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Research Article

FORMULATION DESIGN AND DEVELOPMENT OF ZOLMITRIPTAN ODT

S. Soujanya [1]*, Dr. Y. Ganesh Kumar [2], Dr. A. Madhukar [3], Dr. Damayanthi Dalu [4]

[1,2] Unity College of Pharmacy, Raigir (V), Bhongir (M), Yadadri Bhongir (Dist), Telangana State, INDIA.

[3] Avanthi Institute of Pharmaceutical Sciences, Gunthapally, Abdullapurmet, Hyderabad, Telangana State, INDIA.

[4] MNR College of Pharmacy, Fasalwadi (V), Narsapur (M), Sangareddy, Telangana State, INDIA.

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ABSTRACT

Zolmitriptan is a Selective Serotonin receptor agonist. Used in the acute treatment of Migraine attacks with or without aura and headaches. The current research work is aimed at evolving a formulate and evaluate of a Rapid dispersible tablet dosage form of Zolmitriptan. Who have little or no access to water are also good candidates for orodispersible.Direct Compression technique was employ for combination of pure drug and excipients in the given ratio as an eight compositions. The primed powder blend was then compressed into tablets by the required Superdisintegrants (SSG, CCS and CP) and Polymers. The tablets be evaluate for hardness, thickness, weight variation, friability, Drug Content and Disintegrating Time (Sec) were subjected to a 7 minutes in-vitro drug release studies (USP dissolution rate test apparatus II, 50 rpm, 370C ±0.50C) using phosphate buffer, pH 6.8 as a dissolution medium (900ml). The quantity of Zolmitriptan released from the tablet compositions at dissimilar time intervals is predictable by means of a UV spectroscopy method. The compositions that showed a considerable retardation of the drug release are considered promising. Among the eight compositions, F5 formulation contains Drug to Croscaramellose Sodium (CCS) in ratio 1:2 is optimized based on its ability to till 5 mins of in-vitro dissolution time and its cumulative % drug release was found to be 99.24 %.

KEYWORDS: *Direct Compression technique, Zolmitriptan, Croscaramellose Sodium.*

INTRODUCTION

The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form [1-4]. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations, and also offering advantages over both traditional dosage forms. It provides the convenience of a tablet formulation, and also allowing the ease of swallowing provided by the liquid formulation [5, 6].

MATERIALS AND METHODS

Zolmitriptan was a gift sample from Hetero Labs, Hyderabad, Magnesium Stearate, Microcrystalline Cellulose was used and supplied by Yarrow Chem Products, Mumbai. Sodium Starch Glycolate, Croscaramellose Sodium, Cros povidone, Mannitol was used and supplied by Signet chem, Mumbai, Aerosil was supplied by Loba chemicals, Yarrow Chem Products, Mumbai.

Methodology:

Standardization of Zolmitriptan by UV-Visible spectrophotometry:

Standard calibration of Zolmitriptan in 6.8 Phosphate buffer*:* 100mg of Zolmitriptan was accurately weighed and dissolved in100ml of 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 224 nm.

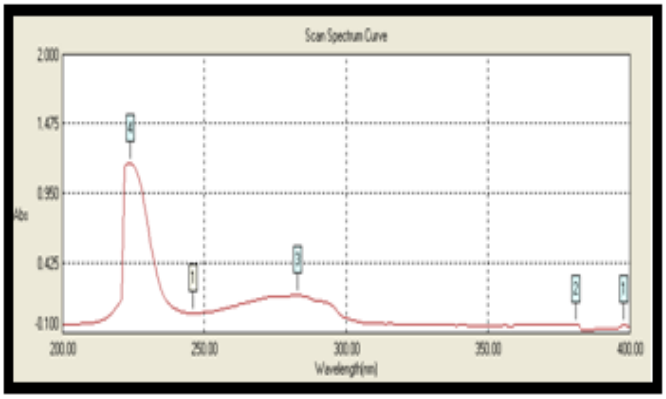

Fig. 1: λ_{max} of Zolmitriptan in pH 6.8 Phosphate buffer

***Corresponding author:**

S. Soujanya

Assistant Professor,

Unity College of Pharmacy,

Raigir (V), Bhongir (M), Yadadri Bhongir (Dist),

Telangana State, INDIA. Contact No: +91-7997540499.

** E-Mail: dindle.me@gmail.com*

Table No. 1: Standard graph of Zolmitriptan in pH 6.8 Buffer

S. No	Concentration	Absorbance
1	0	0
2	1	0.154
3	2	0.294
4	4	0.580
5	6	0.855
6	8	1.079

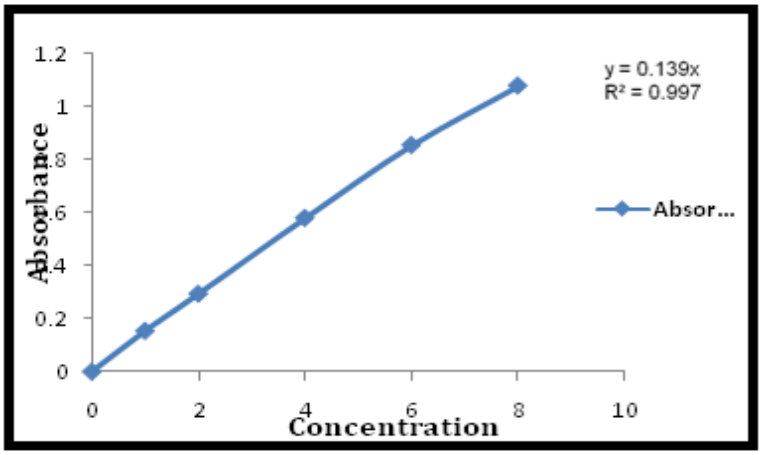

Fig 2: Standard graph of Zolmitriptan in pH 6.8 Buffer

Drug- Excipient Compatibility by FTIR studies:

In the preparation of orodispersible tablet, pure drug and excipient may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug- excipient interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy (Agilent Technologies) was employed to ascertain the compatibility between Zolmitriptan and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure: Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR (Agilent Technologies). FT-IR spectrum of Zolmitriptan was compared with spectrum of Zolmitriptan and polymer. Disappearance of Zolmitriptan peaks or shifting of peak in any of the spectra was studied [7-9].

FTIR Studies:

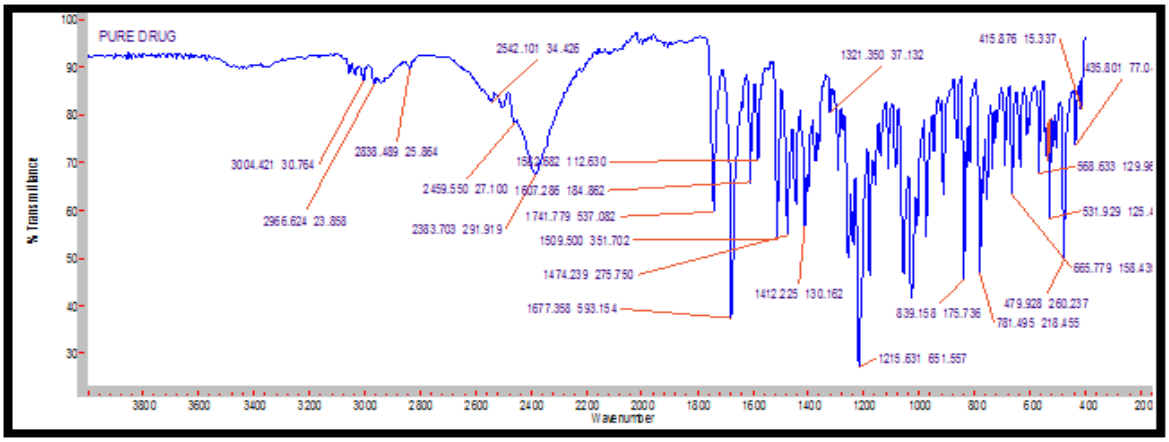

Fig 3: FTIR Graph of Pure Drug (Zolmitriptan)

Evaluation of Tablets:

Precompression Parameters:

(A) Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder.

(B) Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%,

tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder, Vt is the tapped volume of the powder

(C) Angle of Repose (θ): The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h / r$$
$$\theta = \tan^{-1}(h / r)$$

Where, θ is the angle of repose; h is the height in cms,r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

(D) Carr's index (or) % compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = Dt - Db / Dt \times 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

(E) Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = Dt / Db$$

Where, Dt is the tapped density, Db is the bulk density.

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25) [10-12]

Post Compression Parameters:

Weight Variation Test: From each batch twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

Hardness and Friability Test: For each formulation the hardness was determined by using Monsanto hardness tester and Friability of the tablets was checked by using Roche Friabilator. This device subjects tablets to the combined effect of abrasion and shock by utilizing plastic chamber which revolves at 25 rpm dropping the tablets at a distance of 6 inches with an each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed and then % Friability was calculated.

Water Absorption Ratio and Wetting Time: A piece of tissue paper folded twice was placed in a small Petridish containing 6 ml of water. A tablet of known weight was put on the paper and the time required for complete wetting of tablet was measured. The wetted tablet was then weighed; water absorption ratio R was determined using t.

$$R = \frac{Wb - Wa}{Wb} \times 100$$

Where; Wb is weight of tablet before water absorption; Wa is weight of tablet after water absorption

Drug Content Uniformity Study:

Five tablets were weighed individually and powdered. The powder equivalent to 50 mg of Zolmitriptan was weighed and extracted in 6.8 phosphate buffer (100 ml) and the concentration of drug was determined by measuring absorbance at 224nm by spectrophotometer [13-15].

Table No. 2: Precompression Parameters

S. No	Formulation	Angle of repose	Bulk density	Tapped density	Carr's index
1	F1	25.25	0.41	0.52	14.27
2	F2	28.37	0.43	0.51	11.35
3	F3	25.35	0.44	0.53	15.39
4	F4	27.63	0.41	0.56	9.45
5	F5	29.73	0.49	0.54	8.26
6	F6	26.34	0.45	0.52	14.63
7	F7	30.75	0.42	0.55	12.53
8	F8	28.26	0.51	0.57	14.29

Preparation of tablets: Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of pure drug and excipients were mixed thoroughly Magnesium stearate was added as lubricant. Aerosil was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 75 mg of Zolmitriptan.

Table No. 3: Composition of Zolmitriptan

S.No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	**Zolmitriptan**	5	5	5	5	5	5	5	5
2	**Sodium Starch Glycollate**	7.5	12.5	17.5	-----	-----	-----	-----	-----
3	**Cross Caramellose Sodium**	-----	-----	-----	7.5	10	17.5	-----	-----
4	**Cross Povidone**	-----	-----	-----	-----	-----	-----	12.5	17.5
5	**Microcrystalline Cellulose**	QS	QS	QS	QS	QS	QS	QS	QS
6	**Mannitol**	5	5	5	5	5	5	5	5
7	**Magnesium stearate**	2	2	2	2	2	2	2	2
8	**Aerosil**	2	2	2	2	2	2	2	2
	Total weight (mg)	75	75	75	75	75	75	75	75

Table No. 4: Post compression parameters

S. No	Formulation	Weight variation	Thickness (mm)	Hardness (Kg/Cm²)	Friability %	Disintegrating Time (sec)
1	F1	0.38	1.5	2.5	0.53	39
2	F2	0.63	1.3	2.2	0.46	41
3	F3	0.59	2.2	2.1	0.49	46
4	F4	0.72	1.5	2.4	0.57	37
5	F5	0.58	1.4	2.5	0.62	21
6	F6	0.61	1.4	2.7	0.49	38
7	F7	0.72	1.8	2.3	0.51	46
8	F8	0.55	1.6	2.1	0.63	44

***In-Vitro* Drug Release Study:**

Dissolution rate was studied 6.8 phosphate buffer as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5ºC; aliquot of dissolution medium was withdrawn at every 2 minute interval and filtered. The absorbance of filtered solution was checked by UV spectrophotometric method at 224 nm and concentration of the drug was determined from standard calibration curve.

***In-vitro* drug release studies details:**

Dissolution medium : 6.8 phosphate buffer at λ max 224 nm
Dissolution medium volume : 900 ml
Temperature : 37±0.5ºC
Speed of basket paddle : 50 rpm
Sampling intervals : 2 min
Sample withdrawn : 5 ml
Absorbance measured : 224 nm.

***In-Vitro* dissolution studies:**

Table No. 5: Cumulative % Drug Release of the Formulations (F1-F8)

S. No	Time(mins)	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	1	58.46	51.34	49.35	45.41	54.65	49.19	54.35	40.21
3	3	71.36	69.23	64.69	69.24	78.34	69.53	67.56	58.37
4	5	83.28	80.11	79.46	75.35	99.27	72.34	73.29	63.46
5	7	94.22	91.42	88.67	86.29	---	95.13	91.47	84.36

Dissolution release profiles of Compositions:

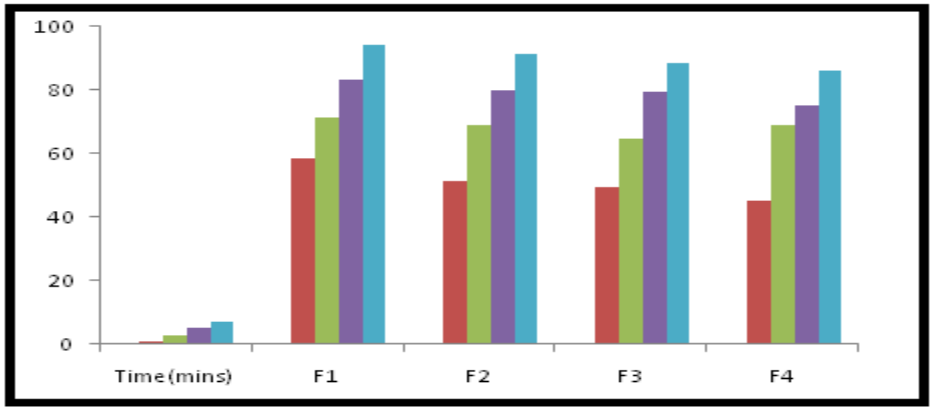

Fig. 4: Dissolution profiles of Compositions F1-F4

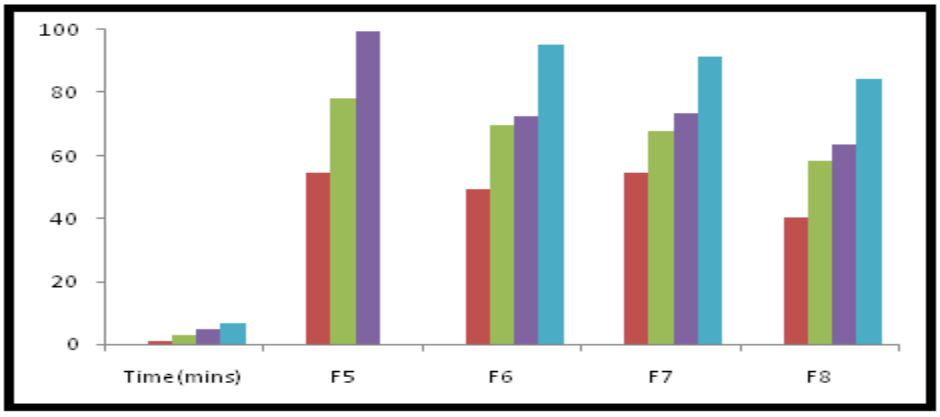

Fig. 5: Dissolution profiles of Compositions F5-F8

RESULTS AND DISCUSSION

Zolmitriptan have an UV absorbance of 224 nm. Solutions ranging from 5 to 25µg/ml were prepared using 6.8 Phosphate buffers separately, absorbance was measured for each solution at λmax of 224 nm using Labindia Double beam UV/ visible spectrophotometer and graph was plotted for absorbance vs. concentration of Zolmitriptan. Standard graph of Zolmitriptan in pH 6.8 Buffer at λ max 224 nm. The drug compatability studies were done by using FTIR and there is no interference to the drug and exipients. Precompression Parameters and post compression parameters were done and they were within the pharmacopoeial limits.

CONCLUSION

The orodispersible tablets of Zolmitriptan were prepared effectively by excipients in dissimilar ratios of through via Superdisintegrants. We can conclude Out of eight compositions using various Superdisintegrants akin to SSG, CCS and CP along with this composition F5 contains Cross Caramellose Sodium shows maximum drug release within 5 minutes of dissolution study. This formulation showed disintegration time of 21 seconds respectively. Thus based on Disintegration time and dissolution profiles, Formulations F5 is optimized to be the best among all the eight compositions.

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