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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF ZOLMITRIPTAN

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ABSTRACT

Zolmitriptan is a serotonin receptor agonist (5-HT1) that is used to treat migraine with or without aura. Its half-life is 2 to 3 hours and undergoes first-pass liver metabolism. The absolute oral bioavailability is approximately 40%. To improve bioavailability and efficacy, Zolmitriptan mucoadhesive buccal tablets made by using mucoadhesive polymers by direct compression technique. The mucoadhesive tablets were evaluated for a series of parameters such as hardness, thickness, weight variation, friability, drug content, in vitro swelling study, in mucoadhesive strength, and *in-vitro* drug release study. A pre-formulation study such as a drug-excipient compatibility study was done by using the IR spectrum. All prepared tablets had a smooth surface and elegant appearance. Tablets were weighing 148-150 mg, hardness was 3.43 to 4.60 kg/cm2, the thickness was 2.80-2.87 mm. Friability and content of the drugs were all within pharmacopeia limits. All tablets reported mild index of swelling. All tablets showed acceptable mucoadhesive strength. Studies of *in-vitro* drug release showed that 84% of the drug was released within 10 hrs. So, these formulations of Zolmitriptan are promising ones as a controlled drug delivery system which can lead to improving bioavailability and greater therapeutic efficacy.

Keywords*:* - Zolmitriptan, Buccal tablets, In vitro drug release, HPMC K4M

INTRODUCTION

Migraine is a neurological disease that affects 5-17% of the general population. Migraine is about 3-4 times more in women than in men. It is also an unpredictable disorder, with attacks that can occur at any time, and patients, therefore, need a medication that enables them to treat their migraine headache anytime a migraine strikes.[1, 2] Headache attacks in migraine cluster usually last from 10 to 180 minutes and can occur several times a day. Most patients have episodes wherein the attacks occur in discrete bouts lasting weeks or months interspersed with periods of complete remission. The precise prevalence of headache clusters is unknown.[3]

Zolmitriptan, a structural analog of serotonin (5- hydroxytryptamine; 5-HT), is a selective (5-HT) 1B/1D agonist. The medication is recommended for treating menses related to acute migraine, with or without aura and cluster headaches. Zolmitriptan mimics serotonin activity by directly activating the brain serotonin receptors and thus contributes to vasoconstriction of the brain's blood vessels. Therefore, reducing sterile inflammation associated with zolmitriptan antidromic neuronal transmission is another mechanism by which acute migraine attacks have been reported to be relieved. Zolmitriptan is currently available commercially as oral (conventional and orodispersible) tablets and a nasal spray. Even though Zolmitriptan is a potent agent, the current oral therapies present drawbacks, such as the slow onset of action, poor bioavailability (40–45%), nausea and inadequate headache relief. Additionally, oral Zolmitriptan has a minimal half-life (1–2 hrs), with the drug completes the first-pass metabolism and is quickly removed by the hepatic and the renal systems. Hence there is a need to formulate into a controlled or sustained dosage form to avoid these demerits.[4]

Buccal drug delivery system has the potential to fill an unmet need in migraine care by providing direct access to the circulation through the inferior vena. Tran mucosal drug delivery routes provide distinct advantages over the systematic delivery of drugs through oral administration. These advantages include possible bypass of first-pass effect, avoidance of presystemic elimination within the GIT, a much better enzymatic flora for drug absorption, noninvasive administration, rapid action, convenient and simply accessible location, self-administrable, drug or excipients suitability that moderately and reversibly damages or irritates the mucous membrane, administers painlessly, quick and has good patient compliance. Water-soluble drugs are considered difficult to deliver within the sort

of sustained or controlled release preparation because of their susceptibility to ‘‘dose dumping phenomenon.’’ Attempts are made to manage their release process by the use of mucoadhesive polymers to attain a once-a-day dose treatment. During this work, develop Buco-adhesive tablets of Zolmitriptan with the subsequent objectives to avoid hepatic first-pass metabolism, to reduce the frequency of administration, overcome the side effects, simplify the treatment regimen, and to get greater therapeutic efficacy to boost patient compliance.[5, 6]

MATERIALS AND METHODS

MATERIALS

Zolmitriptan pure drug was obtained as a gift sample from Cipla Pharmaceutical Mumbai, India. Hydroxypropyl-methyl cellulose K4M (HPMC-K4M) and chitosan were obtained from Loba Chemicals Limited, Mumbai, India. All other analytical grade chemicals used.

METHODS

Identification of drug

The melting point of Zolmitriptan was determined by the capillary method.

Estimation of Zolmitriptan of absorption maxima (λ max)

10 mg of Zolmitriptan has been correctly measured and transferred to a 100 ml volumetric flask. The pure drug was dissolved in 2 ml phosphate buffer pH 6.8 and the volume was made up to 100 ml to produce a 100 µg/ml stock solution.1 ml of this stock solution was diluted again with phosphate buffer pH 6.8 up to 10 ml to get a 10 µg/ml solution. The resulting solution was scanned between 200 nm to 400 nm in a UV-Visible spectrophotometer.

Preparation of calibration curve of Zolmitriptan in phosphate buffer pH 6.8

Weighted exactly 10 mg of Zolmitriptan and transferred to a 100 ml volumetric flask. The pure drug was dissolved in 2 ml phosphate buffer pH 6.8 and the volume was adjusted up to 100 ml using phosphate buffer pH 6.8 to obtain a stock solution of 100 µg/ml (stock solution I). 1 ml of this stock solution was diluted again with phosphate

buffer pH 6.8 up to 10 ml to obtain solution concentration 10 µg/ml (stock solution II). From stock solution, II pipette out 2, 4, 6, 8, 10 ml were transferred to a series of 10 ml volumetric flasks. The volume was made up of phosphate buffer pH 6.8 fluids to give 2, 4, 6, 8 and 10 µg/ml of concentration. The absorbance of these solutions was measured at 225 nm against blank.[7]

Compatibility studies

The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infrared spectra of drug and mixture of drug and excipients were recorded.[8]

Preparation of buccal tablets

The direct compression method was used to prepare mucoadhesive buccal tablets of Zolmitriptan using, chitosan and HPMC K4M as polymers. All the ingredients like including drug, polymers and excipients were weighed accurately according to the batch formula. The drug-polymer combination was mixed and triturated for 15min in a glass mortar to obtain a uniform mixture. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. On a single stroke tablet punching machine, the prepared blend of each formulation was compressed by using a punch (8 mm) to form a tablet according to their weight.

Table No. 1: Composition of Formulations

Ingredients mg/tablet	**F1**	**F2**	**F3**	**F4**	**F5**
Zolmitriptan	10	10	10	10	10
Chitosan	20	40	35	30	50
HPMC K4M	50	30	35	40	20
PVP K-30	8	8	8	8	8
Lactose	29	29	29	29	29
MCC	30	30	30	30	30
Magnesium stearate	2	2	2	2	2
Talc	1	1	1	1	1
Total	150	150	150	150	150

EVALUATION PARAMETERS

Evaluation of Tablets

Tablets are evaluated for the following tests.

1) Weight variation test: Twenty tablets were selected randomly and weighed individually. In determining weight variance, the individual weights were compared to average weights.

2) Hardness: Tablet hardness is defined as the force required to break the tablet in a diametric compression test. Monsanto hardness tester was used to measure the hardness of tablets.

3) Friability: The pre-weighed samples of tablets (10 tablets) were placed in a friabilator which revolves at 25 rpm for 4 min dropping the tablets through a distance of 6 inches with each revolution. Tablets were dedusted and reweighed. This process was repeated for all formulations and the percentage friability was calculated by using the following formula.

$$F = \frac{W\ Initial - W\ Final}{W\ Final} \times 100$$

4) Drug content: To obtain the fine powder, the ten tablets were weighed and ground in a mortar with pestle. Powder equivalent to one tablet mass was dissolved in phosphate buffer (pH 6.8) and filtered through a 0.45-µm filter paper. The filtrate was diluted with phosphate buffer (pH 6.8). The drug content was measured using a UV spectrophotometer at 225 nm using a reference to a standard calibration curve of the Zolmitriptan.

5) Thickness: Digital Vernier caliper was used to determine the thickness of prepared tablets.[9]

6) *In-vitro* drug release study: The USP dissolution test apparatus (apparatus II, paddle-type) was used to in vitro drug release study of tablets. The medium of dissolution was 500 ml of phosphate buffer pH 6.8. The drug release was performed at 37 ± 0.5°C, with a speed of 50 rpm. The backing layer of the tablet was attached to the glass slide by using instant adhesive tape. The slide was placed at the bottom of the dissolution vessel. 5 ml sample was withdrawn at fixed time intervals and maintain sink condition with fresh medium. The

samples were filtered through Whatman filter paper and analyzed spectrophotometrically at 225 nm.[10]

7) Determination of the Surface pH:

The surface pH of the tablets was estimated to predict the potential irritative effects on the bu ccal mucosa of each formulation. The tablets were allowed to swell at 37 ºC, for 2 h in 40 ml isotonic phosphate buffer (IPB) pH 6.7. The surface pH of the swollen tablets was measured using a pH paper. The experiment was carried out in duplicate and the mean surface pH was determined.[11]

8) Swelling index study: The extent of swelling was measured in terms of percentage weight gain by the tablet. One tablet from each batch was weighted as (w_o). Weighted tablets were kept in separate Petri dishes containing 5 ml of phosphate buffer (pH 6.8) from each batch. Each 2 hours duration up to 6 hours the tablet was removed and excess water was carefully blotted using filter paper. The swollen tablets were re-weighed (Wt). The swelling index (SI) of each tablet was calculated according to the following equation. [9, 12]

$$SI = \frac{W0 - Wt}{W0} \times 100$$

9) Mucoadhesive strength: The mucoadhesive potential of each formulation was determined by calculating the force required to detach the formulation form sheep buccal mucosal tissue by using a modified balance. A piece of buccal mucosa was cut from the buccal cavity of the sheep and placed onto each glass vial by the use of a rubber band with a mucosal side. For 5 minutes the vials of buccal mucosa had been held at 37 ° C. Then next vial was attached to the balance in an inverted position with a section of mucosa while the first vial was positioned on a pan adjustable in height. A Tablet of each formulation was put onto the first vial's buccal mucosa. Then the second vial's height was changed so that both vial's mucosa surface came in intimate contact. It took two minutes to ensure intimate tissue contact with the tablet. Then weight in the pan continued to rise until the vials are detached. Therefore, mucoadhesive force expressed as the detachment stress in dyne / cm^2 was calculated using the following equation from the minimal weights which deta ched the tissues from the surface of each formulation. [13, 14]

Detachment stress (dyne/cm^2) = m x g /A

Where, m = weight required for detachment of two vials in grams, g = Acceleration due to gravity [980cm/s^2], A = area of tissue exposed

Figure No. 1: Measurement of Mucoadhesive strength

RESULTS AND DISCUSSION:

Drug Identification and drug-excipient compatibility study

Melting Point

The melting point of Zolmitriptan was found to be 138-139 ºC.

Drug-excipient compatibility study

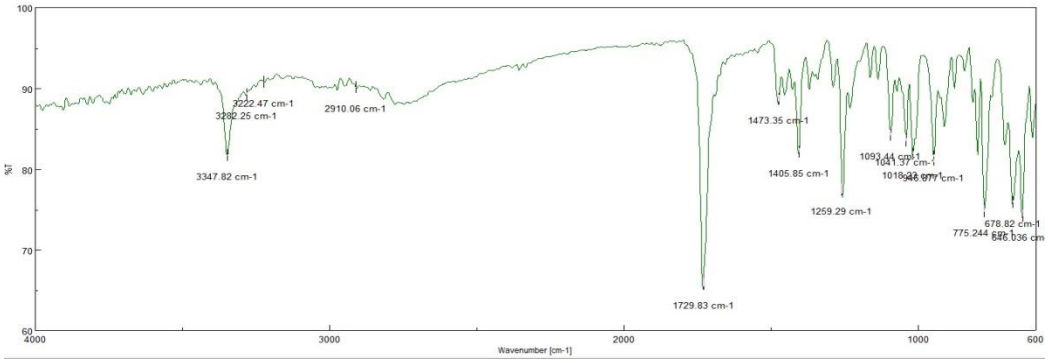

Figure No. 2: FTIR Spectrum of Zolmitriptan

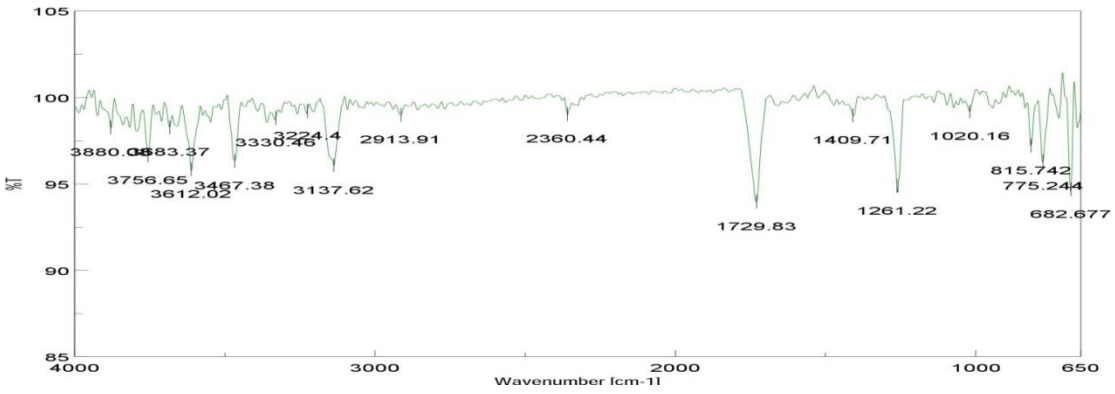

Figure No. 3: FTIR Spectrum of Zolmitriptan and Mixture of Polymer

Weight variation, hardness, thickness, and drug content

All the tablets with different proportions of polymer composition were within the weight range of 149.8 mg to 150.7 mg with SD values 0.3-0.99. The tablet's thicknesses of various formulations were observed to be in the range of 2.81mm to 2.87 mm with SD values of 0.05-0.06 (Table 2).

The mass and thickness of all compressed tablets were within the limit as per USP. The hardn ess of all the tablets was found to be in the range of 3.42 to 4.60 kg/cm^2.

Drug content ranged from 97.95±0.38 to 99.36±0.83 in formulation F1 to F5. The results of content uniformity show all the formulations comply with that prescribed in the Indian pharmacopeia. Friability for all the formulation shown less than 0.90% which is in the acceptable limits which indicate formulations have good mechanical strength.

Surface pH

Surface pH evaluation of oral mucosal dosage forms is an important characterization study. An acidic or alkaline pH may irritate the oral mucosa. The surface pH of all the formulations is in an acceptable pH range of 6.8 to 7 (salivary pH). (Table.2)

Table No. 2: Hardness, Thickness, Weight variations, Friability, Drug content, and Surface pH

Bach Code	Hardness (kg/cm^2) ±SD	Thickness (mm) ±SD	Weight variation (mg) ±SD	Friability (%) ±SD	Drug content (%) ±SD	Surface Ph ±SD
F1	3.43±0.16	2.80±0.06	150.7±0.99	0.67±0.01	98.75±0.88	6.95±0.79
F2	4.50±0.15	2.81±0.05	149.8±0.38	0.57±0.01	99.70±0.34	6.89±0.17
F3	3.52±0.21	2.87±0.06	150.1±0.99	0.55±0.00	97.95±0.38	6.94±0.12
F4	4.54±0.19	2.86±0.06	148.8±0.99	0.51±0.01	98.75±0.88	6.98±0.11
F5	4.60±0.22	2.87±0.06	149.8±0.38	0.87±0.03	99.36±0.83	7.04±0.06

Mucoadhesive Strength

The values of the mucoadhesive strength of Zolmitriptan buccal tablets are given in Figure 4. The formulation F4 shows greater mucoadhesive strength.

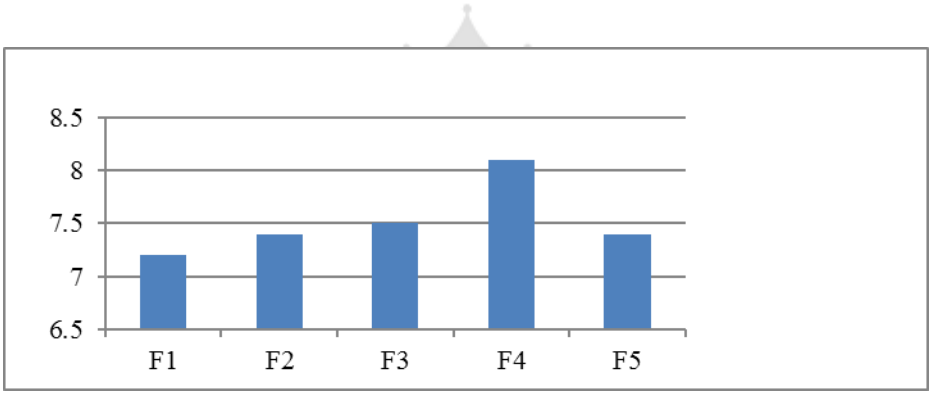

Figure No.4: *In-vitro* mucoadhesive strength of formulations F1 to F5

***In-vitro* drug release study**

In-vitro drug release study was carried out in 6.8 pH buffer using USP apparatus type II at 37 ± 5º C temperature. Batches F1, F2, F3, F4, and F5 showed 84.45, 87.12, 95.34, 93.23 and 88.56 % in vitro drug release in 10 hrs respectively.

Table No. 3: Percent total drug release of formulation F1 to F5

Time (Hrs)	F1	F2	F3	F4	F5
0.25	7.11	9.40	8.34	5.76	6.56
0.5	7.67	12.45	12.56	11.20	9.90
0.75	8.15	17.12	20.13	17.76	14.13
1	9.10	21.30	29.78	23.45	20.25
2	15.20	27.56	34.56	37.08	28.86
3	27.30	30.70	43.23	45.78	37.67
4	34.45	37.89	57.54	52.56	46.13
5	45.15	48.12	63.45	60.80	57.45
6	53.16	56.23	69.44	67.23	65.54
7	67.25	68.56	76.93	74.12	73.90
8	72.25	74.12	81.23	81.67	80.88
9	82.36	86.16	89.17	87.34	84.62
10	84.45	87.12	95.34	93.23	88.56

Swelling study

The swelling study was performed on all the formulations (F1 to F5) for 6 hours. The results of the swelling index were shown in table 4. The swelling index of the tablets was in the range of 33 to 82 %. The highest hydration (swelling) i.e. 85.6% was observed with the formulation F3.

Table No. 4: Swelling Index Profile of Formulation F1 to F5

	Time (Hrs)		
	2	4	6
F1	36.40±0.19	73.15±0.31	85.56±0.11
F2	34.14±0.23	70.34±0.11	80.12±0.14
F3	35.76±0.45	73.77±0.32	85.67±0.28
F4	34.56±0.22	74.45±0.17	83.12±0.32
F5	33.45±0.16	75.50±0.12	82.43±0.27

CONCLUSION

The prepared Zolmitriptan buccal mucoadhesive tablets adhere to the buccal mucous membrane and release the drug in a prolonged and uniform pattern which leads to improvement in patient compliance and drug efficiency.

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