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# DESIGN, DEVELOPMENT AND EVALUATION OF UNIDIRECTIONAL BUCCAL TABLET OF RIZATRIPTAN BENZOATE

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## ABSTRACT

The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are imperilled to first-pass metabolism or are unstable within the rest of the gastrointestinal tract. Rizatriptan Benzoate is subjected to first-pass effect; therefore, formulation of buccal-adhesive dosage form can avoid this effect. This paper describes the preparation of unidirectional mucoadhesive buccal tablet comprising a drug-containing mucoadhesive layer and a drug-free backing layer, by core in cup design. Tablets were obtained by direct compression. The mucoadhesive layer was composed of a mixture of drug and mucoadhesive polymer with release retardant polymer and the backing layer. A two factor, three level, full factorial design was used to optimize amount of Polycarbophil and amount of HPMC K4M so as to get desired mucoadhesion, swelling and rate of drug release. Higher levels of HPMC K4M in the experimental design batches exhibited higher *in-vitro* drug release in the initial hour while the Polycarbophil levels could be related to increase in mucoadhesive strength. Overlay plot comprising a region that satisfied the constraints for all the selected attributes was generated. Formulation containing 6.52% w/w of Polycarbophil and 10% w/w of HPMC K4M was found to be optimum. Checkpoint batches were also prepared to validate the evolved mathematical models. Korsmeyer-Peppas release kinetic model best fitted the optimized batch release profile which showed anomalous diffusion mechanism. It can be concluded that buccal route can be one of the alternatives available for administration of Rizatriptan Benzoate.

## 1. INTRODUCTION

The majority of the drugs are administered through the oral route, which is the most preferred and patient-convenient. Limitations such as enzymatic degradation in the gastrointestinal (GI) tract and low bioavailability of the drug substance due to the first pass hepatic metabolism are important challenges that remain to be accomplished.[1]

The delivery of therapeutic agents, for both local and systemic delivery, via the oral mucosa offers a number of advantages over conventional routes.

- ✓ The oral cavity is convenient and easily accessible. This route is expected to have a higher level of patient compliance than parenteral or rectal routes.
- ✓ Enzyme and acid mediated drug degradation and "first pass metabolism", the two major barriers associated with conventional oral administration, can be avoided via this route.
- ✓ Circulation in the oral cavity mucosa is drained by the internal jugular vein, thus absorbed drugs will enter the systemic circulation directly and will bypass first pass liver metabolism.
- ✓ In case of toxicity buccal drug absorption can be terminated promptly by removing the dosage form from the buccal cavity.
- ✓ Localization of drugs and other formulation adjuvants is possible. Thus, protease inhibitors or penetration enhancers can be incorporated to locally modify the tissue and enhance permeability.
- ✓ Moreover, as being characterized by a rapid cellular turnover (5-6 days), the oral mucosa is less susceptible to damage or irritation potentially related to drugs or excipients used to design the dosage forms.

Potential disadvantages of drug delivery via the oral route include:

- ✓ It has a relatively small surface area compared to other routes, such as the intestine, rectum, and vagina.
- ✓ It has a low permeability of the mucosal membrane and short permanence time of conventional dosage forms due to mechanical stresses and swallowing.
- ✓ When administration of oral drug delivery is attempted, the taste of the drug is an important consideration. This constitutes a limitation to the application of certain drugs via the oral cavity.
- ✓ The need to fabricate dosage forms that are "user-friendly"[2-4]

Rizatriptan Benzoate (RB) is a selective 5-HT (1B/1D) receptor agonist used in the treatment of migraine. Although, it is absorbed well after oral administration, it is extensively metabolized hepatically via oxidative deamination by MAO-A, resulting in oral bioavailability of ~45%.[5]

Thus, the aim of the present work was to develop and characterize a mucoadhesive buccal tablet of Rizatriptan Benzoate using different mucoadhesive polymer and to evaluate mucoadhesion property for its buccal delivery.

## 2. MATERIALS AND METHODS

### 2.1. Materials

Rizatriptan Benzoate was obtained as gift sample from Cipla Ltd, Mumbai., Carbopol 934p (Coral Pharma, Mumbai), PEO WSR 301 and PEO N60K (Dow Ltd, Mumbai), Polycarbophil (Lubrizol, Belgium), Sodium Alginate, Aspartame, HPMC K4M, HPMC K15M and HEC (ACS Chemical, Ahmedabad), Lactose Monohydrate, PEG 4000, Ethyl Cellulose, Cellulose Acetate (Loba chemicals, Thane), Eudragit RS PO (Molychem, Mumbai), Scarlet Red (SDFCL, Mumbai) were used.

### 2.2 Pre-formulation study

#### 2.2.1 Identification of Rizatriptan Benzoate

Identification of Rizatriptan Benzoate was performed by Melting point determination by capillary method, FTIR Spectroscopy and DSC thermogram.

#### 2.2.3 Compatibility study

Physical mixtures of Rizatriptan Benzoate with various excipients were prepared by mixing in weight ratio of 1:1. The prepared mixtures were evaluated for possible interactions via differential scanning calorimetry and Fourier-transform infrared spectroscopy

### 2.3. Methods

#### 2.3.1 Preparation of tablets

**Formulation of core tablet**

- The core tablets were prepared by direct compression method.
- The ingredients Rizatriptan Benzoate, Polycarbophil, HPMC K4M and Lactose Mono-hydrate were accurately weighed as listed in **Table 3** and mixed in geometric proportion.
- The mixture was blended for 20 min in a sealable polythene bag.
- Then mixture is lubricated by adding magnesium stearate and talc and again blended for 2 min.
- The resulting uniform blend was compressed to form the tablets using the 8mm, circular, flat faced punch on lab press compression machine.
- The total weight of each core tablet was kept constant at 100mg.

**Formulation of core-in-cup tablet[6]**

Resulted round shape flat core tablet is recompressed in10mm round shape flat faced punch after adding ethyl cellulose (50 mg) at free three sides around the tablet.

### 2.4 Screening of excipients for mucoadhesive buccal tablet

#### 2.4.1 Screening of mucoadhesive polymer

Screening of mucoadhesive polymer was performed by using placket-burman design.

**Plackett-Burman Screening Design**

A Plackett-Burman screening design was employed to screen the mucoadhesive polymer having significant mucoadhesion. Plackett-Burman designs are screening designs that involve a large number of factors and relatively few runs.[7] They are typically used to identify a few significant factors out of a large set. Five assorted mucoadhesive polymer were evaluated by a total of eight experiments generated from Minitab® 17.0 (trial version). $X_1$ (Amount of Polycarbophil), $X_2$ (Amount of Carbopol 934p), $X_3$ (Amount of Polyethylene oxide N60K), $X_4$ (Amount of Polyethylene oxide 301), and $X_5$ (Amount of Sodium Alginate) were selected as independent variables while Y (mucoadhesive strength) were selected as dependent variable.

The core tablets were optimized for different amount of mucoadhesive polymer. Total weight of core tablet was kept constant as 200 mg.

#### 2.4.2 Screening of backing layer

Optimized core tablets were compression coated with different backing layer. On the basis of literature review Eudragit RSPO, Cellulose acetate, Ethyl Cellulose was tried for preparation of backing layer. Core tablet were carefully placed in the center of the die cavity and filled with coating material. The coating material was compressed using 10 mm flat faced punch by rotary tablet compression machine.

#### 2.4.3 Selection of release retardant polymer and amount of both polymers

On basis of literature review, HPMC K4M, HPMC K15M and HEC (Hydroxy Ethyl cellulose) were selected to check as a release retardant polymer. So, tablets were prepared using these three polymers in combination with Polycarbophil. In all batches, other ingredients are kept constant. Total weight of tablet was 150 mg.

**Table 1: Composition of Tablet for Preliminary Study of Release retardant polymers.**

| Batch | RizatriptanBenzoate | Polycarbophil | HPMC K15M | HPMC K4M | HEC | Lactose | Talc | Magnesiumstearate | Ethyl cellulose |
|---|---|---|---|---|---|---|---|---|---|
| F12 | 5 | 5 | 5 | - | - | 82 | 2 | 1 | 50 |
| F13 | 5 | 10 | 10 | - | - | 72 | 2 | 1 | 50 |
| F14 | 5 | 5 | 10 | - | - | 77 | 2 | 1 | 50 |
| F15 | 5 | 10 | 20 | - | - | 62 | 2 | 1 | 50 |
| F16 | 5 | 5 | 15 | - | - | 72 | 2 | 1 | 50 |
| F17 | 5 | 10 | 30 | - | - | 52 | 2 | 1 | 50 |
| F18 | 5 | 5 | - | 5 | - | 82 | 2 | 1 | 50 |
| F19 | 5 | 10 | - | 10 | - | 72 | 2 | 1 | 50 |
| F20 | 5 | 5 | - | 10 | - | 77 | 2 | 1 | 50 |
| F21 | 5 | 10 | - | 20 | - | 62 | 2 | 1 | 50 |
| F22 | 5 | 5 | - | 15 | - | 72 | 2 | 1 | 50 |
| F23 | 5 | 10 | - | 30 | - | 52 | 2 | 1 | 50 |
| F24 | 5 | 5 | - | - | 5 | 82 | 2 | 1 | 50 |
| F25 | 5 | 10 | - | - | 10 | 72 | 2 | 1 | 50 |
| F26 | 5 | 5 | - | - | 10 | 77 | 2 | 1 | 50 |
| F27 | 5 | 10 | - | - | 20 | 62 | 2 | 1 | 50 |
| F28 | 5 | 5 | - | - | 15 | 72 | 2 | 1 | 50 |
| F29 | 5 | 10 | - | - | 30 | 52 | 2 | 1 | 50 |

**2.4.4 Selection of Permeation enhancer agent:**
On the basis of literature review PEG 4000 was selected for Permeability enhancement. Two batches prepared with 5mg and 10 mg of PEG 4000 was added to Core tablet in both batches, in all batches quantity of other ingredients were kept constant.

**2.4.5 Selection of Sweetening Agent**
On the basis of literature review Aspartame was selected for sweetening agent. With 1mg and 2mg Aspartame was added to core tablet in different two batches, in both batches quantity of other ingredients was kept constant.

**2.4.6 Optimization of key parameters by Factorial design: Design Methodology: $3^2$ full factorial design**
Mucoadhesive strength, *in-vitro* drug release at 8 hrs. and %Swelling Index are important features of buccal tablet have been considered to play significant role in the formulation performance, were taken as dependent or response variables for the study. Amount of HPMC K4M and Amount of Polycarbophil were taken as independent variables. Multiple regression analysis, contour plots and 3D response surface plots were used to study the main and interaction effects of the independent variables on the dependent.

**Table 2. Coded and Decoded value of formulations**

| Batch No. | Coded value | | Decoded value | |
|---|---|---|---|---|
| | Amount of HPMCK4M X1 | Amount of Polycarbophil X2 | Amount of HPMCK4M (mg) X1 | Amount of Polycarbophil (mg) X2 |
| D1 | -1 | -1 | 10 | 5 |
| D2 | 0 | -1 | 20 | 5 |
| D3 | +1 | -1 | 30 | 5 |
| D4 | -1 | 0 | 10 | 10 |
| D5 | 0 | 0 | 20 | 10 |
| D6 | +1 | 0 | 30 | 10 |
| D7 | -1 | +1 | 10 | 15 |
| D8 | 0 | +1 | 20 | 15 |
| D9 | +1 | +1 | 30 | 15 |

**Table 3. Composition of tablet for design batches**

| Ingredients (mg) | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 |
|---|---|---|---|---|---|---|---|---|---|
| Rizatriptan Benzoate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Polycarbophil | 5 | 5 | 5 | 10 | 10 | 10 | 15 | 15 | 15 |
| HPMC K4M | 10 | 20 | 30 | 10 | 20 | 30 | 10 | 20 | 30 |
| Lactose | 77 | 67 | 57 | 72 | 62 | 52 | 67 | 57 | 47 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Magnesium stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Ethyl cellulose (Backing layer) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |

Mucoadhesive strength, *in-vitro* drug release at 8 hrs. and % swelling index obtained at various levels of the two independent variables ($X_1$and $X_2$) were subjected to multiple regressions to yield a second order polynomial equation.

**2.5 Evaluation Parameters**

**2.5.1 Physical characterization of Rizatriptan Benzoate tablets**

The prepared tablets were evaluated for content uniformity, weight variation, thickness, diameter, hardness, and friability. For the determination of content uniformity, one tablet was crushed and the drug was extracted with 250 ml of SSF (pH 6.8).

The solution was then passed through 0.45 Millipore filter and analyzed spectrophotometrically at 225 nm after sufficient dilution with SSF (pH 6.8). The test was done in triplicate.

The weight variation test was carried out according to the British Pharmacopoeia (Commission, 2012), where the weight of twenty tablets was determined using an electronic balance (Shimadzu, Japan) and the weight variation was calculated. The thickness and diameter of ten tablets were determined using a micrometer. The hardness of ten tablets was determined by using Pfizer hardness tester. The friability test was carried out according to British Pharmacopoeia (Commission, 2012), where ten tablets were accurately weighed and placed in the drum of a tablet friabilator (Model DFI- 1, Veego, Bombay, India), which rotated at 25 rpm for a period of 4 min. The tablets were then removed from the drum, dedusted, and accurately weighed. The percentage weight loss was calculated.

**2.5.2 Surface pH**

The microenvironment pH (surface pH) of the buccal tablets was determined in order to investigate the possibility of any side effects *in-vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was decided to keep the surface pH as close to neutral as possible. A combined glass electrode was used for measurement of surface pH. The tablet was allowed to swell by keeping it in contact with 4 ml of distilled water (pH 6.5 ± 0.05) for
2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min.[8]

**2.5.3 *Ex-vivo* mucoadhesion studies**

The *Ex-vivo* mucoadhesive strength was performed after application of the buccal tablet on freshly cut goat buccal mucosa. The fresh goat buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with simulated salivary fluid and adhered to the goat buccal mucosa by applying a light force with a fingertip for 30 seconds. The modified physical balance was adjusted by keeping glass beaker on another side. Water was added by burette and weight of water needed to detach the tablet from goat buccal mucosa was recorded for the measure of mucoadhesive strength in grams.[9]

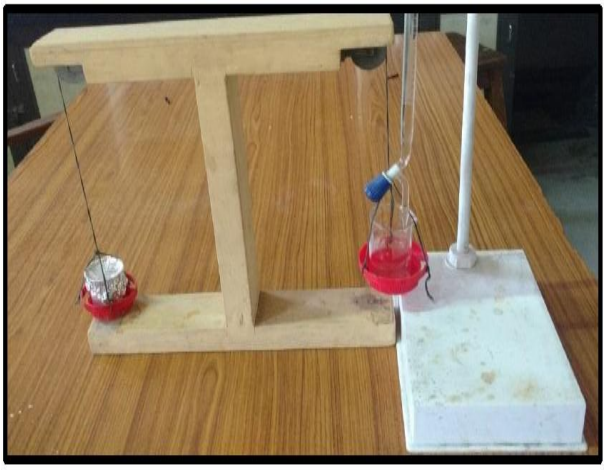

**Fig. 1: Assembly for mucoadhesion strength study.**

**2.5.4 *In-vitro* drug release studies**

The dissolution test was carried out using USP dissolution testing apparatus II. The test was performed at a paddle speed of 50 rpm using 500ml of simulated salivary fluid as the dissolution medium at 37±0.5°C. The tablet was stuck on the slide from the side of backing layer using cyanoacrylate adhesive to mimic unidirectional drug release. An aliquot of 5ml of the sample solution was withdrawn at the interval of 15, 30, 60, 120, 180, 240, 300, 360, 420, 480 min. and the absorbance was measured at 225 nm.[10]

**2.5.5 *In-vitro* swelling rate**

After weighing the tablet ($W_1$), it was immersed in simulated salivary solution maintained at 37°C. The weight at the end of 480 min was reported ($W_2$). The swelling index was determined from the formula:[11]

$$\%\text{Swelling Index} = [(W_2-W_1)/ W_1] \times 100 \quad \text{.....(1)}$$

Where, $W_1$ = initial weight

$W_2$= final weight

**2.5.6 *Ex-vivo* permeation studies**

Diffusion studies were carried out to evaluate the permeability of drug across the goat buccal mucosal membrane using glass surface Franz Diffusion cell. Goat buccal mucosa was obtained from a local slaughter house and was used within 2 hrs. of slaughter.

The tissue was stored in simulated salivary solution upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped in between donor and receiver chambers of the diffusion cells for permeation studies. Receptor compartment contained 20 ml of simulated salivary fluid, while donor compartment was filled with 3ml simulated salivary fluid. The tablet was placed on the mucosal surface in donor compartment, and 2ml

aliquots was removed at suitable intervals from the receptor compartment while the solution being stirred continuously using magnetic stirrer, replacing it with fresh 2 ml medium each time. The experiment was carried out at 37±1°C.[12]

**2.5.7 *Ex-vivo* residence time**

The tablet was applied on the goat buccal mucosa which was fixed on the glass slide with cyanoacrylate glue. The slide was tied to the disintegration apparatus and suspend in the beaker filled with 900 ml simulated salivary fluid. The slide was allowed to reciprocate in the medium until the tablet got detach or erode from the mucosa. The test was performed in triplicate. Time for the detachment of the tablet was recorded as *Ex-vivo* residence time.[12]

**2.5.8 Taste masking evaluation (sensory evaluation)**

For evaluation of taste in human volunteer prior permission of human ethics committee ("Ethiclin" Ethics committee, Saurashtra university, Rajkot) was taken as protocol number SUDPS / ETHICLIN / 05 / 2016 / 03. Taste evaluation was done by taste panels. The method chosen was ranking test. For these 6 human volunteers were selected. The dispersion of the pure drug and formulations were coded and given to the panelists. The intensity of bitterness was asked from panelists and recorded.[13]

**2.5.9 Prediction of the release mechanism**

The drug release profile comparison carried out by curve fitting analysis equations of different mathematical model to drug release profile of optimized formulation.[14-16]

## 3. RESULTS AND DISCUSSION

### 3.1 Pre-formulation studies

#### 3.1.1 Identification of drug

The observed melting point of Rizatriptan Benzoate was found to be 181-183°C. This melting point resembles to melting point reported in reference. The FTIR spectra of pure Rizatriptan Benzoate showing characteristic peaks which are present in reference spectra from IP. The DSC thermograph of Rizatriptan Benzoate showed endothermic peak at 183.14°C depicted in figure 2. This was corresponding to its melting point.

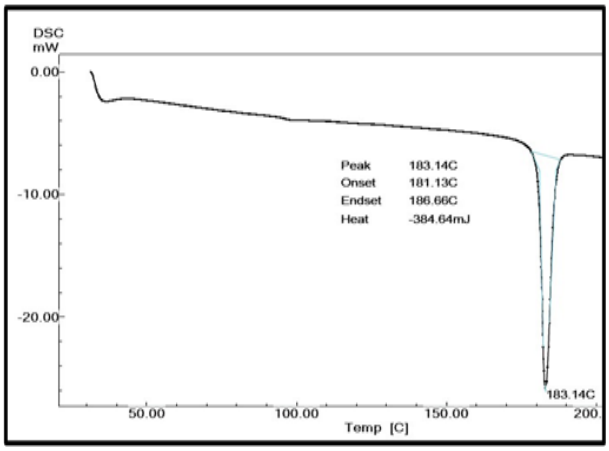


**Fig. 2: DSC thermograph of Rizatriptan Benzoate.**

#### 3.1.2 Compatibility studies

From study of FTIR spectra and DSC thermograph of Rizatriptan Benzoate and Rizatriptan benzoate with physical mixture of excipients. In FTIR spectra of pure Rizatriptan Benzoate shows following peaks 3550, 2943, 1604, 1568, 1502,and 1018 $cm^{-1}$ and Physical mixture shows following peaks 3502, 2947, 1604, 1566, 1504 and 1016 So It was found that functional group peaks of pure drug remain near to same even in physical mixture prepared by using excipients and API in FTIR spectra and In DSC thermograph pure Rizatriptan Benzoate shows peak at 183.14 and physical mixture shows peak at 181.21 which is near to Pure Rizatriptan Benzoate. From observation and identification of peaks in FTIR spectra and DSC thermograph it can be established that API and excipients are compatible.

### 3.2 Screening of mucoadhesive polymer: Plackett-Burman design.

**Table 4. Plackett burman design for Preliminary Study**

| Batch | Polycarbophil (X1) | Carbopol 934p (X2) | PEO N60K (X3) | PEO 301 (X4) | Sodium Alginate(X5) | Mucoadhesive Strength(N) (Y) |
|---|---|---|---|---|---|---|
| **F1** | 1 | -1 | -1 | 1 | -1 | 0.298 |
| **F2** | 1 | 1 | -1 | -1 | 1 | 0.315 |
| **F3** | 1 | 1 | 1 | -1 | -1 | 0.322 |
| **F4** | -1 | 1 | 1 | 1 | -1 | 0.305 |
| **F5** | 1 | -1 | 1 | 1 | 1 | 0.383 |
| **F6** | -1 | 1 | -1 | 1 | 1 | 0.264 |
| **F7** | -1 | -1 | 1 | -1 | 1 | 0.186 |
| **F8** | -1 | -1 | -1 | -1 | -1 | 0.122 |

**Table 5. The Decoded and Coded values of levels for Polymers**

| Polymer (mg) | Low (-1) | High (+1) |
|---|---|---|
| Polycarbophil | 10 | 30 |
| Carbopol 934p | 30 | 45 |
| PEO N 60K | 20 | 40 |
| PEO 301 | 15 | 30 |
| Sodium alginate | 15 | 30 |

As shown in Table 4. Five independent variables were selected, viz. Polycarbophil ($X_1$), Carbopol 934p ($X_2$), Polyethylene oxide N60K ($X_3$), Polyethylene oxide WSR 301 ($X_4$) and Sodium alginate ($X_5$). Mucoadhesive strength(Y) was selected as a dependent factor. As shown in Fig. 3. The Pareto chart revealed that Polycarbophil, Carbopol 934p, PEO 301 and PEO N60K (p value <0.05) showed significant effect on mucoadhesion, However, Polycarbophil showed highest standardized effect on the response variables and was selected as mucoadhesive polymer for further studies.

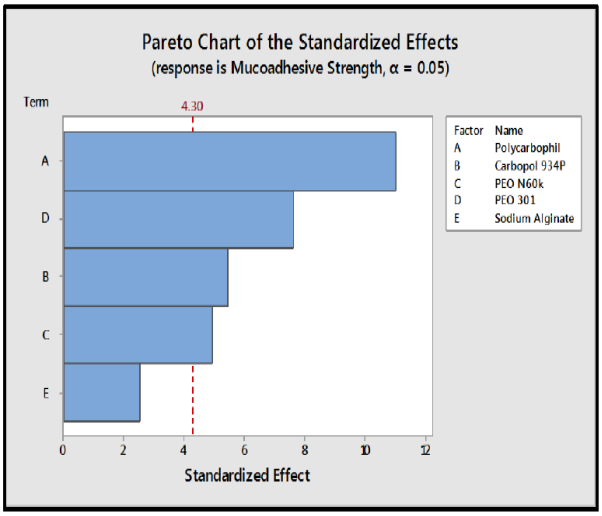


**Fig. 3: Pareto chart for Mucoadhesive strength of Polymer.**

### 3.3 Selection of backing layer: ("cup")

On basis of literature review, Eudragit RSPO, Cellulose acetate, Ethyl cellulose was tried as a backing layer. Other ingredients were kept constant. Mucoadhesive buccal tablets were subjected for dissolution testing condition and observed for the time required for breaking of cup. Ethyl cellulose containing mucoadhesive buccal tablets did not show breaking of cup up to 480 minutes, so selected for further studies.

### 3.4 Selection of release retardant polymer

On basis of literature review, HPMC K4M, HPMC K15M and HEC (Hydroxy Ethyl Cellulose) were selected to check as a released retardant polymer. So, tablets were prepared using these three polymers in combination with Polycarbophil. In all batches, other ingredients were kept constant.

Tablet were prepared by direct compression and dissolution study by USP paddle apparatus (50rpm, 500ml Simulated Salivary Fluid) were done to find out optimum polymer concentration.

### 3.5 Cumulative percentage drug release of preliminary batches

In Batch F12 to F29, different concentrations of different polymers were taken and drug release of each batch was studied. Here, Polycarbophil was used as mucoadhesive polymer, while HPMC K4M, HPMC K15M and HEC were selected as sustained release polymers for screening. From the results, it was found that decreasing the concentration of sustained release polymer provided higher drug release. From the three sustained release polymers, HPMC K15M containing mucoadhesive buccal tablets gives less than 90% drug release at the end of 8 hrs. Which was not desired in case of mucoadhesive buccal tablet so it was not selected for further studies? HPMC K4M was found to be superior for providing sustained release of Rizatriptan Benzoate while in case of HEC it gives 90% of drug release at the end of 6 hrs. So here HPMC K4M selected for further study. Moreover, batch F20 i.e. the batch containing 5 mg Polycarbophil and 10 mg HPMC K4M provided desired drug release.

### 3.6 Selection of Permeation enhancer agent

On the basis of literature review PEG 4000 was selected for Permeability enhancement. Different amount of PEG 4000 was added to Core tablet, in all batches other ingredients were
kept constant.

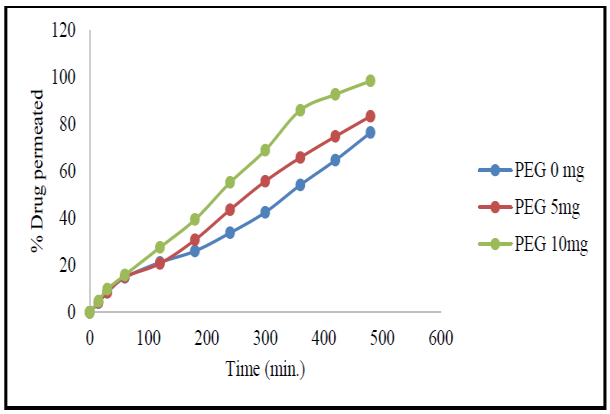


**Fig. 4 *Ex-vivo* permeability of F30-F32.**

Rizatriptan benzoate is BCS class III drug, it having low permeability so to pass through mouth mucosa permeability of drug is rate limiting step for absorption of drug. To enhance permeability of drug PEG 4000 was used. Three batches prepared and evaluated for *Ex-vivo* permeability study. From results obtained presented in figure 4 revealed that with 10 mg PEG 4000 gives desired *Ex-vivo* permeability.

### 3.7 Selection of Sweetening Agent

On the basis of literature review Aspartame was selected for sweetening agent. Different proportion of Aspartame was added to core tablet, in all batches quantity of other ingredients was kept constant.

Evaluation of taste was performed by taste panel. For healthy human volunteer, prior permission of human ethics committee was taken; here 6 healthy volunteers were selected for evaluation of taste. Taste of pure drug and formulation ranked by volunteer given as 0 = Acceptable; 1 = Slightly Bitter; 2= Bitter; 3 = Very Bitter, 4 = Extremely Bitter. It was observed that formulation batch F34 containing 2 mg aspartame given 0 ranks by all volunteers so it will be taken for further study.

### 3.8 Evaluation Parameter of Factorial design batches:

Using $3^2$ full factorial design, nine batches of mucoadhesive buccal tablet of Rizatriptan Benzoate was prepared by direct compression method. Amount of HPMC K4M ($X_1$) and Amount of Polycarbophil($X_2$) were taken as independent variables and mucoadhesive strength, % drug release at 8hrs. and % swelling index taken as dependent variables. The formulations of design batches were evaluated for pre-compressional and post compressional parameters. Optimized batch was derived statistically using desirability function in Design expert® 10 Software. The Model was validated by formulating the check point batch. Short term accelerated stability study was carried out of optimized batch.

### 3.8.1 Physical characteristics of Rizatriptan Benzoate tablets

The prepared tablets were smooth and white in color. Weight variation in case of all tablets was acceptable. The weight variation in case of all the tablets was within ±7.5% of theoretical tablet weight. This fall swell within the acceptance criteria. Friability in case of all the designed tablets was less than 1% w/w indicating suitability of the method used for manufacturing the tablets. The prepared tablet showed maximum thickness of 1.63 mm. Hardness value of all the formulation was in the range of 3-4.5Kg/cm$^2$. To evaluate a tablets potential for efficacy the amount of drug in the tablet need to be monitored from tablet to tablet and batch to batch. The mean drug content was found to be in between range of 97.14% to 99.57%.

### 3.8.2 *Ex-vivo* mucoadhesive strength

**Force of Adhesion (N)= Mucoadhesive Strength * 9.81/1000…….. (2)**

Mucoadhesive strength was found to be increased as Polycarbophil concentration increases. In that batch D5 showed the optimum mucoadhesive strength (0.380 N).

### 3.8.3 Percentage swelling index

Swelling study helps in analysis of important parameters involving drug release mechanism in a matrix system, possibility of water penetration for drug release, lag time of drug release of soluble drug in matrix system.

Swelling index measurements was found to be increased with increasing amounts of HPMC K4M. As Polycarbophil concentration increase swelling index was found to be also increased but effect was not as prominent as with HPMC K4M. In that batch D5 showed the optimum % swelling index.

### 3.8.4 Surface pH study

The maximum and minimum pH values of the formulations were found to be between 6.5 and 7. The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets was within limits. Hence, the formulations may not produce any irritation to the buccal mucosa.

### 3.8.5 *Ex-vivo* residence time

The *Ex-vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablets. The *ex-vivo* residence time was determined by using specially designed disintegration apparatus. As the concentration of bioadhesive polymer increased, the residence time also increased. This examination reveals the mucoadhesive capacity of polymers used in formulations. Polycarbophil had much more effect on the retention time than HPMC K4M and formulation containing higher concentration of Polycarbophil showed higher retention time. So, retention time increases from D1 to D9.

### 3.8.6 *In-vitro* drug release profile of experimental batches

*In-vitro* drug release study data indicated that duration of release of drug was dependent on the percentage of selected polymer used in the formulations. An increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusional path. This leads to decrease in the diffusion of the drug and therefore a reduction in the drug release rate. From the Dissolution profile depicted in fig.

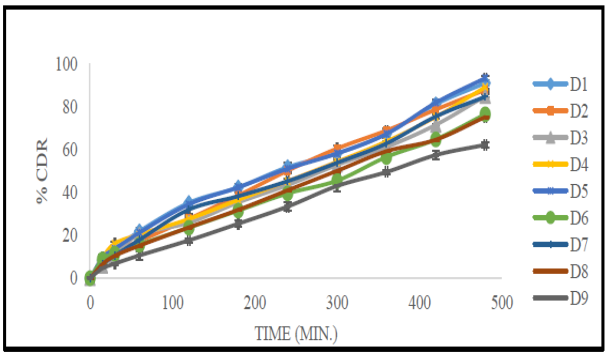


**Fig. 5: Dissolution profile of design batches**

5. It was found that Formulation D5 containing medium concentration of polymers showed highest drug release of 93.23% in 8hours. Formulation D9 containing highest concentration of polymers showed lowest drug release of 62.12% in 8 hours.

**3.8.7 *Ex-vivo* permeability study of design batches**

From *ex-vivo* permeability study it was observed that as Pure drug is having less permeability (76.37 %). To increase permeability of drug, PEG 4000 was used as permeation enhancer. Batch D5 showed maximum Permeability (94.89%).

**3.9 Statistical Analysis for Design Batches**

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses carried out using multiple regression analysis.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_{12} + \beta_{22} X_{22} \quad \text{.....(3)}$$

Where Y is the dependent variable, $\beta_0$ is the arithmetic mean response of experimental runs, and $\beta_1$, $\beta_2$ are regression coefficients for the factor $X_1$ and $X_2$. The main effects ($X_1$ and $X_2$) represent the average result of changing the factor at a time from its low to high values. The interaction terms ($X_1X_2$) showed how the response changed when two factors were simultaneously changed. The polynomial terms ($X_1^2$ and $X_2^2$) are generally included to investigate non-linearity. The fitted equations relating the responses. Mucoadhesive strength, % Drug release after 8 hrs. and % Swelling index observed are shown in the table 6.

**Table 6. Observed dependent variables for $3^2$ full factorial design.**

| Batch No. | Amount of HPMC K4M (X1) | Amount of Polycarbophil (X2) | Mucoadhesive Strength (Y1) (Mean ± SD)* | % CDR at 8 hrs. (Y2) (Mean ± SD)* | % Swelling Index (Y3) (Mean ± SD)* |
|---|---|---|---|---|---|
| D1 | -1 | -1 | 0.273 ± 0.03 | 90.91 ± 0.70 | 114.32 ± 2.09 |
| D2 | 0 | -1 | 0.299 ± 0.01 | 87.72 ± 0.69 | 129.91 ± 3.02 |
| D3 | 1 | -1 | 0.312 ± 0.02 | 84.80 ± 0.71 | 144.65 ± 1.10 |
| D4 | -1 | 0 | 0.367 ± 0.02 | 89.03 ± 0.80 | 132.11 ± 2.33 |
| D5 | 0 | 0 | 0.380 ± 0.04 | 93.23 ± 0.87 | 129.76 ± 2.57 |
| D6 | 1 | 0 | 0.438 ± 0.02 | 76.38 ± 0.86 | 163.63 ± 2.63 |
| D7 | -1 | 1 | 0.502 ± 0.03 | 84.54 ± 1.45 | 118.57 ± 3.42 |
| D8 | 0 | 1 | 0.525 ± 0.03 | 75.09 ± 0.98 | 145.70 ± 3.89 |
| D9 | 1 | 1 | 0.532 ± 0.03 | 62.12 ± 1.04 | 180.23 ± 3.21 |

*Average of three determinations

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficients and the mathematical sign carried: positive or negative. Data were analyzed using Microsoft Excel 2016. R Square Values for Mucoadhesive strength, % Drug release after 8 hrs. and % Swelling index were 0.990, 0.943 and 0.946 respectively indicating good correlation between dependent and independent variables. From multiple regression analysis, it was found that both factors had statistically significant influence on all dependent variables as $p < 0.05$.

Equations for $3^2$ full factorial design for all dependent variables was generated with the aid of Microsoftexcel® 2016.Values of correlation coefficient (R Square) obtained from the result of multiple regression analysis were high enough for all dependent variables suggesting good correlation between response set and independent variables. From the result of ANOVA above table it was found that $F_{cal}$. Values were much greater than $F_{tab}$. For all formulations indicating that all factors had statistically significant effect on all dependent variables.

**3.9.1 $3^2$ model for Mucoadhesive strength**

For Mucoadhesive strength, as seen from figure 6 of response surface plot revealed that the Mucoadhesive strength was change in case of concentration of HPMCK4M and Polycarbophil was varies. The Polynomial equation generated from Microsoft excel® 2016 for Mucoadhesive strength is given below

**Mucoadhesive strength ($Y_1$)**

$$= 0.393 + 0.023X_1 + 0.112X_2 - 0.002X1X_2 - 0.005X_{11} - 0.012X_{22} \ldots \quad (4)$$

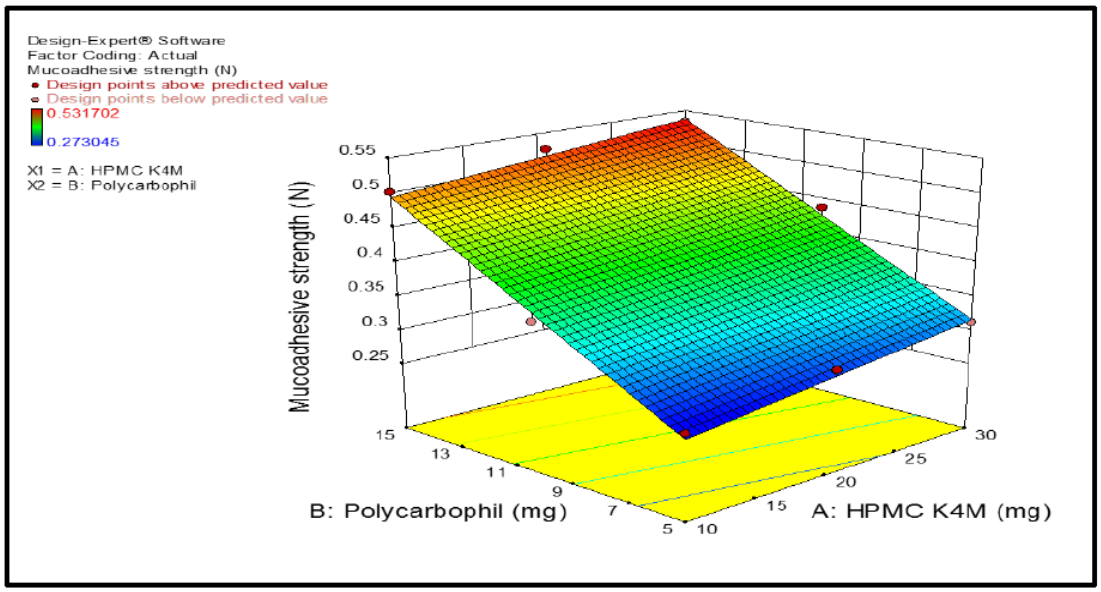


**Fig. 6: Response Surface plot showing the effect of HPMC K4M ($X_1$) and Polycarbophil ($X_2$) on Mucoadhesive Strength ($Y_1$).**

From polynomial equation and coefficient of $X_1$ and $X_2$ it was observed that the Concentration of HPMC K4M and Polycarbophil showed positive effect on Mucoadhesive strength. Increase in their concentration would increase the Mucoadhesive strength and concentration of Polycarbophil was more effective than concentration of HPMC K4M.

### 3.9.2 $3^2$ model for %Drug release at 8 hrs.

For % Drug release at 8hrs. as seen from figure 7 representing the response surface plot revealed that the % Drug release at 8hrs. Was highest in case of concentration of HPMC K4M and Polycarbophil was at low level. The Polynomial equation generated from Microsoft excel® 2016 for % Drug release at 8 hrs. is as given bellow.

**% Drug release at 8 hrs. ($Y_2$)**

**$= 88.91 - 6.86X_1 - 6.94X_2 - 4.07X_1X_2 - 4.05X_{11} - 5.34X_{22}$…. (5)**

From polynomial equation and coefficient of $X_1$ and $X_2$ it was observed that the concentration of HPMC K4M and Polycarbophil showed negative effect on % Drug release. Increase in their concentration would decrease the % Drug release and concentration of HPMC K4M was giving more significant effect on % drug release than concentration of Polycarbophil.

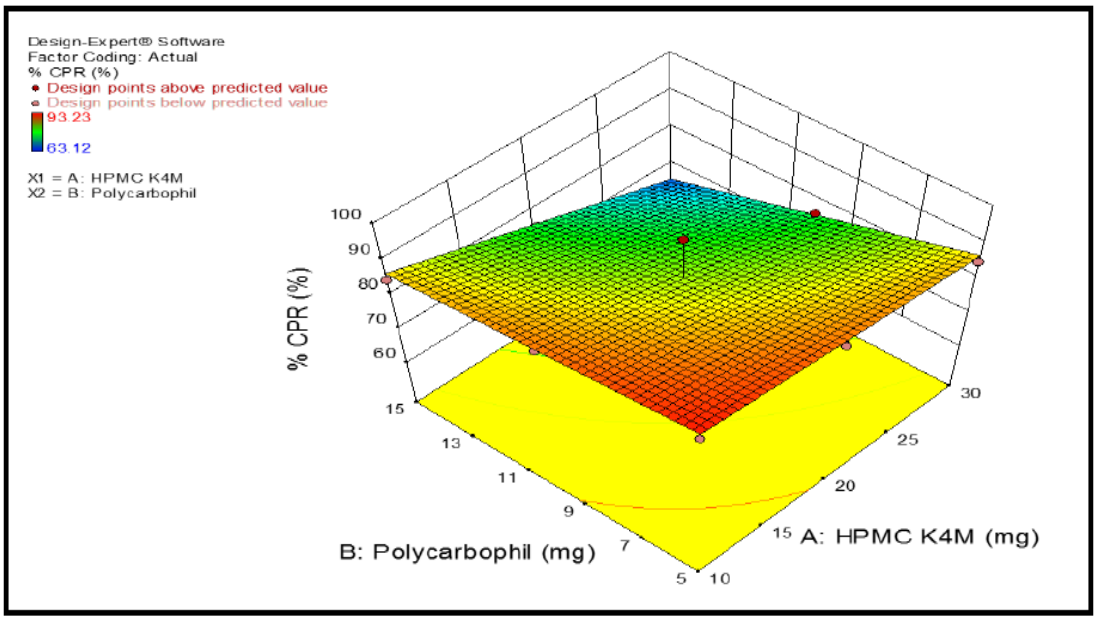


**Fig. 7. Response Surface plot showing the effect of HPMC K4M ($X_1$) and Polycarbophil ($X_2$) on % Drug release at 8 hrs. ($Y_2$).**

### 3.9.3 $3^2$ model for % Swelling index

For % swelling index, as seen from figure 8 representing the response surface plot revealed that the % Swelling index was increase as concentration of HPMCK4M increases. The Polynomial equation generated from Microsoft excel for% Swelling index is given bellow

**%Swelling index ($Y_3$)**
**$= 137.08 + 20.58X_1 + 9.27X_2 + 7.83X_1X_2 + 7.13X_{11} - 2.93X_{22}$….. (6)**

From polynomial equation and coefficient of $X_1$ and $X_2$ it was observed that the concentration of HPMC K4M and Polycarbophil showed positive effect on % Swelling index. Increase in their concentration would increase the % Swelling index and concentration of HPMC K4M was more significant than concentration of Polycarbophil.

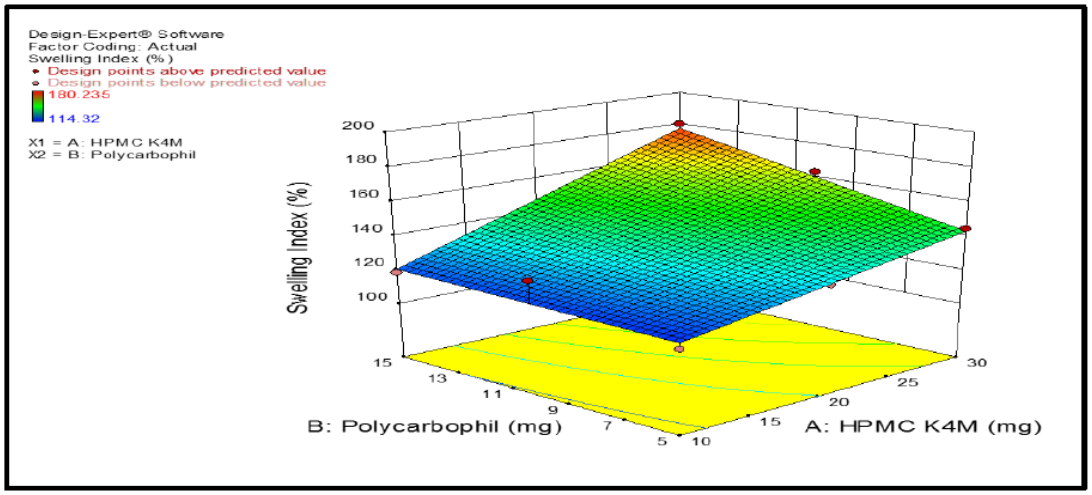


**Fig. 8: Response Surface plot showing the effect of HPMC K4M ($X_1$) and Polycarbophil ($X_2$) on % Swelling index ($Y_3$).**

### 3.10 Desirability approach or Optimization of Experimental design

The optimized formulation was selected based on the criteria of attaining the minimum, target and maximum range of the dependent variables. In this case dependent variables mucoadhesive strength selected in a range (0.3 – 0.4 N), % drug release selected as Maximum and % swelling index selected as minimum target. An overall desirability function dependent on all the investigated formulation variables was used to predict the ranges of variables where optimized formulation might occur. The desirable ranges are from zero to one (least to more desirable, respectively). The restriction value chosen (minimum, target, and maximum) put in Design-Expert 10 software to obtain optimized batch. Optimized batch was prepared by using Amount of HPMC K4M($X_1$) 10mg and Amount of Polycarbophil($X_2$) 6.52mg.

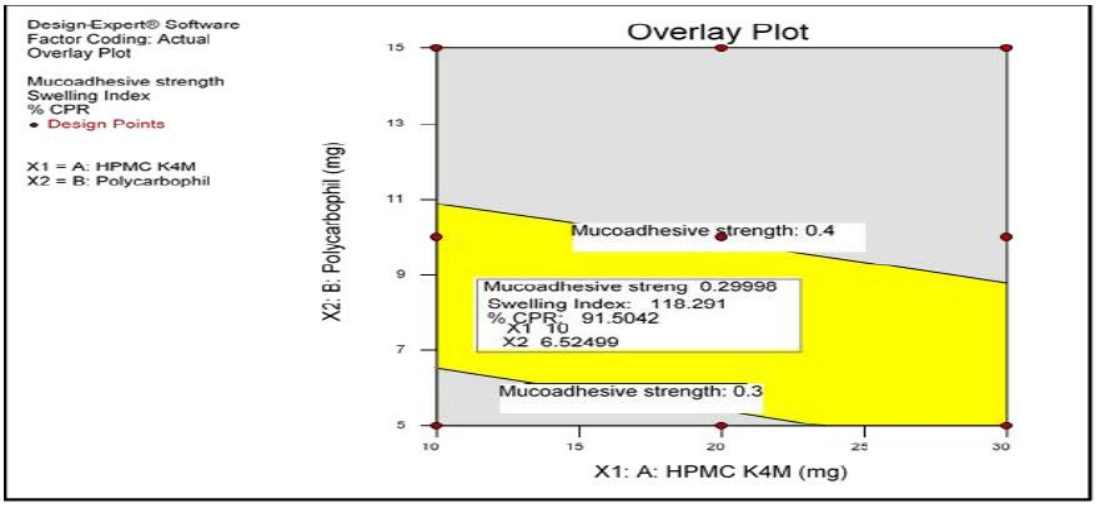


**Fig. 9: Profile of desirability graph.**

### 3.11 Validation by optimized cum check point batch

To confirm the validity of design, the optimized batch was prepared and % relative error was calculated which was found to be less than the 5 % which was indicated goodness of fit in model. It was found that both factor had statistically significant influence on all dependent variables as P <0.05. Thus, both reasons were confirming the validity of design.

**Table 7: Result of check point batch method**

| Response | Predicted value | Experimental value | %Bias |
|---|---|---|---|
| **Mucoadhesive strength (Y1)** | 0.300 N | 0.295 N | -1.66 |
| **% drug release at 8hrs. (Y2)** | 91.50 % | 92.07 % | 0.62 |
| **% swelling index (Y3)** | 118.29 % | 121.04 % | 2.32 |

### 3.12 Curve Fitting Analysis

The best fit model was selected on the basis of relatively higher correlation coefficient value ($R^2$). The method described by Korsemeyer and Peppas was used to describe mechanism of drug release. The diffusion exponent is the indicative of mechanism of drug release from the formulation. The n value is used to characterize different release mechanisms, concluding for values for slab, of n<0.5 for Fickian diffusion mechanism, 0.5<n< 0.89 to non-Fickian transport, 0.89<n<1.15 indicates case II transport or zero order drug release and n>1.15 indicates to supercase II transport.

**Table 8. Drug release kinetic of Optimized batch**

| Kineticmodel | Zero order | First order | Korsemeyer-Peppas Model | Hixon | Higuchi |
|---|---|---|---|---|---|
| **R2value** | 0.9589 | 0.9654 | 0.9901 | 0.9364 | 0.9730 |

The $R^2$ value of Korsemeyer-pappas models is more than other model and n value found to be 0.762, which indicates tablet, follows non-fickian diffusion.

### 3.13 Short-term accelerated stability study

The short-term stability study was carried out for optimized batch at 40± 2°C and 75 ± 5% RH over the period of 30 days.

**Table 9: Result of Short-term stability study of optimized batch.**

| Evaluation Parameters | Before Stability period | After Stability period | %Bias |
|---|---|---|---|
| **Appearance** | White | White | - |
| **%Drug Content** | 97.14 % | 96.25 % | -0.916 |
| **Surface pH** | 6.82 | 6.73 | -1.320 |
| **Mucoadhesive strength(N)** | 0.310 N | 0.302 N | -2.580 |
| **%Swelling index** | 120.08 % | 118.21 % | -1.557 |
| **%Drug release after 8hrs.** | 94.06 % | 93.55 % | -0.542 |

The formulation retained the white appearance. No remarkable change was observed in surface pH, mucoadhesive strength, and % drug release after 8hrs. And swelling index. There was small decrease in swelling index, which led to slightly lower the drug release after 8 hrs. But changes were insignificant. Negligible difference was observed in results obtained during optimization and those after stability study. Thus, the formulation retained the good stability at room temperature and humidity.

### 3.14 Taste evaluation of optimized batch

Taste evaluation carried out in 6 healthy human volunteers. Ranking of taste given in below table. Ranking was given as 0 = Acceptable; 1 = Slightly Bitter; 2= Bitter; 3 = Very Bitter, 4 = Extremely Bitter. The entire 6 volunteer given 0 ranking for optimized batch so it was concluded that bitter taste of Rizatriptan Benzoate was satisfactory masked.

## 4. CONCLUSION

It was concluded that mucoadhesive buccal tablet of Rizatriptan Benzoate provides good concept to bypass the extensive hepatic first-pass metabolism. Formulated tablet using HPMCK4M and Polycarbophil showed good Mucoadhesive Strength, Drug release profile and Swelling Index. The mucoadhesive buccal tablet of Rizatriptan benzoate is promising approach for treatment of migraine which avoid dose related side effect as well as reduce dose frequency by avoiding hepatic first pass metabolism.

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