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Design and Evaluation of Gastroretentive Mucoadhesive Films of Rizatriptan Benzoate

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Abstract

Introduction: Mucoadhesives are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin constituting the major part of the mucus. The use of a mucoadhesive dosage form for drug delivery *via* the gastrointestinal mucosal route increases bioavailability and results in a longer therapeutic impact. Migraine is a prevalent headache illness that places a significant financial and social burden on both the patient and society. It is a puzzling condition characterized by pulsating headaches that are usually limited to one side and occur in bouts lasting 4 to 48 hours and is often associated with nausea, vomiting, sensitivity to light, vertigo, loose motions and other symptoms.

Material and Methods: The Rizatriptan is a selective 5-hydroxytryptamine receptor subtype agonist acute treatment of migraine attacks with or without aura in adult. Mucoadhesive film was prepared by solvent casting method. In this way, gastric mucoadhesive drug delivery system can delay the retention time of a dosage form in the stomach, consequently working on the oral bioavailability of the medication and decrease in dosing recurrence.

Results: All batches showed low dissolvability of polymer since ethyl cellulose eudragit RLPO isn't solvent in water so film was not satisfactory and low collapsing perseverance which prompted film with helpless pliancy and versatility. Out of all cluster, showed great adaptability, collapsing perseverance, high expanding list, mucoadhesive strength and medication discharge so this group was chosen as ideal for factorial design.

Keywords: Migraine; Rizatriptan; Gastro retentive film; Mucoadhesion; Solvent casting method; Ethyl cellulose; Eudragit RLPO

Introduction

The concept of gastric mucosal adhesion was introduced in drug delivery in the early 1980's. Mucosal adhesives are synthetic or natural polymers that interact with the mucous layer covering the surface of the mucosal epithelium, and mucous constitutes the main part of mucus. The use of mucoadhesive formulations for administration through the gastrointestinal mucosal route can increase bioavailability and produce longer therapeutic effects. Migraine is a common headache that places a heavy burden on both individual patients and society. Migraines are generally severe and >80% of patients describes their pain as severe. The overall impact of migraine reflects not only its onset characteristics, but also physical health [1]. Migraine is a mysterious disease characterized by stabbing headaches, usually limited to one side and lasting 4 to 48 hours, often accompanied by nausea, vomiting, sensitivity to light, dizziness, discomfort, and other symptoms. The two main types are migraine with aura, in which the headache precedes visual symptoms or other neurological symptoms, and migraine without aura. Pulsatile dilation of certain large cranial vessels is the direct cause of pain. The pathogenetic mechanism is unclear. Vascular theory believes that initial vasoconstriction or closure of the blood by carotid arteriovenous anastomosis will cause cerebral ischemia and begin to attack. Neurogenic theory believes that it is the expanding inhibition of cortical electrical activity, followed by vascular phenomena. Some triggering events appear to produce neurogenic inflammation of affected blood vessels, which is amplified by retrograde transmission in afferent nerves and the release of drugs such as 5 HT_3, neurokinin, substance P, and calcitonin gene-related peptide [2]. Changes in blood/urine levels of 5HT and its metabolites during migraine attacks, precipitation of 5HT releasing agents, and the efficacy of drugs that have the effect of preventing migraine attacks on the serotonergic system indicate the role of 5HT in disease. Rizatriptan is a selective agonist of the serotonin receptor subtype that is used for the acute treatment of migraine attacks with or without aura in adults. Rizatriptan is used to prevent migraine or to treat basic migraine. Currently,

Rizatriptan is commercially available in conventional tablet form, which is metabolized after oral administration [3]. It is metabolized by type-A monoamine oxidase into an inactive derivative of indoleacetic acid, and a small amount of the active metabolite N mono des methyl rizatriptan is formed, and its bioavailability is low, as high as 45%. It has an elimination half-life of 2 to 3 hours and has an absorption zone in the upper part of the intestine. For these reasons, the gastric mucosal adhesive drug delivery system can extend the residence time of the dosage form in the stomach, thereby increasing the oral bioavailability of the drug and reducing the frequency of administration [4]. In the market, rizatriptan is available in a lyophilized form, which disintegrates quickly. The main disadvantages of this method are that it is very expensive and the product is very sensitive to moisture, freeze-drying is troublesome and produces a fragile and hygroscopic product. The traditional rizatriptan tablet has a short half-life, is quickly cleared from the blood, requires frequent administration, and cannot be released under control, which is necessary to relieve migraine attacks. A new expandable Gastric Retention Dosage Form (GRDF) based on the deployment mechanism. It is made up of a drug loaded polymer film folded into a hard gelatin capsule. Since the dosage form unfolded in 15 to 20 minutes, gastric retention was achieved. The film can be applied to the upper part of the intestine to maintain a sustained level of treatment. This can be achieved through GRDF [5]. Rizatriptan is easily absorbed from the stomach and has a short half-life, it is eliminated quickly from the blood circulation thus require frequent dosing. To avoid this problem, the oral gastro retentive formulation has to be developing in an attempt to release the drug slowly into the gastric region and increase bioavailability and decrease dosing frequency.

Rizatriptan gastro retentive mucoadhesive films were prepared by solvent casting technique. HPMC in the concentration of 1, 2 and 3% w/v, Eudragit RLPO in the concentration of 2 ,4 And 6%, Eudragit L 100 in the concentration 1% and carbopol 971 NF in the concentration 0.3 %were used to prepare the Film. PEG 400 in the concentration of 30% w/w of polymer was used as plasticizer in the preparation of Film. To evaluate the prepared formulations by 'response surface methodology' and developed the optimized formulation [6].

Materials and Methods

Materials

Rizatriptan benzoate was obtained from Cipla Ltd, Vikhroli, India. Hydroxy propyl cellulose, and poly (vinyl alcohol) was received from Dow Chemicals, USA, Eudragit RLPO and Eudragit L100 was gifted by Evonik India Ltd, carbopol 971 NF and ethyl cellulose, PEG-.100,400, Di n-butyl phthalate, di butylsebacate, isopropyl alcohol, dichloromethane, methanol were purchased from SD Fine chemicals, Mumbai. All other chemicals were of analytical grade.

Methods

Drug excipients compatibility study: Drug excipients compatibility testing was performed by mixing drug with polymer in equal proportion and then IR spectrum was noted for mixture. 2-3 mg of sample was mixed with previously dried IR grade potassium bromide and kept in sample cell, the cell was then fitted in sample holder, spectra were recorded with FTIR instrument and the spectral analysis was done [7].

Preparation of gastroretentive mucoadhesive film: Mucoadhesive film was prepared by solvent casting method. HPMC K4M and carbopol 971P NF were dissolved into the mixture of dichloromethane and methanol (1:1). The drug was separately dissolved into Eudragit RLPO and L100 dispersion. Eudragit dispersion containing drug was added into HPMC and carbopol containing dispersion with constant stirring to obtain clear solution. PEG 400 was added as plasticizer with constant stirring. Then it was kept for sonication for 15-20 min for removal of air bubbles. The ready viscous formulation was poured on glass mould, coated with inverted funnel to manage the speedy evaporation of solvent and allowed for drying at temperature for two hours and followed to evaporate the solvent in hot air kitchen appliance for twenty-four hours at 60°C. Once complete drying, gently take away the film for additional studies. The varied films were developed using different compositions of HPMC, carbopol and eudragit polymer [8].

Dose calculation: The total dose-controlled release formulation was calculated as per Robinson Erikson equation using available pharmacokinetic data:

- Dose (X)–5 mg
- Half Life–2-3 hour
- Time to reach peak concentration (TOP)–1 hour
- Time up to which dosage form need to be controlled–8 hours

Elimination rate constant (Ke)=0.693/3=0.231

Loading dose=X_o/Ke*t

=5/0.231*8

=2.70 mg

Desired rate of drug release (K_s) = X_o*ke

=5*0.231

=1.155 mg/hour

Maintenance dose= Ks*t

= 1.155*8

= 9.24 mg

Corrected initial dose=loading dose–(K_s* TOP)

=2.70–(1.155*1)

=1.55 mg

Total dose=Maintenance dose+Corrected initial dose

= 9.24+1.55

= 10.79 mg (10.8 mg)

Dose calculation for gastroretentive mucoadhesive film of Rizatriptan Benzoate

Diameter of glass petri-plates used for formulation of the film=9 ± 0.05 cm

Radius of glass petri-plate used for formulation of film=4.5 cm

Area of glass petri plate=πr^2

$= 3.14 \times (4.5 \times 4.5) = 63.58\ cm^2$

Dose of individual film (2 x 4 cm^2)=10.8 mg

Therefore, for whole petri-plate means for 8 patches to=85.83 mg

Factorial design: A factorial design was used to evaluate two or more factors simultaneously. The treatments are combination of levels of the factors. It was used in experiments of different factors or conditions, on experimental results are to be elucidated. Factorial designs are the designs of choice for simultaneous determination of the effect of several factors and their interactions [9].

Three level full factorial designs: The three level designs are written as a 3 k factorial design. It means that k factor was considered, each at 3 levels. These are usually referred to as low, intermediate and high levels. These levels are numerically expressed as 0, 1 and 2 or -1, 0 and +1. A study, in which there are two factors with 3 levels, is called a 32 factorial design. A 32 randomized full factorial design was constructed where the amounts of HPMC K4M (X_1) and Eudragit RLPO (X_2) were selected as the independent factors. The three levels and two factors were selected.

The experimental design: All other formulation and processing variables were kept invariant throughout the study. The % cumulative drug release was selected as dependent variables.

Evaluation of gastroretentive mucoadhesive films

Unfolding behavior of GRDFs *in vitro*: Films were folded by two methods. In the first method the film was rolled in a single direction, in the second method the film was folded in a zigzag manner and both films were inserted into individual capsule. In each case six capsules were taken for *in vitro* dissolution study in 900 ml aqueous hydrochloric acid pH 1.2 at 37°C ± 0.5°C using the USPXXIII Apparatus (basket) at 50 rpm. Baskets were removed after 1, 15, 60, 240, 480 min and the films were examined for their unfolding behavior [10].

Uniformity of weight: Three films of every formulation were selected randomly and individual weight of each 4 cm × 2 cm film was noted on digital balance. The average weight was calculated [11].

Thickness: Three films of every formulation were selected randomly and film thickness was measured using dial caliper 0-150 × 0.02 mm at three different places and calculates mean value [12].

Folding endurance: Three films of each formulation of size (4 cm × 2 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance.

Determination of drug content: Accurately size (4 cm × 2 cm) of the films taken and dissolved in 100 ml of 0.1 N HCl solution in 100 ml volumetric flask and kept for 24 hours with occasional shaking. Then whole solution was sonicated. After sonication and subsequent filtration, suitable dilutions were made with 0.1 N HCl solutions. The prepared solutions were analyzed by using UV–visible spectrophotometer.

Swelling index (%): Swelling of films was examined in triplicate in simulated gastric fluid (pH 1.2) according to the following procedure. After recording the initial weight of a film (W_1), it was immersed in medium maintained at 37°C for 360 min and then weighed again (W_2).

$$\text{Swelling index} = W_2 - W_1 / W_1 * 100 \quad (1)$$

***In vitro* mucoadhesive strength:** Fresh goat gastric mucosa was obtained from a local slaughter house, placed in saline, and used within 2 hrs of slaughter. The mucosal membrane was cleaned and separated by removing the underlying fat and loose tissues. Bio adhesive strength of the film was measured on a modified physical balance. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by a small plastic cap vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane. The goat gastric mucosa was cut into pieces and washed with 0.1N HCl (pH 1.2). A piece of gastric mucosa was tied to the open mouth of a glass vial, which was placed and tightly fitted in the center of glass beaker. The 0.1N HCl (pH 1.2, 37 ± 2°C) was filled in to the glass beaker in such a way that it makes contact with gastric mucosal surface. The film was stuck to the lower side of flat surface plastic cap with cyanoacrylate adhesive. Two pans of the balance were balanced with 5 g weight on the right-hand side pan. A weight of 5 g was removed from the right-hand side pan, which lowered the pan along with the film over the mucosa. The balance was kept in this position for 5 min contact time, and then slowly the weights were increased on the right hand side pan till the film separated from the mucosal surface.

Mucoadhesive strength was measured as force of adhesion in Newton's by using following formula

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength}/1000 \times 9.81 \quad (2)$$

***In vitro* mucoadhesion time:** The time taken for detachment of film from goat stomach mucosa was measured in 0.1N hydrochloric acid (pH 1.2). This was evaluated by an *in vitro* adhesion testing method, by using *in vitro* dissolution apparatus.

Tensile strength and elongation at break: The tensile strength of the films was determined by isotone tester. It consists of two load cell groups, the lower one was fixed and the upper one was moving. The test film of specific size (4 cm × 2 cm) was fixed

between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms. Mean and standard deviation was calculated and evaluated. The tensile strength was calculated as follows [13].

$$\text{Tensile strength (Kg/mm}^2\text{)} = \frac{\text{Force at break (Kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}} \quad (3)$$

$$\text{Elongation at break (\%)} = \frac{\text{Increase in length}}{\text{Original length (mm)}} \times 100 \quad (4)$$

Scanning Electron Microscopy (SEM): The surface morphology of the films was examined by SEM. The dried films were coated under an argon atmosphere with gold–palladium (Sputter coater, Balzers SCD 004, Liechtenstein) and photographed using a Scanning Electron Microscope (SEM, JSM-6400, Tokyo, Japan).

Drug release studies

Details of test

Dissolution test apparatus: USP XXIII apparatus

Speed: 50 rpm

Stirrer: Basket method

Volume of medium: 900 ml

Sample withdrawal at each time interval: 10 ml

Medium used: 0.1 N HCl (pH 1.2)

Temperature: 37 ± 0.5°C

Dissolution studies were carried out for all the formulations, employing USP XXIII apparatus (basket method) at 37+0.5°C rotated at constant speed of 50 rpm using 900 ml of 0.1 N HCl as the dissolution medium. A sample of films was used in each test. An aliquot of the sample was periodically with drawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The samples were filtered through 0.45 µm Whatman filter paper and analyzed spectrophotometrically. The experiments were performed in triplicate, and average values were reported.

Kinetic treatment of dissolution data: There is variety of formulations that devoted to oral controlled drug release and there is variety of properties that decides the drug release from the formulations. The release patterns can be divided into those that release drug at a slow zero or first order rate and those that provide an initial rapid dose, followed by slow zero or first order release of sustained component. As a matter of fact, controlled release formulations bring engineers and pharmacists to work together with the common aim of realizing more and more effective products. For this purpose, the use of mathematical modeling turns out to be very useful as this approach enables, in the best case, the prediction of release kinetics.

Zero order kinetics: Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t \quad (5)$$

Rearrangement of equation (1) yields:

$$Q_t = Q_0 + K_0 t \quad (6)$$

Where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, Q_0=0) and K_0 is the zero-order release constant expressed in units of concentration/time.

Effect of temperature and humidity: Effect of temperature and humidity on optimized formulation was studied by keeping it at 40°C ± 2°C/75% ± 5% RH in the environmental stability chamber for one month. Samples were analyzed at 0-,1-,2- and 3-month intervals.

- mucoadhesion strength
- % Drug content.
- % Drug release.

Response surface methodology: Response surface method used to examine the relationship between one or more response variables and set of quantitative experimental variables or factors. These methods are employed after one have identified a vital few controllable factor and one want to find the factor setting that optimize the response.

Response surface methodology is used to

- Find factor setting that produce the best response
- Find the factor setting that satisfy operating processes or specification
- Identify the operating procedures that produce demonstrated improvement in product by current conditions
- Model a relationship between the quantitative factors and response.

Results and Discussion

Formulation of gastroretentive mucoadhesive films by factorial design

In order to drug release in 8 hours combination of polymer HPMC K4M and Eudragit RLPO were used in order to study the influence of combination of two factors on the overall drug release and to obtain the optimized formulation by 32 factorial designs was used.

Evaluation of gastroretentive mucoadhesive film

Physical parameters of film: The thickness of formulated Film was ranges from 0.295 ± 0.05 to 0.548 ± 0.012 mm, while the average weight of Film ranges from 332.6 ± 10.1 to 594.9 ±

14.05 mg. The unfolding time of film was ranging from 11–19 min. The content uniformity was observed from 78.52 ± 0.36 to 90.51 ± 1.15. The film did not show any visible cracks even after folding for more than 300 times for all batches. The tensile strength of films was found to be 7.84 to 16.66 kg/mm^2 which are the required strength for gastroretentive films.

Unfolding behavior: GRDFs prepared by both methods were evaluated for their *in vitro* unfolding behavior. The GRDFs prepared by first method have not unfolded properly, but the GRDFs of second method unfolded within 11-19 min (Figure 1).

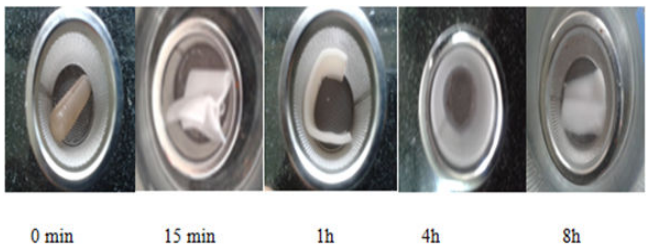

Figure 1: Unfolding behaviour of film.

Swelling index: The swelling property of polymer is important for its mucoadhesion and its drug release pattern. The % swelling of various formulations was in the order of $F_5>F_3>F_6>F_2>F_1>F_4>F_8>F_9>F_7$. The swelling index was directly proportional to the amount of hydrophilic polymer HPMC K4M and hydrophobic polymer Eudragit RLPO. The batch F_5 shows high swelling index due to high content of HPMC K4M and Eudragit RLPO. Whereas F_7 batch showed lowest swelling index due to lower content of HPMC K4M and Eudragit.

Mechanical properties of film: The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, Tensile Strength (TS) and Elongation at Break (E/B). From the result of the mechanical properties *i.e.,* TS and E/B, it was found that TS increases with increase in polymeric content but E/B values decreased with the increase in polymer content (Table 1). Maximum TS was exhibited by formulation F_5 (16.66 kg/mm^{-2}) and minimum was exhibited by formulation F_7 (7.84 kg/mm^{-2}). Maximum E/B was seen with F_7 (54.16% mm^{-2}) and least was observed for F_5 (28.33 kg/mm^{-2}). Addition of Eudragit RLPO in formulations was found to increase in tensile strength. This indicates Eudragit may produce effective cross-linking and strengthen the bonding of polymer chains.

Table 1: Physical parameters of the gastroretentive film.

Parameters batches	Elongation at break (g) ± SD	Tensile strength Kg/mm^2 ± SD	Swelling index (%) ± SD
F1	35 ± 2.5	12.56 ± 0.02	86.60 ± 0.62
F2	33.33 ± 1.44	13.87 ± 0.01	93.30 ± 1.6
F3	30 ± 2.5	15.05 ± 0.05	121.60 ± 4.6
F4	46.66 ± 3.81	10.10 ± 0.01	73.17 ± 1.08
F5	28.33 ± 1.44	16.66 ± 0.01	150.85 ± 3.25
F6	42.5 ± 2.5	11.70 ± 0.05	94.48 ± 4.26
F7	54.16 ± 3.81	7.84 ± 0.02	52.52 ± 3.01
F8	50 ± 2.5	8.58 ± 0.03	55.07 ± 3.27
F9	52.5 ± 2.5	8.06 ± 0.02	54.64 ± 2.44
*Mean ± S.D., n=3			

In-vitro mucoadhesion time

In-vitro residence time was found to be varied from 435.3 ± 3.5 min to 601.6 ± 3.5 min. As the content of HPMC increased, the residence time of film increased. The F_7 formulation showed lowest residence time while F_5 showed the highest residence time; this may be due to high content of hydrophilic polymer HPMC which leads to increased swelling of formulation thus, mucoadhesive bond formation for longer time.

Mucoadhesive strength

Mucoadhesive strength was found to be directly proportional to the concentration of HPMC polymer. This may be due to the formation of strong gel which penetrate deeply into the molecules of mucin and show strong bioadhesion. Thus, formulation F_7 which contain lowest amount of HPMC showed lowest mucoadhesivity while F_5 containing highest amount of HPMC and Eudragit show highest mucoadhesive strength.

In vitro drug dissolution study

To determine whether the availability of Rizatriptan Benzoate was increased by formulating the films, in vitro drug dissolution studies were carried out in 0.1 N HCl (pH1.2) using USP dissolution test apparatus II. The results were tabulated below.

From the above results it is concluded that as the polymer concentration increases the viscosity of the gel layer increases as well as the diffusion path length of the drug increases this cause the less drug release at the higher level of the HPMC and vice versa. The formulation F_3, F_5 and F_6 shows good drug release.

The release kinetics of the formulation was shown in the table, the best fit model for the drug release was found to be Korsmeyer Peppa's. The mechanism involved for the drug release involved diffusion with erosion. The *in vitro* drug release data is fitted into Korsmeyer-Peppa's equation to determine the release exponent, which gives an insight into the mechanism of drug release from the delivery system and is interpreted as n is equal to 0.5, it implies Fickian diffusion (first order release).

Experimental Design and Data Analysis

Percentage drug release (%cdr)

Analysis of Variance for Experimental Matrix (ANOVA): The data were analyzed by ANOVA test. A value of $p<0.05$ was considered as significant. The obtained results (Table 2) were entered in design expert 7.0 software and a model equation was obtained to get the fit result for % CDR.

Table 2: Experimental design of the optimization step.

Formulation	Factor 1 A: HPMC K4M %	Factor 2 B: Eudragit RLPO%	Response 1 %CDR	Response 2: Swelling Index %
F1	2	4	96.17	86.6
F2	3	2	94.88	93.3
F3	3	4	96.29	121.6
F4	2	2	94.6	73.17
F5	3	6	98.12	150.85
F6	2	6	96.85	94.48
F7	1	2	92.62	52.52
F8	1	6	95.7	55.07
F9	1	4	94.68	54.64

Final equation in terms of actual factors

$$\%CDR=+88.27444+2.93500*HPMC\ K4M+1.17750*\ Eudragit\ RLPO+0.020000*\ HPMC\ K4M*\ Eudragit\ RLPO-0.49167*\ HPMC\ K4M^2-0.062917*\ Eudragit\ RLPO^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots(7)$$

Predicted *vs.* actual plot of % CDR: The actual values were obtained from experiments, and the predicted ones were obtained from the models as shown in Table 3. The values prove that the predicted data, which were obtained from the empirical model for percentage drug release, are similar with the experimental results due to their low differences. Linear correlation ship was observed between actual and predicted value.

Table 3: Low and high level for the generation of optimized batch.

Name	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
A:HPMC	Is in range	2	3	1	1	3
B:Eudragit	Is in range	4	6	1	1	3
% CDR	Is in range	96.5	98.12	1	1	3
% Swelling index	Is in range	145	150.85	1	1	3

Effect of experimental variables on the response: The effect of variables on the response was evaluated by design expert software 7.0 and was plotted in each plot, two factors remain constant and the other factor was in given range between its high and low levels, therefore its influence can be seen as a line that represents the demanded response.

Effect o f H PMC K 4M t he % d rug release increases with increases the concentration of HPMC K4M.

Effect of Eudragit RLPO: The % drug release increases with increases the concentration of Eudragit RLPO.

Effect of combined factors: Interaction of AB.

The Figure 2 showed interaction between AB. It can be observed that the increase in % drug release mainly depends upon increasing the concentration of HPMC K4M and Eudragit RLPO. There is no interaction between factors A and B indicates that each variable affects individually in increasing % drug release. The Figure 2 shows that the combined effect of HPMC K4M and Eudragit RLPO which indicates that as increase in HPMC K4M and Eudragit RLPO might be responsible to increase % drug release.

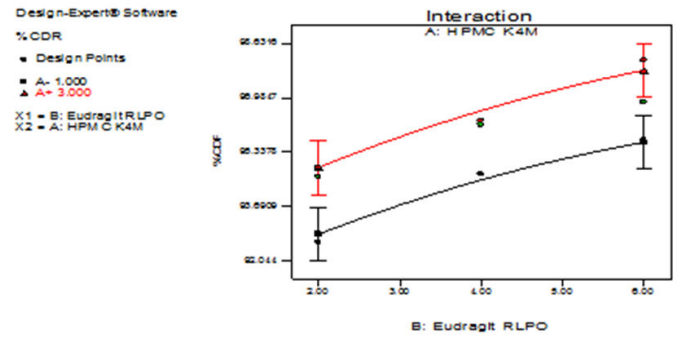

Figure 2: Effect of interaction between factors A and B on the % CDR.

The Figure 3 showed counter plot which concludes that HPMC K4M and Eudragit RLPO concentration increased, percentage drug release increases at the point of prediction. Hence HPMC K4M and Eudragit RLPO had combined effect on percentage drug release.

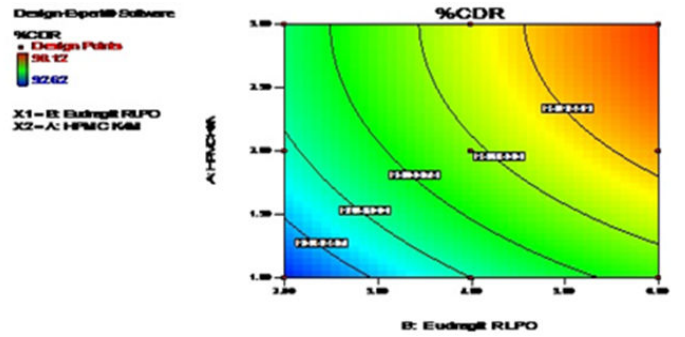

Figure 3: Contour plot of Effect of HPMC K4M and Eudragit RLPO on the % CDR.

Approximation of desired response

The Figure 4 showed relationship between the percentage cumulative drug release on y axis and deviation from the reference point with respect to HPMC K4M and Eudragit RLPO on the X axis. As the concentration of HPMC K4M and Eudragit RLPO is increases, percentage drug release also increases. If still increased the concentration of HPMC K4M and Eudragit RLPO then there is increase in the percentage cumulative drug release. At the point of Perturbation indicates that the levels of the entire 2 variable consider together for optimized response should be at their low-level value.

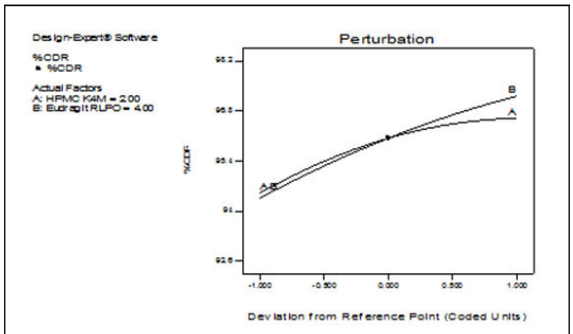

Figure 4: Perturbation plot of % CDR.

Desirability approach

Desirability provides flexibility and giving importance for each response individually. According to the final results, this program suggested some formulations and also predicted their responses containing a probability factor named “desirability” that ranged between 0-1 that the most presumable answer would be the nearest to 1. Data analysis showed that from high levels to low level each factor cause increase in the % CDR in the formulation. This software also suggests some formulations out of the range that was given at first, in regard to the results of analysis. Also, the desirability of each item could be observed. All of the formulation can be chosen for percentage drug release at maximum level.

Swelling index

Analysis of Variance for Experimental Matrix (ANOVA): Significance of this influence was statistically confirmed by ANOVA Test. According to applied 32 experimental designs including 9 experiments was performed to optimize the minimum Swelling Index. The obtained results were entered in design expert software and a model equation was obtained to get the fit result for swelling index.

Final equation in terms of actual factors:

Swelling index=+54.26556-6.56667 *HPMCK4M-4.86917*Eudragit RLPO+6.87500 *HPMC K4M *Eudragit RLPO+3.24667 *HPMC K4M2 -0.26208 *Eudragit RLPO2 (8)

From the equation it was concluded that HPMC K4M (factor A), Eudragit RLPO (factor B) having a individual as well as combined effect on the increasing in swelling index.

Predicted *vs.* actual plot: The actual values were obtained from experiments, and the predicted ones were obtained from the models. The values prove that the predicted data, which were obtained from the empirical model for percentage drug release, are similar with the experimental results due to their low differences. Linear correlation ship was observed between actual and predicted value as shown in Figure 5.

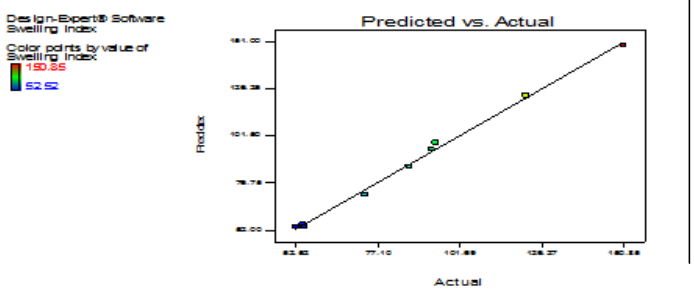

Figure 5: Predicted *vs*. actual values of swelling index.

Effect of experimental variables on the response

The effect of variables on the response was evaluated by design expert software 7.0 and was plotted. In each plot, two factors remain constant and the other factor was in given range between its high and low levels, therefore its influence can be seen as a line that represents the demanded response.

Effect of HPMC K4M: The swelling index increases with increasing the concentration of HPMC K4M.

Effect of Eudragit RLPO: The swelling index increases with increasing the concentration of Eudragit RLPO.

Effect of combined factors: Interaction of AB.

The Figure 6 showed interaction between AB. It can be observed that the decrease in swelling index mainly depends upon decreasing the concentration of HPMC K4M and Eudragit RLPO. There is no interaction between factors A and B indicates that each variable affects individually in decreasing swelling index. The Figure 6 shows that the combined effect of HPMC K4M and Eudragit RLPO which indicates that as decrease in HPMC K4M and Eudragit RLPO might be responsible to decrease swelling index.

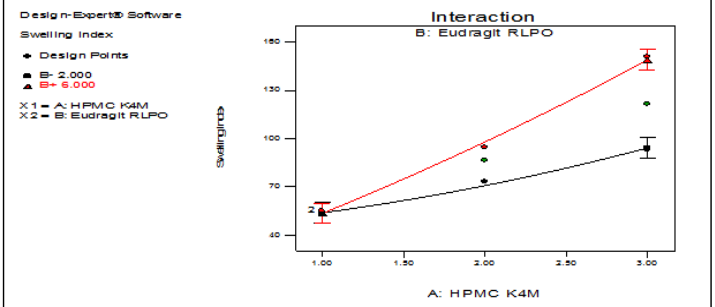

Figure 6: Effect of interaction between factors A and B on the swelling index.

Contour plot

The Figure 7 showed counter plot which conclude that factor A (HPMC K4M) and factor B (Eudragit RLPO) have most significant effect on increase in swelling index. When HPMC K4M and Eudragit RLPO concentration increased, swelling index increases at the point of prediction. Hence HPMC K4M and Eudragit RLPO had combined effect on swelling index.

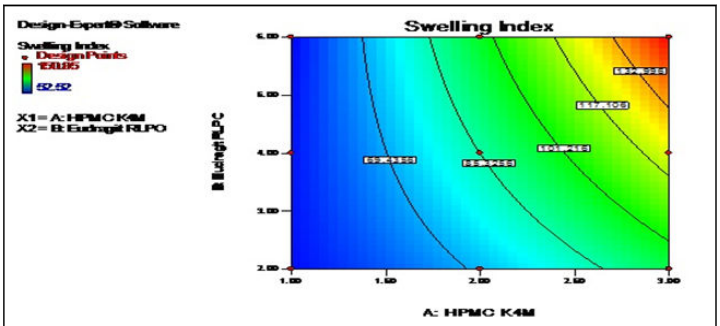

Figure 7: Contour plot of effect of HPMC K4M and Eudragit RLPO on the swelling index.

Approximation of desired response

The Figure 8 showed relationship between the percentage swelling index on y axis and deviation from the reference point with respect to HPMC K4M and Eudragit RLPO on the X axis. As the concentration of HPMC K4M and Eudragit RLPO is increases, percentage swelling index also increases. If still increased the concentration of HPMC K4M and Eudragit RLPO then there is increase in the percentage swelling index. At the point of perturbation indicates that the levels of the entire 2 variable consider together for optimized response should be at their low level value.

Desirability provides flexibility and giving importance for each response individually. According to the final results, this program suggested some formulations and also predicted their responses containing a probability factor named “desirability” that ranged between 0-1 that the most presumable answer would be the nearest to 1.

Data analysis showed that from high levels to low level each factor cause increase in the % swelling index in the formulation. This software also suggests some formulations out of the range that was given at first, in regard to the results of analysis. Also the desirability of each item could be observed. All of the formulation can be chosen for percentage swelling index at maximum level.

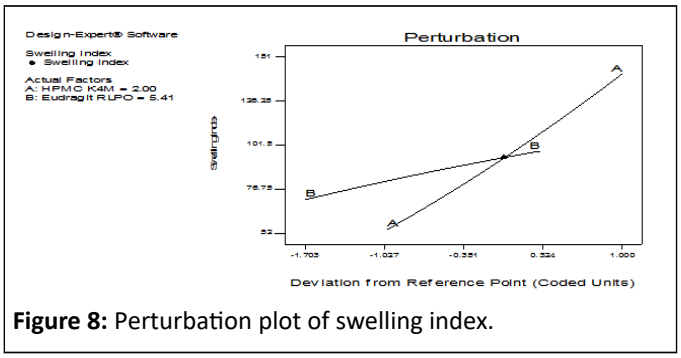

Figure 8: Perturbation plot of swelling index.

Selective formulation for optimized batch

Selected optimized formulation from DE 7.0 suggestions: Out of 11 solutions, solutions 1, 2, and 3 were considered. The optimized solution obtained from the model was formulated and the results are performed in the triplicates for

determination of %CDR, swelling index, unfolding time, mucoadhesive strength, thickness and %drug content, weight uniformity etc. The solution no 2 was found to comply all specifications hence considered optimized

Characterization of Film by Infra-Red spectrophotometer (FT-IR): The IR spectrum of the formulation was recorded and the functional groups where interpreted, it was found that optimized formulation showed functional group of HPMC K_4M, eudragit RLPO, eudragit L100, carbopol 971P NF and rizatriptan benzoate hence it can be concluded that there was no interaction between polymers and drug shown in Figure 9.

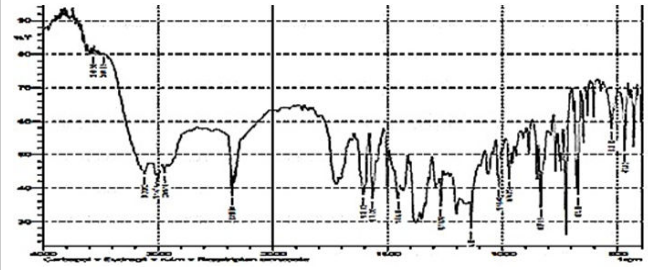

Figure 9: FT-IR spectra of optimized formulation.

Characterization of film by Differential Scanning Calorimeter (DSC): Any possible drug polymer interaction can be studied by thermal analysis. Rizatriptan benzoate exhibits a sharp endothermic peak at 182.60°C shown in Figure 10, which corresponds to its melting point. The Rizatriptan benzoate and other excipients (1:1) exhibit a sharp endothermic peak at 199.64°C. Hence DSC study shows in Figure 10 that there is no any drug polymer interaction [14].

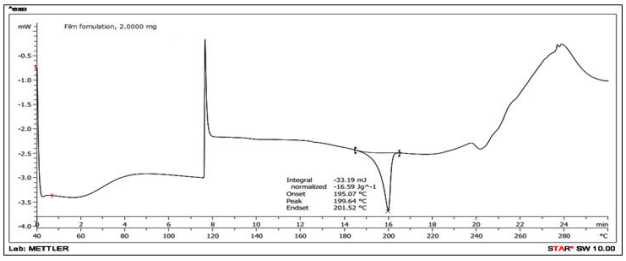

Figure 10: DSC thermogram of optimized formulation.

Morphology of film by SEM: The scanning electron photomicrographs were taken at different magnifications as shown in Figure 11. The SEM photograph showed smooth nonporous surface and uniform dispersion of drug in polymer matrix.

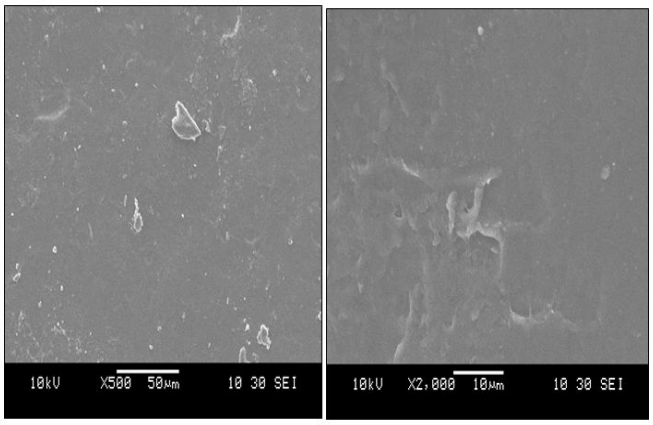

Figure 11: SEM photograph of optimized formulation at different magnification.

Effect of temperature and humidity: Effect of temperature and humidity was studied at 40°C ± 2°C/75% ± 5% RH maintained in environmental stability chamber for six months. An evaluation was done after 0, 1, 2 and 3, 4, 5, 6 months. The results were tabulated in Table 4.

Parameters	Month			
	0	1	2	3
In vitro Mucoadhesion (N) ± SD	0.821 ± 0.015	0.824 ± 0.01	0.821 ± 0.011	0.826 ± 0.013
(%) Drug release ± SD	98.33 ± 0.13	98.47 ± 0.25	98. 36 ± 0.12	98. 27 ± 0.06
(%) Drug content ± SD	88.50 ± 0.31	88.48 ± 0.10	88.20 ± 0.80	88.29 ± 0.21

Table 4: Effect of temperature and humidity on optimized batch.

Conclusion

The current research work demonstrates the successful development of a GRDF for a drug (Rizatriptan benzoate). It consists of a drug loaded polymeric film, folded into a hard gelatin capsule. Gastric retention is achieved due to unfolding of the dosage form in the stomach within 15-20 min of administration. The optimized film formulation showed satisfactory controlled release, mucoadhsion and integrity during the release period. The polymers used in the development of GRDFs were safe and proper combination of these polymers will yield a novel expandable GRDF with good

dissolution, bioadhesion and mechanical performance of the film. The film with zig-zag folding undergoes appropriate unfolding and expansion in acidic media which, combined with good bioadhesion, indicates the gastro retentive potential of the dosage form.

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