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FORMULATION AND EVALUATION OF ZOLMITRIPTAN RAPIMELTS

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ABSTRACT

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. The HPMC K15M polymer is used to prepare minimatrices which further converted to micromatrices. Micromatrices were evaluated for different preformulation parameters, drug content, percentage yield, moisture content and drug release. Based on the drug content and drug release optimized formulation of HPMC is used to prepare rapimelts. The physicochemical compatibility of the drug with other excipients used in the formulations was studied by FTIR analysis. 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. In order to determine the mode of release, the data was fitted into various kinetic models and the optimized formulations followed Krosmeyer peppas model and Higuchi model respectively and n values less than 0.5which indicates Fickian diffusion mechanism of drug release.

KEYWORDS: Zolmitriptan, Micromatrices, Rapimelts, Controlled release, HPMC K15M.

INTRODUCTION

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. A

migraine is a severe, painful headache that is often preceded or accompanied by sensory warning signs such as flashes of light, blind spots, tingling in the arms and legs, nausea, vomiting, and increased sensitivity to light and sound. The excruciating pain that migraines bring can last for hours or even days.[1]

Zolmitriptan (4S)-4-([3-(2-[dimethylamino]ethyl)-1Hindol-5-yl]methyl)-2-oxazolidinone, is a white to almost white powder highly soluble in water (20 mg/ml). It is a BCS (biopharmaceutics classification system) lass-3 drug with high solubility and low permeability. It has a pKa value of 9.52. Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with or without an aura and cluster headaches. It has a selective action on serotonin (5-HT1B/1D) receptors and it is very effective in reducing migraine symptoms, including pain, nausea and photo or phonophobia. It is currently available as a conventional tablet, an oral disintegrating tablet and a nasal spray (2.5 mg and 5 mg/dose). The drawbacks of current oral Zolmitriptan therapies are slow onset of action and low bioavailability (about 40%). Zolmitriptan undergoes highly hepatic first pass metabolism and to solve the problems of hepatic first pass metabolism prepare sublingual tablets.[2] 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.

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.[3]

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[3] (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.[4] ODTs with

good taste and flavor increase the acceptability of bitter drugs by various groups of population.[5]

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.

MATERIALS AND METHODS

Materials

Zolmitriptan obtained as a gift sample from Aurobindo Pharmaceuticals, Hyderabad. HPMC K15M, 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.

Melting Point Determination

Melting point determination was done by using capillary method.

Fourier transform infrared spectroscopy (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 10^0C/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., HPMC K15M 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 1.

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[7-2]

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

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.

$$\%\text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In vitro Drug release study

The drug release was studied using USP type II apparatus at 37 ± 0.5°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 (θ). 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 θ, 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 (θ) was calculated using the following formula.

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

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

Bulk density

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/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.

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

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.

$$\text{Friability} = \frac{\text{Initial weight - Final weight}}{\text{Intitial weight}} \text{X}\,100$$

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 ± 2^0C. 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

Apiece 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 ± 0.5°C and at 50rpm usingthe pH of the dissolution medium was kept at 1.2 for 2 h with 0.1NHCl. Then, 1.7 g of KH2PO4 and 2.225 g of $Na_2HPO_4 \cdot 2H_2O$ 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 (firstorder 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.

$$Q = Q_{\circ} + k_{\circ} t$$

Where Q is the amount of drug dissolved in time t, Q is the initial amount of drug in the solution (most times, Q 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.

$$\ln Qt = \ln Q_{\circ} - k_1 t$$

Where Qt is the amount of drug released in time t, Q0 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.

$$Qt = KHt_{1/2}$$

Where Qt 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 (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

Melting Point Determination

The melting point of Zolmitriptan was found to be in between 138°C to 142°C.

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=0.By observing the IR spectra of pure drug and the all physical mixtures of drug and polymers in figures 5.4 to 5.10 it was found out 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 1-5. 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 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 (Figure 6), 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.

Evaluation of micromatrices

Flow properties

Bulk density of all formulations was in the range of 0.53gm/cc to 0.65gm/cc. Tapped density of all formulations was in the range of 0.59gm/cc to 0.66gm/cc. Carr's index of all the formulations of micromatrices were between 1.32% and 4.70% respectively, which indicates the flow properties of the micromatrices of all formulations are excellent. Hausner's Ratio of all the formulations of micromatrices were between 1.01 and 1.10 respectively which indicates the flow properties of the micromatrices of all formulations are excellent. The micromatrices made with HPMC had an angle of repose ranging from 22.93 to 27.22 indicates that all of the micromatrices made with HPMC had excellent flow properties. The results were depicted in table 4.

Evaluation of micromatrices

Drug content

Drug content of micromatrices formulations made of HPMC were in the range of 91.43 to 96.72% out of which FHC3 had shown comparatively least drug content and FHC2 had shown comparatively highest drug content. Drug content of Micromatrices formulations made of HPMC (FHC) was tabulated in Table 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 HPMC (FHC) 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± 2^0 C and 900ml dissolution medium of 0.1 N HCl. Cumulative % drug release from FHC3 micromatrices shown highest drug release i.e. 96.68%. From this data we can know that with increase in concentration of HPMC there is decrease in drug release. FHC2, FHC3 formulations comparatively had maximum release. FHC6 has the lowest release which had a drug: polymer ratio of 1:6. *In vitro* drug release of Micromatrices formulations made of HPMC is tabulated in Table 6 and curves are as shown in Figure 7.

Optimized formulations for preparation of rapimelts

Out of all formulations of Micromatrices with HPMC as controlled release polymer, based on the above results it was found that FHC3 had optimum flow properties, highest drug content of 96.72 ± 0.07%, acceptable moisture content of 0.50%, and cumulative % drug release of 96.68%. Thus FHC3 was selected as the optimized formulation among the Micromatrices with HPMC polymer for the preparation of Zolmitriptan rapimelts.

Characterization of Micromatrices blends

Bulk density of all formulation blends were in the range of 0.54gm/cc to 0.62gm/cc. Tapped density of all Tablet blends were in the range of 0.56gm/cc to 0.65gm/cc. Carr's index of all the Tablet blends were between 2.70% and 5.16%, which indicate that the flow properties of all the Tablet blends were excellent. Hausner's ratio of all the Tablet blends were between 1.03 and 1.05, which indicates the flow properties of the Tablet blends of all formulations are excellent. Angle of repose of HF2, HF3, HF4 and HF5 were 33.99^{0}C, 34.9^{0}C, 33.4^{0}C and 34.59^{0}C respectively which indicate good flow properties and for HF1 it was 35.35^{0}C indicates fair flow property which does not require any aid. The results were depicted in table 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 4.94 ± 0.02mm to 5.28 ± 0.04mm. The average weights of all formulations were within the permissible limits. Hardness of the Tablet was between 5kg/cm^2 and 6kg/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 in the Tablets were observed for all the formulations. Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 93.57± 1.15% to 97.72 ± 0.49%. The results are shown in table 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 29sec and 48.2sec that is not more than 60sec which is the acceptable limit of an orally disintegrating Tablet. The values of HF4 and HF5 were 29 ± 1.41sec and 32.5 ± 0.70sec which were less than other formulations. This difference may be because of the presence of combination of superdisintegrants in HF4 and HF5.

Wetting time of all the formulations were in the acceptable limit. They were in the range of 37.5sec to 53.5sec.

Dispersion times of all the formulations were in the acceptable limit. They were in the range of 30.85 ± 3.53sec to 51.63 ± 2.82sec. All the formulations passed 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 50.81 to 70.03. The results were shown in Table 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± 2^0C and 900ml dissolution medium of 0.1 N HCl. HF4 shown highest cumulative % drug release i.e. 95.07%. The dissolution data is shown in Table 10 and the dissolution profiles were shown in Figures 8.

Dissolution Kinetics

HF1 (0.9084) and HF4 (0.9974) fit into Higuchi model. HF2 (0.9598), HF3 (0.9626), and HF5 (0.947) follows first order as its R^2 value is highest in first order. 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 11 and the graphs were shown in Figure 9.

Table 1: Composition of Formulations of Zolmitriptan micromatrices.

Formulation Code	Drug : Polymer
FHC1	1:1
FHC2	1:2
FHC3	1:3
FHC4	1:4
FHC5	1:5
FHC6	1:6

Table 2: Composition of micromatrices blend of various formulations of rapimelts.

Ingredients	HC1	HC2	HC3	HC4	HC5
Micromatrices (drug equivalent to 5mg)	30	30	30	30	30
Sodium Starch Glycolate (mg)	-	-	4	2	2
Croscarmellose sodium (mg)	-	4	-	-	2
Cross Povidone (mg)	4	-	-	2	-
Colloidal silicon dioxide (mg)	2	2	2	2	2
Mg. Stearate (mg)	8	8	8	8	8
Microcrystalline cellulose (mg)	56	56	56	56	56
Total weight (mg)	100	100	100	100	100

Table 3: Comparative FTIR Interpretation of Zolmitriptan with Excipients.

S.No	Characteristic bands	Standard wave no. range	Pure drug	HPMC	SSG	CCS	CP
1	Alkane (C-H bending)	1480-1375	1469.76	1465.90	1408.04	1465.90	1463.97
2	Aromatic ring	950-730	939.33	918.12	858.32	777.31	914.26
3	N-H stretching	3560-3200	3325.75	3363.85	3348.42	3348.42	3350.35
4	Secondary amine	1350-1000	1149.57	1228.66	1149.57	1149.57	1166.93
5	Cyclic C=O	1870-1650	1750.93	1743.93	1735.93	1748.36	1749.27

Table 4: Flow properties of Micromatrices.

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio	Angle of repose
FHC1	0.59±0.05	0.61±0.005	2.68±0.02	1.02±0.02	22.93±0.32
FHC2	0.65±0.08	0.66±0.008	1.83±0.02	1.01±0.02	26.14±0.39
FHC3	0.53±0.07	0.59±0.009	4.70±0.13	1.10±0.01	27.12±0.55
FHC4	0.58±0.08	0.63±0.006	.51±0.13	1.09±0.01	27.22±0.57
FHC5	0.62±0.00	0.63±0.008	1.83±0.02	1.018±0.02	26.03±0.20
FHC6	0.63±0.05	0.63±0.006	1.32±0.02	1.01±0.01	23.32±0.43

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

Table 5: Evaluation of micromatrices for drug content and moisture content.

Formulation code	Drug content (%)	Moisture Content (%)
FHC1	91.67 ± 0.02	0.60%±0.004%
FHC2	94.96 ± 0.04	0.70%±0.001%
FHC3	96.72 ± 0.07	0.50%±0.004%
FHC4	91.43 ± 0.49	0.80%±0.002%
FHC5	95.65 ± 0.14	0.50%±0.002%
FHC6	95.56 ± 0.07	0.40%±0.001%

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

Table 6: Cumulative % drug release of Micromatrices with HPMC.

Time(hrs)	FHC1	FHC2	FHC3	FHC4	FHC5	FHC6
0.5	29.46±0.002	27.26±0.052	25.06±0.016	24.71±0.006	22.38±0.004	21.15±0.02
1	32.74±0.112	32.24±0.023	34.33±0.007	30.45±0.009	27.51±0.461	26.71±0.036
2	36.07±0.023	37.66±0.09	42.38±0.009	38.83±0.043	33.03±0.052	32.3±0.021
4	39.29±0.041	42.87±0.05	50.94±0.125	44.56±0.062	39.53±0.021	39.86±0.058
6	45.59±0.145	48.31±0.045	58.01±0.065	49.26±0.007	45.03±0.08	43.51±0.054
8	54.84±0.002	56.41±0.012	65.21±0.522	58.11±0.025	51.14±0.015	49.63±0.009
12	60.34±0.056	64.34±0.027	74.14±0.082	69.53±0.065	62.84±0.04	56.34±0.003
16	66.34±0.064	78.88±0.036	81.28±0.061	76.18±0.065	70.8±0.02	64.59±0.051
20	73.83±0.506	84.93±0.084	89.68±0.035	83.58±0.057	79.43±0.068	73.38±0.401
24	81.18±0.03	90.83±0.029	96.68±0.024	91.33±0.048	88.18±0.009	81.03±0.325

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

Table 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
HF1	0.60±0.041	0.61±0.033	2.86±0.023	1.03±0.051	35.35±0.037
HF2	0.56±0.062	0.58±0.048	2.70±0.30	1.03±0.009	33.99±0.007
HF3	0.54±0.031	0.56±0.08	3.04±0.071	1.03±0.026	34.90±0.051
HF4	0.59±0.09	0.62±0.102	5.16±0.082	1.05±0.049	33.40±0.068
HF5	0.62±0.01	0.65±0.006	4.48±0.044	1.05±0.053	34.59±0.004

Table 8: Evaluation of Rapimelts for Thickness, Weight variation, Hardness, friability and Drug content.

Formulation code	Thickness	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug Content
HF1	4.94 ± 0.02	101.68 ± 0.47	5.5 ± 0.70	0.21 ± 0.11	91.49± 1.12
HF2	5.05 ± 0.04	100.60 ± 0.86	5.5 ± 0.70	0.525 ± 0.17	93.64 ± 1.36
HF3	5.10 ± 0.17	101.23 ± 1.24	6 ± 0	0.495 ± 0.04	95.6 ± 0.24
HF4	5.1 ± 0.08	101.87 ± 0.95	5.5 ± 0.70	0.16 ± 0.01	95.94 ± 0.86
HF5	5.28 ± 0.04	101.47 ± 0.26	5 ± 1.41	0.69 ± 0.05	95.44 ± 1.73

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

Table 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 (%)
HF1	35.4± 2.12	49.5 ± 1.41	39.21 ± 2.82	Uniform	56.94±2.53
HF2	48.2 ± 1.41	46.2 ± 2.82	51.63 ± 2.82	Uniform	70.03±1.18
HF3	37± 1.41	53.5 ± 3.53	38.29 ± 2.82	Uniform	52.46±1.96
HF4	29 ± 1.41	37.5 ± 0.70	30.85 ± 3.53	Uniform	50.81±1.23
HF5	32.5 ± 0.70	44.1 ± 2.82	40.17 ± 0.70	Uniform	60.26±1.59

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

Table 10: Cumulative % drug release of different formulations of rapimelts containing optimized formulations of HPMC Micromatrices.

Time (hrs)	HF1	HF2	HF3	HF4	HF5
0.5	39.12±0.15	38.45±0.019	36.68±0.092	44.92±0.054	42.67±0.015
1	43.35±0.06	41.61±0.061	39.32±0.43	48.47±0.024	45.51±0.078
2	49.18±0.27	47.27±0.044	42.92±0.15	51.85±0.02	51.32±0.054
4	54.45±0.01	51.63±0.061	47.55±0.25	57.72±0.54	54.59±0.452
6	60.22±0.039	57.42±0.18	53.83±0.002	64.27±0.03	59.47±0.84
8	64.56±0.026	61.47±0.025	59.76±0.047	70.28±0.009	63.33±0.05
12	68.69±0.051	66.55±0.066	64.82±0.168	78.32±0.182	71.54±0.0647
16	73.63±0.268	74.72±0.046	70.52±0.177	86.39±0.048	79.41±0.028
20	79.32±0.081	80.28±0.029	76.03±0.854	90.4±0.194	84.57±0.052
24	85.41±.059	88.36±0.073	81.25±0.043	95.07±0.346	91.83±0.049

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

Table 11: Kinetic model fitting data for all formulations.

Formulation code	Zero-order		First-order		Higuchi		Korsmeyer-Peppas		Best fit model
	Slope	R^2	slope	R^2	slope	R^2	slope	R^2	
HF1	7.466	0.782	-0.0146	0.9082	31.39	0.9084	0.216	0.8987	Higuchi
HF2	8.873	0.8262	-0.0182	0.9598	31.95	0.9264	0.2329	0.8896	First-order
HF3	9.074	0.8432	-0.0156	0.9626	33.86	0.9328	0.2428	0.8806	First-order
HF4	7.600	0.8137	-0.0174	0.965	31.96	0.9974	0.232	0.9077	Higuchi
HF5	7.218	0.7979	-0.0194	0.947	30.54	0.9138	0.2205	0.8905	First-order

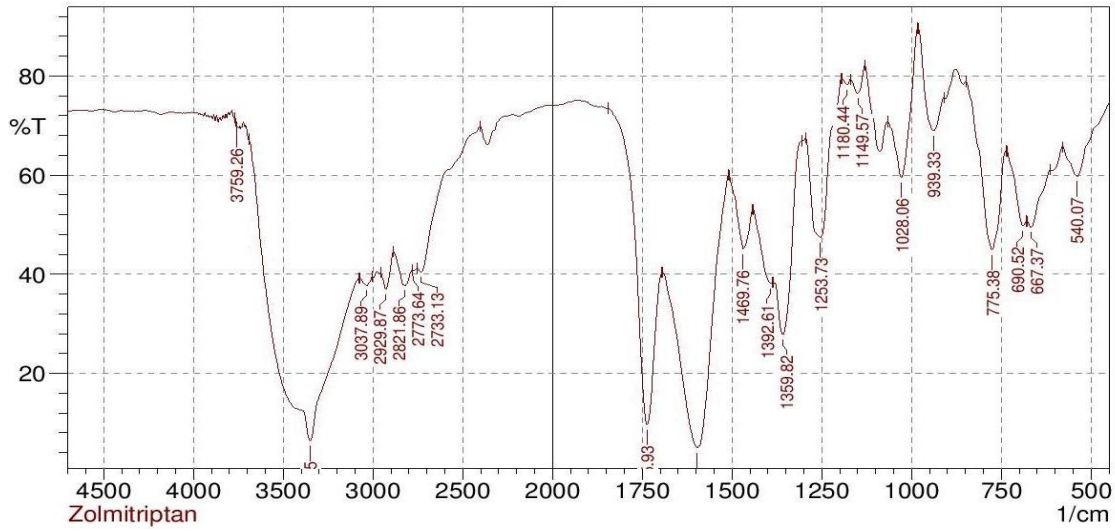

Figure 1: FTIR spectra of Zolmitriptan.

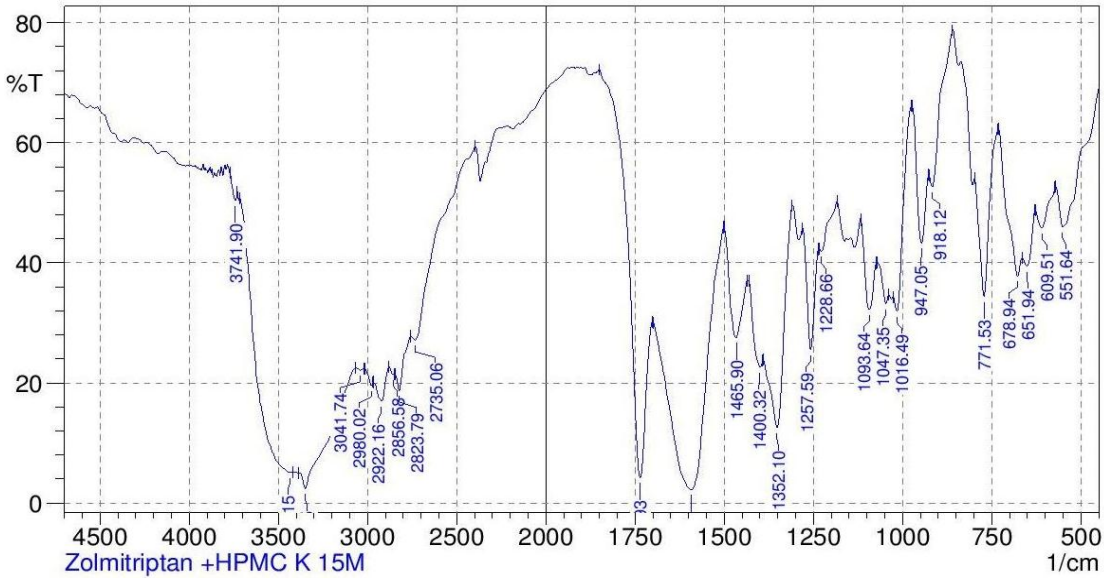

Figure 2: FTIR spectra of Zolmitriptan with HPMC K15M.

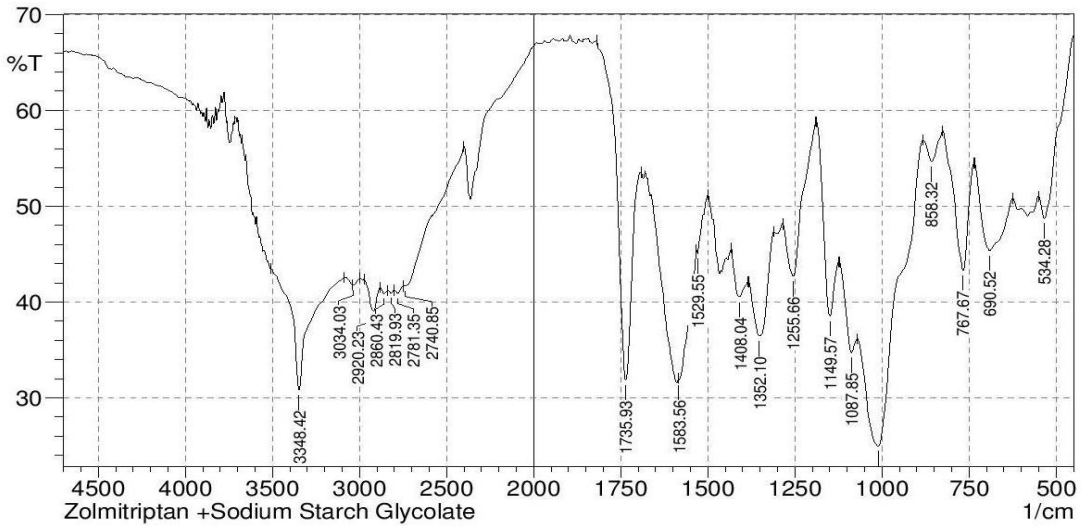

Figure 3: FTIR spectra of Zolmitriptan with Sodium Starch Glycolate.

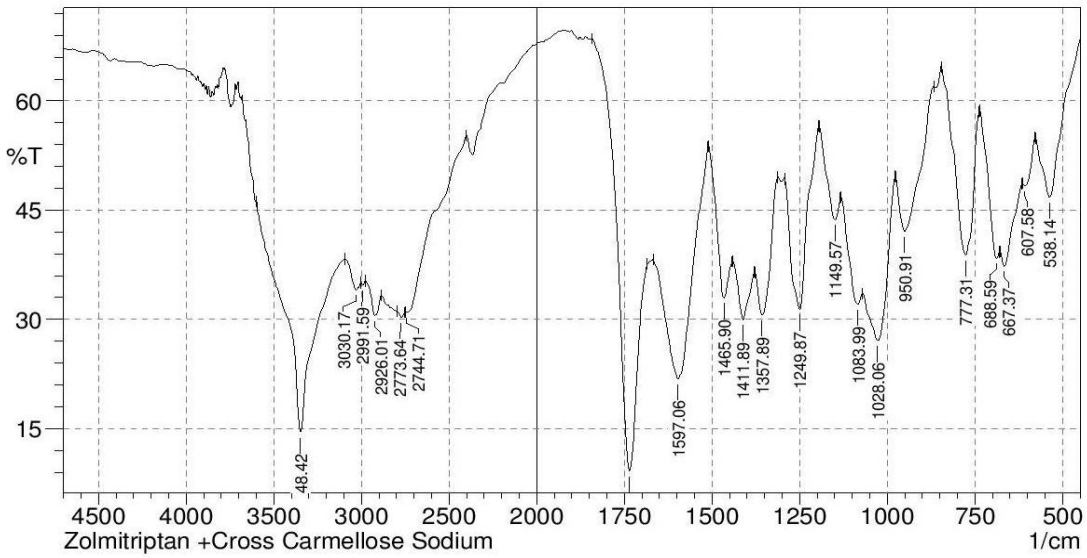

Figure 4: FTIR spectra of Zolmitriptan with Crosscarmellose Sodium.

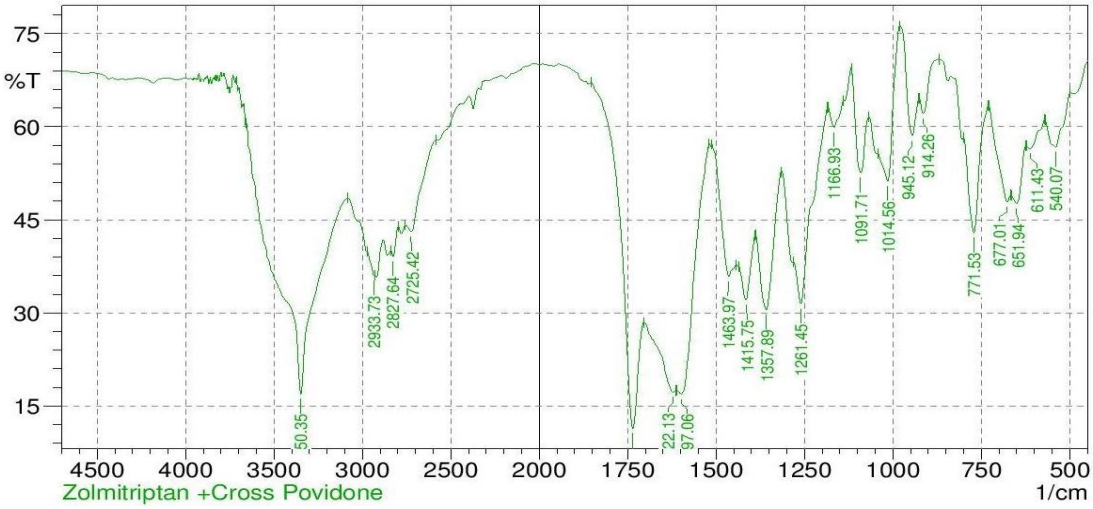

Figure 5: FTIR spectra of Zolmitriptan with Cross Povidone.

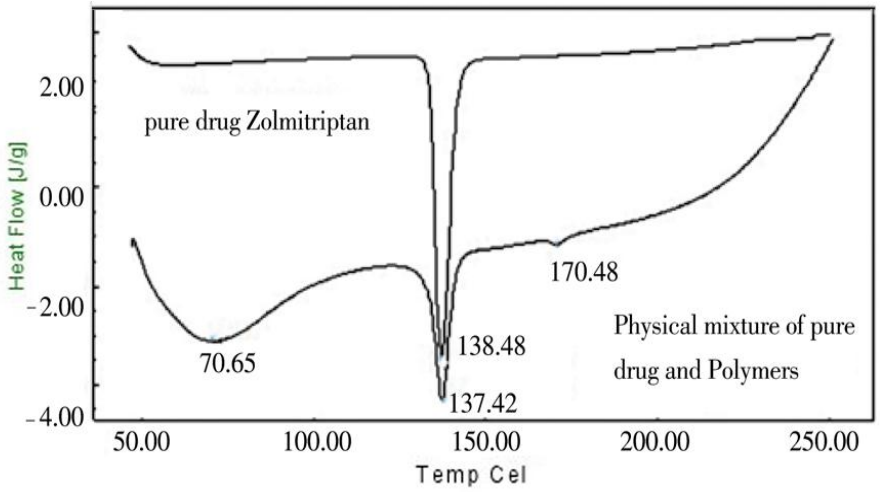

Figure 6: Comparative DSC studies of Zolmitriptan with mixture of Polymers.

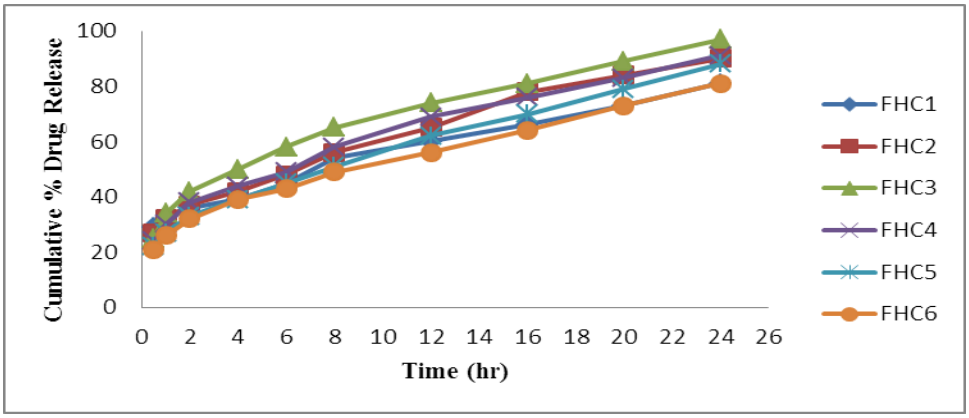

Figure 7: Drug release profiles of Micromatrices with Hydroxy Propyl Methyl Cellulose.

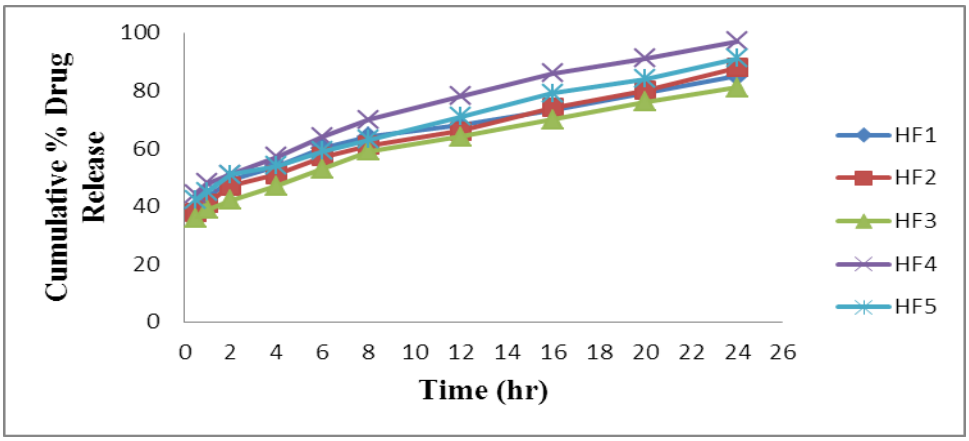

Figure 8: Drug release profiles of rapimelts containing optimized formulations containing HPMC Micromatrices.

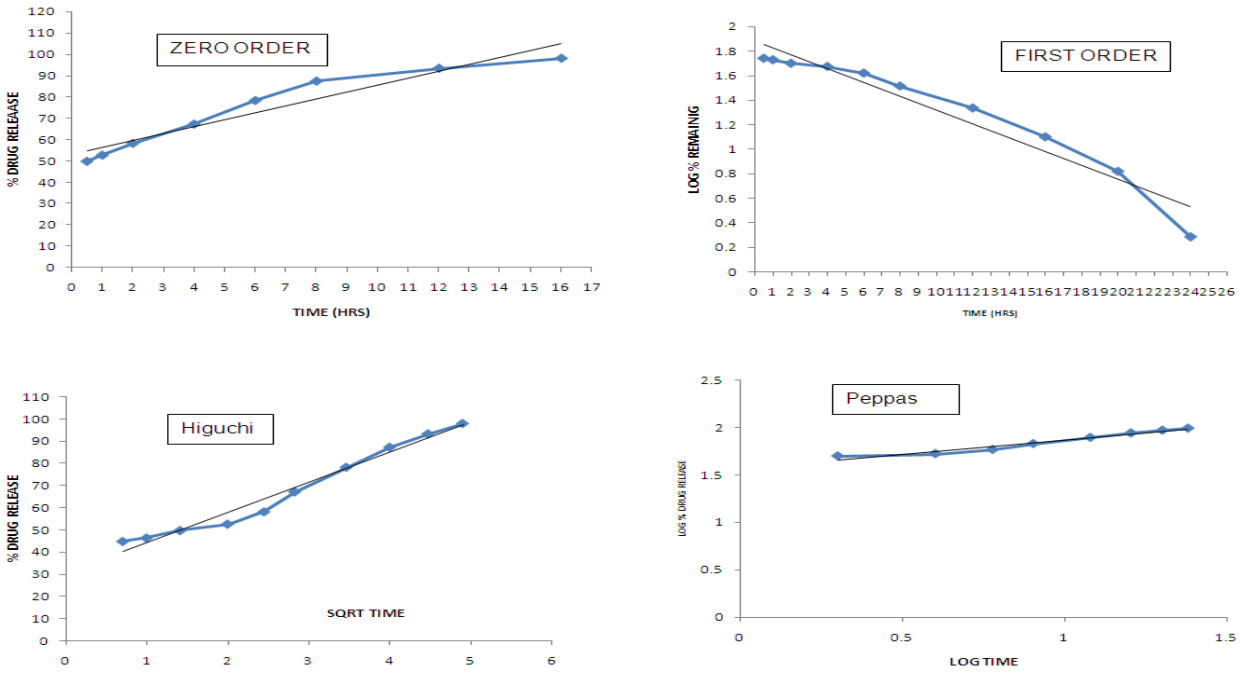

Figure 9: kinetics profiles for formulation HF4.

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 HPMC (FHC). All the evaluation parameters of micromatrices were within the limits. The optimized formulation FHC3 showed the drug content of 96.72 ± 0.07, the cumulative % drug release of 96.68±0.024. Zolmitriptan rapimelts were prepared and evaluated for different parameters. All the evaluation parameters of all the formulations were within the official limits. The optimized formulation HF4 showed the highest drug content of 95.94 ± 0.86, the cumulative percentage drug release of 95.07±0.346. Their formulation includes the combination of superdisintegrants sodium starch glycolate (2%) and crospovidone (2%). The release kinetics showed that the best fit of HF4 followed Higuchi model.

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