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Original Article

Assessing the sustained Release Potential of Rizatriptan as a Matrix Tablet Employing Different Grade of HPMC and Eudragit

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ABSTRACT

To reduce the frequency of administration and improve patient compliance, present studies were aimed to formulate once-daily sustained release matrix tablet of Rizatriptan. The triptan derivatives type of drugs is commonly used for treatment of migraine headaches and Rizatriptan, a 5-HT1 receptor agonist, is one of them. The sustained released Rizatriptan matrix tablet were prepared by wet granulation technique using hydrophilic synthetic polymer like hydroxyl propyl methyl cellulose (HPMC K4M & HPMC K15M) and hydrophobic polymer like Eudragit (Eudragit RSPO and RLPO). Precompression parameters like angle of repose, Carr's index and Hausner's ration were determined to cheek the flow properties of granules, and results satisfied according to the specifications. The sustained release tablets was characterised by FTIR and DSC analysis to know the compatibility between drug and polymers which confirmed the compatibility of drug and polymers. Results of different postcompression parameters such as average thickness, weight variation, friability, hardness, content uniformity and swelling studies satisfied according to pharmacopeia specification. In vitro release study was performed by using USP type-II paddle type eight station dissolution apparatus. The formulation RSRF8 that contained 16.66% of HPMC K4M and K15M each and 13.33% of eudragit RLPO called as optimised formulation as the initial release was 14% with sustained release effect upto 12 h. Further more in vitro release data of optimized formulation (RSRF8) were assessed for mechanism of drug release by using different kinetic model as well as accelerated stability studies were investigated to confirm the stability of dosage forms.

Keywords: Sustained release tablet, Rizatriptan, Matrix tablets, HPMC, Eudragit.

1. INTRODUCTION

Oral drug delivery is the most favoured and advantageous selection among all drug delivery system as the oral route gives greatest dynamic surface area and hence increase residence time of the drug for absorption. Normally

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conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency.[1] These factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.[2] Such dosage forms exhibit better pharmacological effect and prolonged therapeutic activity. Matrix tablets are one of the most commonly used controlled release dosage forms as they release the drug in a controlled manner.[3, 4] Such variety of medication will be beneficial for the chronic disease like asthma, migraine, diabetes, hypertension and inflammation that require consistent plasma level for maintenance therapy.[5]

Rizatriptan, a selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist. Chemically Rizatriptan is expressed as *N*, *N*-dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine. It is used for the treatment of migraine headaches. Migraine headache are the most common disease described as vascular headache that causes a throbbing and pulsating pain around the head. It involves abnormal sensitivity of arteries within the brain resulting in triggers that often lead to rapid changes in the diameter of artery, resulting from spasm. As a result of this other arteries in the brain and scalp dilate resulting in terrible pain in the head. Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the Rizatriptan tablet is about 45%, and mean peak plasma concentrations (Cmax) are reached in approximately 1-1.5 hours (Tmax). Approximately 14% of an oral dose is excreted in urine as unchanged Rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism. The plasma half-life of Rizatriptan in males and females averages 2-3 hours. The recommended starting dose of Rizatriptan is either 5 mg or 10 mg for the acute treatment of migraines in adults.[5, 6]

The objective of the present study was to develop sustained release tablets of Rizatriptan using hydroxyl propyl methylcellulose (HPMC K4M & K15M) and Eudragit (Eudragit RSPO and RLPO) as polymeric retardant materials to reduce the frequency of dosing and to improve the therapeutic efficacy. To optimize the drug release profile of drug under study, distinctive proportions of HPMC along with Eudragit were selected to form different sustained release tablets formulations. The present formulation expected to improve patient compliance as it reduce the frequency of dosing and useful for better management of sustainable migraine.[7, 8]

2. MATERIALS AND METHODS

Materials

Rizatriptan was procured as a gift sample from Hetero Healthcare Ltd Hyderabad, India. HPMC K4M, HPMC K15M polymers were received as gift sample from Glenmark Pharma, Nasik, India. The Eudragit RSPO and RLPO were collected as gift sample from Dr. Reddy's Laboratories Hyderabad, India. Lactose, Starch (Insoluble), talc and magnesium stearate were purchased from S.D. fine chemicals Pvt. Ltd' Mumbai, India. All the ingredients were of laboratory grade. The distilled water used in the process of research work was prepared by double distillation process in the laboratory.

Methods

Formulation of sustained release matrix tablets of Rizatriptan

For preparation of Rizatriptan sustained release matrix tablets, wet granulation methods were adopted and twelve distinct formulations were selected on the basis of different concentration of polymers used. Accurate quantities of all ingredients were weighed and passed through sieve no #80 before their use in formulations. For each formulation specific and accurate quantities of powder like Rizatriptan, HPMC, Eudragit RSPO and RLPO, Starch (Insoluble), and lactose were blended uniformly and passed through #20. Lactose was used as diluent whereas Starch (Insoluble) was used as binder.

Table 1: Composition of different excipients used for sustained release matrix tablets of Rizatriptan

F. No.	Rizatriptan (mg)	HPMC K4M (mg)	HPMC K15M (mg)	Eudragit RSPO (mg)	Eudragit RLPO (mg)	Starch (Insoluble) (mg)	Lactose (mg)	Mg. Stearate (mg)	Talc (mg)	Total wt. (mg)
$RSRF_1$	10	70	-	-	-	15	50	3	2	150
$RSRF_2$	10	-	70	-	-	15	50	3	2	150
$RSRF_3$	10	60	-	10		15	50	3	2	150
$RSRF_4$	10	60	-	-	10	15	50	3	2	150
$RSRF_5$	10	-	60	10	-	15	50	3	2	150
$RSRF_6$	10	-	60	-	10	15	50	3	2	150
$RSRF_7$	10	25	25	20	-	15	50	3	2	150
$RSRF_8$	10	25	25	-	20	15	50	3	2	150
$RSRF_9$	10	40	-	30	-	15	50	3	2	150
$RSRF_{10}$	10	-	40	30	-	15	50	3	2	150
$RSRF_{11}$	10	40	-	-	30	15	50	3	2	150
$RSRF_{12}$	10	-	40	-	30	15	50	3	2	150

A wet lump mass was produced by adding required quantity of distilled water as granulating agent. The aggregates formed were initially dried for 10 min to reduce moisture level and to prevent sticking with sieve during sieving. The aggregates were passed through sieve # 20 to get granules. The granules are dried in hot air oven at 40^{o}C around 20 min to reduce moisture content upto 3-5 %. After lubrication with magnesium stearate and talc the formulations were evaluated for angle of repose, bulk density, compressibility; prior to compression. The evaluated granules were compressed into sustained release matrix tablets on a 10 station rotary tablet punching machine using 8 mm concave

punches. Each tablet contains 10 mg of Rizatriptan as sustained release matrix formulation. The compositions for different formulations are given in **table 1** and same method was followed for all the formulations. Then the prepared tablet formulations were assessed for various postcompression parameters like average thickness, weight variation, hardness, friability, swelling studies, drug content and *in vitro* dissolution studies.[9]

3. EVALUATION

Drug excipients compatibility studies

Drug excipients compatibility studies were done by Fourier Transform Infrared (FTIR) and Differential Scanning Calorimetric (DSC) analysis.

Fourier Transform Infrared (FTIR) spectroscopy:

Fourier transform infrared (FTIR) study was carried out to verify any physical or chemical interaction between the drug and the excipients used in the formulation. 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 obtained pellet was analyzed in FTIR 8400S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. The same procedures were repeated for the analysis of drug and and excipients.[10] The FTIR studies of pure drug Rizatriptan, HPMC, Eudragit and optimised formulation ($RSRF_8$) were carried out and presence of functional groups were compared through obtained spectra.

Differential Scanning Calorimetric (DSC) analysis:

Differential scanning calorimetry, or **DSC**, is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10 ^{0}C/min over a temperature range of 40 to 300 ^{0}C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.[11] The DSC analysis of Rizatriptan, HPMC, Eudragit and physical mixture of drug with excipients used for formulations were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug thermal interaction.

Evaluation of precompression parameters

Angle of Repose (θ)

Angle of repose is a method used to determine flow properties of power and granules from hopper to die cavity during tablet compression process. The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a stainless steel funnel and the size of the orifice was 10 mm and the height from the beginning of funnel to end of orifice was 111 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured.

$$\theta = \tan^{-1}\frac{h}{r}$$

Where θ was called as angle of repose that indicates flow properties of granules, h and r were height and radius of the granule heap respectably. According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle greater than 40^0 indicates poor flow.[12]

Bulk density and tapped density

Bulk density and tapped density is usually measured for powder and granules for determination of compressibility index and Hausner's ratio. Bulk and tapped densities were determined using the methods outlined in the USP. Samples (9–13 g) of sample were passed through a no. 18 sieve into a pre-weighed 25 ml graduated cylinder with 0.5 ml markings. The bulk volume was measured after manually tapping the cylinder two times on a flat table top surface. The tapped volume was measured with the Electrolab ETD-1020 Tap Density Tester after tapping in increments of 500, 750 and 1250 taps with 250 drops per minute. For the determination of both the bulk density (BD) and tapped density (TD) of prepared Rizatriptan sustained release granules of all the formulations, following formula were adopted.[13]

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

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

Compressibility index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of powder and the rate at which it packed down. According to the specification the Carr's index values ranging between 5-15 indicates excellent flow and between 12-16 indicates good flow whereas Values between 33-38 indicates very poor and greater than 40 indicates extremely poor flow.

Compressibility index (Carr's index) of prepared Rizatriptan sustained release granules were calculated by following formula[14]

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

Hausner's ratio

It is another method used for the determination of flow properties of granules and for all the formulations of prepared Rizatriptan sustained release granules; it was determined by using following formula.

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

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, glidant need to be added to improves flow.[15]

Evaluation of postcompression parameters of Rizatriptan sustained release matrix tablets formulations

Average thickness

Measurement of thickness is a process that used to estimate the uniformity in formulation as well as physical appearance can be estimated. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial thickness Gauge, Japan) and the results were expressed as mean values of ten readings, with standard deviations. From each formulation of Rizatriptan sustained release tablets; ten tablets were randomly selected and used for thickness determination. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.[16]

Tablet hardness

Tablet hardness testing, is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage" The breaking point of a tablet is based on its shape. The hardness of all the formulations of prepared Rizatriptan sustained release tablets were measured by using Monsanto hardness tester (Cad Mach). According to specifications of USP; hardness values of 4 to 5 kg/cm^2 is considered as acceptable limit for sustained release tablets. From each formulation the crushing strength of ten sustained release matrix tablets with known weights were recorded in kg/cm^2 and average were calculated with standard deviation. [17]

Friability

Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. Throughout pharmaceutical industry, friability testing has become an accepted technology and the instrument used in to perform this process is called Friabilator or Friability Tester. For any compressed uncoated tablet; friability lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.[18] Previously weighed ten tablets (W_i) from each batch of Rizatriptan sustained release tablets were taken in Roche friabilator (Roche friabilator, Secor India). After hundred revolutions of friabilator; tablets were recovered with cleaning in a soft cloth to make free from dust and the total remaining weight (W_f) was recorded. Friability was calculated by using following formula.

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

Weight variation test

Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression. All the formulations of Rizatriptan sustained release tablets were assessed for weight variation as per USP monograph. Twenty tablets from each batch were weighed collectively and individually using an electronic balance. The average weight was calculated with percent variation of each tablet and the process is repeated thrice to calculate standard deviation. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130 mg or less is 10% whereas for average weight between 130-324 mg is 7.5% and for average weight more than 324 mg 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%.[17, 18]

Content uniformity studies

For determination of content uniformity of the all formulations of Rizatriptan sustained release tablets; twenty tablets from each batch were triturated to form powder. Powder equivalent to one tablet was taken and dissolved in 100 ml of HCl buffer pH 1.2 and heated at 37 ^{0}C for 60 min with constant stirring. The solution was cooled, filtered and after suitable dilution 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 formulation was calculated.[19]

Swelling Index (*SI*)

The swelling behaviour of all formulations of Rizatriptan sustained release tablets were measured by studying its weight gain in the dissolution medium under study. The swelling index were determined by placing the tablets in the basket of dissolution apparatus containing 100 ml of phosphate buffer pH 6.8 as dissolution medium maintaining at 37 ± 0.5 ^{0}C. After every one hour interval and upto 12 h, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.[18, 19]

$$Swelling\ Index\ (SI) = \frac{Wf - Wi}{Wi} \times 100$$

Where W_f and W_i is called as wet and dry weight of the tablet respectively.

***In vitro* drug release study**

The *in vitro* release studies were conducted for all Rizatriptan sustained release matrix tablet formulations using eight stations USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.) maintaining at 37 ± 0.5 ^{0}C. To simulate the physiological conditions of GIT, first 2 h of dissolution was carried out in 900 ml of simulated gastric fluid (SGF, 3.2 mg/ml pepsin in 0.05M HCl, pH 1.2) and the rest of the time in 900 ml of simulated intestinal fluid (SIF, 10 mg/ml pancreatic fluid in phosphate buffer, pH 6.8). At regular intervals of time (every 1 h interval), the aliquots were withdrawn and analyzed for drug using the UV-Visible spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at λmax 226 nm both for HCl buffer pH 1.2 and phosphate buffer pH 6.8. After each sampling an equal volume of fresh dissolution media was added to the dissolution medium. All the dissolution studies were repeated thrice and mean and standard deviation was

calculated. The obtained mean percentage cumulative drug release was plotted with respect to time.[20]

***In vitro* drug release kinetic studies**

The rate and mechanism of release of Rizatriptan from prepared sustained release tablets were analyzed by fitting the dissolution data of optimised formulation ($RSRF_8$) into following exponential equations.

Zero order release equation is calculated by following 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 is calculated by following equation.

$$\log(100 - Q) = log100 - \frac{K_1 t}{2.303}$$

Where, K_1 is the first order release rate constant. When the data are plotted as logarithm of cumulative percent drug remaining versus time, it yields a straight line, indicating that the release follows first order kinetics. The constant K_1 can be obtained by multiplying 2.303 with slope.

The dissolution data was fitted to the following Higuchi's equation.

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

Where, K_2 is the diffusion rate constant. When the data are plotted as accumulative drug released versus square root of time, it yields a straight line, indicating that the drug released by diffusion mechanism. The slope is equal to K_2.

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

$$\log\left(M_t / M_\infty\right) = \log K + n \log t$$

Where *Mt* 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.[19, 20]

Stability studies of optimised formulation

Stress testing of the active pharmaceutical ingredient can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The accelerated condition that chosen for stability study was 40 $^oC \pm 2\ ^oC$/ 75% ± 5% RH(Climatic zone III condition for accelerated testing) using humidity control oven NEC 210R10 (Newtronic Instruments, India) for 90 day. The tablets of optimized batch ($RSRF_8$) were packed in air tight bottles and subjected to accelerated stability studies according to ICH guidelines. The sample were withdrawn from the humidity control oven on 30th day, 60th day and 90th day for evaluation of physicochemical parameters *i.e* physical appearance, weight variation, hardness, friability, swelling index, drug content and *in vitro* drug release characteristics.[21, 22]

4. RESULTS AND DISCUSSION

By comparing the spectra of Rizatriptan drug and optimized formulation $RSRF_8$, the sharp peaks that appear in spectra of Rizatriptan at~ 3120 cm^{-1} also appears in optimized formulation ($RSRF_8$) 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 optimized formulation ($RSRF_8$) with no shifting in the major peaks and there was no additional peaks formed in the optimized formulation, that indicate that no interaction occurred between the Rizatriptan and excipients used in the preparation of different sustained released matrix formulations. The FTIR spectra of Rizatriptan drug and optimised formulation ($RSRF_8$) were shown in **figure 1**.

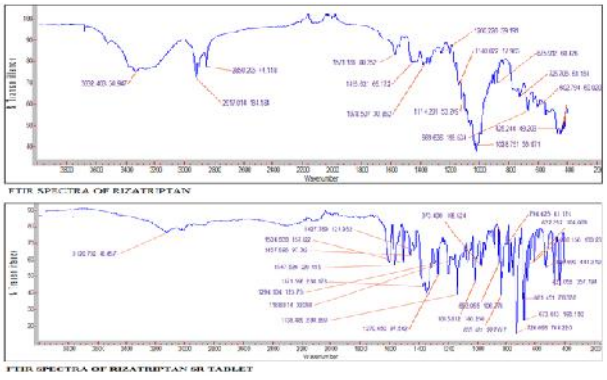


Fig. 1: Drug and Polymers compatibility studies through FTIR analysis

DSC thermogram of pure drug Rizatriptan and optimized formulation ($RSRF_8$) were observed that the endothermic peak appeared between 180-210 ^0C and 150-200 ^0C respectively which indicate that the optimized formulation ($RSRF_8$) is thermodynamically stable by the addition of Rizatriptan. By comparing the DSC thermogram of HPMC

and optimized formulation ($RSRF_8$) it were observed that the endothermic peak that was found between 60-110 ^{0}C with HPMC was also observed with optimized formulation between 90-140 ^{0}C. By comparing the DSC thermogram of Eudragit and optimized formulation ($RSRF_8$) it were observed that the endothermic peak that was found between 200-250 ^{0}C with Eudragit was also observed with optimized formulation between 210-240 ^{0}C. The DSC thermogram of Rizatriptan, HPMC, Eudragit and optimised formulation is shown in **figure 2**.

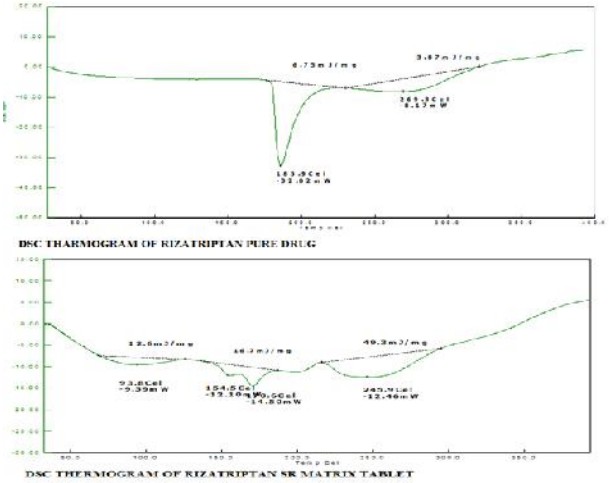


Fig 2: Drug and Polymers compatibility studies through DSC analysis

Angle of repose is suited for particle > 150µm.Values of angle of repose ≤ 25^0 generally indicates the free flowing material and angle of repose ≥ 40^0 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 19.42±0.16 ($RSRF_{10}$) to 24.37±0.19 ($RSRF_5$) *i.e.* granules of Rizatriptan sustained release tablets showed good flow properties.

The bulk densities of Rizatriptan sustained release granules of all formulations were found to be in the range of 0.335±0.03 ($RSRF_5$) to 0.375±0.02 ($RSRF_{11}$) g/cm^3 and the tapped densities were found to be in between 0.402±0.02 ($RSRF_5$) to 0.422±0.04 ($RSRF_{11}$) g/cm^3. This indicates good packing capacity of granules. Measurements of bulk density and tapped density found that density of granules depends on particle packing and density changes as the granules consolidates.

Formulation $RSRF_{11}$ (11.14) showed lowest Carr's index value that expected to have excellent flow properties. All other formulations except $RSRF_5$ (16.66) & $RSRF_{12}$ (16.11) showed Carr's index value less than 16% that indicated good flow properties and values more than 16% indicates presences of more fines with lack of uniformity in particles.

Hausner's ratio is simple method to evaluate stability of powder and granule column and to estimate flow properties. In all formulations the Hausner's ratios values were found 'between' 1.12 ($RSRF_6$) to 1.20 ($RSRF_5$) that indicates good flow characteristics. The precompression characterizations of different batches of sustained released granules are given in **table 2**.

Table 2: Result of precompression parameters of Rizatriptan sustained release granules ($RSRF_1$ – $RSRF_{12}$)

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
$RSRF_1$	0.346±0.02	0.405±0.04	22.24±0.26	14.57	1.17
$RSRF_2$	0.364±0.03	0.413±0.03	21.21±0.31	11.86	1.13
$RSRF_3$	0.352±0.04	0.415±0.05	23.42±0.21	15.18	1.17
$RSRF_4$	0.368±0.02	0.419±0.06	22.52±0.28	12.17	1.14
$RSRF_5$	0.335±0.03	0.402±0.02	24.37±0.19	16.66	1.20
$RSRF_6$	0.372±0.05	0.420±0.04	23.44±0.27	11.42	1.12
$RSRF_7$	0.354±0.03	0.417±0.03	21.51±0.32	15.10	1.17
$RSRF_8$	0.363±0.05	0.421±0.04	21.47±0.35	13.78	1.16
$RSRF_9$	0.362±0.03	0.416±0.05	20.63±0.23	12.98	1.15
$RSRF_{10}$	0.371±0.06	0.419±0.03	19.42±0.16	11.46	1.13
$RSRF_{11}$	0.375±0.02	0.422±0.04	19.56±0.25	11.14	1.13
$RSRF_{12}$	0.349±0.04	0.416±0.06	20.35±0.18	16.11	1.19

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

The surface texture of tablets from all formulations was smooth, white, and circular. Typical tablet defects, such as capping, chipping and picking, were not observed. The average thicknesses of the tablets were ranged from 2.69±0.12 ($RSRF_1$) to 2.80±0.18 mm ($RSRF_{11}$) and the variation observed were within prescribed limits.

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder or granule. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression. Weight variations for different formulations were ranged between 3.37±0.45 ($RSRF_3$) to 4.75±0.55% ($RSRF_6$). The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement.

Tablet hardness testing, is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage. The hardness of all the Rizatriptan sustained released matrix tablets formulations were ranged from 4.43±0.72 ($RSRF_2$) to 5.32±0.63 ($RSRF_{10}$) kg/cm^2 which indicated good handling and transportation characteristics of tablets under study.

Friability test tells how much mechanical stress tablets are able to withstand during their manufacturing, distribution and handling by the customer. The percentage friability of all the formulations was ranged from 0.43±0.06 % ($RSRF_5$) to 0.72±0.03 % ($RSRF_4$). In the present study, the percentage friability for all for formulations was within the prescribed

limits that indicated the product is resistant to wear and tear during handling and transportation.

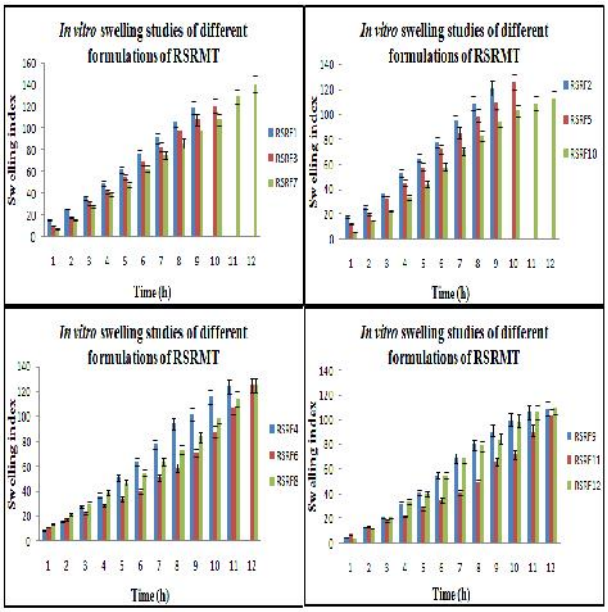
The percentages of drug content for Rizatriptan sustained released matrix tablet formulations ($RSRF_1$ to $RSRF_{12}$) were found to be in between 97.34±1.51 % ($RSRF_2$) to 102.82±1.57 % ($RSRF_{11}$) which were within the acceptable limits. The value ensures good uniformity of the drug content in the tablet. The physicochemical characterizations of different formulation of sustained released tablets are given in **table 3**.

Table 3: Evaluation of postcompression parameters of Rizatriptan sustained release matrix tablets ($RSRF_1$-$RSRF_{12}$)

F. No.	Average hardness (kg/cm^2)	Average weight variation (%)	Average friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)
$RSRF_1$	5.25±0.65	3.45±0.31	0.66±0.02	2.69±0.12	99.51 ±1.43
$RSRF_2$	4.43±0.72	3.52±0.44	0.45±0.05	2.75±0.18	97.34±1.51
$RSRF_3$	5.10±0.71	3.37±0.45	0.54±0.07	2.71±0.16	99.62±1.62
$RSRF_4$	5.16±0.62	3.55±0.53	0.72±0.03	2.73±0.21	98.81±1.26
$RSRF_5$	4.96±0.48	4.42±0.76	0.43±0.06	2.76±0.16	101.16±1.55
$RSRF_6$	4.85±0.59	4.75±0.55	0.61±0.05	2.78±0.18	98.34±1.72
$RSRF_7$	4.90±0.91	3.44±0.62	0.56±0.06	2.74±0.17	97.78±1.58
$RSRF_8$	5.15±0.78	3.72±0.15	0.52±0.04	2.76±0.20	100.53±1.54
$RSRF_9$	5.18±0.55	3.65±0.27	0.53±0.08	2.79±0.16	98.58±1.46
$RSRF_{10}$	5.32±0.63	3.41±0.64	0.68±0.05	2.76±0.15	98.74±1.72
$RSRF_{11}$	5.14±0.85	3.85±0.52	0.52±0.08	2.80±0.18	102.55±1.62
$RSRF_{12}$	5.10±0.69	3.76±0.44	0.72±0.05	2.70±0.20	101.70±1.58

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

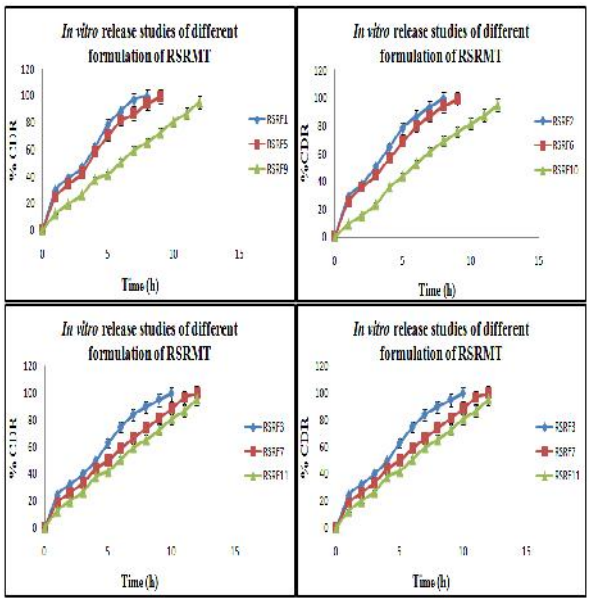
Swelling study was performed on all the formulations ($RSRF_1$ to $RSRF_{12}$) upto 12 hours. The formulation containing more concentration of HPMC K4M, HPMC K15M showed higher swelling indices due to higher hydrophilicity and more water uptake of the polymers. But reverse is observed with the formulations containing higher percentage of eudragit, as it is a hydrophobic polymer. The formulations $RSRF_1$ to $RSRF_6$ those were containing more percentage of HPMC in different proportion, showed higher swelling index whereas the formulation $RSRF_7$ to $RSRF_{12}$ containing more percentage of eudragit showed lower swelling indices as eudragit is a hydrophobic polymer. The formulation $RSRF_1$ and $RSRF_2$ that contains only HPMC showed increasing swelling indices upto 8 hours and decreased the swelling indices due to erosion of hydrophilic polymer. The comparative swelling index for all the formulations were shown as histogram in **figure 3**.



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

Fig 3: Comparative swelling studies of all the formulations with respect to concentration of polymers used

In order to optimise the *in vitro* drug release profile of Rizatriptan sustained released matrix tablets; different hydrophilic matrix polymers *viz.*, HPMC K4M, HPMC K15M and hydrophobic matrix polymer *viz.*, eudragit RSPO and RLPO were used and twelve different formulations were prepared. Between the two grades of HPMC used, HPMC K15M having better controlled release profile than HPMC K4M as it is having higher viscosity. It was observed that using HPMC polymer alone causes initial burst release because drug is hydrophilic in nature and maximum of drug was released upto 8 to 10 h which is noticed in case of formulation $RSRF_1$ and $RSRF_2$. To reduce the initial burst release of drug and to maintain sustained release effect for required period of time, one more hydrophobic polymer *i.e* eudragit RSPO and RLPO was added. The formulation $RSRF_8$ that contained 16.67% of each HPMC K4M & HPMC K15M and 13.33% of eudragit RLPO was considered as optimised formulation as the initial release was 14% and maximum release upto 12 hours. This release profile complies with the prerequisite release profile. Further increase in the concentration of eudragit; the initial release rate was much slower which was not desirable. So 13.33% of eudragit RLPO was considered as optimum. The optimised formulation is supposed to provide once daily medication that may improve patient compliance and may give therapeutic benefit to patient with sustainable migraine. The comparative drug release profiles with respect to concentration of polymers for different formulations were shown in **figure 4**.



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

Fig 4: Comparative dissolution profile of different formulations of Rizatriptan sustained release tablet

The *in vitro* dissolution data of optimised formulation ($RSRF_8$) were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppas kinetic model equation and the graphs were plotted (**Figure 5**). The zero order release plot was found fairly linear as indicated by its highest regression (0.99) values. The release exponent 'n' for optimised formulation $RSRF_8$ was found to be 0.78 ($0.5 < n < 1$), which appeared to indicate an anomalous diffusion coupled with erosion. So in present study *in vitro* drug release kinetic of optimised formulation of Rizatriptan sustained release matrix tablets ($RSRF_8$) followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. The comparative regression values of different kinetic models for the optimised formulation were given in **table 4**.

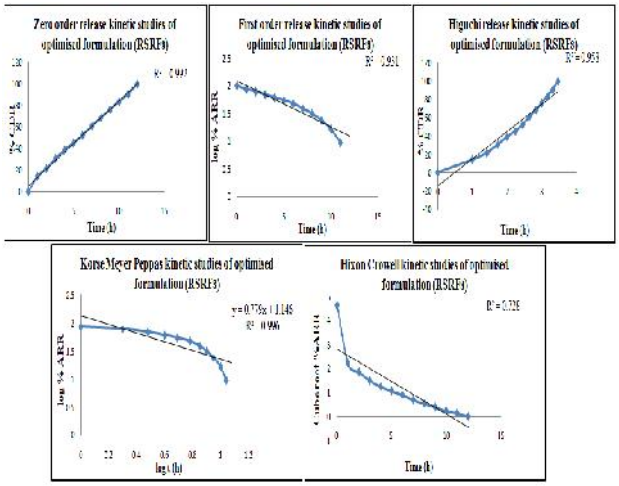


Fig 5: *In vitro* release kinetic studies of optimised formulation ($RSRF_8$)

Table 4: Regression values of *in-vitro* release kinetic study of optimized Rizatriptan sustained release matrix tablet ($RSRF_8$)

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 Peppas model	'n' value of Peppas model
$RSRF_8$	0.99	0.93	0.96	0.73	0.99	0.78

The optimised formulation $RSRF_8$ of Rizatriptan sustained release matrix tablets was selected for the accelerated stability studies. It did not show any significant change in physicochemical characteristics *i.e* physical appearance, weight variation, hardness, friability, swelling studies, drug content and *in vitro* drug release characteristics. More than 90% of the drug had been retained after *in vitro* dissolution studies stored under stressed condition for 3 months. Thus, it was found that the sustained release matrix of Rizatriptan ($RSRF_8$) were stable under accelerated storage conditions for at least 3 month. The results of change in physicochemical characteristics and *in vitro* release profile of optimised formulation at different time interval in accelerated stability conditions were shown in **table 5.**

Table 5: Comparative physicochemical characterization of optimized batch ($RSRF_8$) 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	Smooth, white, circular, concave surface without any cracks	No change	No change	No change
2	Weight variation	3.72±0.15	3.72±0.14	3.71±0.18	3.71±0.14
3	Hardness	5.15±0.78	5.08±0.42	5.02±0.62	4.95±0.66
4	Friability	0.52±0.04	0.55±0.05	0.58±0.02	0.61±0.04
5	Average thickness	2.76±0.20	2.75±0.31	2.75±0.24	2.75±0.22
6	Swelling index	125 ±3.16	121 ±2.34	118 ±2.33	106 ±2.19
7	Drug content	100.53±1.54	99.25±1.52	98.56±1.82	95.72±1.44

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

5. CONCLUSION

In the above research findings, sustained release matrix tablet of Rizatriptan were successfully developed by weight granulation techniques. The major challenge in these studies was to design a sustained release matrix tablet that can provide sustained release effect upto 12 h by using different grade of hydrophilic polymer HPMC and hydrophobic polymer eudragit. The main objective of using hydrophobic polymer eudragit with HPMC was to prevent the burst release effect the hydrophilic drug under study which was successfully developed. Formulation $RSRF_8$ that contained 16.66% of each HPMC K4M HPMC K15M and 13.33% of eudragit showed 14% of drug release within first hour that may be essential to elicit pharmacological response and showed sustained release upto 12 h with almost complete release (99.48%) emerged as optimised formulation. FTIR and DSC studies revelled that there is no chemical and

thermal interaction between drug and excipients used in the present studies. The precompression and postcompression parameter estimations satisfied according to pharmacopoeia specification. Kinetic of *in vitro* drug release of $RSRF_8$ followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. The accelerated stability studies for the optimised formulation were reviled that the formulation was stable without any remarkable physicochemical changes. Thus the results of the current study clearly indicate a promising potential of the Rizatriptan sustained release matrix tablets system as an alternative to the conventional dosage form as it enhance bioavailability of the Rizatriptan by producing a sustained release effect and can be therapeutically beneficial for sustainable migraine. However, further clinical investigations are needed to assess the utility of this system for patients suffering from sustainable migraine.

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