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FORMULATION DESIGN AND *IN-VITRO* EVALUATION OF ZOLMITRIPTAN GASTRORETENSIVE FLOATING MATRIX TABLETS FOR MANAGEMENT OF MIGRAINE

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ABSTRACT: Objective: The objective of the present investigation was to formulate and evaluate hydrodynamically balanced floating matrix controlled drug delivery system of Zolmitriptan by increasing its residence time and improves the bioavailability. **Methods:** Twelve different formulations of floating tablets were prepared using direct compression technique with hydrophilic polymers such as HPMC K4M, K15M, K100M and hydrophobic polymer like ethyl cellulose in different ratios. Dry powder blends of all the formulations were evaluated for precompression parameters and all the formulations were evaluated for post compression parameters after compression into tablet. Characterization of the prepared formulation was done by FTIR and DSC analysis. *In-vitro* dissolution studies were carried out for all the formulations and optimised formulation was analysed for kinetic as well as mechanism of drug release. Accelerated stability studies were carried out for the optimised formulation at stressed temperatures/humidity conditions *i.e* 40 ± 2 °C/ 70 ± 5 % RH. **Results:** The evaluation results of precompression and postcompression parameters revealed that all formulations comply with the specification of official pharmacopoeias. From DSC and FTIR studies revealed that there were no interaction between the drug and polymers and formulations were thermally stable. Out of all the formulation developed, formulation F₁₁ containing 25% of HPMC K100M and 12.5% of ethyl cellulose showed optimum *in vitro* drug release upto 99% at the end of 12 h. The formulations that contain more than 12.5% of NaHCO₃ had floating time more than 12h. Kinetic of *in vitro* drug release of optimized formulation F₁₁ found to be zero order having drug release mechanism as anomalous diffusion coupled with erosion. Accelerated stability studies of optimised formulation F₁₁ showed a little change in physicochemical properties as well as drug release profiles at the end of 90 days indicating all the formulations were stable. **Conclusion:** From the above experimental results it was ensured that Zolmitriptan sustained release floating matrix tablet was a successful formulation with several advantages.

INTRODUCTION: Gastroretensive drug delivery systems were designed to prolong the residence time of drug in the GIT. Gastric retention can be prolonged by using floating, mucoadhesive, swelling and high density systems.

These systems release the drug in gastric fluid for prolong period before it reaches its site of absorption and thereby ensures optimal bioavailability of drugs having stability and more solubility in gastric fluids¹. Various approaches have been pursued over the last three decades, to increase the retention of oral dosage forms in the stomach.

The most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include a) co-administration of the DDS with pharmacological agents that slow gastric motility,

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b) bioadhesive systems, c) size increasing systems, which are either due to expansion and shape modification and d) density controlled systems which are either, high density systems or floating systems. Among the above methods used for gastric retention floating systems are most commonly used now-a-days. Floating systems are less dense than that of gastric fluid and so remain buoyant in stomach for extended period of time. While the system is floating over the gastric contents, the drug is slowly released at the desired rate.

This results in an increase in the gastro retention time and decrease in fluctuation in plasma drug concentration. Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are: A. Effervescent System, and B. Non-Effervescent System. Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it float on the gastric fluid. The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract.

The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. Floating matrix tablets are type of sustained release drug delivery system which floats on gastric fluids for longer period of time by generating CO₂ gas or by swelling and release the drug for prolonged period of time. Prolonging of drug release can be achieved by use of various polymers like various grade of HPMC, Eudragit, chitosan, carbopol, guar gum and xanthum gum².

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 is a selective serotonin receptor agonist used in the acute treatment of migraine. 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 3 hours. Zolmitriptan is a white to 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 3 to 4 times in a day³.

MATERIAL AND METHODS:

Materials:

Zolmitriptan was a gift sample from Dr Reddy's laboratories Ltd, Hyderabad. HPMC K4M, HPMC K15M, HPMC K100M, and ethyl cellulose polymers were received as gift sample from Glenmark Pharma, Nasik, India. Talc and magnesium Stearate from S.D. fine chemicals Pvt. Ltd' Mumbai, India. Microcrystal line cellulose was procured from Signet Chemicals. All other ingredients used were of analytical grade and purchased from SD fine chemicals Pvt Ltd, Mumbai, India.

Methods:

Formulation of Zolmitriptan floating matrix tablets:

Zolmitriptan floating matrix tablets were formulated by direct compression method. All the powders passed through 40 mesh sieve. The required quantity of Zolmitriptan, various polymers 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 precompression parameters like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio etc.

The evaluated mixture of powder was directly compressed (8 mm diameter, circular flat faced punches) on a 10 station rotary tablet punching machine (SHAIMAC Technology Pvt. Ltd, Hyderabad, India). Each tablet contained 10 mg of Zolmitriptan. All the tablets were stored in airtight

containers for further study^{4, 5}. The compositions of different excipients used for the formulation of

Zolmitriptan floating matrix tablet were shown in **Table 1**.

TABLE 1: DIFFERENT FORMULATIONS OF ZOLMITRIPTAN FLOATING MATRIX TABLETS

Formulations (mg)	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	F ₁₀	F ₁₁	F ₁₂
Zolmitriptan	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	40	-	-	45	-	-	50	-	-	-	-	-
HPMC K15M	-	40	-	-	45	-	-	50	-	-	-	-
HPMC K100M	-	-	40	-	-	45	-	-	50	50	50	50
Ethyl cellulose	15	15	15	15	15	15	15	15	15	20	25	30
NaHCO ₃	15	15	15	20	20	20	25	25	25	25	25	25
MCC	97	97	97	87	87	87	77	77	77	72	67	62
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Analytical Method for the *in-vitro* Estimation of Zolmitriptan in the formulations:

Scanning: From the stock solution, a suitable concentration (10µg/ml) was prepared with pH 1.2 Hydrochloric acid buffer solutions and UV scan was taken between 200-400 nm. The absorption maxima of 283 nm was selected and utilized for further studies.

Standard Plot: From the stock solution, 5, 10, 15, 20, 25 and 30 µg/ml solutions of Zolmitriptan were prepared in pH 1.2 hydrochloric acid buffer solutions. The absorbance was measured at 283 nm and a graph of concentration versus absorbance was plotted. Standard plot data of Zolmitriptan in pH 1.2 hydrochloric acid buffer solutions is reported⁶.

Evaluation of pre-compression parameters of dry powder blend of all formulations:

Angle of Repose (θ):

This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. The 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 granules formed.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

According to the specifications the angle of repose value less than 25° indicates excellent flow whereas angle between 25°-30° indicates good flow. The angle between 30°-40° indicates passable flow and angle greater than 40° indicates very poor flow^{7,8}.

Bulk density:

Both the loose bulk density (LBD) and tapped bulk density (TBD) were determined. The quantity of 2 gm of powder from each formula, previously lightly shaken to break any agglomerates formed; was 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 2.5 cm at second interval. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas.

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}}$$

Compressibility Index (Carr's index):

The flow ability of powder can be evaluated by comparing the loose bulk density (LBD) and tapped bulk density (TBD) of powder and the rate at which it packed down.

Compressibility index (Carr's index) is calculated by following formula

$$\text{Carr's index (\%)} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

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 fair-passable where as between 23-25 indicates poor. Between 33-38 indicates very poor and greater than 40 indicates extremely poor^{7,8}.

Hausner's ratio:

The Hausner's ratio of prepared Zolmitriptan floating tablets dry powder blends were determined by following formula.

$$\text{Hausner's ratio} = \frac{TBD}{LBD}$$

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^{7,8}.

Content uniformity:

The 200 mg of dry powder blends containing equivalent quantity of 10mg of Zolmitriptan was dissolved in 100ml of P^H 1.2 HCl buffer and heated at 37 °C for 15-20 minutes with stirring. The cooled solution was passed through a Whatmann (no. 1) filter paper and analyzed spectrophotometrically at 283 nm after sufficient dilution with P^H 1.2 HCl buffer⁶.

Evaluation of Zolmitriptan floating matrix tablets:

Thickness:

From each batch ten Zolmitriptan floating tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Caliper (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of ten readings, with standard deviations¹⁰.

Tablet Hardness:

The Zolmitriptan floating tablets hardness was measured by using Monsanto hardness tester. From each batch the crushing strength of ten floating tablets with known weights were recorded in kg/cm² and average was calculated and presented with standard deviation¹¹.

Friability:

Previously weighed 10 tablets from each batch were taken in Roche friabilator (Roche friabilator,

Pharma labs, Ahmedabad, India). After 100 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 formula¹².

Percentage friability = (Initial weight – Final weight)/ Initial weight × 100

Weight variation test:

All formulated Zolmitriptan floating 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 calculated¹⁶.

Content uniformity:

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and dissolved in 100 ml of P^H 1.2 HCl buffer. The solution was filtered, suitably diluted and the Zolmitriptan content was measured by using UV Spectrophotometer (Elico, India) at 283 nm. Each measurement was carried out in triplicate and the average drug content in the floating tablet was calculated^{17,18}.

In Vitro Buoyancy Test:

The prepared floating tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200ml P^H 1.2 HCl buffer (temp. 37±0.50C). The time required for the tablet to rise to the surface for floating was determined as the floating lag time and floating duration of all tablets was determined by visual observation^{10,11}.

In -Vitro Drug Release:

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Lab India DS 8000, Mumbai, India) at 37 ± 0.5°C. The studies were performed with rotation speed of 50 rpm using 900ml dissolution medium of P^H 1.2 HCl buffer. 5ml of the samples were withdrawn at one hour intervals and replaced with an equal volume of buffer. The Zolmitriptan release at different time intervals was measured using an ultraviolet visible spectrophotometer (Analytical Technology Ltd, Spectro 2080) at 283 nm after suitable dilution. The study was performed in triplicate^{25,26}.

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 P^H 1.2 HCl buffer. 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 (Wt). The swelling index (SI) of each tablet was calculated according to the following equation^{10,11}.

$$S.I. = \{(Wt-W_0) / W_0\} \times 100$$

Where W₀ = initial weight, W_t = final weight

Characterization of the drug release profile:

The rate and mechanism of release of Zolmitriptan from prepared floating matrix tablets were analyzed by fitting the dissolution data into following exponential equations²¹.

Zero order release equation:

$$Q = K_0 t$$

Where Q is the amount of drug released at time t and K₀ is the zero order release rate constant.

The first order equation:

$$\ln(100 - Q) = \ln 100 - K_1 t$$

Where, K₁ is the first order release rate constant.

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

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

Where, K₂ 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:

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

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^{21, 22}.

Drug excipients compatibility studies:**FTIR study:**

Fourier transform infrared (FTIR) study was performed to verify any physical or chemical interaction between the pure drug and the polymers. The FTIR studies of pure drug Zolmitriptan, HPMC K100M, ethyl cellulose and optimised formulation (F₁₁) were carried out. It was performed by potassium bromide (KBr) pellet method. The pure drug was triturated with KBr and pellet was prepared by setting the pressure to 100 kg/cm² 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 procedure was repeated for the analysis of drug and individual excipients²⁰.

DSC Studies:

The DSC analysis of Zolmitriptan, HPMC K100M, ethyl cellulose, optimised formulation (F₁₁) 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^oC. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min²².

Stability studies:

The stability studies of optimised formulation (F₁₁) were carried out according to ICH guidelines. The optimized formulation was subjected to stability study at 40 °C ± 2 °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 release study²⁴.

RESULTS AND DISCUSSION:

The loose bulk densities of dry powder blends of all formulations were found to be in the range of 0.209 to 0.292 g/cm³ and the tapped densities were found to be in between 0.291 to 0.390 g/cm³. This indicates good packing capacity of granules. Bulk density and tapped density measurements found that density of a powder depends on particle packing and that density changes as the powder

consolidates. Values of Carr's index below 15% usually show good flow characteristics, but readings above 25% indicate poor flowability. Carr's index was found to be between 13.79 to 31.69 that indicate good to average flow properties.

Formulations F4, F1 and F2 having more 25% Carr's index which indicates pore flow properties and 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 to be between 1.16 to 1.46 that indicates good flow and the formulation

having more than 1.25 requires adding glidant to improve flow properties. Angle of repose is suited for particle > 150 μ m. Values of angle of repose \leq 30 generally indicates the free flowing material and angle of \geq 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 20.97 to 24.27 *i.e.* dry powder blends was of good flow properties. The results of precompression parameters of each formulation were given in **Table 2**.

TABLE 2: EVALUATION PARAMETERS OF DRY BLENDS OF ZOLMITRIPTAN FLOATING MATRIX TABLET POWDERS FORMULATIONS F₁- F₁₂

F. No.	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index	Hausner's ratio	Drug Content (%)
F ₁	0.232±0.04	0.323±0.06	24.19±0.14	28.17	1.39	98.39±0.10
F ₂	0.291±0.05	0.390±0.08	23.38±0.08	25.38	1.34	99.73±0.09
F ₃	0.264±0.02	0.328±0.14	21.91±0.04	19.51	1.24	99.48±0.08
F ₄	0.209±0.06	0.306±0.07	24.27±0.12	31.69	1.46	98.92±0.11
F ₅	0.218±0.07	0.291±0.09	22.53±0.10	25.09	1.33	99.26±0.12
F ₆	0.242±0.06	0.299±0.10	24.72±0.06	19.06	1.23	99.42±0.08
F ₇	0.256±0.04	0.316±0.05	23.44±0.13	18.98	1.23	99.26±0.06
F ₈	0.248±0.08	0.321±0.08	22.73±0.15	22.74	1.29	98.40±0.14
F ₉	0.275±0.10	0.319±0.07	21.62±0.10	13.79	1.16	101.60±0.10
F ₁₀	0.289±0.08	0.341±0.11	20.76±0.11	15.25	1.18	102.62±0.12
F ₁₁	0.284±0.11	0.334±0.06	20.97±0.08	21.33	1.17	99.43±0.13
F ₁₂	0.269±0.05	0.322±0.09	21.84±0.10	16.46	1.20	99.27±0.06

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

The physical parameters of the all the formulations of Zolmitriptan floating matrix tablets were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed.

The physicochemical characterizations of different batches of Zolmitriptan floating tablets are given in **Table 3**.

TABLE 3: EVALUATION OF POST-COMPRESSION PARAMETERS OF ZOLMITRIPTAN FLOATING MATRIX TABLETS FORMULATION F₁- F₁₂

F. No.	Average hardness (kg/cm ²)	Average Weight Variation (mg)	Average friability (% w/w)	Average thickness (mm)	Content uniformity (%)	Floating lag time (sec)	Floating durations (Hour)
F ₁	4.84±0.6	201±1.81	0.49±0.02	3.21±0.12	99.54±1.8	46±0.9	08±0.2
F ₂	4.52±0.2	203±1.12	0.51±0.04	3.28±0.09	100.28±1.7	38±0.8	09±0.4
F ₃	4.79±0.4	202±2.24	0.52±0.03	3.27±0.08	101.83±1.6	39±0.7	08±0.5
F ₄	4.15±0.6	201±2.20	0.65±0.02	3.22±0.10	98.19±1.8	27±0.6	10±0.4
F ₅	4.22±0.5	199±1.81	0.61±0.05	3.24±0.08	99.27±1.5	28±0.8	11±0.5
F ₆	4.21±0.1	202±1.31	0.58±0.06	3.22±0.07	98.39±1.6	25±0.9	10±0.6
F ₇	4.02±0.4	199±2.12	0.73±0.02	3.24±0.11	99.74±1.8	15±1.1	14±0.5
F ₈	4.05±0.5	201±1.61	0.72±0.04	3.23±0.09	101.52±1.7	16±0.5	15±0.4
F ₉	3.98±0.4	202±1.53	0.75±0.03	3.25±0.12	99.68±1.4	12±0.8	13±0.5
F ₁₀	4.07±0.3	198±1.42	0.78±0.05	3.24±0.08	98.09±1.7	10±0.6	14±0.3
F ₁₁	4.68±0.2	202±1.30	0.79±0.04	3.21±0.08	99.64±1.2	10±0.9	15±0.1
F ₁₂	4.11±0.5	201±1.63	0.72±0.06	3.29±0.09	98.91±1.4	12±0.7	14±0.2

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

The thickness of the tablets were ranged between 3.21 ± 0.08 to 3.29 ± 0.09 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 198 ± 1.42 to 203 ± 1.12 mg. 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. The hardness of all the Zolmitriptan floating matrix tablets formulations were ranged from 4.84 ± 0.6 to 3.98 ± 0.4 kg/cm². By increasing the concentration of sodium bicarbonate the hardness usually decreased that noticed in case of formulation F₁₀, F₁₁ and F₁₂. The percentage friability of all the formulations were ranged from $0.49 \pm 0.02\%$ to $0.79 \pm 0.04\%$ and also the % friability were found more by increased concentration of sodium bicarbonate.

In the present study, the percentage friability for all for formulations was within the prescribed limits. The percentages of drug content for F₁ to F₁₂ were

found to be in between 98.09 ± 1.7 to 101.83 ± 1.6 of Zolmitriptan floating matrix tablet formulations which were within the acceptable limits. The results of post compression parameters of each formulation were given in **Table 3**.

Swelling study was performed on all the formulations (F₁ to F₁₂) for 12 hours. The result of swelling index was shown in **Fig 1**. Formulations that contains HPMC K100M polymer showed higher swelling indices as compared with other formulations containing HPMC K4M and HPMC K15M. The direct relationship was observed between swelling index and polymer concentration and type, and as polymer concentration increases in floating matrix tablets, swelling index was found to increase but swelling index were found to be decreased by increasing the concentration of ethyl cellulose. The swelling indexes of all the formulations were plotted with respect to time (hour) in the form of histogram and shown in **Fig. 1**.

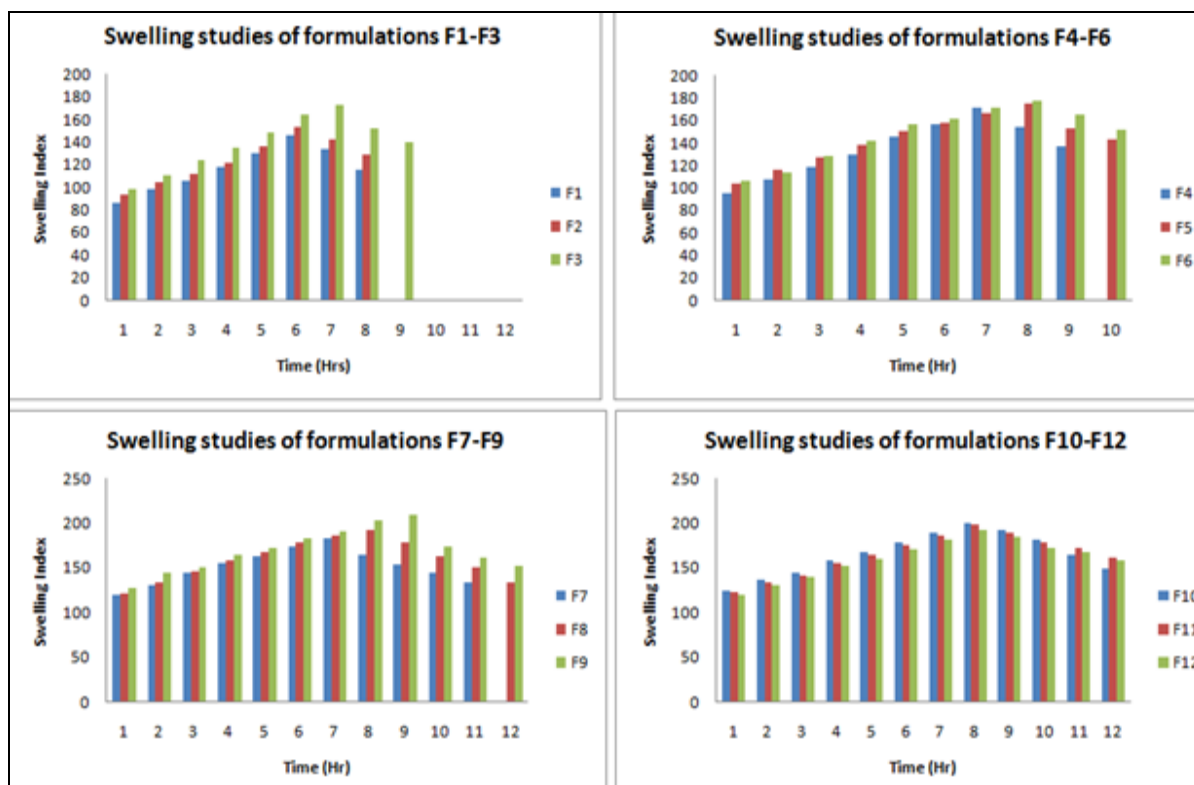


FIG.1: SWELLING STUDIES OF ZOLMITRIPTAN FLOATING MATRIX TABLET FORMULATION F1-F12

All the batches of floating tablets were found to exhibit short floating lag times due to presence of gas generating agent, sodium bicarbonate. The buoyancy properties of various Zolmitriptan

floating matrix tablets were given in **Table 3**. The floating lag time of all formulations was less than 60 seconds and the floating lag time decreased due to increased concentration of sodium bicarbonate.

Floating durations were varied from 8 hours to more than 12 hours. From formulations F7 to F12 which contained 12.5% of sodium bicarbonate showed an optimum floating duration of more than 12 hours.

In order to optimise the *in vitro* drug release of Zolmitriptan floating matrix tablets different hydrophilic matrix polymers *viz.*, HPMC K4M, HPMC K15M, HPMC K100M and hydrophobic matrix polymer *viz.*, ethyl cellulose were used and 12 different formulations were prepared. The drug release profiles of different formulations were shown in **Fig 2**. Between the three grades of HPMC used, HPMC K100M having better controlled release profile than other two grades of HPMC. By increasing the concentration of HPMC the prolong release effect increases and it was found optimum at HPMC polymer concentration of 25%.

It was observed that using HPMC polymer alone causes initial burst release because drug is hydrophilic in nature and maximum release upto 10 hours. So one more hydrophobic polymer *i.e* ethyl cellulose was added to reduce the initial burst release. F₁₁ formulation that contained 25% of HPMC K100M and 12.5% of ethyl cellulose was considered as optimised formulation as the initial release was 10% and maximum release upto 12 hours.

Further increase in the concentration of ethyl cellulose the initial release rate was much slower which was not desirable. So 12.5% of ethyl cellulose was considered as optimum. The plots of cumulative percentage drug release with respect to time for all the formulations were shown in **Fig.2**.

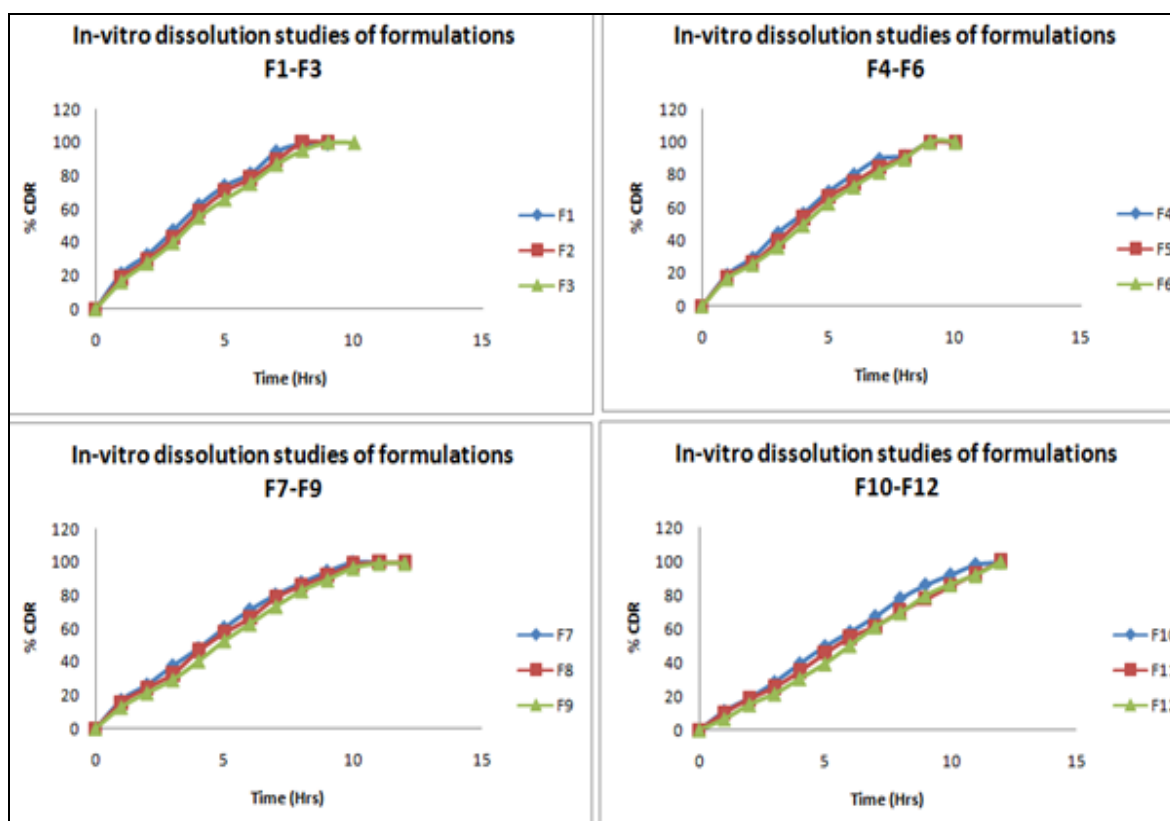


FIG.2: IN VITRO STUDIES OF ZOLMITRIPTAN FLOATING MATRIX TABLET FORMULATION F1-F12

The *in vitro* dissolution data were fitted in different kinetic models *viz.* zero order, first order, Higuchi and Korse Meyer- Peppas equation and the graphs were plotted **Fig.3**. The zero-order plots were found to be fairly linear as indicated by their high regression values for F₁₁ formulation. The release

exponent 'n' for optimised formulation F₁₁ was found to be 0.93 ($0.5 < n < 1$), 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 Zolmitriptan floating matrix tablet followed

Release kinetic followed zero order kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. The comparative regression

values of all the kinetic profiles were shown in **Table 4**.

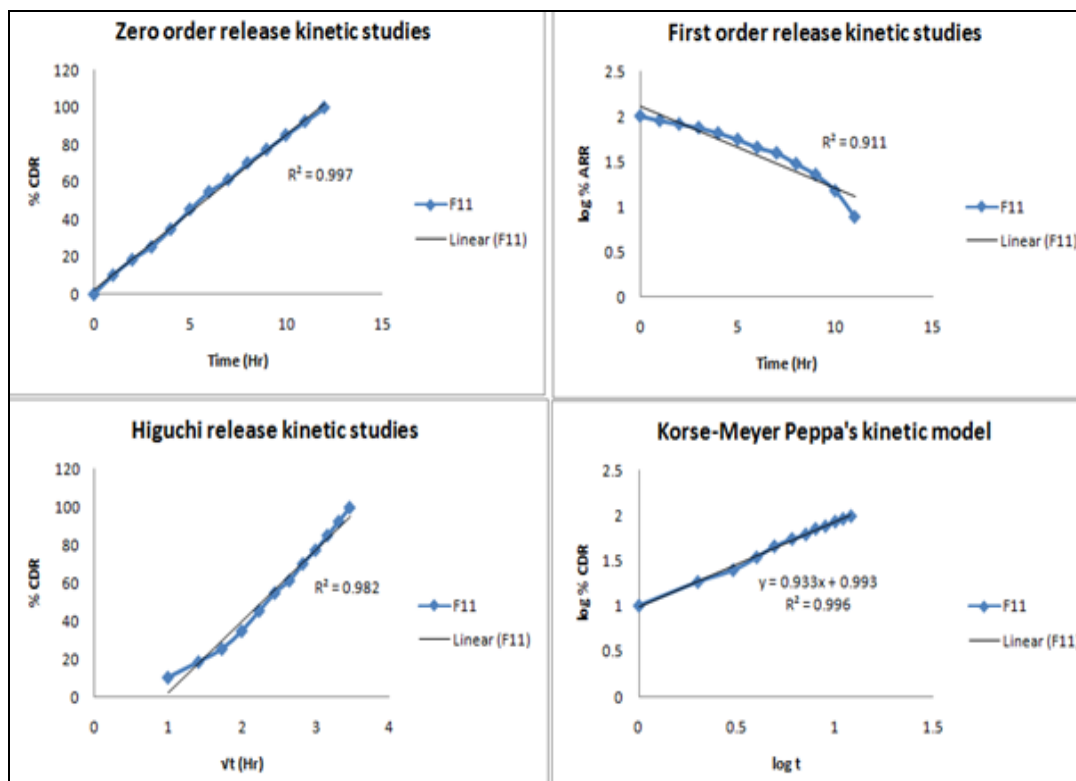


FIG.2: IN VITRO STUDIES OF ZOLMITRIPTAN FLOATING MATRIX TABLET OPTIMISED FORMULATION (F11)

TABLE 4: REGRESSION VALUES OF IN-VITRO RELEASE KINETIC STUDY OPTIMIZED ZOLMITRIPTAN FLOATING MATRIX TABLET (F₁₁)

Formulation	R ² value of Zero order	R ² value of 1 st order	R ² value of Higuchi model	R ² value of Peppas's model	"n" value of Peppas's model
Optimized Zolmitriptan floating matrix Tablet (F ₁₁)	0.997	0.911	0.982	0.996	0.933

The FTIR spectra of Zolmitriptan exhibits peak due to N-H stretching at 3342.41/cm, C = O stretching at 1730.03/cm, and C = C stretching at 1650.0/cm. These values were meeting the reported values. The FTIR spectra of optimised formulation F₁₁ (Zolmitriptan + Excipients) exhibit peak due to N-H stretching at 3332.76/cm, C=O stretching at 1735.00/cm, and C = C stretching at 1647.10/cm.

Thus it is evident that all the characteristic peaks that were present in the spectra of pure drugs replicated in the same region in the spectra of optimised formulations of Zolmitriptan floating matrix tablet indicating that there is no significant interaction between the drugs and the polymers. The FTIR spectra of drug, polymers and optimised formulations were shown in **Fig.4**.

DSC study was conducted on the selected formulations. DSC thermogram of pure Zolmitriptan shows sharp endothermic peak at 141.5 °C. Similar endothermic peaks were obtained at 201.1°C for the optimized Zolmitriptan floating matrix tablet formulations prepared with HPMC K100M, and ethyl cellulose.

The endothermic that appears at 76.4 °C for HPMC K100M and at 102 °C for ethyl cellulose also appears the similar peaks at 94.6 °C in optimised formulation F₁₁. Presence of all peaks indicates that all ingredients are compatible with Zolmitriptan potassium and there is no incompatibility between the selected ingredients. DSC thermogram of optimised formulation, drug and polymers are shown in **Fig. 5**.

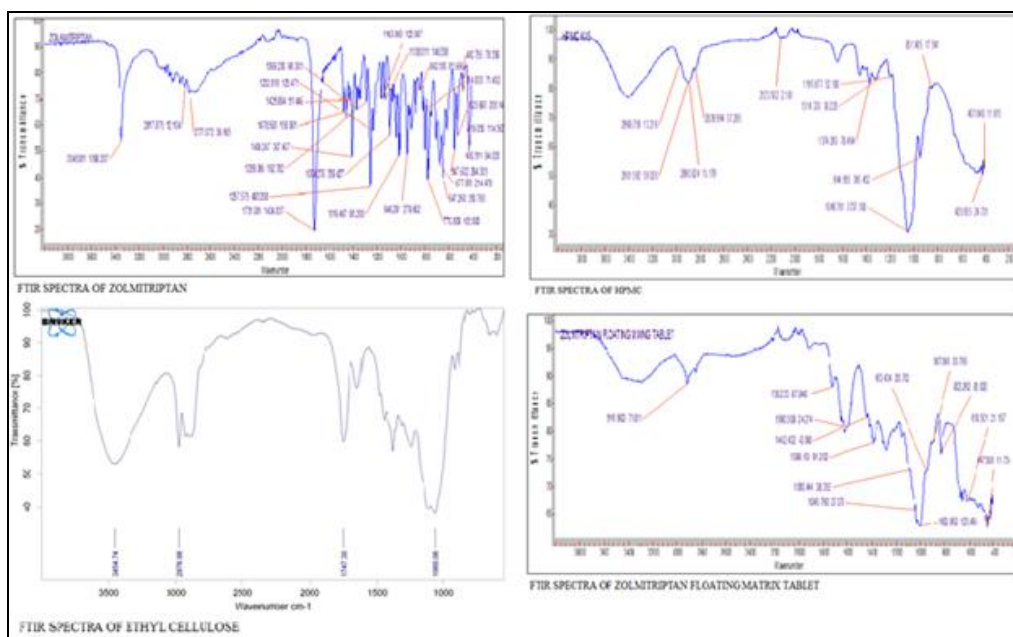


FIG.4: FTIR STUDIES OF PURE DRUG, POLYMER AND OPTIMISED FORMULATION (F11)

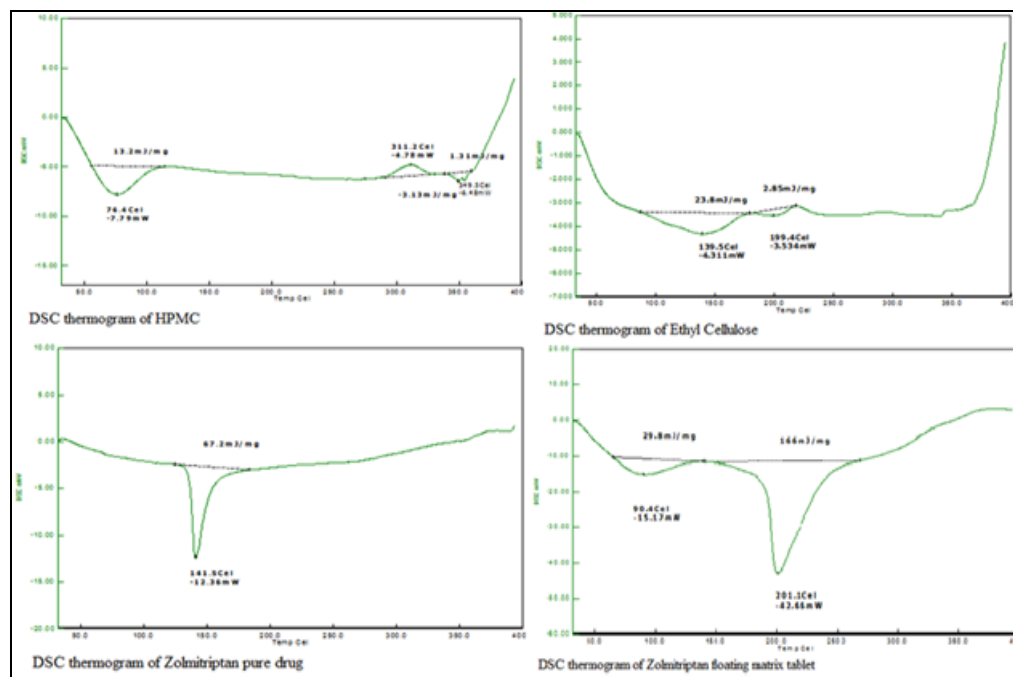


FIG.5: DSC STUDIES OF PURE DRUG, POLYMER AND OPTIMISED FORMULATION (F11)

The optimised formulation F₁₁ was selected for the accelerated stability studies. The results of in-vitro release profile of optimised formulation at different time interval for accelerated stability conditions were shown in **Table 5**. The Zolmitriptan floating matrix tablets did not show any significant change

in physicochemical parameters and *in vitro* drug release characteristics. Thus, it was found that the floating tablets of Zolmitriptan (F₁₁) were stable under short term storage conditions for at least 3 months.

TABLE 5: IN-VITRO RELEASE STUDIES OF OPTIMISED FORMULATION (F₁₁) AT ACCELERATED STABILITY CONDITIONS

Time (Hr)	Initial	15 days	30 days	45 days	60 days	90 days
1	10.27	10.02	09.49	08.64	07.14	04.69
2	18.52	18.14	17.36	16.06	14.52	12.03
3	25.39	25.06	24.15	23.34	22.46	20.14

4	34.83	34.21	33.08	32.43	30.56	27.36
5	45.42	45.20	44.72	43.65	41.19	38.48
6	54.84	54.25	53.31	52.26	50.72	46.82
7	61.35	61.06	60.42	59.10	57.28	54.65
8	70.22	69.56	68.09	66.92	64.52	62.19
9	77.44	76.82	75.19	73.45	71.83	68.61
10	85.17	84.91	83.28	82.04	80.86	77.36
11	92.48	92.04	91.44	90.23	88.74	85.19
12	99.87	99.17	98.23	96.46	94.63	92.38

CONCLUSION: In the present work Zolmitriptan floating matrix tablet were successfully developed. The major challenge in this work was to study the effect of various low density polymers on *in vitro* release rate of floating tablet of Zolmitriptan. The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of drug. Different types of low density matrix forming polymers HPMC K4M, HPMC K15M, HPMC K100M, and Ethyl cellulose were studied. The main objective of using hydrophobic polymer ethyl cellulose with HPMC was to prevent the burst release effect the hydrophilic drug under study with hydrophilic polymer like HPMC which was successfully developed.

The Sodium bicarbonate was added in varying concentrations as a gas generating agent to improve the floating capacity of tablet. Formulation F₁₁ containing 25% of HPMC K100M and 12.5% of ethyl cellulose showed controlled drug release for 12h (99%) emerging as optimised formulation. By increase in polymer concentration of both the polymer the drug release profile were much slower. Kinetic of *in vitro* drug release of optimized formulation F₁₁ found to be zero order having drug release mechanism as anomalous diffusion coupled with erosion.

FTIR studies revealed that there is no chemical interaction between drug and polymers. DSC studies proved that no thermal interaction between the drug Zolmitriptan and polymer used in the present studies. The stability studies were carried out according to ICH guideline and selected F₁₁ formulation were stable at 40 °C ± 2 °C/ 75% ± 5% RH up to 3 months. *In vitro* floating studies were carried out which indicated that gastric residence time could be increased by the floating principle upto 12 hours and was considered desirable for improving bioavailability of the drugs that having more solubility in gastric fluids. Thus from the

results of the current study clearly indicate, a promising potential of the Zolmitriptan floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system for patients suffering from migraine.

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