Original Research Article

Preparation and evaluation of sublingual tablets of zolmitriptan

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Abstract

Aim: Zolmitriptan is a 5-HT receptor agonist (1B/1D). It is used in the acute treatment of migraine having low bioavailability about 40% orally due to hepatic first pass metabolism. The purpose of the present research was to formulate fast acting sublingual tablets of zolmitriptan. **Materials and Methods:** Sublingual tablets were prepared using ispaghula husk powder, gellan gum, sodium alginate as super disintegrating polymers and citric acid, tartaric acid and camphor as permeation enhancers by direct compressible technique and evaluated for weight variation, thickness, friability, content uniformity, hardness, disintegration time, wetting time, *in-vitro* drug release, *in-vitro* and *ex-vivo* permeation study. Stability study of optimized formulation was performed as per ICH (International Conference on Harmonisation) guideline. **Results:** The *in-vitro* disintegration time of the optimized formulation (D5) was 9 ± 2 s and all formulations showed 100% of dissolution within 6 ± 2 min. Formulation containing 4% of gellan gum (D5) showed highest disintegration and 2% of citric acid formulation (P3) showed highest permeation 88% within 30 min and *ex-vivo* permeation was 52% within 30 min. Optimized formulation was stable for 1 month during stability study as per ICH guideline. **Conclusion:** The sublingual tablet formulation gives better results using natural super disintegrant for fast onset of action.

Key words: *Ex-vivo* permeation, natural super disintegrants, permeation enhancers, sublingual tablets, zolmitriptan

INTRODUCTION

Sublingual administration of the drug means placement of the drug under the tongue. The absorption of the drug through the sublingual route is 3-10 times greater than the oral route.[1] Different formulations such as tablets, films and spray are useful for sublingual administration of drug.[2,3] The task of formulation of sublingual dosage form is very challenging. The challenges are mechanical strength, disintegration time, taste masking, mouth feel, sensitivity to the environmental condition and cost etc.[4,5]

Zolmitriptan (4S)-4-([3-(2-[dimethylamino]ethyl)-1Hindol-5-yl]methyl)-2-oxazolidinone, is a white to almost white powder highly soluble in water (20 mg/ml). It is a BCS (biopharmaceutics classification system) Class-3 drug with high solubility and low permeability. It has a pKa value of 9.52.[6] Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with or without an aura and cluster headaches. It has a selective action on serotonin (5-HT1B/1D) receptors and it is very effective in reducing migraine symptoms, including pain, nausea and photo - or phonophobia.[7,8] It is currently available as a conventional tablet, an oral disintegrating tablet and a nasal spray (2.5 mg and 5 mg/dose). The drawbacks of current oral zolmitriptan therapies are slow onset of action and low bioavailability (about 40%). Zolmitriptan undergoes highly hepatic first pass metabolism and to solve the problems of hepatic first pass metabolism prepare sublingual tablets.[9-11]

A migraine is a severe, painful headache that is often preceded or accompanied by sensory warning signs such as flashes of light, blind spots, tingling in the arms and legs, nausea, vomiting and increased sensitivity to light and sound. The excruciating pain that migraines bring can last for hrs or even days. Migraine treatment and prevention focus on avoiding triggers, controlling symptoms and taking medicines. Over-the-counter medications such as naproxen, ibuprofen, acetaminophen and other analgesics like aspirin with caffeine are often the first abortive therapies to eliminate the headache or substantially reduce pain. Zolmitriptan undergoes highly hepatic first pass metabolism and to solve the problems of hepatic first pass metabolism prepare sublingual tablets.[9-11]

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Present study was aimed to prepare zolmitriptan sublingual tablets using direct compression technique. The different proportions of super disintegrants such as ispaghula seed husk powder, gellan gum, sodium alginate and permeation enhancers were optimized.[12]

MATERIALS AND METHODS

Zolmitriptan was kindly supplied by Aurobindo Pharma Ltd, India. Ispaghula husk powder (1086 cP) was purchased from Unjha market, Gujarat, India. Gellan gum (849 cp) was procured from Hi Media Laboratories, Pvt., Ltd., Mumbai, India. Sodium alginate (350 cp), citric acid, tartaric acid and camphor were procured from Finar Chemicals Ltd, Ahmedabad, India.

Compatibility study

Fourier transform infrared (FT-IR) spectrophotometric study

The infrared spectrum of the native drug zolmitriptan was recorded on a FT-IR Spectrophotometer in the range of 4000-400/cm and 1/cm resolution. Infrared spectra of zolmitriptan and excipients mixture were recorded using KBr mixing method on FT-IR instrument (FT-IR-8400S, Shimadzu, Kyoto, Japan). Results are shown in Figures 1 and 2.

Differential scanning calorimeter (DSC) study

DSC study was carried out using Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) instrument. DSC thermogram of pure drug zolmitriptan and mixture (zolmitriptan + excipients) were taken. DSC aluminum cells were used as sample holder and blank DSC aluminum cell was used as a reference. 2-3 mg sample was used for analysis. Thermograms were recorded over the range of 20°C-200°C at a constant rate of 20°C/min under nitrogen purge at 20 ml/min. Results are shown in Figures 3 and 4.[13]

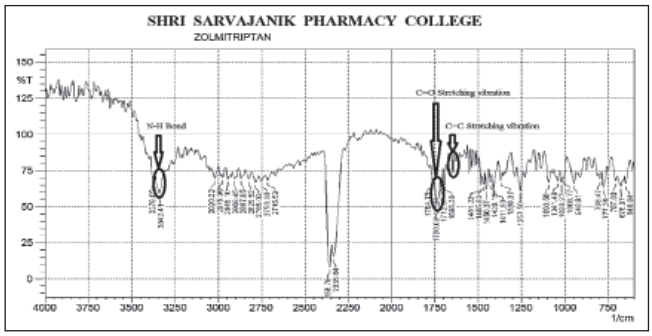

Figure 1: Fourier transform infrared of zolmitriptan pure drug

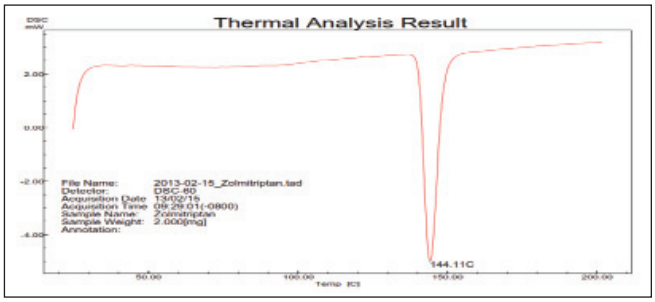

Figure 3: Differential scanning calorimeter spectrum of zolmitriptan

Powder characteristics

Powder mixture showed minimum Carr's index, Hausner's ratio and angle of repose. The mixture had good flow properties. So we had gone through direct compression. Results of powder characteristics are shown in Table 1.

Fabrication of sublingual tablets

The sublingual tablets were prepared by direct compression technique. Accurate amount of the active ingredient and all additives were homogeneously blended by passing through 80# screen sieve. Tablets were directly compressed by double rotary tablet compression machine (Rimek 10 station minipress) equipped with 8 mm flat faced punch and die set. The compression force and mass of all tablets were kept constant and each tablet contained 2.5% (2.5 mg) of zolmitriptan.[14]

Selection of superdisintegrant

The compositions for selection of super disintegrant for the sublingual tablets are shown in Table 2. Batch P1 to P9 were preapared to evaluate permeation enhancer. Composition of batch P1 to P9 is shown in Table 3.

Evaluation of batches D1 to D9

Hardness

The hardness of the tablets was determined by Monsanto hardness tester. A tablet hardness of about 3-4 kg is considered to be adequate for mechanical stability. Determinations were made in triplicate. Results of hardness are shown in Table 4.

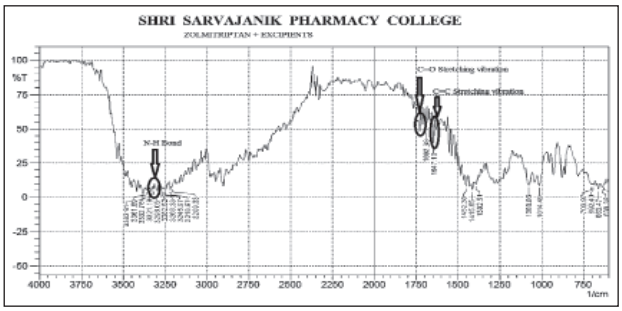

Figure 2: Fourier transform infrared of zolmitriptan and excipients

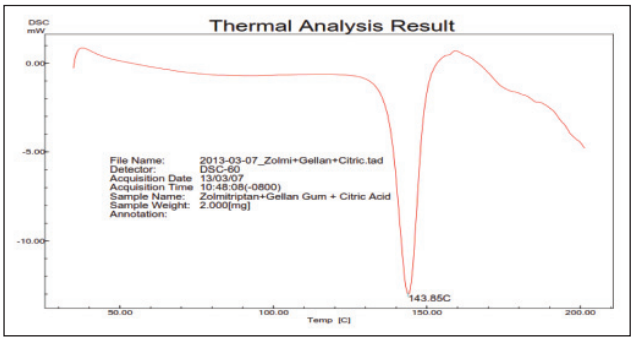

Figure 4: Differential scanning calorimeter spectrum of zolmitriptan and excipients

In-vitro disintegration test

In the USP (United States Pharmacopoeia) disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual dosage form. The test was carried out using tablet disintegration apparatus (model ED-2 L, Electrolab, Mumbai, India). *In-vitro* disintegration test was carried out using a modified disintegration method ($n = 6$) using disintegration tester at 37°C ± 0.5°C in distilled water. The tablets were kept in the basket and noted the time taken for the tablet to disintegrate completely into smaller particles and results are shown in Table 4.

Table 1: Powder characteristics

Powder mixture				
Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Carr's index	Hausner's ratio	Angle of repose
0.435	0.484	10.124	1.11	26.22°

Wetting time

The tablet was placed at the center of 2 layers of absorbent paper fitted into a petri dish. After the paper was thoroughly wetted with

Table 2: Composition of batches D1-D9

Formula	D1	D2	D3	D4	D5	D6	D7	D8	D9
Ingredients	Quantity in mg								
Drug	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	75	75	75	75	75	75	75	75	75
MCC	15	13	11	15	13	11	15	13	11
Sodium alginate	2	4	6	—	—	—	—	—	—
Gellan gum	—	—	—	2	4	6	—	—	—
Ispaghula seed husk powder	—	—	—	—	—	—	2	4	6
Menthol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium saccharin	2	2	2	2	2	2	2	2	2
Mg stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Total weight	100 mg								

MCC: Microcrystalline cellulose

Table 3: Composition of batches P1-P9

Formula	P1	P2	P3	P4	P5	P6	P7	P8	P9
Ingredients	Quantity in mg								
Drug	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	75	75	75	75	75	75	75	75	75
MCC	12	11.5	11	12	11.5	11	12	11.5	11
Gellan gum	4	4	4	4	4	4	4	4	4
Citric acid	1	1.5	2	—	—	—	—	—	—
Camphor	—	—	—	1	1.5	2	—	—	—
Tartaric acid	—	—	—	—	—	—	1	1.5	2
Menthol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium saccharin	2	2	2	2	2	2	2	2	2
Mg stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Total weight	100 mg								

MCC: Microcrystalline cellulose

Table 4: Evaluation parameters of batches D1-D9

Batch codes	Average hardness (kg/cm²)	Disintegration time (s) *n*=6	Wetting time (s) *n*=3	Friability (%)	% assay (*n*=3)
D1	3.6	12.61±0.55	9.61±0.23	0.59	98.43±0.01
D2	3.8	13.45±0.58	14.49±0.49	0.44	102.08±0.10
D3	3.9	16.53±0.85	20.90±0.39	0.31	101.04±0.04
D4	3.0	9.95±0.40	7.23±0.22	0.81	100.14±0.01
D5	3.1	9.82±0.11	7.00±0.10	0.34	100.01±0.01
D6	3.5	13.13±0.98	9.10±0.14	0.42	100.60±0.01
D7	2.9	11.35±0.26	8.50±0.49	0.91	99.74±0.03
D8	3.0	11.61±0.51	8.97±0.04	0.86	101.90±0.01
D9	3.2	11.42±0.48	8.25±0.58	0.80	101.30±0.04

distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. Results of wetting time are shown in Table 4.

Assay

Tablets (n = 5) were weighed individually and the drug was extracted in distilled water and the solution was filter by whatman filter paper. The absorbance was measured at 224 nm after suitable dilution using a Shimadzu ultraviolet (UV)-1601 (UV/visible is double beam spectrophotometer). Results of drug content are shown in Table 4.

Friability

The tablets were tested for friability testing using Roche friabilator. For this test, six tablets were weighed and subjected to the combined effect of abrasion and shock in the plastic chamber of friabilator revolving at 25 rpm for 4 min and the tablets were then dusted and reweighed. Results are shown in Table 4.

In-vitro drug release study

Dissolution study was conducted for all the formulations using USP dissolution rate test apparatus type-II (TDT-08 L Electrolab, Mumbai, India.). A total volume of 900 ml of distilled water was taken in dissolution apparatus, which was maintain at 37°C ± 0.5°C at 100 rpm. Ten milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 2 min intervals and filtered by whatman filter paper. Samples were analyzed spectrophotometrically at 224 nm. Results are shown in Figure 5.

In-vitro permeation study

In-vitro permeation studies were carried out with modified Franz's diffusion cells (D.K. Scientific, Ahmedabad, India). The medium used for these studies was phosphate buffer (pH 7.4), maintained at 37°C ± 0.5°C. Cellulose dialysis membrane was used as a permeation barrier. Samples were collected at predetermined time intervals (0, 5, 8, 15, 20, 30, 45, 60, 90 and 120 min). Samples were analyzed for drug content with a UV spectrophotometer set at 224 nm. All permeation studies were three replicates for each formulation. Results are shown in Table 5 and Figure 6. The calibration curve for zolmitriptan, in phosphate buffer, was linear from 1 to 8 µg/ml (r^2 = 0.999). Compositions of formulas are shown in Table 3.

Ex-vivo permeation study was carried out using goat sublingual mucosa 2 cm × 2 cm dimension using Franz's diffusion cell. Results are shown in Table 6.

Stability study of the optimized formulation

Short Term Stability study was carried out according to ICH guidelines Q1C at 40°C ± 2 °C/75 ± 5% RH for 1 month for optimized batch P3. The optimized formulation sealed in aluminum foil was also kept at room temperature and humidity condition. At the end of studies, samples were analyzed for the % drug release and drug content.

Table 5: *In-vitro* permeation data within 30 min

Batch codes	% permeation
Batch P1	21.69±1.46
Batch P2	38.85±0.91
Batch P3	88.12±0.09
Batch P4	7.15±1.02
Batch P5	10.28±1.87
Batch P6	15.74±0.57
Batch P7	11.81±0.49
Batch P8	15.09±1.69
Batch P9	31.19±0.91

Table 6: *Ex-vivo* permeation study of optimized batch D5 and P3

Batch code	D5	P3
Time (min)	% CPR	
0	0	0
5	0.01	13.52
8	0.15	19.44
15	0.95	32.35
20	4.25	39.03
30	11.21	52.84
45	15.01	60.86
60	17.37	68.73
90	28.51	88.88
120	35.33	101.93

CPR: Cumulative percentage drug release

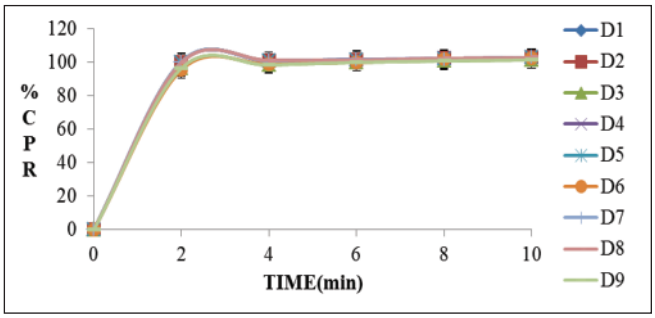

Figure 5: *In-vitro* drug release profile of batches D1 to D9

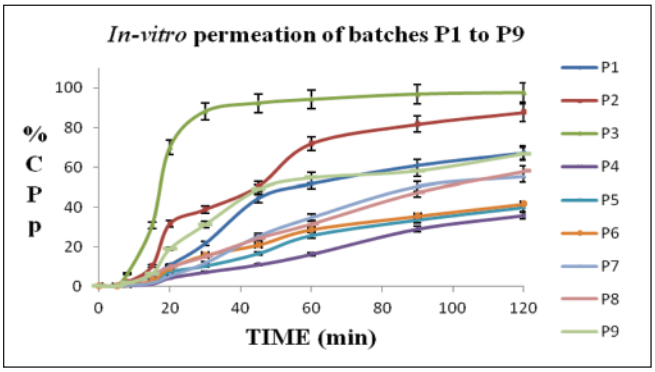

Figure 6: *In-vitro* permeation of batches P1 to P9

RESULTS AND DISCUSSION

FT-IR spectrophotometric study for compatibility

The FT-IR of zolmitriptan exhibits peak due to N-H stretching at 3342.41/cm, C = O stretching at 1730.03/cm, and C = C stretching at 1650.0/cm. These values were meet the reported values. The FT-IR of mixture (zolmitriptan + Excipients) exhibit peak due to N-H stretching at 3332.76/cm, C = O stretching at 1735.00/cm, and C = C stretching at 1647.10/cm. From results of FT-IR data it was concluded that there is no interaction between zolmitriptan pure drug and mixture (zolmitriptan + excipients) as shown in Figures 1 and 2.

DSC study

In both thermo grams [Figures 3 and 4] peak was very sharp. Pure drug melted at 144.11°C and mixture (pure drug + excipients) melted at 143.85°C. DSC Thermogram results showed that there was no change in melting point of the drug; hence, there was no incompatibility between drug and excipients.

Selection of super disintegrant

All prepared tablets (batch D1 to D9) complied with the pharmacopoeial required specifications for the weight variation and content uniformity tests. Results of hardness, friability, disintegration time, wetting time and assay are represented in Table 4. Hardness test showed an average hardness of tablets ranging from 2.9 to 3.9 kg/cm^2. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. Disintegration time of Batch D4 and D5 were 9.95 ± 0.40 s and 9.82 ± 0.11 respectively, which were prepared with gellan gum shown minimum disintegration time among all batches. Batch D5 shows minimum wetting time 7.00 ± 0.10 s among all batches.

In-vitro permeation study

It was observed that permeability was increased as increase in concentration of permeation enhancer from 1%, 1.5% and 2% in all the batches P1 to P9. The % permeation of batch P3 (2% citric acid) was maximum (88.12 ± 0.09) amongst all batches. Hence 2% of citric acid was optimized as permeation enhancer (Table 5).

Ex-vivo permeation study

Ex-vivo permeation study was conducted for 120 min for batch D5 and batch P3. Percentage permeation at 30 min of batch D5 was 11.21% and permeation of batch P3 was 52.84% (Table 6).

Stability study

The optimized formulation (batch P3) stored at 40 ± 2°C/75 ± 5% for 3 months. After storage at 40 ± 2°C/75 ± 5%, cumulative percentage drug release, disintegration time, hardness and % drug content were nearly similar to the initial results. Hence, it was clear that the drug and the formulation were thermally stable as well as not affected by the high humidity at 40 ± 2°C/75 ± 5%. Similarity, value f2 for batch P3 was 97.80. Hence, we can conclude that formulation is stable.

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