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Formulation Design and *in vitro* Evaluation of Zolmitriptan Immediate Release Tablets using Primojel and AC-Di-Sol

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Abstract

The objective of the present study was to develop an immediate release tablet of Zolmitriptan using different concentration of Primojel and AC-Di-Sol as superdisintegrant with a view to obtain rapid disintegration in gastric P^H and to achieve quick action for acute migraine. Zolmitriptan is a selective serotonin receptor agonist used in the acute treatment of migraine. Ten different formulations of Zolmitriptan immediate release tablets were prepared using direct compression technique. Different Precompression and post compression characterization of tablet was carried out and the result satisfied according to the pharmacopoeia specifications. *In vitro* release studies were carried out in USP II paddle type dissolution apparatus for different formulations and the formulation containing 4% of Polyplasdone-XL giving best release profile because of highest similarity factor and lowest difference factor. *In vitro* release kinetic studies like zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppa's kinetic model were carried out for optimised formulation. The optimised formulation followed Peppa's kinetic model with drug release mechanism was anomalous diffusion coupled with erosion. Drug and excipients compatibility studies were carried out through FTIR and DSC analysis. FTIR and DSC studies revelled that there is no interaction between drug and different excipients used in the formulation. Accelerated stability studies were carried out for optimised formulation to confirm the stability of dosage forms.

Key words: Zolmitriptan, Immediate release tablets, Primojel, AC-Di-Sol, Antimigraine

INTRODUCTION

The oral route of drug administration is one of the most popular routes of drug administration. The tablets are still the most commonly used dosage forms due to its continuous development and implementation of innovative ideas to overcome the basic drawbacks of the existing formulations. Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques. Immediate release dosage forms are most commonly formulated when rapid response is required. This also serves as an advantage for patient compliance. Sometimes immediate release dosage forms are used as one of layer in a bilayer tablet as loading dose for quick on set of action. Superdisintegrant is the vital component along with various common excipients like diluents, binder, lubricants, glidant etc used for the preparation of immediate release tablets. The immediate release tablets are usually prepared by using various superdisintegrant like sodium starch glycolate (Primojel™), crosscarmellose (AC-Di-Sol™) and different grade of crosspovidone (Polyplasdone-XL™) etc for quick and easy disintegration of tablets.[1] Tablet manufacturing by direct compression has increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency.[2] As direct compression is more economic, reducing the cycle time and straight forward in terms of good manufacturing practice requirements. On the other hand wet granulation not only increases the cycle time, but also not suitable for thermolabile and moisture sensitivity active ingredients. So pharmaceutical industry is now focusing increasingly on this process.[3, 4]

Zolmitriptan is a selective serotonin receptor agonist used in the acute treatment of migraine. 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. Zolmitriptan binds with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors leading to cranial blood vessel constriction. It is having oral bioavailability 40% and plasma half-life 2.5-3 hours. Zolmitriptan is almost white powder slightly soluble in water (1.3 mg/ml at 250°C) but shows greater solubility in 0.1M hydrochloric acid belonging to class III of BCS classification. The recommended starting dose is 1.25 or 2.5 mg. The maximum recommended single dose is 5mg 2 to 3 times in a day.[6]

The basic objective of present studies were to formulate and in vitro evaluation studies of immediate release tablets of Zolmitriptan using super disintegrant like sodium starch glycolate (Primojel™) and crosscarmellose (AC-Di-Sol™) with a view to obtain rapid disintegration when taken through oral route, permitting a rapid onset of action during acute migraine attack.[5]

Table 1: Compositions of different formulations of Zolmitriptan immediate release tablets

Formulations(mg)	$ZIRF_1$	$ZIRF_2$	$ZIRF_3$	$ZIRF_4$	$ZIRF_5$	$ZIRF_6$	$ZIRF_7$	$ZIRF_8$	$ZIRF_9$	$ZIRF_{10}$
Zolmitriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Avicel 101	82	80	78	76	82	80	78	76	78	78
PVP K30	10	10	10	10	10	10	10	10	10	10
Primojel	2	4	6	8	-	-	-	-	2	4
AC-Di-Sol	-	-	-	-	2	4	6	8	4	2
Mg. stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2	2	2	2	2	2	2	2	2	2
Total wt.	100	100	100	100	100	100	100	100	100	100

MATERIALS AND METHODS

Materials

Zolmitriptan was procured as a gift sample from Glenmark Pharma, Nasik, India. The superdisintegrant sodium starch glycolate (Primojel™) and crosscarmellose (AC-Di-Sol™) were also obtained as a gift sample from Dr. Reddy's laboratories Pvt. Ltd. The diluent Micro crystalline cellulose (Avicel 101) was purchased from Otto Manufacturers. Lactose, PVP K30, 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

Analytical method for the *in vitro* estimation of Zolmitriptan in the formulations

Primary stock solution of Zolmitriptan having concentration of 1000µg/ml was prepared using HCl buffer P^H 1.2. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10µg/ml was prepared using same HCl buffer P^H 1.2. The prepared secondary stock solution was then scanned by a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400nm to 200nm, and the λmax for solution was determined and it was found as 283 nm was selected and utilized for further studies. The secondary stock solution was then diluted using same HCl buffer P^H 1.2 to form a series of concentration of 2, 4, 6, 8, and 10 µg/ml and corresponding absorbance were measured at λmax of 283nm. For obtaining the calibration curve of pure Zolmitriptan, measured absorbencies were plotted against corresponding concentrations.[5, 6]

Formulation of Zolmitriptan immediate release tablets ($ZIRF_1$-$ZIRF_{10}$)

For the preparation of immediate release tablets of Zolmitriptan direct compression method were adopted. The formulation composition of different batch is shown in **table 1**. All the powders passed through 40 mesh sieve. The required quantity of Zolmitriptan, various superdisintegrants and fillers were mixed thoroughly. Magnesium stearate and talc were finally added as a lubricant and glidant respectively. The dry blends were tested for various pre compression parameters like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio etc. The evaluated mixture of powder was directly compressed (6 mm diameter, circular concave faced punches) on a 10 station rotary tablet punching machine (SHAIMAC Technology Pvt. Ltd, Hyderabad, India). Each tablet contained 2.5 mg of Zolmitriptan. All the tablets were stored in airtight containers for further study.[1, 7]

Evaluation of precompression parameters of dry blend powders of Zolmitriptan immediate release tablet formulations

Angle of Repose (θ)

The dry blend powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powders formed.

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

Where θ was called as angle of repose, h and r were height and radius of the powder 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.[5, 8]

Bulk density and tapped density

Both the bulk density (BD) and tapped density (TD) of prepared Zolmitriptan immediate release dry blend powders of all the formulations were determined using the following formulas.[7, 9]

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

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

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. Compressibility index (Carr's index) of prepared Zolmitriptan immediate release dry powders blend were calculated by following formula

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

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. "Between" 33-38 indicates very poor and greater than 40 indicates extremely poor.[7, 10]

Hausner's ratio:

The Hausner's ratios of prepared Zolmitriptan immediate release dry powders blend were determined by 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.[5, 11]

Evaluation of postcompression parameters of Zolmitriptan immediate release tablets formulations

Average thickness

From each formulation (ZIRT); ten 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.[7, 11]

Tablet Hardness

The hardness was measured for all the formulations of Zolmitriptan immediate release tablets by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten immediate release 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 3-4 Kg for immediate release tablet is considered as acceptable limit.[5, 12]

Friability

Previously weighed ten tablets from each batch (ZIRT) were taken in Roche friabilator (Roche friabilator, Secor India, Delhi, India). After hundred revolutions of friabilator tablets were recovered. The tablets were then made free from dust 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 compress tablet that lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.[7, 13]

Weight variation test

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%. All formulations of Zolmitriptan immediate release tablets were evaluated 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 and percent variation of each tablet was calculated.[5, 14]

Content uniformity

For determination of content uniformity of the all formulations (ZIRF); twenty tablets were taken and triturated to form powder. Powder equivalent to one tablet was taken and dissolved in 100 ml of HCl buffer P^H 1.2 and heated at 37 ^{0}C for 15 to 20 minutes with constant stirring. The solution was cooled, filtered and after suitable dilution the Zolmitriptan content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 283 nm. Each measurement was carried out in triplicate and the average drug content in each formulation was calculated.[15]

Wetting time and water absorption ratio

Wetting time reflects the disintegration process of the tablet formulation. Lesser the wetting time more is the disintegration rate. For the wetting time determination, twice folded tissue paper was placed in a petri dish having an internal diameter of 6.5 cm containing 10 ml of HCl buffer P^H 1.2 containing methylene blue (0.1% w/v). A tablet from each formulation of Zolmitriptan immediate release tablets was carefully placed on the surface of the tissue paper in the petri dish. The time required for the dye to reach the upper surface of the tablet was recorded as wetting time. Measurements were carried out in triplicate and standard deviations were also determined.[6, 16]

Water absorption ratio (R), can be estimated by simple procedure include weighing (W_b) of the tablet prior to the placement on the Petri dish, then after recording the wetting time. The wetted tablet was removed and reweighed (W_a). The water absorption ratio was determined according to the following equation.

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

***In-vitro* disintegration time (D_t)**

According to USP the disintegration apparatus for oral tablets is used without the covering plastic disks and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements whereas < 2 min for immediate release dosage form. The test was carried out using tablet disintegration apparatus (model EI D-16, Electrolab, Mumbai, India). *In-vitro* disintegration test was carried out using a modified disintegration method (n = 6) using disintegration tester maintained at 37°C ± 0.5°C in HCl buffer P^H 1.2. The tablets were kept in the basket and the time taken for the tablet to disintegrate completely into smaller particles was noted.[7, 17]

***In-vitro* drug release (dissolution) study**

The *in-vitro* dissolution study was conducted for all the formulations (ZIRF) using an eight station USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.). A total volume of 900 ml of HCl buffer P^H 1.2 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 each 5 min intervals and filtered by Whatmann filter paper. Samples were analyzed spectrophotometrically at 283 nm for determination of Zolmitriptan that were released from immediate release tablets.[5, 18]

Calculation of similarity and difference factors for Zolmitriptan immediate release tablets

The optimized formulation of the Zolmitriptan immediate release tablets was chosen according to comparative

dissolution study with a reference marketed product of ZOMIG TAB (AstraZeneca) containing Zolmitriptan 2.5mg, employing the similarity factor (f_2) and difference factor (f_1) equation introduced by Moore and Flanner.

The similarity factor (f_2) adopted by the U.S. Food and Drug Administration (FDA) was used to evaluate the similarity in release profiles between the two pharmaceutical preparations. The similarity factor, which is a logarithmic transformation of the sum squared error of differences between the test preparation and reference preparation, was calculated by the following equation:

$$f2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} \times 100\right\}$$

Where R_t and T_t are the accumulated release rates of the reference preparation and test preparation at the predetermined time points, respectively, and n represents the number of the time points. The value of the similarity factor is between 0 and 100. The value 100 indicates that the test and reference profiles are identical; the more it approaches 0, the more dissimilarity of the two preparations occurs. Generally, if $f_2 > 50$, the release profiles are considered to be similar, and the larger the f_2 value, the higher the similarity.

Difference factor (f_1) measures the percent error between two drug release curves over all time points.

$$f1 = \frac{\sum_{t=1}^{n}|Rt - Tt|}{\sum_{t=1}^{n} Rt} \times 100$$

Dissolution profile was considered satisfactory if $f1$ values lies below 15 (nearing zero, more it approaches towards zero more similarity is the product.[5, 6]

Characterization of the *in vitro* drug release profile

The rate and mechanism of release of Zolmitriptan from prepared immediate release tablets were analyzed by fitting the dissolution data 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.

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

Where, K_1 is the first order release rate constant.

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.

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

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

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 *W*o 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.[6, 7]

Drug and excipients compatibility studies

Drug and excipients used for the formulation of different batch of Zolmitriptan immediate release tablets were analysed for any possible physical and chemical interactions through FTIR and DSC studies.

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transforms infrared (FTIR) spectroscopy studies were performed to find out the peaks that indicates presence of a particular functional group in the pure drug and the excipients used. If the functional groups present in pure drug reflects in the formulations than the drug and excipients are said to be compatible with each other. The FTIR studies were carried out for pure drug Zolmitriptan and physical mixture of drug and all excipients (optimised 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, individual excipients and for physical mixture of drug and excipients.[19, 22]

Differential Scanning Calorimetric (DSC) analysis:

Another method of estimating the physical interaction between drug and excipients used for the formulation of different dosage form is thermal analysis by DSC or TGA techniques. In the present studies the DSC analysis of Zolmitriptan and physical mixture of drug with excipients (optimised formulation) used for formulation of Zolmitriptan immediate release tablets were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10^o C/min over a temperature range of 40 to 300^{o}C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.[20, 21]

Stability studies of optimised formulation

The short term stability studies of optimised formulation of Zolmitriptan immediate release tablet were carried out according to ICH guidelines. The optimized formulation was subjected to accelerated stress condition at 40 ^{o}C ± 2 ^{o}C/ 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.[6, 22]

RESULTS AND DISCUSSION

The bulk densities of Zolmitriptan immediate release dry powder blends of all formulations were found in the range of 0.347±0.05 to 0.396±0.09 g/cm^3 and the tapped densities were found in between 0.412±0.09 to 0.475±0.07 g/cm^3. This indicates good packing capacity of dry powder blends. Bulk density and tapped density measurements found that density of dry powder blends depends on particle packing and that density changes as the powder consolidates. Values of Carr's index for all the formulations were found below 16% that usually indicates good flow characteristics except the formulations $ZIRF_1$, $ZIRF_2$, $ZIRF_4$ and $ZIRF_5$ which may be due to lake of uniformity in powder sizes and presences of more fine particles in those formulations.

Hausner's ratio is simple method to evaluate stability of power and granule 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 values were ranged from 1.14 to 1.25 that indicates good flow characteristics of dry powder blends.

Angle of repose is suited for particle > 150μm.Values of angle of repose ≤ 25 generally indicates the free flowing material and angle of repose ≥ 40 suggest a poor flowing material. The angle of repose is indicative of the flowability of the dry powder or granules. The angle of repose of all formulations fell within the range of 24.66±0.16 to 20.68±0.10 *i.e.* dry powder blends of Zolmitriptan immediate release tablet showed good flow properties and suitable for direct compression. The results of precompression parameters for all the formulations were given in **table 2**.

Table 2: Evaluation of precompression parameters of Zolmitriptan Immediate release dry powder blends ($ZIRF_1$ – $ZIRF_{10}$)

F. No.	Bulk density (gm/ml)	Tapped density(gm/ml)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
$ZIRF_1$	0.359±0.08	0.448±0.08	24.66±0.16	19.86	1.25
$ZIRF_2$	0.388±0.09	0.464±0.06	23.29±0.12	16.38	1.20
$ZIRF_3$	0.347±0.05	0.412±0.09	24.84±0.17	15.78	1.19
$ZIRF_4$	0.369±0.07	0.442±0.06	23.73±0.11	16.52	1.20
$ZIRF_5$	0.392±0.06	0.475±0.07	23.65±0.19	17.47	1.21
$ZIRF_6$	0.378±0.07	0.435±0.08	22.72±0.14	13.10	1.15
$ZIRF_7$	0.367±0.05	0.421±0.05	23.46±0.16	12.83	1.15
$ZIRF_8$	0.376±0.08	0.428±0.08	21.85±0.12	12.15	1.14
$ZIRF_9$	0.384±0.06	0.450±0.05	20.68±0.10	14.67	1.17
$ZIRF_{10}$	0.396±0.09	0.454±0.09	21.78±0.16	12.78	1.15

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

The physical parameters such as hardness, average weight variation, average friability and average thickness of the all the formulations of Zolmitriptan immediate release tablets were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The average thicknesses of the tablets were ranged between 3.76±0.14 to 3.88±0.15mm. All the batches showed uniform thickness and those were within range. Weight variations for different formulations were found to be 098±1.62 to 102±1.45mg. The acceptable average percentage variation for tablet formulations having weight 100mg is 10% and all the formulations fall within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement.

The average hardness of all the Zolmitriptan immediate release tablet formulations was ranged from 3.44±0.6 to 3.91±0.5 kg/cm^2. By increasing the concentration of superdisintegrant concentration the hardness usually decreased that noticed in case of formulation $ZIRF_4$, $ZIRF_8$, $ZIRF_9$ and $ZIRF_{10}$. The percentage friability of all the formulations were ranged from 0.46±0.08% to 0.77±0.05% and also the % friability were found more by increased concentration of superdisintegrant concentration. In the present study, the percentage friability for all for formulations was within the prescribed limits. The percentages of drug content for $ZIRF_1$ to $ZIRF_{10}$ were found to be in between 97.48±1.60 to 102.57±1.48 of Zolmitriptan immediate release tablet formulations which were within the acceptable limits. Disintegration time were determined for all the formulations and it was found that by increasing concentration of superdisintegrant, the disintegration time decreases; but increase in concentration above 6% the hardness value decreases.

The wetting time of all the formulations were found between 68±0.41 to 110±0.38 second. For the case of wetting time by increasing the concentration of superdisintegrant the wetting time decreases those were noticed in case of formulations of $ZIRF_4$, $ZIRF_8$, $ZIRF_9$ and $ZIRF_{10}$. Between sodium starch glycolate (Primojel) and cross carmellose (AC-Di-Sol), former showed less wetting time than later at equal concentrations. The water absorption ratio of formulations $ZIRF_1$ to $ZIRF_{10}$ was found in the range of 15.46±0.24 to 44.45±0.39. By increasing the concentration of superdisintegrant the water absorption ratio increased that might be due to increase in the porosity of the formulation with increase in superdisintegrant concentration. The physicochemical characterizations of different batches of Zolmitriptan immediate release tablets are given in **table 3**.

Table 3: Evaluation of Post-compression parameters of Zolmitriptan immediate release tablets

Formulation code	Average Hardness (kg/cm^2)	Average Weight Variation (%)	Friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)	D_t (Sec)	Wetting time (Sec)	Water absorption ratio
$ZIRF_1$	3.91±0.5	102±1.67	0.46±0.08	3.86±0.14	101.68±1.62	260±1.23	108±0.35	15.46±0.24
$ZIRF_2$	3.75±0.6	99±2.54	0.61±0.06	3.81±0.17	102.57±1.48	172±1.16	92±0.44	17.62±0.35
$ZIRF_3$	3.62±0.5	98±2.71	0.67±0.05	3.85±0.18	99.45±1.81	116±1.43	84±0.65	29.45±0.28
$ZIRF_4$	3.44±0.6	102±1.52	0.73±0.04	3.78±0.14	102.56±1.74	114±1.52	69±0.56	31.36±0.27
$ZIRF_5$	3.84±0.7	102±1.45	0.48±0.07	3.80±0.18	97.48±1.60	228±1.58	110±0.38	18.44±0.34
$ZIRF_6$	3.71±0.5	98±1.62	0.58±0.06	3.76±0.14	98.72±1.55	184±1.86	102±0.47	24.51±0.30
$ZIRF_7$	3.59±0.8	102±2.06	0.68±0.08	3.84±0.19	99.64±1.44	112±1.42	89±0.29	30.67±0.42
$ZIRF_8$	3.48±0.9	101±1.67	0.77±0.05	3.85±0.15	98.75±1.72	109±0.88	76±0.42	32.78±0.35
$ZIRF_9$	3.67±0.4	100±1.85	0.65±0.08	3.86±0.17	101.31±1.68	102±1.36	74±0.74	41.81±0.27
$ZIRF_{10}$	3.62±0.8	101±1.92	0.68±0.05	3.88±0.15	102.42±1.47	108±1.76	68±0.41	44.45±0.39

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

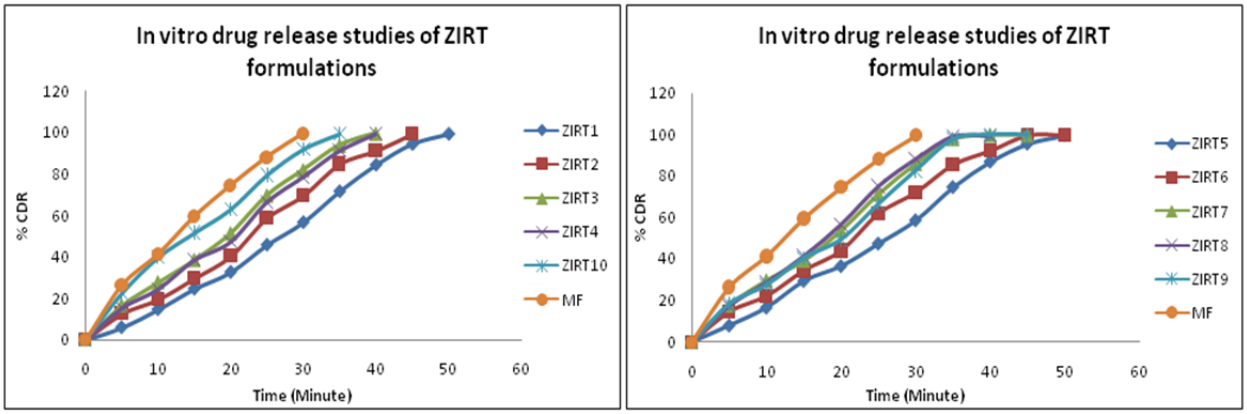


Figure 1: Comparative *in vitro* release studies of all the formulations (ZIRF1-ZIRF10) with marketed formulation

The *in vitro* drug release characteristics of Zolmitriptan immediate release tablets were studied in HCl buffer P^H 1.2 dissolution medium for a period of 45 minutes using USP type-II (paddle type) dissolution apparatus. The rate of dissolution increased by increasing the concentration of superdisintegrant upto an optimum concentration of 6%. The formulation $ZIRF_7$ having 6% of AC-Di-sol released 99.78% of the drug in 35 minute whereas formulation $ZIRF_3$ having 6% of Primojel released 99.54% of the drug in 40 minute When both the superdisintegrants were used in combination in total concentration of 6% it showed some better dissolution profile and released almost all the drug within 35 minute that were noticed in case of formulation $ZIRF_9$ and $ZIRF_{10}$. Formulation $ZIRF_{10}$ having superdisintegrant concentration of 6% (2% AC-Di-Sol™ and 4% Primojel™) release the drug upto 99% within 30 minutes and have shown similar dissolution profile with selected marked formulations. MCC (Avicel 101) was used as diluents as it is having good disintegrating capacity then other diluents so it was used in all the formulations. The dissolution profiles of all the formulations ($ZIRF_1$ to $ZIRF_{10}$) were shown in **figure 1**.

The similarity factors (f_1) and difference factor (f_2) play a very important role in comparing the test formulations release profile with standard marketed formulation. When the two dissolution profiles are identical, the value of f_2 is 100 and when the dissolution of one product (test or reference) is completed before the other begins, f_2 can be rounded to zero. Thus, the value of f_2 ranges from 0 to 100. If a difference between the test and the reference products is 10%, and this average absolute difference is substituted in the equation, f_2 becomes 50. Two dissolution profiles are considered "similar" when the f_2 value is between 50 and 100. A higher f_2 value indicates closeness between the two dissolution profiles. However, the equation is only applicable in comparing curves in which the average differences between the reference and the test formulation profiles is less than 100 and the amount of drug released in percent. The percent error is zero when the test and the drug reference profiles are identical, and increases proportionally with the dissimilarity between the two dissolution profiles. It is generally accepted that values of f_1 between 0 and 15 do not indicate dissimilarity. The dissolution profiles all the batches of prepared immediate release tablets in the present investigation were shown in **table 4**. Among all the formulations, $ZIRF_{10}$ showed highest f_2 value (57.84) and lowest f_1 value (10.72) was considered as best formulation.

Table 4: Similarity (f_2) and difference factor (f_1) with dissolution profile of all formulations ($ZIRF_1$ to $ZIRF_{10}$)

F. No.	f_1	f_2	Dissolution profiles
$ZIRF_1$	53.02	23.34	Dissimilar
$ZIRF_2$	39.73	29.50	Dissimilar
$ZIRF_3$	26.29	38.54	Dissimilar
$ZIRF_4$	28.33	36.94	Dissimilar
$ZIRF_5$	48.18	25.33	Dissimilar
$ZIRF_6$	34.69	32.37	Dissimilar
$ZIRF_7$	23.09	41.08	Dissimilar
$ZIRF_8$	20.58	43.72	Dissimilar
$ZIRF_9$	23.69	40.55	Dissimilar
$ZIRF_{10}$	**10.72**	**57.84**	**Similar**

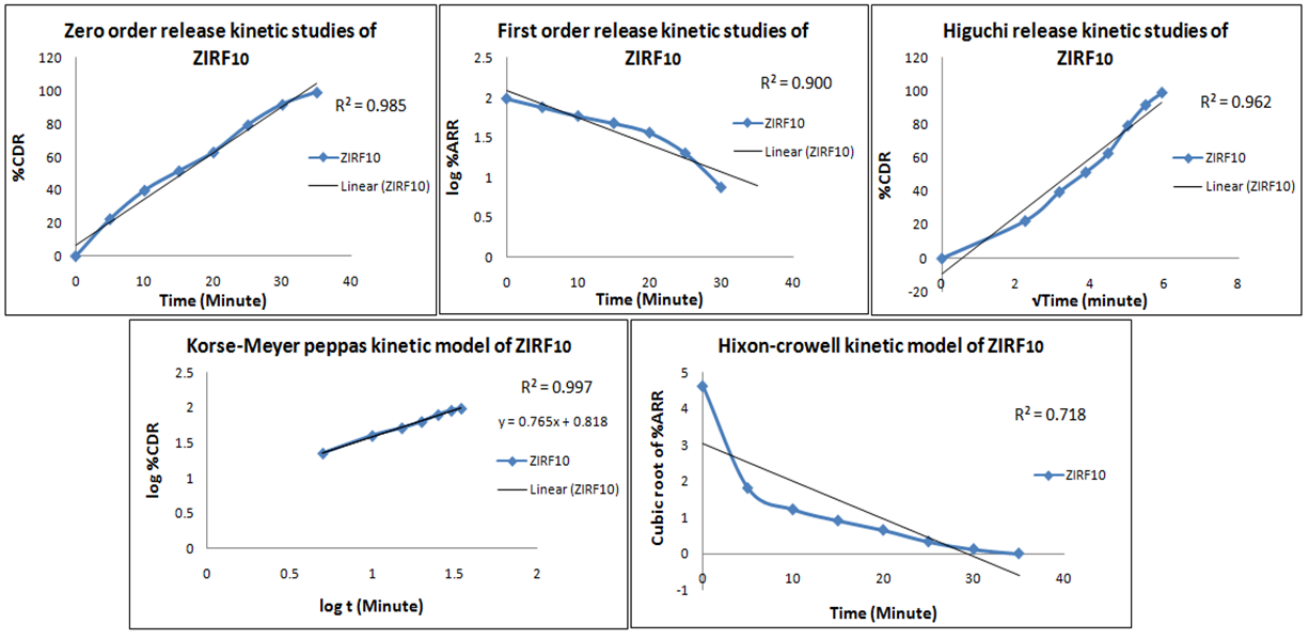


Figure 2: Different kinetic studies of *in vitro* release profile for optimised formulation $ZIRF_{10}$

Table 5: Regression values of *in-vitro* release kinetic study optimized Zolmitriptan immediate release Tablet ($ZIRF_{10}$)

Formulation code	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
$ZIRF_{10}$	0.985	0.900	0.962	0.718	0.997	0.765

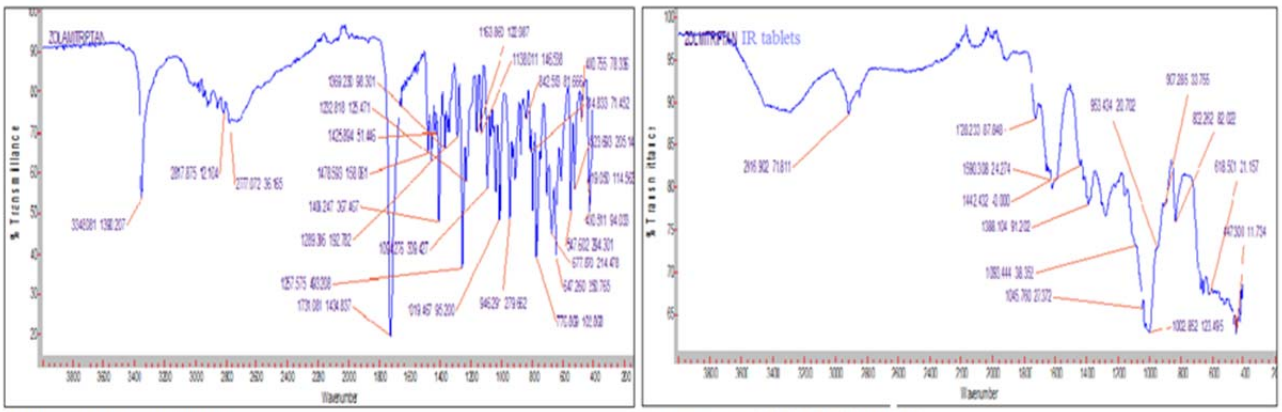
On the basis of highest f_2 and lowest f_1 value, the formulation $ZIRF_{10}$ was chosen for drug release kinetic and mechanism of release studies. The *in vitro* dissolution data of Zolmitriptan immediate release tablets ($ZIRF_{10}$) were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixson-Crowell and Korse Meyer- Peppas equation; and the graphs were plotted **figure 2**. The Korse-Mayer Peppa's kinetic plots were found to be fairly linear as indicated by their highest regression values (0.997) for $ZIRF_{10}$ formulation. The release exponent 'n' for optimised formulation $ZIRF_{10}$ was found to be 0.765 ($0.5 < n < 1$), that 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 Zolmitriptan immediate release tablet followed Peppas release kinetic model and the drug release mechanism was said to be anomalous diffusion coupled with erosion. The regression values of all the release kinetics were presented in the **table 5**.

Compatibility studies by FTIR and DSC:

From the FTIR studies it was found that the spectra of Zolmitriptan exhibits peak due to N-H stretching at 3342.41 cm^{-1}, C = O stretching at 1730.03 cm^{-1}, and C = C stretching at 1650.0 cm^{-1}. These values were complying with the reported values. The FTIR spectra of optimised formulation $ZIRF_{10}$ (Zolmitriptan with all the Excipients) exhibit peak due to N-H stretching at 3332.76 cm^{-1}, C = O stretching at 1735.00 cm^{-1}, and C = C stretching at 1647.10 cm^{-1}. Thus it is evident that all the characteristic peaks that were present in the spectra of pure drugs replicated almost in the same region in the spectra of optimised formulations

of Zolmitriptan immediate release tablet indicating that there is no significant interaction between the drugs and the excipients. The FTIR spectra of pure drug Zolmitriptan and optimised formulations were shown in **figures 3**.

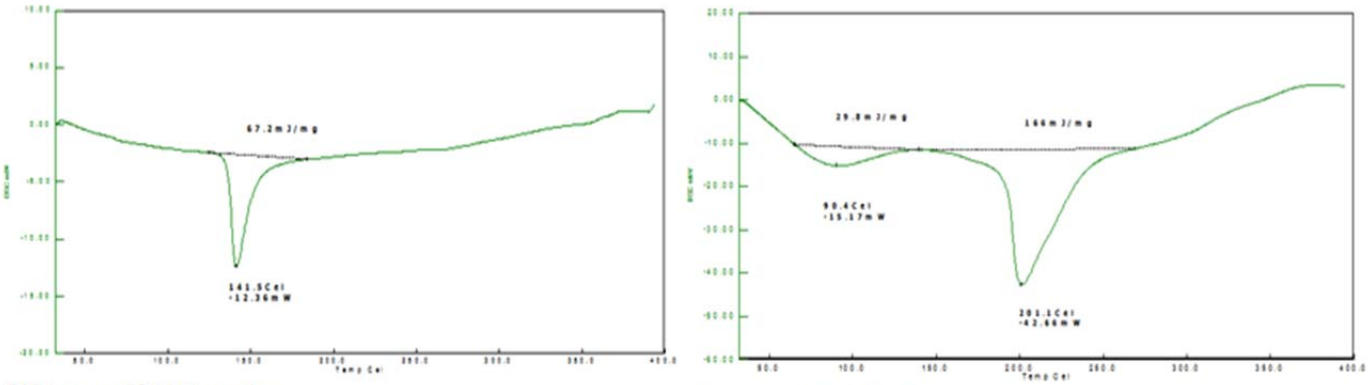
DSC study was conducted for pure drug Zolmitriptan and optimised formulation ($ZIRF_{10}$). DSC thermogram of pure Zolmitriptan shows sharp endothermic peak at 141.5 °C and similar endothermic peaks were obtained at 201.1°C for the optimized Zolmitriptan immediate release tablet formulations. The peaks appeared at higher temperature may be due to presence of other ingredients. The shifting of endothermic peaks to exothermic peaks was not observed in the thermogram of optimised formulation under study. Presence of similar kind of peaks indicated that all ingredients were compatible with Zolmitriptan potassium and there is no incompatibility between the drug and selected ingredients. DSC thermogram of pure drug and optimised formulation are shown in **figure 5**.



FTIR SPECTRA OF ZOLMITRIPTAN

FTIR SPECTRA OF OPTIMISED FORMULATION

Figure 3: Compartibility studies through FTIR analytical technique



DSC thermogram of Zolmitriptan pure drug

DSC thermogram of optimised formulation

Figure 4: Compartibility studies through DSC analytical technique

The optimised formulation ($ZIRF_{10}$) of Zolmitriptan immediate release tablets was selected for accelerated stability studies. The optimised formulation ($ZIRF_{10}$) Zolmitriptan immediate release tablets did not show any significant changes in physicochemical parameters and *in vitro* drug release characteristics. More than 90% of the drug had been retained in the *in vitro* dissolution studies after 90days of exposure to accelerated stress condition. Thus, it was found that the immediate release tablets of Zolmitriptan ($ZIRF_{10}$) were stable under short term accelerated storage conditions for at least 3 months.

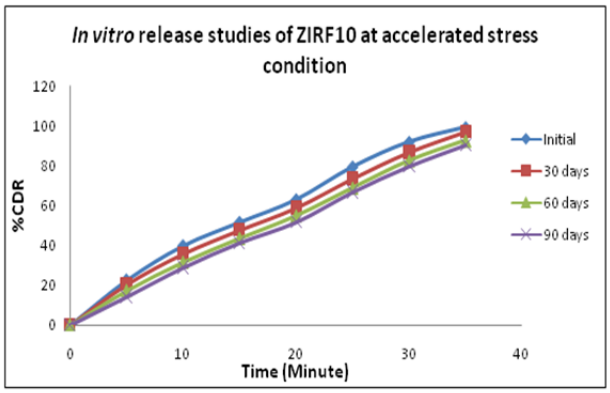


Figure 5: Comparative *in vitro* release profile of optimised formulation at accelerated stressed condition

CONCLUSION

In the present investigation Zolmitriptan immediate release tablets were successfully developed. The major challenge in this work was to study the effect of Primojel and AC-Di-Sol on *in vitro* release rate of immediate release tablet of Zolmitriptan. The immediate release drug delivery system was a promising approach to achieve quick release of drug and beneficial for acute diseases like migraine. FTIR and DSC studies revealed that the drug and excipients were compatible with each other and formulation is thermally stable. Direct compression methods were adopted for the preparation of Zolmitriptan immediate release tablets and the evaluation results of all the precompression parameters for dry blend of drug and excipients were satisfied the acceptance criteria that showed excellent flow properties. All the postcompression parameters like average thickness, hardness, friability, weight variation and disintegration also fall within acceptable limit. Formulation $ZIRF_{10}$ containing 2% of AC-Di-Sol and 4% of Primojel showed complete drug release within 35 minute (>99%) emerging as optimised formulation and using both the superdisintegrant in combination it gave better drug release profile. The formulation $ZIRF_{10}$ had also showed highest similarity factor and lowest difference factor when it was compared with the standard marketed formulation and considered as best formulation in dissolution profile point of view. By increase in superdisintegrant concentration the drug release profile became faster but the hardness and friability of the formulation were severely affected. Kinetic of *in vitro* drug release of optimized formulation $ZIRF_{10}$ found to follow Peppa's kinetic model having highest R^2 value with drug release mechanism as anomalous diffusion coupled with erosion. The stability studies were carried out according to ICH guideline and selected $ZIRF_{10}$ formulation were stable at accelerated stressed condition up to 3 months with a little change in physicochemical as well as drug release characteristics of the formulations. Thus from the results of the current study clearly indicate, a promising potential of the Zolmitriptan immediate release tablets drug delivery system can be used as an alternative to the conventional dosage form because it release the drug quickly and useful for the acute condition of migraine. However, further clinical studies are needed to assess the utility of this system for patients suffering from migraine.

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