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Comparison Of Ranolazine With Telmisartan In The Treatment Of Mild To Moderate Hypertension

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Abstract

The objective of the present study was to develop and compare fast-dissolving oral films of Anti-Hypertensive drugs Ranolazine and Telmisartan using a solvent casting technique. A response surface methodology experimental design was applied to optimize fast-dissolving film using Box-Behnken experimental design. The concentrations of X1 (mango kernel, 100–400 mg), X2 (MDX 0–100 mg), and X3 (PG, 15–30%) were preferred as independent factors for Ranolazine films. The concentrations of X1 (Mango kernel, 100–300 mg), X2 (Maltodextrin, 200–350 mg), and X3 (Propylene glycol, 15–30%) were selected as independent variables for Telmisartan. Y1 (Tensile Strength; MPa), Y2 (Disintegration Time; Sec), Y3 (Folding Endurance; Folds), Y4 (Elongation; %), and Y5 (% drug release; min) were considered as dependent variables for both drugs. Various physicochemical parameters like weight variation, thickness, folding endurance, and drug content were evaluated. Ranolazine films' maximum bio-adhesive strength and highest ex-vivo mucoadhesion time were 52.43±0.31 gm and 182 min observed for F6. Telmisartan-optimized films F4 had the highest ex-vivo mucoadhesion duration and maximal bioadhesive strength of 49.82 gm and 189 min, respectively. Ex-vivo muco irritation was performed by using fresh sheep oral mucosa. The Pharmacokinetic plasma parameters of Telmisartan-optimized films F4 results displayed improved absorption compared to RZ-OFDFs F6.

Keywords: Ranolazine, Telmisartan, Anti-Hypertensive, Box-Behnken experimental design, Pharmacokinetics.

Introduction

The oral route of administration is the most accepted route for therapeutic agents because of the low cost and ease of administration leads to high levels of patient compliance. About 60% of all dosage forms are 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 patients, including geriatric, pediatric, and dysphasic patients associated with many medical conditions as they have difficulty

swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are disinclined to receive solid preparations due to fear of choking dosage forms. One study showed that 26% of patients had difficulty 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 pediatric patients, as well as traveling 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 to 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 for water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste, and improved patient compliance.

Hypertension is a "lifetime" condition and, if left untreated, leads to lethal complications. The rennin–angiotensin system plays an important role in the regulation of normal blood pressure (BP) and also in the pathogenesis and maintenance of essential hypertension [5]. Currently, drugs that attenuate the action of angiotensin II and act as antihypertensive agents by different mechanisms are available, which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). One of the newer agents in this class is telmisartan. 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 [6]. It acts by inhibiting sodium channels due to which a reduction in the intracellular calcium levels takes place, leading to a decrease of tension in the heart muscle (myocardium). Therefore, comparison studies of both drugs in terms of pharmacokinetics and permeation profile are done.

Materials and Methods

Materials

Ranolazine and Telmisartan were purchased from Hetero Pvt Ltd. in Hyderabad; Gattefosse India Pvt Ltd. provided the mango kernel and HPMC E15; and SD Fine-Chem Limited provided the HPMC E5.

Methods

Preparation of RZ-OFDFs and Telmisartan-OFDFs

The solvent casting method (SCM) was applied to prepare RZ-OFDFs and Telmisartan-OFDFs separately. Briefly, the polymeric materials, used at different weight ratios, 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 amounts (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 [7]. At the end, when the dispersion was found clear, requisite amounts of aspartame (24.3 mg) and mannitol (24.3 mg) were added to 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 aluminum sachet, and stored in a desiccator until further assessment.

Experimental Design for RZ & Telmisartan 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) [8]. 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.

For RZ-OFDFs, 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).
For Telmisartan-OFDFs, the independent variables, the concentrations of X1 (mango karnel, 100-300 mg), X2 (MDX, 200-350 mg), and X3 (PG, 15-30%) were chosen. Table 1 lists the dependent variables as Y1 Folding endurance (folds), elongation (%), disintegration time (sec), and tensile strength (MPa), and percent drug release (T5; min).
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 [9]. 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 drug'loaded ODFs with desirable mechanical properties.

Table 1: Full factorial design (BBD) for Ranolazine and Telmisartan OFDFs

Parameter	Ranolazine			Telmisartan		
	Low (-1)	Medium (0)	High (+1)	Low (-1)	Medium (0)	High (+1)
Independent Variables				**Independent Variables**		
X1: Mango Kernel (mg)	100	250	400	100	200	300
X2: MDX (mg)	0	50	100	200	275	350
X3:PG (%)	15	22.5	30	15	22.5	30
Dependent variables				**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					

3-D Response Surface plots were developed using mathematical models to predict the association between chosen factors and variables. To obtain thin and quickly disintegrating ODFs with desired mechanical characteristics, the optimal formulation design space was developed.

Evaluation of OFDFs

Appearance

The general appearance and elegance of the films were identified visually, including shape, color, presence of an odor, taste, surface texture, etc [10].

Weight variation studies

The individual weight of three samples (2x2 cm) of each formulation was determined using an analytical balance. The results were analyzed for mean and standard deviation [11].

Thickness and Diameter

The thickness of 3 films (2x2 cm) of each formulation was measured using a Digital thickness measurement apparatus and the results were analyzed 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. Both drug 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 drug contents in OFDFs [13].

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

Folding endurance
The 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 and telmisartan OFDFs [15]. Each film was measured in triplicate.

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

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 [16].

Ex-vivo permeation studies
The formulated film of 2×2cm diameter was cut and placed over the goat oral mucosa membrane [17]. 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 of up to 5 hours and were analyzed 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 fresh sheep oral mucosa purchased from a local slaughterhouse. The epithelial tissues of mucosa were fixed in 10% neutral buffered formalin for 2 h, washed with distilled water for 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 colored with eosin [18]. 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 and telmisartan-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 [19]. 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 and 275 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 [20]. 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 RZ- 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

Optimization of Telmisartan Oral Fast Dissolving Film using BBD Design

The range of Tensile Strength (Y1) for all batches was 1.26±0.12 to 8.96±0.02 Mpa. Similarly, the Disintegration Time (Y2) was 15.34±1.24 to 46.35±2.04 sec, Folding endurance (Y3) was 124±1.37 to 354±2.41 folds, Elongation (Y4) was 10.85±0.43-23.16±0.13% and cumulative percentage of drug released in 5 minutes (Y5) was 43.211.84-89.610.48% .

Table 3: Summary of Telmisartan Oral Fast Dissolving Film using BBD Design

Run	X1	X2	X3	Y1	Y2	Y3	Y4	Y4
1	200	275	22.5	1.26±0.12	35.62±1.02	158±3.51	18.52±0.34	73.26±2.31
2	200	275	22.5	1.43±0.14	29.04±0.65	160±2.64	16.59±1.26	78.32±0.54
3	200	275	22.5	1.29±0.13	21.52±1.38	157±2.18	17.53±0.52	76.84±1.26
4	300	350	22.5	8.96±0.02	15.34±1.24	354±2.41	23.16±0.13	89.61±0.48
5	100	350	22.5	5.42±0.13	21.84±3.02	283±3.05	19.62±0.48	64.72±2.04
6	300	275	30	3.16±0.14	18.43±2.16	279±1.64	13.48±0.69	59.02±2.15
7	200	350	30	5.48±0.15	20.48±1.59	259±2.51	16.05±0.52	77.04±3.25
8	100	275	15	1.34±0.16	46.35±2.04	124±1.37	10.85±0.43	43.21±1.84
9	200	200	15	2.69±0.24	37.05±0.34	167±2.18	12.96±0.11	49.86±1.95
10	200	275	22.5	3.48±0.08	29.31±1.28	139±3.29	14.03±0.27	75.14±3.75
11	200	200	30	2.19±0.16	23.06±1.24	186±2.47	16.27±0.13	56.24±1.64
12	100	275	30	3.02±0.01	18.93±3.01	134±3.61	11.86±0.62	63.25±2.95
13	300	200	22.5	3.26±0.11	16.35±2.46	395±2.05	21.86±0.42	60.48±1.48
14	200	275	22.5	2.51±0.12	34.62±1.35	148±1.49	16.92±2.43	77.03±1.57
15	200	350	15	4.59±0.04	41.26±1.28	195±2.43	20.54±1.29	53.29±1.39
16	300	275	15	3.85±0.05	26.35±1.29	213±2.13	18.53±2.31	56.39±1.64
17	100	200	22.5	6.59±0.03	20.13±2.34	186±1.35	16.52±0.69	73.51±2.04

*All the readings are expressed as mean ± standard deviation (n=3)

Influence of independent variables on Tensile strength (TS)

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

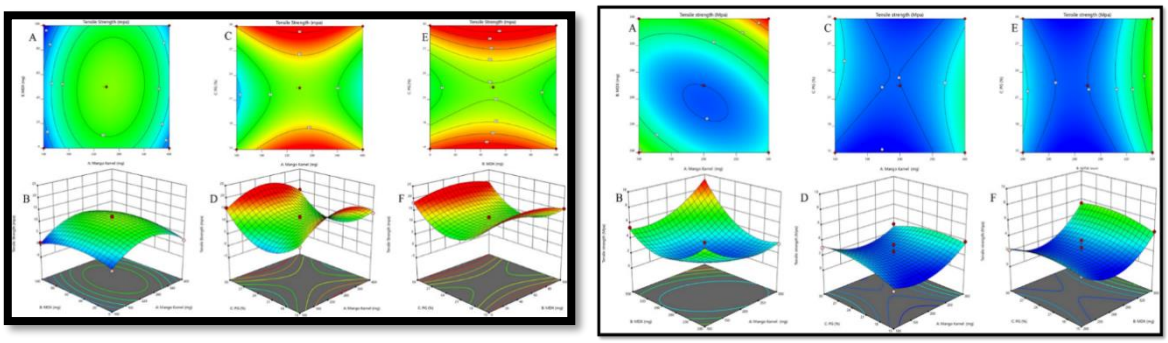

Figure 1: Counter and 3D response surface plots of RZ & Telmisartan OFDF's showing the effect of independent variables on tensile strength (Y1).

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 = +1.99 +0.3575A +1.22B +0.1725C +1.72AB -0.5925AC +0.3475BC +1.58A2 +2.48B2 -0.7357

Surface Plot showed that as the amount of mango karnel increased, the tensile strength of the film also increased. On the other hand, value of mango karnel moved from lower range to higher range, the thickness of the matrix system also increases. It was concluded from the surface plot that combine effect of polymer greatly affected on tensile strength of the system so it is necessary to maintain the optimum concentration to achieve the desired results.

Influence of independent variables on in vitro disintegration time

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

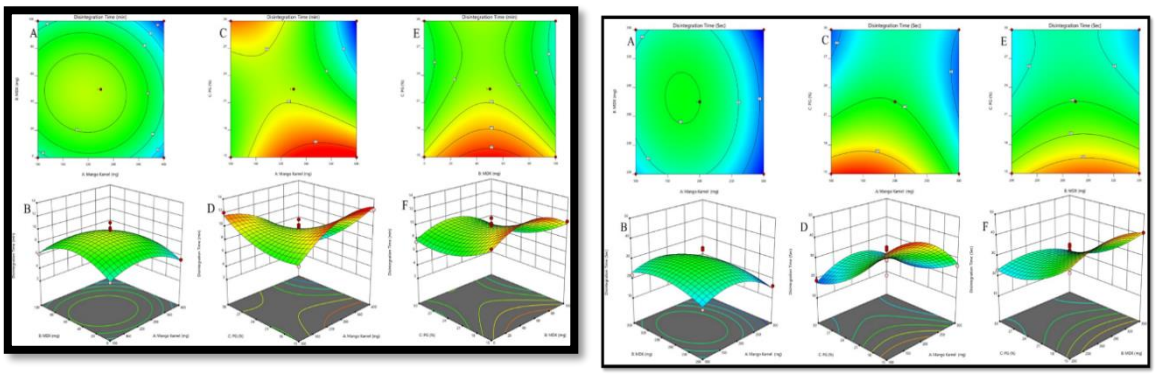

Figure 2: Counter and 3D response surface plots of RZ & Telmisartan OFDF's showing the effect of independent variables on disintegration time (min) (Y2).

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.

Disintegration Time = +30.02 -3.85A +0.2913B -8.76C -0.6800AB +4.88AC -1.70BC -7.28A2 -4.33B2 +4.77C2

According to the surface plot, the length of the film's disintegration rose as the quantity of mango karnel grew. On the other hand, as value of MDX moved from lower to higher range, the disintegration time of the matrix system also increases. When the concentration of the plasticizer raised, the disintegration time increased, while it was noted that the disintegration time dropped as the concentration of the polymer increased.

Influence of independent variables on Folding Endurance

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

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. 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.

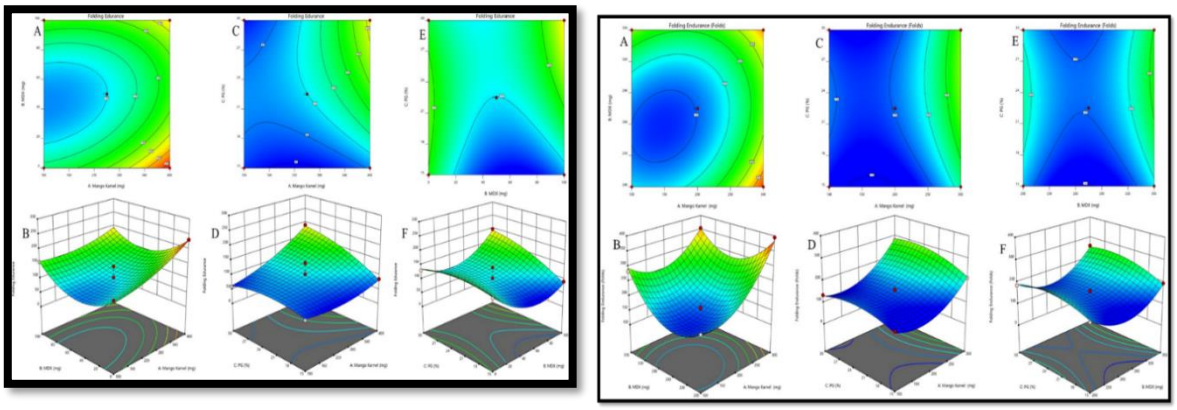

Figure 3: Counter and 3D response surface plots of RZ & Telmisartan OFDF's showing the effect of independent variables on Folding endurance (Y3).

Folding Endurance = +152.40 +64.25A +19.63B +19.88C -34.50AB +14.00AC +11.25BC +68.92A2 +83.17B2 -33.82C2

The Folding Endurance of the mouth dissolving films was discovered to be between 124±1.37-354±2.41 folds. The quadratic model showed that the quantity of propylene glycol, maltodextrin, and mango karnel had a substantial impact on the folding endurance. Surface Plot showed that as the amount of mango karnel increased, the the film's duration of disintegration time also increased. On the other hand, value of MDX moved from lower range to higher range the thickness of the matrix system also increases.

Influence of independent variables on Elongation (%)

The average %E of RZ-OFDFs ranged from 22.15±0.96 to 58.94±1.32%. 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].

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

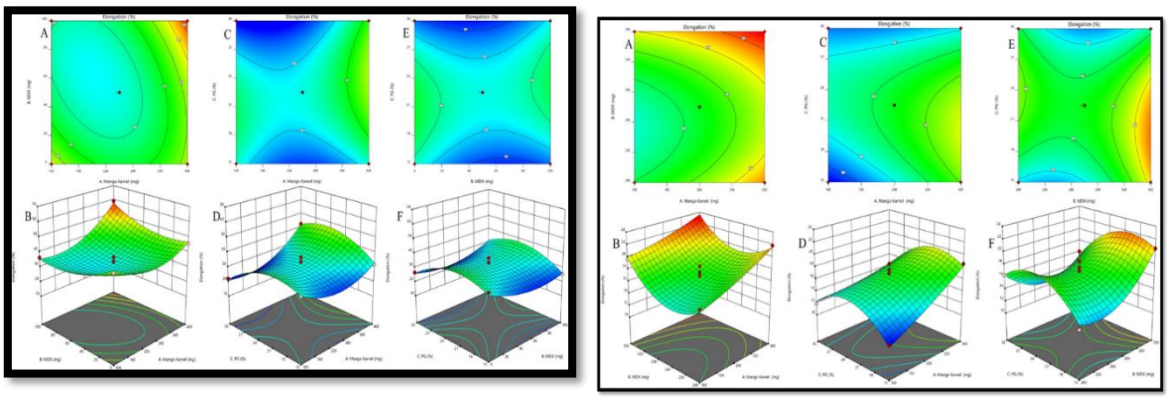

Figure 4: Counter and 3D response surface plots of RZ & Telmisartan OFDF's showing the effect of independent variables on Elongation analysis (%) (Y4).

Elongation = +16.72 +2.27A +1.47B -0.6525C -0.4500AB -1.52AC -1.95BC +0.3985A2 +3.17B2 -3.44C2

The films' elongations were determined to be between 10.85±0.42 and 23.16±0.13%. Surface Plot showed that as the amount of mango karnel increased, the Elongation of the film also increased. On the other hand, value of MDX moved from lower to higher range, the folding endurance of the matrix system also increases.

Influence of independent variables on in vitro drug release

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

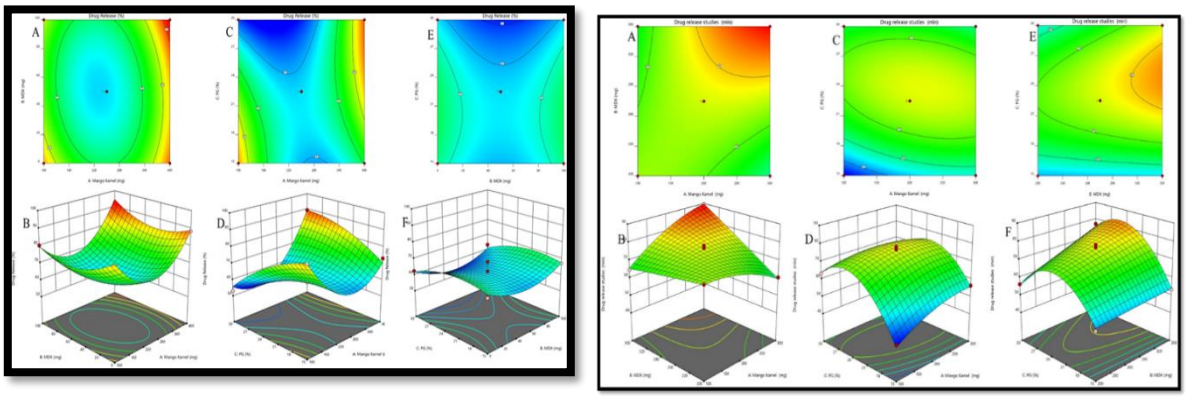

Figure 5: Counter and 3D response surface plots of RZ & Telmisartan OFDF's showing the effect of independent variables on in vitro drug release studies (%) (Y5).

Drug release studies = +76.12 +2.60A +5.57B +6.60C +9.48AB -4.35AC +4.34BC -3.84A2 -0.1990B2 -16.81 C2.

The total proportion of drugs released in 5 min from the mouth Dissolving films were discovered to be between 43.21±1.84-89.61±0.48% . From the in vitro drug release investigation, it was shown that drug release increased as plasticizer concentration increased and reduced as polymer concentration increased. As a result, the figure depicted the common impact of plasticizer and polymer concentration. The contour plot for formulation batch F1 to F17 shows that drug release rose as plasticizer concentration increased, whereas drug release reduced as polymer concentration increased.

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	Ranolazine			Telmisartan		
	Optimum Condition			Optimum Condition		
	Predicted values	Experimental values	Error	Predicted values	Experimental values	Error
Y1	13.677	4.53±0.94	3.017	9.334	8.96±0.02	1.04
Y2	0.800	4.32±1.39	0.1851	13.691	15.34±1.24	0.892
Y3	254.745	185.34±7.12	1.3744	357.858	354±2.41	1.010
Y4	56.132	58.94±1.32	0.9523	23.160	23.16±0.13	1
Y5	98.569	92.46±0.59	1.066	90.207	89.61±0.48	1.006

At X1:300, X2:350, and X3:22.5, the maximum function value was attained. The experimental results were found to be in a close resemblance to the expected results.

Evaluation of Films

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

Ranolazine							Telmisartan					
F. No	Adhesiveness	Film Clarity	Surface appearan	Drug content (%)	Weight (mg)	Av. pH ± SD	Adhesiveness	Film Clarity	Surface appearan	Drug content (%)	Weight (mg)	Av. pH ± SD
1	Non-adhesive	Homogenous	Transparent	97.23±1.25	32.56±0.25	6.5±0.2	Non-adhesive	Homogenous	Transparent	97.01±1.25	19.34±0.25	6.75±0.2
2				98.36±0.96	36.51±0.13	6.3±0.1				98.36±0.96	18.52±0.13	7.03±0.1
3				97.26±0.35	33.24±0.46	6.1±0.3				98.01±0.35	16.37±0.46	6.91±0.3
4				99.34±1.24	38.02±1.25	6.2±0.1				99.87±1.24	23.03±1.25	6.82±0.1
5				99.82±0.38	41.26±0.34	6.8±0.5				99.02±0.38	18.64±0.34	6.98±0.5
6				98.31±0.75	34.25±1.10	6.4±0.4				98.63±0.75	15.34±1.10	6.94±0.4
7				98.02±0.62	43.16±0.12	6.7±0.2				97.94±0.62	18.85±0.12	6.67±0.2
8				97.06±0.15	35.78±2.34	6.9±0.2				98.31±0.15	16.32±2.34	6.79±0.2
9				98.35±0.27	32.01±2.51	6.5±0.1				97.34±0.27	20.87±2.51	6.85±0.1
10				100.24±1.0	35.06±0.36	6.6±0.4				98.15±1.03	24.31±0.36	7.01±0.4
11				102.34±1.0	38.79±4.31	6.3±0.3				97.32±1.02	28.69±4.31	6.98±0.3
12				101.12±1.1	42.01±2.18	6.5±0.1				98.34±1.13	17.01±2.18	7.06±0.1
13				102.40±1.2	32.11± 0.07	6.2±0.2				99.08±1.24	22.08±0.07	6.82±0.2
14				99.68±0.49	39.26±0.54	6.4±0.2				97.34±0.49	20.39±0.54	6.79±0.2
15				98.73±0.56	38.76±0.37	6.8±0.1				98.73±0.56	18.04±0.37	7.01±0.1
16				100.28±0.3	41.25±0.85	6.9±0.4				97.82±0.38	18.38±0.85	7.35±0.4
17				101.32±0.3	45.39± 0.82	6.5±0.2				99.03±0.35	19.69±0.82	7.12±0.2

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. Film with RZ-OFDFs 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.

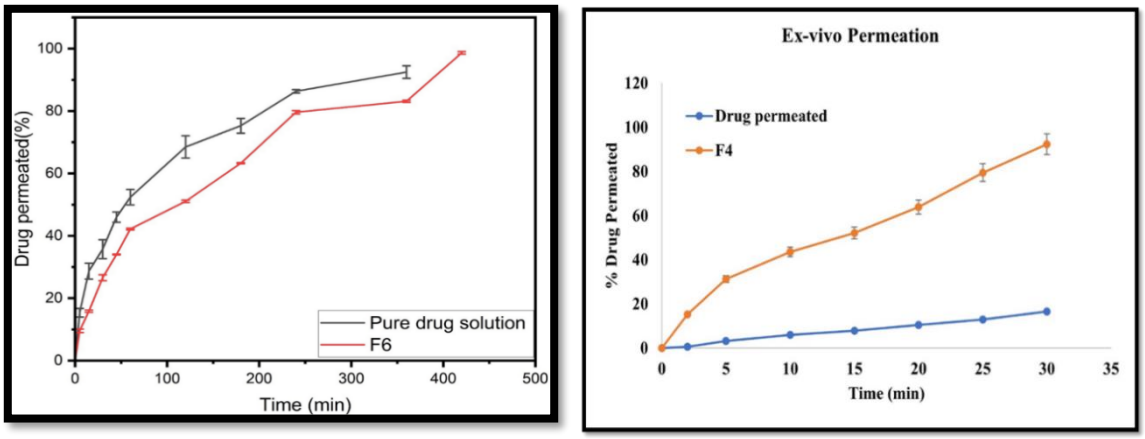

Figure 6: Ex vivo permeation of RZ & telmisartan OFDF through rat oral mucosa

Investigations were done on the drug permeation of telmisartan pure drug solution and optimum film. Optimized films (F4) and drug solution dissolved in 15 and 8 min, respectively. A film with an enhanced

formulation that contains mango karnel at 52.39% and 42.19%, respectively, demonstrated the penetration of telmisartan-OFDFs and telmisartan over 30 minutes in Fig. 18. As a result, the improved formulation F4 may improve the penetration of drugs through the oral mucosa and serve as a unique 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.

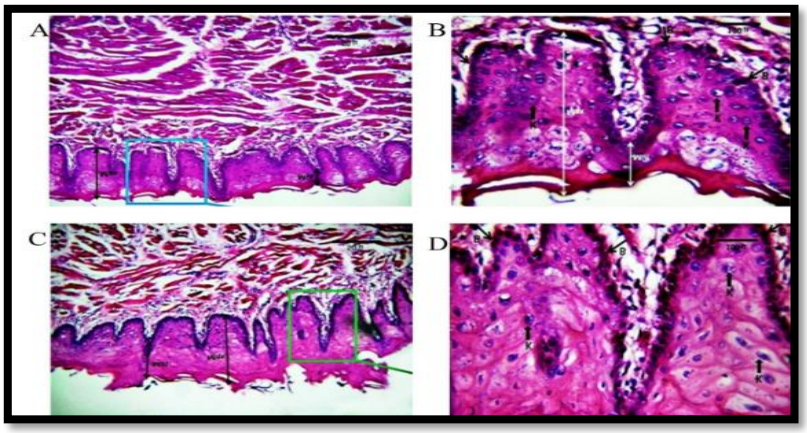

Figure 7: Histopathological evaluation of before contact with oral mucosa (A&B) after contact with fast dissolving film (F6) (C& D).

Optimized F4 formulation was used in the current investigation to Eosin staining for ex vivo muco irritation. Eosin also causes a noticeable reddening of red blood cells. In research, it is the most often employed dye.

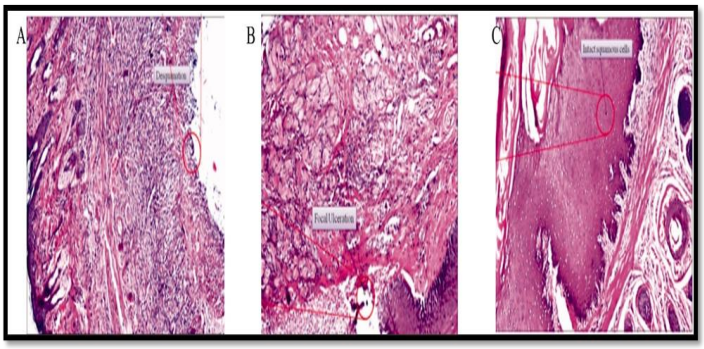

Figure 8: Representative photomicrographs (100x) of sections of (a) the control group of rats, (b) the group of rats receiving plain pure drug solution and (c) the group of rats receiving optimized oral fast-dissolving films (F4).

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. 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].

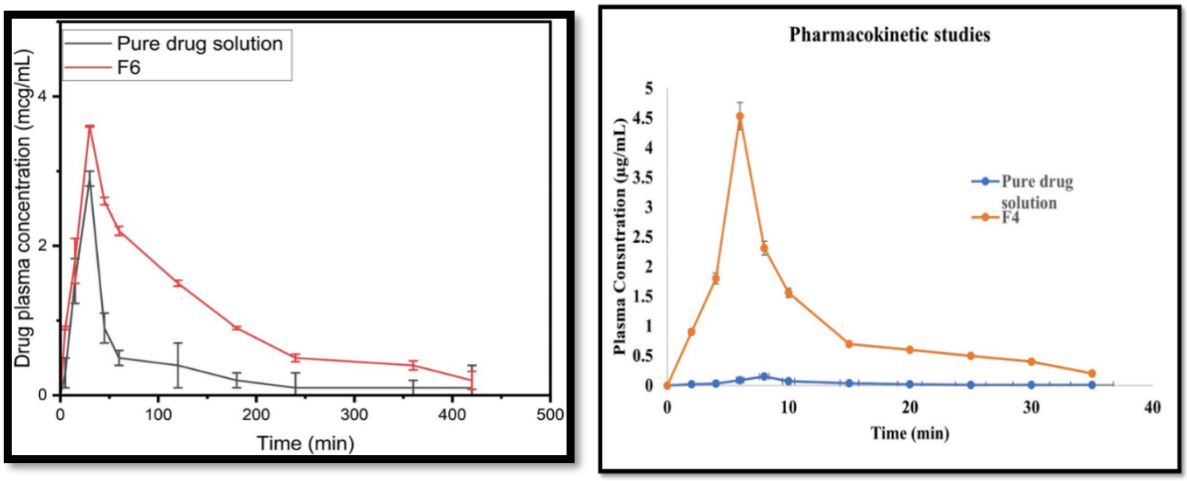

Figure 9: Pharmacokinetics profile of RZ and Telmisartan after oral administration of OFDFs

The lowest average plasma concentrations were obtained when Telmisartan was dosed as aqueous suspensions. In contrast to the AUC found for the aqueous drug solution, the AUC was 30 times higher when Telmisartan was delivered as oral fast-dissolving films. A Cmax of 4.586 g/mL, obtained with the optimized oral rapid dissolving films, was 29.02 times greater than aqueous solution. Oral fast dissolving films have a strong chance of having a higher Cmax without changing the Tmax since the Tmax (35 min) obtained after oral fast dissolving films dosage was the same as that obtained for aqueous solutions (35 min). These findings show that, in comparison to aqueous suspensions, absorption is much higher when telmisartan is formulated as oral fast-dissolving films.
The Pharmacokinetic plasma parameters of Telmisartan-optimized films F4 results displayed improved absorption compared to RZ-OFDFs F6.

Conclusion

The current study's goal was to use solvent casting to form and evaluate fast-dissolving oral films of the antihypertensive drugs Telmisartan and Ranolazine. Box-Behnken experimental design with response surface methods was used to optimise fast-dissolving film. For both drug-loaded films, the concentrations of X1 (mango kernel), X2 (maltodextrin), and X3 (propylene glycol) were preferred as independent parameters. For both medicines, the dependent variables were Y1 (Tensile Strength; MPa), Y2 (Disintegration Time; Sec), Y3 (Folding Endurance; Folds), Y4 (Elongation; %), and Y5 (% drug release; min). Numerous physicochemical characteristics were assessed, including drug content, weight fluctuation, thickness, and folding endurance.In comparison to RZ-OFDFs F6, the pharmacokinetic plasma characteristics of Telmisartan-optimized films F4 showed better absorption.

References

1. A. Srinivas, D.V.R.N. Bhikshapathi. Fast Dissolving Oral Films of Pramipexole HCl monohydrate: Preparation and in vitro evaluation. Research J. Pharm. and Tech. 2018;11(3):1001-1008.
2. Anjana anil and Preethi Sudheer. International Journal of Pharmaceutical Sciences. 2018; (2):121-129.
3. Anusha J, Prasanna MR, Jyothi P and Lakshmana Rao A. Indian Journal of Pharmacy and Pharmacology. 2016;3(4):221-224.
4. Ashish Gorle and Girish Patil. Development and Evaluation of Fast Dissolving Film of Amlodipine Besylate. International Journal of Chem Tech Research. 2017;10(4):334-344.
5. Bhagat BV, Darkunde SA. Orodispersible Film: A Novel Drug Delivery System. Research J. Pharm. And Tech.7 (10) 2014; 1196- 1200
6. D. Jayaprakash, N. Swathi. Formulation and Characterization of Rosuvastatin Mouth dissolving films for the treatment of Hyperlipidemia. Research J. Pharm. and Tech. 2021;14(2):997-1002.
7. D. Maheswara Reddy, C. Madhusudhana Chetty, Y. Dastagiri Reddy, P. Komali, B. Sri Divya, S. Sandhya Rani. Formulation and Evaluation of Fast Dissolving Buccal Patches of Tenofovir Disoproxil Fumarate. Research J. Pharm. and Tech. 2021; 14(1):225-230.
8. Deepak Sharma, Daljit Kaur, Shivani Verma, Davinder Singh, Mandeep Singh, Gurmeet Singh and Rajeev

Garg. Fast Dissolving Oral Films Technology: A Recent Trend for an Innovative Oral Drug Delivery System. International Journal of Drug Delivery. 2015;(7):60-75.

9. Sumedha Bansal, Gopal Garg. Design and Optimization of Fast Dissolving Film of Losartan. Research J. Pharm. and Tech. 2014;7(11):1211-1218.
10. Deepthi PR and Kumar KS: Formulation and Evaluation of Amlodipine Besylate Oral Thin Films. Int J Pharm Sci Res. 2016; 7(1): 199-05
11. Gangurde A. B., Bairagi V. A., Borse K. Design and Quality Control of fast Dissolving Atorvastatine Calcium and Amlodipine Besylate Tablets. Research J. Pharm. and Tech. 2018;11(6):2424-2428.
12. John Oluwasogo Ayorinde, Michael Ayodele Odeniyi , Olalekan Balogun-Agbaje. Formulation and Evaluation of Oral Dissolving Films of Amlodipine Besylate Using Blends of Starches with Hydroxypropyl Methyl Cellulose. Polim. Med., 2016; 46(1):45–51
13. K. Adinarayana Reddy, Y. Srinivasa Rao. Formulation and in Vivo Evaluation of Granisetron HCl mouth Dissolving films in Healthy Human Volunteers. Research J. Pharm. and Tech. 2018;11(1):236-244.
14. Nikhlesh Birla, Kavita Mandloi, Rampal Mandloi, Sujit Pillai. Formulation and Evaluation of Quick Dissolving Films of Promethazine Hydrochloride. Research J. Pharm. and Tech. 2017;10(4):1025-1028.
15. Ramani Gade, Aparna Ayunampudi, Anitha Makineni, Murthy TEGK, Chandu Babu Rao and Sreekanth Nama. Design and Development of Pravastatin sodium Fast Dissolving Films from natural mucilage of Ocimum bacilicum seeds, International Journal of Pharma Research and Review. 2014;17-27.
16. Ramya Deepathi and Sathish Kumar. Formulation and Evaluation of Amlodipine Besylate oral thin films. International Journal of Pharmaceutical Science and Research, 2016; 7(1):199-205.
17. Reddy PS, Murthy KVR. Formulation and Evaluation of Oral Fast Dissolving Films of Poorly Soluble Drug Ezetimibe Using Transcutol Hp. Indian J of Pharmaceutical Education and Research. 2018;52(3):398-407.
18. Sudhir Maddela, Buchi N. Nalluri. Development of Rizatriptan Mouth Dissolving Films: A Fast-Absorbing Drug Delivery System for Effective Treatment of Migraine. Research J. Pharm. and Tech. 2019;12(6):2907-2916.
19. Nitesh S Chauhan, Alka Tomar, Kiran Sharma and Ashu Mittal. Umakant Formulation and Evaluation of fast dissolving oral film of Dicyclomine as potent route of buccal delivery. International Journal of Drug Development and Research. IJDDR. 2011;(2):408-417
20. Puja Chaurasiya, Rajesh Kharel, Manasa Deepa R, Rajashekhar V and Sridhar KA. Review on Oral Fast Dissolving Films A Novel Drug Delivery System, Asian Journal of Research in Chemistry and Pharmaceutical Sciences. 2016;(4):165-175.