Fast Dissolving Sublingual Films of Zolmitriptan : A Novel treatment approach for Migraine Attacks

Prachi Pandey*, Sonam Chauhan

Babaria Institute of Pharmacy, BITS edu campus, Vadodara - Mumbai NH # 8, Varnama, Vadodara - 391240, Gujarat. INDIA.

ABSTRACT

Zolmitriptan, 5- Hydroxy tryptamine agonist is a new generation anti-migraine drug showing the oral bioavailability of only 40% as a result of hepatic first pass metabolism. The present research work is aimed to prepare sublingual dosage form of the Zolmitriptan with the purpose to achieve quick onset of action in management of severe migraine attacks. Fast dissolving sublingual films of Zolmitriptan were thus prepared by solvent casting method. Water soluble polymer hydroxyl propyl methyl cellulose E50 was used as film forming polymer. Polyethylene glycol 400 and propylene glycol were used as plasticizers. Sucralose was added as a sweetener and peppermint oil as flavoring agent. The formulations prepared were evaluated for their uniformity of weight, surface pH, folding endurance, disintegration time, mucoadhesion time, tensile strength, % elongation, content uniformity and % drug release. The FTIR studies showed no interaction between drug and polymer. From the observations of evaluation results, it was concluded that formulation F3 containing 10% PEG 400 and 3% PG for films prepared using HPMC E 50 was the best formulation among all other formulations. Films showed excellent stability for at least for 4 weeks when kept at RT as well as at 400C and 75% RH.

Key words: Zolmitriptan, fast dissolving sublingual film, film forming polymer HPMC E50.

INTRODUCTION

For the last two decades, there has been an enhanced demand for more patient compliant dosage forms.[1] The cost involved and time consumed in the development of a single new chemical entity has made it mandatory for pharmaceutical companies to reconsider delivery strategies to improve the efficacy of drugs that have already been approved.[2] Therefore, pharmaceutical Industries are now directed towards reformulating existing drugs into new drug delivery systems.[3] The oral route is considered to be the ideal route for the administration of therapeutic agents. It is more acceptable from patient compliance aspects due to low cost and ease of administration. However, significant constraints are associated with oral administration such as hepatic first pass effect and drug degradation due to enzymes.[2,4] The pediatric and geriatric patients find it difficult to take solid preparations due to fear of choking.[5] Fast dissolving tablets can be the option to resolve the problem, but it is also associated the fear of choking due to the size and shape.[6] Thus absorptive mucosa can be considered as potential site for drug administration including mucosal linings of nasal, rectal, vaginal, ocular and oral cavity.[2] The oral cavity is highly acceptable by the patients because of several reasons like high mucosal permeability, rich blood supply and short healing time after damage. Sublingual drug delivery can bypass the first pass metabolism and avoid drug elimination without absorption. Such factors make sublingual cavity a feasible site for achieving the systemic therapeutic effects of drug.[7] Sublingual route can be considered as a novel route of administration because of immediate onset of pharmacological action. Sublingual drug administration means placement of the dosage form under the tongue. From here the drug gets absorbed and reaches directly into the blood stream through the ventral surface of the tongue and

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Correspondence Address
Prof . Prachi Pandey
Babaria Institute of Pharmacy, BITS edu campus, Vadodara - Mumbai , NH # 8, Varnama, Vadodara - 391240, Gujarat. INDIA.
E-mail: prachipandey21@gmail.com

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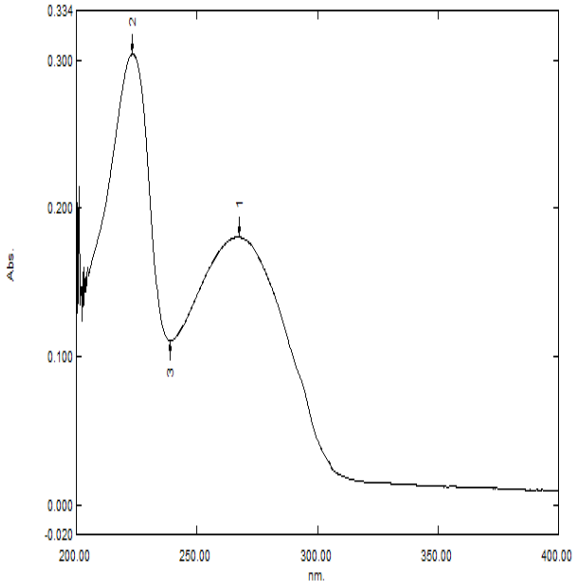

Figure. 1: UV Spectrum analysis of Zolmitriptan in Phosphate buffer pH 6.8 λ_{max} 223.4 nm

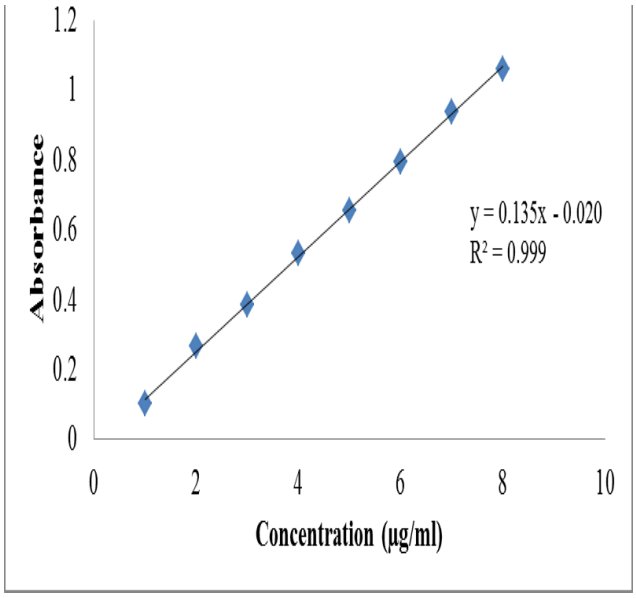

Figure. 2: Standard plot of Zolmitriptan in phosphate buffer pH 6.8

the floor of the mouth. This route provides the better alternative for the dysphagic patients, children, and geriatrics or to the patients who are mentally retarded, uncooperative, nauseated or on reduced intake of liquids. The sublingual area of oral cavity is more permeable than buccal area.[8]

Migraine is a neurobiologically based clinical syndrome characterized by recurrent episodic attacks of head pain.[9] It may be unilateral or bilateral, throbbing in quality and exacerbated by physical activity.[10] Studies on epidemiology show that >90 % migraine patients experience nausea during migraine attacks and > 70 % experience vomiting. Hence, during attacks, patients prefer to avoid the intake of liquid.[11] The anti-migraine drug, Zolmitriptan is serotonin 5-HT1B/1D agonist.[9] The absorption of Zolmitriptan from GIT is high but it undergoes extensive first pass metabolism giving the oral bioavailability of only 40%.

The aim of the study is to prepare fast dissolving sublingual film of zolmitriptan to achieve rapid onset of action as required during the migraine attacks. The fast dissolving sublingual films of Zolmitriptan prevents its first pass metabolism. It also eliminates patient's fear of choking as well as need of liquid or water for oral administration of dosage form, also the patient will get rapid onset of action.

MATERIAL AND METHODS

Zolmitriptan was received as gift sample from Cipla Pharmaceuticals Ltd., Mumbai, India. Hydroxymethyl propyl cellulose was procured from Sulab laboratories, Vadodara. Polyethylene glycol 400 and Propylene glycol were obtained from Suvidhinath lab, Vadodara. Sucralose was obtained from Sunrise Remedies, Ahmedabad and Peppermint oil was obtained from Chemydes laboratory, Vadodara.

Drug polymer compatibility studies

The interaction study between drug and polymer was carried out using FTIR. The KBr discs of drug and polymer in the ratio of 1:1 was prepared and spectra were obtained

UV Spectrum Analysis of Zolmitriptan

The solution of Zolmitriptan in phosphate buffer pH 6.8 was prepared and scanned in the range of 200-400 nm to get the maximum wave length and UV spectrum was obtained (Figure 1).

Standard plot of Zolmitriptan in Phoshphate buffer pH 6.8

The pure drug sample i.e. 10 mg of Zolmitriptan was accurately weighed on the digital balance, dissolved in phosphate buffer pH 6.8 and volume was made up to 100 ml using phosphate buffer pH 6.8. From the above prepared solution, 10 ml was withdrawn and diluted to 100 ml. From the prepared stock solution as mentioned above (i.e.10 µg/ml) 1 ml was pipetted out and diluted with phosphate buffer pH 6.8 up to 10 ml to give the solution of 1 µg/ml. Subsequently, aliquots of 2 to 8 ml of stock solution (10 µg/ml) were serially diluted with phosphate buffer pH 6.8 up to 10 ml to get a concentration range of 2 to 8 µg/ml concentration. The absorbance of each solution was measured at 223.4 nm against phosphate buffer pH 6.8 as a blank. The procedure was carried out in triplicate and average absorbance was considered (Figure 2 & 3).

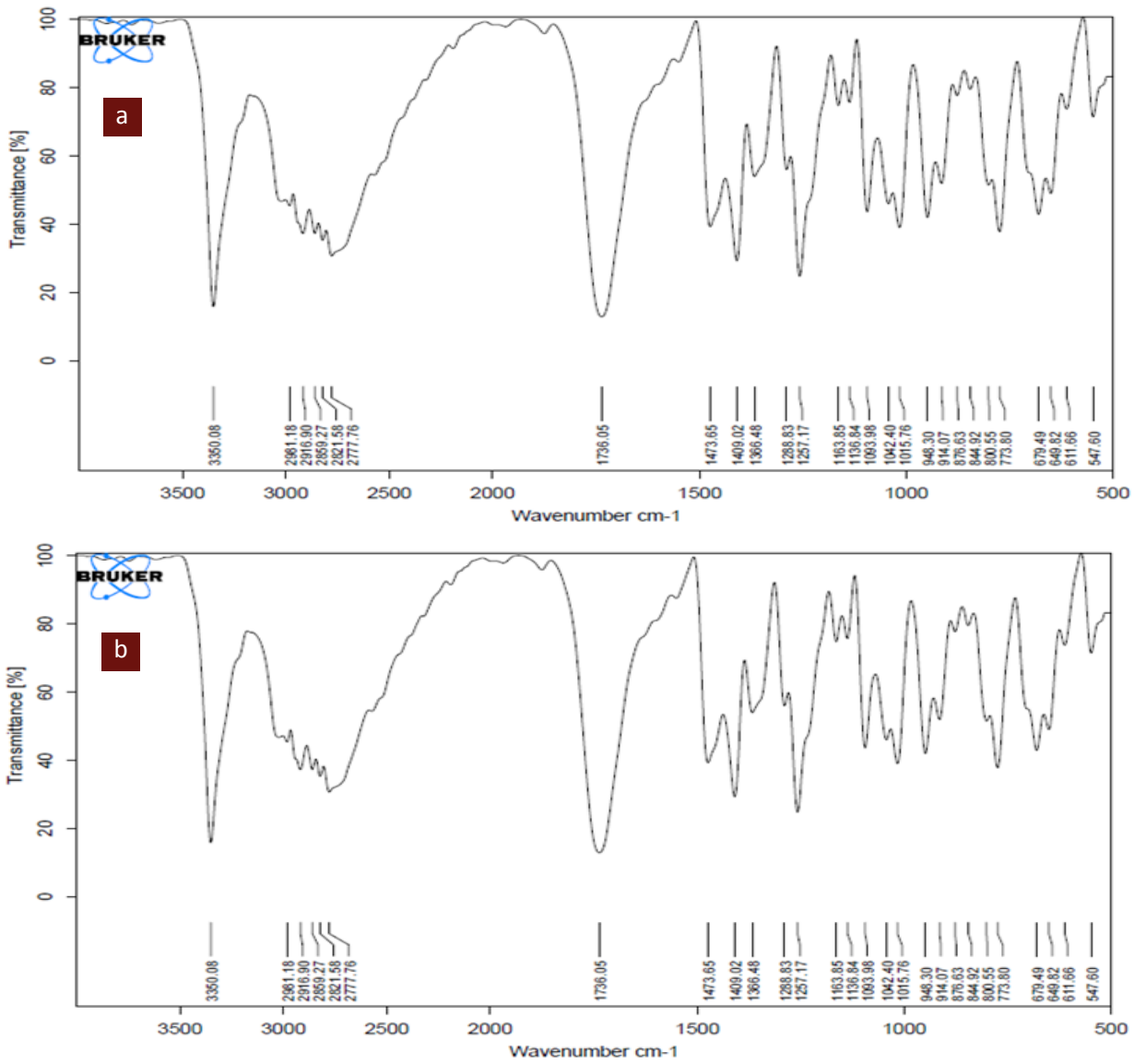

Figure. 3: FTIR spectra of (a) Pure Zolmitriptan (b) Physical mixture of Zolmitriptan and HPMC E50

Method of preparation of fast dissolving sublingual film of Zolmitriptan

Films were prepared using solvent casting method. The aqueous solution I was prepared by dissolving HPMC E50 in cold water and keeping it aside for 4 hours to remove the air bubbles. Solution II was prepared by dissolving sucralose, peppermint oil and plasticizers i.e. polyethylene glycol 400 and propylene glycol. Solution II was then added to solution I and it was then casted on to petri plates and dried at RT for 24 hours. After drying, films were carefully removed from plates, cut in to required size (2 x 1) cm. The samples were then evaluated for various tests (Table I).

Thickness

The thickness of the film was measured using digital verneir calipers. The thickness of each film was determined at six different locations and standard deviation was calculated.

Weight Variation

An area of 2 cm^2 of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.[12]

Folding endurance

The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This gives an indication of the brittleness of film.[12] Folding endurance was determined manually by repeatedly folding the film at the same place several times till it breaks.[13]

Tensile strength

Tensile strength was measured by the apparatus fabricated in the laboratory. A film of area 2 cm^2 was cut which did not contain any air bubble. It was then fixed

Table 1: Composition of Zolmitriptan Sublingual Films

Formulation	Zolmitriptan (mg)	HPMC E50 (mg)	PEG 400 (ml)	PG (ml)	Sucralose (mg)	Peppermint oil (ml)	Citric acid (mg)	Water upto (ml)
F1	80	600	1.0	0.1	50	0.3	70	10
F2	80	600	1.0	0.2	50	0.3	70	10
F3	80	600	1.0	0.3	50	0.3	70	10
F4	80	600	1.5	0.1	50	0.3	70	10
F5	80	600	1.5	0.2	50	0.3	70	10
F6	80	600	1.5	0.3	50	0.3	70	10
F7	80	600	2.0	0.1	50	0.3	70	10
F8	80	600	2.0	0.2	50	0.3	70	10
F9	80	600	2.0	0.3	50	0.3	70	10

to the assembly and the weight that was required to break the film was noted as well as film elongation was noted using the pointer fixed to the assembly. Tensile strength was measured using the formula given below:

Tensile strength = Break force / w.t (1+ΔL/L)

Where,

w, t and L are width, thickness and length of film; ΔL is increase in length of film.[5]

Percent Elongation

It was determined by the increase in the length of the film just before the breaking of the film. The formula used for calculating % Elongation is as shown below:

% Elongation = [Final length – Initial length]/ Initial length x 100.[14]

Surface pH

The oral film was slightly wetted with the help of water. Then the pH of film was measured by bringing the electrode in contact with the surface of the oral film. This study was performed for six batches of each film formulation and mean ± S.D was calculated.[15]

Disintegration time

In vitro disintegration time was measured visually in a beaker containing 25 ml phosphate buffer pH 6.8 and swirling the media every 10 s. The disintegration time was noted as the time when the film starts to break.[11]

Uniformity of drug content

The film of 1 x 2 cm^2 was cut and dissolved in phosphate buffer pH 6.8 and volume made to 100 ml in volumetric flask. Then 1 ml was withdrawn from this solution and made to 10 ml. the absorbance of this solution was measured at 223.4 nm using UV visible spectrophotometer and the concentration was calculated. By correcting the dilution factor, the drug content was calculated. The test was performed in the triplicates and the standard deviation was calculated.[16]

In vitro dissolution

Dissolution study of film was performed in USP type II apparatus using 300 ml phosphate buffer pH 6.8 at 50 rpm speed and 37 ± 0.5^0 C temperature. The samples were withdrawn at the time intervals of 30 sec and analyzed spectrophotometrically.[15]

Ex vivo mucoadhesion time

The mucoadhesion time was measured by fixing the goat buccal tissue on the internal side of a beaker. The film was wetted with small volume of simulated salivary fluid and was pasted to the mucosa by applying a light

Table 2 : Evaluation of Physico-Mechanical Parameters of Fast Dissolving Sublingual Film of Zolmitriptan

Formulation Code	Thickness (mm)	Weight (mg)	Folding endurance	Tensile strength (N/ mm^2)	% Elongation
F1	0.10 ± 0.020	51 ± 1.00	> 300	5.2 ± 0.03	28.5 ± 0.11
F2	0.12 ± 0.005	53 ± 1.00	>300	6.8 ± 0.01	32.3 ± 0.08
F3	0.11 ±0.011	52 ± 1.00	>300	7.1 ± 0.05	35.0 ± 0..16
F4	0.09 ± 0.005	49 ± 1.00	152	3.2 ± 0.10	18.0 ± 0.12
F5	0.16 ± 0.010	56 ± 1.40	209	3.6 ± 0.13	19.0 ± 0.32
F6	0.15 ± 0.005	55 ± 1.15	>300	8.6 ± 0.04	40.6 ± 0.10
F7	0.10 ± 0.005	51 ± 0.57	124	2.0 ± 0.10	12.1 ± 0.13
F8	0.12 ± 0.010	54 ± 1.00	>300	4.4 ± 0.10	27.3 ± 0.09
F9	0.15 ± 0.005	54 ± 1.53	>300	5.9 ± 0.06	29.4 ± 0.14

Table 3: Surface Ph, Mucoadhesion Time, Disintegration Time and Drug Content of Sublingual Film of Zolmitriptan

Formulation Code	Surface pH	Mucoadhesion time (s)	Disintegration time (s)	Drug content (%)
F1	6.63 ± 0.05	192 ± 3.00	36 ± 4.50	99.1 ± 0.40
F2	6.61 ± 0.04	162 ± 1.00	32 ± 4.04	97.9 ± 0.50
F3	6.63 ± 0.02	168 ± 2.00	49 ± 0.57	99.9 ± 0.23
F4	7.01 ± 0.01	121 ± 5.00	30 ± 2.00	97.8 ± 0.52
F5	6.68 ± 003	130 ± 1.40	28 ± 3.50	98.0 ± 0.74
F6	7.04 ± 0.01	202 ± 1.15	43 ± 0.57	93.3 ± 0.20
F7	6.53 ± 0.03	177 ± 5.00	20 ± 1.00	100.1 ± 1.29
F8	7.08 ± 0.02	125 ± 2.00	23 ± 2.00	98.3 ± 0.40
F9	6.41 ± 0.03	95 ± 2.53	26 ± 2.00	98.1 ± 0.50

force with a fingertip. The beaker was filled with 200 ml of phosphate buffer pH 6.8 and kept at 37 °C. A 50 rpm stirring rate was applied and, the time taken for the film to completely erode or detach from the mucosa was observed as the mucoadhesion time.[17]

Stability studies

The stability study of the formulated film was carried out under different experimental conditions. The film was wrapped in butter paper and then packed in aluminum foil and kept at room temperature in stability chamber at 45–50^{0}C and 75% RH for the period of 45 days. After this period, films were characterized for drug content and other evaluation parameters.[18]

RESULTS AND DISCUSSION

In the present study, fast dissolving sublingual film formulations of Zolmitriptan were prepared by solvent casting method using HPMC E50 as film forming polymer, Propylene glycol and Polyethylene glycol 400 as plasticizers in various ratios, Sucralose as sweetener and Peppermint oil as flavoring agent. The effect of different concentration of plasticizers on tensile strength of film formulations was studied.

Fast dissolving sublingual films of zolmitriptan were evaluated for the various evaluation parameters. The films were prepared by using varying concentrations of different plasticizers with constant concentration of film forming polymer. All the prepared films were transparent, non-sticky, flexible and good in appearance.

The slight difference in the thickness of films could be attributed to the uneven surface of the plate. The individual weight of the films was measured and weight variation was calculated. The slight difference in the weight could be proportionately related to the variation in the film thickness. The pH of all the formulations was found in the range of 6.61 to 7.08. This shows that all the films prepared were of neutral pH.

All the films showed good folding endurance and most of them showed folding endurance of more than 300. The tensile strength of formulation F6 was found to be highest with the highest % elongation. It was seen from the results that formulations with lower concentrations of PEG 400 (F1, F2, F3) and the higher concentration of propylene glycol (F3, F6, F9), showed better folding endurance, tensile strength as well as % elongation (Table 2). The disintegration time of the films was found to be in the range of 20 – 49 sec. The higher disintegration time of could be attributed to higher concentration of film forming polymer as well as the mucoadhesive nature of this polymer (Table 3).

The formulations F1, F3, F5, F7, F8 and F9 showed better drug content of above 98 %. The reason of slight variation in the drug content of the prepared film can be attributed to the difference in the thickness of the film. Almost total amount of drug was found to be released from the formulations within 180 – 240 sec i.e. 3 – 4 min. Formulations F1, F3 and F7 showed the best drug release of more than 98% within 4 min. Thus from drug content and drug release evaluation data, it could be said that three formulations F1, F3 and F7 shows better drug content as well as drug release profile (Figure 4).

The films showed good stability at both RT and accelerated conditions for the period of 45 days. There was no significant change in mechanical properties, drug content and drug release of the film. This shows that the film will remain stable to the wear and tear that occurs during its handling and transportation.

CONCLUSION

The results of the studies indicated that HPMC E50 could be used as a film forming polymer for the formulation of sublingual film of Zolmitriptan. All the films prepared using HPMC E50 showed acceptable mechanical properties. The in vitro disintegration time of all the formulation batches was found to be within 20-49 sec. On the basis of tensile strength, drug content

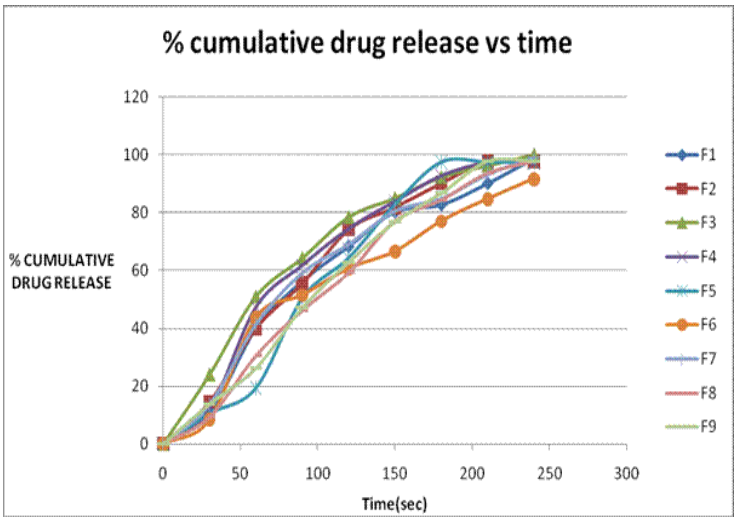

Figure 4: *In-vitro* dissolution of formulations in simulated salivary fluid pH 6.8

and *in vitro* dissolution, formulation F3 was found to be the promising formulation showing better strength and good drug release profile. Also this formulation was stable for a period of 45 days with no significant change in drug content and drug release profile. Thus it could be said that the fast dissolving sublingual film of Zolmitriptan could be a better option for acute treatment of migraine attacks compared to the available conventional dosage forms.

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