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## Formulation Design and Evaluation of Controlled Release Zolmitriptan Rapimelts

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### ABSTRACT

**Aim** The purpose of this study was to prepare controlled release Zolmitriptan rapimelts. These rapimelts are in the form of Tablets which were prepared by direct compression.

**Method** Ethyl cellulose polymer is used to prepare micromatrices which further converted to micromatrices. Micromatrices were evaluated for different parameters such as drug content, flow properties, percentage yield, moisture content, taste evaluation and drug release. Based on the drug content and drug release optimized formulation of ethyl cellulose were used to prepare rapimelts. The physicochemical compatibility of the drug with other excipients used in the formulations was studied by FTIR analysis.

**Results** The results obtained showed no physicochemical incompatibility between the drug and other excipients used in the formulations. The prepared Tablets were evaluated for different parameters such as thickness, weight variation, hardness, friability, drug content, disintegration time, water absorption ratio, wetting time, dispersion time and wetting volume. The Tablets were also evaluated for *in vitro* drug release in 0.1N HCl for 24hrs in USP Type II dissolution apparatus.

**Conclusion** In order to determine the mode of release, the data was fitted into various kinetic models and the optimized formulations followed Krosmeier peppas model and Higuchi model respectively and n values less than 0.5 which indicates Fickian diffusion mechanism of drug release.

**Keywords:** Zolmitriptan, Micromatrices, Rapimelts, Controlled release, Ethyl cellulose.

### INTRODUCTION

Oral drug delivery is the most widely utilized route for administration among all the routes that have been explored for systemic delivery of drugs via various pharmaceutical products of different dosage forms. A fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these disciplines involved in the design and optimization of the system [1].

Over a decade, the demand for development of orally disintegrating Tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating Tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia [1] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications [2]. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

Orally disintegrating Tablets are also called as orodispersible Tablets, quick disintegrating Tablets, mouth dissolving Tablets, fast disintegrating Tablets, fast dissolving Tablets, rapid dissolving Tablets, porous Tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently European Pharmacopoeia has used the term orodispersible Tablet for Tablets that disperse readily within 3 min in mouth before swallowing [3].

Zolmitriptan [4, 5] is an oral selective 5-hydroxytryptamine (5-HT) receptor agonist that binds to human recombinant 5-HT and 5-HT receptors. Migraine symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides through nerve endings in the trigeminal system. The therapeutic effects of Zolmitriptan are most likely due to the agonistic effects at the 5-HT raptors on intracranial blood vessels and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release. After Zolmitriptan is absorbed through oral administration, its peak plasma concentrations occur in two hours.

Zolmitriptan is a new Anti Migraine drug. Its higher Solubility in water is 272 mg/ml results in burst effect with sudden peak levels of drug in blood. The half-lives of Zolmitriptan is 3hr. Use of the Zolmitriptan SR formulation may diminish side effects that are related to the rapid rise in the plasma concentrations of Zolmitriptan with immediate release because of slower absorption profile than IR treatment.

Several works has been done on Zolmitriptan to improve its bioavailability since it has high first pass metabolism. Extended release Zolmitriptan capsules were prepared and they improved bio availability, then sustained release wax matrix Tablets were prepared with enhanced bioavailability.

This work includes development of extended release micromatrices which also aids taste masking and further this will be formulated into orally disintegrating Tablets using different superdisintegrants. Thus this dosage form improves the bioavailability as well as improves patient compliance.

These Zolmitriptan Rapimelts initially includes the preparation of micromatrices by Mass Extrusion method, thus gives a novelty where up till now spray drying method and freeze drying methods are used. This method is cost effective and gives a matrix form where drug release can be controlled by polymers and low dose of drug is needed. Later these micromatrices were punched into Tablets using different concentrations of Super disintegrants and in different combinations where the effect of Super disintegrants

can also be studied. Thus Oral Disintegrating tablets of Zolmitriptan with sustained release of drug can be obtained.

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## MATERIALS AND METHODS:

### Materials

Zolmitriptan obtained as a gift sample from Aurobindo Pharmaceuticals, Hyderabad. Ethyl cellulose, Magnesium stearate, microcrystalline cellulose, And Colloidal Silicon Dioxide were purchased from S.D. Fine chemical Pvt Ltd, Mumbai. Crosscarmellose sodium, Sodium starch glycolate and Cross Povidone obtained as a gift sample from Aurobindo Pharmaceuticals, Hyderabad. The remaining chemicals and reagents used are of analytical grade.

### Methods

#### Preformulation studies

Before formulation of drug substances into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

#### Calibration curve of Zolmitriptan in distilled water

The stock solution of Zolmitriptan was freshly prepared by dissolving 100mg of Zolmitriptan in few ml of distilled water (5ml) in a 100ml volumetric flask and then make up the solution upto the mark using distilled water for obtaining the solution of strength 1000µg/ml (stock I). 1ml of this solution is diluted to 100ml with distilled water to obtain a solution of strength 10µg/ml (stock II). From this secondary stock 1, 2, 3, 4, 5, 6, 8, and 10 ml were taken separately in 10ml volumetric flasks and made up to 10ml with distilled water, to produce 1, 2, 3, 4,5, 6, 8, and 10µg/ml respectively. The absorbance was measured at 228nm using a UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight line equation was generated to facilitate the calculation of amount of drug. This procedure is repeated 3 times and the average value will be taken into consideration.

#### Calibration curve of Zolmitriptan in phosphate buffer of pH 6.8

The stock solution of Zolmitriptan was freshly prepared by dissolving 100mg of Zolmitriptan in few ml of phosphate buffer pH 6.8 (5ml) in a 100ml volumetric flask and then make up the solution upto the mark using distilled water for obtaining the solution

of strength 1000µg/ml (stock I). 1ml of this solution is diluted to 100ml with of phosphate buffer pH 6.8 to obtain a solution of strength 10µg/ml (stock II). From this secondary stock 1, 2, 3, 4, 5, 6, 8, and 10ml, were taken separately in 10 ml volumetric flasks and made up to 10ml with of phosphate buffer pH 6.8, to produce 1, 2, 3, 4, 5, 6, 8, and 10µg/ml respectively. The absorbance was measured at 228nm using a UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug. This procedure is repeated 3 times and the average value will be taken into consideration.

#### **Calibration curve of Zolmitriptan in 0.1 N HCl**

The stock solution of Zolmitriptan was freshly prepared by dissolving 100 mg of Zolmitriptan in few ml of 0.1 N HCl(5ml) in a 100ml volumetric flask and then make up the solution upto the mark using distilled water for obtaining the solution of strength 1000µg/ml (stock I). 1ml of this solution is diluted to 100ml with of 0.1 N HCl to obtain a solution of strength 10 µg/ml (stock II). From this secondary stock 1, 2, 3, 4, 5, 6, 8, and 10ml, was taken separately in a 10 ml volumetric flask and made up to 10ml with of 0.1 N HCl, to produce 1, 2, 3, 4, 5, 6, 8, and 10µg/ml respectively. The absorbance was measured at 228nm using a UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug. This procedure is repeated 3 times and the average value will be taken into consideration.

#### **Fourier transform infrared spectrophotometry (FTIR)**

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

#### **Differential Scanning Calorimeter (DSC) studies**

The DSC is performed to check for any interaction between excipients and drug; and to find the effect of temperature and compression forces. DSC is a thermo analytical technique in which the difference in amount of heat required to increase the temperature of sample and reference are measured as function of temperature. Both sample and reference are maintained at same

temperature throughout the experiment. Samples are placed in aluminium pans and thematically sealed. The heating rate was 10<sup>0</sup>C/min using nitrogen as perge gas. The DSC instrument was calibrated for temperature using Indium. In addition for the enthalpy calibration Indium was sealed in Aluminium pans with sealed empty pan as reference.

#### **Formulation [6]**

##### **Preparation of micromatrices**

Slightly modified procedure for extrusion was followed. The weighed polymer i.e., ethyl cellulose and the drug in the ratios mentioned in Table 1 are taken in a motor and triturated to get a uniform mass. To the above mixture isopropyl alcohol (wetting agent) was added drop wise to form an extrudable mass. This mass was extruded using an extruder. These extrudates were cut into minimatrices using a sterile blade. These minimatrices were dried in a desiccator overnight. The dried minimatrices were further reduced the size to micromatrices. The composition of micromatrices is shown in Table No.1.

**Table No 1: Composition of Formulations of Zolmitriptan micromatrices**

<b>Formulation Code</b>	<b>Drug : Polymer</b>
<b>FEC1</b>	1:1
<b>FEC2</b>	1:2
<b>FEC3</b>	1:3
<b>FEC4</b>	1:4
<b>FEC5</b>	1:5
<b>FEC6</b>	1:6

##### **Preparation of Zolmitriptan rapimelts**

Tablets containing 5mg of Zolmitriptan were prepared by direct compression method and the various formulae used in the study are shown in Table No.2. The drug, diluents and superdisintegrants were passed through sieve # 40. Accurately weighed quantities of the above ingredients were taken in a mortar and mixed geometrically. Aerosil and magnesium stearate and Micro crystalline cellulose were passed through sieve, mixed and blended with initial mixture in a poly-bag. The powder blend was compressed into Tablets on a multiple station rotary punch tableting machine using 8mm concave punch.

#### **Evaluation**

##### **Evaluation of micromatrices [7-12]**

Micromatrices were evaluated for the parameters like drug content, moisture content and *In vitro* release study.

Table No 2: Composition of micromatrices blend of various formulations of rapimelts

Ingredients	EC1	EC2	EC3	EC4	EC5
<b>Micromatrices (drug equivalent to 5mg)</b>	22.5	22.5	22.5	22.5	22.5
<b>Sodium Starch Glycolate (mg)</b>	-	-	4	2	2
<b>Croscarmellose sodium (mg)</b>	-	4	-	-	2
<b>Cross Povidone (mg)</b>	4	-	-	2	-
<b>Colloidal silicon dioxide (mg)</b>	2	2	2	2	2
<b>Mg. Stearate (mg)</b>	8	8	8	8	8
<b>Microcrystalline cellulose (mg)</b>	63.5	63.5	63.5	63.5	63.5
<b>Total weight (mg)</b>	100	100	100	100	100

**Drug content**

Micromatrices of drug equivalent to 5mg were weighed and dissolved in minimum amount of methanol. This solution is filtered and the filtrate is taken in a 100ml volumetric flask and made up the volume with distilled water. This solution was analyzed for Zolmitriptan content by measuring absorbance at 228nm.

**Moisture content**

Moisture was determined by loss on drying. Micromatrices were dried at ambient temperature by keeping 1000mg of microspheres in desiccators until a constant weight was achieved. The % moisture content was calculated using the following formula.

$$\% \text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 10$$

**In vitro Drug release study**

The drug release was studied using USP type II apparatus at  $37 \pm 0.5^\circ\text{C}$  and at 50rpm using 900ml of 0.1 N HCl as dissolution medium. 1ml of the sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically at 228nm. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved was calculated.

**Characterization of micromatrices blend [13-17]**

The quality of Tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested are as given below:

**Angle of repose**

The frictional force in a loose powder can be measured by the angle of repose ( $\theta$ ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle  $\theta$ , is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose ( $\theta$ ) was calculated using the following formula:

$$\tan \theta = \frac{\text{Height of the pile}}{\text{radius of the base of the pile}}$$

where  $\theta = \tan^{-1} (h / r)$   $\theta$  = angle of repose

**Bulk density**

Density is defined as weight per unit volume. Bulk

density,  $\rho_b$ , is defined as the mass of the powder divided by the bulk volume and is expressed as  $\text{gm}/\text{cm}^3$ . The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 15 g powder blend introduced into a dry 100 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled

apparent volume was read. The bulk density was calculated using the following formula.

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Apparent volume of powder}}$$

#### **Tapped density**

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped 500 times initially followed by an additional taps of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, tapped density was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the following formula.

$$\text{tapped density} = \frac{\text{Weight of sample}}{\text{tapped volume of powder}}$$

#### **Carr's index (%)**

The compressibility index (Carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the carr's index which is calculated using the following formulas:

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

#### **Hausner's ratio**

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

#### **Evaluation of Zolmitriptan rapimelts [18-25]**

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Following parameters were evaluated:

#### **Tablet thickness**

The thickness in millimeters (mm) was measured individually for 10 pre weighed Tablets by using micrometer (screw gauge). The average thickness and standard deviation were reported.

#### **Weight variation**

Twenty Tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of three batches were calculated. It passes the test for weight variation, if not more than two of the individual Tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

#### **Tablet hardness**

Hardness of Tablet is defined as the force applied across the diameter of the Tablet in order to break the Tablet. The resistance of the Tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of 6 Tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

#### **Friability**

The friability values of the Tablets were determined using a Roche-type friabilator. Accurately weighed six Tablets were placed in Roche friabilator and rotated at 25rpm for 4 min. The Tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original Tablets. Percentage friability was calculated using the following equation.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

#### **In Vitro Disintegration test**

The disintegration time was measured using disintegration apparatus. One Tablet was placed in each tube of the basket. The basket with bottom surface made of a stainless steel screen (mesh no. 10) was immersed in water bath at  $37 \pm 2^{\circ}\text{C}$ . The time required for complete disintegration of the Tablet in each tube was determined using stop watch. The range is 30sec to 1min.

#### **Dispersion time and uniformity of dispersion**

Modified method for dispersion time and uniformity of dispersion was used. To a shaft a screen of #20 mesh size was attached where the Tablet was hold. This was placed in a beaker containing 100 ml of water and stirred gently. The time required for complete dispersion of the Tablet was noted. Absence of any of the particles in the mesh indicates uniformity of the dispersion.

#### **Wetting time**

A piece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of buffer solution simulating saliva, pH 6.8 in which eosin (water soluble dye) was dissolved. The dye solution was used to identify the complete wetting of the Tablet surface. A Tablet was carefully placed on the paper at room temperature and the time taken for the complete wetting was noted. Three Tablets from each formulation were randomly selected and the average wetting time was calculated.

#### **Water absorption ratio**

A piece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of buffer solution simulating saliva, pH 6.8 in which eosin (water soluble dye) was dissolved. The dye solution was used to identify the complete wetting of the Tablet surface. A Tablet was weighed and was carefully placed on the paper at room temperature ( $W_b$ ). The wetted Tablet was reweighed ( $W_a$ ). Water absorption ratio, R, was then determined according to the following equation

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where  $W_a$  and  $W_b$  are the weights before and after water absorption, respectively.

#### **Drug content**

Ten Tablets were weighed from each formulation, powdered and equivalent to 5mg of Zolmitriptan were weighed and dissolved in sufficient quantity of methanol and filtered. The filtrate was made up to a volume of 100 ml with 0.1 N HCl. The solutions were suitably diluted with buffer 0.1 N HCl and the content of was estimated spectrophotometrically at 228nm 0.1N HCl buffer as a blank.

#### **In vitro Drug release study**

The drug release was studied using USP type II apparatus at  $37 \pm 0.5^\circ\text{C}$  and at 50rpm using the pH of

the dissolution medium was kept at 1.2 for 2 h with 0.1NHCl. Then, 1.7 g of  $\text{KH}_2\text{PO}_4$  and 2.225 g of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  were added, adjusting the pH to 6.8 with 1.0M NaOH. The release rate analysis was done. 1ml of the sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved was calculated.

#### **Model fitting for drug release kinetics [26-30]**

Drug release kinetics can be analyzed by various

mathematical models, which are applied considering the amounts of drug released from 0 to 24hrs. Following equations presents the models tested. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined. The following plots were made: cumulative % drug release versus time (zero order kinetic model); log cumulative % drug remaining versus time (first order kinetic model); cumulative % drug release versus square root of time (Higuchi model).

#### **Zero order kinetics**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$Q = Q_0 + k \cdot t$$

Where Q is the amount of drug dissolved in time t,  $Q_0$  is the initial amount of drug in the solution (most times,  $Q_0 = 50$ ) and K is the zero order release constant.

#### **First order kinetics**

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in a theoretical basis. The following relation can also express this model:

$$\ln Q_t = \ln Q_0 - k_1 t$$

Where  $Q_t$  is the amount of drug released in time t,  $Q_0$  is the initial amount of drug in the solution and K is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

#### **Higuchi model**

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. In a general way it is possible to resume the Higuchi model to the following expression:

$$Q_t = K H t^{1/2}$$

Where  $Q_t$  is amount of drug released in time  $t$  and  $KH$  is release rate constants. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems (Costa et al., 1996) and matrix Tablets with water soluble drugs.

### Korsmeyer–Peppas model

Korsmeyer et al. (1983) developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time ( $t$ ). An equation that can be described in the following manner:

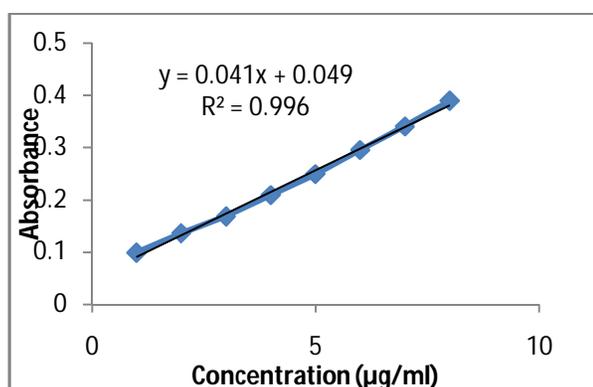
$$M_t / M_\infty = at^n$$

where  $a$  is a constant incorporating structural and geometric characteristics of the drug dosage form,  $n$  is the release exponent, indicative of the drug release mechanism, and the function of  $t$  is  $M / M_\infty$  (fractional release of drug). Peppas (1985) used this  $n$  value in order to characterize different release mechanisms, concluding for values for a slab, of  $n = 0.5$  for Fick diffusion and higher values of  $n$ , between 0.5 and 1.0, or  $n = 1.0$ , for mass transfer following a non-Fickian model.

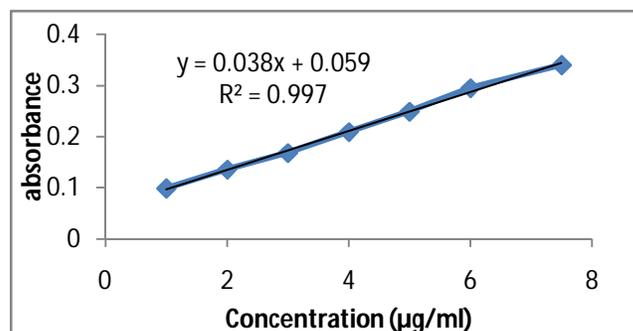
## RESULTS AND DISCUSSION

### Calibration curves of Zolmitriptan in different media

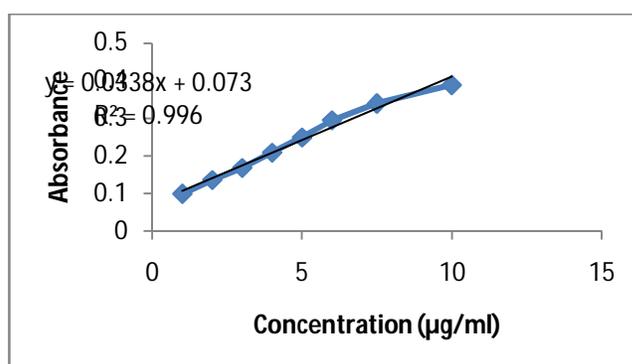
Standard graph of Zolmitriptan in different media was plotted by taking concentration ranging from 1 to 10  $\mu\text{g/ml}$ . the standard graphs were shown in Fig. no 1, 2 and 3.



**Fig No.1: Calibration graph of Zolmitriptan in Distilled water**



**Fig No.2: Calibration graph of Zolmitriptan PBS pH 6.8**



**Fig No.3: Calibration graph of Zolmitriptan in 0.1N HCl**

### Fourier Transform Infrared Spectrophotometry

The spectra for pure Zolmitriptan and for the physical mixture of Zolmitriptan and all the polymers were determined to check the intactness of the drug in the polymer mixture using FTIR Spectrophotometer by disc method.

1469.76-Alkane(C-H bending), 939.33-Aromatic ring, 3325.75- O-H stretching, 1149.57- Secondary amine, 1750.93-Cyclic C=O. By observing the IR spectra of pure drug and the all physical mixtures of drug and polymers, it was found that none of the above mentioned groups were affected by those polymers. Thus it can be said that there was no interaction between the drug and any of the polymers. The FTIR spectra's of pure drug and physical mixture of drug and excipients are shown in figure numbers 4-8. The FTIR interpretation data were shown in Table no. 3

### Comparative DSC studies of Zolmitriptan with mixture of Polymers

The DSC thermogram of pure Drug Zolmitriptan showed characteristic endothermic peak at 138.48°C

Table No.3: Comparative FTIR Interpretation of Zolmitriptan with Excipients

S.No	Characteristic bands	Standard wave no. range	Pure drug	EC	SSG	CCS	CP
1	Alkane (C-H bending)	1480-1375	1469.76	1469.76	1408.04	1465.90	1463.97
2	Aromatic ring	950-730	939.33	873.75	858.32	777.31	914.26
3	O-H stretching	3560-3200	3325.75	3330.35	3348.42	3348.42	3350.35
4	Secondary amine	1350-1000	1149.57	1259.52	1149.57	1149.57	1166.93
5	Cyclic C=O	1870-1650	1750.93	1745.93	1735.93	1748.36	1749.27

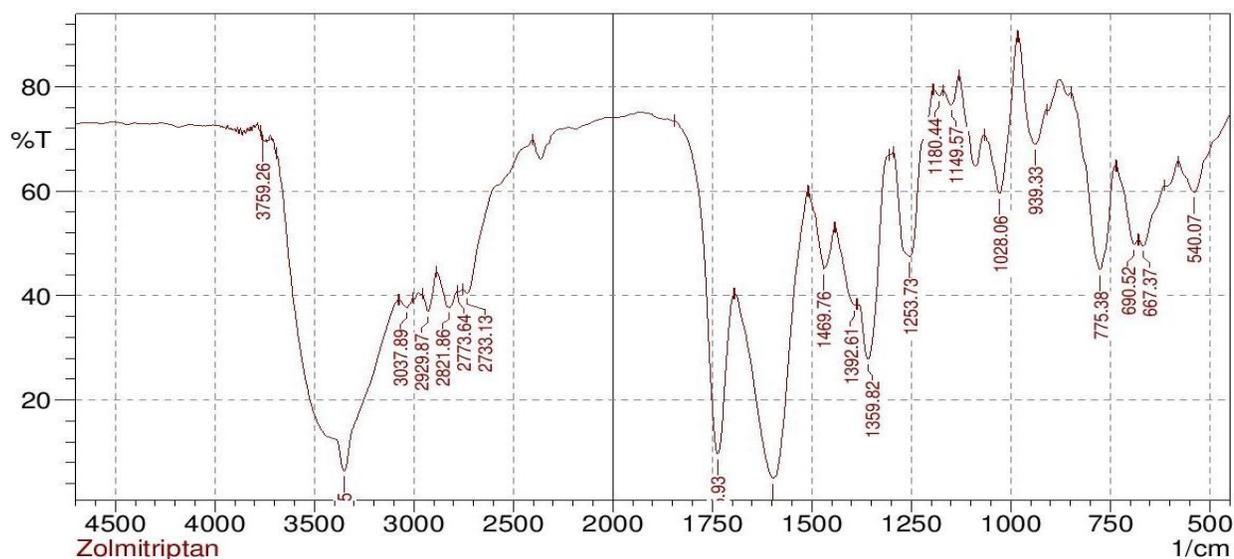


Fig No.4: FTIR spectra of Zolmitriptan

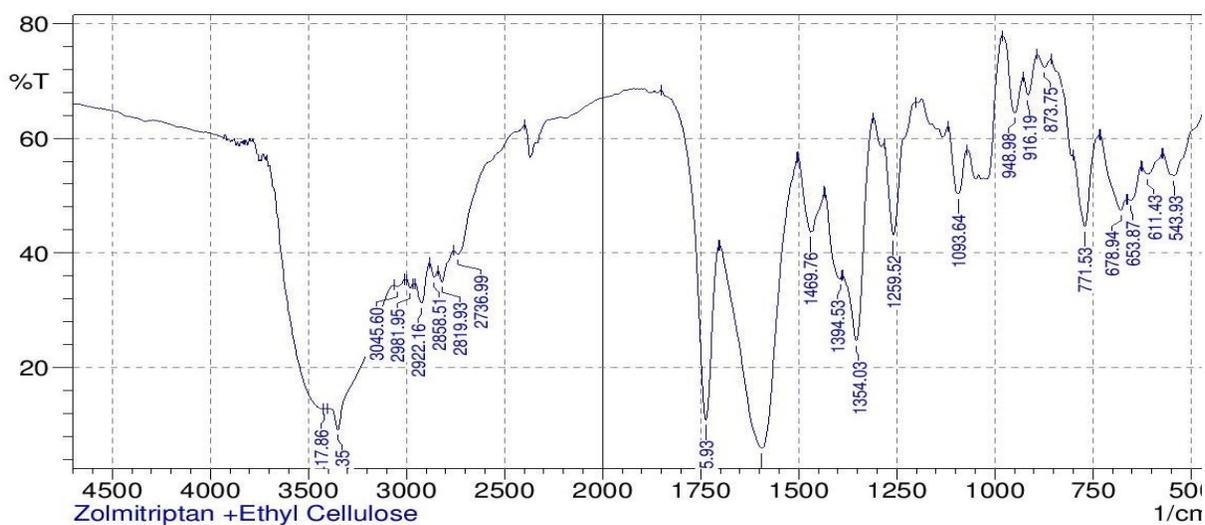
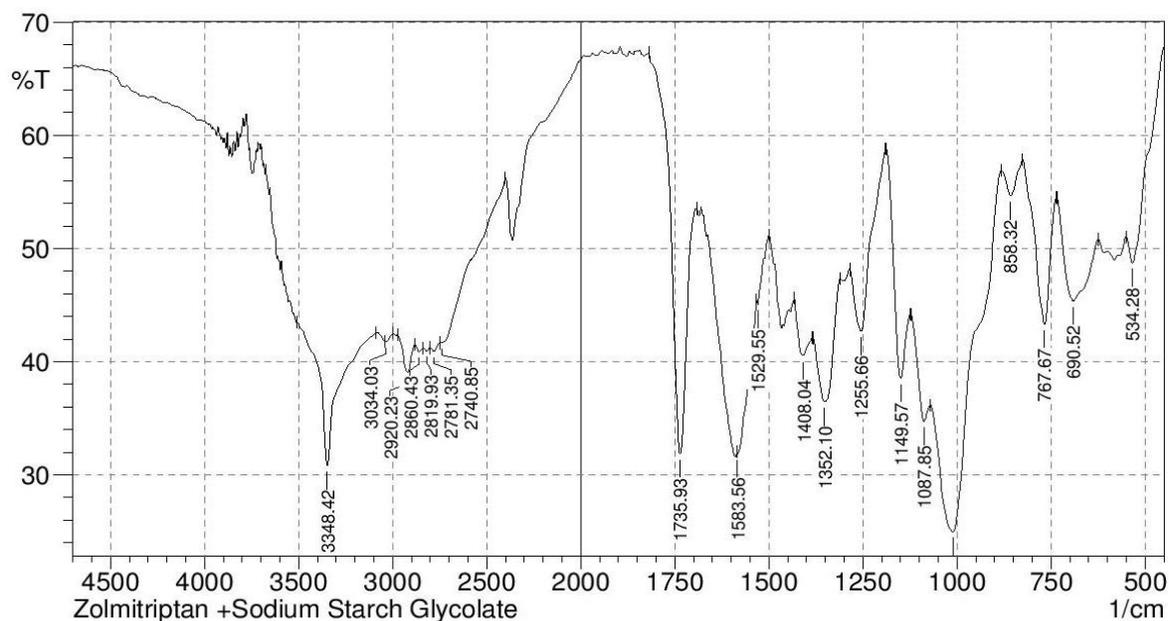
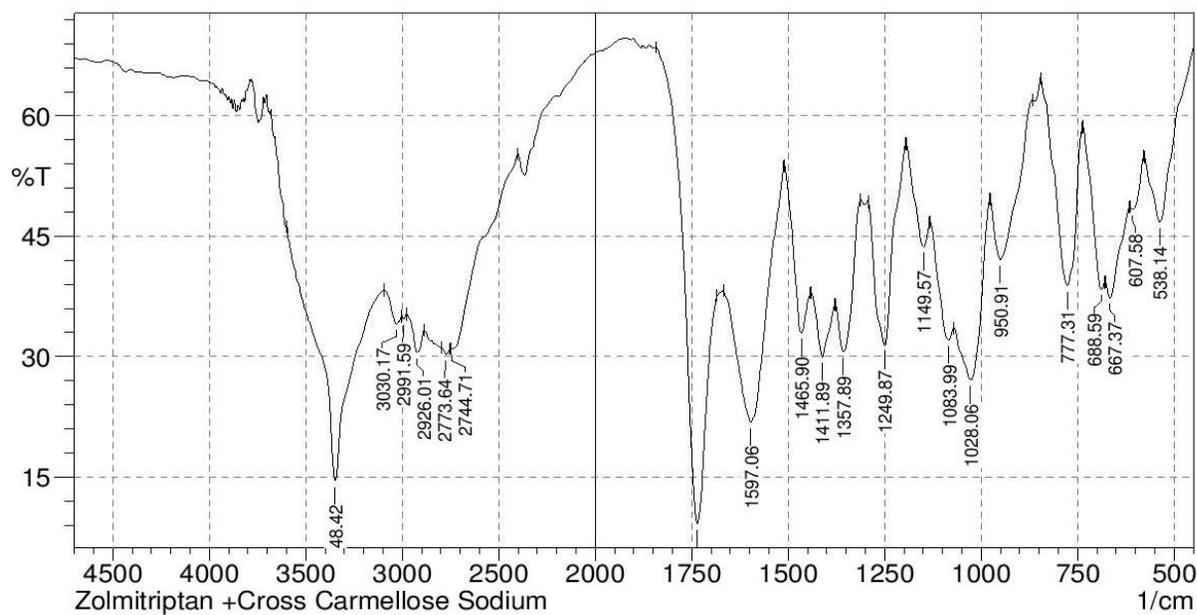


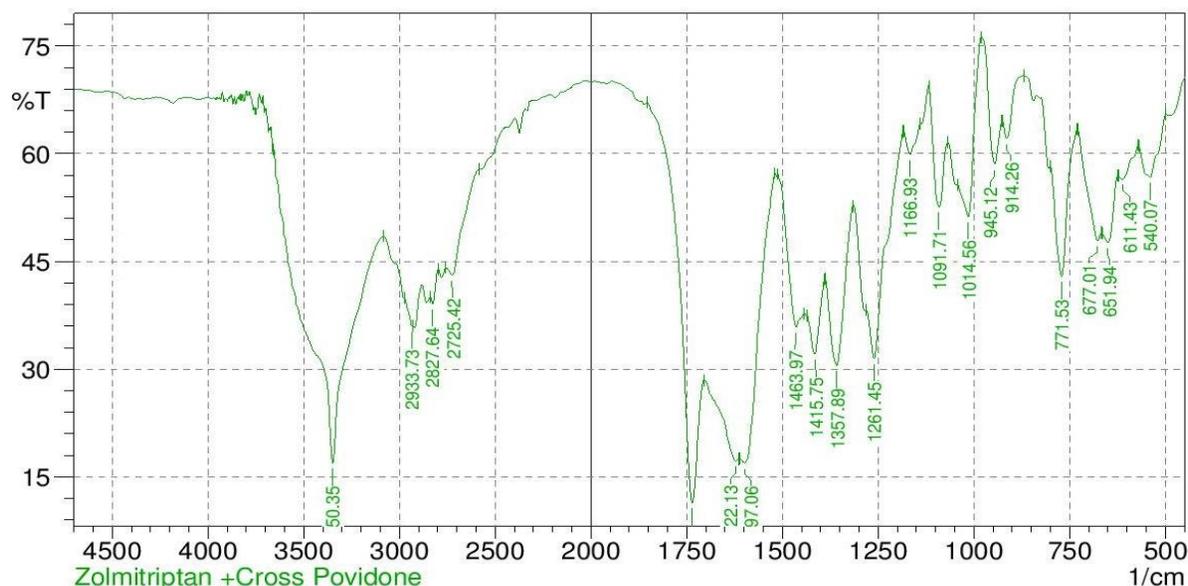
Fig No.5: FTIR spectra of Zolmitriptan with Ethyl Cellulose



**Fig No.6: FTIR spectra of Zolmitriptan with Sodium Starch Glycolate**



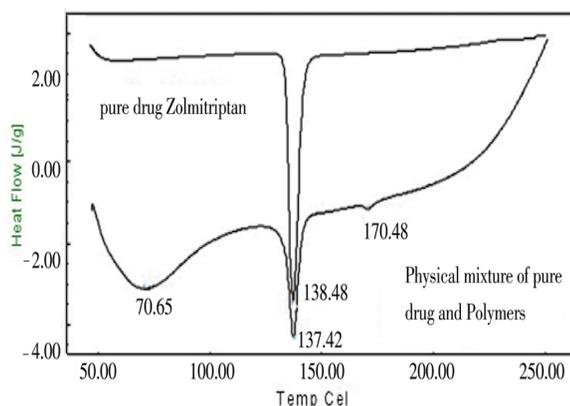
**Fig No.7: FTIR spectra of Zolmitriptan with Crosscarmellose Sodium**



**Fig No.8: FTIR spectra of Zolmitriptan with Cross Povidone**

indicating melting point of pure Drug. The DCS is performed to check for any interaction between excipients and Drug. It also finds the effect of temperature and compression forces.

From the thermogram (Fig. no 9), the endothermic peak of drug with mixture of polymers is obtained at 137.42°C. The melting point of pure drug ranges from 136°C -141°C. Thus there exists a negligible difference and is within the range. Therefore it implies good compatibility and physical stability of the drug with polymers and there is no effect of temperature and compression forces on Drug stability.



**Fig No.9: Comparative DSC studies of Zolmitriptan with mixture of Polymers**

#### Evaluation of micromatrices:

##### Flow properties:

Bulk density of all formulations was in the range of 0.48gm/cc to 0.54gm/cc. Tapped density of all formulations was in the range of 0.52gm/cc to 0.56gm/cc. Carr's index of all the formulations of micromatrices made with ethyl cellulose were between 2.10% and 4.14% respectively, which indicates the flow properties of the micromatrices of all formulations are excellent. Hausner's Ratio of all the formulations of micromatrices made with ethyl cellulose were between 1.02 and 1.10 respectively which indicates the flow properties of the micromatrices of all formulations are excellent. The micromatrices made with ethyl cellulose had an angle of repose ranging from 26.05 to 27.27 indicates that all of the micromatrices made with ethyl cellulose had excellent flow properties. The results were depicted in Table no. 4.

#### Evaluation of micromatrices

##### Drug content

Drug content of micromatrices formulations made of ethyl cellulose were in the range of 91.55 to 96.52% out of which FEC4 had shown comparatively least drug content and FEC2 had shown comparatively highest drug content. The other formulations FEC1, FEC3, FEC5 and FEC6 having  $95 \pm 0.01\%$ ,  $93.935 \pm$

Table No. 4: Flow properties of Micromatrices

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio	Angle of repose
FEC1	0.53±0.01	0.55±0.01	2.81±0.05	1.02±0.05	26.05±0.47
FEC2	0.53±0.09	0.54±0.010	2.53±0.04	1.02±0.04	26.36±0.50
FEC3	0.54±0.08	0.55±0.008	2.10±0.03	1.02±0.03	27.37±0.33
FEC4	0.53±0.08	0.54±0.008	2.19±0.03	1.02±0.03	27.27±0.21
FEC5	0.48±0.03	0.52±0.004	4.14±0.073	1.10±0.08	26.19±0.57
FEC6	0.54±0.04	0.56±0.004	3.02±0.69	1.03±0.01	25.21±0.53

n=3±S.D (All the values are average of three determinations)

Table No.5: Evaluation of Micromatrices for drug content and moisture content

Formulation code	Drug content (%)	Moisture Content (%)
FEC1	95 ± 0.01	0.40%±0.002%
FEC2	96.52 ± 0.2	0.10%±0.003%
FEC3	93.935 ± 0.07	0.20%±0.004%
FEC4	91.55 ± 0.14	0.50%±0.001%
FEC5	94.385 ± 0.09	0.70%±0.005%
FEC6	92.61 ± 0.21	0.30%±0.003%

n=3±S.D (All the values are average of three determinations)

0.07% 94.385 ± 0.09%, and 92.61 ± 0.21% respectively. Drug content of Micromatrices formulations made of Ethyl Cellulose (FEC) was tabulated in Table No.5.

#### Moisture content

All the formulations had moisture content less than 1% indicating that they can be used in direct compression process of production of rapimelts. Moisture content of Micromatrices formulations made of Ethyl Cellulose (FEC) is reported in Table No.5.

#### In vitro drug release study

Dissolution studies were conducted for a period of 24 hours using USP dissolution apparatus II at an rpm of 50 and at a temperature of 37± 2° C and 900ml dissolution medium of 0.1 N HCl. Cumulative % drug release of micromatrices formulations made of ethyl cellulose after 24 hour time interval was found to be FEC1 had 89.93%, FEC2 had 97.52%, FEC3 had %84.63, FEC4 had 79.48%, FEC5 had 73.18%, and FEC6 had 72.68%. From this data we can know that with increase in concentration of ethyl cellulose there is decrease in drug release. FEC2 formulation had

maximum release. FEC6 has the lowest release which had a drug: polymer ratio of 1:6. *In vitro* drug release of Micromatrices formulations made of Ethyl Cellulose was tabulated in Table No.6 and curves are as shown in Fig. No.10.

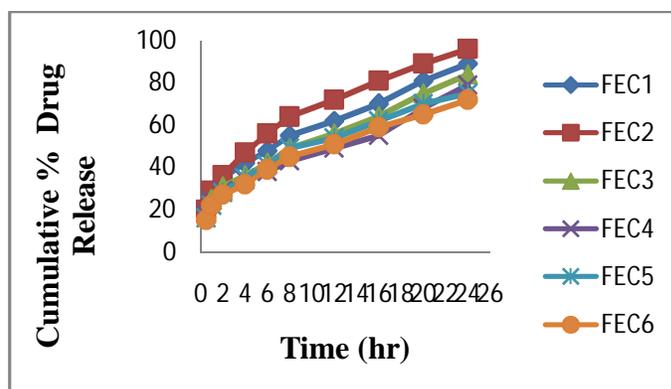


Fig No.10: Drug release profiles of Micromatrices with Ethyl Cellulose

**Table No.6: Cumulative % drug release of Micromatrices with Ethyl Cellulose.**

Time(hrs)	FEC1	FEC2	FEC3	FEC4	FEC5	FEC6
0.5	22.18±0.002	20.64±0.054	19.48±0.025	18.05±0.058	16.29±0.042	15.59±0.024
1	29.16±0.031	29.92±0.002	25.31±0.057	24.88±0.014	22.91±0.003	22.81±0.054
2	35.8±0.004	36.57±0.028	31.47±0.053	29.59±0.027	28.59±0.005	27.4±0.023
4	42.03±0.001	47.73±0.004	36.52±0.028	34.5±0.093	35.17±0.071	32.54±0.017
6	48.65±0.061	56.54±0.008	42.18±0.060	38.03±0.048	41.6±0.005	39.57±0.024
8	55.86±0.023	64.65±0.012	49.49±0.053	43.93±0.042	49.61±0.005	45.15±0.096
12	62.19±0.025	72.29±0.063	56.98±0.075	49.39±0.036	54.89±0.024	51.69±0.091
16	70.99±0.056	81.54±0.035	64.59±0.042	55.94±0.034	62.44±0.057	59.04±0.025
20	81.73±0.041	89.43±0.052	75.93±0.054	68.43±0.021	70.58±0.024	65.28±0.043
24	89.93±0.022	97.52±0.041	84.63±0.025	79.48±0.018	73.18±0.077	72.68±0.033

n=3±S.D (All the values are average of three determinations)

#### **Optimized formulations for preparation of rapimelts:**

Out of all formulations of Micromatrices with Ethyl Cellulose as controlled release polymer, based on the above results it was found that FEC2 had optimum flow properties, highest drug content of  $96.52 \pm 0.21\%$ , acceptable moisture content of 0.1%, and cumulative % drug release of 97.52%. Thus FEC2 was selected as the optimized formulation among the Micromatrices with Ethyl Cellulose polymer for the preparation of Zolmitriptan rapimelts.

#### **Characterization of Micromatrices blends:**

Bulk density of all formulation blends were in the range of 0.53gm/cc to 0.55gm/cc. Tapped density of all Tablet blends were in the range of 0.54gm/cc to 0.57gm/cc. Carr's index of all the Tablet blends containing ethyl cellulose micromatrices were between 2.19% and 3.95%, which indicate that the flow properties of all the Tablet blends were excellent. Hausner's ratio of all the Tablet blends containing ethyl cellulose micromatrices were between 1.022 and 1.04, which indicates the flow properties of the Tablet blends of all formulations are excellent. Angle of repose of EF2, EF3 and EF5 were  $35.22^{\circ}\text{C}$ ,  $35.22^{\circ}\text{C}$ , and  $35.53^{\circ}\text{C}$  respectively indicates fair flow property which does not require any aid and the other formulations EF1, and EF4 were  $33.69^{\circ}\text{C}$  and  $34.98^{\circ}\text{C}$  respectively indicates good flow properties. The results were depicted in Table No. 7.

#### **Evaluation of Rapimelts for Thickness, Weight variation, Hardness, friability and drug Content:**

Thicknesses of tablets of all the formulations were in the range of  $4.93 \pm 0.02\text{mm}$  to  $5.16 \pm 0.08\text{mm}$ . The average weights of all formulations were within the

permissible limits. Hardness of the Tablet was between  $5\text{kg}/\text{cm}^2$  and  $6\text{kg}/\text{cm}^2$  and was maintained for all the batches in order to minimize the effect of hardness on the drug release because the effect of polymer concentration is the only area of interest. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. The weight loss was found to be in between 0.16% and 0.72% which shows that all the formulations comply with the friability test. Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from  $93.57 \pm 1.15\%$  to  $97.72 \pm 0.49\%$ . The results of thickness, weight variation, hardness, friability and drug content are shown in Table No.8.

#### **Evaluation of rapimelts for *In vitro* disintegration time, Wetting time, Dispersion time, Uniformity of Dispersion and Water absorption ratio (%)**

The *In vitro* disintegration values of all formulations in Phosphate Buffer PH 6.8 were in between 28.5sec and 50sec that is not more than 60sec which is the acceptable limit of an orally disintegrating Tablet. The values of EF4 and EF5 were  $28.5 \pm 0.70\text{sec}$  and  $31 \pm 1.41\text{sec}$  which were less than other formulations. The values are as follows: EF1 had  $31 \pm 1.41\text{sec}$ , EF2 had  $40.1 \pm 1.41\text{sec}$ , and EF3 had  $38.5 \pm 0.70\text{sec}$ . This difference may be because of the presence of combination of superdisintegrants in EF4 and EF5.

Wetting time of all the formulations were in the acceptable limit. They were in the range of 35.5sec to 45.97sec.

Dispersion times of all the formulations were in the acceptable limit. They were in the range of  $31.98 \pm 1.41\text{sec}$  to  $48.5 \pm 2.12\text{sec}$ . All the formulations passed

**Table No.7: Flow properties of Micromatrices blend**

Formulation code	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index	Hausner's Ratio	Angle of Repose
EF1	0.55±0.06	0.57±0.050	3.95±0.049	1.04±0.026	33.69±0.061
EF2	0.53±0.024	0.57±0.011	3.38±0.025	1.03±0.09	35.22±0.35
EF3	0.55±0.012	0.56±0.067	2.19±0.071	1.02±0.015	35.22±0.029
EF4	0.53±0.190	0.54±0.026	2.53±0.036	1.03±0.02	34.98±0.048
EF5	0.54±0.007	0.55±0.071	2.59±0.001	1.03±0.074	35.53±0.055

**Table No.8: Evaluation of Rapimelts for Thickness, Weight variation, Hardness, friability and Drug content**

Formulation code	Thickness	Weight variation (mg)	Hardness (Kg/cm <sup>2</sup> )	Friability (%)	Drug Content
EF1	4.93 ± 0.02	100.79 ± 2.23	5.5 ± 0.70	0.55 ± 0.02	93.57 ± 1.15
EF2	5.02 ± 0.02	102.29 ± 1.34	5 ± 1.41	0.29 ± 0.02	94.59 ± 1.01
EF3	5.04 ± 0.01	100.9 ± 0.63	6 ± 1.41	0.72 ± 0.01	95.9 ± 0.69
EF4	5.16 ± 0.08	101.77 ± 1.11	5 ± 0	0.625 ± 0.04	97.72 ± 0.49
EF5	5.11 ± 0.12	101.45 ± 0.28	5.5 ± 0.70	0.475 ± 0.10	96.94 ± 1.29

n=3±S.D (All the values are average of three determinations)

through #22 no. sieve without any precipitate remaining and thus all of them were uniform. Water absorption ratios (%) of all the formulations were in the acceptable limit. They were in the range of 50.23 to 61.81. Drug content in the Tablets were observed for all the formulations. The results were shown in Table No.9.

#### In vitro dissolution studies

Dissolution studies were conducted for a period of 24 hours using USP dissolution apparatus II at an rpm of

50 and at a temperature of 37± 2<sup>o</sup>C and 900ml dissolution medium of 0.1 N HCl. Cumulative % Drug release of rapimelts having ethyl cellulose micromatrices after 24 hour time interval was found to be EF1 had 80.99%, EF2 had 82.55%, EF3 had 85.71%, EF4 had 98.21%, and EF5 had 91.23%. From this data we can know that. EF4 and, EF5 formulations had maximum release. The dissolution data is shown in Table No.10 and the dissolution profiles were shown in Fig. No.11.

**Table No.9: Evaluation of rapimelts for *In vitro* disintegration time, Wetting time, Dispersion time, Uniformity of Dispersion, Water absorption ratio (%)**

Formulation code	Disintegration time (sec)	Wetting time (sec)	Dispersion time (sec)	Uniformity of dispersion	Water absorption ratio (%)
EF1	31 ± 1.41	39.5 ± 0.70	35.93 ± 2.82	Uniform	50.23±2.14
EF2	40.5 ± 1.41	42.5 ± 0.70	48.5 ± 2.12	Uniform	61.81±0.67
EF3	38.7 ± 0.70	45.97 ± 0.70	46.82 ± 2.12	Uniform	58.69±1.12
EF4	28.5 ± 0.70	35.5 ± 0.70	31.98 ± 1.41	Uniform	58.69±1.12
EF5	31 ± 1.41	43 ± 1.41	39.4 ± 0.70	Uniform	57.64±1.71

n=3±S.D (All the values are average of three determinations)

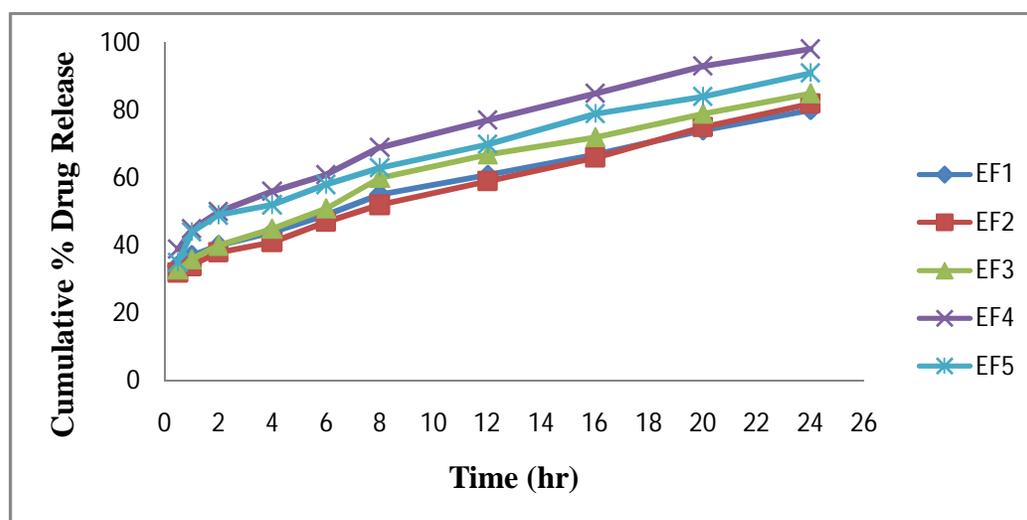
**Table No.10: Cumulative % drug release of different formulations of rapimelts containing optimized formulations of ethyl cellulose Micromatrices.**

Time (hrs)	EF1	EF2	EF3	EF4	EF5
0.5	34.27±0.15	32.22±0.055	33.58±0.180	39.34±0.019	35.11±0.059
1	37.41±0.06	34.31±0.06	36.32±0.034	45.61±0.044	44.32±0.041
2	40.65±0.04	38.59±0.170	40.99±0.24	50.78±0.051	49.22±0.032
4	44.5±0.091	41.43±0.061	43.57±0.088	56.31±0.060	52.41±0.076
6	49.68±0.026	47.17±0.035	47.65±0.019	61.33±0.04	58.31±0.021
8	55.33±0.015	57.75±0.021	51.83±0.034	69.79±0.28	63.81±0.085
12	61.67±0.063	59.34±0.067	60.58±0.071	77.46±0.07	70.97±0.024
16	67.88±0.092	66.94±0.054	75.64±0.03	85.12±0.019	79.68±0.052
20	74.34±0.035	75.6±0.158	79.63±0.190	93.56±0.062	84.56±0.071
24	80.99±0.043	82.5±0.240	85.71±0.042	98.21±0.08	91.23±0.05

n=3±S.D (All the values are average of three determinations)

**Table No.11: Kinetic model fitting data for all formulations**

Formulation code	Zero-order		First-order		Higuchi		Korsmeyer-Peppas		Best fit model
	Slope	R <sup>2</sup>	slope	R <sup>2</sup>	slope	R <sup>2</sup>	slope	R <sup>2</sup>	
EF1	13.96	0.8587	-	0.9015	39.04	0.9383	0.2602	0.9055	Higuchi
EF2	11.42	0.8643	-	0.8739	37.45	0.9382	0.2541	0.8897	Higuchi
EF3	9.248	0.8592	-	0.9429	34.41	0.9384	0.2526	0.8793	First-order
EF4	11.85	0.7702	-	0.9016	38.64	0.9097	0.2237	0.9518	Korsmeyer-Peppas
EF5	8.761	0.7955	-	0.9396	31.67	0.9253	0.2413	0.9505	Korsmeyer-Peppas

**Fig No.11: Drug release profiles of rapimelts containing optimized formulations containing Ethyl Cellulose Micromatrices**

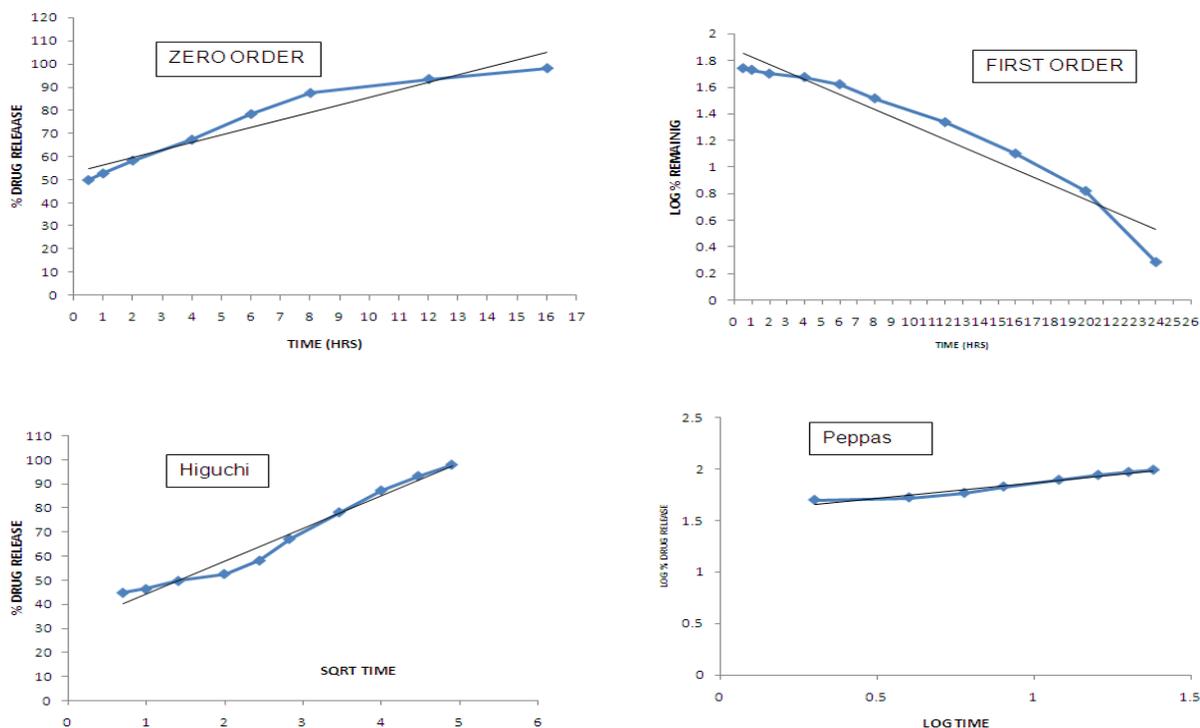


Fig o.12: Kinetic profiles for formulation EF4

### Dissolution Kinetics:

EF1 and EF2 formulations fit into Higuchi model as they have highest  $R^2$  values of 0.93823 and 0.9382 respectively. EF3 (0.9429) follows first order as its  $R^2$  value is highest in first order. EF4 (0.9518) and EF5 (0.9535) follows Peppas model. The  $n$  values of all the formulations are below 0.5 and thus the drug release mechanism follows Fickian diffusion. The first order for some of the formulations may be due to the action of other excipients used in Tableting. The release kinetics was shown in Table No.11 and the graphs were shown in Fig. No.12.

### CONCLUSION

The Rapimelts containing Zolmitriptan micromatrices were successfully prepared by Mass Extrusion method and direct compression method. Micromatrices were prepared by mass extrusion method with drug: polymer ratios of ethyl cellulose (FEC). All the evaluation parameters of micromatrices were within the limits. The optimized formulation FEC2 showed the drug content of  $96.52 \pm 0.2$ , the cumulative % drug release

of  $97.52 \pm 0.041$ . Zolmitriptan rapimelts were prepared and evaluated for different parameters. All the evaluation parameters of all the formulations were within the official limits. The optimized formulations EF4 showed the highest drug content of  $97.72 \pm 0.49$ , the cumulative percentage drug release of  $98.21 \pm 0.08$ . Their formulation includes the combination of superdisintegrants sodium starch glycolate (2%) and croscopolidone (2%). The release kinetics showed that the best fit of EF4 followed Krosmeier Peppas and Higuchi model respectively. Out of the formulations EF4 is selected as the best since the drug release followed Krosmeier Peppas model which is best suited for matrix type sustained release dosage form where the drug release is by Fickian diffusion.

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