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BUCCAL MUCOADHESIVE TABLET DRUG DELIVERY SYSTEM OF RIZATRIPTAN AGAINST SUSTAINABLE MIGRAINE BY USING METHOCEL K100LV, CARBOPOL 934P AND JAGUAR GUM: DESIGN, DEVELOPMENT AND *IN VITRO* EVALUATION

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Abstract:
The present research was expected to foster buccal mucoadhesive tablet of Rizatriptan utilizing mucoadhesive polymers like Methocel K100LV, Carbopol 934P and Jaguar gum by direct pressure technique. The dry power combination of medication and polymers were assessed for precompression parameters to guarantee flow properties during tablet compression. FTIR and DSC results showed no proof of interaction between the Rizatriptan and mucoadhesive polymers utilized for formulations. The detailed mucoadhesive buccal tablets were assessed for physicochemical properties like hardness, friability, thickness consistency, weight variation, swelling studies and moisture absorption studies. The formulated buccal tablets were additionally assessed for mucoadhesive strength, in vitro drug delivery and ex vivo drug permeation through cellulose acetic acid derivation layer. Ex vivo mucoadhesive strength and in vitro discharge studies showed that formulation RBMT$_4$ containing 20% of Methocel K100LV and 10% of Jaguar gum showed adequate bioadhesive strength and displayed optimum medication release (99.64% after 10hrs). The Stability of best mucoadhesive buccal still up in the air in artificial human saliva and it was found that both Rizatriptan and buccal tablets were steady in human saliva. The plan mucoadhesive buccal tablets of Rizatriptan expected to have delayed restorative impact with improved tolerance consistence by keeping away from first pass metabolism.

Keywords: *Antimigraine, Mucoadhesion, Rizatriptan, Methocel K100LV, Carbopol 934P, Jaguar gum*

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1. INTRODUCTION:

Buccal medication delivery system gives direct admittance to the systemic circulation through the inner jugular vein bypassing the first pass metabolism that prompts high bioavailability. In addition, the buccal cavity is effectively available for self-medicine and medication absorption is ended in the event of harmfulness by removing the dosage form from the buccal cavity.[1] Buccal medication delivery system uses mucoadhesive polymers which become cling to the buccal mucosa upon hydration and thus go about as targeted or controlled/sustained delivery system. Different mucoadhesive dosage forms proposed for oral medication conveyance which incorporate glue adhesive tablets, adhesive patches, adhesive gels, strip, ointment and discs. Different benefits are fast beginning of activity, non-invasive organization, advantageous and effectively open site, self-administrable, low enzymatic action, reasonableness for drugs or excipients that gently and reversibly, harms or disturbs the mucosa, effortless organization, simple medication withdrawal, modest and have predominant patient consistence.

Rizatriptan, a particular 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist. Chemically Rizatriptan is communicated as N, N-dimethyl-2-[5-(1H-1,2,4-triazol-1-ylmethyl)- 1H-indol-3-yl]ethanamine. It is utilized for the treatment of headache migraines. Headache migraine are the most widely recognized illness portrayed as vascular migraine that causes a throbbing and pulsating agony around the head.[3] It includes strange affectability of conduits inside the mind bringing about triggers that regularly lead to quick changes in the measurement of course, coming about because of fit. Because of this different supply routes in the cerebrum and scalp widen bringing about horrible torment in the head. The mean oral outright bioavailability of the Rizatriptan tablet is around 45%, and mean peak plasma concentrations (Cmax) are reached in roughly 1-1.5 hours (Tmax). Roughly 14% of an oral portion is discharged in urine as unaltered Rizatriptan while 51% is discharged as indole acetic acid metabolite, demonstrating generous first pass metabolism. The plasma half-existence of Rizatriptan in males and females 2-3 hours. The recommended starting dose of Rizatriptan is either 5 mg or 10 mg for the intense therapy of headaches in adults.[4]

Thus, in the current review an attempt had been made to figure mucoadhesive buccal tablet for Rizatriptan utilizing distinctive blend of polymers to keep away from first pass metabolism, for delayed impact and to get more noteworthy therapeutic efficacy for further developing patient compliance.[5]

2. MATERIALS AND METHODS:

2.1 Materials

Rizatriptan was acquired as a gift test from Hetero Healthcare Ltd Hyderabad, India. The mucoadhesive polymer like Methocel K100LV, Carbopol 934P and Jaguar gum were bought from Indian Drugs, Hyderabad. Pharmatose, PVP K30, Titanium dioxide, Saccharin, Talc and magnesium Stearate were bought from S.D. fine synthetic substances Pvt. Ltd' Mumbai, India. All the ingredients were of research facility grade. The distilled water utilized during the time spent examination work was ready by twofold refining process in the laboratory.

2.2 METHODS:

2.2.1 Drug excipients compatibility studies

Drug excipients compatibility studies were performed by FTIR and DSC studies.

2.2.1.1 Fourier Transform Infrared (FTIR) spectroscopy:

Fourier transform infrared (FTIR) study was performed to check any physical or chemical interaction between the unadulterated medication and the excipients utilized. The FTIR investigations of unadulterated API Rizatriptan and the actual blend that contains that multitude of fixings with unadulterated API were done. It was performed by potassium bromide (*KBr*) pellet method. The samples were triturated with *KBr* and pellet was prepared by setting the pressure to 100 kg/cm^2 for 2 min. The acquired pellet was investigated in FTIR 8400S, Shimadzu, Japan. The peaks that were acquired for the unadulterated medication, polymers and formulation, portrayed for the presence of various functional group and guaranteed that there was no additional peaks shaped which ordinarily demonstrates development of new functional group.[6,7]

2.2.1.2 Differential Scanning Calorimetric (DSC) analysis:

One more strategy for assessing the actual collaboration among medication and polymers utilized for the formulation of different dosage form is warm examination by DSC or TGA procedures. In the current examinations the DSC investigation of Rizatriptan and the actual blend that contains that large number of fixings with unadulterated API utilized for formulation of buccal mucoadhesive tablets were done utilizing a Shimadzu DSC 60, Japan; to assess any conceivable polymer drug thermal interactions. Precisely gauged 5 to 6 mg tests were airtight fixed in aluminium crucible and heated at consistent pace of 10 ^{o}C/min over a temperature

range of 40 to 300°C. Inert atmosphere was kept up with by cleansing nitrogen gas at a stream pace of 50 ml/min.[9]

2.2.2 Formulation of Rizatriptan mucoadhesive matrix tablets

Rizatriptan mucoadhesive tablets were detailed by direct compression strategy. All the powders went through sieve number #40. The necessary amount of Rizatriptan, different polymers and fillers were blended completely by process of trituration. The dry mixes were dried at 40°C for 15 minutes to decrease moisture content so the last level of moisture in powder stayed in a range of 2-5 %. Magnesium stearate and powder were at last added as a lubricant and glidant separately. The dry mixes were tried for different pre-pressure boundaries like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio etc. The assessed combination of powder was straightforwardly compacted (6 mm breadth, round level confronted punches) on a 10 station rotating tablet punching machine (SHAIMAC Technology Pvt. Ltd, India). The formulation composition of various cluster is displayed in table 1. The total weight of every tablet is 150mg and it contains 10 mg of Rizatriptan. Every one of the tablets were put away in hermetically sealed compartments for additional study.[10,11]

Table 1: Formulation of Rizatriptan mucoadhesive matrix tablets ($RBMT_1$ to $RBMT_8$)

Formulations (mg)	$RBMT_1$	$RBMT_2$	$RBMT_3$	$RBMT_4$	$RBMT_5$	$RBMT_6$	$RBMT_7$	$RBMT_8$
Rizatriptan	10	10	10	10	10	10	10	10
Methocel K100LV	15	20	25	30	-	-	-	-
Carbopol 934P	-	-	-	-	15	20	25	30
Eudragit L100	-	-	-	-	-	-	-	-
Jaguar gum	30	25	20	15	30	25	20	15
Pharmatose	124	124	124	124	124	124	124	124
PVP K30	15	15	15	15	15	15	15	15
Mg stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3
Titanium dioxide	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Saccharine	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Total	150	150	150	150	150	150	150	150

2.2.3 Evaluation of precompression parameters of dry powder blend of all formulations ($RBMT_1$-$RBMT_8$)

2.2.3.1 Angle of Repose (θ):

The angle of repose was then calculated by measuring the height and radius (r) of the heap of powder formed.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Angle of repose is an important parameter that is used to find out the flow properties of powder and that is indicated as maximum angle possible between the surface of a pile of powder and the horizontal plane. The dry powder blends from different formulations were allowed to flow through the funnel fixed to a stand at definite height (h). According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle "between" 25^0-30^0 indicates good flow. The angle "between" 30^0-40^0 indicates passable flow and angle greater than 40^0 indicates very poor flow. [5]

2.2.3.2 Bulk density:

Both the bulk density (BD) and tapped density (TD) of prepared dry powder blends of all the formulations were determined. The quantity of 2 gm of powder blends from each formulation, previously lightly shaken to break any agglomerates formed; were introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at second interval. The tapings were continued until no further changes in volume were noted. BD and TD of prepared powder blends of all formulations were calculated using the following formulas.[11, 12]

$$BD = \frac{weight\ of\ the\ granule}{volume\ of\ the\ packing}$$

$$TD = \frac{weight\ of\ the\ granule}{tapped\ volume\ of\ the\ packing}$$

2.2.3.3 Compressibility Index (Carr's index):
Carr's index of prepared dry powder blends were calculated by following formula

$$Carr's\ index\ (\%) = \frac{TD-BD}{TD} \times 100$$

Compressibility index (Carr's index) is important parameters to determine the flow properties of powder and granules. According to the specification the Carr's index values "between" 5-15 indicates excellent flow where as "between" 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable where as "between" 23-25 indicates poor and "between" 33-38 indicates very poor and greater than 40 indicates extremely poor. [6, 7]

2.2.3.4 Hausner's ratio:
The Hausner's ratios of prepared dry powder blends were determined by following formula.

$$Hausner's\ ratio = \frac{TD}{BD}$$

Hausner's ratios are also another parameter to determine the flow properties of powder and granules. According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), where as greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, added glidant normally improves flow. [11, 12]

2.2.4 Evaluation of Post-compression Parameters of all formulations ($RBMT_1$-$RBMT_8$)
2.2.4.1 Thickness
Ten tablets from each formulation of prepared tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.[9]

2.2.4.2 Tablet Hardness
Hardness of all the formulations of prepared tablets under study was measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten tablets with known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 5 kg/cm^2 for tablet is considered as acceptable limit.[10]

2.2.4.3 Friability
Previously weighed ten mucoadhesive tablets from each batch were taken in Roche friabilator (Roche friabilator, Secor India). After100 revolutions of tablets were recovered from friabilator and made free from dust using a soft muslin cloth and the total remaining weight was recorded. Friability was calculated from the following formula.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

Where W_i and W_f were the initial and final weight of the tablets before and after friability test. For any compressed tablet, the lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.[9]

2.2.4.4 Weight variation test
All formulated tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.[13, 14]

2.2.4.5 Content uniformity
Twenty Rizatriptan mucoadhesive sustained release tablets were taken and triturated to form powder and powder equivalent to one tablet was taken and dissolved in 100 ml of phosphate buffer pH 6.8 and heated at 37 ºC for 15 to 20 minutes with stirring. The solution was filtered, suitably diluted and the Rizatriptan content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 226 nm. Each measurement was carried out in triplicate and the average drug content in each Rizatriptan mucoadhesive sustained release tablets was calculated.[15]

2.2.4.6 Swelling index study
The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling index of all formulation was studied. One tablet from each batch was kept in a Petridis containing 2% agar gel plates with the core facing the gel surface and incubated at 37±1 °C. The tablet was removed every two hour interval up to 12 hour and excess water blotted carefully using filter paper. The swollen tablets were re-weighed (W_t). The swelling index (SI) of each tablet was calculated according to the following equation.[15, 16]

$$SI = \frac{(W_t - W_0)}{W_0} \times 100$$

Where W_0 = initial weight, W_t = weight after time t

2.2.4.7 Measurement of bioadhesive force

Bioadhesive force of the tablets was measured on a specially designed modified physical balance.[13] The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side. The height of the total set-up was adjusted to accommodate a glass container of 6.6 cm height. In order to find out the bioadhesion strength first buccal tablet (n = 3) was stacked to the glass slide with the help of the knob, which was situated at the base of the physical balance. Five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then, the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e. total weight minus 5 g was taken as a measure of the bio-adhesive strength.[12, 13] By using this weight, bio-adhesive force for all the formulations of Rizatriptan buccal mucoadhesive tablets were calculated using following equation

$$N = (W \times g)/1000$$

Where N is bio adhesive force, W is the weight required for the detachment of two vials in grams, and g is the acceleration due to gravity.

2.2.4.8 *In vitro* drug release study

The *in vitro* dissolution study was conducted for all the formulations using an eight station USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.). A total volume of 900 ml of phosphate buffer pH 6.8 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 5ml of aliquots were periodically withdrawn and the same volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 1 hour intervals and after filtering by Whatmann filter paper, were analyzed spectrophotometrically at 227 nm for determination of Rizatriptan that were released from mucoadhesive sustained release tablets.[12]

2.2.4.9 *In vitro* permeation study

In vitro permeation studies were carried out in a modified Franz's diffusion cells. The medium used for these studies was phosphate buffer pH 6.8, maintained at 37°C ± 0.5°C. Cellulose acetate dialysis membrane was used as a permeation barrier. Samples were collected at each one-hour interval upto12h and analyzed for drug content with a UV spectrophotometer set at 227 nm. The permeation studies for all the formulations of Rizatriptan mucoadhesive tablets were carried out thrice and average were taken.[11, 13]

2.2.4.10 *Ex vivo* permeation study of buccal mucoadhesive tablets

Ex vivo permeation study of prepared Rizatriptan mucoadhesive buccal tablet was carried out on goat buccal mucosa membrane (as semi permeable membrane) using modified Franz diffusion cell with a diffusion area of 17.35 cm^2 with the acceptor compartment volume capacity of 45 ml and maintained at 37 ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The mucoadhesive tablet was placed into the donor compartments and clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 6.8 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. 5 ml samples were withdrawn at pre-determined time intervals and replaced with 5ml of same fresh buffer. Then the sample were analyzed using an UV spectrophotometer at 227 nm for the amount of Rizatriptan absorbed through buccal mucosa.[16]

2.2.4.11 Mechanism and kinetic of *in vitro* drug release:

The rate and mechanism of release of Rizatriptan from prepared buccal mucoadhesive tablet were analyzed by fitting the dissolution data into following exponential equations.

Zero order release equation:

$$Q = K_0 \, t$$

Where Q is the amount of drug released at time t and K_0 is the zero-order release rate constant.

The first order equation:

$$\log(100 - Q) = log100 - K_1 \, t$$

Where, K_1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

$$Q = K_2 t^{1/2}$$

Where, K_2 is the diffusion rate constant.

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems:

$$\log\left(\frac{M_t}{M_\infty}\right) = \log K + n\, logt$$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug release after infinite time, K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation.

Hixson-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

$$W_0{}^{1/3} - W_t{}^{1/3} = K_s t$$

Where *Wo* is the initial amount of drug, *Wt* is the remaining amount of drug in dosage form at time *t*, and K_S is a constant incorporating the surface volume relation. The graphs are plotted as cube root of percent drug remaining versus time.[17, 18]

2.2.4.12 Stability studies of best formulation

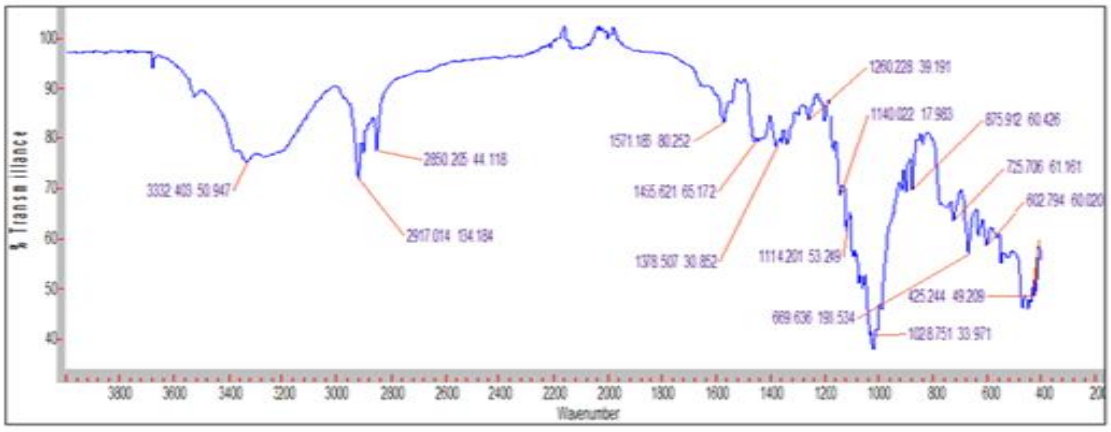
The stability studies of optimised formulation of Rizatriptan buccal mucoadhesive sustained release tablet were carried out according to ICH guidelines. The optimized formulation was subjected to accelerated stress condition at 40 ºC ± 2 ºC/ 75% ± 5% RH for 90 days. After that period the product was evaluated for friability, hardness, weight variation, thickness, drug content and *in vitro* drug release study.[18, 19]

2.2.4.13 Stability in human saliva

Stability studies of the buccal tablet were performed for optimized formulation in artificial saliva. The artificial saliva was prepared by using material such as Sodium chloride (NaCl) {0.4 gm/lit}, Potassium chloride (KCl) {0.4 gm/lit}, Calcium chloride ($CaCl_2.2H_2O$) {0.8 gm/lit}, Sodium di hydrogen phosphate ($NaH_2PO_4.2H_2O$) {0.78 gm/lit}, Sodium Sulfide ($NaS.9H_2O$) {0.005 gm/lit} and Urea {1 gm/lit}. The prepared artificial saliva was filtered through a Whatmann filter paper. The buccal tablet was placed in separate Petri dishes containing 5 ml of artificial saliva and placed in a temperature-controlled oven for 9h at 37°C ± 0.2 °C at regular intervals (0, 3, 6, and 9 h), the buccal tablet was examined for change in colour, surface area, and integrity.[20]

2.3 RESULTS AND DISCUSSION:

The spectra of Rizatriptan drug and physical mixture of mucoadhesive formulation were compared and found that, the sharp peaks that appear in spectra of Rizatriptan at~ 3120 cm^{-1} also appears in physical mixture at~ 3268 cm^{-1} due to presence of C-H functional group. The characteristic IR absorption peaks of Rizatriptan at ~1569 cm^{-1} (C=N stretch), at ~ 1567 cm^{-1} (C-N stretch), at ~1475 cm^{-1} (C-H bend), and at ~1317 cm^{-1} (C-O bend) were also present in the physical mixture with no shifting in the major peaks and there was no additional peaks formed in the physical mixture of mucoadhesive formulation, that indicate that no interaction occurred between the Rizatriptan and excipients used in the preparation of different mucoadhesive sustained released matrix formulations. The FTIR spectra of Rizatriptan drug and physical mixture of mucoadhesive were shown in **figure 1**.



FTIR SPECTRA OF RIZATRIPTAN PURE DRUG

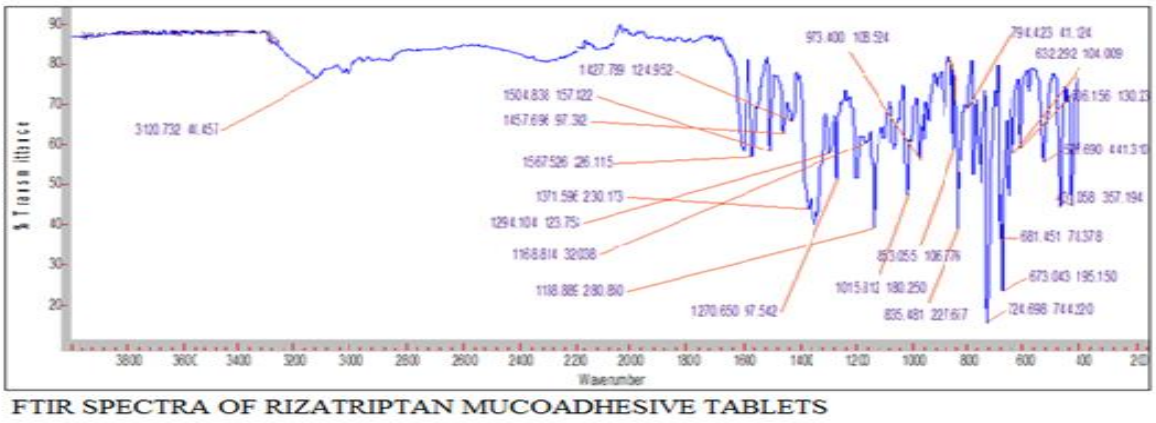


Fig. 1: Drug and Polymers compatibility studies through FTIR analysis

DSC thermogram of pure drug Rizatriptan and physical mixture of mucoadhesive formulation were observed that the endothermic peak appeared between 180-210 ^{0}C and 150-200 ^{0}C respectively which indicate that the physical mixture of optimized formulation is thermodynamically stable by the addition of Rizatriptan. From the above DSC studies it was observed that the formulation is thermodynamically stable as it required marginally more heat than pure drug because of existence of different excipients with drug. No shifting of peaks from endothermic to exothermic was also noticed. The DSC thermogram of Rizatriptan and physical mixture of polymer used for optimized formulation is shown in **figure 2**.

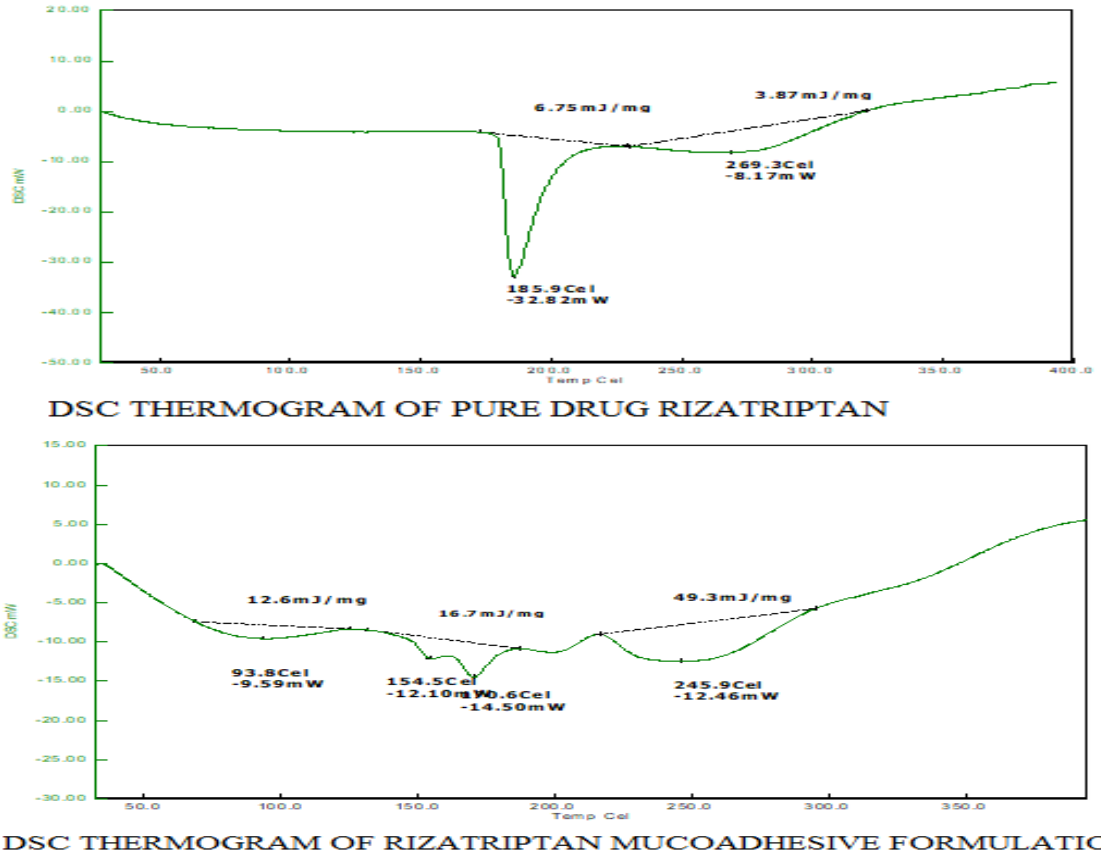


Fig. 2: Drug and Polymers compatibility studies through DSC analysis

Evaluations of precompression parameters were usually carried out to ensure the tyre of flow properties of dry powder and granules during tablet punching.

The bulk densities of dry powder blends of all formulations were found to be in the range of 0.265±0.06 to 0.297±0.05 g/cm^3 and the tapped densities were found to be in between 0.304±0.06 to 0.344±0.06 g/cm^3. Bulk density and tapped density measurements found that density of a powder depends on particle packing and that density changes as the powder consolidates. This indicates good packing capacity of powder blends.

Values of Carr's index below 16 usually show good flow characteristics, but readings above 23 indicate poor flowability. Carr's indexes of all the formulations were found "between" 08.41 to 15.11 that indicate excellent to passable flow properties. All the Formulations having Carr's index less than 16 which indicates good flow properties due to presences of more fine particles.

Hausner's ratio is simple method to evaluate stability of powder column and to estimate flow properties. Low range was observed of Hausner's ratio that indicates good flow ability. In all formulations the Hausner's ratios were found "between" 1.09 to 1.17 that indicates good flow and all the formulation having Hausner's ratios less than 1.25 indicates improve flow properties.

Angle of repose is suited for particle > 150µm.Values of angle of repose ≤ 25 generally indicates the free-flowing material and angle of ≥ 40 suggest a poor flowing material. The angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 19.52±0.16 to 22.28±0.23 *i.e.* dry powder blends were of good flow properties.

The evaluation results of all precompression parameters for the formulation $RBMT_1$ to $RBMT_8$ were shown in the **table 2**.

Table 2: Precompression parameters of dry powder blends of Rizatriptan mucoadhesive matrix tablet formulations $RBMT_1$- $RBMT_8$

F. No.	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index	Hausner's ratio
$RBMT_1$	0.265±0.08	0.306±0.04	22.28±0.23	13.39	1.15
$RBMT_2$	0.276±0.06	0.313±0.07	21.45±0.21	11.82	1.13
$RBMT_3$	0.292±0.06	0.344±0.06	20.36±0.24	15.11	1.17
$RBMT_4$	0.276±0.07	0.308±0.07	21.42±0.24	10.39	1.12
$RBMT_5$	0.294±0.08	0.321±0.08	22.18±0.17	08.41	1.09
$RBMT_6$	0.265±0.06	0.304±0.06	20.71±0.21	12.83	1.14
$RBMT_7$	0.297±0.05	0.331±0.05	21.43±0.24	10.27	1.11
$RBMT_8$	0.283±0.08	0.318±0.08	19.52±0.16	11.01	1.12

All values are expressed as average± SD; (n=3)

All the physical parameters were found to be satisfactory after compression of Rizatriptan mucoadhesive matrix tablets. Typical tablet defects, such as chipping and picking, capping was not observed. The average thickness of the tablets was ranged between 4.21±0.16 to 4.45±0.16 mm. All the batches showed uniform thickness and it were within acceptable limits. Weight variations for different formulations were found to be 4.18±0.24 to 4.42±0.32%. The average percentage deviation of all tablet formulations was found within the limit, and hence passed the test for uniformity of weight as per official requirement. The hardness of all the Rizatriptan mucoadhesive matrix tablets formulations were ranged from 5.16±0.6 to 5.52±0.4 kg/cm^2 that were according to the specification. The percentage friability of all the formulations were ranged from 0.66±0.06% to 0.46±0.06% and found within the prescribed limits. The percentages of drug content of the entire formulations of Rizatriptan mucoadhesive matrix tablet ($RBMT_1$ to $RBMT_8$) were found "between" 98.93±1.5 to 101.52±1.6 which were within the acceptable limits. The results of various post compression characterizations of different formulations of prepared Rizatriptan mucoadhesive tablets are given in **table 3**.

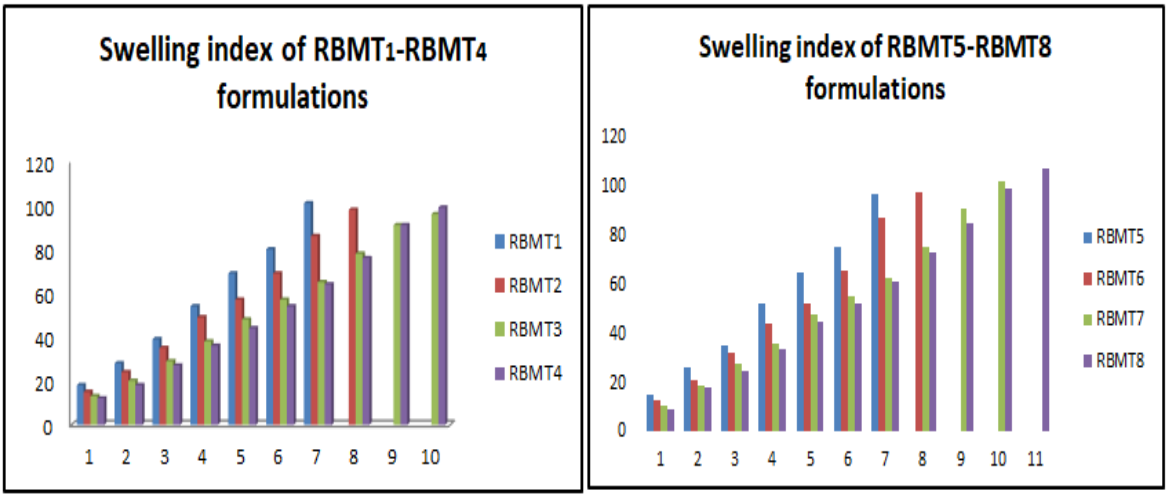
Table 3: Evaluation of post-compression parameters of Rizatriptan mucoadhesive matrix tablets formulation $RBMT_1$- $RBMT_8$

F. No.	Average hardness (kg/cm^2)	Average Weight Variation (%)	Average friability (% w/w)	Average thickness (mm)	Content uniformity (%)	Bioadhesive strength (N)
$RBMT_1$	5.23±0.7	4.23±0.21	0.54±0.08	4.34±0.15	100.25±1.2	0.362±0.004
$RBMT_2$	5.41±0.4	4.24±0.26	0.56±0.05	4.21±0.16	99.65±1.7	0.412±0.003
$RBMT_3$	5.25±0.5	4.18±0.24	0.46±0.06	4.36±0.18	100.43±1.5	0.421±0.004
$RBMT_4$	5.52±0.4	4.31±0.27	0.51±0.07	4.42±0.14	99.75±1.4	0.472±0.003
$RBMT_5$	5.16±0.6	4.42±0.32	0.58±0.05	4.35±0.12	101.52±1.6	0.345±0.002
$RBMT_6$	5.31±0.4	4.30±0.28	0.66±0.06	4.45±0.16	100.85±1.8	0.373±0.002
$RBMT_7$	5.32±0.6	4.21±0.42	0.49±0.08	4.62±0.13	98.93±1.5	0.495±0.004
$RBMT_8$	5.40±0.6	4.32±0.31	0.62±0.04	4.24±0.15	99.51±1.7	0.536±0.002

All values are expressed as average± SD; (n=3)

Determination of bioadhesive force is important parameters for mucoadhesive formulation as it decides to what extend the formulation will adhere to the mucosa membrane. Bioadhesive forces were determined for all the formulations ($RBMT_1$-$RBMT_8$). The formulations that contained higher concentration of carbopol 934P showed more bioadhesive force then other formulations. Formulation $RBM8_8$ having 20% of carbopol 934P and 10% Jaguar gum had highest bioadhesive force (0.536±0.002). Next to carbopol 934P, the formulations that contained higher concentration of Methocel K100LV showed better bioadhesive force that was noticed from the formulation $RBMT_1$ and $RBMT_4$. Lower bioadhesive force was noticed for the formulations containing higher concentration of natural polymer 'Jaguar gum' that was observed in case of formulation $RBMT_1$ and $RBMT_5$.

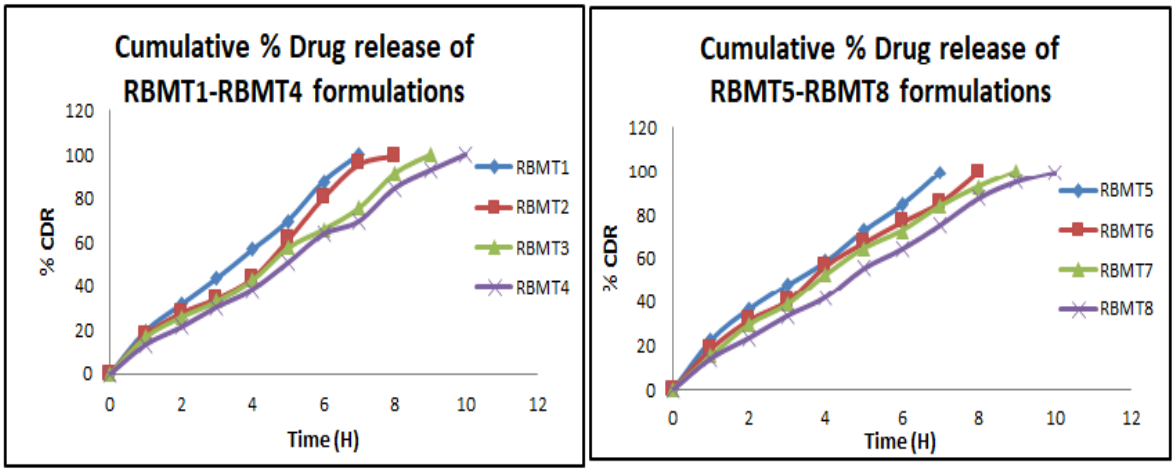
Swelling study was performed on all the formulations ($RBMT_1$ to $RBMT_8$) for 10 hours. The result of swelling index was shown in **figure 3**. The formulation that contains more percentage of Jaguar gum showed higher swelling indices due to higher hydrophilicity and more water uptake of the polymers. The formulation $RBMT_1$ and $RBMT_5$ that contains 20% of Jaguar gum showed higher swelling indices then other formulations upto after 7 hour but the formulation started bulk erosion as Jaguar gum is a natural polymer. When the % of Methocel K100LV increases, the swelling index persist for longer period of time which indicates that the formulation can deliver the drug in a more sustain manner that is noticed in case of $RBMT_4$.



All values are expressed as mean± SD; (n=3)

Fig. 3: Histogram showing Swelling index of Rizatriptan mucoadhesive matrix tablets formulations

In order to find out best *in vitro* drug release along with adequate bioadhesive force, different hydrophilic matrix polymers *viz.*, Carbopol 934P, Methocel K100LV and Jaguar gum were used for 8 different formulations of Rizatriptan mucoadhesive matrix tablets. The drug release profiles of different formulations were shown in **figure 4**. In these studies, Methocel K100LV was usually used for sustained release effect with better bioadhesive strength then Carbopol 934P. It was noticed that the formulation containing higher percentage of Methocel K100LV have better release profile with good mucoadhesive strength. $RBMT_4$ formulation that contained 20% of Methocel K100LV and 10% of jaguar gum, released the drug upto 10 hr and could be considered as best formulation as the initial release was 13.42% and maximum release upto 10 hr and had remarkable bioadhesive strength that may be adequate criteria for bioadhesive formulation. Formulation $RBMT_5$ containing 20% of Jaguar gum and 10% of Carbopol 934P showed an initial burst release of 22.53% with maximum release up to 6 hour and also had lowest bioadhesive strength. More percentage of Jaguar gum in formulation indicated lower bioadhesive strength with release of drugs with less time.



All values are expressed as mean± SD; (n=3)

Fig. 4: Comparative dissolution profile of different formulations of Rizatriptan mucoadhesive matrix tablet formulations

Ex vivo permeation studies (diffusion studies) were carried out for best formulation ($RBMT_4$) using goat buccal mucosa and compared with *in vitro* drug release studies (dissolution studies). The results of this studies shows that, the cumulative percentage of drug release for *in vitro* dissolution studies was 99.64% within 10 hour where it was 88.72% within 10 hour for *ex vivo* studies. The difference in drug release profiles may be attributed due to low permeability of the drug. Both the release profile were correlated on point to point basis and the correlation co-efficient was found 0.9961 which indicates good co-relation level between *in vitro* and *ex vivo* release profile which was shown in **table 4 and figure 5**.

Table 4: *In vitro* and *Ex vivo* comparative of release profile of optimized formulation $RBMT_4$

Time (Hr)	*In vitro* cumulative % drug release (Dissolution study)	*Ex vivo* cumulative % drug release (Diffusion study)
1	13.42±1.2	6.37±1.3
2	21.34±1.3	13.51±1.4
3	30.55±1.4	22.62±1.2
4	38.34±1.4	32.45±1.5
5	50.47±1.1	39.52±1.2
6	63.53±1.2	49.47±1.1
7	69.38±1.3	58.64±1.3
8	84.34±1.4	69.45±1.4
9	92.48±1.5	80.64±1.5
10	99.64±1.6	88.72±1.7

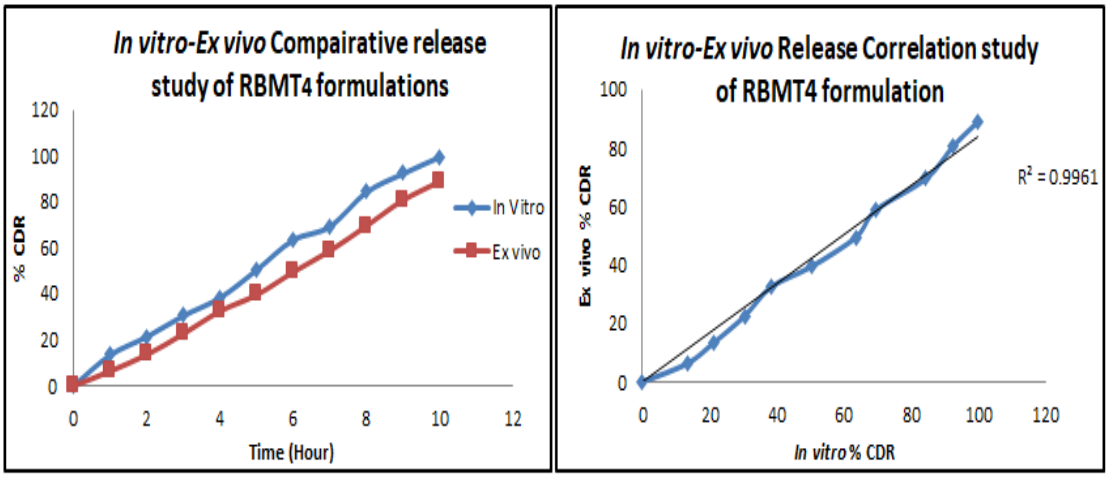


Fig. 5: *In vitro* and *Ex vivo* comparative of release profile of best formulation $RBMT_4$

The *in vitro* dissolution data of best formulation $RBMT_4$ were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppa's kinetic model and the graphs were plotted (**Figure 6 & 7**). The zero-order plots were found to be fairly linear as indicated by their highest regression values. The release exponent 'n' for optimised formulation $RBMT_4$ was found to be 0.91 ($0.5 < n < 1$), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study *in vitro* drug release kinetic of optimised formulation of Rizatriptan mucoadhesive matrix tablets followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion.

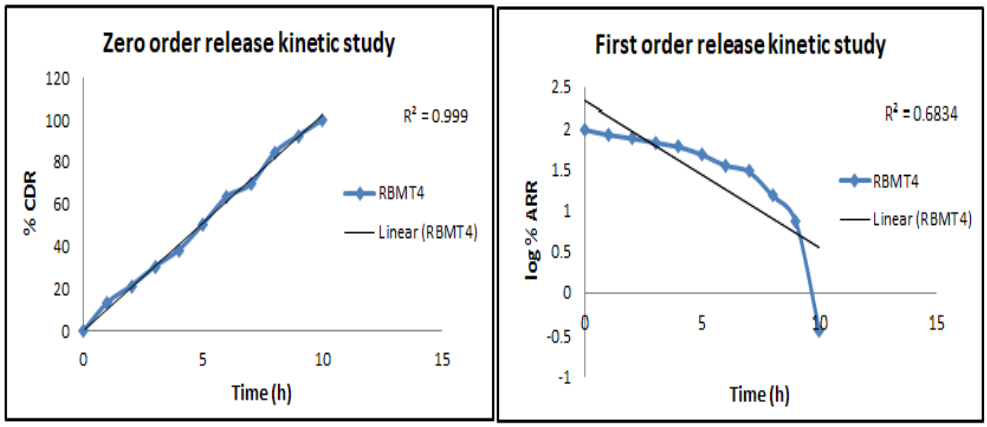


Fig. 6: I*n vitro* release kinetic plot of best formulation of Rizatriptan mucoadhesive matrix tablet (RBMT$_4$)

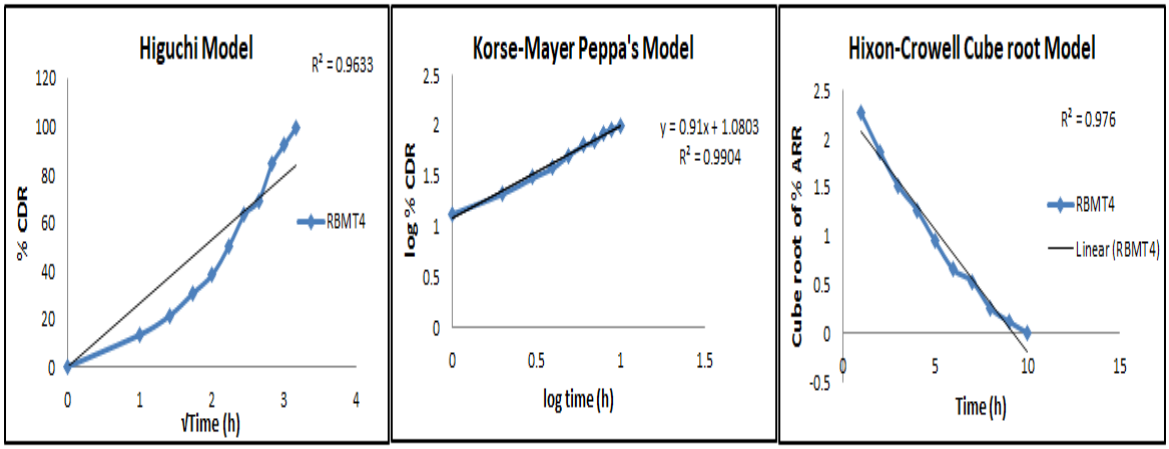


Fig. 7: Mechanism of i*n vitro* release plot of best formulation of Rizatriptan mucoadhesive matrix tablet (RBMT$_4$)

Table 5: Regression values of *in vitro* release kinetic study optimized Rizatriptan mucoadhesive matrix tablet (RBMT$_4$)

Formulation	R^2value of Zero order	R^2 value of 1st order	R^2value of Higuchi model	R^2value of Hixon-Crowell model	R^2value of Peppa's model	'n' value of Peppa's model
RBMT$_4$	0.999	0.6834	0.9653	0.976	0.9904	0.91

The best formulation (RBMT$_4$) was under gone for the accelerated stability studies. The results of *in vitro* release profile of the best formulation at different time interval for accelerated stability conditions were shown in **figure 8**. The Rizatriptan mucoadhesive matrix tablets did not show any significant change in physicochemical parameters *i.e* physical appearance, weight variation, hardness, friability, swelling studies, drug content, bioadhesive strength and *in vitro* drug release characteristics. Thus, it was found that the mucoadhesive tablets of Rizatriptan (RBMT$_4$) were stable under short term storage conditions for at least 3 months.

Table 6: Comparative physicochemical characterization of RBMT$_4$) at accelerated conditions (40 ° C ± 2 ° C/ 75% ± 5% RH)

Sl. No.	Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
1	**Physical appearance**	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
2	**Weight variation**	4.31±0.27	4.24±0.18	4.19±0.32	4.12±0.21
3	**Hardness**	5.52±0.4	5.63±0.6	5.71±0.5	5.83±0.5
4	**Friability**	0.51±0.07	0.57±0.05	0.63±0.06	0.68±0.04
5	**Swelling index**	99 ±1.25	96±1.38	94 ±1.46	92 ±1.72
6	**Drug content**	99.75±1.4	97.57±1.5	95.26±1.6	92.75±1.2
7	**Bioadhesive strength (N)**	0.432±0.003	0.424±0.005	0.417±0.003	0.410±0.005

All values are expressed as mean± SD; (n=3)

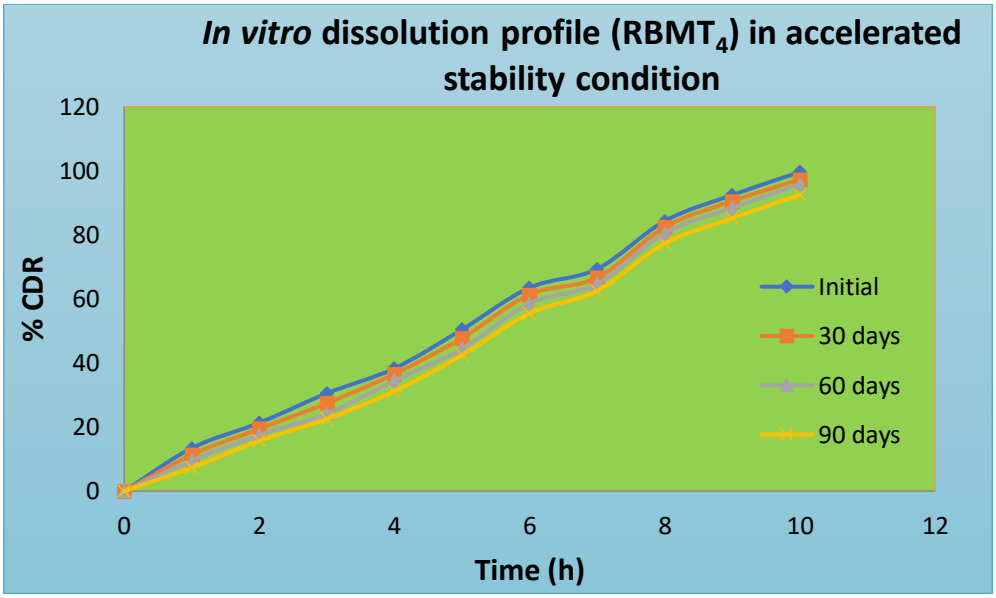


Fig. 8: Comparative *in vitro* dissolution profile of (RBMT$_4$) at accelerated conditions (40 ° C ± 2 ° C/ 75% ± 5% RH)

The stability studies on acted in artificial human salivation that was ready in the lab would be more precise to impersonate the strength of the Rizatriptan mucoadhesive buccal tablet in oral cavity *in vivo*. In light of the consequences of *ex vivo* mucoadhesion, *in vitro* release studies, formulation RBMT$_4$ was chosen for stability study. Stability studies in prepared artificial human saliva showed no adjustment of the shade of tablets, which would have occurred assuming medication was unsteady in human saliva. Results uncover that the buccal tablets are having adequate steadiness in the prepared artificial human saliva. The thickness and diameter of tablets somewhat changed because of expanding of the

polymers in prepared artificial saliva but buccal tablets didn't implode till the finish of studies affirming that the tablet strength was adequate.

2.4 CONCLUSION:

In the current research study Rizatriptan buccal mucoadhesive matrix tablet was effectively developed. The significant test in this work was to concentrate on the impact of different low-density polymers on *in vitro* release rate of buccal mucoadhesive of Rizatriptan with satisfactory bioadhesive strength for prolonging the drug residence time in buccal mucosa. The mucoadhesive strength and *in vitro* drug release impact of various kinds of low-density matrix framing polymers Methocel K100LV, Carbopol 934P and Jaguar gum were studied. FTIR studies on delighted that there is no chemical interaction between drug and polymers. DSC studies on demonstrated that no thermal ineraction between the medication Rizatriptan and polymer utilized in the current investigations. The hydrophilic polymer like Methocel, Carbopol 934P, Jaguar gum having great bioadhesive strength which was effectively evolved. Formulation $RBMT_4$ that contained 20% of Methocel K100LV and 10% Jaguar gum showed supported medication release for 10 hour (almost 100%) and had sufficient bioadhesive strength, arisen as best formulation. Increase in proportion of hydrophilic polymer (Jaguar gum) caused initial burst release effect. *In vitro* drug release profiles of best formulation were compared with *ex vivo* drug diffusion studies and *in vitro-ex vivo* correlation was established. Kinetic of *in vitro* drug release of optimized formulation $RBMT_4$ found to be zero order having drug release mechanism as anomalous diffusion coupled with erosion. The stability studies were carried out in artificial human saliva and the optimised formulation were found to be stable without any remarkable physical changes. Accordingly, from the consequences of the current concentrate unmistakably show, a promising capability of the Rizatriptan buccal mucoadhesive system as an option in contrast to the ordinary dose structure as it improves bioavailability of the Rizatriptan by bypassing the first pass metabolism and by producing sustained release effect for long term Migraine. In any case, further clinical investigations are expected to evaluate the utility of this framework for patients experiencing Migraine.

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REFERENCES:

1. Jain NK. Controlled and Novel Drug Delivery, 1st edn., CBS Publishers, New Delhi, 2004;236-55.
2. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm 1999; 178: 11-22.
3. Remunnan Lopez C, Portero A, Vila Jato JL, Alonso MJ. Design and evaluation of Chitosan / Ethocel mucoadhesive bilayered devices for buccal drug delivery. J Control Release 1998; 55: 143-52.
4. Kumria R, Gupta V, Bansal S, Wadhwa J, Nair AB. Oral buccoadhesive films of ondansetron: Development and evaluation. Int J Pharma Investig 2013; 3:112-8.
5. Vishnu M. Patel, Bhupendra G. Prajapati, and Madhabhai M. Patel, Formulation, Evaluation, and Comparison of Bilayered and Multilayered Mucoadhesive Buccal Devices of Propranolol Hydrochloride, AAPS PharmSciTech 2007; 8 (1)
6. Shanker G, Kumar CK, Gonugunta CS, Kumar BV, Veerareddy PR. Formulation and evaluation of bio adhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS Pharma Sci Tech 2009; 10:530-9.
7. Vishnu M. Patel, Bhupendra G. Prajapati, Harsha V. Patel, and Karshanbhi M. Patel, Mucoadhesive Bilayer Tablets of Propranolol Hydrochloride, AAPS PharmSciTech 2007; 8 (3) Article 77.
8. Panda N, Panda KC, Reddy AV, Reddy GV; Process Optimization, Formulation and Evaluation of Hydrogel {Guargum-G-Poly(Acrylamide)} Based Doxofylline Microbeads. Asian Journal of Pharmaceutical and Clinical Research, 2014; 7(3): 60-65.
9. Medline plus A. Service of the U.S National Library of Medicine and the National Institutes of Health. Available from: http://www. medlineplus.gov [Last accessed on 2008].
10. Patel VM, Prajapati BG, Patel HV, Patel KM. Mucoadhesive bilayer tablets of Propranolol hydrochloride. AAPS PharmSciTech, 2007; 8:E77.
11. Patel VM, Prajapati BG, Patel MM. Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of Propranolol hydrochloride. AAPS PharmSciTech, 2007; 8:22.
12. Zafar R and Panda N: Formulation Design and *In Vitro* Evaluation of Zolmitriptan Gastroretensive Floating Matrix Tablets for Management of

Migraine. Int J Pharm Sci Res 2015; 6(9): 3901-12.doi: 10.13040/IJPSR.0975-8232.6(9).3901-12.
13. Shanker G, Kumar CK, Gonugunta CS, Kumar BV, Veerareddy PR. Formulation and evaluation of bio adhesive buccal drug delivery of Tizanidine hydrochloride tablets. AAPS Pharma Sci Tech, 2009; 10:530-9.
14. S.Velmurugan*, P.Srinivas, formulation and *in vitro* evaluation of Losartan potassium mucoadhesive buccal tablets, Asian J Pharm Clin Res, Vol 6, Issue 3, 2013, 125-130.
15. S. Fatima, N. Panda, AV Reddy, S Fatima "Buccal Mucoadhesive Tablets of Sumatriptan Succinate for Treatment of Sustainable Migraine: Design, Formulation and In Vitro Evaluation"Int. J. of Pharm. Res. & All. Sci. 2015;4(3):114-126
16. Abidunnisa Begum, Niranjan Panda, Sujitha Bajjuri, Kanhu Charan Panda; Assessing the sustained Release Potential of Rizatriptan as a Matrix Tablet Employing Different Grade of HPMC and Eudragit, International Journal of Pharma Research and Health Sciences, 2018; 6 (1): 2119-28, e-ISSN: 2348-6465, DOI:10.21276/ijprhs.2018.01.08
17. Prasanna RI, Anitha P, Chetty CM. Formulation and evaluation of bucco-adhesive tablets of Rizatriptan. Int J. Pharma Investig 2011; 1:182-91.
18. Swapnil R.Chaudhari, Amol A.Harsulkar, Design and in- vitro evaluation of mucoadhesive buccal tablets of carvedilol, Int.J.PharmTech Res.2012,4(4)
19. Panwar MS, Tanwar YS. Evaluation of stability of Diltiazem hydrochloride floating microspheres at normal and accelerated conditions. J Pharm Biomed Sci.2015;05(01):57-60.
20. S Bhanja, P. Ellaiah, SK Martha, P K Sahu, SP Tiwari, BB Panigrahi, D Das, Formulation and *in vitro* evaluation of mucoadhesive buccal tablets of Timolol maleate, Int J Pharm Biomed Res 2010, 1(4), 129-134.
21. Prajapati ST, Patel PB, Patel CN. Formulation and evaluation of sublingual tablets containing Rizatriptan. Int J Pharma Investig, 2012; 2:162-8.
22. Gupta A, Garg S, Khar RK. Measurement of bioadhesive strength of mucoadhesive buccal tablets: Design of an *in vitro* assembly. Indian Drugs 1993; 30:152-5.
23. Rana Abu-Huwaij, Rana M. Obaidat, Kamal Sweidan, and Yusuf Al-Hiari, Formulation and In Vitro Evaluation of Xanthan Gum or Carbopol 934-Based Mucoadhesive Patches, Loaded with Nicotine, AAPS PharmSciTech, Vol. 12, No. 1, March 2011.