based on result of disintegration time (DT), mucoadhesive strength, flow properties, and dissolution study of all trials, TM-3 and IBH-1 were selected for further compression into bilayer tablets as per Table 3 (On Rotary Tableting machine Cip D-8 Lab Press). Direct compression approach was used for the preparation of bilayer tablets. Both immediate release layer and mucoadhesive layer blend compressed into tablets separately for preliminary evaluations. After optimization, one layer filled in die cavity and compressed at very low pressure to reduce the interparticulate distance with void volume. Then, another layer blend poured on first layer and main compression force applied so as to attach first layer with second layer for the formation of bilayer tablets [34,35].

Characterization of bilayer tablets

Appearance

Physical appearance of tablets was checked visually for layer separation or any other defect.

Weight of tablet

Weight of single layer and bilayer tablets checked using analytical weighing balance (Shimadzu AUX 220) and average calculated.

Dimensions of tablets

Thickness and diameter of single and bilayer tablets measured with digital Vernier caliper (Aerospace).

Hardness

Hardness of tablet is mechanical strength which protects it during transportation and storage. It was measured by Monsanto hardness tester (Rolex). Readings were noted in triplicate and average calculated (Expressed in Kg/cm^2) [36].

Friability

Determination of friability or dust generation was performed by fribilator (Electrolab EF-2 USP). Approximately, 6.5 g weight of bilayer tablets taken, weighed, and noted as W1. These tablets were dropped in friabilator compartment. After dropping friabilator started for 100 revolutions at speed of 25 rpm (revolutions per minute). After completion of 4 min, tablets dedusted manually and final weight taken as W2. % Friability was calculated using below formula,

% Friability=Initial weight of tablets (W1)−Weight of tablets after 100 rpm (W2)/Initial weight of tablets

Disintegration test for IR layer

DT of IR IBH layer tablet was determined using Electrolab disintegration test apparatus (ED-2L USP). Six number of IR tablets were dropped separately in 6 glass tubes held in 1 liter beaker containing water maintained at 37±2°C. DT of each tablet noted by carefully observing the tablet breaking and passing from 10# screen at bottom of glass tube.

Swelling index (% SI)

Weighed individual tablet of TMZ and placed in Petri dish containing 20 ml of 0.1N HCl incubated at 37±0.5°C. These tablets were removed at regular time interval of 1h, removed excess solvent using tissue paper, and weighed on analytical balance. SI was calculated using below formula,

SI=Weight of tablet at interval−Initial weight of tablet/Initial weight of tablet × 100

In vitro dissolution study

Dissolution study of TMZ layer tablets were carried out using USP type II dissolution tester (Electrolab TDT-08L) with paddle speed of 50 rpm, 900 mL of 0.1 N HCl as dissolution medium. Aliquot of 5 mL withdrawn at specified time intervals and replaced with equal volume of fresh dissolution medium kept at 37±0.5°C to maintain sink condition. And samples were analyzed by UV-Visible spectrophotometer (Jasco V-630). Then, percentage drug release calculated and plotted the graph of % drug release versus time.

Mucoadhesive strength

Modified lab scale mucoadhesive test apparatus portrayed in Fig. 1. It was used for the measurement of mucoadhesive strength. In this test, gut mucosa procured from local slaughter cut into circular pieces washed with distilled water and then using 0.1N HCl. One mucosal tissue piece kept in between two discs, which holds tissue at its place in a beaker containing 0.1N HCl as solvent maintained at 37°C to mimic stomach condition. Two sides of weighing balance kept at equal state. Right pan of balance attached to probe which was attached to mucoadhesive tablet by adhesive material. Empty beaker was kept on the left side of the pan, in which water was added in drop wise manner until tablet detaches from mucosal tissue. Mass of water drops required to detach the mucoadhesive tablet from gut mucosal tissue was noted and mucosal strength (Force of detachment) was calculated using below mentioned formula,

$$F=M\times G/A,$$

Where, M=Mass of water added into beaker
G=Acceleration due to gravity (980 cm/s^2)
A=Area of tissue exposed ($A=\pi r^2$)

Determination of Kinetics

Data obtained from dissolution study were fitted into different drug release kinetics model such as zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas model. Mechanism of drug release from matrix tablets was determined based on regression

Table 3: Composition of bilayer tablet blends

Serial number	Composition of mucoadhesive bilayer tablets					% w/w
	TMZ layer (TM-3)	mg/tablet	% w/w	IBH layer (IBH-2)	mg/tablet or % w/w	
1	TMZ	35.0	15.22	Ivabradine HCl	5.00	3.34
2	Steric acid	3.5	1.52	Avicel PH 112	134	89.35
3	Benecel K200 M	77.5	33.70	Cabosil	1.5	1.0
4	Kollidon SR	60	26.08	Vivasol	4	2.66
5	Xanthan Gum	50.0	21.74	Klucel ultra pharm	3	2.0
6	Colloidal Silicon dioxide	2.5	1.09	FD and C Yellow 5	1	0.66
	Lubrication					
7	Stearic acid	1.5	0.65	Magnesium Stearate	1.5	0.99
		230	100		150.00	100
Weight of bilayer tablet (mg)		380				

Table 3 portrayed composition of bilayer tablets with TMZ mucoadhesive layer and IBH immediate release layer. %: Percentage, w/weight by weight, FD&C: Food, Drug and cosmetic

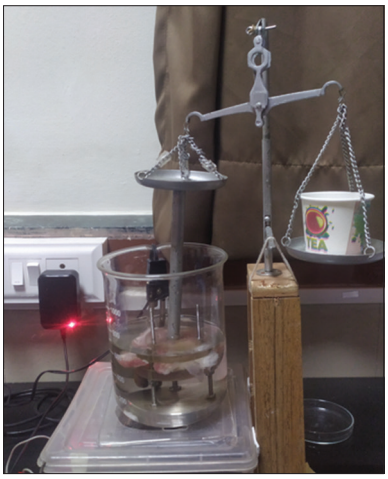

Fig. 1: Modified lab scale mucoadhesive test apparatus [37]

values R^2. Zero-order model relates to release rate is independent of concentration of API, first-order model relates to release rate is dependent on concentration of API, Higuchi model relates to diffusion mechanism, and Hixson-Crowell model relates to erosion mechanism while Korsmeyer-Peppas model relates diffusion mechanism [38].

Stability study of bilayer tablets

Stability study was conducted as per ICH (International Council for Harmonization) guidelines. Bilayer tablets with TM-3 and IBH-1 layer kept at 40°C±2 and 75±5% RH in HDPE (High density polyethylene) bottles till 6 months time. Sample withdrawn at specified time intervals, that is, 1, 2, 3, and 6 months to check appearance, weight, thickness, diameter, hardness, friability, mucoadhesive strength, and *in vitro* drug release.

In vivo gastroretentive study

Animal study protocol was approved by Institutional Animal Ethics Committee, Committee for the Control and Supervision of Experiments on Animals (CCSEA) Reg. No. 2030/PO/RcBiBt/S/18/CCSEA with Proposal no. CRY/2425/200. *In vivo* study of TMZ tablets of TM-3 batch containing combination of Kollidon SR, Benecel K200M, and xanthan gum polymers was performed on New Zealand White rabbits (2–2.5 Kg body weight) by X-ray imaging method. Tablets of 5.0 mm diameter containing 18% barium sulfate were selected for study and given to rabbit. Before that animals were kept for acclimatization for 7 days. And radiograph captured just before administration of tablet to ensure absence of radio-opaque material inside stomach. Radiograph image taken by keeping constant distance between animal and X-ray source for all images. X-ray imaging study was carried out for 24 h to study *in vivo* retention time [13,38,39].

RESULT AND DISCUSSION

FTIR

FTIR spectra of pure drug, combination of IBH and TMZ showed in Fig. 2. Only excipients and mixture of drug and excipients depicted characteristic peaks of major functional groups represented in Table 4. Hence, it was confirmed that both the drug were in pure form, no interactions hence compatible with each other.

DSC

DSC thermogram of IBH, TMZ, combination of both, and drug-excipient mixture showed sharp endothermic peak at 239.15°C and 194.87°C for TMZ and IBH, respectively, (Fig. 3) in melting range; therefore, it indicates no interaction, decomposition, and compatibility with each other.

Fig. 3 demonstrated DSC (A-C) thermogram of both API individually and in combination while D and E showed overlay thermogram of API with excipients.

Visual appearance of API

Both IBH and TMZ were white crystalline powders when observe in well-illuminated place.

Melting point

Melting point of IBH was found to be 194.3±1.5°C and TMZ was 233.6±1.5°C. Reported range of melting point of IBH and TMZ was 191–196°C and 231–235°C, respectively. Hence, observed melting point both the API was in good agreement with the reported values that indicate the identity and purity.

UV spectroscopy

Absorbance spectrum of IBH and TMZ displayed maximum absorbance (λ-max) at 287 nm and 232 nm in 0.1N HCl, as showed in Fig. 4. This also confirmed the API identity and purity.

Flow properties of IBH and TMZ blends

Flow properties of blends displayed in Table 5. Due to Benecel, K200 M TMZ layer blend exhibited poor to very poor flow and it was improved in combination of Kollidon SR. All the trials of IBH IR layer displayed passable flow.

Post compression evaluation

Post compression parameters such as weight, thickness, diameter, and hardness of individual layer measured and presented in below Table 6.

Stability study results of bilayer tablets

Evaluation and stability study results of bilayer tablets for physical parameters, mucoadhesive strength, and dissolution time presented in Table 7.

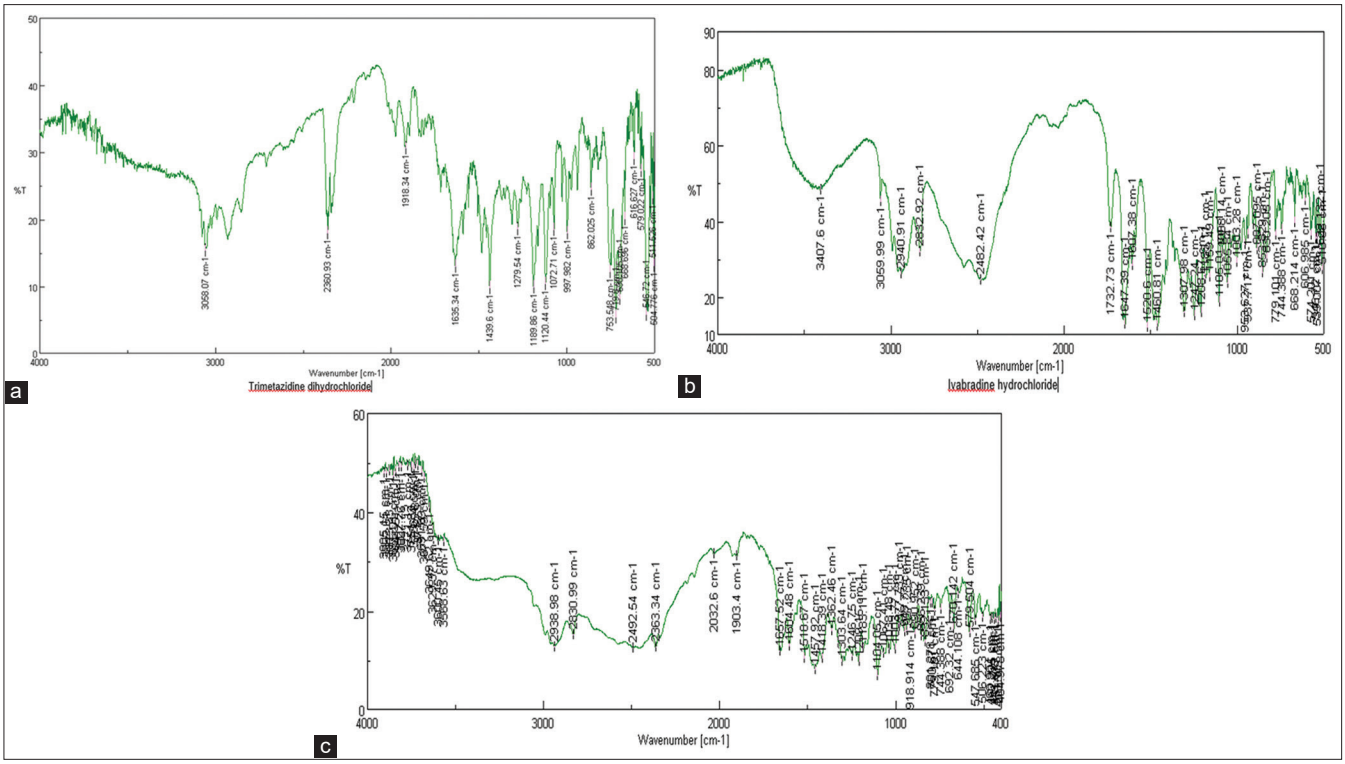

Fig. 2: (a-c) Fourier-transform infrared spectroscopy spectra of trimetazidine dihydrochloride, Ivabradine hydrochloride and combination of both

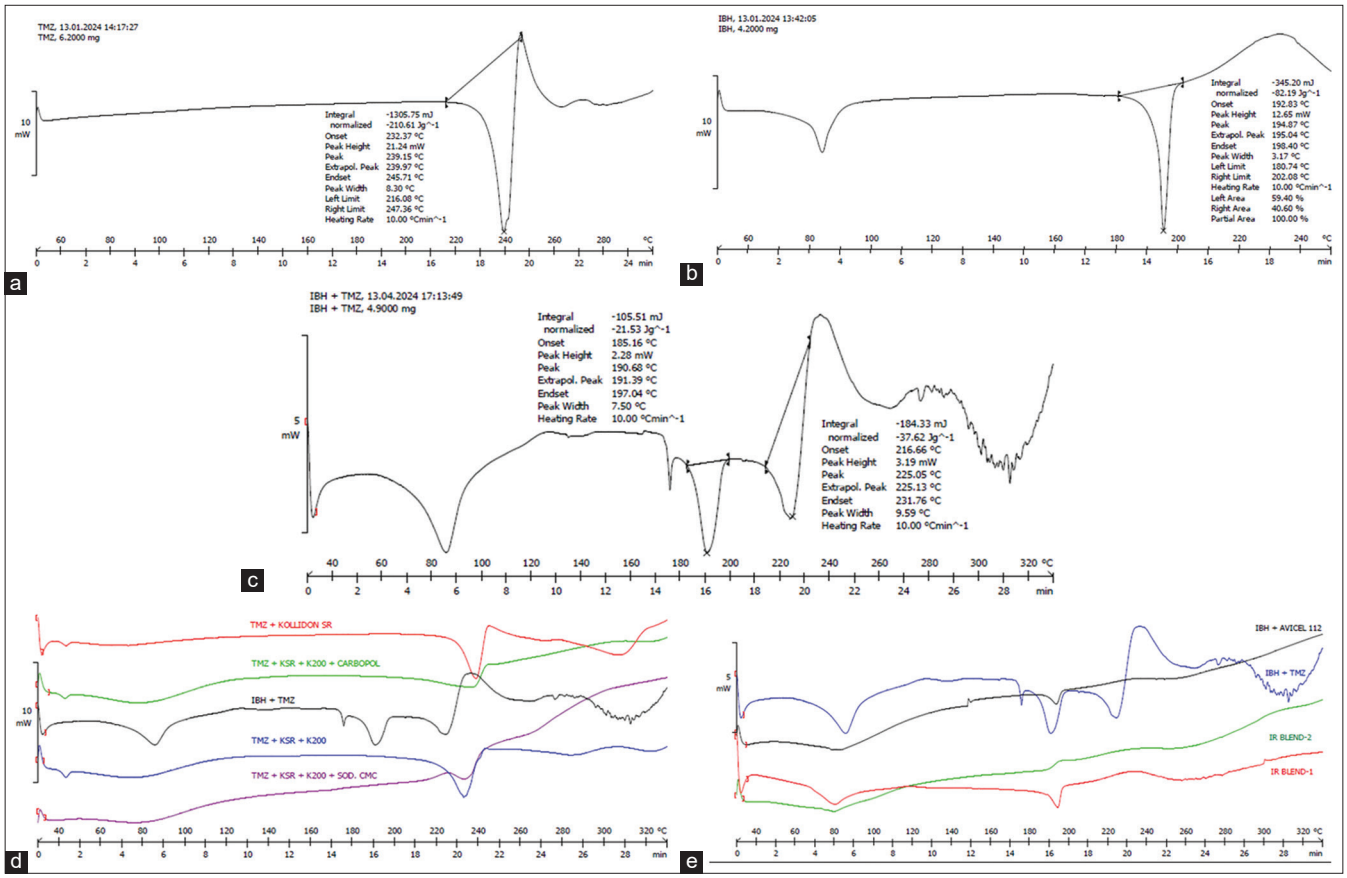

Fig. 3: Differential scanning calorimetry thermogram of (a) TMZ, (b) IBH, (c) IBH+TMZ, (d) TMZ+mucoadhesive polymers, and (e) IBH+IR excipients. TMZ: Trimetazidine dihydrochloride, IBH: Ivabradine hydrochloride

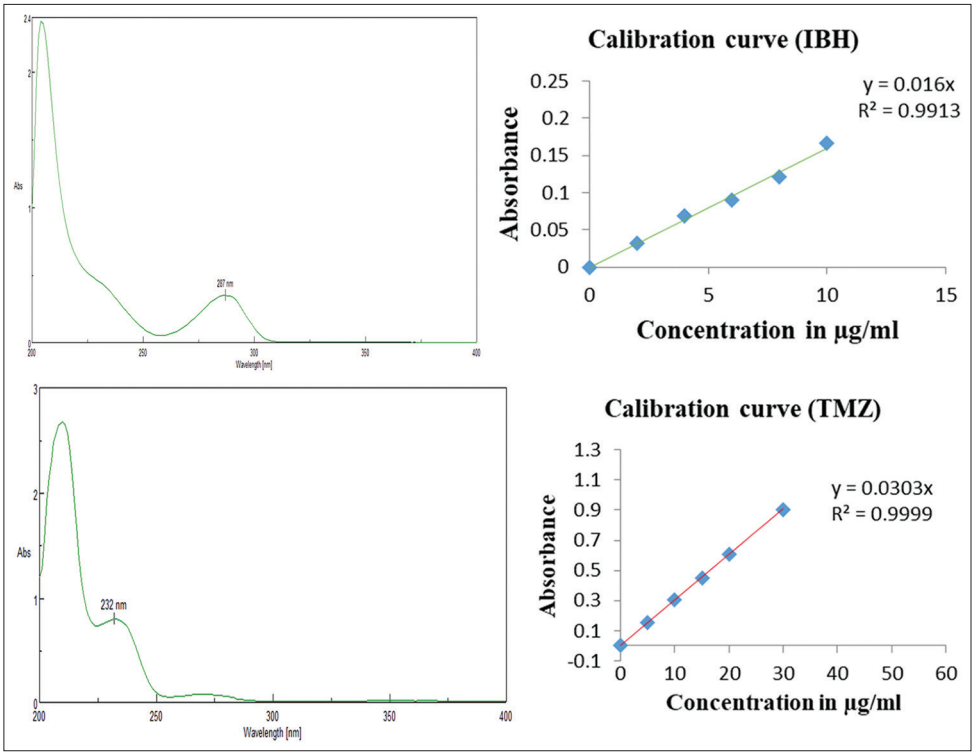

Fig. 4: Ultraviolet spectroscopy: λ-max and calibration curve of ivabradine hydrochloride and trimetazidine dihydrochloride in 0.1N HCl. µg/mL: microgram per milliliter, λ-max: Maximum absorbance

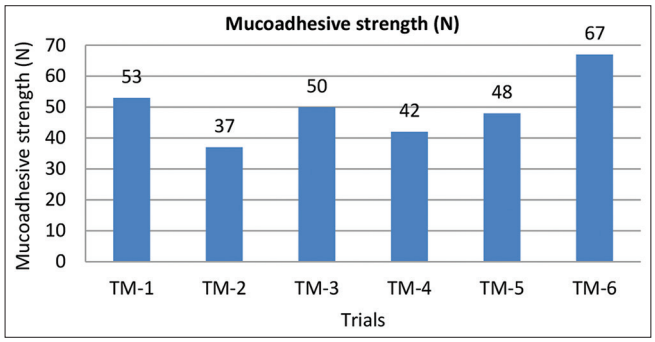

Fig. 5: Mucoadhesive strength of trimetazidine dihydrochloride layer

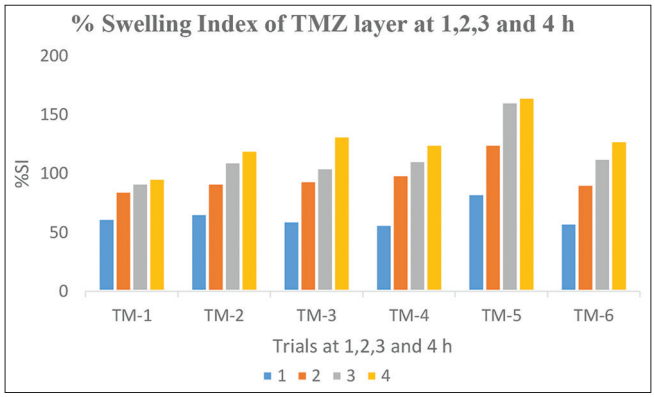

Fig. 6: % swelling index of trimetazidine dihydrochloride layer tablets

Mucoadhesive strength

Mucoadhesive strength of TMZ layers trials depicted in below Fig. 5. TM-6 resulted in highest mucoadhesive strength 67N as it contains

Table 4: Interpretation of Fourier-transform infrared spectroscopy spectra of both active pharmaceutical ingredient

Serial number	Ivabradine hydrochloride		Trimetazidine dihydrochloride	
	Functional group	Wavenumber (cm^{-1})	Functional group	Wavenumber (cm^{-1})
1	O-CH3	1105.01	C=N Stretching	1635.34
2	C=O	1647.49	C-O Stretching	1072.71
3	C-H Stretching	2940.91	-C=C aromatic stretching	1500.00
4	C-N Stretching	1307.98		
5	C=C Stretching	1520.60		

Carbopol-974P with Benecel K200M, then TM-1 (53N) in which Benecel K15 M with guar used as polymer and TM-3 showed 50 N as it contains xanthan gum and Benecel K200 M.

SI of TMZ layer tablets (% SI)

% SI of all mucoadhesive layer tablets is presented in below Fig. 6.

In vitro dissolution

% TMZ release from all mucoadhesive layer tablets is presented in Fig. 7. All the trials released drug in extended pattern without burst effect.

In vitro drug release kinetics

Drug release kinetics were calculated from *in vitro* release data and portrayed in Table 8.

All the models such as zero order, first order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell applied to all TMZ trials. R^2 value of

Table 5: Flow properties of IBH and TMZ blends

Parameters trial number	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
TMZ Mucoadhesive layer blend					
TM-1	0.361±0.00	0.519±0.00	30.408±0.35	1.437±0.01	Poor
TM-2	0.331±0.00	0.509±0.00	35.027±0.71	1.539±0.02	Very poor
TM-3	0.344±0.00	0.483±0.00	28.753±0.71	1.404±0.01	Poor
TM-4	0.350±0.00	0.531±0.01	34.209±1.00	1.520±0.02	Very poor
TM-5	0.360±0.01	0.517±0.01	30.408±0.35	1.437±0.01	Poor
TM-6	0.267±0.01	0.500±0.02	46.531±1.16	1.871±0.04	Very very Poor
IBH immediate release layer blend					
IBH-1	0.382±0.00	0.505±0.01	24.491±0.22	1.324±0.00	Passable
IBH-2	0.384±0.00	0.506±0.01	24.230±1.02	1.320±0.02	Passable
IBH-3	0.374±0.00	0.494±0.00	24.499±0.78	1.325±0.01	Passable

Table 5 showed blend analysis results for both TMZ and IBH layer trials. g/mL: gram per milliliter, SD: standard deviation, IBH: Ivabradine hydrochloride, TMZ: Trimetazidine dihydrochloride. All the values in table expressed as mean±standard deviation based on triplicate measurements

Table 6: Post compression parameters of individual layers

Parameters trialnumber	Weight±SD (mg) (n=10	Thickness±SD (mm) (n=10)	Diameter±SD (mm) (n=10)	Hardness±SD (kg/cm^2) (n=5)
TMZ mucoadhesive layer tablets				
TM-1	229.7±0.95	3.83±0.02	10.02±0.01	8.4±0.5
TM-2	228.9±1.20	3.81±0.02	10.02±0.01	8.5±0.3
TM-3	228.9±2.13	3.82±0.02	10.02±0.01	8.4±0.1
TM-4	229.4±1.43	3.76±0.02	10.02±0.01	8.9±0.2
TM-5	229.9±1.45	3.75±0.02	10.03±0.01	9.2±0.1
TM-6	230.8±1.99	3.67±0.01	10.03±0.01	9.8±0.4
IBH immediate release layer tablets				
IBH-1	149.4±0.97	2.91±0.02	10.01±0.01	4.8±0.1
IBH-2	149.0±0.94	2.90±0.02	10.02±0.01	4.5±0.3
IBH-3	149.2±1.03	2.91±0.02	10.01±0.01	4.8±0.1

Table 6 represented results of post compression parameters. mm: millimeter, kg/cm^2: kilogram per centimeter square, SD: standard deviation, IBH: Ivabradine hydrochloride, TMZ: Trimetazidine dihydrochloride. All the values in table expressed as mean±standard deviation

Table 7: Result of stability study at 40°C–75% RH for 6 months

Parameters	Stability study results at 40°C–75% RH for 6 months			
Stability study (time points in months)	**Initial**	**1**	**3**	**6**
Appearance	Uncoated bilayer tablets with two distinct layers, circular in shape, yellow immediate release layer and white to off white mucoadhesive layer			
Weight (mg)	376.9±1.44	382.3±1.16	385.1±1.1	385.1±1.1
Thickness (mm)	5.21±0.03	5.24±0.02	5.23±0.02	5.30±0.02
Diameter (mm)	10.02±0.01	10.03±0.01	10.03±0.01	10.06±0.02
Hardness (kg/cm^2)	14.5±0.72	13.7±0.60	13.2±0.6	13.2±0.6
Friability (%)	0.31±0.06	Not done		
DT (s)	4±1	5±1	5±1	5±1
Mucoadhesive strength (N)	51.15±1.42	52.09±0.33	52.96±3.16	53.46±1.95
Dissolution time	Immediate layer released 100% drug within 5 min while mucoadhesive layer controlled the drug release up to 12 h in all time points of stability study			

Table 7 portrayed stability study results of bilayer tablets for 6 months at 40–75 temperature and RH condition. N: Newton, RH: Relative humidity. All the values in table expressed as mean±standard deviation

TM-1 and TM-3 showed best fit for Korsmeyer-Peppas model while Higuchi model fits well for Trial-2, 4, 5, and 6. R^2 value of TM-3 trial fitted to Korsmeyer-Peppas model; therefore, n (release exponent) was determined. Moreover, it was 0.475 that confirmed drug release followed Fickian diffusion and tablet released the drug mainly by diffusion mechanism rather than polymer erosion.

Table 8: *In vitro* drug release kinetics of TMZ trials

Drug release kinetics/model	TM-1	TM-2	TM-3	TM-4	TM-5	TM-6
Zero order	0.909	0.902	0.915	0.921	0.944	0.957
First order	0.984	0.828	0.897	0.911	0.864	0.757
Higuchi	0.996	0.994	0.997	0.996	0.998	0.990
Korsmeyer-Peppas	0.998	0.990	0.998	0.993	0.994	0.979
Hixson-Crowell	0.317	0.578	0.586	0.586	0.615	0.627

Table 8 indicates drug release kinetics for TMZ mucoadhesive trials. TMZ: Trimetazidine dihydrochloride

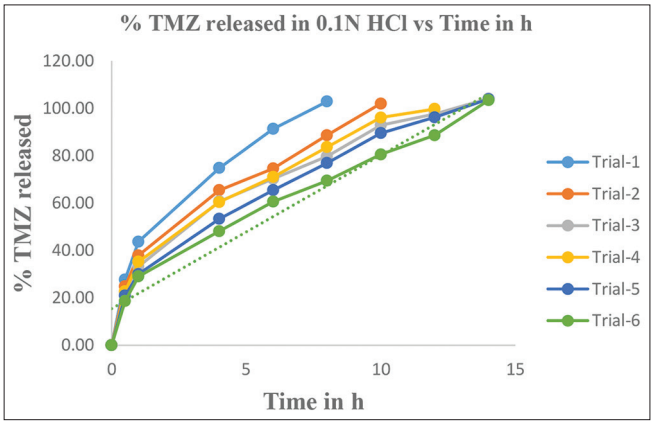

Fig. 7: Dissolution study of trimetazidine dihydrochloride in 0.1 N HCl

In vivo study by X-ray imaging

Images taken after administration of mucoadhesive tablets in X-ray imaging study for 24 h, revealed that mucoadhesive tablets of trial-3

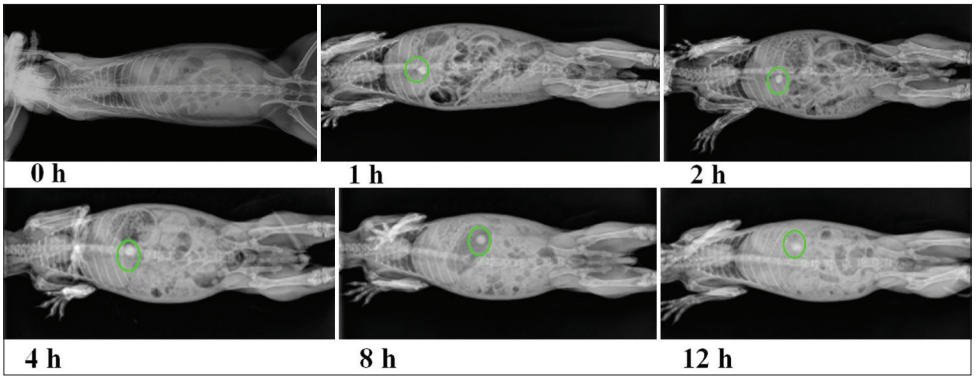

Fig. 8: X-ray imaging study of trimetazidine dihydrochloride mucoadhesive layer at 0, 1, 2, 4, 8, and 12 h in New Zealand white rabbits.

retained in stomach of New Zealand white rabbit for more than 12 h. Fig. 8. displayed the X-ray images at 0, 1, 2, 4, 8, and 12 h.

DISCUSSION

Results of DSC, IR, UV spectroscopy, and melting point of both the API confirmed the purity, identity, and compatibility between drug-drug and drug excipient. Bilayer mucoadhesive tablet consisting IBH in IR layer and TMZ in sustained release layer successfully compressed using simple direct compression method. Flow properties of tablet blends checked, wherein Trial TM-3 showed comparatively good (Poor) flow among all the trials whereas all IBH IR layer trials showed passable flow. Considering the results of flow, mucoadhesive strength, dissolution study, and % SI of TM-3 and IBH-2 trial based on DT were selected for further bilayer compression. Compressed bilayer tablets were evaluated for physical properties, DT of IR IBH layer, dissolution study, mucoadhesive strength of TMZ layer, and % SI. Combination of Benecel K200M with xanthan gum demonstrated good mucoadhesion, flow, % SI, and extended drug release compare to other polymers. Carbopol (in TM-6 trial) controlled the drug release; however, due to moisture sensitivity, it affected flow properties and may impact stability of tablets. *In vivo* study in New Zealand white rabbit by X-ray imaging confirmed the gastric retention of TMZ mucoadhesive tablet was more than 12 h.

CONCLUSION

From the obtained results, it can be concluded that bilayer mucoadhesive tablets of TMZ and IBH successfully prepared using simple, cost-effective direct compression method. Mucoadhesive trial of TMZ containing combination of Kollidon SR, Benecel K200M, and xanthan gum showed best result with respect to flow properties, mucoadhesive strength, and drug retardation without burst release. Kollidon SR contributed for improvement of flow as well as sustained drug release. Benecel K200M formed matrix and also contributes in bio adhesion. In IBH layer, Vivasol (crosscarmellose) showed faster disintegration which resulted quick drug release while Avicel-112 as diluent that imparted good compressibility and passable flow properties. *In vivo* study confirmed the gastric retention of TMZ mucoadhesive layer. This combination in bilayer tablet would improve the effectiveness by reducing the dosing frequency and enhancing the patient compliance in angina.

This *in vivo* study would support in further optimization by design of experiment that could improve the gastric retention and extend the release of TMZ. This composition may be suitable for other combination therapy depending on the properties of active, patient condition, and dose.

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AUTHORS' CONTRIBUTIONS

Author SJ contributed in investigation, writing, methodology, and collection of data while AP contributed in conceptualization, review, editing, and supervision. All authors reviewed the data and approved the draft copy for submission.

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CONFLICTS OF INTEREST

All authors declare that they have no financial interest or relationship that influence the work presented in this research paper.

REFERENCES

1. Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 2019;11(3):129.doi:10.3390/pharmaceutics11030129, PMID 30893852
2. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. Front Pharmacol. 2021;12:618411. doi: 10.3389/fphar.2021.618411, PMID 33679401
3. Iglesias N, Galbis E, Romero-Azogil L, Benito E, Lucas R, Garc MG. In-depth study into polymeric materials in low-density gastroretentive formulations. Pharmaceutics. 2020;12(7):636. doi: 10.3390/pharmaceutics12070636
4. Raza A, Bukhari NI, Karim S, Hafiz MA, Hayat U. Floating tablets of minocycline hydrochloride: Formulation, *in-vitro* evaluation and optimization. Future J Pharm Sci. 2017;3(2):131-9. doi: 10.1016/j.fjps.2017.05.001
5. Gande S, Yamsani MR. Formulation and evaluation of floating gastroretentive drug delivery system of diltiazem hydrochloride. Int J Pharm Bio Sci. 2013;4(2):538-48.
6. Vrettos N, Roberts CJ. Gastroretentive technologies in tandem with controlled-release strategies: A potent answer to oral drug bioavailability and patient compliance implications. Pharmaceutics. 2021;13:1591. doi: 10.3390/pharmaceutics13101591
7. Nigusse B, Gebre-Mariam T, Belete A. Design, development and optimization of sustained release floating, bioadhesive and swellable matrix tablet of ranitidine hydrochloride. PLoS One. 2021;16(6):e0253391. doi:10.1371/journal.pone.0253391, PMID 34170952
8. Naseem F, Shah SU, Rashid SA, Farid A, Almehmadi M, Alghamdi S. Metronidazole based floating bioadhesive drug delivery system for potential eradication of *H. pylori*: Preparation and *in vitro* characterization. Polymers (Basel). 2022;14(3):519. doi: 10.3390/polym14030519, PMID 35160508
9. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their *in vivo* success: A recent update. Asian J Pharm Sci. 2016;11(5):575-84. doi: 10.1016/j.ajps.2016.04.007
10. Vinchurkar K, Sainy J, Khan MA, Mane S, Mishra DK, Dixit P. Features and facts of a gastroretentive drug delivery system-a review. Turk J Pharm Sci. 2022;19(4):476-87. doi: 10.4274/tjps.galenos.2021.44959, PMID 36047602
11. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019;11(4):193. doi: 10.3390/pharmaceutics11040193,

PMID 31010054
12. Vantimitta SR. Novel approaches of gastro retentive drug delivery system: A review. Int J Health Sci (Qassim). 2022;6:3464-76. doi: 10.53730/ijhs.v6nS1.5549
13. Patil S, Talele GS. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. Drug Deliv. 2015;22(3):312-9. doi: 10.3109/10717544.2013.877099, PMID 24471787
14. Chatterjee B, Amalina N, Sengupta P, Mandal UK. Mucoadhesive polymers and their mode of action: A recent update. J App Pharm Sci. 2017;7(5):195-203. doi: 10.7324/JAPS.2017.70533
15. Bakhrushina E, Anurova M, Demina N, Kashperko A, Rastopchina O, Bardakov A, *et al*. Comparative study of the mucoadhesive properties of polymers for pharmaceutical use. Open Access Maced J Med Sci. 2020;8(A):639-45. doi: 10.3889/oamjms.2020.4930
16. Hossain MS, Banik S, Moghal MM, Bhatta R. Swelling and mucoadhesive behavior with drug release characteristics of gastoretentive drug delivery system based on a combination of natural gum and semi-synthetic polymers. Marmara Pharm J. 2018;22(2):286-98. doi: 10.12991/mpj.2018.66
17. Ford TJ, Berry C. Angina: Contemporary diagnosis and management. Heart. 2020;106(5):387-98. doi: 10.1136/heartjnl-2018-314661, PMID 32054665
18. Rousan TA, Thadani U. Stable angina medical therapy management guidelines: A critical review of guidelines from the European Society of Cardiology and National Institute for health and care excellence. Eur Cardiol. 2019;14(1):18-22. doi: 10.15420/ecr.2018.26.1, PMID 31131033
19. Tarkin JM, Kaski JC. Trimetazidine: Is there a role beyond angina? Eur Heart J Cardiovasc Pharmacother. 2018;4(2):67-8. doi: 10.1093/ehjcvp/pvx029, PMID 29554292
20. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, *et al*. Expert consensus document: A "diamond" approach to personalized treatment of angina. Nat Rev Cardiol. 2018;15(2):120-32. doi: 10.1038/nrcardio.2017.131, PMID 28880025
21. Pavasini R, Camici PG, Crea F, Danchin N, Fox K, Manolis AJ, *et al*. Anti-anginal drugs: Systematic review and clinical implications. Int J Cardiol. 2019;283:55-63. doi: 10.1016/j.ijcard.2018.12.008, PMID 30538056
22. Ferrari R, Pavasini R, Camici PG, Crea F, Danchin N, Pinto F, *et al*. Anti-anginal drugs-beliefs and evidence: Systematic review covering 50 years of medical treatment. Eur Heart J. 2019;40(2):190-4. doi: 10.1093/eurheartj/ehy504, PMID 30165445
23. Ferrari R, Censi S, Squeri A. Treating angina. Eur Heart J Suppl. 2019;21(Suppl G):G1-3. doi: 10.1093/eurheartj/suz190, PMID 31736659
24. Balla C, Pavasini R, Ferrari R. Treatment of angina: Where are we? Cardiology. Cardiology. 2018;140(1):52-67. doi: 10.1159/000487936, PMID 29874661
25. Sankaraiah J, Sharma N, Naim MJ. Formulation and evaluation of fixed-dose combination of bilayer tablets of atazanavir sulfate and ritonavir 300 Mg/100 Mg. Int J Appl Pharm. 2021;13(5):60-72. doi: 10.22159/ijap.2021v13i5.41860
26. Ramoleta T, Schellack N, Bronkhorst E. An overview of ivabradine. S Afr Fam Pract. 2016;58(6):36-9. doi: 10.4102/safp.v58i6.4572
27. Giavarini A, De Silva R. The role of ivabradine in the management of angina pectoris. Cardiovasc Drugs Ther. 2016;30(4):407-17. doi: 10.1007/s10557-016-6678-x, PMID 27475447
28. Sathyamurthy I, Newale S. Ivabradine: Evidence and current role in cardiovascular diseases and other emerging indications. Indian Heart J. 2018;70(Suppl 3):S435-41. doi: 10.1016/j.ihj.2018.08.008, PMID 30595304
29. Liang M, Puri A., Devlin G. Heart rate and cardiovascular disease: An alternative to beta blockers. Cardiol Res Pract. 2009;2009:179350. doi: 10.4061/2009/179350
30. Harahap Y, Lusthom W, Prasaja MM, Hardiyanti, Azmi F, Felicia V, *et al*. Bioequivalence of trimetazidine modified release tablet formulations assessed in Indonesian subjects. J Bioequiv Availab. 2013;5(3):117-20. doi: 10.4172/jbb.1000144
31. Ajabnoor A, Mukhtar A. Effect of trimetazidine on the functional capacity of ischemic heart disease patients not suitable for revascularization: Metaanalysis of randomized controlled trials. PLoS One. 2022;17(2):e0263932. doi: 10.1371/journal.pone.0263932, PMID 35148340
32. Srinivas K, Sambhaji J, Manjeeta G, Sofi J. Trimetazidine 80 mg once daily: A novel formulation developed with multi-layer microgranular technology (MLMT) and its clinical benefits. Int J Pharm Res Appl. 2021;6(4):11-6. doi: 10.35629/7781-06041116
33. Chappidi SR, Bhargav E, Marikunte V, Chinthaginjala H, Vijaya Jyothi M, Pisay M, *et al.* A cost effective (QbD) approach in the development and optimization of rosiglitazone maleate mucoadhesive extended release tablets - *in vitro* and *ex vivo*. Adv Pharm Bull. 2019;9(2):281-8. doi: 10.15171/apb.2019.032, PMID 31380254
34. Momin MM, Kane S, Abhang P. Formulation and evaluation of bilayer tablet for bimodal release of venlafaxine hydrochloride. Front Pharmacol. 2015;6:144. doi: 10.3389/fphar.2015.00144, PMID 26217229
35. Aleti R, Baratam SR, Jagirapu B, Kudamala S. Formulation and evaluation of metformin hydrochloride and gliclazide sustained release bilayer tablets: A combination therapy in management of diabetes. Int J Appl Pharm. 2021;13(5):343-50. doi: 10.22159/ijap.2021v13i5.41339
36. Saikia R, Sahu BP. Development and evaluation of bilayer tablets for immediate and controlled release of metformin hydrochloride. Int J Curr Pharm Res. 2017;9(5):173-9. doi: 10.22159/ijcpr.2017v9i5.22182
37. More A, Mahangade A. Modified Mucoadhesive Test Apparatus. Indian Design Patent Application no: 379351-001; 2024
38. Rajeswari S, Kudamala S, Murthy KV. Development, formulation and evaluation of a bilayer gastric retentive floating tablets of ranitidine HCl and clarithromycin using natural polymers. Int J Pharm Pharm Sci. 2017;9(9):164-77. doi: 10.22159/ijpps.2017v9i9.20290
39. Sankar R, Jain SK. Development and characterization of gastroretentive sustained-release formulation by combination of swelling and mucoadhesive approach: A mechanistic study. Drug Des Dev Ther. 2013;7:1455-69. doi: 10.2147/DDDT.S52890, PMID 24348022