DESIGN, FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILMS OF ANTI-HYPERTENSIVE DRUG

Medisetty Gayatri Devi, Dr.R.Santosh Kumar*
GITAM Institute of Pharmacy, GITAM Deemed to be University
Vishakhapatnam, Andhrapradesh-530045
***Corresponding Authors:Dr.R.Santosh Kumar**
drsantoshrada@gmail.com

Abstract

The objective of present study was to develop fast dissolving oral films of Anti-Hypertensive drug Ranolazine using solvent casting technique. A response surface methodology experimental design was applied for the optimization of fast dissolving film using Box-Behnken experimental design. The concentration of X1 (mango kernel, 100–400 mg), X2 (MDX 0–100 mg), and X3 (PG, 15–30%) were preferred as independent factors. Y1 (Tensile Strength; MPa), Y2 (Disintegration Time; Sec), Y3 (Folding Endurance; Folds), Y4 (Elongation; %), and Y5 (% drug release; min) were considered as dependent variables. Various physico-chemical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption parameters like mucoadhesive strength were evaluated. Results revealed that prepared films showed good physical characteristics, no drug-polymer interaction from FTIR was observed. The in vitro release study revealed that F6 formulation showed maximum release in 20 min. The maximum bio adhesive strength and highest ex-vivo mucoadhesion time of 52.43±0.31 gm and 182 min was observed for F6. In-vitro drug release after 20 min was found out to be 82% for F6 and for marketed tablet and pure drug solution was found to be above 65 to 74% for 6hr. Ex-vivo muco irritation was performed by using a fresh sheep oral mucosa. The Pharmacokinetic plasma parameters results displayed improved absorption of RZ-OFDFs compared to RZ intragastric suspensions in the rats. The optimized formulation was subjected to stability studies which indicated that F6 was stable up to 6 months.

Key words: Ranolazine, Oral fast dissolving films, solvent casting technique, in-vitro drug release, ex vivo mucoadhesion studies, plasma Pharmacokinetic study, stability studies.

Introduction

Oral route of administration is the most accepted route for therapeutic agents because of the low cost and ease of administration lead to high levels of patient compliance. About 60% of all dosage forms are the oral solid forms and the most accepted oral solid dosage forms are

tablets and capsules [1]. The oral drug delivery systems still need some advancement to be made because of some drawbacks related to particular class of patients which includes geriatric, paediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many paediatric and geriatric patients are disinclined to receive solid preparations due to fear of choking dosage forms. One study showed that 26% of patients practiced difficulty in swallowing tablets. The most general complaint was tablet size, followed by surface form and taste [2]. The difficulty of swallowing tablets was more evident in geriatric and paediatric patients, as well as travelling patients who may not have ready access to water.

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastrointestinal tract [3]. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms [4]. These dosage forms possess certain specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance.

Ranolazine is acetanilide and piperazine derivative having anti – ischemic properties. It was approved in the year 2006 by USFDA for the treatment of angina pectoris. It acts by inhibiting sodium channels due to which reduction in the intracellular calcium levels takes place, leading to decrease of tension in heart muscle (myocardium).

Materials

Ranolazine was purchased from Hetero Pvt Ltd. Hyderabad, Mango kernel from Gattefosse India Pvt. Ltd, HPMC E15 from Gattefosse India Pvt. Ltd, HPMC E5 from SD Fine-Chem Limited.

Methods

Preparation of RZ-OFDFs

The solvent casting method (SCM) was applied to prepare RZ-OFDFs. Briefly, the polymeric materials, used at different weight ratios (Mango kernel = 100–400 mg; MDX = 0–100 mg), were dissolved in purified water (5 mL) and mixed for 2 h with a magnetic stirrer (RT 10 P, IKA, Königswinter, Germany) at 2000 rpm to obtain a homogenized solution. Separately, RZ (10 mg) and citric acid (50 mg) were dissolved in distilled water (5 mL) containing different

plasticizer amount (15–30%) under continuous stirring for an additional 1 h at room temperature (RT). This drug-containing solution was added dropwise into the polymeric solution with continuous stirring and made up to a final volume of 10 mL [9]. At the end, when the dispersion was found clear, requisite amounts of aspartame (24.3 mg) and mannitol (24.3 mg) were added in the preparation under mechanical stirring. The obtained transparent and homogenized solution was kept aside for 6 h to remove the entrapped air or bubbles. Finally, the solution was decanted into a 61 cm^2 substrate, followed by drying at RT for 24 h. The resulting films were cautiously cut into 3 × 2 cm2 size, packed in an aluminium sachet, and stored in a desiccator until further assessment.

Experimental Design for RZ-OFDFs

The response surface design (RSD) was employed using three factors and three levels through Design Expert® software (version-10, Stat-Ease, Inc. Minneapolis, MN, USA) [10]. The software presents seventeen experiments for each of the factors being considered. The analysis of variance (ANOVA) table revealed that a polynomial quadratic equation was the most suitable model to represent the data.

$$Y=b0+b1\times1+b2X2+b3X3+\cdots+b12X1X2+b13X1X3+b23X2X3+b123X1X2X3 \quad (1)$$

Equation (1) shows that Y is the selected dependent variables (response); b1, b2, b3, … are the regression coefficients for the factors (independent variables); and X1, X2, X3, … are the coded levels of the associated factors.

The concentration of X1 (mango karnel, 100–400 mg), X2 (MDX 0–100 mg), and X3 (PG, 15–30%) were preferred as independent factors. Y1 (Tensile Strength; MPa), Y2 (Disintegration Time; Sec), Y3 (Folding Endurance; Folds), Y4 (Elongation; %), and Y5 (% drug release T5; min) were considered dependent variables (Table 1). The independent and dependent variables were statistically analyzed employing Design-Expert software and relating the studied independent variables with the dependent variables at a 95% level of significance. Mathematically created models produced three-dimensional (3-D) response surface plots to forecast the correlations between selected factors and variables. The optimum formulation design space was created to achieve thin and fast disintegrated RZT-ODFs with desirable mechanical properties.

Table 1: Formulation parameters for RZ-OFDFs Full factorial design (BBD)

Parameter	Low (-1)	Medium (0)	High (+1)
Independent Variables			
X1: Mango Kernel (mg)	100	250	400
X2: MDX (mg)	0	50	100

X3:PG (%)	15	22.5	30
Dependent variables			
Y1: Tensile Strength (Mpa)	Minimize		
Y2: Disintegration Time (Sec)	Minimize		
Y3: Folding Endurance (Folds)	Maximize		
Y4: Elongation (%)	Maximize		
Y5: % drug release T5 (min)	Maximize		

Evaluation of OFDFs

Appearance

The general appearance and elegance of film was identified visually, which include shape, colour, presence of an odour, taste, surface texture etc [11].

Weight variation studies

The individual weight of three samples (2x2 cm) of each formulation was determined using an analytical balance. The results were analysed for mean and standard deviation.

Thickness and Diameter

The thickness of 3 films (2x2 cm) of each formulation was measured using Digital thickness measurement apparatus and the results were analysed for mean and standard deviation [12].

Drug Content Uniformity

Briefly, OFDFs (2×2 cm2) were dissolved in 100 mL artificial salivary fluids (pH = 6.8) and homogenized for 15 min using an ultra-sonication bath. The supernatant was collected by centrifugation at 10,000 rpm (10 min), and 20 µL was loaded into the HPLC system. RZ concentrations were determined using a Shimadzu® (model SPD-15c, Shimadzu Corporation, Kyoto, Japan) HPLC system equipped with a Shimadzu® UV detector (u-2600). The following equation calculated the RZT contents in OFDFs [13].

$$\text{RZ contents (\%)} = \frac{Actual\ amount\ of\ Drug}{Theoritical\ amount\ of\ RZ} X100$$

Folding endurance

Folding endurance of 3 films of each batch was determined by repeatedly folding one film at the same place up to 200 times till it broke or folded, which is considered satisfactory to reveal good patch properties [14].

Tensile Strength

The mechanical properties of the film were measured using an Instron testing apparatus (model: UH6430, Beijing, China) and a 50 kg weighted cell. Each sample (2 × 2 cm2) was held vertically between two clamps. The upper clamp tugged the films at 100 mm per min while the lower clamp was stationary. Once the film was broken, the following formulae

were used to estimate the TS and %E of RZ-OFDFs [15]. Each film was measured in triplicate.

$$\textbf{TS (\%)} = \frac{\textit{Load force at failure}}{\textit{strip thickness}} \textit{X strip width}$$

Percent moisture absorption

The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminium chloride up to 86% relative humidity. After 3 days, the films were taken out and weighed [16].

$$\textbf{\% moisture absorption} = \frac{\textit{Final weight} - \textit{intial weight}}{\textit{intial weight}} \textit{X100}$$

Percent moisture loss

The films were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The percentage moisture absorption and moisture loss were calculated using the formula:

$$\textbf{Percent moisture loss} = \frac{\textit{intial weight} - \textit{Final weight}}{\textit{intial weight}} \textit{X100}$$

Surface pH

The film was allowed to swell by keeping it in contact with 5 ml distilled water for one hour at room temperature. The surface pH was measured by placing a pH paper on the surface of the swollen film [17].

Swelling Index

Oral fast dissolving film units were weighed individually (W1) and placed separately on 2% agar gel plates and incubated at 37^0C ± 1^0C. At every 30 mins regular intervals, the films were removed and adhering gel was removed carefully with tissue paper [18]. The weight of the swollen film was W2. Percentage swelling was calculated using the formula.

$$\textbf{S.I} = \frac{W2 - W1}{W1} \textit{X100}$$

Where, S.I = Swelling Index; W2 = Weight of swollen film after time t; W1 = Weight of film before placing in beaker.

Solid state characterization

Fourier Transform Infrared (FTIR) Spectroscopy

The substantial molecular interactions between the drug and film-forming materials were explored through FTIR spectrophotometer (model: Excaliber series UMA-500, Bio-Rad, Hercules, CA, USA) using KBr disk method. The scanning spectra of the samples were achieved in the range of 400–4000 cm^{-1} [19].

Differential Scanning Calorimetry (DSC) Analysis

Thermal analysis of the samples was performed by DSC apparatus (model: SKZ1052C-1L, SKZ industrial Co., Ltd., Jinan, Shandong, China). Samples were accurately weighed and placed in a DSC aluminum pan under a nitrogen atmosphere. The samples were heated from 40 to 250 °C at a heating rate of 20 °C per minute, and the XRD diffraction patterns were recorded [20].

X-ray Diffractometric (XRD) Analysis

The X-ray diffraction pattern of the samples, i.e., pure drug, MDX, mango karnel, and RZ loaded OFDFs, were scanned by Rigaku Mercury instrument (model: CCD, Tokyo, Japan) with Cu K-α line of copper (radiation source operated at 45 kV and 40 mA at of 5 to 50° (2 θ) range to confirm the crystal form or crystal form transformation of the materials used in the formulation of the film. The scan temperature was 25 degrees Celsius, and the time was set at five microseconds per minute [21].

Morphological Characterizations

Scanning Electron Microscopy (SEM)

The outer macroscopic structure of the oral fast dissolving film was investigated by Scanning Electron Microscopy with a S4800 TYPE II scanning electron microscope (Hitachi high technologies, Japan), operating at 15kV [22]. The sample was fixed on a SEM-stub using double-sided adhesive tape and then coated with a thin layer of gold.

Determination in- vitro bio adhesion strength

Mucoadhesive strength was determined by using modified physical balance method, for which goat oral mucosa was collected from local slaughter house and stored in saline solution. The mucosal and film surface was wetted with few drops of 0.01 N HCl and on the left pan film 50 gm weight was placed for 5 min to allow the initial contact of mucoadhesion. Then drop wise water was added in beaker of right pan till the detachment of film from the mucous membrane was observed [23]. Then weight of water present in right pan beaker was determined, using following formula,

Mucoadhesive strength = weight of beaker + weight of water – weight of empty beaker

After determination of mucoadhesive strength, Force of adhesion was calculated using formula,

$$\textbf{Force of Adhesion (N)} = \textbf{(Mucoadhesive Strength)}/1000 \times 9.81$$

Determination of ex-vivo mucoadhesion time

The ex vivo residence time of RZ-OFDFs was evaluated by assessing the time required for these films to detach from goat oral mucosal membrane fixed in a well stirred beaker. The

goat oral mucosa was fixed on the internal side of a beaker with cyanoacrylate glue. The film (2x2cm) was wetted with 50µl of phosphate buffer pH 6.8 and was pasted to the goat oral tissue by applying a light force with fingertip for one minute [24]. The beaker was filled with 250 ml phosphate buffer pH 6.8 and kept at 37± 0.5 °C. After 2 minutes the beaker was magnetically stirred at 50 rpm stirring rate to simulate the oral cavity environment. The time taken for the patch to completely erode or detach from the mucosa was observed as the ex vivo mucoadhesion time.

Disintegration time

In-vitro disintegration time was determined visually in a Petri dish containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrate.

In-vitro drug release studies (Diffusion study)

Franz diffusion cell having 10 mm diameter and 16 ml capacity was used to study in-vitro diffusion of oral fast dissolving film. Dialysis membrane (Himedia) of molecular weight of 12000 – 14000 kDa was used as diffusion membrane. Before experiment, pieces of dialysis membrane were soaked in phosphate buffer (PB) pH 6 for 24 hrs [25]. After 20 minutes of pre-incubation time, 10 mg of oral fast dissolving film was placed in the donor chamber. Then for next 4 hours, samples were periodically withdrawn from the receptor compartment with simultaneous replacement of same amount of fresh phosphate buffer solution. The withdrawn solutions were further assayed at 257 nm by a spectrophotometer.

Ex-vivo permeation studies

The formulated film of 2×2cm diameter was cut and placed over the goat oral mucosa membrane [26]. The donor compartment was then placed and the whole assembly was placed on a magnetic stirrer, and the solution in the receptor compartment was continuously stirred. The temperature was maintained at 37 ± 2ºC. Samples of 1 ml were withdrawn at time different time intervals up to 5 hours and were analysed at 272 nm spectrophotometrically for drug content against blank. The receptor phase was replenished with an equal volume of phosphate buffer each time the sample was withdrawn. The percentage of the released drug was calculated.

Ex-vivo muco irritation by histological examination

Ex-vivo muco irritation of optimized oral fast dissolving films was performed by using a fresh sheep oral mucosa was purchased from local slaughter house. The epithelial tissues of mucosa were fixed in 10% neutral buffered formalin for 2 h, washed with distilled water up to 1 h and dehydrated with graded ethanol (60%, 80%, 90%, 95% and 100%). Then it is

treated with xylene for permeation and embedded with liquid paraffin. After 8 h the samples were cut in 4 µm thick sections on a microtome with a surgical blade and conveniently coloured with eosin [27]. The photograph of both controlled untreated and RA oral fast dissolving film subjected to simple diffusion in sheep oral mucosa.

In Vivo Pharmacokinetic (PK) Studies

Experimental Animals

Sprague–Dawley (SD) rats (180–220 g) provided by the animal care and use committees of Gitam University (Visakhapatnam, AP) were utilized. (Approval No. IAEC/GU/2023/012)

PK Experimental Design

The rats were kept in stable condition (12 h light/dark cycle at 23 ± 2 °C) with free access to food and water. Overnight fasted rats were divided randomly into two groups, each containing six rats. Before administering optimized OFDFs (F4), 50 µL of DI water was placed into the mouth using a micropipette. The film (1 cm^2) was sliced in half and placed on the tongue of rats (group 1). As a control, RZ marketed tablets equivalent to the dose of the film were crushed and filled in mini capsule shells (size 9). The prepared capsules were fixed in an applicator and intragastrically administered to group 2 animals. All samples were extracted using the liquid-liquid extraction method. Approximately 0.4 mL blood was extracted from retro-orbital plexus in micro-centrifuge heparinized tubes at 10, 30, 60, 90, 180, 360, and 540 min after treatment and instantaneously centrifuged for 20 min at 5000 rpm. The collected plasma (180 µL) was extracted with 1.8 mL dichloromethane to separate plasma proteins and vortex for 2 min [28]. Following centrifugation (10,000 rpm, 10 min), the organic phase was cautiously shifted to a clean micro-tube for dryness by employing a nitrogen evaporator. The collected residues were reconstituted using mobile phase (120 µL) and zolmitriptan (ZMT) (10 µL) of 10 µg·mL−1 as an internal standard. A 20 µL sample was introduced into the HPLC apparatus. HPLC instrument and chromatographic conditions were comparable, modified flow rate of 1.5 mL·min−1 and wavelength of 225 nm were employed for drug analysis in plasma.

Statistical Analysis

The statistical variances among the results were calculated employing Origin Pro and ANOVA. The student t-test was used to statistically assess and compare the PK parameter values between the two groups [30]. When the p-value was less than 0.05 or more than 0.05, the difference between the group means was considered statistically significant or non-significant

Results & Discussion

Optimization of Oral Fat Dissolving Film Composition

A response surface methodology experimental design was applied for the optimization of fast dissolving film using Box-Behnken experimental design, as it requires few runs with three or four variables. Here three variables at three levels were studied using total 17 runs.

Table 2: Box-Behnken design 3^3full factorial for optimization of RZ-OFDFs

Run	X1	X2	X3	Y1	Y2	Y3	Y4	Y5
1	250	0	15	18.39±0.23	10.52±0.59	142.36±5.34	35.26±0.25	65.34±2.31
2	100	0	22.5	1.36±1.25	6.43±3.18	135.28±8.27	47.02±0.34	88.35±0.96
3	250	50	22.5	12.48±0.59	8.32±2.31	102.39±6.31	36.91±1.02	59.82±3.25
4	250	100	15	15.84±0.43	10.57±1.34	90.58±5.29	25.45±6.35	67.13±1.42
5	250	50	22.5	11.59±1.26	8.56±2.01	141.05±9.34	32.15±2.04	68.12±3.67
6	400	100	22.5	4.53±0.94	4.32±1.39	185.34±7.12	58.94±1.32	92.46±0.59
7	100	100	22.5	1.25±0.35	6.28±3.24	156.28±8.34	36.42±5.67	80.31±0.63
8	250	100	30	18.34±0.81	6.35±0.67	196.34±5.16	29.58±2.05	63.24±0.58
9	250	50	22.5	10.98±0.46	11.07±0.59	95.34±4.32	33.85±1.03	62.17±1.27
10	100	50	30	16.02±2.03	12.04±0.43	59.38±5.12	22.15±0.96	53.02±2.03
11	250	0	30	18.34±1.69	7.53±0.67	130.47±6.02	26.59±0.37	62.45±3.04
12	100	50	15	10.52±0.45	8.41±0.28	64.52±9.37	33.01±0.28	86.49±0.13
13	250	50	22.5	12.43±0.21	10.27±0.41	80.59±8.02	28.37±0.48	58.36±2.34
14	250	50	22.5	11.95±0.38	9.95±0.35	79.16±4.13	30.42±0.86	60.32±0.62
15	400	0	22.5	2.25±0.27	5.37±0.18	231.05±8.65	45.94±0.53	88.37±0.53
16	400	50	15	13.86±0.16	12.48±1.26	85.67±10.29	32.16±1.24	73.12±0.37
17	400	50	30	15.72±0.35	3.95±2.04	189.52±9.37	42.51±2.30	89.35±1.24

Influence of independent variables on Tensile strength (TS)

The TS analysis demonstrated that as the proportion of MTX and PG to mango kernel increases, the TS of RZ-OFDFs decreases, as shown in Table 2.

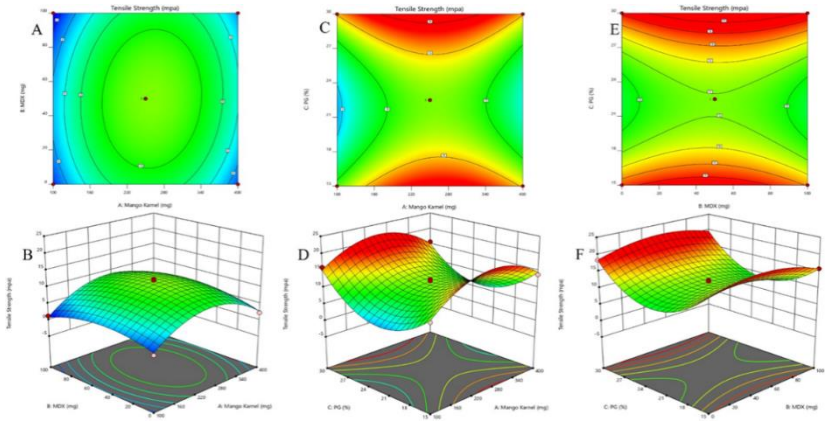

Figure 1: Counter and 3D response surface plots showing the effect of independent variables on tensile strength (Y1).

For instance, RZ-OFDFs plasticized with an equivalent amount of PG, only Mango Kernel-based films (F2, F11, and F15) showed lowest TS and higher % Elongation than the composite formulation of MDX and mango kernel (F4, F8, and F17). This could be attributed to the facile insertion of low MW hydrophilic plasticizer into the polymeric strands, thus preventing the connection between the mango kernel [33]. The TS of RZ-OFDFs improved with increasing mango kernel amounts, as shown by Equation (1), which suggested that mango kernel (X1) amounts positively influenced TS.

Tensile Strength = +11.89 +0.9013A -0.0475B +1.23C +0.5975AB -0.9100AC +0.6375BC -6.62A2 -2.92B2 +8.76C2

Influence of independent variables on in vitro disintegration time

According to Table 2, all formulations were disintegrated in 4.32±1.39 to 12.48±1.26 min; therefore, based on previous researches disintegration times were in the acceptable range [44].

Disintegration Time = +9.63 -0.8800A -0.2912B -1.51C -0.2250AB -3.04AC -0.3075BC -1.78A2 -2.26B2 +1.36C2

As shown in Fig. 2, increasing the concentration of mango kernel and MDX increased disintegration time, but this amount was negligible. Increasing the concentration of mango kernel and MDX increased thickness of each film, thus disintegration time was increased. \This behaviour could be due to the lipid structure of mango kernel powder and PG has lower hydrophilicity than MDX in film formulations.

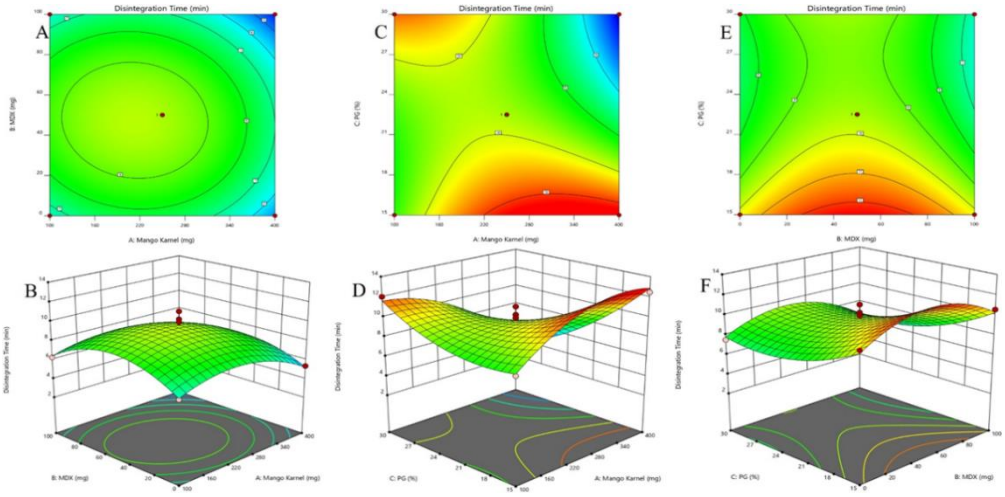

Figure 2: Counter and 3D response surface plots showing the effect of independent variables on disintegration time (min) (Y2).

Influence of independent variables on Folding Endurance

The physical strength of the produced formulations was determined by their FE, which ranged from 59.38±5.12 to 231.05±8.65, respectively. F1 comprised 15% PG showed considerably lower FE compared to F2 (PG 22.5%), F4 (PG 22.5%), or F5 (PG 30%) at fixed proportion of polymeric materials. It is attributed to the electrostatic force amongst the polymers and PG molecules that were not strong enough to overcome the hydrogen bonding interactions due to the low level of PG in RZ-OFDFs [30]. The multiple linear regression for the response FE (Y3) was represented as follows in Equation (3):

Folding Endurance = +99.71 +34.51A -1.33B +24.07C -16.68AB +27.25AC +29.41BC +18.56A2 +58.72B2 -18.49C2

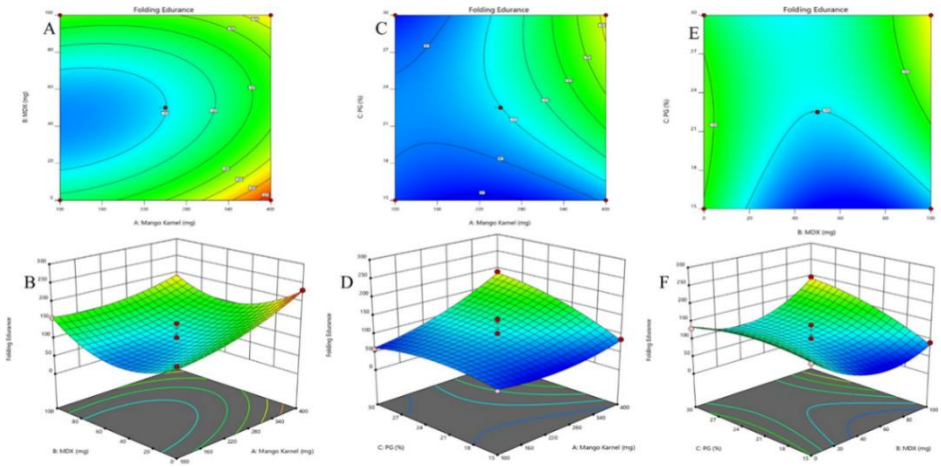

Figure 3: Counter and 3D response surface plots showing the effect of independent variables on Folding endurance (Y3).

Accordingly, it was anticipated that increase in the mango kernel, MDX, concentrations was related to the FE of RZ-OFDFs. Figure 3 displays that at fixed X1 (mango karnel), an increase in PG (%) concentration substantially increased FE of the films. Similarly, at a fixed level of X2, enhancement in both plasticizer and MDX dramatically increased the FE (Figure 3B). When the X3 percentage was maintained constant, the FE substantially increased as the ratio of X1 and X2 increased. Figure 3 showed that the maximum level of PG (30%) to any polymeric material ratio considerably enhanced the FE of RZ-OFDFs.

Influence of independent variables on Elongation (%)

The average %E of RZ-OFDFs ranged from 22.15±0.96 to 58.94±1.32%, as revealed in Table 2. The mango kernel-containing films (F1, F11, and F15) had a lower %E than the composite films of MDX-mango kernel (F6, F9, and F17), as shown in Figure 4. This could be because mango kernel-MDX utilizes a diverse range of bonding mechanisms than MDX alone [32]. The PG amount in film ($p < 0.05$) significantly increased the %E. At the

equivalent polymer amount, film plasticized with 15% PG (F1, F4, and F13) showed a lower %E than that comprised of 30% PG (F3, F5, and F14). This could be due to introducing low MW and highly hydrophilic PG that increased the polymer chain's molecular mobility and, in turn, increased the elasticity and decreased the rigidity of the RZ-OFDFs [33]. Equation (4) describes the multiple linear regression coefficients for the dependent variable %E (Y4).

Elongation = +32.34 +5.12A -0.5525B -0.6313C +5.90AB +5.30AC +3.20BC +8.99A2 +5.75B2 -8.87C2

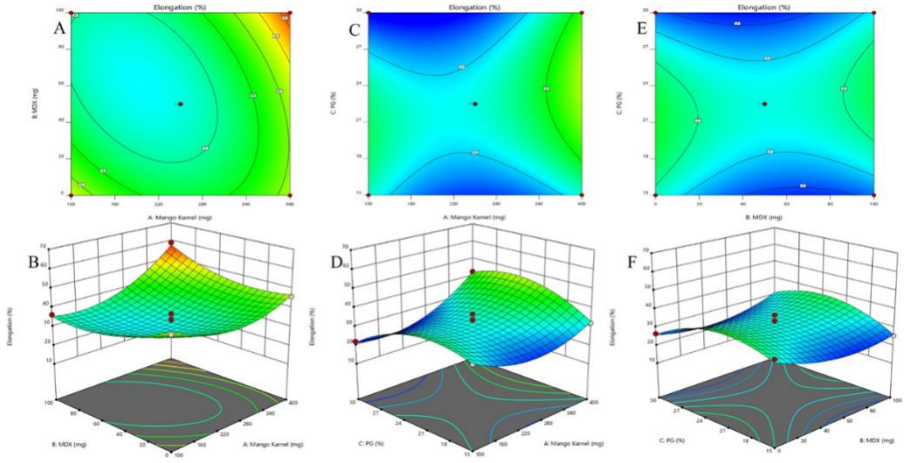

Figure 4: Counter and 3D response surface plots showing the effect of independent variables on Elongation analysis (%) (Y4).

Influence of independent variables on in vitro drug release

According to Table 2, F6 and F17 formulations released maximum amount of RZ (about 100%).

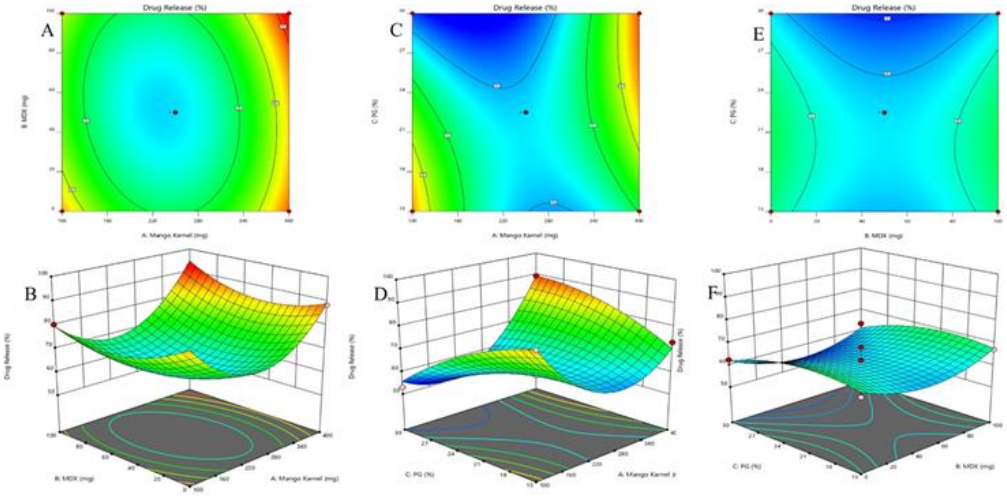

Figure 5: Counter and 3D response surface plots showing the effect of independent variables on in vitro drug release studies (%) (Y5).

Based on BBD method, the quadratic model was selected by software for response Y5. This model for response Y5 is expressed as follow:

Drug Release = +61.76 +4.39A -0.1712B -3.00C +3.13AB +12.43AC -0.2500BC +18.28A2 +7.33B2 -4.55C2

Optimization and validation of film formulation

The optimum desirability of 0.904 was achieved when optimum factor levels were fixed at 398.185 mg of mango kernel, 99.999 mg of MDX, 30.00 % of PG. Finally, their validation was calculated and there was an acceptable deviation between the experimental and predicted values based on suggested models.

Table 4. Comparative levels of predicted and experimental responses obtained at optimum condition.

Responses	Optimum Condition		
	Predicted values	Experimental values	**Error**
Y1	13.677	4.53±0.94	3.017
Y2	0.800	4.32±1.39	0.1851
Y3	254.745	185.34±7.12	1.3744
Y4	56.132	58.94±1.32	0.9523
Y5	98.569	92.46±0.59	1.066

Evaluation of Films

Appearance

RZ fast dissolving films were homogenous, clear and flexible. PG in the formulations played its plasticizer role and gave a film better transparency. The film-forming capacity of polymers and the physical appearance of all formulations were visually examined, ensuring transparency, bubbles-free, and a smooth surface.

Table 5: Feasibility, pH and drug content (%) determination of RZ-OFDFs.

F. No	Adhesiveness	Film Clarity	Surface appearance	Drug content (%)	Weight (mg)	Av. pH ± SD
1	Non-adhesive	Homogenous	Transparent	97.23±1.25	32.56±0.25	6.5±0.2
2	Non-adhesive	Homogenous	Transparent	98.36±0.96	36.51±0.13	6.3±0.1
3	Non-adhesive	Homogenous	Transparent	97.26±0.35	33.24±0.46	6.1±0.3
4	Non-adhesive	Homogenous	Transparent	99.34±1.24	38.02±1.25	6.2±0.1
5	Non-adhesive	Homogenous	Transparent	99.82±0.38	41.26±0.34	6.8±0.5
6	Non-adhesive	Homogenous	Transparent	98.31±0.75	34.25±1.10	6.4±0.4
7	Non-adhesive	Homogenous	Transparent	98.02±0.62	43.16±0.123	6.7±0.2
8	Non-adhesive	Homogenous	Transparent	97.06±0.15	35.78±2.34	6.9±0.2

9	Non-adhesive	Homogenous	Transparent	98.35±0.27	32.01±2.51	6.5±0.1
10	Non-adhesive	Homogenous	Transparent	100.24±1.03	35.06±0.36	6.6±0.4
11	Non-adhesive	Homogenous	Transparent	102.34±1.02	38.79±4.31	6.3±0.3
12	Non-adhesive	Homogenous	Transparent	101.12±1.13	42.01±2.18	6.5±0.1
13	Non-adhesive	Homogenous	Transparent	102.40±1.24	32.11 ± 0.07	6.2±0.2
14	Non-adhesive	Homogenous	Transparent	99.68±0.49	39.26±0.54	6.4±0.2
15	Non-adhesive	Homogenous	Transparent	98.73±0.56	38.76±0.37	6.8±0.1
16	Non-adhesive	Homogenous	Transparent	100.28±0.38	41.25±0.85	6.9±0.4
17	Non-adhesive	Homogenous	Transparent	101.32±0.35	45.39 ± 0.82	6.5±0.2

Weight variation studies

Average weight was found in range of 32.1 ± 0.007 mg and 45.39 ± 0.892 mg. The optimized F-6 film was found to have thickness of 34.25±1.103 mg.

Drug Content uniformity

The amount of RZ in each OFDFs ranged within the defined range of 97.0 to 102.4%, demonstrating that the drug was distributed consistently among all formulae, which complies with USP standards.

Surface pH

The surface pH of all formulations was within ± 0.5 units of the neutral pH and hence no mucosal irritation was expected and ultimately achieve patient compliance.

Thickness and Diameter

Film thickness should be controlled within a range of 0.12 ± 0.01 cm and 0.35 ± 0.06 cm ± 5% variation of standard value. The optimized F-6 film was found to have thickness of 0.17 ± 0.078 cm.

Percent moisture absorption

The percent moisture absorption study was done over a period of 3 days and the results were found to be varied between 3.9±0.51% to 8.3 ±1.82 %. The composite films of mango kernel and MDX showed significantly more water content than the only mango kernel-based formulations due to the exceptionally hygroscopic nature of MDX. This phenomenon is attributed to the hydrophilic nature of polymeric materials. Additionally, the amount of water increased proportionally as the PG level in the composite OFDFs increased. The hydrophilic properties of plasticizer could drive this interaction, resulting in a substantial hydrodynamic complex of mango kernel-MTX-PG, thus enhancing film moisture contents.

Microbial contaminations and bulkiness of the film can be reduced by presence of low moisture content but low moisture content can make film completely dried and brittle. Hence gelatin film found more brittle as compared to mango kernel.

Percent moisture loss

The results of percent moisture loss varied between 1.21 ± 0.42% to 3.40 ±0.41 %. It is found that increase in the viscosity of the polymer causes retention of moisture capacity and thus slow decline of percent moisture loss. Less moisture capacity is observed in F-6 and high moisture absorbing capacity in F-17. Mango kernel shows less moisture loss and mango kernel & MDX shows higher moisture loss. There is inverse relationship between percentage moisture loss and percentage moisture absorption.

Table 6: Results of Thickness, moisture absorbance and % moisture loss

F. No	Thickness	% Moisture absorption	% Moisture loss
1	0.21±0.01	4.2±0.61	1.36±0.21
2	0.34±0.05	5.3±0.82	1.59±0.39
3	0.26±0.06	3.9±0.51	2.04±0.18
4	0.12 ± 0.01	5.6±0.34	1.21±0.42
5	0.28±0.05	6.8±.52	3.02±0.16
6	0.17 ± 0.07	4.3±0.46	2.94±0.42
7	0.32±0.04	6.9±0.31	2.86±0.38
8	0.13±0.01	5.2±0.29	2.75±1.24
9	0.22±0.03	7.3±0.13	1.59±1.26
10	0.34±0.06	8.1±0.27	1.36±1.23
11	0.32±0.04	6.9±0.15	1.85±1.02
12	0.26±0.02	7.2±0.34	2.04±0.04
13	0.28±0.04	7.5±1.25	1.36±0.06
14	0.19±0.01	8.3 ±1.82	2.49±0.02
15	0.32±0.03	6.4±1.03	2.94±0.31
16	0.29±0.04	6.8±0.95	3.35±0.25
17	0.35 ± 0.06	8.1±0.72	3.40 ±0.41

Swelling Index

All the films hydrated very quickly and reached 80% hydration after just few minutes. Maximum hydration (115-120%) was obtained with formulations containing mango kernel i.e., F1 & F2. Films containing only mango kernel showed a slightly lower hydration by 4-

8%. Fragmentation was already evident at 60 minutes in all formulae. This higher fragility of the films might be due to the larger swelling in water of this polymer. The faster the swelling of the polymer is the faster the initiation of drug diffusion and formation of adhesive bonds resulting in faster initiation of bio adhesion.

Solid state Characterizations

The pure RZ clearly showed characteristics peaks at 1563 cm^{-1}, and 1606 cm^{-1} corresponding to C=O stretching. The most critical absorption peak appeared at 1372, attributed to C-N stretching in tertiary amines. C-O stretching in the carboxylic acid peak was noticed at 1295 cm−1 [45]. C-O and Hydrogen bond stretching was observed in the MDX IR spectrum at 1013 cm^{-1} and 991 cm^{-1}, respectively [46]. A strong absorption peak was observed in the mango kernel spectrum at 3297 cm^{-1}, which indicates repeating units of -OH in mango kernel. Another strong peak at 2923 cm^{-1} and 846 cm^{-1} was attributed to the C-H bond of the alkane compound and α –D-glucopyranose configuration, respectively [47]. The existence of major RZ peaks and lack of shifting or generation of new peaks in the optimized film formulation (F6) confirmed the compatibility of RZ drugs with their excipients used for the formulation of RZ-OFDFs [48].

Overly plot

DSC

The DSC thermogram of RZ exhibits a sharp endothermic peak at 120.04 °C, which corresponds to its melting point. Thus, the thermogram of RZ conferred its anhydrous and crystalline state [1]. No characteristic peak was detected in the thermogram of MTX, which might be due to its amorphous nature. [40]. The peaks of crystallization or melting were not observed in the DSC thermogram of mango kernel, suggesting that mango kernel was amorphous. This might be because a steric interference of neighbouring bulky side chains limits the rotation of glycosidic linkages in the mango kernel backbone, and these results agree with the reported ones [41]. While preparing the PM, partial disorientation of the organized crystalline structure of RZ occurs, which could justify by the low drug amount to film-forming components in the ternary PM system resulting in the lowest intensity endothermic peak in the DSC thermograph of PM, as previously reported [42]. In addition, no significant difference was observed in the blank film compared to the RZ-loaded film. The absence of a drug peak in the RZ-OFDFs thermogram suggested significant molecular miscibility and consistent drug distribution in film fabricating constituents [6].

XRD

The presence of intense, sharp peaks at 15.8, 18.7, 20.9, 22.1, and 24.9 in the XRD diffract gram of pure RZ demonstrates that active RZ exists in pure crystalline form. The broad peak at 18.3 in the MDX and mango kernel XRD patterns confirmed the amorphous nature of polymers [31,43]. Some distinctive RZ peaks were observed in the physical mixture. Therefore, the hallo pattern of RZ-OFDFs demonstrates the transition of all discrete peaks into a broad peak at 19.3, indicating the loss of crystallinity of RZ and its transformation into an amorphous state [44].

Morphological studies

SEM photograph of physical mixture reveals a stable crystalline nature, as shown in Figure 18 A [6]. In contrast, the SEM image of RZ-OFDFs reveals a homogeneous surface devoid of cracks or transverse ridges (Figure 1B). The findings suggested adequate miscibility and a consistent dispersion of RZ throughout the OFDFs [28].

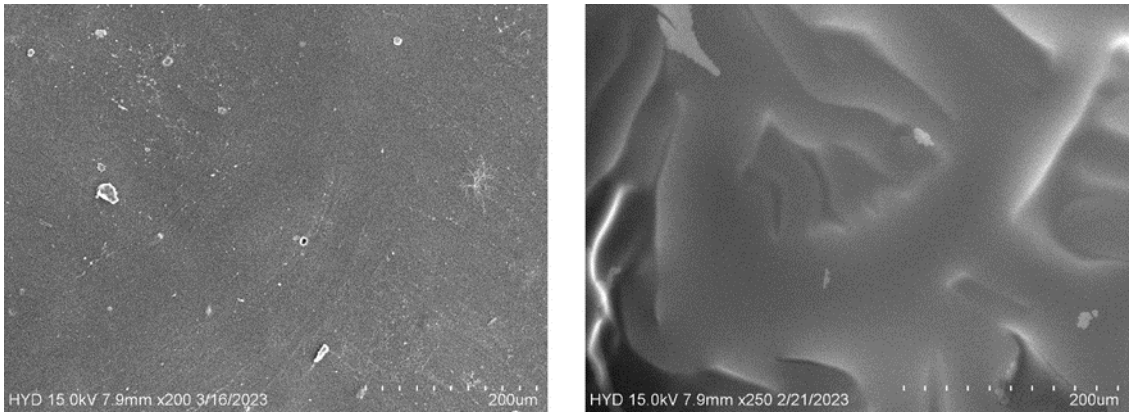

Figure 18. Scanning electron microscopic images of (A) physical mixture, (B) RZ-OFDFs.

Determination of in- vitro bio adhesion (Mucoadhesive) strength

Different polymeric combinations showed variations in mucoadhesive strength of films. Bio adhesion strength was found in range of 30.25 to 52.43 gm for F1-F17 formulae. The maximum mucoadhesive strength has observed in the formulation F6.

Determination of ex-vivo mucoadhesion time

Film mucoadhesion time varied from 90 to 182 min in various batches. But F6 showed the highest adhesion time of 182 min whereas the films from F2 showed the lowest mucoadhesion time of 91 min. This difference depends upon several factors that affect the effectiveness of such a formulation. In fact, when using mango kernel, mucoadhesion time always resulted high, because the polymer although manifesting decisively higher swelling is

less water affined and hence tends to retain its structure better than HPMC E15 that, in turn, is better dissolved.

Table 7: Results of In vitro bio adhesion and Ex-vivo mucoadhesion time

F. No	In vitro bio adhesion	Ex-vivo mucoadhesion time
1	30.25±0.02	91±2.35
2	36.59±0.54	92±1.39
3	38.49±0.69	124±1.42
4	45.37±0.82	135±2.31
5	42.01±0.76	142±2.05
6	52.43±0.31	182±3.27
7	40.37±0.02	164±1.46
8	36.08±0.42	90±1.28
9	39.35±0.36	102±1.28
10	32.51±0.51	135±1.34
11	36.02±.28	110±1.05
12	39.58±.37	127±2.39
13	42.07±0.52	106±1.52
14	43.28±0.34	115±2.04
15	43.16±0.29	138±1.36
16	41.09±0.35	143±0.95
17	43.21±0.42	103±1.42

In-vitro drug release studies

Marketed Tablet form of RZ showed considerably poor releases pattern compared to films. It is also observed that rate of RZ release is related to swelling index and mucoadhesive strength, which again depends on properties and composition of basic matrix forming polymers in the various film formulations.

Good swelling index and bucco adhesive strength of formulation F6 in proportions of mango karnel and MDX relates well with the maximum cumulative percentage release of RZ. Different kinetic models were used to analyse the in- vitro release data. In vitro drug release of prepared film showed that RZ was rapidly released during the first 4 min (30%), and the release was completed after 15 min. Percent drug release after 12 min was found out to be

82% for film code F6 and for marketed tablet and pure drug solution was found to be above 65 to 74%. We also evaluated all the data of drug released of batches and it showed that prepared oral fast dissolving films follows Higuchi pattern of drug release.

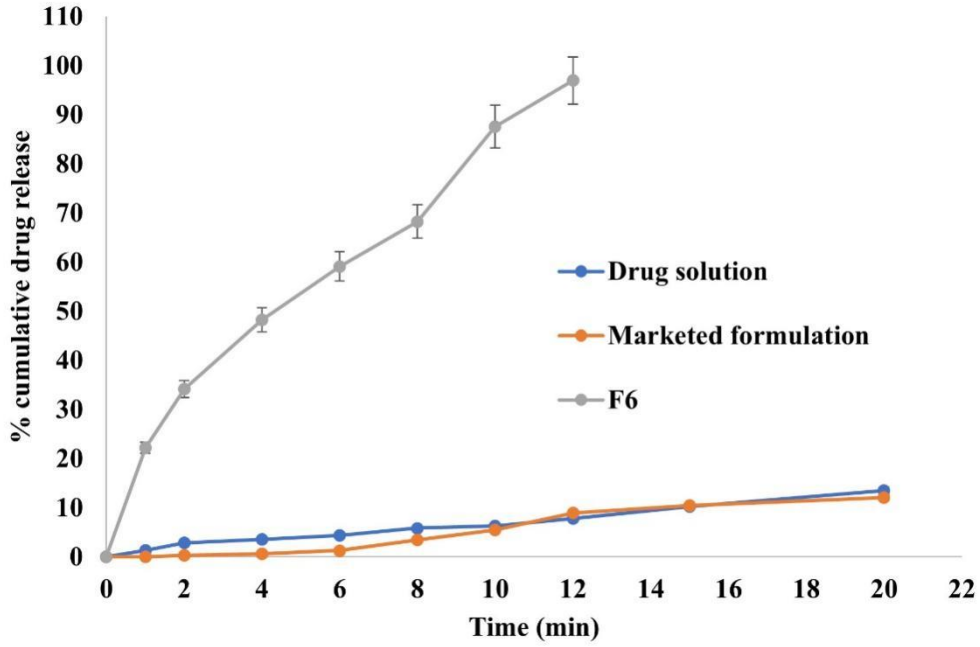

Figure19: Invitro drug release studies of drug solution, optimized formulation and marketed tablet

Ex vivo drug permeation studies

Optimized films and drug solution were disintegrated on rat oral mucosa in 15 and 8 min respectively which was slower than that in PBS solution.

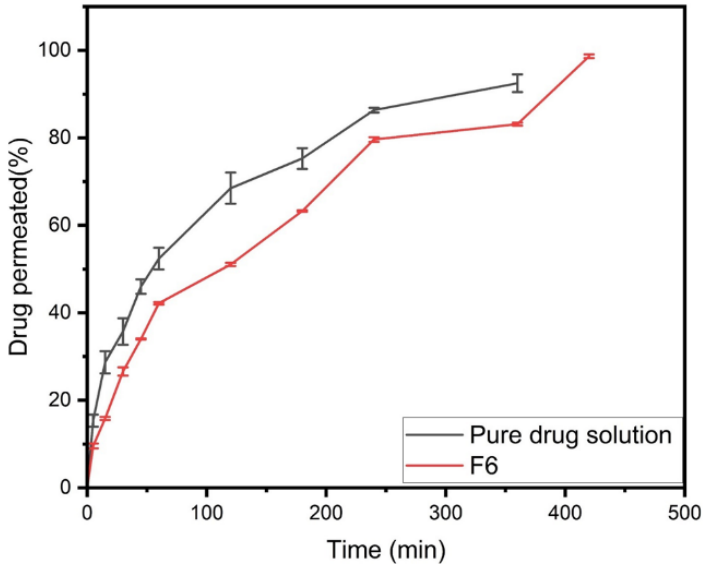

Figure 20: Ex vivo permeation of RZ from film through rat oral mucosa

In Fig. 20, film with optimized formulation containing mango kernel showed 52.39 % and 42.19 % penetration of RZ-OFDFs and RZ over 1h respectively. As we can observe, films on oral mucosa were not completely dissolved within 3h. Therefore, optimized formulation F6 could potentially enhance permeation of drugs through oral mucosa and can be used as a novel structure for mucoadhesive fast dissolving films.

Ex-vivo muco irritation by histological examination

In present study optimized F6 formulation taken for ex-vivo muco irritation by histological examination study using eosin stain. Eosin is a fluorescent acidic compound that binds to positively charged compounds like proteins, collagen, muscle fibers and stains them dark red or pink. Results compared with untreated oral mucosa. (Figure 21)

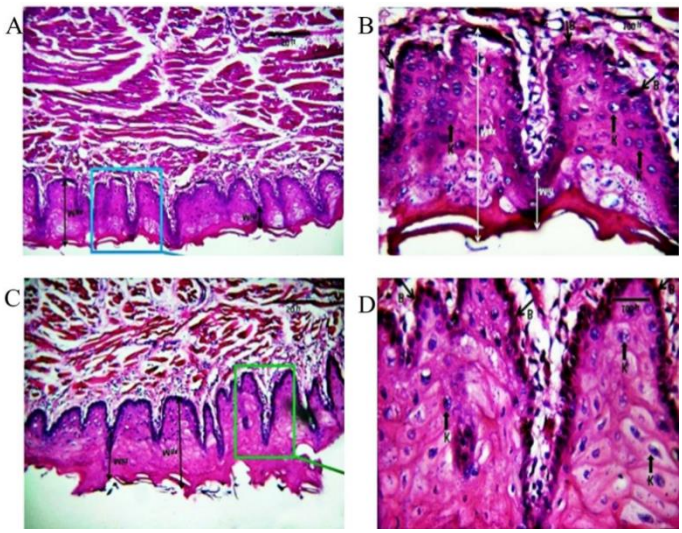

Figure 21: Histopathological evaluation of before contact with oral mucosa (A&B) after contact with fast dissolving film (F6) (C& D).

Pharmacokinetics Study

The Cmax of RZ-OFDFs and RZ intragastric suspensions were 2.44 ± 0.34 μg·mL−1 and 1.56 ± 0.37 μg·mL^{-1}, respectively, with significant difference ($p < 0.05$), reaching the peak at 0.5 h. The AUC_{0-t} among the two groups was 5.89 ± 0.94 μg·h·mL^{-1} and 2.82 ± 1.02 μg·h·mL^{-1}, with significant differences ($p < 0.05$). The MRT of the two formulations was 2.9 ± 0.7 h and 2.3 ± 0.9 h, respectively, indicating that the retention time of RZ in vivo was nearly similar.

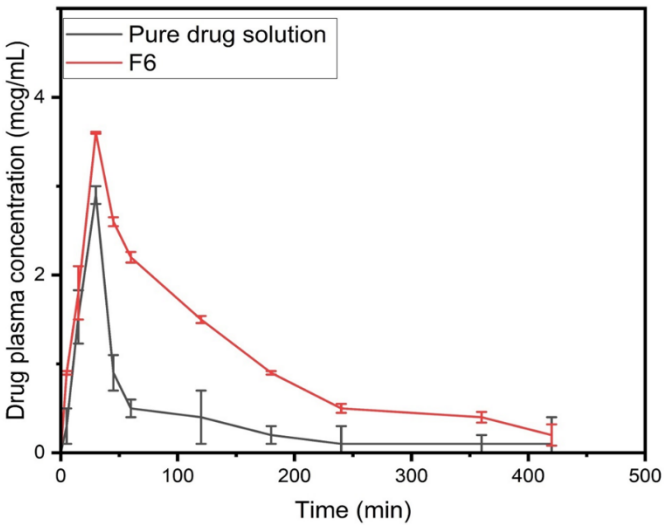

Figure22: Pharmacokinetics profile of RZ after oral administration of OFDFs and intragastric suspension at a dose of 10 mg·kg−1 to rats.

The above results show improved absorption of RZ-OFDFs compared to RZ intragastric suspensions in the rats. This can be attributed to the faster disintegration and dissolution of OFDFs leading to rapid absorption of RZ from the oral mucosa which undoubtedly resulted in a decreased pre-systemic biotransformation and degradation of the digestive tract environment [16].

Table 8: Pharmacokinetics profile of RZ after oral administration of OFDFs and intragastric suspension

Pharmacokinetics Parameter	**Drug Solution**	**F6**
Intercept	-0.00335	-0.00286
Slope	1.197327	1.328397
C0 (mcg/ml)	-0.00772	-0.00658
K(hr-1)	-89.7878	-105.367
Dose (mg)	15.75168	21.30084
Vd (mL)	10	10
Vd (L)	634.853	469.465
t1/2 (hr)	0.634853	0.469465
Clearance (L/hr)	-4.89992	-3.08767
AUC 0-t (µg.h/mL)	13.25	13.5
AUC 1-t (µg.h/mL)	153.375	-0.45257
AUC t-inf (µg.h/mL)	-12.9564	-30.409
AUC Total (µg.h/mL)	153.6686	-17.3616
C max	4.012	0.932
T max	32.06	45.18

Stability Studies

All the characteristics of formulation F-6 were found stable even after 6 months period. The overall stability of developed RZ oral films under the given conditions found out to be satisfactory. No significant changes in appearance and surface morphology of oral film sample of F-6 in before and after stability studies has been observed in scanning electron microscopy (SEM) analysis. Uniform surface morphology indicates uniform drug distribution throughout film during shelf life (Figure 23).

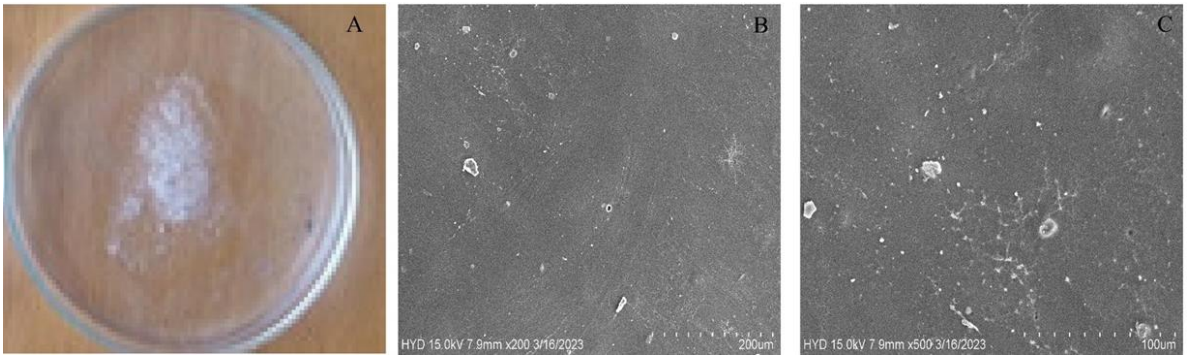

Figure 23: A) stability studies of Human Saliva, B) SEM images of before stability and C) SEM images of After stability

Table 9: Physicochemical evaluation of formulation F-6 during stability studies

Parameters	40°C+ 2 / 75+ 5% RH				Room Temperature			
	0 Days	1 Month	3 Month	6 Month	0 Days	1 Month	3 Month	6 Month
Physical appearance	No Change	No change	No Change	No change	No Change	No Change	No change	No Change
Thickness (mm)	0.17± 0.07	0.15±0.01	0.13±0.02	0.12±0.01	0.17± 0.07	0.17 ± 0.07	0.16±0.01	0.15±0.02
FE	185.34±7.12	180±2.38	176±3.15	173±6.12	185.34±7.12	182±5.34	180±2.19	176±0.59
pH	6.4±0.4	6.2±0.25	6.1±0.01	5.8±0.23	6.4±0.4	6.4±0.01	6.3±0.01	6.1±0.02
SI (%)	110±1.25	106±0.29	102±0.42	99±0.13	110±0.53	108±0.28	106±0.42	103±0.31
TS (Mpa)	4.53±0.94	4.42±0.13	4.36±0.24	4.31±0.12	4.53±0.94	4.52±0.13	4.49±0.24	4.46±0.01
Drug Content (%)	98.31±0.75	98.31±0.75	98.31±0.75	98.31±0.75	98.31±0.75	98.31±0.75	98.31±0.75	98.31±0.75

Conclusion

The objective of present study was to develop fast dissolving oral films of Anti-Hypertensive drug Ranolazine using solvent casting technique. A response surface methodology experimental design was applied for the optimization of fast dissolving film using Box-

Behnken experimental design. Various physic mechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption parameters like mucoadhesive strength, drug excipients interaction studies, in vitro drug release and stability studies were evaluated. The in vitro release study revealed that F6 formulation showed maximum release in 20 min. The maximum bio adhesive strength and highest ex-vivo mucoadhesion time of 52.43±0.31 gm and 182 min was observed for F6. The Pharmacokinetic plasma parameters results displayed improved absorption of RZ-OFDFs compared to RZ intragastric suspensions in the rats. The optimized formulation was subjected to stability studies which indicated that F6 was stable up to 6 months. The result suggests that the developed films of Ranolazine could perform the better than conventional dosage form leading to improved efficacy and better patient compliance.

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