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FORMULATION AND EVALUATION OF BUCCAL STRIPS OF ZOLMITRIPTAN

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ABSTRACT

The present study was aimed to formulate and evaluate buccal strips of zolmitriptan using hydroxypropyl methyl cellulose and PVA. Zolmitriptan is having poor bioavailability (40-50%) by oral route, there is an effort made to increase its bioavailability by formulating it in the form of buccal dosage forms. In the present research work, zolmitriptan buccal strips were prepared by solvent casting method using different polymers like hydroxypropyl methyl cellulose & poly vinyl alcohol (in different ratios), PEG 400 as plasticizer, aspartame as sweetener and Kyron T-314 used as a superdisntegrant. The suitable plasticizer and its concentration were selected on the basis of flexibility and tensile strength of the strip. All the prepared strips showed smooth surface and elegant texture. FT-IR studies revealed that, there was no interaction between drug and excipients used. The thickness and folding endurance of the strips were found in the range of 0.121 to 0.165mm and 264 to 291.13. Moisture content and moisture uptake of the strips were found in the range of 3.9 to 6.98% and 4.10 to 9.44%. The surface pH of the buccal strips was found in the range of 6.43 to 6.80. Disintegration times of buccal strips were in the range of 18.15 to 38.33 sec and absence of bitterness in the strips. Drug content of buccal strips were found in the range of 76.6 to 96.6 % per $2cm^2$. Among all the developed formulations, the formulation F2 containing HPMC E-10 showed optimum drug release of 98.13%. The results of *in vitro* drug release, *ex vivo* diffusion drug release and *in vivo* bio availability studies were found to be satisfactory. The stability studies as per ICH guide lines suggesting that there was no significant change in drug content and *in-vitro* release. It was concluded that buccal strips of zolmitriptan can be developed by solvent casting technique with enhanced dissolution rate, better increased bioavailability, patient compliance and effective therapy.

INTRODUCTION

Fast dissolving films are gaining attractiveness as an alternative to fast dissolving tablets as they eliminate patient's fear of chocking and overcome patient impediments. Fast dissolving films generally consists of plasticized hydrocolloids or blends which can be laminated by using techniques such as hot-melt extrusion and solvent casting. Additionally, they also provide easy delivery of drug under emetic condition. An oral strip, are the new drug delivery system for delivery of drugs through oral cavity and was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which when placed on the patient's tongue or any oral mucosal tissue gets instantly wet by saliva and rapidly hydrates and adheres onto the site

of application and dissolves rapidly [1-3]. Oral strips are able to reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats [4]. Oral strips are a group of flat films which are administered into the oral cavity and recently they have become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral strip has become a novel and widely accepted form by consumers for delivering vitamins and personal care products [5]. Zolmitriptan is a selective 5-hydroxytryptamine receptor sub type agonist indicated for the acute treatment of migraine with or without aura in adults. Zolmitriptan binds with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors leading to cranial blood vessel constriction. The therapeutic activity of zolmitriptan for the treatment of migraine headache can most likely be attributed to the agonist effects at the $5HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release. The dose of zolmitriptan is 1.25 to 10 mg per day by oral route, 2.5 to 10 mg per day by intranasal route. Elimination half life and bioavailability of zolmitriptan is 3 hours and 40% [6]. The aim of the study was to formulate buccal strip of zolmitriptan by using a combination of polymers i.e., HPMC E10, HPMC E15, Poly Vinyl Alcohol and Kyron T-314 in different concentrations; Kyron T-314 as a superdisintegrant, Polyethylene glycol and Glycerine as a plasticizer, Aspartame as a sweetening agent allowing fast reproducible drug dissolution in oral cavity thus bypassing first pass metabolism, to enhance the convenience and compliance by the elderly and paediatric patients

MATERIALS AND METHODS

Materials: Zolmitriptan obtained gift sample from Apotex Pharmachem, Bangalore. HPMC E10, HPMC E15 obtained as gift sample from Colorcon Asia Pvt Ltd., Verna, Goa and Kyron T-314 obtained gift sample from Corel Pharmachem, Ahmedabad.

METHODS

Preformulation studies

Melting point determination

Melting point of drug was determined by using Thiele's tube method in which the pure drug is placed in a capillary tube which was fused at one end. The capillary tube was tied to the thermometer and the temperature at which drug starts melting was noted down [6].

Drug-polymer Compatibility studies using FT-IR

Compatibility studies were carried out to know the possible interactions between zolmitriptan, polymer and excipients used in the formulation. Physical mixtures of drug, polymer and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using Tensor 27, Bruker optics FTIR (ATR) spectroscopy. FTIR spectrum of pure drug and polymers were determined seen in between 600- 4000cm^{-1} [7]. The IR peaks of Zolmitriptan when mixed with excipients compared with pure Zolmitriptan (Figure 2).

Preparation of Zolmitiyptan buccal strips

Table 3 shows the composition of all the formulation of buccal strips of Zolmitriptan. Polymeric solution HPMC/PVA were prepared by using distilled water with continuous stirring for 4 h. Specified amount of zolmitriptan was dissolved in the ethanol solution kyron T-314 (superdisintegrant), polyethylene glycol (plasticizer), glycerine and tween 80 was added above ethanol solution containing drug and stirred at 100 rpm to form a homogenous solution. The homogenous solution was incorporated into the polymeric solution after levigation with 30% polyethylene glycol of polymer weight. The solution was casted into petri dishes (90mm) and dried in hot air oven at 40°C for 24 h.

Evaluation of buccal strips of zolmitriptan

Physical appearance and surface texture

Appearances of buccal strips were checked simply with visual inspection and evaluation of texture by feel or touch [8].

Weight uniformity: The weight variation test was carried out by using analytical balance. In this weight variation test, three strips from each batch were weighed individually and the average weight was calculated [8].

Thickness uniformity: Thickness of the strips was measured at three different places using a screw gauge and mean values were calculated [8].

Folding endurance: Folding endurance of the strips was determined by repeatedly folding the strips (approximately 2×2 cm) at the same place till it broke. The number of times strips could be folded at the same place, without breaking gives the value of folding endurance [8].

Drug content uniformity study: The strips were tested for drug content uniformity by using Shimadzu 1700 UV-Visible spectrophotometric. Strips of $2cm^2$ were cut from the three different places of the casted strips sheet. Each strip was placed in 100ml volumetric flask and dissolved in pH 6.8 phosphate buffer. After suable dilutions the absorbance was measured at 223nm and drug content uniformity calculated [8].

Surface pH: Surface pH was determined for the strips were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of strips and allowing equilibrate for 1min [8].

Disintegration test: Disintegration test was performed using USP disintegration testing apparatus. The strips were placed in the tubes of the basket and the operated until strips disintegrate completely. The disintegration time was recorded [8].

Percentage of moisture content: The buccal strips were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the strips were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using following formula [9].

$$\text{Percentage of moisture content} = \frac{Initial\ weight - final\ weight}{initial\ weight} \times 100$$

Percentage of moisture uptake: The buccal strips were weighed accurately and placed in a desiccator containing100ml of saturated solution of aluminium chloride, which maintains 86% relative humidity (RH). After 3 days, films were taken out and weighed. The moisture uptake was calculated using the formula [9].

$$\text{Percentage moisture uptake} = \frac{Initial\ weight - final\ weight}{initial\ weight} \times 100$$

Figure 1: Tensile strength measurement

Tensile strength measurement: This tensile strength of the buccal strips was performed by using Instron tensile strength apparatus. Instron tensile strength apparatus was shown in Figure 1. The strips were cut into strips of 1 inch width and 15cm length. The strips were fixed to the upper and lower jaws of the tensile strength in such a way that the length of the strip between the jaws was initially 10cm. The force required to break the strips was measured. The test was repeated for all the formulations [9].

$$\text{Tensile strength} = \frac{Force\ at\ break}{Initial\ cross\ sectional\ area\ of\ the\ sample(mm2)}$$

***In vitro* drug release study:** *In vitro* dissolution of zolmitriptan buccal strips was studied in USP XXIV dissolution test apparatus a 900 ml pH 6.8 phosphate buffer

solution was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.5°c throughout the experiment. One strip was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of pipette at specified time intervals and analysed by measuring the absorbance at 223 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percent cumulative drug release of zolmitriptan was calculated and plotted against time [9-11].

***Ex vivo* permeation studies:** *Ex vivo* diffusion study of pure drug was carried out using sheep buccal mucosa tissue, which was procured from local slaughter house and placed in 6.8 phosphate buffer. Isolation of the epithelium was done mechanically by using scissors and forceps. The studies were carried out by using Franz diffusion cell. It consists of upper cylindrical compartment open from above and containing the porcine buccal mucosa at its base. Lower compartment was in the form of a closed cylinder having the sampling port and had Teflon coated magnetic bead at the base. The junction between the two compartments was designed in such a manner that the buccal membrane did not shift from its place [12]. The donor compartment was filled with1ml pH 6.8 phosphate buffer containing 20% of methanol. The receptor compartment contains the 50ml pH 6.8 phosphate buffer having 20% methanol to maintain sink conditions. The whole assembly was maintained at 37±1°C. One ml of sample was withdrawn from receptor compartment and replaced with the same amount of fresh medium. The withdrawn samples were diluted suitably, and then absorbance was measured at 223nm. The percentage cumulative drug diffused was calculated.

***In vivo* studies:** The study was conducted with the approved *in vivo* study design and protocol (Protocol approval number: IAEC/ABMRCP/2012-13/39) and as per the guidelines prescribed by the IAEC**.** Before starting the experimentation (8-10 H) food was stopped to all the animals. Food and water was not given to animals up to 2 h after the start of the study**.** Each animal (female) (n=3) in the first group was administrated a buccal strip (2.5 mg) irrespective of the body weight. The rabbit's mouth was opened, tongue was elevated and the strip was placed between the cheek and gingival. Two ml of water was added to surface of the strip before administering. The mouth was shut for 1 min, to avoid chewing or swallowing of the strip. Two ml of water was administered after dosing. Blood was withdrawn from rabbits at pre-determined time intervals such as 0 min, 10 min, 30 min, 60 min, 90 min and 120 min through marginal ear vein [13].

Analysis of blood samples

1ml of blood withdrawn from female rabbit at the pre-determined time intervals (0, 10min, 20min, 30min, 60min, 90min and 120min) through marginal ear vein and transferred into commercially available anticoagulant-treated tubes (e.g. EDTA-treated) using a multi sample needle. Blood samples were centrifuged for 6mins at 4000 RPM. The supernatant solution (plasma) 0.4ml was collected and transferred into centrifuged tubes, then 1ml of 0.05M methanolic hydrochloride solution was added to precipitate product. Again centrifuged the mixture for 6 mins at 4000 RPM. The supernatant solution 1ml separated and 4ml of 0.05M Methanolic hydrochloride solution was added. The absorbance of solution was measured. Finally calculated C_{max} and T_{max} were calculated.

Stability studies

The optimized buccal strips of zolmitriptan (F2) were packed in glass containers, which were tightly sealed with aluminium foil. The strips were stored at 30 ± 2°C/ (65 ± 5 % RH) for 2 months and evaluated for their physical appearance, drug content and *in vitro* drug release at specified intervals of time [14-16].

RESULTS AND DISCUSSION

Preformulation studies

Melting point of zolmitriptan pure drug was found to be 146°C and which was

found to be in the range of 144- 150°C. The drug was found to be in pure form. It was observed that all the characteristics peaks of zolmitriptan were present in the combination spectra indicating the compatibility of the drug with the polymer used. It was concluded that the obtained drug was in pure form. FT-IR study showed that there was no major change in the position of peak obtained in drug alone and in a mixture of drug with excipients, which showed that there was no interaction between drug and excipients in Figure 2. The observations were shown in Table 1 and Table 2. From the obtained spectra it

Physical appearance and surface texture of strips: The Physical appearance and surface texture were checked simply with visual infection of strips and by feel or touch. From the observation it was predicted that the strips are having smooth surface and they are elegant enough to see**.**

Weight uniformity: The weight of prepared strips was determined by using digital balance and the observations of all strips were given in Table 4. Weight uniformity was found in the range of 29.9 ±0.378 to 37.4 ± 0.68 mg. All the formulations were found within limits.

Thickness uniformity: The average thickness of all strips was shown in Table 4. Thicknesses of strips were found in the range of 0.121 ± 0.0028 to 0.165 ± 0.005. All the formulations were found to be within limits.

Folding endurance: The folding endurance of the strips was determined by repeatedly folding the buccal strips at the same place till it broke. The folding endurance of all formulations was given in Table 4. The results showed that the folding endurance was found in the range of 264 ± 1.527 to 291.3 ± 3.605. It was revealed that the buccal strips of all formulations having appropriate strength.

Drug content uniformity: Buccal strips prepared with various polymers were subjected to drug content uniformity Shimadzu-1700 UV spectrophotometer at 223nm. The results were revealed in Table 4. The drug content of all formulations were found in the range of 76.6±1.242 to 96.6±1.358 % suggesting that drug was uniformly dispersed throughout all strips. Among all the formulations F_2 showed very good drug content uniformity.

Surface pH: The surface pH was lying in the range of 6.43 to 6.80. The observations were shown in Table 5. The surface pH of all the strips was within the range of salivary pH (6.5±5). No significant difference was found in surface pH for different formulation. Hence buccal strips will not cause any damage to the buccal mucosa.

Disintegration studies: The observation was tabulated in Table 5**.** From the results, disintegration times for all the formulations were found in the range of 18.15 to 38.33sec. The disintegration time was lying within the pharmacopeia limit.

Percentage of moisture content & moisture uptake: The results were tabulated in Table 5. Moisture content and Moisture uptake of buccal strips were found to be in the range of 3.9 to 6.98% and 4.10 to 9.44%.

Tensile strength studies: Tensile strength indicates the strength of strip and the risk of film cracking. From the studies it was revealed that there was no sign of cracking in prepared buccal strips, which might be attributed to the addition of the plasticizer, PEG-400 and glycerine. Tensile strength of formulated films was ranges from 2.8 to 5.37N. The outcomes of tensile strength of films were shown in Figure 3.

In vitro **drug release studies:** The observations of release of drug from different formulations were revealed in Figure 4**.** From the results, it was revealed that, formulations (F2) showed maximum amount of drug release (98.13%) and formulation F8 showed minimum amount of drug release (76%) in 30mins. The order of drug diffused from various formulations was found to decrease in the following order such as F2> F1 > F3 > F4 > F5 > F6 > F7 >F8. Drug release was more rapid in strips containing tween 80 because of the surfactants causing wetting of strip.

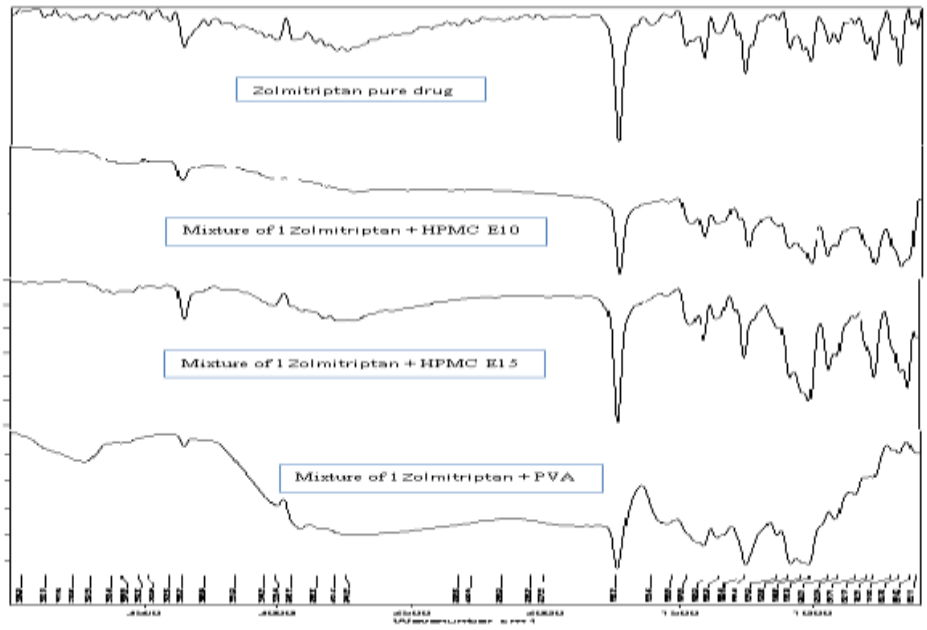

Figure 2: FT-IR spectra of pure drug and mixture of pure drug and pure drug with polymer

Table 1: FTIR spectra of zolmitriptan pure drug

Vibrations	Drug sample
C=O stretch	1732.73 cm^{-1}
N-H bending	3352.23 cm^{-1}
-C-H- aromatic	2958.30 cm^{-1}
-C-H- aliphatic	3044.35 cm^{-1}
-CH3 aromatic	1412.87 cm^{-1}

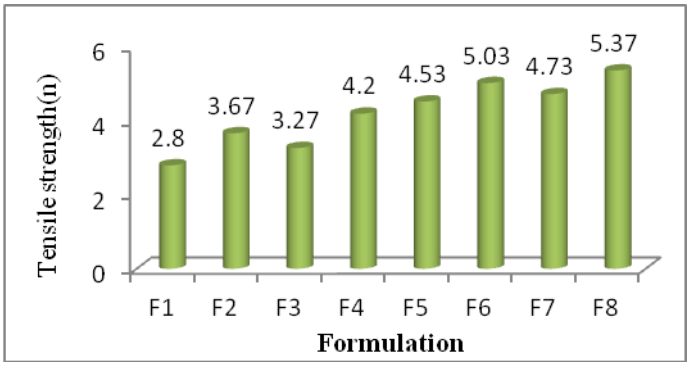

Figure 3: Tensile strength profile of zolmitriptan buccal strips

Table 2: FTIR spectra of pure drug + polymer mixtures

Vibrations	Drug + HPMC	Drug + HPMC E15	Drug + PVA
C=O stretch	1728.98 cm^{-1}	1731.16 cm^{-1}	1732.82 cm^{-1}
N-H stretch	3344.07 cm^{-1}	3348.00 cm^{-1}	3348.10 cm^{-1}
-C-H- aliphatic	2817.83 cm^{-1}	2909.56 cm^{-1}	2914.15 cm^{-1}
-C-H- aromatic	3012.18 cm^{-1}	3010.39 cm^{-1}	3004.13 cm^{-1}
-CH3 aromatic	1412.08 cm^{-1}	1420 cm^{-1}	1418 cm^{-1}

Table 3: Formulation chart of buccal strips of zolmitriptan

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Zolmitriptan	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg
HPMC E10	150mg	300mg	-	-	-	-	150mg	150mg
HPMC E15	-	-	150mg	300mg	-	-	-	-
PVA	-	-	-	-	150mg	300mg	150mg	300mg
PEG 400	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
Kyron T 314	75mg	75mg	75mg	75mg	75mg	75mg	75mg	75mg
Aspartame	40mg	40mg	40mg	40mg	40mg	40mg	40mg	40mg
Tween 80	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml

Table 4: Evaluation parameters of buccal strips of zolmitriptan

Formulation code	Weight uniformity* (mg)	Thickness uniformity*(mm)	Folding Endurance*	Drug content uniformity* (%)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
F1	31.0 ± 0.173	0.123 ± 0.003	289.6 ± 3.605	95.60 ± 1.537
F2	29.9 ± 0.378	0.121 ± 0.003	291.3 ± 3.605	96.60 ± 1.358
F3	33.7 ± 1.060	0.133 ± 0.003	273.0 ± 2.543	93.30 ± 1.746
F4	32.4 ± 0.360	0.131 ± 0.003	285.0 ± 2.645	90.50 ± 1.100
F5	35.7 ± 0.400	0.150 ± 0.005	264.0 ± 1.527	76.60 ± 1.242
F6	37.4 ± 0.560	0.165 ± 0.005	265.6 ± 1.527	81.30 ± 0.996
F7	33.6 ± 0.450	0.141 ± 0.030	274.6 ± 2.081	88.26 ± 1.416
F8	36.4 ± 0.850	0.151 ± 0.003	286.3 ± 1.154	84.40 ± 0.889

* n = 3

Table 5: Evaluation parameters of buccal strips of zolmitriptan

Formulation code	Moisture content* (%)	Moisture uptake* (%)	Disintegration time*(sec)	Surface pH* Mean + SD
F1	5.23 ± 0.11	5.53 ± 0.015	20.50 ± 3.605	6.64 ± 0.032
F2	3.90 ±0.32	5.96 ± 0.020	18.15 ± 3.605	6.80 ± 0.020
F3	5.74 ±0.21	6.59 ± 0.020	24.24 ± 2.543	6.43 ± 0.020
F4	6.11 ±0.33	7.33 ± 0.015	29.12 ± 2.645	6.74 ± 0.030
F5	6.98 ±0.43	9.44 ± 0.015	38.33 ± 1.527	6.47 ± 0.010
F6	4.54 ±0.54	4.10 ± 0.015	25.14 ± 1.527	6.55 ± 0.030
F7	6.23 ±0.42	5.34 ± 0.015	29.34 ± 2.081	6.79 ± 0.010
F8	4.35 ± 0.38	6.78 ± 0.015	31.13 ± 1.154	6.72 ± 0.026

* n = 3

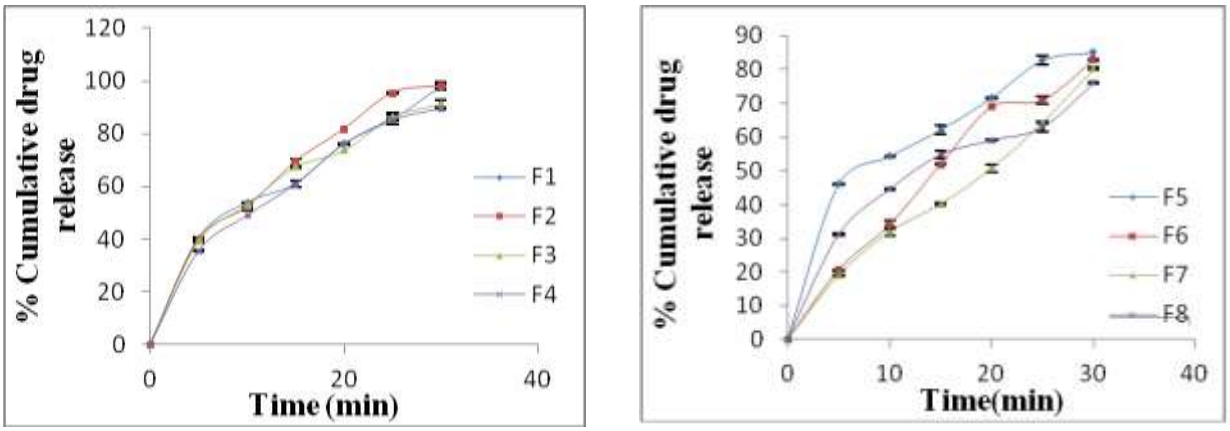

Figure 4 Percentage cumulative drug release profile of zolmitriptan buccal strips

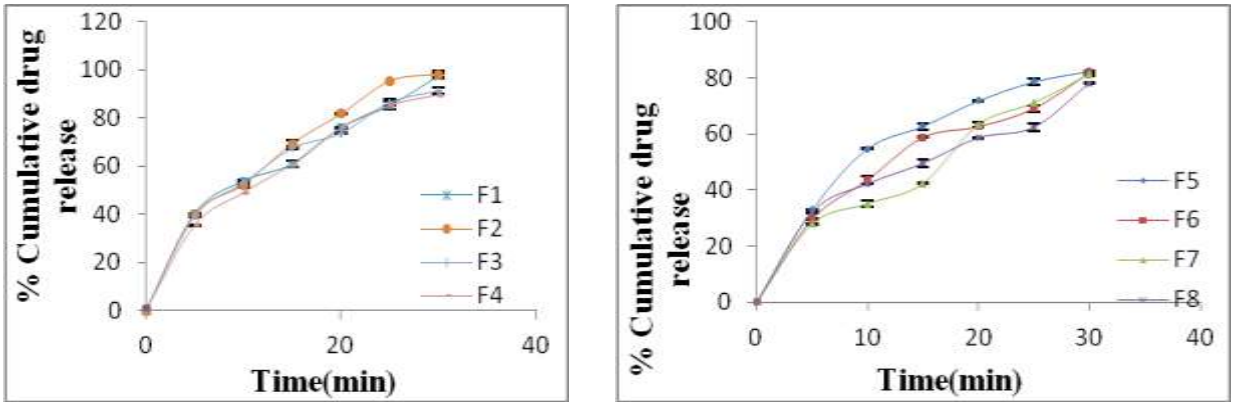

Figure 5 Percentage cumulative drug release data of zolmitriptan buccal strips

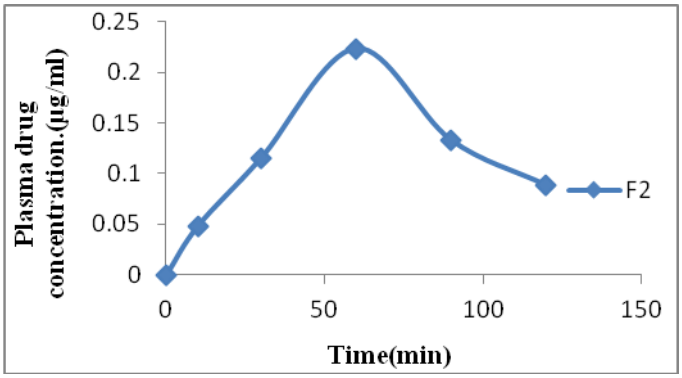

Figure 6 Mean plasma concentration-time data of zolmitriptan buccal strips

Table 6: *In vitro* drug release profile of optimized formulation (F2) after stability studies at 30 ± 2°C / 65 ± 5% RH

Formulation Code	%CDR* Mean ± SD		
	0th Day	**30th Day**	**60th Day**
F2	98.13 ± 0.66	98.10± 0.82	96.09± 0.79

* n = 3

Table 7: *Ex vivo* drug diffusion profile of optimized formulation (F2) after stability studies at 30 ± 2°C / 65 ± 5% RH

Formulation Code	%CDR* Mean ± SD		
	0TH DAY	**30 DAYS**	**60 DAYS**
F2	95.01± 0.55	94.36± 0.01	94.01± 0.23

* n = 3

Table 8: Buccal strip properties of optimized formulation (F2) after stability studies At 30 ± 2°C / 65 ± 5% RH

Time (Days)	Weight uniformity* (mg) Mean ± SD	Disintegration* (sec)* Mean ± SD	Folding endurance* (Numbers) Mean ± SD	Drug content* (%) Mean ± SD
0	29.9	18.15	291	96.6
30	29.6	17.96	289	95.8
60	29.5	17.90	286	95.3

*n = 3

Buccal strips containing HPMC E10 showed maximum release compared to other buccal strips containing HPMC E15 and polyvinyl alcohol. As the concentration of HPMC E10 increases the drug release rate also increases. As the viscosity of the HPMC increases the drug release rate decreases. The formulation (F2) was predicted as optimized formulation based on drug content and drug release.

Ex vivo drug diffusion studies

The *ex vivo* drug diffusion study was carried out for the optimized formulation (F2) in pH 6.8 phosphate buffer solution for 30mins using sheep buccal mucosa. The diffusion studies were carried out using Franz diffusion cell. The diffusion results were depicted in Figure 5. It was observed from the results that, optimized formulation (F2) showed drug release (95.10%) in 30mins.

Pharmacokinetic studies

In vivo studies were carried out for optimized formulation (F2) using rabbits. The mean plasma concentration-time data of buccal strips of zolmitriptan was shown in Figure 6. The peak plasma concentration (C_{max}) attained by formulation F2 was 0.2234±0.25 µg/ml following oral administration, respectively. The times required for attaining peak plasma concentration by drug following oral administration were 60mins. The time required for a drug to decrease by half ($t_{1/2}$) were found to be 60mins following oral administration respectively.

Stability studies

Stability studies were carried out for the optimized formulation F2, at 30 ± 2°C / 65± 5% RH for 2 months. Stability studies results were shown in Table 6-8. There was no significant change in the ***in vitro*** release of F2on 0^{th} day (98.13%), 30^{th} day (98.10%) and 60^{th} day (96.09%). The *ex vivo* drug diffusion study showed that there is no significant difference in the drug release after 0^{th} day (95.10%), 30^{th} (94.36%) and 60^{th} day (94.01) at 30 ± 2°C (65± 5% RH). After stability studies, it was found that there is no significant change in the weight variation, disintegration time, folding endurance and drug content. It was concluded that formulation (F2) was stable at 30 ± 2°C (65± 5% RH) after 2 months stability study.

CONCLUSION

From the present study, it may be concluded that buccal strips of zolmitriptan can be prepared by solvent casting method using polymers HPMC E10, E15 and PVA in different concentrations and superdisintegrants Kyron T-314. It was concluded that formulation (F2) was considered as best formulation with fast onset of action, improved bioavailability, drug release rate, patient compliance and effective therapy.

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