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Original Article

Formulation and evaluation of fast dissolving sublingual films of rizatriptan benzoate

[1]Afaf Ramadan, [1]Shereen El-Adawy, [2*]Heba Hamdi

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt
[2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), Cairo, Egypt

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ABSTRACT

Rizatriptan benzoate is anti-migraine drug which has oral bioavailability of 47% due to hepatic first pass metabolism. The present study investigated the possibility of developing fast dissolving sublingual films to provide rapid drug onset. Nine formulae were prepared with different concentrations 1%, 2%, and 3% of carboxymethyl cellulose, hydroxypropyl methylcellulose E6 and E15 as water soluble polymers, by solvent casting technique. The prepared films were subjected to characterization for thickness, weight variations, folding endurance, surface pH, disintegration time, drug content and in-vitro drug release. Compatibility between drug and polymers were studied. Film with 1% CMC was disintegrated in time of 30 seconds with rapid drug release 100% in 120 seconds. Stability study was carried out within 90 days for formulae chosen F1, F2, F4 and F7. They were stored at 40 ^{o}C/45% RH and 50 ^{o}C/45% RH. Highest percent drug remained was detected in formula F1 which was evaluated for in vivo release studies using human volunteers. The peak serum concentration (C_{max}), half time ($T_{½}$), time for maximum plasma concentration (T_{max}) and area under curve (AUC) were calculated. T_{max} for the sublingual film was faster than conventional oral route.

Key words: Rizatriptan benzoate, fast dissolving sublingual film, solvent casting technique, stability studies, pharmacokinetics.

INTRODUCTION

Mouth dissolving films, a new drug delivery system for the oral delivery of drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro-mucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of lyophilysates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets [1]. Oral dissolving films can be administered without water, anywhere, anytime. Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity. Oral dissolving films are flexible and portable so they provide ease in transportation during consumer handling and storage, suitability for geriatric and pediatric patients, who experience difficulties in swallowing, mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated [2,3].

Migraine is a recurrent headache disorder with intense pain that may be unilateral (one-sided) and accompanied by nausea or vomiting as well as photosensitivity (sensitivity to light) and phonosensitivity (sensitivity to sound). The lifetime prevalence is 25% in women and 8% in men. Migraine also affects about 5% to 10% of children and adolescents. Some people who have migraine headaches experience an aura (temporary disturbance of the senses or muscles) in the

***Corresponding Author Address:** Heba Hamdi Ahmed Tolba, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, October University for Modern Sciences and Arts, P.O. Box: ,12591Zip Code: 2104, Giza, Egypt; E. mail: Hebahamdi67@yahoo.com*

minutes before the onset of pain. The aura may consist of seeing flashing lights, having numbness or tingling in the face or extremities, having a disturbed sense of smell, or having difficulty speaking. However, only about one-third of individuals who have migraine headaches experience auras. Migraines are painful but fortunately are not life-threaten in [4].

The new generation anti-migraine drug, rizatriptan benzoate is an orally active serotonin 5-HT_1 receptor agonist that potently and selectively binds to 5-HT_1B/1D subtypes. Chemically it is N, N dimethyl-5-(1H-1, 2, 4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate. The initial gut absorption of rizatriptan is high (90%); however, the compound undergoes moderate first-pass metabolism, which limits the bioavailability to 47%. So orally fast dissolving sublingual films of rizatriptan prevent its first-pass metabolism and eliminate the need of intake of water by the patient during the migraine attack and provide fast onset of action which would be beneficial to migraine sufferers in resuming their functional abilities as soon as possible [2,5].

MATERIALS AND METHODS

Materials: Rizatriptan benzoate was purchased from Baoji Guokang Bio-Technology Co., Ltd, (China). Aspartame was obtained as a gift sample from Sedico Pharmaceutical Cairo Company (Egypt). Mannitol, potassium dihydrogen phosphate and disodium hydrogen phosphate dibasic and propylene glycol were purchased from El-Nasr Pharmaceutical Company, Cairo (Egypt). Hydroxypropyl methylcellulose (E15, E6) polymer and carboxymethy cellulose (low viscosity) polymer were obtained as a gift sample from Cairo Pharmaceutical Company, Cairo (Egypt). Rizact-10mg tablets were kindly supplied by Cipla pharmaceutical company , Mumbai (India). Sumatriptan internal standard was purchased from Baoji Guokang Bio-Technology Co., Ltd, (China). Analytical grade chemicals and HPLC grade solvents were used.

Methodology

Drug polymer compatibility

a- Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra of pure rizatriptan benzoate, mixture of rizatriptan benzoate and CMC, mixture of rizatriptan benzoate and HPMC E6 and mixture of rizatriptan benzoate and HPMC E15 obtained by FTIR Spectrophotometer (Shimadzu IR-345,Japan) using potassium bromide pellets. Samples were scanned from 4000 to 400 cm^{-1} [6].

b- Differential scanning calorimetry (DSC): DSC analysis of pure rizatriptan benzoate, mixture of rizatriptan benzoate and CMC, mixture of rizatriptan benzoate and HPMC E6, and mixture of rizatriptan benzoate and HPMC E15 were carried out using a differential scanning calorimeter (Shimadzu DSC-60, Japan) to evaluate any possible drug-polymer interaction. Samples (2 mg) were heated in a hermetically sealed aluminum pans in temperature range of 25 to 350 ºC at heating rate of 10 ºC /min under nitrogen flow of 40ml/min [6].

Spectrophotometric scanning of rizatriptan benzoate: Scanning for rizatriptan benzoate was carried out by UV spectrophotometer in phosphate buffer pH6.8.Ten mg of rizatriptan benzoate was dissolved in phosphate buffer of pH 6.8 in a volumetric flask and made up the volume with the respective medium to obtain a stock solution of 100.0 µg/ml. Appropriate dilution was made with buffer and the solution was subjected to spectrophotometric scanning of UV wavelength ranging from 200 - 400 nm against phosphate buffer pH 6.8 as a blank and detects the maximum peak of absorption [7].

Standard plot of rizatriptan benzoate in phosphate buffer pH 6.8: The standard plot of rizatriptan benzoate was prepared in pH 6.8 phosphate buffer. Appropriate dilutions were made with buffer to obtain test solution ranging from 10 to 60 µg/ml. The above solution was measured spectrophotometrically at wave length 275 nm. A procedural constant (K) was calculated from the reciprocal of the slope of the best fitting line representing the calibration curve [7].

Method of preparation of fast dissolving sublingual film of rizatriptan benzoate: Fast dissolving oral film containing carboxymethyl cellulose CMC and hydroxyprobyl methyl cellulose HPMC were prepared by the solvent casting technique. Accurately weighed rizatriptan benzoate dissolved in the distilled water using magnetic stirrer (Stuart, Germany). Mannitol, aspartame and propylene glycol (PG) were added to the previous dispersion under constant stirring to sure that all previous ingredients were dissolved. CMC or HPMC was added portion wise under constant stirring and was left on magnetic stirrer for 1 hour and the resultant homogeneous solution was introduced into water bath at 30 ºC for one hour to get rid of all air bubbles then poured into a petri dish, then film was dried in an oven at 50 ºC for 24 hour. After drying, films were removed with the help of sharp blade and kept in desiccators for 24 hours before cutting into small pieces with area of 2×2 cm^2 so that each piece containing 10 mg of

rizatriptan benzoate. Films with air bubbles, cuts or imperfections were excluded from study. Selected films were subjected to different evaluation parameters. Different concentrations of CMC (1%, 2% and 3%), HPMC E6 (1%, 2% and 3%), and HPMC E15 (1%, 2% and 3%) were added to prepare different formulations of fast dissolving films [8].

Evaluation parameters for fast dissolving films

a- Thickness: Thickness of the film was measured using digital Vernier Calliper (Starrett 3732, Germany) with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film, average and SD were calculated. Weight variation of four centimeter square of the film was cut at three different places from the casted film. The weight of each film and weight variation were calculated [2,9,10].

b- Folding endurance: Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value [2,11].

c- Surface pH: The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode of PH meter (Jenway, 3510 pH Meter) in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported [12].

d- In-vitro disintegration: The disintegration study was carried out using disintegration tester (Erweka ZT224, Germany). The disintegration was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5 ºC The film was carefully kept in a basket .The disintegration time is the time passed for the film to start to break or disintegrate. The results were expressed as mean of three determinations [13,14].

e- Drug content: Drug content determination of the film was carried out by dissolving the film of 4 cm^2 in 100 ml pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. One ml was withdrawn from previous solution and completed to 10 ml of phosphate buffer pH 6.8 in 10 ml volumetric flask. The drug concentration was then evaluated spectrophotometrically at λ max of 275 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded [2].

f- In-vitro dissolution: The dissolution study was carried out using USP Type II (paddle type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5 ºC at 100 rpm. Aliquots of 5 ml were taken at different time intervals (1, 2, 3, 4 and 5 mints) which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37±0.5 ºC. Rizatriptan benzoate in the samples was then determined spectrophotometrically at λ max of 275 nm. The results were expressed as mean of three determinations [15].

Stability study: Stability study was carried out at two different storage conditions, at 40 ºC/45% RH and at 50 ºC/45% RH for 90 days using stability chamber (MMM Climacell- Germany). Each film of formulations F1, F2, F4 and F7 was packed in aluminum foil and plastic tape in petri dish and covered with foil. After 90 days the films were evaluated for the physical appearance, thickness, weight variations, folding endurance, surface pH, disintegration time, drug content and in-vitro drug release.

In vivo Release Studies

a- Pharmacokinetic analysis: F1 was found as the best suitable formula and the pharmacokinetic studies of this rizatriptan benzoate rapidly disintegrating sublingual film were compared with oral marketed rizatriptan tablets (Rizact-10 mg, Cipla, Mumbai). Six healthy male volunteers were classified into two groups, the first group (n=3) administrated rizatriptan benzoate sublingual film (F1) which contained 10 mg of rizatriptan benzoate. The second group (n=3) received comparator marketed preparation of oral rizatriptan tablet (Rizact-10mg, Cipla, Mumbai). Blood samples are withdrawn after pre specified time intervals (0,0.25, 0.5, 0.75, 1, 2, 4, 6 and 8 hr) [16]. All the subjects were informed of the aim and risk involved in the study .The inclusion criteria for volunteer selection were based on the age (18–45 years),body mass index (between 18.5 and 24.9 kg/height^2), general physical examination, and laboratory tests like liver enzymes were done. The work was approved and subjected to review by an Institutional Ethics Committee. The procedures followed while dealing with human subjects were based on International Conference on Harmonization, E6 Good Clinical Practice (ICH, E6 GCP) guidelines [17]. The samples were centrifuged at 1811 ×g at 4 ◦C for 15min and plasma was separated, stored at −20 ◦C until use [18].

b-Analysis of blood samples

LC-MS/MS instrumentation and conditions: For quantitative analysis the HPLC system consisted of

an Agilent 1200 system, solvent delivery module, quaternary pump, autosampler, and column compartment (Agilent Technologies, Germany). The detector used was an Agilent 6420 triple quad mass spectrometer (TQ-MS) controlled by Mass Hunter software. The TQ-MS conditions utilized were a gas temperature of 330 ºC, gas flow of 12 L/min, nebulizer pressure of 35 psi, capillary voltage of 4000 v, and cell accelerator voltage of 7 v. The dwell, fragmentor voltage of 135, and collision energy (CE) were optimized and a positive mode was applied. The mobile phase consisted of 0.1% formic acid buffer: methanol (25: 75 *v/v*), and the flow rate was set at 0.25mL/min for isocratic conditions. Quantitation was done using MRM mode to monitor protonated precursor → product ion transition of *m/z* 395.33 33 precursor ions to *m/z* 182.17 with collision energy of 30 eV for rizatriptan and *m/z* 298.15 precursor ion to *m/z* 241.15, with collision energy of 15 eV for sumatriptan. The separation was performed on an Agilent Zorbax Eclipse Plus-C18 column, 4.6 x 150 mm, 5 µm (Agilent Technologies, USA) maintained at 40 °C.

Preparation of Stock and Working Solutions

***a- Preparation of stock solution of rizatriptan standard*:** About 10 mg of rizatriptan standard was weighed placed into a 100 ml standard flask and dissolved using mobile phase 0.1% formic acid buffer: methanol (25: 75 *v/v*) to have a solution of 100 µg/ml. The working standard solution was prepared by taking 10 ml from the above solution in 100 ml mobile phase to obtain a solution of 10 µg/ml.

b-Preparation of stock solution of internal standard: About 10 mg of sumatriptan standard was weighed, placed into a 100ml standard flask and dissolved using mobile phase 0.1% formic acid buffer: methanol (25: 75 *v/v*) to have a solution of 100 µg/ml. The working standard solution was prepared by taking 10 ml from the above solution in 100 ml mobile phase to obtain a solution of 10 µg/ml.

Plasma standard calibration curve: It was prepared by spiking 1 ml of blank plasma with 1 ml of the internal standard working solution and appropriate volumes of Rizatriptan working solution to produce concentrations ranging from (0.25-60 ng/mL). The mixture was vortexed (Vortex Genie, Scientific industries, USA) for one minute and then centrifuged (Sigma, Germany) for ten minutes at 3000 r.p.m. The upper layer was separated and transferred to another tube filtered through 0.45 µm millipore filter for analysis using MS/MS. The calibration curve was obtained by plotting the chromatographic peak area ratios (Rizatriptan/ Sumatriptan) against the corresponding nominal Rizatriptan concentration added. Samples were prepared and injected directly into HPLC.

Evaluation of pharmacokinetic parameters: Pharmacokinetic parameters were measured by non-compartmental analysis using (PK Solver 2.0) software. For the determination of pharmacokinetic parameters mean serum concentrations (n=3) were used. The AUC for serum concentration versus time (AUC_{0-t}) and ($AUC_{0-\infty}$) were calculated by linear trapezoidal rule. Peak serum concentration (C_{max}) and time to reach this concentration (T_{max}) will be observed.

RESULTS AND DISCUSSION

Drug Incompatibility Studies

a- Fourier Transform Infrared Spectroscopy (FTIR): Figure (1) represented FTIR spectra of pure rizatriptan benzoate exhibited characteristic peaks at 3121 cm^{-1} (aromatic secondary amine N-H stretching), 2974 cm^{-1} (aromatic C-H stretching), 1604 cm^{-1} (C=O five member cyclic stretching) and 1210 cm^{-1} (C-N aliphatic amine stretching). All these peaks appeared in rizatriptan benzoate mixtures with different polymers in figures 2, 3 and 4.

b- Differential scanning calorimetry (DSC): Rizatriptan benzoate exhibits a sharp endothermic peak at 179.16°C shown in Figure (5), which corresponds to its melting point. The rizatriptan benzoate and CMC exhibit a sharp endothermic peak at 179.16ºC, rzatriptan benzoate and HPMC E6, rizatriptan benzoate and HPMC E15 exhibit a sharp endothermic peak at 179.16ºC, shown in Figures 6, 7 and 8 respectively. Hence DSC study shows that there is no any drug polymer interaction.

UV Scanning and standard calibration of rizatriptan benzoate: Figure (9) represented UV spectrophotometer scanning for rizatriptan benzoate showed in maximum absorption wave length at 275 nm in phosphate buffer pH6.8. Standard calibration for rizatriptan benzoate was carried out in phosphate buffer pH6.8 at 275 nm with the range of 10 to 60 µg/ml giving a best fitting line and slope was determined.

Formulation and Evaluation of fast dissolving films loaded with rizatriptan benzoate: Evaluation of fast dissolving films loaded with rizatriptan benzoate showed that the weight of film was ranged from 33± 0.000 mg of 1 % HPMC E15 film to 189±0.002 mg of 3% CMC film. The variation in weight is due to difference in the amount added as we increase the percentage of polymer; the

weight is increased and there is difference in different chemical structure of polymers as CMC more density than HPMC [19]. Films prepared at 1% w/v concentration with both polymers were very thin, clear transparent brittle and easily broken [14]. Films with 2 and 3% w/v concentration for both polymers were clear, transparent, and easily separated. The thickness varied in the range from 0.064±0.004 of 1 % HPMC E15 mm to 0.266±0.020 mm of 3% CMC film. All the strips were found to contain an almost uniform quantity of the drug as per content uniformity studies indicating reproducibility of technique. As per the IP requirements, the films found to meet the criteria for content uniformity as drug content in the film was evaluated and the values were found to be between 87± 0.730 and 104±0.041 for the different formulations. As all the formulations contained different amounts of polymer hence folding endurance was measured manually and it was ranged from 141±1.527 times to 356±0.577 times. The folding endurance was increased as the concentration of the polymer increased. In vitro disintegration study showed that some batches of fast dissolving film disintegrate in 21±1.527 seconds and others in 70.333±1.527 seconds. In vitro disintegration time was found to increase with increase in the amount of polymer used in the formulation. F4 formula was found to give minimum disintegration time 21±1.52 seconds as compared to other preparation results shown in table (2). The surface pH of the films was ranged from 5.8±0.305 and 6.6±0.264. Since surface pH films were found to be around neutral pH, there will not be any kind of irritation to mucosal lining of the oral cavity [12].

Dissolution of rizatriptan benzoate from different formulations of fast dissolving films: The in vitro release of the drug from formula F1 to F9 in phosphate buffer pH 6.8 was shown in figures (10, 11 and 12), it was obvious that the release rate was decreased with higher amount of CMC, HPMC E6 and HPMC E15 in formulation. After 2 minute 100% of the drug was released from formula (F1) CMC as film former polymer with increasing the percentage from 1% to 3% the time for release of drug was prolonged from 2 minute to 5 minutes respectively. It was found that the release of drug from formulae F4, F5 and F6 containing HPMC E15 1, 2 and 3% respectively decreased from 101±1.527 to 43±0.321 after 3 minutes. It was found that the release of drug from formulae F7, F8 and F9 containing HPMC E6 1, 2 and 3% respectively decreased from 96±1 to 62.666±2.516 % after 3 minutes. So it was found that the release of drug decreased on replacing CMC with HPMC this may be due to H-bonding between HPMC and carboxylic acid OH in rizatriptan benzoate [20].

Stability study: The stability study of the drug formula F1, F2, F4 and F7 was shown in figure 13 and 14 carried out at 40 ºC/45% RH and 50 ºC/45% RH for a period of 90 days respectively. It was noticed that F1 showed the least percentage of drug degradation. The percent of drug remained after 90 days were 99.3 % and 98.9% at 40 ºC/45% RH and 50 ºC/45% RH, respectively. This indicated that F1 is the best formula regarding stability study. On the other hand, the other formulae showed lower percent of drug remained and they could be ranked as F1> F2> F7> F4.

In vivo Release Studies

Pharmacokinetics parameters: Table (5) and figure 15 showed the comparison between the pharmacokinetic parameters of rapidly disintegrating sublingual film (F1) and oral marketed drug conventional tablets (Rizact-10 mg), it was shown that the fast dissolving film of rizatriptan benzoate reached the systemic circulation in time less than conventional tablet formula as the formulae F1 reach the maximum concentration after 0.333 while conventional tablet formula reaches C_{max} in blood after one hour which delays the therapeutic effect of the drug. The AUC_{0-8} for fast dissolving sublingual film and conventional tablet were found to be 142.958±14.914 and 91.958±10.897 respectively which may indicate that higher amount absorbed from F1 than conventional tablet formula and may enhance the drug bioavailability.

CONCLUSION

The fast dissolving films containing rizatriptan benzoate were prepared to obtain rapid onset of action and increased bioavailability. Various cellulose derivatives like CMC and HPMC were employed for their film forming properties of which CMC showed promising physicochemical properties as compared to all other grades therefore; it was selected for further studies. Prepared film with 1% CMC was transparent with smooth surface and acceptable mechanical properties. There was no interaction between drug and polymer. Film was disintegrated in 30 seconds. Drug release was found to be 100% in 60 seconds. F1 was the best formula in its stability (highest T_{90}, 0.8927 year) and was subjected to pharmacokinetic studies in comparison with oral marketed rizatriptan tablets (Rizact-10 mg, Cipla, Mumbai). It was concluded that fast dissolving film of rizatriptan benzoate reached the systemic circulation in time less than conventional tablet formulation (0.333 hr) , the maximum concentration of fast dissolving film 50 ng/ml while the conventional product was 25 ng/ml and

the AUC $_{0-\infty}$ for fast dissolving film were more than the marketed drug which indicate higher amount absorbed than conventional tablet formula and enhance the drug bioavailability. Thus, F1 is a promising formula as fast dissolving film for rizatriptan benzoate.

Table 1. Composition of different film formulations containing rizatriptan benzoate.

Formula No.	Rizatriptan Benzoate (g)	CMC (g)	HPMC E15 (g)	HPMC E6 (g)	Mannitol (g)	Aspartame (g)	PG (ml)	Water up to (mls)
F1	0.125	0.2	-	-	0.008	0.008	0.4	20
F2	0.125	0.4	-	-	0.008	0.008	1	20
F3	0.125	0.6	-	-	0.008	0.008	2	20
F4	0.125	-	0.2	-	0.008	0.008	0.4	20
F5	0.125	-	0.4	-	0.008	0.008	1	20
F6	0.125	-	0.6	-	0.008	0.008	2	20
F7	0.125	-	-	0.2	0.008	0.008	0.4	20
F8	0.125	-	-	0.4	0.008	0.008	1	20
F9	0.125	-	-	0.6	0.008	0.008	2	20

Table 2. Evaluation of physico-mechanical parameters and drug content of fast dissolving films loaded with rizatriptan benzoate.

Formula	weight variation (mg)	Thickness (mm)	Surface pH	Disintegration time (Sec)	Drug content (%)	Folding endurance (no. of folds)
F1	42 ±0.000	0.090±0.010	6.5±0.057	30.000±1.000	102.5±1.664	150±1.500
F2	78± 0.002	0.186±0.011	6.1±0.305	32.900±0.173	102.05±0.011	237±1.527
F3	189±0.002	0.23±0.020	6.6±0.264	57.666±1.154	91.89±0.770	290±0.0163
F4	30±0.000	0.064±0.004	6.4±0.251	21.333±1.527	92.966±1.094	141±1.527
F5	78±0.000	0.130±0.017	6.5±0.264	56.333±1.527	91.443±0.767	184±1.214
F6	151±0.002	0.213±0.015	6.4±0.300	70.333±1.527	87.190±0.74	230±1.081
F7	33±0.001	0.1±0.010	6.4±0.200	24.333±0.577	101.106±0.291	210±0.200
F8	83± 0.002	0.176±0.025	6.1±0.057	52.333±0.577	104.04±0.555	281±1.527
F9	143±0.003	0.266±0.015	6.4±0.300	68.000±1.000	102.043±0.115	356±0.577

Table 3. Kinetic data of accelerated stability testing of rizatriptan benzoate fast dissolving sublingual film at 40 ºC and 50 ºC/ 45%RH.

Mechanism of degradation (Zero-order)						
Formula	**K_{40} $(days)^{-1}$**	**K_{50} $(days)^{-1}$**	**E_a (cal/mole)**	**Calculated $K_{20}(days)^{-1}$**	**$t_{(1/2)}$ (year)**	**$t_{(90)}$ (year)**
F1	0.040087	0.045252	2435.044	0.030687	4.4639	0.8927
F2	0.072294	0.08514	3286.162	0.050407	2.71758	0.5435
F4	0.089729	0.090418	153.6906	0.08822	1.55263	0.3105
F7	0.078753	0.08625	1827.039	0.064446	2.12559	0.4251

Table 4. The plasma concentrations of rizatriptan benzoate after sublingual treatment with fast dissolving film and marketed drug.

Concentration of drug in plasma (ng/ml)								
(F1 containing 10 mg of rizatriptan benzoate)					**(marketed drug containing 14.25 mg of rizatriptan benzoate)**			
Time (Hours)	**volunteer (1)**	**volunteer (2)**	**volunteer (3)**	**Average**	**volunteer (4)**	**volunteer (5)**	**volunteer (6)**	**Average**
0	0	0	0	0.000	0	0	0	0.000
0.25	47	53	49	49.666	4	7	4	5.000
0.5	48	49	45	47.333	10	11	10	10.33333
0.75	39	42	38	39.666	20	16	20	18.66667
1	34	38	31	34.333	26	23	26	25.000
2	23	26	21	23.333	19	15	19	17.66667
4	12	16	15	14.333	12	9	12	11.000
6	7	11	9	9.000	8	6	8	7.333333
8	4	7	6	5.666	5	4	5	4.666667

Table 5. Comparison between pharmacokinetics parameters of rizatriptan benzoate fast dissolving film formula (F1) and oral marketed drug (Rizact-10 mg).

PK Parameter	**C_{max} (ng/ml)**	**$t_{½}$ (hr)**	**K (hr^{-1})**	**t_{max} (hr)**	**AUC_{0-8} (ng.hr/ml)**	**$AUC_{0-\infty}$ (ng.hr/ml)**
Fast dissolving Sublingual film (F1)	50±2.645	2.995±0.408	0.234±0.034	0.333±0.144	142.958±14.914	168.007±23.270
Oral marketed tablet (Rizact-10)	25±1.732	3.235±0.159	0.2205±0	1±0	91.958±10.897	113.650±12.596

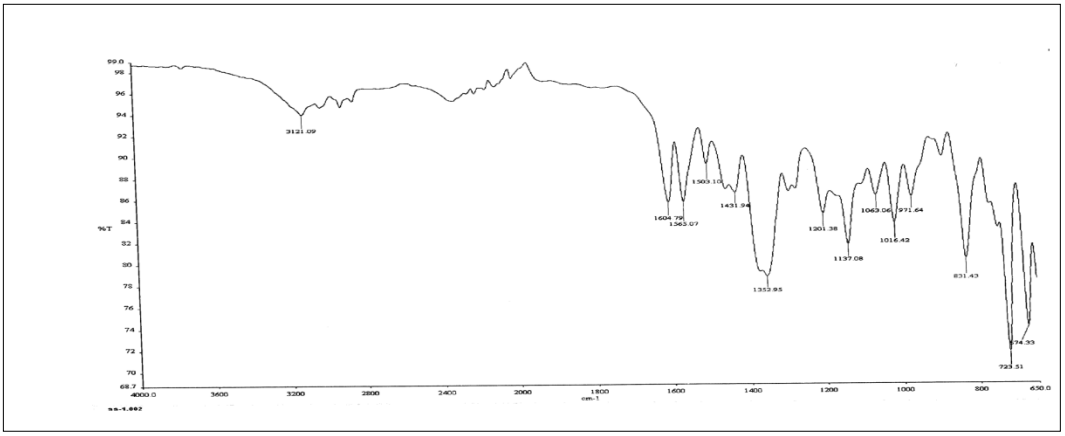

Figure 1. FTIR spectra for pure rizatriptan benzoate

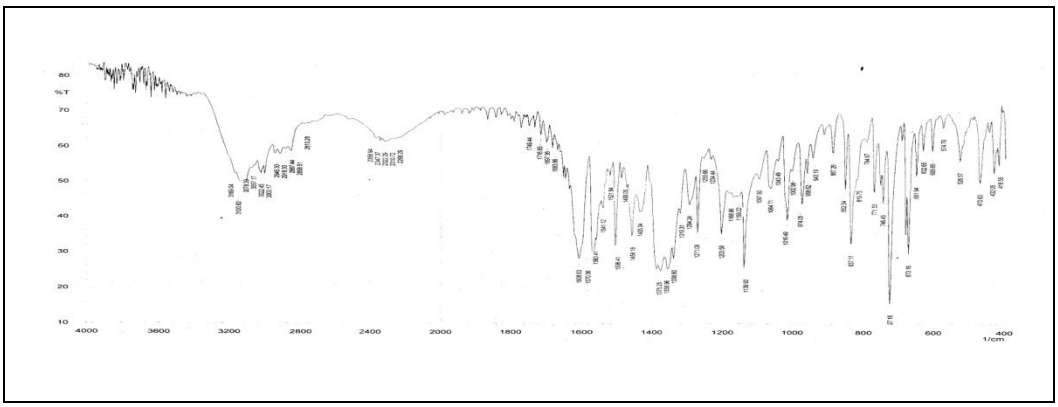

Figure 2. FTIR spectra for physical mixture of rizatriptan benzoate and CMC

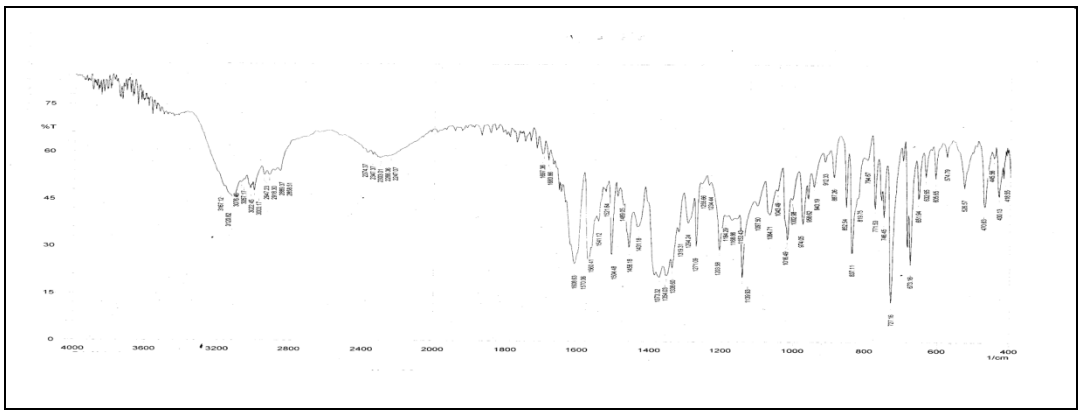

Figure 3. FTIR spectra for physical mixture of rizatriptan benzoate and HPMC E6 LV

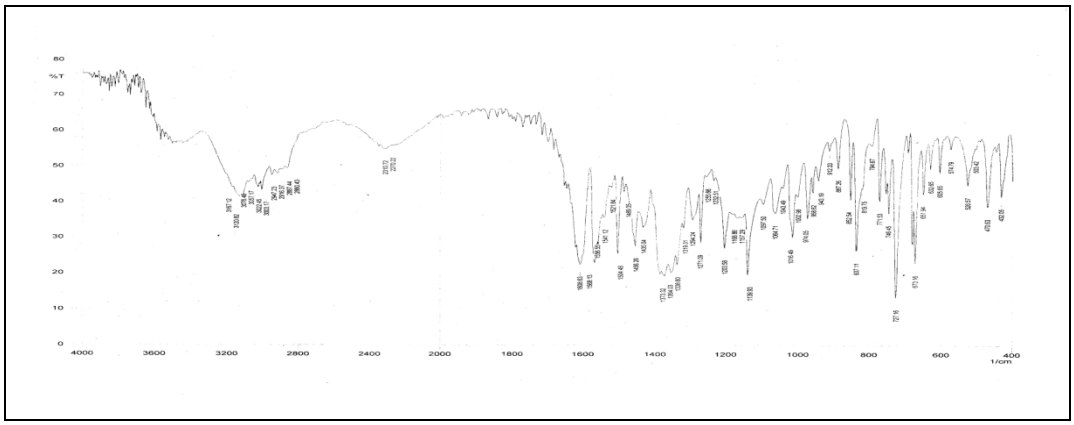

Figure 4. FTIR spectra for physical mixture of rizatriptan benzoate and HPMC E15 LV

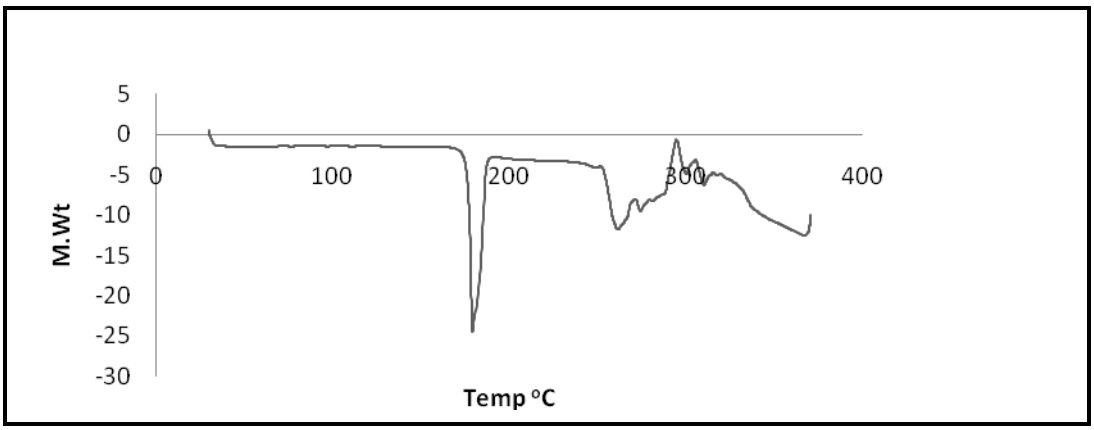

Figure 5. DSC thermal analysis of rizatriptan benzoate

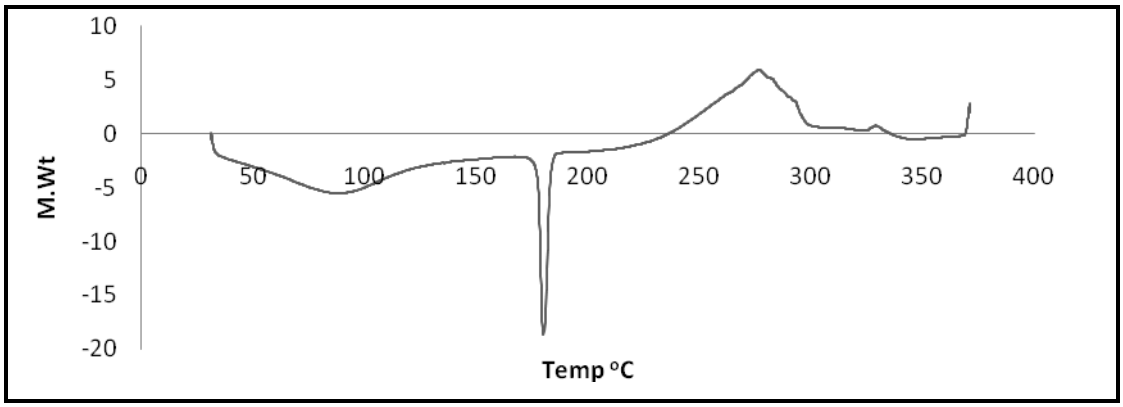

Figure 6. DSC thermal analysis of rizatriptan benzoate and CMC (LV)

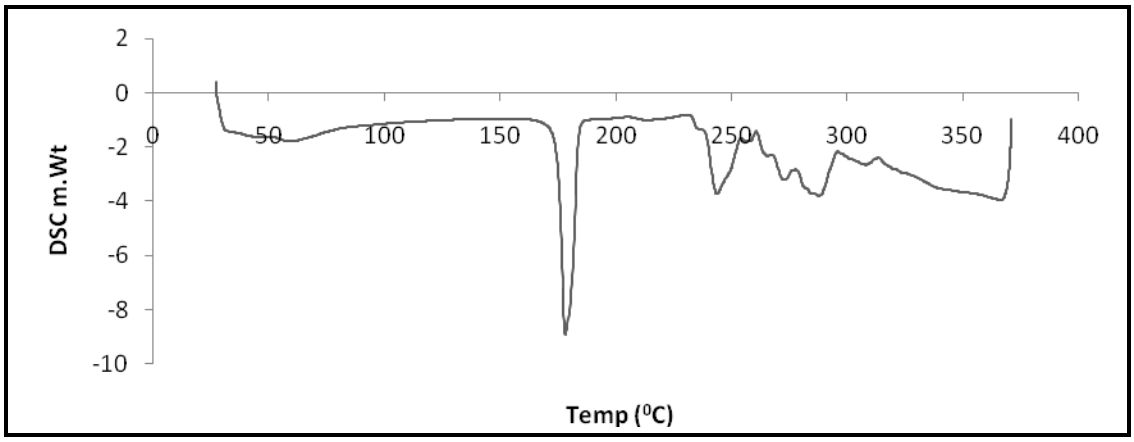

Figure 7. DSC thermal analysis of rizatriptan benzoate and HPMC E6 (LV)

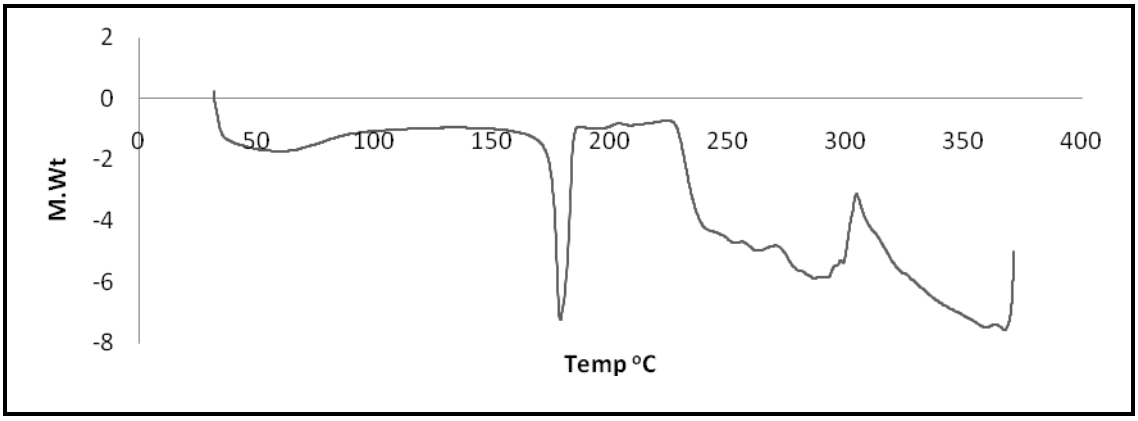

Figure 8. DSC thermal analysis of rizatriptan benzoate and HPMC E15 (LV**)**

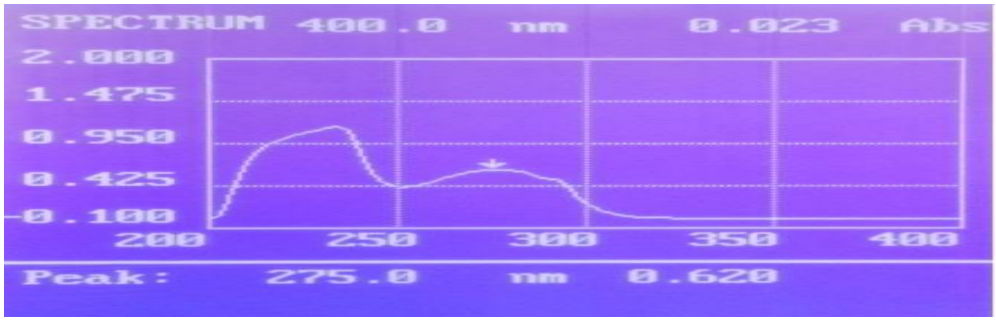

Figure 9. UV scanning of rizatriptan benzoate

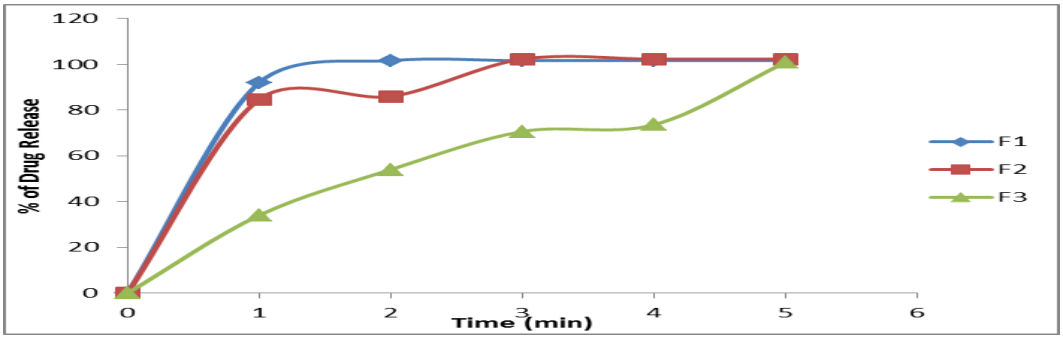

Figure 10. Plot of in vitro release of rizatriptan benzoate from formulae F1, F2 and F3 containing CMC with 1%, 2% and 3%, respectively

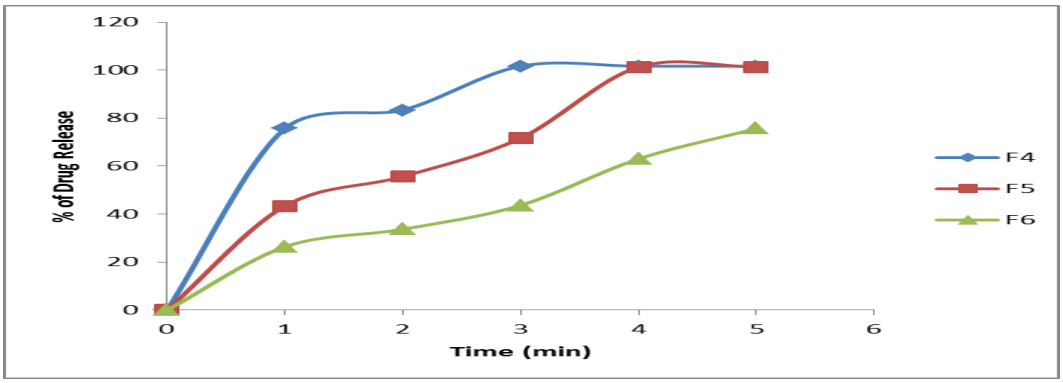

Figure 11. Plot of in vitro release of rizatriptan benzoate from formulae F4, F5 and F6 containing HPMC E15 with 1%, 2% and 3%, respectively

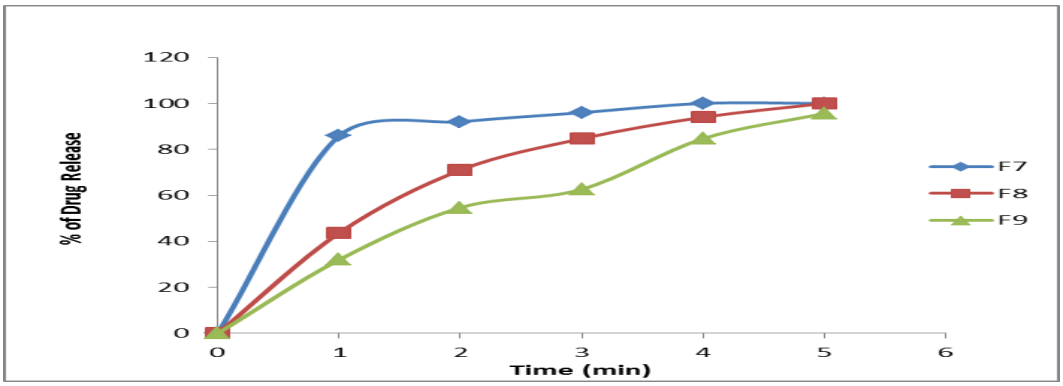

Figure 12. Plot of in vitro release of rizatriptan benzoate from formulae F7, F8 and F9 containing HPMC E6 with 1%, 2% and 3%, respectively

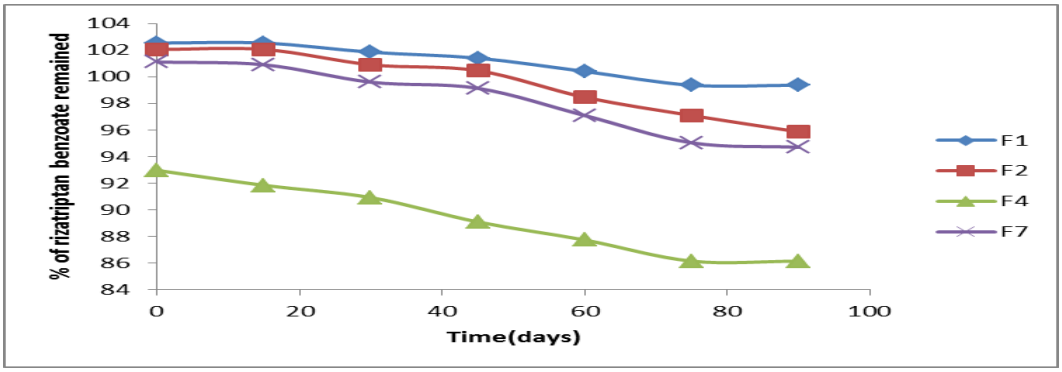

Figure13. Cumulative drug releases of formulae F1, F2, F4 and F7 under accelerated conditions 40 ^{0}C±2 ^{0}C (45±5% RH) after 90 days

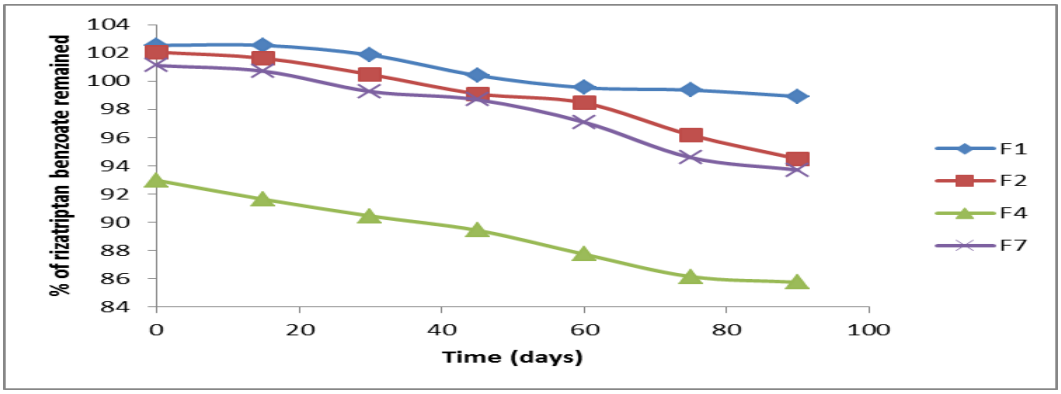

Figure14. Cumulative drug releases of formulae F1, F2, F4 and F7 under accelerated conditions 50 ^{0}C±2 ^{0}C (45±5% RH) after 90 days

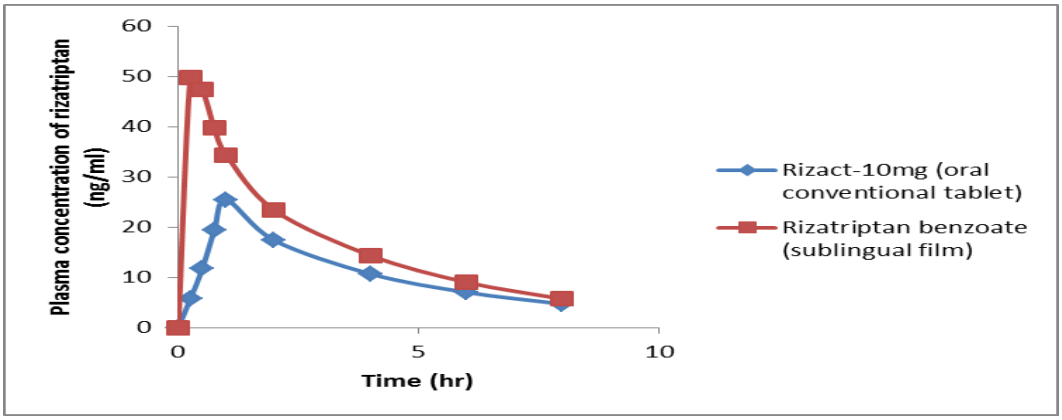

Figure15. The plasma concentration time curve of rizatriptan benzoate sublingual film and oral (marketed formulation) administration

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