Formulation and Evaluation of Fast Disintegrating Zolmitriptan Sublingual Tablets

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Abstract

The drug delivery via sublingual drug route is considered to be a one of promising alternative to oral route and quick entry of drug into the systemic circulation can be possible. A diseases state such as migraine, considering pharmacological response was fast which is an important criteria. In the present study sublingual tablets of a potent anti-migraine drug of zolmitriptan 5mg per tablet were prepared. The powdered materials are compressed by direct compression method incorporating various pharmaceutical excipients. The super disintegrates were used are sodium starch glycolate, cross carmellose sodium, cross povidone. The flow properties of powder are important in handling and processing operations. The blend was examined for angle of repose, Carr's compressibility index and Hausner's ratio. The Angle of repose was determined by using conventional fixed funnel method. The Carr's compressibility index and Hausner's ratio were calculated from Bulk and tapped density of the zolmitriptan sublingual powder. The tablets were studied for physiochemical properties and dissolution efficiency. The optimised formulation was used for *in vivo* studies on rabbit as an animal model. The optimised formulation was disintegrated rapidly and from the dissolution studies, it was within the limits of compendia.

This specially reveals that the concentration range of mannitol, cross povidone and avicel 102 are in the appropriate ratios and are formulated in good proportions. From *in vivo* studies it showed that optimised formulation containing cross povidone has the minimum T_{max} and $T_{1/2}$ values (P<0.05), and show effective therapeutic Cmax when compared to clinical dose and it's a promising alternate to oral administration route in acute management of migraine.

Keywords: Fast disintegrating sublingual tablets, Pharmacokinetics, LC-MS/MS.

Introduction

Cluster headache is rare but extremely debilitating disorder that is characterised by the rapid onset of unilateral , per orbital headache that quickly escalates to maximum intensity, patients routinely report the pain of an attack as being the most severe they have ever experienced. Based on the definition of the International Headache Society attacks headache typically last for 15 to 180 minutes when it is untreated and subjected by one more cranial autonomic features such as ipsiletaral, conjunctival injections, lacrimation and rhinorrhoea or nasal congestion (1,2). In this case rapid onset of pharmacological effect is an often desired from drugs. This can be possible through parenteral route of

administration, but this method, sometime may give some inconvenience to the patient. Therefore there is a need to develop such new, non parenteral, and convenient dosage forms using other administration routes where the drug rapidly dissolved and immediately available for the systemic circulation (3).

Sublingual administration can offer an attractive alternative route of oral administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation, bypassing the enzyme degradation in the gut and liver. In addition to the thin sublingual mucosa (about 190 μm compared to 500-800 μm of the buccal mucosa) and the abundance of blood supply at the sublingual reason allow excellent drug penetration (absorption) to achieve high plasma drug concentration with a rapid onset of action. A well established example is nitroglycerin which is used for the treatment of acute angina (4). Zolmitriptan is a second- generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea, and photo or phono phobia. It is currently available as a oral tablet, an orally disintegrating tablet and a nasal spray (2.5 mg and 5 mg per dose) (5,6). In present study, we have developed zolmitriptan fast disintegrating sublingual tablets using pharmaceutical excipients in appropriate proportions (7), and manufactured with optimal techniques. For this reason, the developed sublingual tablet formulations were evaluated with basic tablet physicochemical tests, *in vitro* release studies and *in vivo* studies using rabbit as the animal model.

Materials and Methods

Zolmitriptan was kindly supplied by Suven Pharma Limited Hyderabad, India. Sodium starch glycollate, cross carmellose sodium, cross povidone, avicel pH102, aspartame, mannitol and magnesium stearate were supplied as gift sample by Cheminova Remedies, Hyderabad, India. All 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 zolmitriptan were prepared using the method of direct compression. The excipients used were mannital (8), avicel pH102 (diluent), sodium Starch glycollate (9, 10), cros carmellose sodium, cros povidone (super disintegrant) (11-13), aspartame (sweetening agent), 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 test sieves) and finally magnesium stearate was added for lubrication and triturated well. Different concentrations of excipients were used to prepare different formulations of sublingual tablets. The blended material was compressed on 8mm standard concave punch using a minipress (RIMEK, India). The total weight of tablet was 150 mg.

Evaluation of sublingual tablets

Micromeritic properties of zolmitriptan powder formulations: The flow properties of powder are important in handling and processing operations. The blend was examined for angle of repose, Carr's compressibility index and Hausner's ratio. The Angle of repose was determined by using conventional fixed funnel method. The Carr's index or % compressibility can be expressed using the following formula

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where D_t is tapped density of the powder and D_b is bulk density of the powder.

Hausner's ratio were calculated from bulk and tapped density of the zolmitriptan sublingual powder formulation and it is expressed as

$$\text{Hausner's ratio} = \frac{D_t}{D_b}$$

Where D_t is tapped density and D_b is bulk density.

***Determination of physiochemical parameters*:** Drug content uniformity (14) was determined by dissolving the crushed tablets in mobile phase (90:10 %(v/v)) mix buffer (pH 4.0) and acetonitrile respectively and filtered through 0.45 μm membrane filter and degas. It was made necessary dilutions and analysed using High Performance Liquid Chromatography (HPLC - Agilent 1100 series, USA)at the wavelength of 210nm .The liquid chromatography equipped with UV detector and column YMC-pack ODS-AQ (150x4.6mm, 5μm) was used. Isocratic elution was carried out at a flow rate 1.0 ml/min. The injection volume was 10μl and the column temperature was 30° C. Weight variation test was done by weighing 20 tablets, and individual tablet weights were compared with calculated average weights.

The thickness and diameter of the tablets was measured with a vernier calliper (Mututoyo, Japan). The strength of tablet is expressed as tensile strength (N: Newton). The tablet crushing load was the force required to break a tablet into two halves by applying compression. It was measured using a tablet Hardness tester (Tab machines, India).The Friability test is performed to assess the effects of friction and shocks, which may often cause tablet to chip, cap or break. Friabilator (Electrolab, India) was used for this purpose. Pre-weighed twenty tablets was placed in the Friabilator and operated for 100 revolutions (15). The tablets was dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

Wetting time of the tablets was performed by placing the tablet on tissue paper which was placed in a petri dish of 6.5cm in diameter containing 10ml of water at room temperature, and the time for complete wetting was recorded. *In vitro* disintegration time was carried out using a modified disintegration method (n=6) using disintegration tester (Lab India, DS 1400, India) at 37± 0.5°C in distilled water. The tablet was kept in the basket and noted the time taken for the tablet to disintegrate completely into smaller particles (16).

In vivo disintegration time was carried out by placing a tablet in the floor of the mouth of the volunteer (n=6) and the time required for complete disintegration in the mouth was noted. The taste and mouth feel was also observed (17). *In vitro* dissolution for all the formulations were studied (13), employing a USP Dissolution test apparatus type II (Paddle method (Lab India, DS 14000, India)) at a rotating speed of 50 rpm according to US FDA guidelines. The medium used for these dissolution tests was 500 ml of 0. 1N hydrochloric acid maintained at 37±0.5°C. The solution was filtered though a 0.45μ pore size (PVDF filter) .The samples were collected at predetermined time intervals (5,10,15,20,30,45 and60 min) and analysed for drug content with a UV-Visible spectrophotometer (Schimadzu, model UV1601, Japan) set at 223nm. All the dissolution studies were made six replicate (n=6) to ensure a high sample power and confidence in the results. The calibration curve for zolmitriptan in 0.1N hydrochloric acid was linear from 1-8 μg per ml (r^2>0.99).

***Scanning Electron Microscopy (SEM)*:** The surface characteristics of the zolmitriptan sublingual tablets and standard zolmitriptan were examined using Scanning Electron Microscope (SEM)(Scanning Electron Microscopy, JEOL 5400, Japan) . Samples were fixed on a brass stub

using double sided adhesive tape and were made electrically conductive by coating with five to six times and formed a thin layer of gold, then 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 (tablet), standard zolmitriptan, zolmitriptan physical mixture without drug, physical mixture with drug and sublingual zolmitriptan formulations. Using differential scanning calorimeter (DSC 6, Perkin Elmer, USA) curves of the samples were obtained. The samples were heated in hermetically sealed aluminium fans over a temperature range of 35°C - 350°C at a constant rate of 10.0°C per min under nitrogen purge at 20ml /min.

Powder X-Ray Diffractometry (PXRD): Physical mixture with drug, standard zolmitriptan and sublingual zolmitriptan formulation were measured using X-Ray powder diffract meter (XRD x' pert PRO MPD PAN Analytical, USA). The diffraction pattern was measured using Ni filtred Cu Ka (45kV/40mA) radiation. 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 (FT-IR): Infrared spectrum peaks of placebo(tablets), physical mixture without drug, physical mixture with drug, zolmitriptan sublingual formulation was compared with zolmitriptan reference standard using FT-IR spectrophotometer (Perkin Elmer Spectrum one series, USA) by KBr pellet method. The scanning range was in between 400 to 4000 cm^{-1} and 1 cm^{-1} resolution.

Pharmacokinetic analysis: Physicochemical properties of formulation nine (F9) was selected and pharmacokinetic studies of sublingual tablets were compared with intravenous administration

(18-20).The experimental protocol approved by institutional animal ethics committee (Vimta Labs, Pre clinical Division, Hyderabad, India, Study number: VLL/0611/NG/D007). Six male New Zealand rabbits (1.4 -2 kg) were purchased from Sainath agencies, Hyderabad, India. All rabbits were housed in stainless steel cages (size approximately width 45X length 60X height 35cm). Rabbits were housed separately; the cases were equipped with facilities for holding pellet food and drinking water in bottle with stainless steel sipper tube. All rabbits were free access to reverse osmosis (RO) generated potable water, standard animal diet (provimi animal nutrition). During the study, the room temperature and relative humidity was maintained at 22°C ± 3°C and 30% - 70% RH respectively. Prior to treatment, initiation rabbits subjected to randomization based on their body weights and distributed equally into two groups (21, 22).

Each animal (n=3) in first group was administrated single sublingual tablet (5mg) irrespective of the body weight under mild anaesthesia (isoflurane). The rabbit mouth was opened, tongue was elevated by using a flat forceps, tablet and small amount of water was added to surface of the tablet before administering. It was placed underneath of the mouth by using forceps (30). The mouth was closed for few minutes, to avoid chewing or swallowing of the tablet (23-25) Group-II rabbits were received intravenous preparation of zolmitriptan (standard, 5mg per kg body weight) according to body weight. 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 hours). The samples were centrifuged (Cetrifuse, thermoscientific X3R, USA) and serum was separated, stored at -20°C.

Analysis of blood samples: Study sample, calibration curve samples and quality control

samples were transferred to a pre labelled ria vials and added 20μ of internal standard (rizatriptan 2 μg /ml) was added and vortexed, 2.5 ml of diethyl ether: dichlomethane (70:30) was added and shaken for 15 minutes, then centrifuged for 10 minutes at 20°C at 400 rpm. The supernatant was transferred into pre labelled ria vial, evaporated under a stream of nitrogen at 35°C until it completely dried, reconstituted the dried residue 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 mass spectrophotometer, API 2000, USA). The Devilosil ODS-3 column (4.6x150mm, 3.5 μm) and the oven temperature was maintained at 40°C and mobile phase was 0.1% formic acid: acetonitrile (25 :75 V/V) with a flow rate of 0.45ml/min and an injection volume with 10μl. The total run time was about 4 minutes and the electron spray ionization was performed in the selected ion monitoring mode. The detection ions were at mass-to-charge ratios m/z of 288.2amu (parent) to 182amu (product) and 270.2amu (parent) to 201amu (product) for zolmitriptan tablets and internal standard rizatriptan respectively. The chromatograms were analysed by using 1.4-2 version software and the concentration of zolmitriptan was calculated. Pharmacokinetic parameters were calculated by non-compartmental analysis using WinNonlin (R) 5.2 software.

Pharmacokinetic parameters: The following parameters were primarily calculated from *in vivo* study. The Peak serum concentration attained by the drug (Cmax) and its time required to attain peak serum concentration (Tmax) (26-29) where obtained directly from the plasma concentration time profile. The area under the curve (AUC0-t) was calculated by using trapezoidal rule method. The AUC0-8 , time taken for a test items undergoing decay to decrease by half ($T_{1/2}$) was calculated (31) and the volume of distribution (Vd), clearance of the drug is calculated (Cl) . The bioavailability (%F) was estimated (32-34).

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, was used to determine significance among all possible pairs of formulations and interactions. The level of statistical significance was chosen as p≤0.05 (ANOVA).

Results and Discussion

Preparation of zolmitriptan sublingual tablets: Total nine formulations of zolmitriptan sublingual tablets were prepared using three super disintigrents (sodium starch glycolllate, cross carmellose sodium and cross povidone) with variation in there percentage (2-6%) and variation in excipients. The diluents used were mannitol and avicel pH 102. The composition of zolmitriptan sublingual formulation was shown in Table 1.

The micromeritic properties of the zolmitriptan powder formulations are vital in handling processing operations because the dose uniformity and ease of filling into container is detected by the powder flow properties. The powder flow properties can be accessed from Angle of repose, Carr's index and Hausner's ratio. The results for powder formulations were represented in Table 2. Our results indicate small angle of repose (<33°) assuring good flow properties for formulations. In addition to this Carr's index and Hausner's ratio were also less than 14 and 1.17 respectively ensuring all nine formulations resulted in good mixing, flow ability and compressible characteristics. Table 3 and 4 shows the physiochemical characterization of sublingual formulations. Drug uniformity results

were found to be good among different batches of tablets and the percentage of the drug content was more than 97.5% (P<0.05). The results also showed acceptable and homogeneous distribution of drug in all tablets. The average weight of the tablet in all formulations ranged from 150.07 ± 0.06 mg to 151.37 ± 0.23mg. All tablets prepared in this study meet the USP requirements for weight variation <2% (USP 31).The diameter and thickness of the formulations ranged from 8.03± 0.06mm to 8.17± 0.06mm and from 3.1±0.00mm to 3.2±0.00 mm respectively. All the formulations of tablets indicated good mechanical strength (4-5kg/cm 2), where as friability is less than 0.5%, indicating the friability was within the compendia limits (USP 31), which showed that the tablets possess good mechanical resistance.

In vitro disintegration study: The disintegration time of the tablets was one of the most important parameter which is supposed to be optimised in the development of sublingual tablets. In this present study, all the tablets were disintegrated in the range varied from 84.3±0.58s to 7.7±0.58s. As per USP, the disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without covering plastic disks and 2 minutes is the time limit specified as an acceptable limit for tablet disintegration fulfilling the official requirements (<2minutes) for sublingual tablets (USP31).

All of our formulations meet the requirements for disintegration. Out of all, the formulation 9 (F9) was quickly disintegrated compared to other formulations and showed disintegration time of 7.7±0.58s.The *in vivo* disintegration time was in the range of 115.33± 0.58s to 12.33±0.58s and the time was found to be 12.33±0.58s for formulation nine (F9). The wetting time and water absorption was 66.0±1.0s to 5.0±1.0s and 154.32±0.01% to 90.75±0.01% respectively. It was observed in formulation 9

(F9), the tablet wetted and disintegrated completely within 5s.

In vitro dissolution study: Table 5 showed the dissolution profile of zolmitriptan from all formulations. After starting the experiment, more than 85% of drug was dissolved within 15 minutes. According to the literature, amount of drug dissolved from sublingual tablets must exceed 80% in 15 min. Therefore the resulted dissolution profile met the above-mentioned requirement. The formulation nine (F9) showed 100.34± 1.19 dissolution efficiency in 15 min than other formulations, Which contains 6% cross.povidone, shown less disintegration time and more dissolution efficiency. Hence formulation 9(F9) was selected as optimized formula and is characterised.

Scanning Electron Microscopy (SEM): The surface morphology of sublingual zolmitriptan formulation and standard zolmitriptan and were examined by scanning electron microscopy (Fig.1). The SEM micrographs reveal that there is no segregation or deposition of particles on the surface of sublingual tablets.

Differential scanning calorimetry (DSC): The thermo tropic behaviour, the physical states of the drug in sublingual tablets were ascertained from the DSC thermo grams of placebo (tablet), physical mixture without drug, standard zolmitriptan, physical mixture with drug and zolmitriptan sublingual formulation (F9). It is shown from Fig. 2 that the onset of peak for standard zolmitriptan was found to at 136°C; a sharp intensive peak at 140°C was observed. In the zolmitriptan sublingual tablets and physical mixture with drug, there is a small peak was noticed at 138°C (135°C-140°C). The small size of peak is attributed to the fact that the amount of zolmitriptan in physical mixture with drug and tablets was less than 10% by weight. The peak at 169°C in all the formulations except in standard
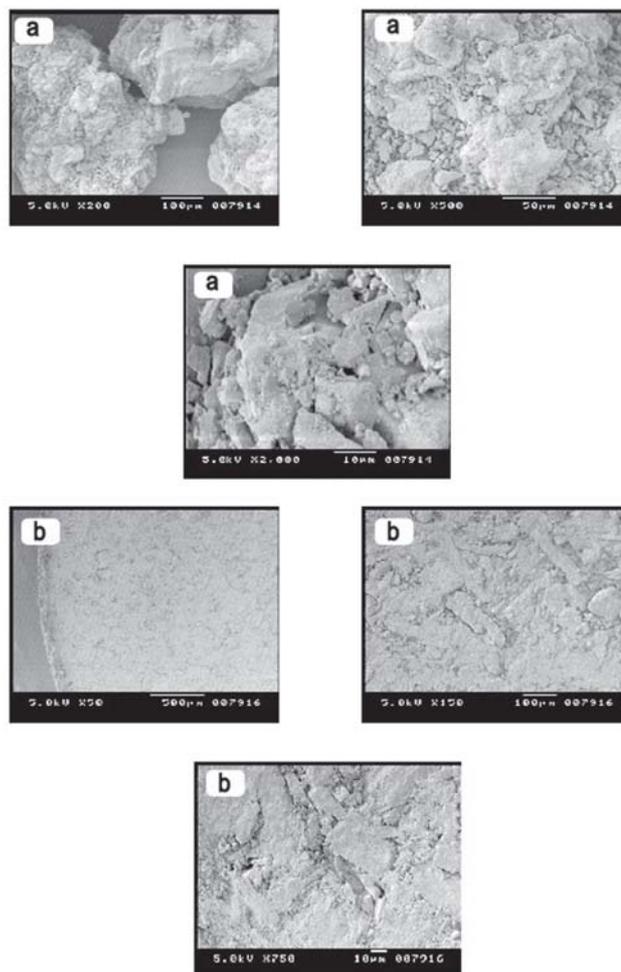
Fig. 1. Scanning electron microscope images of a) Zolmitriptan standard   b) Zolmitriptan sublingual tablets

zolmitriptan was due the presence of excipients. This shows that there was no polymorphic change occurring in these formulations.

Powder X-Ray diffraction study (PXRD): The pure drug showed numerous characteristic high intensity diffraction peaks demonstrating the crystalline nature of the drug (Fig. 3). The peak at about 19.32(2θ) corresponds to main peak in standard zolmitriptan. The same peak was also found in physical mixture with drug and in zolmitriptan sublingual tablets at 19.32(2θ). This indicates that the crystallinity of zolmitriptan was not changed in physical mixture with drug and in zolmitriptan sublingual formulation.

Fourier transform infrared spectroscopy (FTIR): FTIR spectra are of placebo(tablet), physical mixture without drug, physical mixture with drug, standard zolmitriptan and zolmitriptan sublingual formulation (Fig. 4). The pure zolmitriptan exhibits characteristic peaks at $3350 cm^{-1}$(aromatic secondary amine N-H stretching), $2974 cm^{-1}$(aromatic C-H stretching),
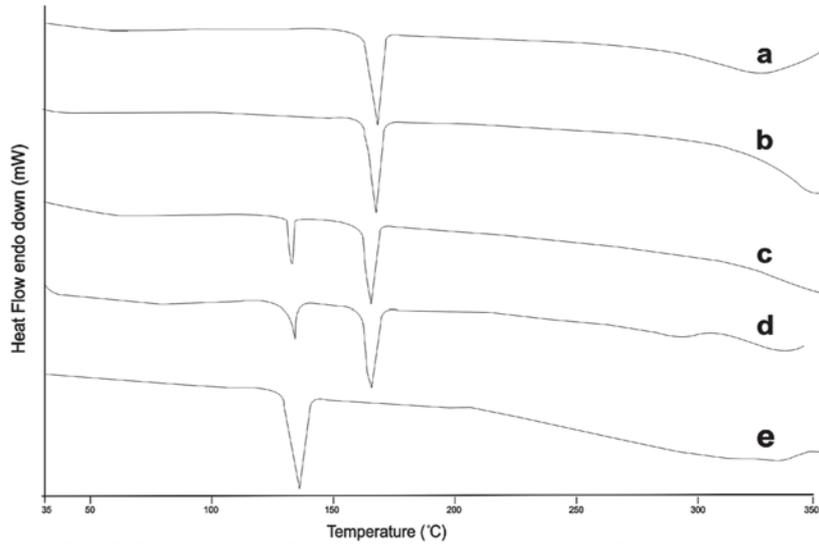
Fig.2. DSC thermograms of a) Placebo b) Physical mixture without drug c) Physical mixture with drug d) Sublingual Zolmitriptan Tablet e) Zolmitriptan Standard
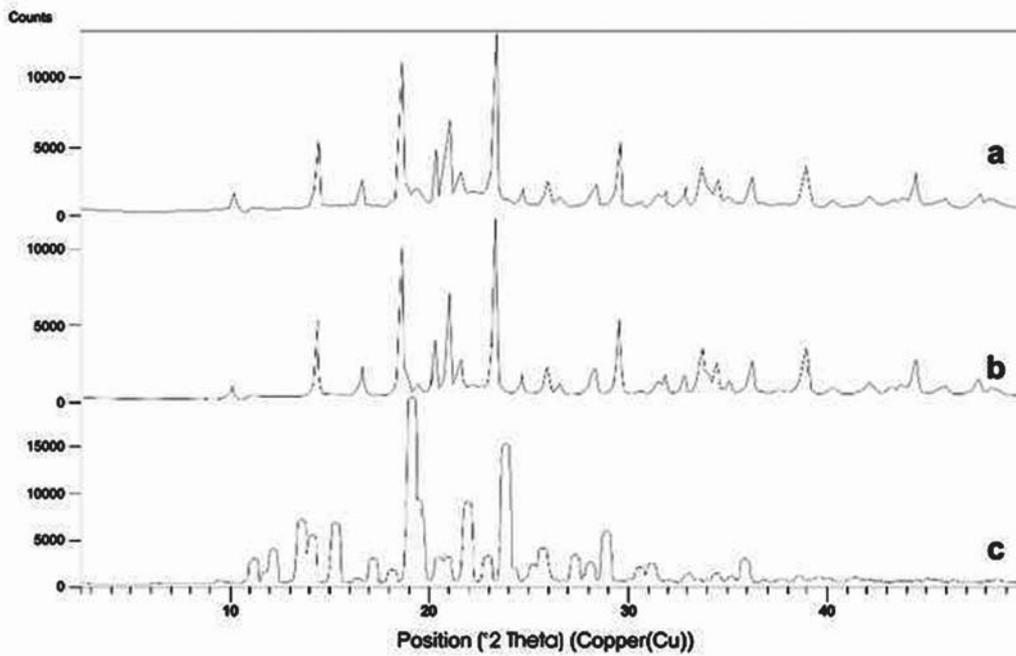
Fig. 3. Powder X-ray diffraction patterns of a) Zolmitriptan sublingual tablets b) Zolmitriptan physical mixture with drug c) Zolmitriptan standard.
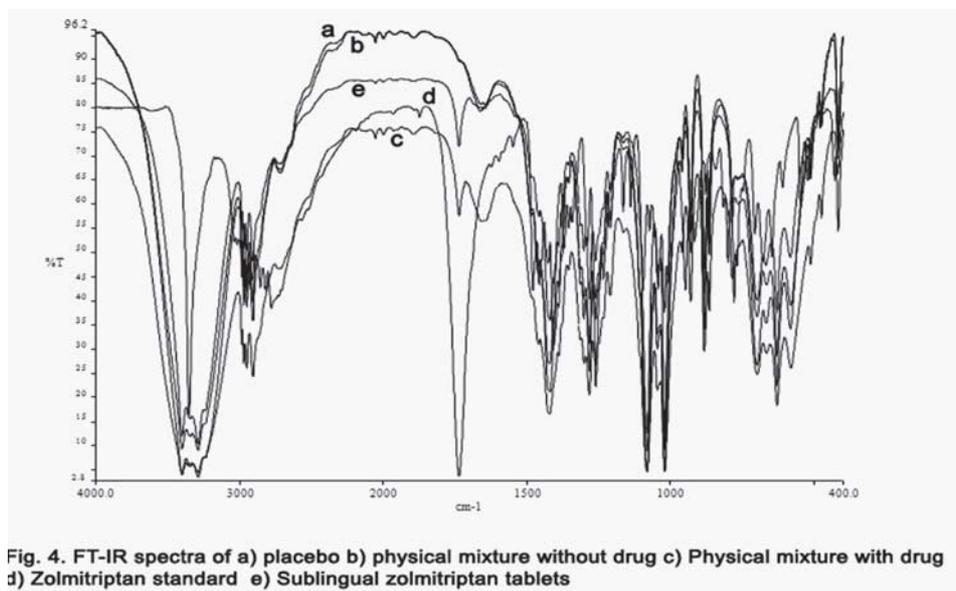
Fig. 4. FT-IR spectra of a) placebo b) physical mixture without drug c) Physical mixture with drug d) Zolmitriptan standard e) Sublingual zolmitriptan tablets
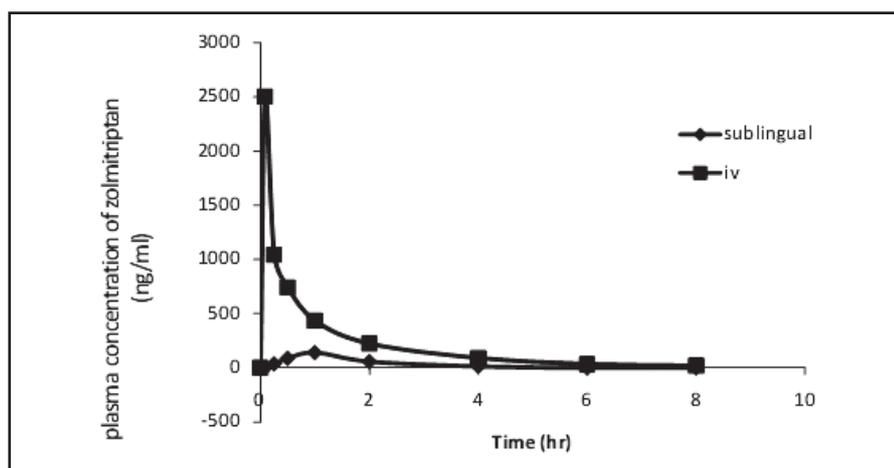

Figure 5. The plasma concentration time curve of zolmitriptan sublingual tablets and intravenous (Zolmitriptan standard) administration. Results are expressed as the mean± SD (n=3)

1736 cm^{-1} (C=O five member cyclic stretching), 1259 cm^{-1} (C-N aliphatic amine stretching) (Fig. 4). All these peaks have appeared in zolmitriptan formulation(F9) at 3292 cm-1 (aromatic secondary amine N-H stretching), 2970cm-1(aromatic C-H stretching), 1736 cm^{-1} (C=O five member cyclic stretching), 1260 cm^{-1}(C-N aliphatic amine stretching), indicate no chemical interaction during formulation of zolmitriptan tablets.

Pharmacokinetic studies :The optimised formulation was chosen according to *in vitro* results by means of exhibiting fast disintegration and dissolution profile. Formulation nine (F9) was directly included for *in vivo* experiments.

Formulation and evaluation of Zolmitriptan

Table 1. Composition of the Zolmitriptan formulations

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zolmitriptan	5	5	5	5	5	5	5	5	5
Sodium Starch Glycollate	3	6	9	-	-	-	-	-	-
Cross Carmellose Sodium	-	-	-	3	6	9	-	-	-
Cross Povidone	-	-	-	-	-	-	3	6	9
Avicel 102	39.75	36.75	33.75	39.75	36.75	33.75	39.75	36.75	33.75
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(mg)	150	150	150	150	150	150	150	150	150

Each tablet contains 5mg of Zolmitriptan.

Table 2. Powder flow properties of the Zolmitriptan formulations Data are expressed as mean ± SD. (n=3).

Code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hausner's ratio
F1	32.4±0.1	0.23±0.01	0.26±0.01	11.39±0.25	1.15±0.03
F2	32.00±0.11	0.31±0.01	0.35±0.01	11.54±0.19	1.13±0.00
F3	31.6±0.18	0.22±0.01	0.25±0.01	12.01±0.48	1.13±0.01
F4	31.1±0.17	0.25±0.01	0.29±0.01	13.64±0.27	1.16±0.01
F5	31.3±0.04	0.25±0.01	0.28±0.01	10.86±0.61	1.12±0.00
F6	30.4±0.13	0.25±0.00	0.28±0.01	11.74±1.78	1.13±0.02
F7	30.0±0.13	0.27±0.01	0.30±0.01	10.11±0.20	1.11±0.01
F8	30.4±0.13	0.25±0.00	0.28±0.01	10.84±0.23	1.11±0.02
F9	29.8±0.14	0.26±0.01	0.29±0.01	10.46±0.21	1.12±0.00

Sterile solution of zolmitriptan at a concentration of 5mg/kg body weight was used to calculate relative bioavailability. The mean serum concentration-time data of zolmitriptan following the administration of the sterile solution formula via intravenous and sublingual tablet formulations is shown in Figure 5. Table 6 showed pharmacokinetic parameters for both the formulations. Peak serum concentration attained by drug was 140.62 ± 18.39ng/ml and 2500.85±1004.02 ng/ml following sublingual and intravenous administration respectively. Time required for attaining peak serum concentration by drug, following sublingual and intravenous administration was 1 hr and 0.083 hr respectively .Area under the curve AUC0-24 was found to be 231.77±81.50 ng.hr/ml and 1712.74±606.65 ng.hr/ml for sublingual and intravenous administration respectively.AUC0-8 was calculated and was found to be 295.131±15.40 and 1750.45±619.57 ng.hr/ml respectively for sublingual and intravenous administration. Time

Table 3. Physicochemical properties of sublingual tablets of Zolmitriptan Data are expressed as mean ± SD. (n=3).

Code	Content uniformity (%)	Thickness(mm)	Hardness (Kg/cm^2)	Friability (%)
F1	98.06±0.89	3.17±0.06	4.33±0.58	0.28±0.02
F2	98.76±1.30	3.13±0.06	4.33±0.58	0.18±0.01
F3	99.09±0.19	3.17±0.06	4.33±0.58	0.13±0.01
F4	102.9±0.62	3.10±0.06	4.66±0.58	0.24±0.01
F5	103.31±0.56	3.20±0.00	4.33±0.29	0.30±0.01
F6	97.66±0.41	3.17±0.06	4.16±0.29	0.33±0.01
F7	101.82±0.33	3.20±0.00	4.16±0.29	0.29±0.01
F8	101.23±0.41	3.10±0.00	4.5±0.50	0.33±0.01
F9	102.23±0.42	3.17±0.06	4.33±0.29	0.30±0.02

Table 4. Physicochemical properties of sublingual tablets of Zolmitriptan Data are expressed as mean ± SD. (n=3).

Code	Average tablet weight(mg)	Diameter (mm)	DT (seconds)	*In vivo* DT (seconds)	Wetting Time (seconds)	Water Absorption Ratio (%)
F1	151.3 ±0.04	8.03±0.06	84.3 ±0.58	115.33±0.58	66±1	154.32±0.01
F2	151.37±0.23	8.07±0.06	57.7±0.58	104.67±0.58	55.67±0.58	147.22±0.01
F3	151.33±0.58	8.13±0.06	53.7±0.58	82.33±0.58	43.67±0.58	141.06±0.00
F4	151.23±0.12	8.13±0.06	16.0±1.0	33.0±0.00	15.3±0.58	129.06±0.00
F5	151.13±0.12	8.13±0.06	15.67±0.58	31.67±0.58	14.3±0.58	121.32±0.00
F6	151.5±0.10	8.17±0.06	15.0±1	27.0±0.00	12.3±0.58	117.68±0.00
F7	150.07±0.06	8.13±0.06	11.3±0.58	25.33±0.58	10.67±0.58	109.45±0.00
F8	151.17±0.06	8.10±0.00	9.3±0.58	20.0±0.0	6.67±0.58	106.18±0.01
F9	151.03±0.06	8.17±0.06	7.7±0.58	12.33±0.58	5±1	90.75±0.01

required for a drug to decrease by half (ie T1/2) was found to be 0.86hr and 1.66 hr following sublingual and intravenous administration. Volume of distribution for a drug (vd) was 20914.02±657.47 ml and 0.458±0.16 ml following sublingual and intravenous administration. Clearence of the drug was found to be 16964.75±885.29 ml/hr and 3079.49±654.44 ml/ hr following sublingual and intravenous administration. Percentage availability (% F) was found to be 20.

The therapeutic dose of zolmitriptan oral dose in rabbits is 0.083 mg/kg. In current study, 5 mg/kg was administered to rabbits which correspond to 1.25 mg/kg in humans. In conclusion, the mean plasma concentration time profile for zolmitriptan 5 mg tablet by sublingual

Table 5. *In Vitro* Release profile of the Zolmitriptan formulations Data are expressed as mean ± SD. (n=3).

Time (Min)/ Code(%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	71.16 ± 2.93	78.83 ± 2.52	83.52 ± 1.01	77.72± 0.73	81.04± 0.81	84.13± 0.46	79.15± 0.78	80.89± 0.81	85.49± 0.46
10	78.17± 3.60	83.29 ± 3.70	93.75± 1.74	84.93± 0.80	84.87± 0.54	95.17± 0.90	86.95± 0.49	88.94± 0.65	97.10± 0.54
15	85.15 ± 2.49	93.32 ± 3.04	97.37 ± 0.69	91.92± 0.82	88.70± 0.27	96.08± 0.54	97.28± 0.59	97.21± 0.40	100.34± 1.19
20	91.90 ± 1.62	98.67 ± 0.64	97.60± 0.20	97.25± 0.81	95.42± 0.75	98.38± 0.29	97.05± 0.95	97.67± 0.40	102.41± 0.49
30	97.47 ± 1.25	101.71 ± 1.41	99.41± 0.64	99.13± 0.72	99.74± 0.92	99.52± 0.66	101.64± 0.99	101.58± 0.38	102.86± 0.40
45	98.68 ± 2.56	103.10 ± 0.40	102.81 ± 0.80	99.13± 0.72	99.74± 0.92	100.91± 0.62	102.09± 0.69	102.73± 0.68	103.10± 0.41
60	102.62 ± 1.75	103.57 ± 0.68	103.50 ± 0.12	101.21± 0.85	102.35± 0.87	102.97± 0.08	103.01± 0.77	102.50± 0.39	103.33± 0.09

Table 6. Pharmacokinetic Parameters of Zolmitriptan sublingual tablets in rabbits following administration of Optimised Zolmitriptan sublingual tablets (F9) and Intravenous administration.

PK parameters	Sublingual tablets (5 mg/tablet)	Intravenous administration (5 mg/kg)
C_{max}(ng/ml)	140.62±18.39	2500.85±1004.02*
T_{max}(hr)	1±0	0.083±0*
AUC(0-t) (ng.hr/ml)	231.77±81.50	1712.74±606.65*
AUC(0-8) (ng.hr/ml)	295.13±15.40	1750.45±619.57*
T1/2 (hr)	0.86±0.02	1.67±0.645*
CL (ml)	16964.75±885.29	3079.49±654.44*
VD (ml)	20914.02±657.47	0.458±0.16*
%F		20

Data are expressed as mean ± SD. (n=3). *Significant difference at $P \leq 0.05$ vs control.

route show initially it is very rapid absorption of drug and reached an average 80% of eventual Cmax within 1 hour and 5 mg/kg intravenous route show time to peak plasma concentration within 1 hour. zolmitriptan 5 mg tablet by sublingual route in rabbits show effective therapeutic Cmax (140.62 ng/ml) when compared to clinical dose by oral route (5.6 ng/ml)(26).

Conclusions

All tablets met the compendia limits in terms of physicochemical parameters, disintegration and dissolution studies. When given sublingually, zolmitriptan is well absorbed, and its bioavailability by this route is significantly. From this study, the optimised sublingual tablets of zolmitriptan appeared to be

a promising alternative to oral drug administration route in acute management of migraine.

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