ORIGINAL ARTICLE

# Application of Box-Behnken design to formulate and optimize multipolymeric fast dissolving film of rizatriptan benzoate

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The present investigation aims at formulation and optimization of multipolymeric fast dissolving film of rizatriptan benzoate. Three film forming polymers namely hydroxypropyl methylcellulose (HPMC), maltodextrin and polyvinylalcohol were explored using Box-Behnken experimental design to derive optimized fast dissolving film formulation using desirability function. Analysis of variance (ANOVA) was performed for five dependent variables tensile strength, folding endurance, load at yield, percentage elongation and percentage drug release in 30 s ($Q_{30}$). Mathematical regression equations were derived by applying ANOVA and validated using checkpoint batches. Results of the experimental design exposed that the effect of independent factors HPMC and maltodextrin significantly influenced the mechanical properties and percentage drug release from the film. Optimized batch was derived based on set criteria using desirability function. Reponses of the optimized formulation were tensile strength (500 N/m$^2$), folding endurance (203), load at yield (15.06 N/m$^2$), percentage elongation (4.56%) and $Q_{30}$ (60.03%) falling under acceptable limits. High percentage drug release from the film in simulated saliva and simulated gastric fluid reveal fast dissolving characteristics. Fast dissolving dosage form can help patients with diseases like migraine.

*Key words:* *Box-Behnken design, desirability function, fast dissolving films, rizatriptan benzoate, similarity factor*

## INTRODUCTION

Patient non-compliance is emerging as a major hurdle in drug delivery to pediatric and geriatric patients. Non-compliance due to dysphagia is a common problem of all age groups, especially the elderly, stroke victims and bed ridden patients. They face difficulty in chewing or swallowing solid preparations, probably due to fear of choking.[1,2] Besides treatment of bed ridden, mentally ill, uncooperative or nauseated patients produce additional challenge to drug delivery. On the other hand, drugs with high first pass metabolism or drugs requiring quick onset of action need to be absorbed quickly after oral administration. Many novel dosage alternatives and technologies have emerged now a day in this horizon to overcome such difficulties.[3,4]

Fast dissolving oral delivery systems have emerged as a solution to overcome several drawbacks of conventional oral drug delivery. Fast dissolving films represent one of such delivery system. Fast dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within few minutes when placed in the mouth without drinking or chewing. Upon ingestion, fast dissolving film quickly dissolved into the saliva which act as a carrier for dissolution or dispersion of medicament and facilitate its absorption in the normal way. Drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. This may significantly improve bioavailability of medicament as compared to the standard dosage forms.[5,6]

Among the several methods available, solvent casting technique is commonly utilized for fast dissolving film formation. The main ingredient of the film formulation is the film forming polymer, based on which the films may be monopolymeric (containing only one polymer)

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or multipolymeric (containing two or more polymers). Films prepared from single polymer may give desired low dissolution time, but at the same time such films may experience moderate to poor mechanical properties or other problems like hygroscopicity, stickiness etc. which may result in handling, packaging and other problems. Hence to overcome such shortcomings, combination of two or more polymers may be utilized to formulate films with desired characteristics.[7,8]

Rizatriptan benzoate (RZB) is a potent, highly selective $5HT_{1B/1D}$ agonist with rapid onset of action for acute treatment of migraine.[9] Migraine is a common, frequently incapacitating, headache disorder that imposes a substantial burden on both the individual patient and society. RZB is available in the market in the form of conventional tablet and orally disintegrating tablet. The epidemiological studies in migraine reveal that the vast majority of patients (>90%) have experienced nausea during a migraine attack and more than 50% have nausea with the majority of attacks.[10,11] Similarly, most (almost 70%) have vomited at some time during an attack and of these patients, almost one-third vomit in the majority of attacks.[12] RZB is absorbed quickly from gut but undergoes moderate first pass metabolism which limits its oral bioavailability to about 45%. RZB is having low dose, short half-life of 2-3 h, molecular weight of 392 g/mol and requisite of fast onset of action makes it suitable for formulated as fast dissolving films.[13,14]

In the present research, focus has been made to deliver RZB through multipolymeric fast dissolving film containing three hetero polymers hydroxypropyl methylcellulose (HPMC) (E-15), maltodextrin and polyvinylalcohol (PVA). Among several film forming polymers, five widely used polymers were selected and screened by forming monopolymeric films containing fixed amount of other ingredients. Optimized amount of sweetener, plasticizer and flavor to be adapted to the further experimental batches was determined by preliminary formulation study. Since critical parameters in the development of a fast dissolving film are mechanical properties, the influence of the type and the concentration of plasticizers on flexibility, tensile strength and stickiness; monopolymeric films were evaluated based on these properties. After preliminary screening, formulation and optimization of fast dissolving films was carried out using Box-Behnken experimental design.[15]

## MATERIALS AND METHODS

### Materials

RZB was a kind gift from Cipla Ltd. (Mumbai, India). HPMC (15 cps), polyvinyl pyrrolidone (K-30), PVA, Methyl cellulose (A-6) and maltodextrin were gifted by Astron Research Pvt. Ltd. (Ahmedabad, India). Plasticizer (propylene glycol) was produced from Suvik Hitek Pvt. Ltd. Gandhinagr, India. Coloring agent (Allura red AC), flavoring agent (strawberry) and sweetener (alitame) were obtained from Xylopia Research Center, Ahmedabad, India. All other chemicals used were of analytical grade.

### Methods

#### *Polymer screening*

Five monopolymeric films trial batches $T_1$-$T_5$ were prepared to screen three polymers on the basis of film characteristics such as film forming capacity, mechanical and physical characteristics and dissolving time [Table 1].

#### *Preparation of mouth dissolving film*

Fast dissolving films were prepared by solvent casting technique. Preliminary trials were carried out to determine optimized amount of plasticizer, sweetener and flavor. Requisite amount of the drug, polymer, plasticizer, coloring agent, sweetener and flavor were dissolved in 18 ml distilled water. It was stirred for 10 min on a magnetic stirrer (Remi Magnetic Stirrer Bath 2 MLB, Mumbai, India) and the final volume (20 ml) was made with distilled water with stirring. It was stirred further for 10 min and was kept aside to remove the entrapped air bubbles. Resulting casting solution was casted on flat, square-shaped aluminum foil covered plastic mold having surface area of 4 × 4 cm and was dried at 40°C in a hot air oven. The dried film was carefully removed from the mould and was cut into size of 2 $cm^2$ size required for testing. Cut films were kept in desiccator for 1 day and covered with aluminum foils. The films were stored in an air tight container until further use.

### Experimental design

Formulation optimization process was carried out using a Box-Behnken design, as it requires few runs with three or four variables. Here three variables at three levels were studied using total 17 runs.[16] Layout of the Box-Behnken design is represented in Table 2. Effect of three factors $X_1$ (HPMC K-15), $X_2$ (Maltodextrin) and $X_3$ (PVA) on mechanical properties of film and percentage drug release in 30 s ($Q_{30}$) in distilled water were studied by Box-Behnken design. A set of points lying at the midpoints of each edge of the multidimensional design cube as well as replicated center points were utilized to construct mathematical models and response surfaces using Design Expert® software (Version 7.0.0, Stat-Ease Inc., Minneapolis, MN, USA). Derived models were validated using three checkpoint batches $CHK_1$-$CHK_3$.

In order to determine the reliability of the equations that describe the influence of the independent variables over the dependent variables, three additional checkpoint experiments ($CHK_1$, $CHK_2$ and $CHK_3$) were conducted in triplicate. The percentage relative error (%RE) for each response was calculated using Equation 1.

$$\%RE = \frac{\text{Predicted value} - \text{Experimental value}}{\text{Predicted value}} \times 100 \quad (1)$$

**Table 1: Polymer screening**

| Ingredients | Amount for 20 ml casting solution | | | | |
|---|---|---|---|---|---|
| | T1 | T2 | T3 | T4 | T5 |
| Rizatriptan benzoate (mg) | 58.12 | 58.12 | 58.12 | 58.12 | 58.12 |
| Hydroxypropylmethycellulose E-15 (mg) | 90 | – | – | – | – |
| Maltodextrin (mg) | – | 90 | – | – | – |
| Polyvinyl pyrrolidone K-30 (mg) | – | – | 90 | – | – |
| Methyl cellulose A-6 (mg) | – | – | – | 90 | - |
| Polyvinyl alcohol (mg) | – | – | – | – | 90 |
| Glycerol (mg) | 15 | 15 | 15 | 15 | 15 |
| Colouring agent (10% w/v solution) (ml) | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 |
| Sweetener (mg) | 20 | 20 | 20 | 20 | 20 |
| Flavor (ml) | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 |
| Film forming capacity | ++ | ++ | – | – | + |
| Physical characteristics | Transparent film, good texture | Transparent film, good texture | Semitransparent and sticky film with poor texture | Semitransparent and brittle film, average texture | Transparent but slightly brittle film, good texture |
| Tack (dryness) test | 2 | 4 | 1 | 3 | 1 |
| Folding endurance | 157 | 97 | 159 | 70 | 133 |
| Dissolving time (s) | 85 | 57 | 35 | 36 | 54 |

++: Good, +: Average, −: Poor. Dryness test: 5. Perfectly dry, 4. Dry, 3. Slightly tacky, 2. Tacky, 1. Very tacky

## Measurement of mechanical properties

Five mechanical properties namely load at yield, tensile strength, elastic modulus, percentage elongation and folding endurance of films were evaluated. Mechanical properties of the film were studied using Instron universal testing machine with 5 kg load cell (Model F.4026, Instron Ltd. NITK, Surathkal, Japan). Film strip with dimension 20 × 10 mm was held between two clamps positioned at a distance of 2 cm. Strip pulling speed was set at 60 mm/min. The values of mechanical properties were recorded when the film broke. Measurements were run in triplicate for each film.[17]

## Physicochemical evaluation of film

### *Morphology study*

The surface morphology of the optimized batch OB was studied using scanning electron microscopy (SEM; JEOL JSM-5200, Tokyo, Japan). The thickness of the film was measured using digital Vernier Calliper. The thickness was measured at six different spots of the film to determine average film thickness with standard deviation.

### *Surface pH*

Deviation of film surface pH on either side from neutral pH may produce discomfort or irritation of the mucosal membrane. Hence attempt was made to keep surface pH as close to neutral as possible. Surface pH of the film was measured using previously reported method.[17,18] Equally cut strip of 1 × 1 cm was placed in a petri dish and moistened with 1 ml of distilled water for 1 min. The surface pH was measured by micro probe pH electrode (pH Cal, Electroquip, Mumbai, India). Test was performed in triplicate ($n = 3$).

### *In vitro disintegration and dissolving time*

Film strip (2 × 2 cm) of each batch was placed in 25 ml of simulated saliva, kept mildly agitated by swirling every 10 s. The disintegration time is the time when a film starts to break or disintegrate. The dissolving time is the time when the film completely dissolves.[19]

### *In vitro dissolution studies*

The dissolution was carried out using USP dissolution apparatus type II (Model TDT-00T, Electrolab, Mumbai, India) in 500 ml simulated saliva (pH 6.8; 37°C ± 0.5°C; 50 rpm).[20,21] Film strip of 2 × 2 cm was tied to a 3 × 3 cm solid block. It was put into the bowl of dissolution apparatus. 5 ml samples were withdrawn at the time interval of 10 s and filtered through 0.45 $\mu$ filter. Samples were analyzed using spectrophotometrically at 225 nm (1800 ultraviolet (UV)-visible spectrophotometer, Shimadzu, Kyoto, Japan). An equal volume of the fresh dissolution media, maintained at the same temperature, was added after withdrawing the sample.

### *Drug content uniformity*

Film from each batch was cut five in strips of 1 × 1 cm from different places. Each film strip was dissolved separately in 100 ml of distilled water using mechanical shaker. The resulting solutions were filtered and analyzed at 225 nm in a UV-Visible Spectrophotometer (1800 UV-visible spectrophotometer, Shimadzu, Japan) using the placebo patch (patch without drug) solution as blank.[22] The average of five strips was taken as the content of drug in one film strip.

### Drug-excipient interaction study

The pure RZB and film of optimized batch were separately mixed with IR grade potassium bromide. Infrared spectra were taken over a wave number of 4000-400/cm using an infrared spectrophotometer (FTIR-8400S, Shimadzu, Japan).

### Stability study

Stability testing was performed as per International Conference on Harmonization guidelines conditions at intermediate (30°C ± 2°C/65% ± 5% RH) and accelerated storage conditions (40°C ± 2°C/75% ± 5% RH) for a period of 3 months. Aluminum foil wrapped film strips were put in clean, dry, air tight, moisture proof glass bottles, kept away from light and transferred to the stability chamber (Thermolab, Mumbai, India). The strips were characterized for mechanical and physicochemical properties at regular intervals of 1 month.

## RESULTS AND DISCUSSION

### Polymer screening

As shown in Table 1, monopolymeric films were having different characteristics according to the film forming polymer utilized. Batches $T_1$, $T_2$ and $T_5$ containing polymers HPMC E-15, maltodextrin and PVA, respectively; produced films of acceptable characteristics. Among these, batch $T_1$ showed comparatively higher dissolving time while batch $T_5$ resulted in brittle film. Batch $T_2$ could produce films with desired properties but having poor folding endurance. To overcome these drawbacks, combination of polymer characteristics at different levels to derive optimized film formulation with improved characteristics was accessed by applying Box-Behnken design.

### Preparation and optimization of mouth dissolving film

Box-Behnken experimental batches were prepared employing three screened polymers as independent factors. Five dependent variables namely tensile strength ($R_1$), folding endurance ($R_2$), load at yield ($R_3$), percent elongation ($R_4$) and $Q_{30}$ ($R_5$) were measured for experimental and checkpoint batches prepared using independent variables HPMC E-15 ($X_1$), maltodextrin ($X_2$) and PVA ($X_3$) [Tables 2 and 3a represents layout of Box-Behnken design and measured responses, respectively. Moreover, prepared batches were evaluated for physicochemical parameters as listed in Table 3b].

Stepwise multivariate linear regression analysis of variance (ANOVA) was performed to derive the model predictor equations for each dependent variable separately employing Design Expert® software (Version 7.0.0, Stat-Ease Inc., Minneapolis, MN, USA). Equation 2 represents a statistical model incorporating mathematical terms derived for individual responses

$$R = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{23} X_2 X_3 + \beta_{13} X_1 X_3 + \beta_{123} X_1 X_2 X_3 \quad (2)$$

Where R is the dependent variable, $\beta 0$ is the arithmetic mean response of all the runs, and bi (i = 1-3) is the estimated coefficient for the factor $X_i$ (i = 1-3). The main effects, i.e., $X_1$, $X_2$, and $X_3$, correspond to the average result of changing one factor at a time while the interaction terms, i.e., $X_1X_2$, $X_2X_3$, $X_1X_3$, and $X_1X_2X_3$, show how the response changes when two or more factors are simultaneously changed. The statistical evaluation of the results was carried out by ANOVA using Design Expert® software (Version 7.0.0, Stat-Ease Inc., Minneapolis, MN, USA).

The ANOVA table represents regression analysis for the full and derived models [Table 4]. The applied design was further validated by the standard error graph, which shows the standard error of prediction for areas in the design space. For acceptable criterion, this graphs to have relatively low standard error (approximately 1.0 or lower) across the region of interest. Figure 1 shows the standard error graph of applied $3^2$ full factorial designs in 2D and 3D view, which indicates the standard error in the range of 0.60-1.00 reflecting efficacious prediction power of proposed factorial design.[23]

Full and reduced mathematical models were derived for each response. The significant factors in the equations were selected using a stepwise forward and backward elimination

**Table 2: Layout of Box-Behnken design**

| Batch | $X_1$: HPMC E-15 | $X_2$: Maltodextrin | $X_3$: PVA |
|---|---|---|---|
| $BB_1$ | −1 | −1 | 0 |
| $BB_2$ | −1 | 0 | −1 |
| $BB_3$ | −1 | 0 | 1 |
| $BB_4$ | −1 | 1 | 0 |
| $BB_5$ | 0 | −1 | −1 |
| $BB_6$ | 0 | −1 | 1 |
| $BB_7$ | 0 | 0 | 0 |
| $BB_8$ | 0 | 1 | −1 |
| $BB_9$ | 0 | 1 | 1 |
| $BB_{10}$ | 1 | −1 | 0 |
| $BB_{11}$ | 1 | 0 | −1 |
| $BB_{12}$ | 1 | 0 | 1 |
| $BB_{13}$ | 1 | 1 | 0 |
| $BB_{14}$ | 0 | 0 | 0 |
| $BB_{15}$ | 0 | 0 | 0 |
| $BB_{16}$ | 0 | 0 | 0 |
| $BB_{17}$ | 0 | 0 | 0 |
| $CHK_1$ | −0.58 | 0.12 | −0.65 |
| $CHK_2$ | 0 | −0.82 | 0.52 |
| $CHK_3$ | 0.81 | 0.1 | 0.75 |
| **Transformed coded to actual levels** | | | |
| **Independent variables** | **Actual level of factor (mg)** | | |
| | **−1** | **0** | **1** |
| HPMC E-15 | 20 | 40 | 60 |
| Maltodextrin | 15 | 30 | 45 |
| PVA | 18 | 36 | 54 |

HPMC: Hydroxypropyl methylcellulose, PVA: Polyvinylalcohol

for the calculation of regression analysis. According to the probability function, insignificant terms (significance level = 5%, $P \geq 0.05$) were excluded to derive reduced models.[24,25] Reduced equations derived for each independent variable are shown below in Equations 3-7:

$$R_1 = 527.56 + 97.31X_1 + 35.48X_2 - 11.74X_3 \quad (3)$$

$$R_2 = 233.09 + 44.19X_1 - 17.99X_2 + 45.28X_3 - 26.2X_1X_2 \quad (4)$$

$$R_3 = 12.18 + 4.69X_1 - 2.7X_2 + 0.89X_3 - 0.38X_1X_2 + 0.66X_1^2 + 1.24X_2^2 \quad (5)$$

$$R_4 = 4.77 + 0.95X_1 + 0.34X_2 - 0.16X_3 \quad (6)$$

$$R_5 = 63.99 + 5.23X_1 - 5.30X_2 + 2.1X_3 - 274X_1^2 - 0.56X_3^2 \quad (7)$$

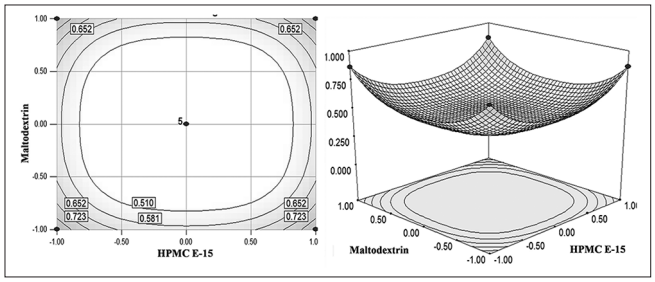


**Figure 1:** Standard error graph in 2D and 3D

**Table 3a: Responses of Box-Behnken and checkpoint batches**

| Batch code | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| | Tensile strength ($N/m^2$) | Folding endurance | Load at yield ($N$) | Percent elongation (%) | $Q_{30}$ (%) |
| $BB_1$ | 388.4±3.4 | 219.7±2.4 | 12.4±0.3 | 3.2±0.5 | 55.7±3.1 |
| $BB_2$ | 452.9±2.4 | 100.5±3.2 | 7.3±0.7 | 4.1±0.7 | 63.5±3.9 |
| $BB_3$ | 416±3.3 | 250.7±1.4 | 8.8±0.7 | 3.8±0.5 | 58.9±2.8 |
| $BB_4$ | 459.3±6.8 | 189±0.7 | 6.6±0.3 | 4.3±0.2 | 66.8±4.0 |
| $BB_5$ | 490.8±5.4 | 203.4±1.5 | 15.4±1.7 | 4.6±0.1 | 60.3±3.7 |
| $BB_6$ | 472±1.2 | 280.8±2.2 | 17.3±2.0 | 4.3±0.3 | 56.4±3.7 |
| $BB_7$ | 533.6±7.3 | 234.2±1.6 | 12.1±1.2 | 4.8±0.2 | 64.2±3.2 |
| $BB_8$ | 574.1±8.4 | 174.1±4.4 | 9.5±0.9 | 5.1±0.7 | 70.3±4.1 |
| $BB_9$ | 560±2.1 | 263.3±3.0 | 11.7±1.1 | 4.8±0.4 | 66.3±1.2 |
| $BB_{10}$ | 603.1±1.7 | 307±2.8 | 20.7±2.1 | 5.5±0.4 | 66.3±4.2 |
| $BB_{11}$ | 635.7±4.5 | 260.2±1.1 | 17±1.7 | 5.9±0.9 | 73.5±3.8 |
| $BB_{12}$ | 611.6±7.7 | 305.6±5.7 | 18.5±1.7 | 5.5±0.5 | 69.2±3.1 |
| $BB_{13}$ | 644.7±1.5 | 240.6±3.2 | 16.4±1.4 | 6.1±0.6 | 77.7±2.2 |
| $BB_{14}$ | 525.8±8.8 | 228.7±3.9 | 12±1.0 | 4.7±0.3 | 64±2.7 |
| $BB_{15}$ | 530±4.2 | 232.2±4.2 | 12.6±1.5 | 4.9±0.4 | 64.7±2.8 |
| $BB_{16}$ | 538.9±1.4 | 237.4±1.7 | 11.8±0.8 | 4.8±0.3 | 63.2±2.8 |
| $BB_{17}$ | 531.6±1.7 | 235.1±2.0 | 12.2±0.5 | 4.7±0.3 | 64.3±2.5 |
| $CHK_1$ | 476.3±2.2 | 168.9±2.1 | 8.69±0.7 | 4.28±0.5 | 61.3±3.0 |
| $CHK_2$ | 512.7±0.7 | 278.5±3.3 | 15±1.4 | 4.32±0.2 | 56±3.1 |
| $CHK_3$ | 584.4±3.7 | 285±1.9 | 16.55±1.3 | 5.33±0.3 | 69.9±3.1 |

Influence of individual terms in above equations can be depicted by their corresponding coefficients. Positive sign of all the coefficients of factor $X_1$ (HPMC E-15) represents its positive influence on all the responses. It was depicted from Equations 3, 6 and 7 that maltodextrin exhibits positive influence over tensile strength, percentage elongation and $Q_{30}$. On the other side, PVA demonstrated negative influence over these three responses. Other interaction and quadratic terms of the quadratic equation illustrated positive influence over load at yield and negative influence over folding endurance. They were found to be insignificant for tensile strength and percentage elongation. The trend of magnitude of the effect of independent variable on $Q_{30}$ was found to be maltodextrin >HPMC E-15>>PVA.

Derived mathematical models were further validated through three random checkpoint batches. Table 5 enlists the experimental values and predicted values of each response. The %REs revealed that differences between observed and predicted values were insignificant, which proved derived mathematical models valid. Therefore derived mathematical models were employed for optimization by desirability criteria. Figure 2 represents the response surfaces of all responses and overlay plot.

On the basis of specified criteria, a set of possible combinations were derived according to the desirability function using Design Expert® software (Version 7.0.0, Stat-Ease Inc., Minneapolis, MN, USA). The combination of independent variables with highest desirability (desirability value = 0.804) was selected as optimized batch OB. Composition of batch OB is represented in Table 6.

**Table 3b: Physical evaluation of simplex lattice batches**

| Batch | Thickness (μm) | Surface pH | Drug content (%) | Dissolving time (s) | Elastic modulus |
|---|---|---|---|---|---|
| $BB_1$ | 356±28 | 6.5±0.3 | 99.34±1.57 | 67±4.3 | 10547±210 |
| $BB_2$ | 421±43 | 6.7±0.2 | 98.24±2.01 | 68.2±3.3 | 13945±137 |
| $BB_3$ | 520±37 | 7.1±0.1 | 99.34±2.46 | 71.5±5.7 | 11493±245 |
| $BB_4$ | 738±24 | 6.5±0.2 | 97.84±3.2 | 64.4±4 | 18864±177 |
| $BB_5$ | 655±33 | 6.5±0.3 | 99.89±1.82 | 65.5±5.1 | 10873±276 |
| $BB_6$ | 477±49 | 6.7±0.4 | 98.33±2.0 | 61.8±5.2 | 10139±282 |
| $BB_7$ | 425±21 | 7.2±0.1 | 97.69±3.23 | 63.8±5.7 | 13769±328 |
| $BB_8$ | 552±49 | 6.8±0.2 | 98.89±2.17 | 69.2±3.3 | 19243±333 |
| $BB_9$ | 611±28 | 6.9±0.2 | 97.90±1.54 | 66.3±2.9 | 18753±198 |
| $BB_{10}$ | 493±34 | 6.9±0.1 | 98.74±2.11 | 65.9±3.4 | 12385±172 |
| $BB_{11}$ | 375±29 | 6.5±0.4 | 97.4±3.3 | 63±2.7 | 12942±293 |
| $BB_{12}$ | 584±44 | 7.0±0.3 | 98.3±2.3 | 70.3±3.7 | 13721±198 |
| $BB_{13}$ | 483±38 | 6.6±0.2 | 97.4±3.3 | 64.6±4.0 | 19543±207 |
| $BB_{14}$ | 500±41 | 6.9±0.3 | 97.4±3.3 | 62.9±2.1 | 13731±230 |
| $BB_{15}$ | 433±28 | 7.2±0.4 | 97.4±3.3 | 63.4±4.2 | 13691±193 |
| $BB_{16}$ | 529±28 | 6.8±0.1 | 97.4±3.3 | 68.3±5.3 | 13573±205 |
| $BB_{17}$ | 683±28 | 6.9±0.4 | 97.4±3.3 | 62.7±3.0 | 13643±267 |

**Table 4: ANOVA results (*P* value) of the effect of independent variables on response variables**

| Regression | df | SS | MS | *F* value | $R^2$ |
|---|---|---|---|---|---|
| Tensile strength, $N/m^2$ | | | | | |
| FM | 9 | 87394.21 | 9710.47 | 99.59 | 0.9923 |
| RM | 3 | 86927.74 | 28975.91 | 327.84 | 0.9870 |
| Folding endurance | | | | | |
| FM | 9 | 37938.61 | 4215.4 | 24.99 | 0.9698 |
| RM | 4 | 37353.05 | 9338.26 | 63.44 | 0.9548 |
| Load at yield, *N* | | | | | |
| FM | 9 | 249.73 | 27.75 | 202.43 | 0.9962 |
| RM | 6 | 249.66 | 41.61 | 404.6 | 0.9959 |
| Percentage elongation, % | | | | | |
| FM | 9 | 8.44 | 0.94 | 48.44 | 0.9842 |
| RM | 3 | 8.34 | 2.78 | 155.29 | 0.9729 |
| $Q_{30}$, % | | | | | |
| FM | 9 | 510.97 | 56.77 | 167.12 | 0.9954 |
| RM | 5 | 510.75 | 102.15 | 432.48 | 0.9949 |

df: Degree of freedom, SS: Sum of squares, MS: Mean square, ANOVA: Analysis of variance, FM: Full model, RM: Reduced model

**Table 5: Validation by checkpoint batches**

| Response | Batch code | Experimental value | Predicted value | Percentage of relative error |
|---|---|---|---|---|
| Tensile strength, $N/m^2$ | $CHK_1$ | 476.3 | 483.01 | 1.39 |
| | $CHK_2$ | 512.7 | 492.36 | 4.13 |
| | $CHK_3$ | 584.4 | 601.12 | 2.78 |
| Folding endurance | $CHK_1$ | 168.9 | 177.69 | 4.95 |
| | $CHK_2$ | 278.5 | 271.39 | 2.62 |
| | $CHK_3$ | 285 | 298.92 | 4.66 |
| Load at yield, *N* | $CHK_1$ | 8.69 | 8.77 | 0.92 |
| | $CHK_2$ | 15 | 15.69 | 4.40 |
| | $CHK_3$ | 16.55 | 16.85 | 1.80 |
| Percentage elongation, % | $CHK_1$ | 4.28 | 4.36 | 1.92 |
| | $CHK_2$ | 4.32 | 4.41 | 2.00 |
| | $CHK_3$ | 5.33 | 5.45 | 2.26 |
| $Q_{30}$, % | $CHK_1$ | 61.3 | 63.64 | 3.68 |
| | $CHK_2$ | 56 | 58.40 | 4.11 |
| | $CHK_3$ | 69.9 | 68.66 | 1.80 |

**Table 6: Optimized formulation for film containing RZB (Batch OB)**

| Formulation ingredients | Amount per film |
|---|---|
| RZB (mg) | 14.53 |
| HPMC E-15 (mg) | 9.8 |
| Maltodextrin (mg) | 3.79 |
| PVA (mg) | 4.5 |
| Propylene glycol (ml) | 0.05 |
| Alitame (mg) | 2 |
| Strawberry flavour (ml) | 0.0125 |
| Allura red AC (mg) | 0.0125 |

RZB: Rizatriptan benzoate; HPMC: Hydroxypropyl methylcellulose, OB: Optimized batch

### Physicochemical evaluation of film

SEM image of optimized batch OB represents interconnected arrangement of polymers. Absence of drug crystals revealed uniform distribution of drug throughout the film and physical stability of the drug [Figure 3]. Prepared experimental batches films thickness ranged within 300-750 $\mu$m. Surface pH of all experimental formulations was found in vicinity to neutral. Thus probability of irritation due to pH difference was nullified.

*In vitro* disintegration time and dissolving time were about 5 and 70 s respectively. It disclosed the effect of combining two or more polymers which resulted in reduction of overall disintegration and dissolution time. Besides, synergistic effect was observed on folding endurance, i.e., folding endurance of batch OB was higher than that of monopolymeric films. Drug content of all the batches were found within pharmacopoeia limits.

Drug release pattern of Box-Behnken batches and batch OB in simulated saliva are represented in Figure 4. The figure illustrates that drug release profile of batch OB followed desired pattern and >80% drug was released within 40 s.

### Drug-excipients interaction study

Fourier transform infrared spectrum of pure RZB and physical mixture of formulation of batch OB are shown in Figure 5. Characteristic peaks of RZB were observed near region of 3430/cm (N-H stretch); 2938/cm, 2888/cm (CH3, CH2 stretch); 1608/cm (C-C stretch); 1569/cm (N-H bend); 1446, 1377 (CH2, CH3 bend); 1271, 1140, 1016 (C-N stretch). These peaks were retained in the spectrum of physical mixture.

### Stability study

The stability study of the optimized formulation OB was carried out at intermediate and accelerated storage conditions. For films stored at intermediate storage conditions, no significant changes were observed in mechanical and physicochemical properties till 3 months. Although films stored at accelerated conditions showed comparatively poor mechanical properties after 3 months storage. It may be due to effect of higher humidity on polymer characteristics. Hence proper storage conditions are required to be labeled on package.

## CONCLUSION

Findings from the investigation revealed that combination of two or more polymers at appropriate levels may result in fast dissolving film with improved characteristics as compared to monopolymeric film. Some limitations such as high dissolving time, low folding endurance, poor appearance etc. may be improved by formulating multipolymeric films as compared to corresponding monopolymeric films. This study utilized some of the widely used polymers to improve characteristics of monopolymeric films. Similar formulations can be prepared

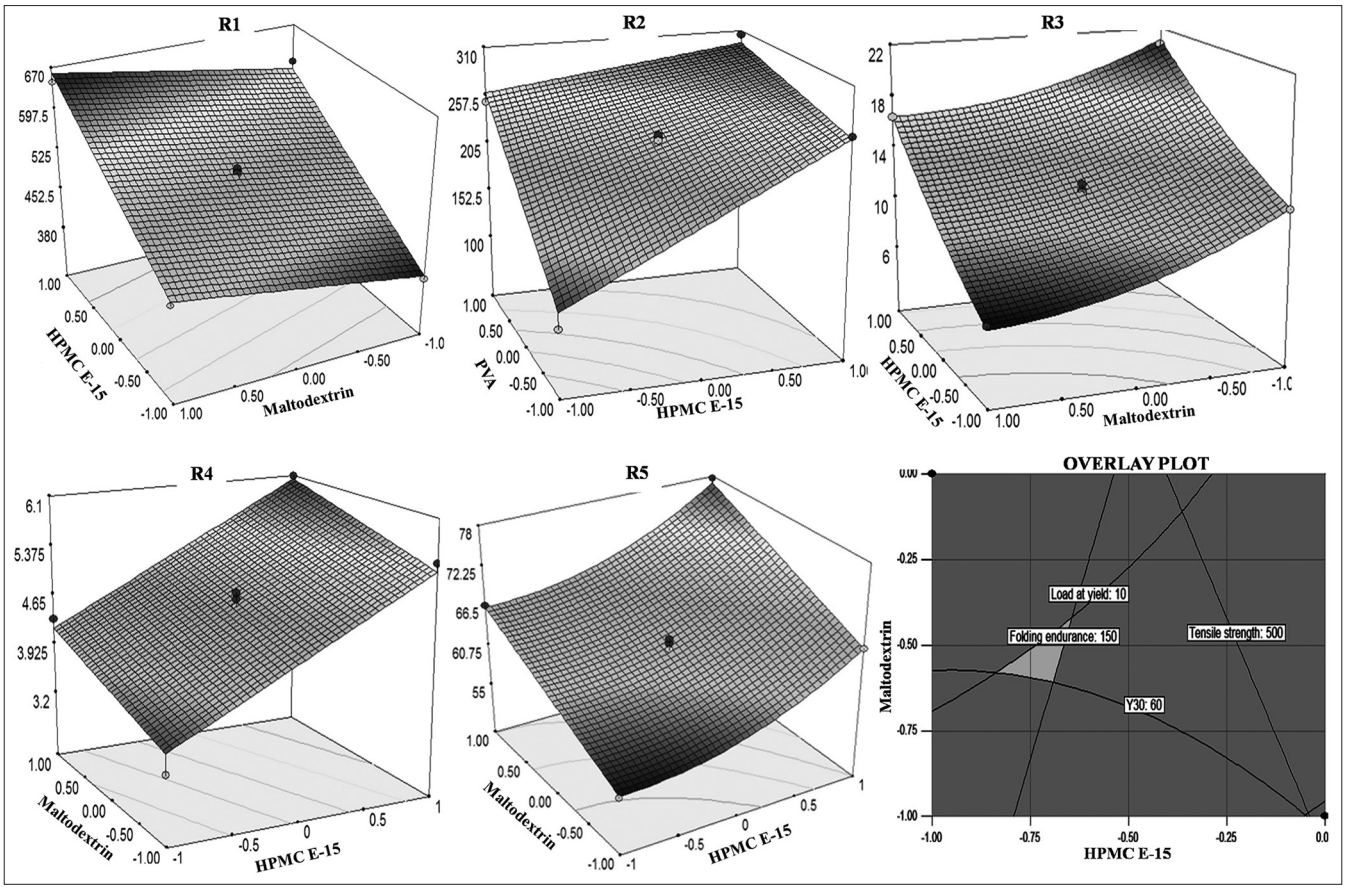


**Figure 2:** Contour plots for dependent responses (*R*1-*R*5) and overlay plot

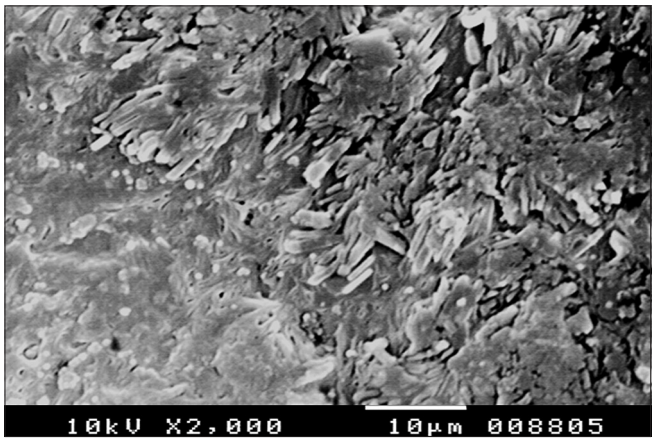


**Figure 3:** Scanning electron microscopy of optimized batch film

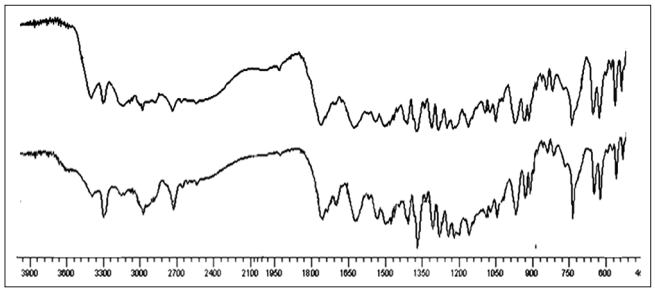

**Figure 5:** Fourier transform infrared spectra of (a) rizatriptan and (b) physical mixture of batch OB formulation

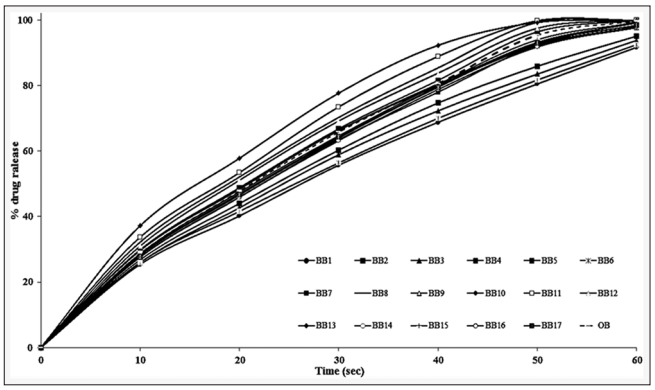


**Figure 4:** *In vitro* drug release profiles of experimental batches

by combining other polymers also. Evaluation of the optimized batch OB revealed that the limitations of HPMC E-15, maltodextrin and PVA were overcome by suitable combination all three polymers. Further studies can be carried out in future to overcome present limitations of this dosage form.

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