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FORMULATION AND EVALUATION OF FAST DISINTEGRATING RIZATRIPTAN BENZOATE SUBLINGUAL TABLETS

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Rizatriptan benzoate is a potent and selective 5-$HT_{IB/ID}$ receptor agonist and is effective for the treatment of acute migraine. Sublingual formulation has the advantage of offering fast relief from migraine due to faster drug delivery. The present study involves the formulation and evaluation of fast disintegrating sublingual tablets of rizatriptan benzoate to produce intended effects. The sublingual rizatriptan benzoate tablets were prepared by the method of direct compression. The superdisintegrants used were sodium starch glycolate, cross carmellose sodium and cross povidone. The powder flow properties of all formulations were evaluated for diameter, thickness, weight variation, hardness, friability, wetting time, water absorption ratio, drug content, in vitro and in vivo disintegration time as well as in vitro release and were found to be satisfactory. The optimised formulation containing cross povidone disintegrated very fast and in vitro drug release was very high. The optimised formulation was characterised by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD) and fourier transform infrared spectroscopy (FTIR). Based on disintegration and dissolution studies, the optimised formulation was also evaluated for in vivo release studies using rabbit model. The peak serum concentration (C_{max}), half time needed for item to decay ($T_{½}$), time for maximum plasma concentration (T_{max}) and area under curve (AUC) were calculated. T_{max} for rizatriptan tablet was faster in sublingual route when compared to oral route. Rizatriptan tablet by sublingual route in rabbit shows effective therapeutic C_{max} when compared to clinical dose and it is a promising alternative to oral administration route in acute management of migraine.

Keywords: Rizatriptan benzoate, Fast disintegrating sublingual tablets, Pharmacokinetics, LCMS/MS

INTRODUCTION

Migraine is a frequently occurring headache that imposes a burden on both the individual patient and society. Rizatriptan benzoate is a potent and selective 5-$HT_{IB/ID}$ receptor agonist used for the treatment of migraine headache (Sunitha, Tejal and Ankit 2010; Pranzatelli 1999). The absorption is very rapid but the bioavailability is 40% due to extensive first pass effect. The half life of the drug is around 2–3 hours. In conventional tablets the onset of action is slow. So there is a need to formulate a dosage form which gives fast relief from headache, while at the same minimising the first pass effect to improve its bioavailability.

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The sublingual route usually produces faster onset of action as compared with oral route. A small quantity of saliva is sufficient for these formulations. The drug is absorbed partially or completely into the systemic circulation from the sublingual mucosal blood vessels, thus producing faster onset of action and bypasses hepatic first-pass metabolic process (Birudaraj, Berner and Shen 2005; Ishikawa *et al*. 2001; Price *et al*. 1997).

In the present study, the fast disintegrating sublingual tablets were prepared by the method of direct compression using various pharmaceutical excipients. The excipients used were avicel pH 102, sodium starch glycolate, cross carmellose sodium, cross povidone, mannitol, aspartame and magnesium stearate (Rameshwari and Jeya 2009). The developed sublingual tablets were evaluated for physical parameters, in vitro release studies and in vivo release studies using rabbit as the animal model.

METHODS

Rizatriptan benzoate was kindly supplied by Natco Pharma Limited (Hyderabad, India). Sodium starch glycolate, cross carmellose sodium, cross povidone, avicel pH 102, aspartame and magnesium stearate were supplied as gift samples by Cheminova Remedies (Hyderabad, India). Analytical grade chemicals and HPLC grade solvents were used. Double distilled water was used throughout the experiment.

Formulation of Fast Disintegrating Sublingual Tablets

Sublingual tablets of rizatriptan benzoate were prepared by the method of direct compression. The excipients used were mannitol, avicel pH 102 (diluent), sodium starch glycollate, cross carmellose sodium, cross povidone (super disintegrant), aspartame (sweetening agent) and magnesium stearate (lubricant). Accurate amount of the active ingredient and all additives were homogenously blended using geometric dilution after passing through sieve number 60 (standard sieve size) and finally magnesium stearate was added for lubrication and triturated well (Biradar, Bhagavati and Kuppasad 2006). Different quantities of excipients were used to prepare various formulations of sublingual tablets. The blended material was compressed on 8 mm standard concave punch using a minipress table punching machine (RIMEK, India). The total weight of formulation was made up to 150 mg (Keny, Chrisma and Lourenco 2010).

Evaluation of Sublingual Tablets

Micromeritic properties of rizatriptan powder formulations

The flow properties of powder are vital in handling and processing operations. The flow properties were obtained by measuring angle of repose, Carr's compressibility index and Hausner's ratio. The angle of repose was determined by using conventional fixed funnel method. From the bulk and tapped density, the Carr's compressibility index and Hausner's ratio of rizatriptan benzoate powders were calculated. The diameter and thickness of the tablets was measured with vernier callipers (Mututoyo, Japan).

Weight variation

After direct compression, 20 tablets were selected randomly and the average tablet weight was calculated. All the tablets were made sure to not deviate from the average weight by more than ±10%.

Hardness

The tablet crushing strength was determined by applying a force that is required for breaking of a tablet into two halves. This was measured using hardness tester (Tab Machines, India). Three tablets were randomly selected from each formulation and the average hardness was noted.

Friability

This test was performed to determine the effects of friction and shock. Pre-weighed sample of 10 tablets was placed in the friabilator (Electrolab, India) and rotated at 25 rpm for about 4 min. The tablets were dedusted and reweighed, and the friability percentage was calculated. Compressed tablets should not lose more than 1% of weight.

Wetting time

The tablet's wetting time was measured by using a simple procedure. A piece of tissue paper was cut circularly (10 cm diameter) and placed on a petridish containing 10 mL of water at room temperature. A tablet is placed on the surface of the tissue paper and the time required for the complete wetting of the tablet was noted (Honey, Nishant and Vikas 2008).

Drug content uniformity

Drug content uniformity was determined by crushing 20 tablets in a mortar. An amount equivalent to 10 mg of rizatriptan was dissolved in mobile phase. The mobile phase consisted of a 80:20% v/v mixture of buffer (pH 3.5) and acetonitrile, which was previously filtered through 0.45 µm nylon membrane filter and degassed. Appropriate dilutions were made and analysed using high performance liquid chromatography (HPLC; Agilent 1100 series, USA) at the wavelength of 225 nm. The liquid chromatography was equipped with a UV detector and a Zorbax SB phenyl, 5 µm (250 mm x 4.6 mm) column. Isocratic elution was carried out at a flow rate 1.0 mL/min. The injection volume was 10 µL and the column temperature was maintained at 30°C. The system was equilibrated for at least 30 min until a steady baseline was obtained.

Disintegration time

In vitro disintegration time was determined using a modified disintegration method (n=5) by using disintegration tester (Lab India, DS 1400, India) at 37±0.5°C in distilled water. The tablet was carefully kept in a basket. The time taken for the tablet to disintegrate completely into smaller particles were noted. For in vivo disintegration, the tablet was placed on the floor of mouth of volunteers (n=5) and the time taken for complete disintegration in the mouth was noted.

In-vitro release studies

All the formulations were studied for in vitro drug dissolution using USP dissolution test apparatus type II [paddle method (Lab India, DS 14000, India)] (Toshihiro, Masae and Yoshinori 2003) at a rotating speed of 50 rpm; 900 mL of water was used and maintained at 37±0.5°C. A tablet containing equivalent to 10 mg of rizatriptan was placed in each basket and the solutions were filtered through a 0.45 µm pore size (PVDF filter). The samples were collected at 5, 10, 15, 20, 30, 45 and 60 min and analysed for drug content using UV-visible spectrophotometer (Schimadzu, model UV1601, Japan) set at 282 nm. All dissolution studies were made in six replicates (n=6) to ensure a high sample power and confidence in the results. The calibration curve for rizatriptan in water was linear from 11.2–65.2 µg/mL (r^2>0.99).

Scanning Electron Microscopy (SEM)

The surface characteristics of the rizatriptan sublingual tablets and standard rizatriptan were examined by scanning electron microscope [Scanning Electron Microscopy (SEM), JEOL 5400, Japan]. Samples were placed on a brass stub using adhesive tape (Rahul, Zahra and Farhan 2009) and were made electrically conductive by vaccum sputter coating with gold, done five to six times, to form a thin layer of gold. SEM images were recorded at acceleration voltage of 5 kv.

Differrential Scanning Calorimetry (DSC)

The molecular state of the drug was evaluated by performing DSC analysis of placebo, physical mixture with drug, sublingual rizatriptan formulation and rizatriptan standard using a differential scanning calorimeter (DSC 6, Perkin Elmer, USA). The samples were heated in hermetically sealed aluminium pans over a temperature range of 35°C–350°C at a constant rate of 10.0ºC per min under nitrogen purge at 20 mL/min.

Powder X-ray Diffractometry (PXRD)

The powder X-ray diffraction patterns of sublingual rizatriptan tablets, physical mixture with rizatriptan and rizatriptan standard were measured using X-ray powder diffractometer (XRD x'pert PRO MPD, PANalytical, USA). The diffraction pattern was measured using Ni filtered Cu Kα (45 kV/40 mA) radiation (Takao *et al.* 2005). The samples were measured between the angular range of 2°–50°(2θ) using 0.017° steps and a 10 s counting time per step.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectrum peaks of placebo (tablet), physical mixture without drug, physical mixture with drug and rizatriptan sublingual formulation was compared with rizatriptan reference standard using FTIR spectrophotometer (Perkin Elmer Spectrum one series, USA) by KBr pellet method. The scanning was in between 400 to 4000 cm^{-1} and with 1 cm^{-1} resolution.

In vivo Release Studies

Pharmacokinetic analysis

Formulation nine (F9) was found as the best suitable formulation and the pharmacokinetic studies of this sublingual rizatriptan tablets were compared with oral marketed rizatriptan tablets (Rizact-10 mg, Cipla, Mumbai). The experimental protocol was approved by institutional animal ethics committee (Vimta Labs, Pre Clinical division, Hyderabad, India; study number: VLL/0611/NG/D006). Six male New Zealand rabbits (1.5–2.0 kg) were purchased from Sainath Agencies (Hyderabad, India). All rabbits were housed in stainless steel cages (size approximately 45 cm width × 60 cm length × 35 cm height). Rabbits were housed separately (Gu, Simons and Simons 1999), the cases were equipped with facilities for holding pellet food and drinking water in bottle with stainless steel sipper tube. All animals had free access to reverse osmosis (RO) generated potable water and standard animal diet (Provimi Animal Nutrition India Pvt. Ltd., Doddaballapur, Bangalore, India). During the study, the room temperature and relative humidity (RH) was maintained at 22±3°C and 30%–70% RH, respectively. Prior to treatment, rabbits were subjected to randomisation based on their body weights and distributed equally into two groups.

Each animal (n=3) in the first group was administrated a single sublingual tablet (10 mg) irrespective of the body weight under mild anaesthesia (isoflurane). The rabbit's mouth was opened, tongue was elevated and the tablet was placed underneath. Small amount of water was added to surface of the tablet before administering. The mouth was shut for 1 min, to avoid chewing or swallowing of the tablet. The rabbits from second group received comparator i.e. marketed preparation of rizatriptan tablet orally. Two mL of water was administered after dosing. Animals were bled at pre-determined time points through marginal ear vein (0, 0.83, 0.25, 0.5, 1, 2, 4, 6 and 8 h). The samples were centrifuged (Cetrifuse, Thermoscientific X3R, USA) and, serum was separated and stored at –20°C (Mutasem *et al.* 2006).

Analysis of blood samples

Study samples, calibration curve samples and quality control samples were transferred to pre labelled ria vials and 20 µL of internal standard (Zolmitriptan, 10 µg/mL) was added and vortexed, followed by addition of 2.5 mL of diethyl ether:dichloromethane (70:30), placed in shaker for 15 min and then centrifuged for 10 min at 20°C at 400 rpm. The supernatant (organic layer) was transferred into pre-labelled ria vial, evaporated under a stream of nitrogen at 35°C until completely dried; the dried residue was reconstituted with 0.2 mL of mobile phase and vortexed. Samples were loaded into pre-labelled auto-injector vials and 10 µL of samples were injected onto LC-MS/MS system containing HPLC (Perkin Elmer PE 200 series) and MS (API 2000, USA). The Devilosil ODS-3 column (4.6 × 150 mm, 3.5 µm; Nomura Chemical Co. Ltd., Japan) and the column oven temperature was maintained at 40°C. Mobile phase was 0.1% formic acid buffer:methanol (25:75, v/v) with a flow rate of 0.45 mL/min and the injection volume was 10 µL. The total run time was about 4 min and the electron spray ionisation was performed in the selected ion monitoring mode. The detection ions were at mass-to-charge ratios (m/z) of 270.20 amu (parent) to 201.0 amu (product) and 288.20 amu (parent) to 182.0 amu (product) for rizatriptan sublingual tablets and internal standard zolmitriptan respectively. The

chromatograms were analysed by using 1.4-2 version software and the concentration of rizatriptan was calculated. Pharmacokinetic parameters were calculated by non-compartmental analysis using WinNonlin® 6.1 software (Pharsight Corporation, USA).

Pharmacokinetic parameters

The following pharmacokinetic parameters were calculated primarily for the oral study. The peak serum concentration attained by the drug (C_{max}), time required to attain peak serum concentration (T_{max}), the area under the curve (AUC_{0-24}) and ($AUC_{0-\infty}$), time taken for a test item undergoing decay to decrease by half ($T_{1/2}$), the volume of distribution (Vd) and clearance of the drug (Cl) was estimated.

Statistical Analysis

Statistical analysis was expressed as mean±standard deviation (SD) and performed with repeated measures which controls the experimental wise error at rate α=0.05 which was used to determine significance among all possible pairs of formulations and interactions. The level of statistical significance was chosen as $p \leq 0.05$.

RESULTS

Preparation of Rizatriptan Sublingual Tablets

Fast disintegrating sublingual tablets of rizatriptan were prepared using direct compression method. Nine formulations were prepared. The composition of rizatriptan benzoate sublingual formulations is shown in Table 1. The powder flow properties were assessed from Angle of repose, Carr's Compressibility Index and Hausner's ratio. The Carr's Compressibility Index and Hausner's ratio were ≤15 and ≤1.18, respectively. The comparison of powder flow characteristics of the rizatriptan benzoate sublingual formulations are shown in Table 2.

Tables 3 and 4 show the physical parameters of all sublingual formulations. The diameter and thickness of the formulations ranged from 8.0±0.0 mm to 8.07±0.06 mm and from 3.10±0.00 mm to 3.2±0.00 mm, respectively. The average weight of the tablet in the formulations ranged from 147.96±0.06 mg to 153.5±0.25 mg. All the formulations of tablets indicated good mechanical strength (4–5 kg/cm^2). The friability was less than 0.5%, indicating that it is within the compendia limits, which showed that the tablets possess good mechanical strength. Drug content uniformity results were found to be good among all the formulations. The percentage of the drug content was more than 95.5% ($p<0.05$). All tablets disintegrated in the range of 80.33±0.58 s to 7.33±0.58 s. Less than 2 min was obtained for sublingual tablet formulations (USP31). All formulations met the requirements for disintegration test. Formulation 9 (F9) quickly disintegrated compared to other formulations, with disintegration time of 7.33±0.58 s.

Table 5 shows the *in vitro* release profile of rizatriptan benzoate from all the formulations. More than 85% of drug dissolved within 15 min. F9 showed 97.47±0.36 dissolution efficiency in 15 min. Based on disintegration and dissolution efficiency F9 was selected as the optimum formulation and was characterised.

Table 1: Composition of the rizatriptan sublingual formulations.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rizatriptan benzoate	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Sodium starch glycollate	3	6	9	–	–	–	–	–	–
Cross carmellose sodium	–	–	–	3	6	9	–	–	–
Cross povidone	–	–	–	–	–	–	3	6	9
Avicel 102	30.25	27.25	24.25	30.25	27.25	24.25	30.25	27.25	24.25
Aspartame	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Mannitol	100	100	100	100	100	100	100	100	100
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150	150	150	150

Note: Each tablet contains equivalent to 10 mg of rizatriptan

Table 2: Compressed tablet properties of the rizatriptan sublingual formulations.

Formulation	Angle of repose (θ)*	Bulk density (gm/mL)*	Tapped density (gm/mL)*	Compressibility Index (I)*	Hausner's ratio*
F1	32.6±0.10	0.22±0.01	0.26±0.01	14.87±0.98	1.18±0.01
F2	32.1±0.12	0.30±0.01	0.34±0.01	11.64±0.21	1.13±0.00
F3	31.6±0.13	0.22±0.01	0.25±0.01	12.01±0.48	1.14±0.01
F4	31.0±0.12	0.25±0.01	0.29±0.01	13.64±0.27	1.16±0.01
F5	30.9 ±0.13	0.25±0.01	0.28±0.01	10.59±0.21	1.13±0.00
F6	30.4±0.13	0.25±0.01	0.28±0.01	10.59±0.21	1.13±0.02
F7	29.8±0.12	0.26±0.00	0.30±0.01	13.48±0.27	1.15±0.02
F8	30.3±0.13	0.25±0.01	0.28±0.01	10.84±0.23	1.12±0.01
F9	29.7±0.13	0.26±0.01	0.29±0.01	10.46±0.21	1.12±0.00

Note: *All values represent mean±SD, n=3.

Scanning Electron Microscopy (SEM)

The surface morphology of sublingual rizatriptan benzoate formulation and standard rizatriptan benzoate were examined by scanning electron microscope (Fig. 1). The SEM micrographs reveal that there was no segregation or deposition of particles on the surface of sublingual tablets.

Table 3: Physical parameters of the rizatriptan sublingual formulations.

Formulation	Assay %***	Thickness (mm)***	Hardness (kg/cm²)**	Friability %***	Weight variation (mg)***
F1	95.92±0.04	3.2±0.01	4.0±0.0	0.29±0.0	153.5±0.25
F2	95.80±0.03	3.10±0.0	4±0.5	0.30±0.0	151.33±0.06
F3	95.79±0.03	3.15±0.01	4.0±0.0	0.25±0.0	150.07±0.06
F4	96.14±0.04	3.18±0.01	4.0±0.0	0.25±0.0	153.27±0.06
F5	95.77±0.04	3.10±0.0	4.17±0.29	0.30±0.0	147.96±0.06
F6	95.81±0.03	3.09±0.01	4.0±0.0	0.32±0.0	150.60±0.0
F7	96.23±0.04	3.18±0.01	4.0±0.0	0.29±0.0	151.46±0.10
F8	95.98±0.01	3.20±0.01	4.17±0.29	0.37±0.0	151.72±0.02
F9	96.03±0.04	3.10±0.00	4.0±0.0	0.35±0.0	152.34±0.03

Notes: ***All values represent mean±SD, n=20
**All values represent mean±SD, n=6

Table 4: Physical parameters of the rizatriptan sublingual formulations**.**

Formulation	Diameter (mm)***	In vitro disintegration time (s)**	In vivo disintegration time (s)**	Wetting time (s)*	Water absorption ratio (%)*
F1	8.03±0.00	80.33±0.58	110.33±0.51	65.33±0.58	156.73±0.0
F2	8.03±0.06	58.33±0.58	100.33±0.51	53.67±0.58	147.36±0.01
F3	8.05±0.06	54.67±0.58	80.33±0.51	42.33±0.58	141.55±0.00
F4	8.03±0.06	20.0±0.0	38.33±0.51	15.33±0.58	129.07±0.0
F5	8.03±0.06	19.0±0.0	35.67±0.51	14.33±0.58	121.36±0.0
F6	8.07±0.06	14.33±0.58	29.33±0.51	12.33±0.58	118.20±0.01
F7	8.07±0.06	11.0±0.00	28.33±0.51	9.33±0.58	109.58±0.0
F8	8.07±0.06	9.33±0.58	20.33±0.51	7.33±0.58	105.73±0.0
F9	8.07±0.06	7.33±0.58	13.67±0.51	5.33±0.58	94.17±0.0

Notes: *All values represent mean±SD, n=3
**All values represent mean±SD, n=6
***All values represent mean±SD, n=20

Differential Scanning Calorimetry (DSC)

The DSC thermograms of placebo (tablet), physical mixture with rizatriptan, rizatriptan sublingual tablets F9 and rizatriptan standard were studied. The endothermic peaks of rizatriptan standard appeared at 183°C and in the sublingual tablets and physical mixture it was found at 179°C. The small size of peak is attributed to the fact that the amount of rizatriptan in tablets and physical mixture with drug was around 15%. It shows that drug exist in crystalline form in formulation without having polymorphic change (Fig. 2). The

peak at 169°C in all the formulations except in standard rizatriptan was due to the presence of excipients. This was further confirmed by PXRD.

Powder X-ray Diffraction (PXRD)

PXRD studies were done to reveal the crystalline modification of the drug during formulation of tablets. The more intensive peak was obtained at 18.84 (2θ) for rizatriptan standard. Similarly, in sublingual tablets and in physical mixture a peak at about 18.74 (2θ) appeared, showing the crystalline nature of the drug in formulations (Fig. 3).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of placebo, physical mixture without drug, physical mixture with drug, rizatriptan sublingual formulation and standard rizatriptan are shown in Figure 4. The pure rizatriptan benzoate exhibited characteristic peaks at 3120 cm^{-1} (aromatic secondary amine N-H stretching), 2974 cm^{-1} (aromatic C-H stretching), 1608 cm^{-1} (C=O five member cyclic stretching) and 1270 cm^{-1} (C-N aliphatic amine stretching). All these peaks appeared in rizatriptan sublingual formulation (F9) at 3291 cm^{-1} (aromatic secondary amine N-H stretching), 2948 cm^{-1} (aromatic C-H stretching), 1608 cm^{-1} (C=O five member cyclic stretching) and 1281 cm^{-1} (C-N aliphatic amine stretching).

Pharmacokinetic Studies

The optimum formulation was chosen based on in vitro results by means of exhibiting fast disintegration and dissolution. F9 was included in in vivo study. The mean serum concentration-time data of rizatriptan (n=3) following sublingual and oral administration is shown in Figure 5. Table 6 shows pharmacokinetic parameters for both the formulations. The peak serum concentration attained by drug was 235.23±22.89 ng/mL and 486.34±262.75 ng/mL following sublingual and oral administration, respectively. The times required for attaining peak serum concentration by drug following sublingual and oral administration were 0.5 h and 1.33 h, respectively. The times required for a drug to decrease by half ($t_{1/2}$) were found to be 1.333 h and 1.024 h following sublingual and oral administration, respectively.

DISCUSSION

Rizatriptan sublingual tablets were prepared using direct compression method. Nine formulations were prepared using various excipients of different proportions. All the powder formulations showed small angle of repose (<33°) indicating good flow properties for all formulations. The average weight, friability and hardness were within compendial limits which shows that all formulations of tablets possessed good mechanical strength. The wetting time and water absorption were found to be 65.33±0.58 s to 5.33±0.58 s and 156.73±0.0% to 94.17±0.0%, respectively. It was observed that in F9 the tablet wetted and disintegrated completely within 5.33 s. Drug content uniformity was within acceptable limits, which indicates a homogenous distribution of drug in tablets.

Table 5: In-vitro release profile of the rizatriptan sublingual formulations.

Time (min)/ Code	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
5	82.50±0.61	82.58±0.50	81.10±0.75	82.25±0.66	81.65±0.55	83.48±0.78	83.22±0.28	84.19±0.86	85.87±0.54
10	85.34±0.99	85.43±0.65	82.49±0.24	85.90±0.88	87.32±0.52	88.09±0.30	87.72±0.11	88.42±0.52	89.46±0.34
15	86.33±0.51	85.69±0.02	87.14±0.87	87.18±0.14	88.60±0.29	90.75±0.83	95.74±0.59	96.61±0.43	97.47±0.36
20	87.74±0.30	87.91±0.91	89.26±0.56	89.59±0.75	91.01±0.96	92.57±0.36	96.02±0.43	96.89±0.27	98.19±0.17
30	89.16±0.58	88.34±0.26	89.96±0.76	90.59±0.41	92.14±0.79	96.63±0.45	96.86±0.44	96.90±0.68	98.47±0.12
45	93.69±0.44	94.08±0.69	98.63±0.28	96.26±0.44	96.53±0.17	97.20±0.39	97.56±0.04	98.30±0.45	99.05±0.38
60	96.25±0.04	98.20±0.69	99.05±0.17	98.39±0.42	98.80±0.07	98.88±0.07	99.25±0.02	99.57±0.37	99.76±0.14

Note: All values represent mean±SD, n=6

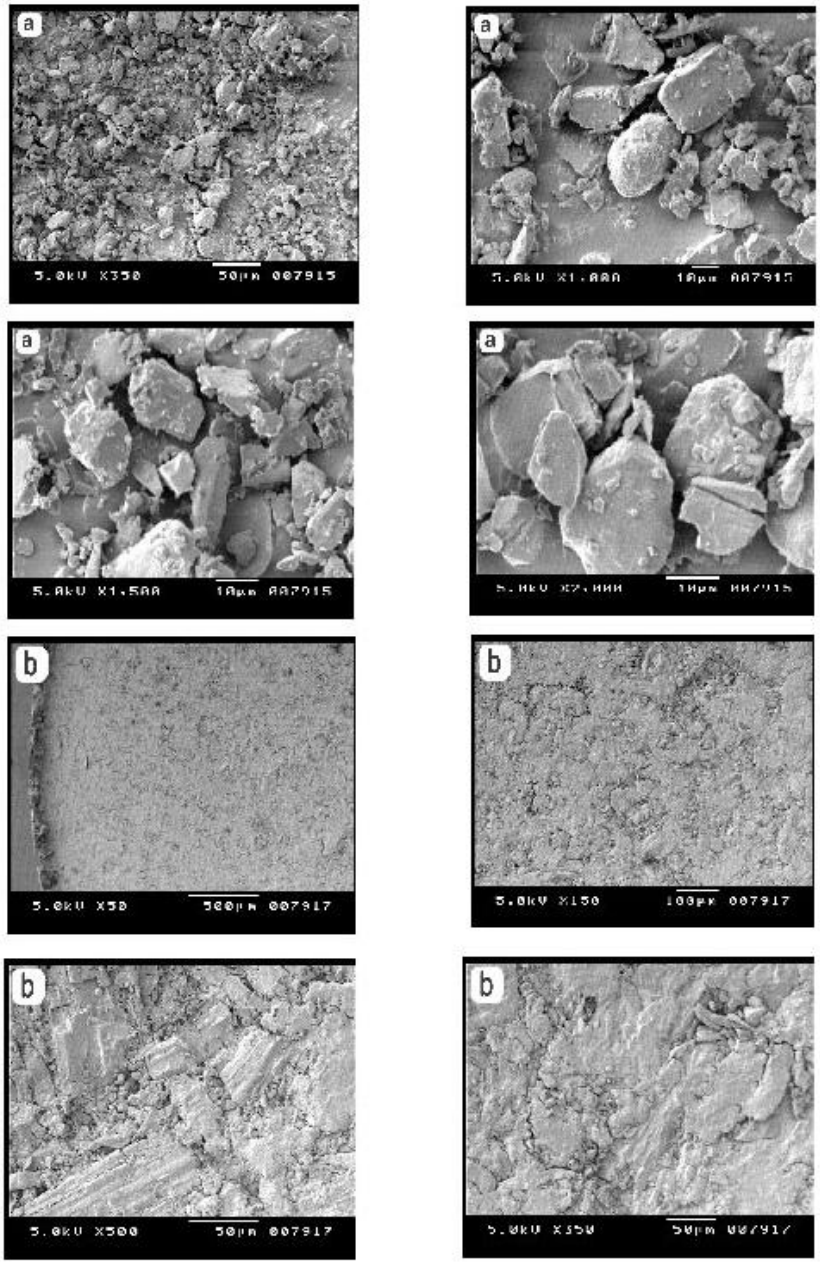

Fig. 1: Scanning electron microscope images of (a) rizatriptan standard and (b) rizatriptan sublingual tables (F9).

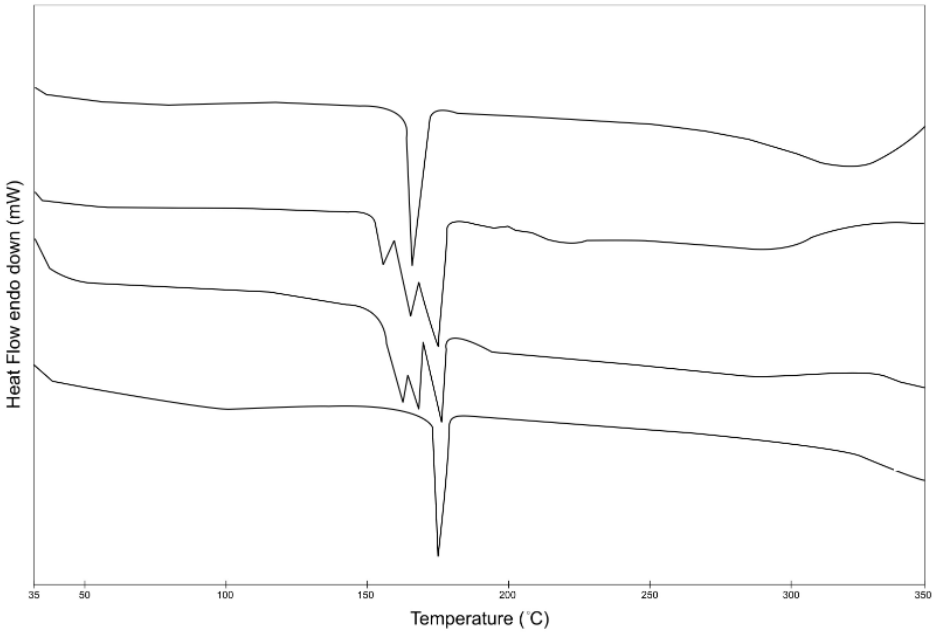

Fig. 2: DSC themograms of rizatriptan standard, sublingual rizatriptan tablets, rizatriptan physical mixture with drug and placebo.

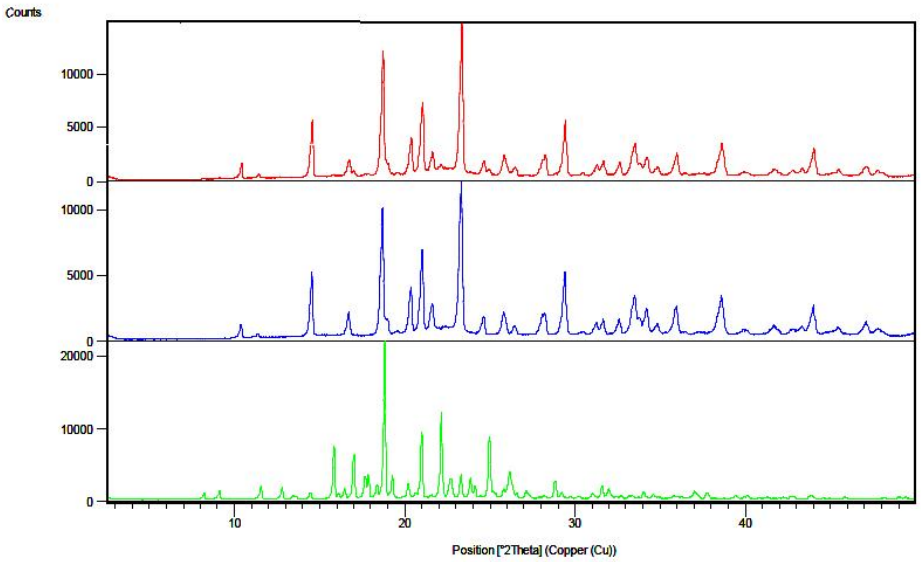

Fig. 3: PXRD patterns of rizatriptan standard, rizatriptan physical mixture with drug and sublingual tablets.

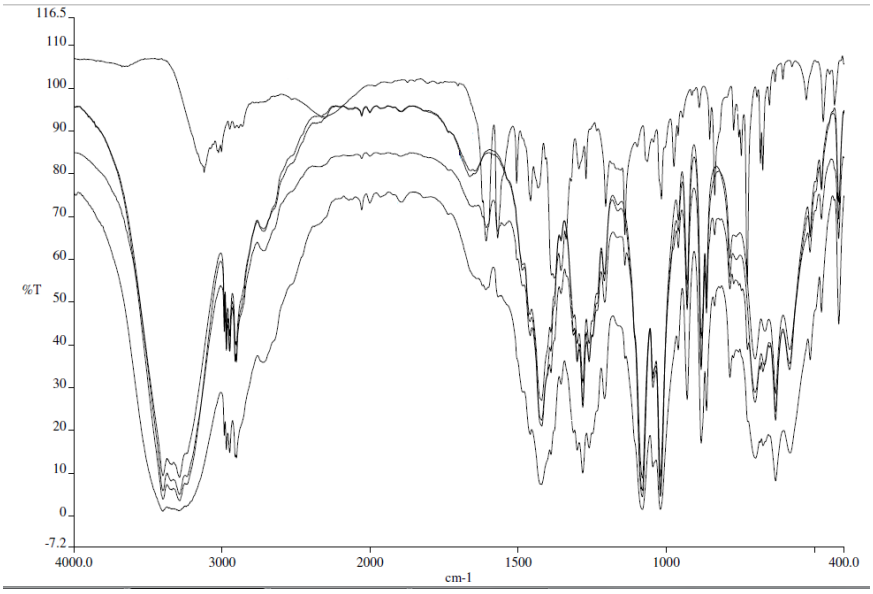

Fig. 4: FTIR spectra of physical mixture with drug, placebo, physical mixture without drug, rizatriptan sublingual tablets and rizatriptan standard.

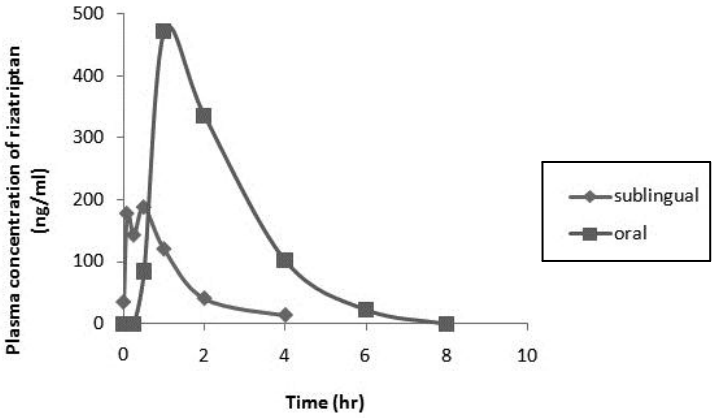

Fig. 5: The plasma concentration time curve of rizatriptan sublingual tables and oral (marketed formulation) administration. Results are expressed as the mean ± SD (n=3)

In the present study, all formulations of tablets disintegrated immediately (<2 min). The in vitro disintegration time of the tablets is an important parameter that should be optimised in the development of sublingual tablets. The tablet disintegration was affected by wicking and swelling of disintegrant (Jinichi *et al.* 2006). F9, which contained 6% of cross povidone, disintegrated more quickly as compared with other formulations. The in vivo disintegration time was in the range of 110.33±0.51 s to 13.67±0.51 s and the time was found to be 13.67±0.51 s for F9. Cross povidone exhibits high capillary activity and pronounced hydration capacity, faster disintegration and dissolution. It swells

rapidly in water without getting gel formation due to its high cross link density (Mohanchandran, Sindhumol and Kiran 2011). As a result, the cross povidone-containing tablets quickly wicks the saliva into the tablet which generates the volume expansion and the hydrostatic pressure to provide rapid disintegration in the mouth (Rudnic *et al.* 1980).

The SEM pictures showed no evidence of negative crystalline structure in the sublingual tablet formulation. The DSC and PXRD studies showed the crystalline nature of the drug in the formulations. The FTIR spectrum of sublingual tablets indicated the drug and excipients did not undergo any chemical interaction. Based on fast disintegration and dissolution efficiency, F9 was included in vivo study. The times required to attain peak serum concentration, following sublingual and oral administration were 0.5 h and 1.33 h, respectively. Area under the curve AUC_{0-t} was found to be 475.49±97.02 ng.h/mL and 1083.31±385.62 ng.h/mL for sublingual and oral administration respectively. In the current study, even though the plasma concentrations of sublingual tablets were lower compared to oral tablets, the C_{max} (235 ng/mL) achieved with sublingual route elicits the pharmacological activity. As reported in the literature for 10 mg human dose, the concentrations achieved after conversion factor from rabbit to man would be 6.38 ng/mL (Suzanne *et al.* 2006). The elimination is increased in sublingual tablets probably due to rapid transport across the single epithelial cell layer of the sublingual mucosa into the interstitial fluid then into the venous circulation down the concentration gradient and due to bioavailability. The mean plasma concentration-time profiles for rizatriptan 10 mg tablet by sublingual and oral route show a comparable time to peak plasma concentration. The time to achieve maximum plasma concentration (T_{max}) for rizatriptan 10 mg tablet was faster in sublingual route of administration when compared to oral route. Rizatriptan 10 mg tablet by sublingual route in rabbits show effective therapeutic C_{max} when compared to clinical dose (Suzanne *et al.* 2006; Chen *et al*. 2005; Jun *et al*. 2005).

Table 6: Pharmacokinetic parameters of rizatriptan sublingual tablets and oral tablets (10 mg/tablet).

PK parameters	*Sublingual tablets	Oral administration
C_{max} (ng/mL)	235.23±22.89	486.34±262.75
T_{max} (hr)	0.5±0.43	1.33±0.58
AUC_{0-t} (ng.h/mL)	475.49±97.02	1083.31±385.62
$AUC_{0-\infty}$ (ng.h/mL)	235.23±92.37	1298.55±307.46
$T_{1/2}$ (h)	1.34±0.18	1.02±0.15
Cl (mL)	18672.04±3173.86	7922.97±1875.93
Vd (mL)	36376.57±10917.33	11908.99±4491.57

Note: *Significant difference at $p \leq 0.05$ vs control

CONCLUSION

All tablets met the compendia limits in terms of physical parameters, disintegration and dissolution efficiency. When given sublingually, rizatriptan is well absorbed, and its bioavailability by this route is significantly enhanced with the addition of cross povidone. From this study, the optimised rizatriptan sublingual tablets appeared to be a promising alternative to oral administration route in acute management of migraine.

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