RIZATRIPTAN BENZOATE FAST DISSOLVING TABLETS FOR QUICK RELIEVE OF MIGRAINE: DESIGN, DEVELOPMENT AND CHARACTERIZATION

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ABSTRACT

Objective: Rizatriptan benzoate (RB) is a new generation anti-migraine drug. After oral administration, the peak plasma concentrations (t_{max}) occur in about 1 to 2.5 hrs depending on the formulation and the bioavailability which is about 40 to 45%. Food may delay the t_{max} by about 1 hour. The aim of this work was to design and develop fast dissolving tablets of RB to improve the bioavailability and patient compliance applying the Mixture Experimental Design. **Methods:** Twenty formulations were prepared by direct compression each containing 14.53 mg of RB equivalent to 10 mg Rizatriptan with different proportions of superdisintegrants (X_1-X_3) according to the experimental design. The independent factors selected were the percentages of: Croscarmellose sodium (X_1), Explotab (X_2) and Polyplasdone XL 10 (X_3). The dependent variables investigated were: hardness (Y_1), disintegration time (Y_2) and cumulative % drug release after 10 minutes (Y_3). The formulations were evaluated for the pre-compression parameters to assess the powder compressibility and flowability (bulk and tapped density, Hausner's ratio, Carr's index and angle of repose) as well as the post-compression parameters (weight variation, friability, hardness, disintegration time, wetting time, water absorption ratio, drug content and in-vitro drug release). The optimized formulation was prepared and evaluated in the same manner. **Results:** All the evaluated parameters, either for powder blend or for the compressed tablets, were within the acceptable limits. The values of dependent variables ranged between 3.13-3.68 kg/cm^2; 12.23-21.81 sec; and 94.44-99.83% for Y_1, Y_2 and Y_3 respectively. Polynomial regression equations for the variables (Y_1-Y_3) were generated and the quantitative effects of X_1-X_3 at different levels on Y_1-Y_3 could be predicted. Surface response and contour plots were plotted. The optimal ratios of different disintegrants were used to prepare the optimized formulation. The difference between the predicted and the observed data for the optimized formula were minimal. **Conclusions:** The use of direct compression technique and the mixture experimental design succeeded to produce fast dissolving tablets of RB with optimal hardness, minimal disintegration time and maximal in vitro drug release. The quantitative effects of the selected factors tested on the different variables were explored. Based on the obtained results, fast dissolving tablets of RB could be a potential dosage form for quick relieve of migraine patients.

Key words: Fast Dissolving tablets, Rizatriptan benzoate, Experimental Design

INTRODUCTION

The oral cavity is still the attractive site for drug administration because of ease and versatility of use. Fast dissolving tablets, also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and quick disintegrating tablets, disintegrate in the mouth without chewing and there is no need for water to facilitate swallowing ***(Chopda et. al., 2014)***.

All fast dissolving tablets approved by FDA are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in the mouth in less than 3 minutes before swallowing. Such a tablet disintegrates into smaller granules, or melts in the mouth to a gel-like structure and allows easy swallowing by patients ***(Patidar et. al., 2011).***

One of the advantages of orodispersible tablets is to provide quick onset of action within few seconds as the oro-mucosal absorption of drug occurs directly from the site of administration to the systemic circulation avoiding first pass metabolism. Various techniques have been used to formulate fast dissolving tablets. The most common preparation methods are molding, lyophilization, direct compression, cotton-candy, spray drying, and sublimation **(*(*Parakh and Gothoskar, 2003; *Evren et al., 2014*)**. Each one of these has advantages and disadvantages.

Direct compression represents one of the techniques that require the incorporation of superdisintegrants into the formulation and the use of highly water soluble excipients to achieve fast tablet disintegration ***(Indurwade, 2002).*** This technique does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile drugs. It is inexpensive, most convenient and produces tablets of sufficient mechanical integrity without the use of complicated unit operations ***(Parshu et al., 2012)***.

Design of Experiments (DOE), also called statistical experimental design, is a well-established concept for planning of experiments and generating useful data. An important application of DOE is the preparation and modification of mixtures. It involves the changing in mixture composition and exploring how such changes will affect the properties of the mixture in an attempt to find the formulation (or formulations) that produce the best response **(*Cornell, 1990, Eriksson et al., 1998; Martinello et al., 2006*)**.

Rizatriptan benzoate (RB) is a potent and selective 5-hydroxytryptamine$_{1B/1D}$ receptor agonist and is considered more effective than the traditional triptans for the treatment of acute migraine attack ***(Sanders et al., 2006).*** A 10 mg dose of Rizatriptan is equipotent to a 100 mg of sumatriptan, the traditional antimigraine drug ***(Martindale, 2002)***. RB has poor bioavailability (40 to 45%) may be because of liver metabolism and incomplete drug absorption and its t_{max} is 1 to 2.5 hrs depending on the formulation. On oral administration of intact tablet, it was found that food may delay the t_{max} by about 1 hr. As migraine sufferers have markedly reduced functional ability, they would be benefited from quick treatment that helps them to resume their functional activities as quickly as possible.

The objectives of this study were to design and develop fast dissolving tablets of RB in order to solve the problem of difficulty in swallowing leading to better patient compliance, improve onset of action to enhance both the safety and efficacy of drug molecules. DOE was applied to study the effects of superdisintegrant concentrations on the hardness, disintegration time and dissolution time. DOE was also to generate the optimized formulation which was prepared and characterized in the same manner.

MATERIAL AND METHODS

Materials

RB was obtained from Zhejiang Supor Pharmaceuticals Co. Ltd. (Shaoxing, China); Croscarmellose sodium (Ac-Di-Sol, "modified cellulose gum NF", was obtained from FMC Corporation (Philadelphia, PA, USA); Explotab (Sodium Starch Glycolate), Emcocel®90M (Microcrystalline Cellulose) and Pruv® (Sodium Stearyl Fumarate) were obtained from JRS Pharma (GMBH & Co. KG, Rosenberg, Germany); Crospovidone NF (Polyplasdone XL10) from ISP Technologies, (Ashland, KY, USA); Pearlitol® 200SD-Mannitol was obtained from Roquette Freres, (France); Aerosil 200 was obtained from Cabot Corporation, (Boston, MA, USA); Aspartame was obtained from Nutrasweet LTD. All other materials were of analytical grades and were used without further purification.

Methods

Experimental Design

A mixture experimental design of the Extreme vertices model was employed to statistically optimize the combination of superdisintegrants for development of RB fast dissolving tablets with optimal hardness, minimal disintegration time and maximal in vitro drug release. Generation and evaluation of the DOE was performed with Statgraphics® Centurion XV Software Version 15.2.05 (StatPoint Technologies, Inc., Warrenton, VA, USA). The selected superdisintegrants: Croscarmellose sodium (X_1), Explotab (X_2), and Polyplasdone XL 10 (X_3) were used in different proportions for construction of 20 formulae in randomized runs by the mixture design. The dependent variables investigated were the hardness (Y_1), in vitro disintegration time (Y_2) and the cumulative % release of RB from fast dissolving tablets after 10 min (Y_3). Table 1 summarizes the independent factors and intervals selected to perform the mixture design.

Table 1: Factors and intervals selected to perform the mixture of superdisintegrants

Independent Factors	**Level**	
	Low	High
Croscarmellose sodium (X_1)	0.0	0.6
Explotab (X_2)	0.0	0.7
Polyplasdon XL 10 (X_3)	0.0	0.5

Formulation of RB fast dissolving tablets

RB fast dissolving tablets were prepared by Direct Compression Technique. All the ingredients RB, Croscarmellose sodium, Explotab, Polyplasdon XL 10, Pearlitol, Emcocel and Aspartame were sifted through # 40 mesh and weighed, placed in bin blender and mixed for 15 minutes at 14 rpm followed by lubrication with sodium stearyl fumarate (which was previously sifted through # 60 meshes) for 5 min at 14 rpm ***(Hindustan et al., 2010).*** The lubricated blends ready for compression were compressed into tablets using flat face 8 mm size punch to get tablet of 100 mg using single punch Erweka Tablet compression machine (XL8D-type). The composition of batches as per the mixture design was shown in Table 2.

Table 2: Composition of RB fast dissolving tablets according to the mixture design:

Run code	RB	X_1	X_2	X_3	Emcocel	Pearlitol®	Aspartame	Aerosil 200	Pruv® JRS
F1	14.53	3	2	0	30	44.47	5	0.5	0.5
F2	14.53	3	0	2	30	44.47	5	0.5	0.5
F3	14.53	1.5	3.5	0	30	44.47	5	0.5	0.5
F4	14.53	0	3.5	1.5	30	44.47	5	0.5	0.5
F5	14.53	2.5	0	2.5	30	44.47	5	0.5	0.5
F6	14.53	0	2.5	2.5	30	44.47	5	0.5	0.5
F7	14.53	2.34	1.96	0.7	30	44.47	5	0.5	0.5
F8	14.53	2.34	0.96	1.7	30	44.47	5	0.5	0.5
F9	14.53	1.59	2.71	0.7	30	44.47	5	0.5	0.5
F10	14.53	0.84	2.71	1.45	30	44.47	5	0.5	0.5
F11	14.53	2.09	0.96	1.95	30	44.47	5	0.5	0.5
F12	14.53	0.84	2.21	1.95	30	44.47	5	0.5	0.5
F13	14.53	3	1	1	30	44.47	5	0.5	0.5
F14	14.53	2.25	2.75	0	30	44.47	5	0.5	0.5
F15	14.53	2.75	0	2.25	30	44.47	5	0.5	0.5
F16	14.53	0.75	3.5	0.75	30	44.47	5	0.5	0.5
F17	14.53	0	3	2	30	44.47	5	0.5	0.5
F18	14.53	1.25	1.25	2.5	30	44.47	5	0.5	0.5
F19	14.53	1.67	1.92	1.41	30	44.47	5	0.5	0.5
F20	14.53	3	2	0	30	44.47	5	0.5	0.5

Pre-compression evaluation of the powder blend:

The blend of each formula was evaluated by mass-volume relationship (for bulk and tapped density, Hausner's ratio, and Carr's index) and flow properties (angle of repose) to evaluate the compressibility and flow properties ***(Kumara et al., 2012).***

Post compression evaluation of the tablets

Weight variation test

The weight variation test was carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly selected from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated ***(Nyol et al., 2013).***

Friability test

The friability was measured in an Erweka Friabilator, type PTF1 (Pharmatest, Hainburg, Germany). In each run 20 tablets were carefully dedusted, weighed and rotated in the tester 100 times at 25 rpm then the tablets were dedusted and weighed again. Percentage friability was calculated from the loss in weight as given in the following equation.

Friability % (% loss in weight) = [(W1 - W2) / W1] × 100

Where W1 and W2 were tablet weights before and after test, respectively **(Battu *et al.*, 2007)**.

Hardness test

Tablet crushing strength or hardness (i.e. the force required to break a tablet in a diametric compression) was measured using 4M tablet hardness tester (Schleuniger, Switzerland) **(Battu *et al.*, 2007)**.

In vitro disintegration time

In-vitro Disintegration time was measured by dropping a tablet in a beaker containing 5 ml of pH 6.8 Phosphate buffer at 37±0.5° and the time required for complete dispersion was determined. Three tablets from each formulation were randomly selected and in-vitro disintegration times were determined ***(Mohire et al., 2009)*.**

Wetting time and water absorption ratio

The wetting time of the tablet was measured by placing a tablet on a piece of tissue paper folded twice in a small Petri dish (Internal diameter = 6.5 cm) containing ten millimeters of water. Eosin, a water soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time. Water absorption ratio (R) was then determined according to the following equation.

$R = [(Wa - Wb)/Wb] \times 100$ Where Wb and Wa were tablet weights before and after water absorption, respectively **(Battu *et al.*, 2007; Mukeshi *et al.*, 2009)**.

Drug content uniformity

The assay of tablets was performed by HPLC using Agilent 1200 Series, Agilent Technologies (Deutschland GmbH, Waldbronn, Germany), and SUPLECO Analytical-C18 column (250×4.6 id mm, 5 µm). The mobile phase used was triethylamin:acetonitrile (90:10) ***(Que et al., 2006)*.** The flow rate was set as 1.8 ml/min with a column temperature of 25°. The injected volume was 20 µl and an UV detector was used (226 nm).

For content uniformity test, ten tablets of each batch were weighed and powdered. Aliquot of this powder containing RB equivalent to 10 mg of Rizatriptan was accurately weighed, suspended in approximately 50 ml of 0.1 N HCl and shaken for 15 min. Final volume was adjusted to 100 ml with 0.1 N HCl and filtered (Whatmann No.1 filter paper). From this 10 ml was diluted to 100 ml. The final volume was made by taking 2 ml of above solution and diluted to 10 ml with 0.1 N HCl. Absorbance of this solution was recorded against a reagent blank and the mean percent drug content was calculated as an average of three determinations ***(Keny et al., 2010)*.**

In vitro release studies

In vitro dissolution of RB fast dissolving tablets was studied in USP dissolution test apparatus type II employing a paddle stirrer at 50 rpm using 900 ml of water at 37±0.5° as dissolution medium ***(Que et al., 2006)*.** One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specific intervals of time (2 min) filtered through (Whatmann No.1 filter paper) and analyzed for drug content by measuring the absorbance at 280 nm using UV/Vis spectrophotometer against a reagent blank (water). The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent drug released was calculated and plotted against time ***(Keny et al., 2010)*.**

RESULTS AND DISCUSSION

Evaluation of powder blends

The flow properties of powder blends of the formulations were evaluated and illustrated in Table 3. Bulk density of various formulations was found to be in the range of 0.487-0.514 g/cm^{3}and the tapped density ranged from 0.571 to 0.601 g/cm^3. From the observed data, the powder blends of all the formulations had Hausner ratio and Carr's index values ranging from 1.14 to 1.21 and 12.80 to 17.73 %, respectively. The angle of repose ranged from 20.11 to 27.49°. The results provide strong evidence that these blends had excellent flow properties and could be used for tablet manufacture by direct compression. In general, powders with angles of repose greater than 60° would have unsatisfactory flow properties, while powders with minimum angle of repose up to 25° would have excellent flowability **(Carr, 1965).**

Table 3: Evaluation of powder blend of drug and excipients

Run Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Carr's index (%)	Angle of repose (°)
F1	0.514 ± 0.007	0.593 ± 0.005	1.15	13.32	22.13 ± 0.143
F2	0.501 ± 0.006	0.588 ± 0.009	1.17	14.79	23.84 ± 0.125
F3	0.494 ± 0.009	0.571 ± 0.005	1.15	13.45	26.15 ± 0.119
F4	0.502 ± 0.005	0.583 ± 0.006	1.16	13.89	20.93 ± 0.257
F5	0.495 ± 0 .007	0.574 ± 0.007	1.15	13.76	26.49 ± 0.243
F6	0.504 ± 0.006	0.578 ± 0.008	1.14	12.80	20.11 ± 0.132
F7	0.491 ± 0.008	0.584 ±0 .004	1.18	15.92	26.89 ± 0.174
F8	0.497 ± .005	0.582 ± 0.004	1.17	14.60	21.46 ± 0.221
F9	0.499 ± .004	0.589 ± 0.007	1.18	15.28	24.70 ± 0.413
F10	0.487 ±0 .005	0.583 ±0.003	1.19	16.46	24.26 ± 0.227
F11	0.494 ± 0.005	0.587 ± 0.006	1.18	15.84	27.49 ± 0.322
F12	0.487 ± 0.004	0.592 ± 0.003	1.21	17.73	22.23 ± 0.040
F13	0.503 ± 0.009	0.596 ± 0.006	1.18	15.60	20.12 ± 0.082
F14	0.499 ± 0.007	0.598 ± 0.006	1.19	16.55	26.55 ± 0.262
F15	0.502 ± 0.007	0.587 ± 0.008	1.16	14.48	21.27 ± 0.092
F16	0.506 ± 0.009	0.596 ± 0.005	1.17	15.10	23.90 ± 0.143
F17	0.504 ± 0.005	0.597± 0.007	1.18	15.57	24.54 ± 0.234
F18	0.503 ± 0.004	0.601 ± 0.006	1.19	16.30	22.20 ± 0.093
F19	0.502 ± 0.005	0.592 ± 0.006	1.17	15.20	22.98 ± 0.212
F20	0.506 ± 0.007	0.594 ± 0.005	1.17	14.8	22.13 ± 0.142

Evaluation of tablets

The results of the evaluation parameters for the developed tablets were shown in Table 4. Weight variation was found within the specification of the USP limits. The average weight of 20 tablets of all formulations was found to be in the range of 98.85 to 101.5 mg. The ranges of friability and hardness were 0.25 to 0.46%, and 3.13 to 3.68 kg/cm^2, respectively. The lower friability results (<1.0 %) indicate that the tablets may not break during handling on machines

and/or shipping. Wetting time and water absorption ratio ranged from 11.30 to 18.57s and 66.74 to 77.30%, respectively. Drug content of all the formulations was in the range of 97.78 to 100.35%.

All formulations showed in vitro disintegration time less than 22 seconds. The *in vitro* disintegration time was rapid with Polyplasdone XL10 containing formulae (12.23, 13.30 and13.82 sec for F5, F6 and F18, respectively) and delayed with Explotab containing formulae (20.53, 20.73, 20.84 and 21.81 sec for F17, F4, F14 and F3, respectively), while Croscarmellose sodium containing formulae were midway between both groups. The rapid disintegration obtained with Polyplasdone XL 10 might be explained by the fast uptake of water from the medium, followed by swelling and bursting. In contrast, croscarmellose sodium and Explotab are characterized by high gelling tendency which causes swelling of tablet mass with subsequent retardation of disintegration.

Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that Explotab is disintegrated by swelling mechanism leading to longer wetting time. Polyplasdone XL 10 and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling **(Yutaka *et al.*, 2002)**. After contact with water, the tablets containing Explotab swelled, the outer edge appeared gel-like. Tablets containing Polyplasdone XL 10 quickly wicked water and were hydrated, but were soft as compared with tablets prepared with croscarmellose sodium and Explotab. The centers of the tablets with Explotab and croscarmellose sodium remained dry and hard **(Kakade *et al.*, 2010).**

In vitro dissolution studies of the prepared tablets were performed in water using USP dissolution apparatus type II at different time intervals as presented in (Figures 1-4). All formulations showed maximum dissolution rate of more than 94.44 % within 10 minutes. The rapid dissolving concept in case of RB could particularly be of a great importance in relieving migraine attacks. Formulations F18, F11, and F13 which contained combinations of the three superdisintegrants with different proportions showed drug release of 99.83, 99.69, and 98.49% respectively (Figures 3 and 4), at the end of 10 minutes with the order of relative efficiency as Polyplasdone XL 10 >Croscarmellose sodium >Explotab. Formulations F5, F15, and F2 which contained high concentrations of superdisintegrants, Polyplasdone XL 10, and croscarmellose sodium have recorded drug release of 98.15, 97.87, and 97.45% respectively, at the end of 10 minutes (Figures 1 and 3). Whereas, the remainder of the formulations which contained two different superdisintegrants in alternative concentration in absence of the third one, and formulations which contained high amount of Explotab had the lowest % of drug release (96.28, 95.87, and 95.62% in F4, F9, and F14) at the end of 10 minutes (Figures1-3). This was probably due to formation of viscous plugs by Explotab particles.

Table 4: Evaluation data of the prepared RB fast dissolving tablets

Run code	Weight (mg)	Friability (%)	Hardness (kg/cm^2)	Disintegration time (sec.)	Wetting time (sec.)	Water absorption ratio	Drug content (%)	Drug release (%)
F1	99.87±0.45	0.27±0.01	3.65±0.06	17.84±0.17	18.57±0.33	70.37±0.50	98.34±0.15	94.44±0.22
F2	98.85±0.45	0.31±0.01	3.44±0.06	16.74±0.13	14.53±0.33	68.77±0.50	99.47±0.15	97.45±0.15
F3	101.3±0.20	0.46±0.01	3.63±0.02	21.81±0.36	15.34±0.28	70.27±0.57	99.75±0.27	94.49±0.26
F4	99.82±0.10	0.39±0.03	3.61±0.04	20.73±0.11	14.46±0.48	68.91±0.44	99.46±0.32	96.28±0.46
F5	99.47±0.15	0.26±0.02	3.27±0.05	12.23±0.18	15.52±0.12	67.54±0.37	100.23±0.38	98.15±0.68
F6	100.3±0.40	0.39±0.02	3.51±0.04	13.30±0.25	16.13±0.23	66.74±0.39	98.51±0.20	96.77±0.29
F7	99.23±1.14	0.46±0.02	3.43±0.03	16.27±1.09	15.25±0.22	70.12±0.21	99.62±0.47	97.14±0.41
F8	99.27±0.95	0.28±0.03	3.36±0.08	15.64±0.46	13.79±0.21	73.41±0.36	99.70±0.21	98.35±0.48
F9	100.4±0.12	0.33±0.02	3.59±0.08	19.87±0.44	12.79±0.83	75.15±1.20	97.78±0.25	95.87±0.56
F10	99.87±0.45	0.44±0.01	3.39±0.06	19.84±0.09	13.53±0.33	71.97±0.50	98.76±0.15	96.32±0.24
F11	100.3±0.60	0.42±0.03	3.37±0.05	16.72±0.11	14.84±0.26	69.87±0.26	100.35±0.25	99.69±0.26
F12	99.27±0.95	0.45±0.03	3.16±0.08	14.64±0.46	13.57±0.21	74.41±0.36	99.81±0.21	98.92±0.48
F13	100.1±0.55	0.37±0.03	3.17±0.05	15.07±0.14	12.56±0.17	77.30±0.37	99.98±0.31	98.49±0.29
F14	99.89±0.45	0.28±0.01	3.67±0.06	20.84±0.15	11.30±0.33	75.97±0.50	98.39±0.15	95.62±0.37
F15	99.77±0.15	0.34±0.01	3.13±0.05	16.56±0.19	13.69±0.28	72.06±0.92	99.73±0.47	97.87±0.29
F16	100.0±0.21	0.25±0.02	3.55±0.08	19.63±0.13	12.13±0.32	76.85±0.25	99.20±0.46	96.64±0.27
F17	99.97±0.76	0.34±0.02	3.48±0.05	20.53±0.16	13.26±0.27	75.69±0.81	99.75±0.30	96.46±0.38
F18	101.5±0.12	0.34±0.02	3.32±0.08	13.82±0.44	13.19±0.83	69.15±1.20	100.07±0.25	99.83±0.56
F19	100.2±0.66	0.29±0.02	3.25±0.07	14.31±0.27	15.82±0.08	75.92±0.18	99.17±0.20	97.31±0.21
F20	100.3±0.60	0.28±0.03	3.68±0.05	17.79±0.11	17.49±0.26	70.87±0.26	98.31±0.25	94.58±0.26

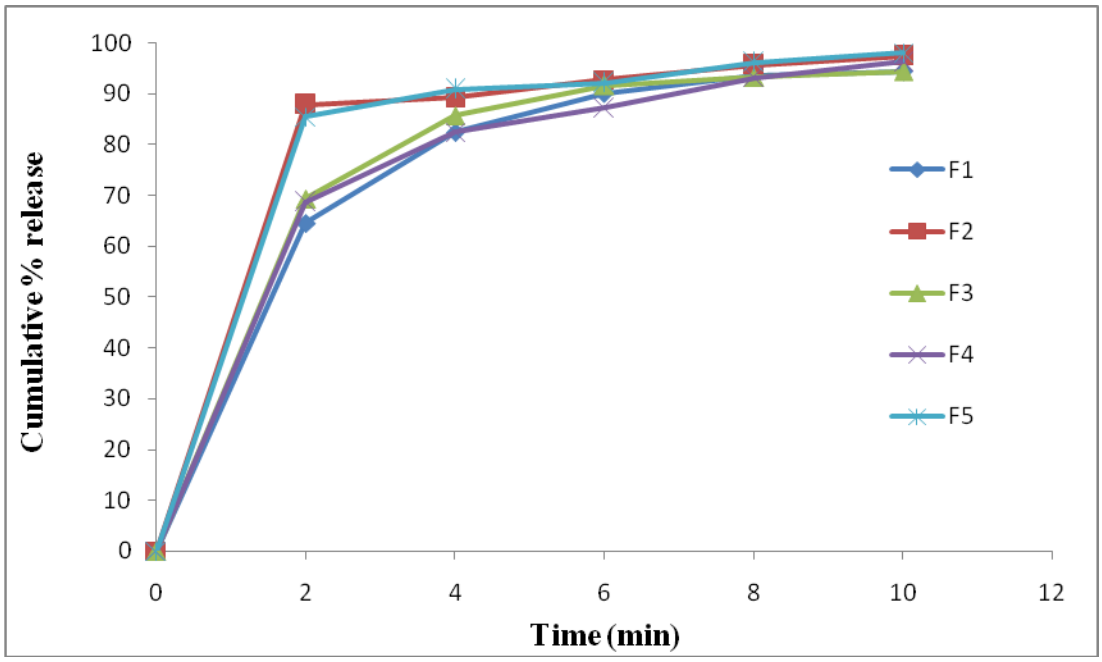

Figure 1: In-Vitro release Profile of formulation F1, F2, F3, F4 and F5

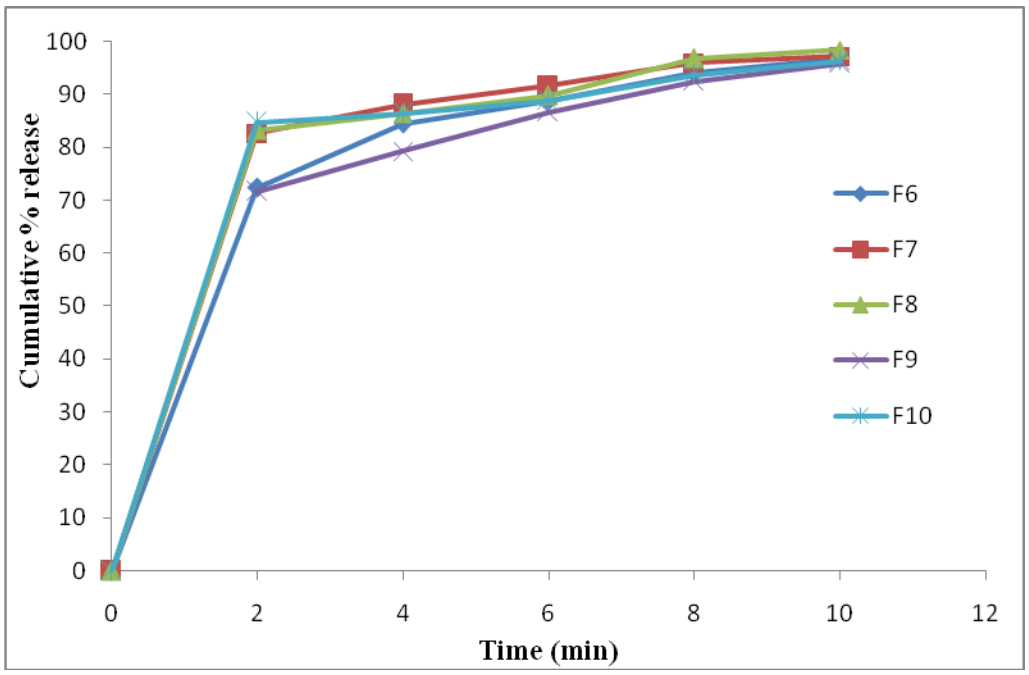

Figure 2: In-Vitro release Profile of formulation F6, F7, F8, F9 and F10

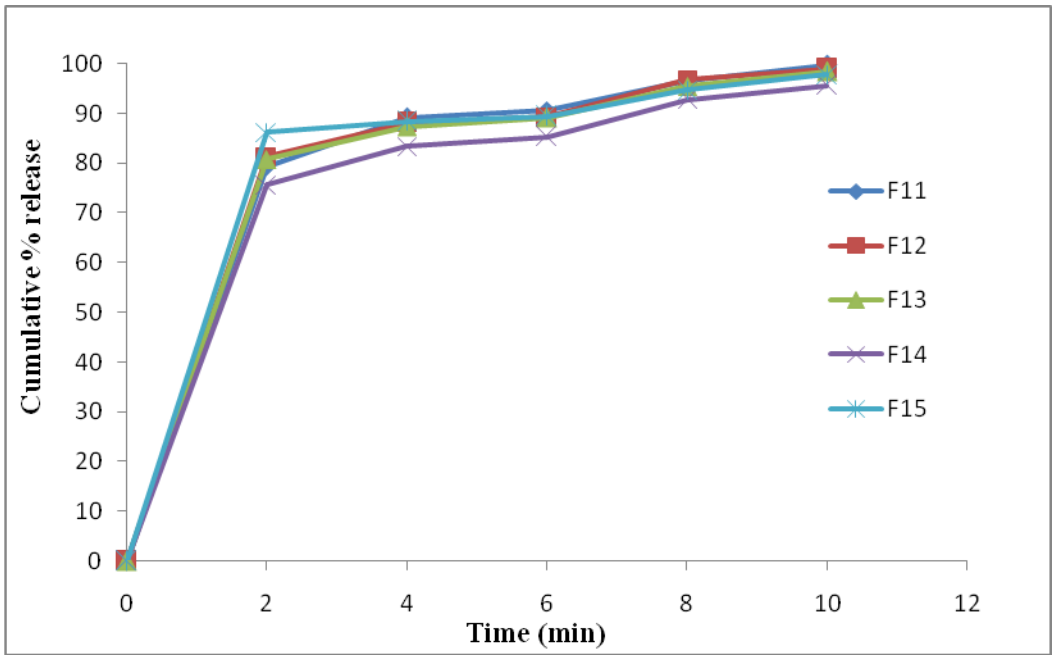

Figure 3: In-Vitro release Profile of formulation F11, F12, F13, F14 and F15

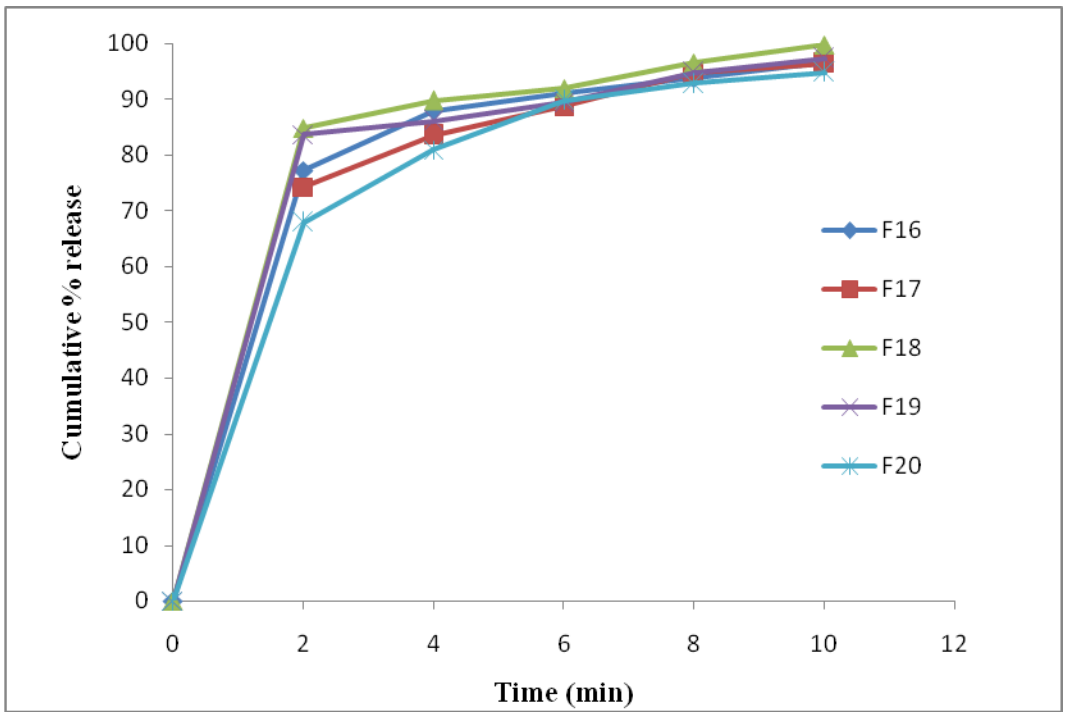

Figure 4: In-Vitro release Profile of formulation F16, F17, F18, F19 and F20

Optimization of the Formulation

Fitting of Data to the Model

According to the design, the experimental runs, their factor combinations and the levels of experimental units used in the study as well as the other formulation additives used in direct compression of tablets are summarized in Table 2. In order to determine the levels of factors which yielded optimal hardness, minimum disintegration time and maximal % drug release in 10 minutes, mathematical relationships were generated between the dependent factors and independent variables. Using the aforementioned software, the model was fitted to the data. Regression analysis of the data was carried out in SAS (Statistical Analysis System) by a linear model. ANOVA studies represented in tables (5-7) showed that there is a statistically significant relationship between the dependent variables and the components at the 99% confidence level indicated by *P-value* (*P-value* was < 0.01 for all the dependent variables).

The R-Squared statistic indicated that the model as fitted explains 55.304% of the variability in hardness, 55.919% of the variability in disintegration time and 63.191% of the variability in cumulative % release. The adjusted R-squared statistic, which is more suitable for comparing models with different numbers of independent variables, was 50.0461%, 50.733% and 58.859 % in case of hardness, disintegration time and cumulative % release, respectively.

Table 5: ANOVA for hardness:

Source	*Sum of Squares*	*Df*	*Mean Square*	*F-Ratio*	*P-Value*
Linear Model	0.332059	2	0.166029	10.52	0.0011
Total error	0.268361	17	0.0157859		
Total (corr.)	0.60042	19			

Table 6: ANOVA for disintegration time:

Source	*Sum of Squares*	*Df*	*Mean Square*	*F-Ratio*	*P-Value*
Linear Model	85.9602	2	42.9801	10.78	0.0009
Total error	67.7604	17	3.98591		
Total (corr.)	153.721	19			

Table 7: ANOVA for *in vitro* dissolution:

Source	*Sum of Squares*	*Df*	*Mean Square*	*F-Ratio*	*P-Value*
Linear Model	30.7707	2	15.3853	14.59	0.0002
Total error	17.9248	17	1.0544		
Total (corr.)	48.6955	19			

In order to understand the mathematical relationship between independent factors and dependent variables, regression equations were generated for each variable ($Y1$, $Y2$ and $Y3$) and listed in table 8.

Table 8: Regression Equations of the fitted models

Response	Equation
Hardness (*Y*1)	= 3.436 X_1 + 3.747 X_2 + 2.981 X_3
Disintegration time (Y_2)	= 16.34 X_1 + 22.575 X_2 + 10.666 X_3
In vitro dissolution (Y_3)	= 96.325 X_1 + 94.321 X_2 + 101.815 X_3

Three-dimensional (3D) Response Surface and* Contour *Plots:

Based on the model polynomial functions, Three-dimensional (3D) plots for the measured variables were formed to assess the change of the response surface as well as to provide better understanding of the relationship between the dependent factors and independent variables. Response surface and contour plots of estimated response surface for the variables *Y*1, *Y*2 and *Y*3 were represented in Figures (5–10). These Figures, showed the effect of components; Croscarmellose sodium % (*X*1), Explotab % (*X*2), and Polyplasdone XL10 % (*X*3), on the properties of the prepared RB fast dissolving tablets *Y*1 (hardness), Y_2 (disintegration time) and Y_3 (cumulative % release after 10 minutes).

The three components of the mixture were located at the corners of the triangle and the center corresponds to the mixture in equal parts. The white regions displayed in the figures represent areas not applied in the regressions, because of the constraints of the components. Consequently, variations on the mixture composition influence hardness (Y_1), disintegration time (Y_2), and cumulative % release after 10 minutes (Y_3). All regression equations of the fitted linear model for all investigated responses showed positive values for all components of the mixture demonstrating their positive effect on the responses.

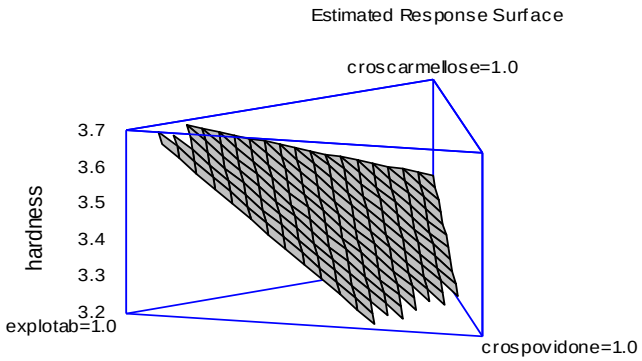

Figure 5: Response surface plot (3D) showing the effect of *X*1, *X*2, and *X*3 on *Y*1 response.

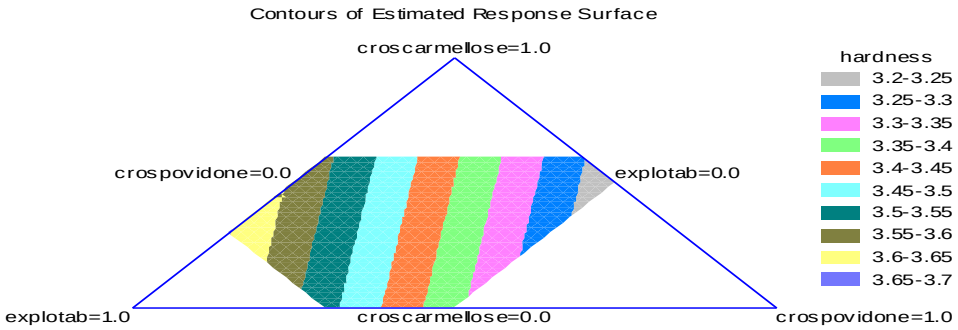

Figure 6: Contour plot of estimated response surface showing the effect of *X*1, *X*2, and *X*3 on *Y*1 response.

The regression equation and the triangular dimensional contours figure (6) demonstrated that higher proportions of Explotab (X_2) and lower proportions of both X_1 and X_3 increased the hardness of the tablet. The yellow areas in Figure 6, close to the corner of Explotab in the triangle represent the highest hardness of the formulations. On the other hand, the disintegration time (Y_2) was shown to be influenced by the mixture composition. From the contour plot (Figure 8) the shorter disintegration time was obtained at the midpoint between croscarmellose and polyplasdone XL10 with lower level of explotab which appeared in the gray area. The same finding was observed for cumulative % release (*Y*3) and was shown to be influenced by the mixture composition as displayed in Figure 10. The maximum % of drug release (98.8-99.4%) was achieved at the center of the distance between croscarmellose and polyplasdone XL10 with lower level of explotab which appeared in the yellow area.

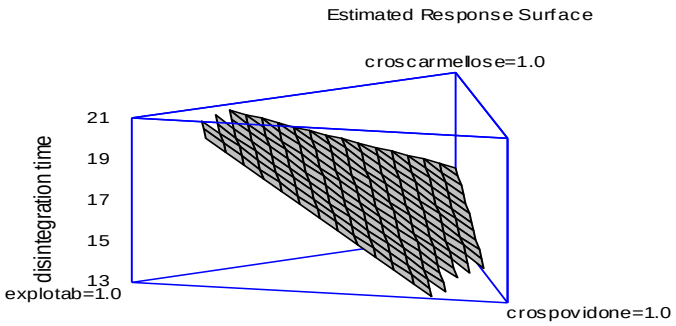

Figure 7: Response surface plot (3D) showing the effect of *X*1, *X*2, and *X*3 on *Y*2 response.

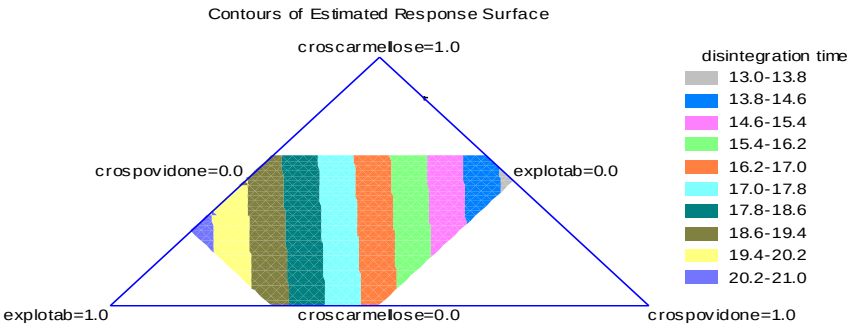

Figure 8: Contour plot of estimated response surface showing the effect of *X*1, *X*2, and *X*3 on *Y*2 response

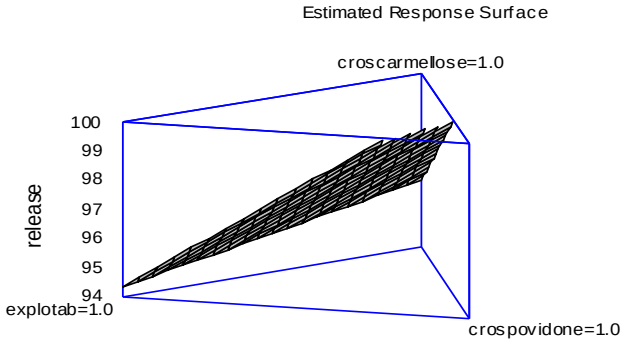

Figure 9: Response surface plot (3D) showing the effect of *X*1, *X*2, and *X*3 on *Y*3 response.

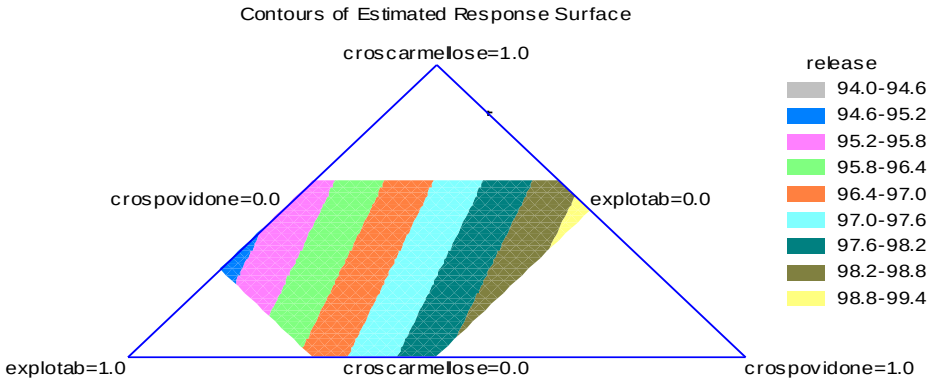

Figure 10: Contour plot of estimated response surface showing the effect of *X*1, *X*2, and *X*3 on *Y*3 response.

Prediction of the Optimized RB fast dissolving formulation

After generating the model regression equations to relate the dependant factors and independent variables, the process was optimized for the dependent variables. The optimization goals for the dependent variables were set to achieve optimal hardness, minimal disintegration time and maximal in vitro % release. The final optimal experimental factors were calculated using the canonical analysis, which allows the compromise among various dependent variables and searches for a combination of independent factor levels that jointly optimize a set of responses by satisfying the requirements for each variable in the set. The optimal calculated parameters were: Croscarmellose sodium was 0.58%, Explotab was 1.92% and Polyplasdone XL10 was 2.5%.

To confirm the validity of the calculated optimal factors, determination of the dependent variables (the hardness, disintegration time and in vitro drug release profile) was carried out. Table 9 illustrated the observed and predicted values for the dependent variables for the optimized RB fast dissolving tablet. Minimal differences were observed between the observed and predicted values.

Table 9: Optimum Desirability.

Factor	*Optimum*	*Response*	*Predicted*	*Observed*	*Residuals*
Croscarmellose	0.58	Hardness	3.328	3.37	0.042
Explotab	1.92	disintegration time	15.896	14.69	-1.206
Polyplasdone XL10	2.5	Release	98.30	99.58	1.278

CONCLUSIONS

The use of direct compression technique and the mixture experimental design succeeded to produce fast dissolving tablets of RB with optimal hardness, minimal disintegration time and maximal in vitro drug release. The quantitative effects of the selected factors tested on the different variables were explored. Based on the obtained results, fast dissolving tablets of RB could be a potential dosage form for quick relieve of migraine patients.

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ريزاتريبتان بنزوات أقراص سريعة الذوبان لتخفيف الصداع النصفى: تصميم, تطوير وتوصيف

للدكتور

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ريزاتريبتان بنزوات هو أحد عقاقير الجيل الجديد من مضادات الصداع النصفى ويصل أعلى تركيز له فى الدم بعد تناوله عن طريق الفم من 1 ساعة الى 2.5 ساعة اعتمادا على الصياغة، هذا وتبلغ نسبة اتاحته الحيوية 40 - 45% ويؤخروجود الطعام وصول العقار الى اعلى تركيز فى الدم بحوالى ساعة. لذا كان الهدف من هذه الدراسة هو تصميم وتطوير أقراص سريعة الذوبان لعقار الريزاتريبتان بنزوات لتحسين التوافر الحيوى له واستحسان قبوله لدى مرضى الصداع النصفى.
وقد تم استخدام نموذج الخليط التجريبى وطريقة الكبس المباشر فى تحضير عشرين صيغة تحتوى كل واحدة منهم على 14.53 مجم من الريزاتريبتان بنزوات مع نسب مختلفة من المواد المساعدة على سرعة تفتت الأقراص، وكانت العوامل المستقلة هى: نسبة الكروس كارميللوز، اكسيبلوتاب والبولى بلاسدون اكس ال، بينما اعتبر كل من درجة الصلابة، زمن التفتت ونسبة انطلاق العقار من الأقراص بعد 10 دقائق عوامل تابعة.
و قد تم أولا تقييم مخلوط المساحيق من حيث مدى قابليتها للتدفق والكبس، ثم كبست هذه المساحيق مباشرة الى أقراص، وتم تقييم هذة الأقراص وكانت ضمن الحدود المقبولة، كما تم دراسة تأثير مستوى كل مادة من المواد التى تساعد على درجة الصلابة، زمن التفتت ونسبة انطلاق العقار من الأقراص بعد 10 دقائق.
وتم الوصول الى صيغة مثلى تحتوى على نسب معينة من المواد المساعدة على سرعة التفتت وتم تحضيرها وتقييمها من حيث درجة الصلابة، زمن التفتت ونسبة انطلاق العقار من الأقراص بعد 10 دقائق. وقد اشارت النتائج ان للصيغة المثلي أفضل درجة صلابة، وأقل زمن تفتت وأقصى نسبة انطلاق للعقار من الأقراص بعد 10 دقائق مما يسمح لها بالامتصاص السريع داخل الفم وظهور الأثر العلاجى السريع في تخفيف الآم الصداع النصفى. وخلصت الدراسة الي نجاح تقنية الكبس المباشر ونموذج الخليط التجريبى للاقراص في استمثال صيغة تحقق الغرض المرجو منها في زيادة الاتاحة الحيوية للعقار.