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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF ZOLMITRIPTAN MOUTH DISSOLVING TABLETS

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ABSTRACT

The present study was carried out on Zolmitriptan Mouth dissolving tablets were prepared by direct compression method and different concentration super disintegrants like croscarmellose sodium, polyplasdone XL and Explotab were used in mouth dissolving tablets. A total of 9 formulations were prepared and evaluated for various pre and post compression parameters like angle of repose, bulk density, tapped density, carr's index, hausner's ratio, weight variation, hardness, friability, thickness, wetting time, drug content, *in vitro* disintegration time, *in vitro* drug release. The *in vitro* disintegration time of the optimised formulation (F3) of Zolmitriptan was found to be 28 sec. Release rate of drug was 99.65% within 12 hours. FTIR studies showed good compatibility between drug and excipients.

KEYWORDS: Zolmitriptan, Croscarmellose Sodium, Crospovidone, Sodium starch glycolate, Mouth dissolving tablets.

INTRODUCTION

Zolmitriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors. Drug IUPAC name (4S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1,3-oxazolidin-2-one. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists, and has only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3 or 5-HT_4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1, dopamine2; muscarinic, or benzodiazepine receptors. It is a triptan, used in the acute treatment of migraine attacks[1,2,3] with or without aura and cluster headaches. Zolmitriptan is used for the acute treatment of migraines with or without aura in adults. Zolmitriptan is not intended for the prophylactic therapy of migraine[4,5.6] or for use in the management of hemiplegic or basilar migraine.[7,8,9,10] Zolmitriptan is available as a swallowable tablet, an oral disintegrating tablet, and a nasal spray, in doses of 2.5 and 5 mg. People who get migraines from aspartame should not use the disintegrating tablet which contains aspartame. According to a study of healthy volunteers, food intake seems to have no significant effect on the effectiveness of Zolmitriptan in both men and women.

MATERIALS AND METHODS

Zolmitriptan obtained from the Natco pharma ltd kothur telangana India *Sodium starch glycolate, Crosspovodone,* Crosscamellose sodium, Aspartame, Microcrystalline cellulose, Magnesium stearate, Manitol were purchased from SD fine chemical private Ltd, Mumbi, Maharastra.

Methodology

Preparation of Zolmitriptan Mouth dissolving tablets by direct compression method

Drug and different concentrations of super disintegrates and sweetening agent were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using 6mm round flat faced punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Composition of Zolmitriptan Mouth dissolving tablets

Materials (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zolmitriptan	5	5	5	5	5	5	5	5	5
Crospovidone	6	9	12	-	-	-	-	-	-
Croscaramellose sodium	-	-	-	6	9	12	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	6	9	12
Aspartame	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2	2	2	2
Mannitol	41.5	40	38.5	41.5	40	38.5	41.5	40	38.5
MCC	41.5	40	38.5	41.5	40	38.5	41.5	40	38.5
Total weight	100	100	100	100	100	100	100	100	100

EVALUATION OF PRE-COMPRESSION PARAMETERS OF POWDER BLEND ANGLE OF REPOSE

Angle of repose was determined using funnel method .The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula.

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

BULK DENSITY

Apparent bulk density (ρ_b) was determined by pouring the powder blend into a graduated cylinder. The bulk volume ($V_{b)}$ and weight of the powder (M) were determined.

$$\rho_b = M / V_b$$

TAPPED DENSITY

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend was measured. The tapped density (ρ_t) was calculated using the following formula.

$$\rho_t = M / V_t$$

COMPRESSIBILITY INDEX OR CARR'S INDEX

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index.

$$\text{Carr's Index} = \rho_b - \rho_t / \rho_b * 100$$

Where ρ_t = tapped density
ρ_b = bulk density

HAUSNER'S RATIO (H)

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

$$\text{Hausner's ratio (H)} = \rho t/\rho b$$

Where ρ_t = tapped density
ρ_b = bulk density

EVALUATION OF POST COMPRESSION PARAMETERS OF ZOLMITRIPTAN MDTs:

Different quality control tests were performed for all the MDT formulations to check whether these have met the specifications given in USP along with other In-vitro tests like wetting time and water absorption ratio.

Various tests performed are:

WEIGHT VARIATION TEST

20 tablets were randomly selected from each formulation and their individual weights and average weight of all 20 tablets was calculated by weighing on an electronic balance (Shimadzu, AUX 220, Shimadzu Corp, Japan). The Mean ± S.D. were noted.

THICKNESS

Randomly 10 tablets were taken from each formulation and their thickness was measured using a Micrometer. Average thickness and standard deviation values were calculated. The tablet thickness should be controlled within a ± 5% variation of standard value.

HARDNESS

The tablet hardness of different formulations was measured using the monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 2.5 kg / cm^2 is considered acceptable for uncoated tablets.

The hardness for MDTs should be preferably 2.5 to 3 kg/cm^2.

FRIABILITY

This test was performed using a laboratory friability tester known as roche friabilator. 20 tablets were weighed and placed in a plastic chambered friabilator

attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were de - dusted and reweighed. Percentage loss of tablet weight was calculated. Friability values below 1% are generally acceptable.

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} * 100$$

Where W_1 = Initial weight of 10 tablets.
W_2 = Final weight of 10 tablets.

WETTING TIME

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A water-soluble dye phenolphthalein was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface (Abdelbary et al, 2009). A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The wetting time was recorded using a stopwatch.

WATER ABSORPTION RATIO (R)

The weight of the tablet before keeping in the petridish was noted (W_b) using digital balance. The wetted tablet from the petridish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = (W_a - W_b) / W_b * 100$$

W_a= Weight of the tablet after absorption
W_b= Weight of the tablet before absorption

***IN VITRO* DISPERSION TIME**

In vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5°c and the time required for complete dispersion was determined.

To check for reproducibility, the measurements were carried out in triplicates (n=3). The dispersion time was recorded using a stopwatch.

***IN VITRO* DISINTEGRATION TIME**

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of pH 6.8 phosphate buffer. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature.

The time required for water to reach the upper surface of the tablets and completely wet them and break down into small particles was noted as the *in vitro* disintegration time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The disintegration time was recorded using a stopwatch.

IN VITRO DISSOLUTION STUDIES

Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm. 0.1N HCL was used as dissolution medium (900ml) and was maintained at 37 ± 1^0C. Samples of 5ml were withdrawn at predetermined intervals (5, 10, 15, 20 and 30), filtered and replaced with 5ml of fresh dissolution medium.

The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 227 nm by using ultra violet double beam spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed on drug, optimized formulation using Agilent FTIR. The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

The percent weight variation for all the formulation is tabulated in Table. All the tablets passed weight variation test as the % variation was within the pharmacopoeia limit of ±10%. It was found to be from 95 mg to 105 mg. The weight of all the tablets was found to be uniform. This is due good flow property and compressibility of all the formulations.

The thickness of the tablets was measured by using Vernier caliper by picking the tablets randomly. The mean values are shown in table 5. The values are almost uniform in all formulations. Thickness was found in the range from 3.25±0.20 mm to 3.43±0.21mm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.

The results of hardness are given in table 5 Hardness test was performed by Monsanto hardness tester. Hardness was maintained to be within 3.0±0.10 kg/cm2 to 4.0±0.21kg/cm2. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and posses good mechanical strength with sufficient hardness.

The results are tabulated in table 5 was found well within the approved range (<1%) in all the formulation. Friability was in between 0.42% to 0.73%. Results revealed that the tablets possess good mechanical strength.

The content uniformity was performed for all nine formulations and results are shown in table. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 97.68 % and 99.91 % of Zolmitriptan. The results indicated that in all the formulations the drug content was uniform.

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. The results are shown in table this was determined as per I.P for all the formulations. All the formulations show disintegration time less than 60 seconds. Crospovidone has high water uptake and swelling pressure which leads to faster disintegration. Sodium starch glycolate shows disintegration time in between and Croscarmellose sodium shows more disintegration time.

From the above dissolution data, The rapid dissolution was observed in formulations F1, F2, release 79.75%, 99.28%, of drug respectively, at the end of 15 minutes and formulation F3 releases 99.65% at the end of 12 minutes. formulations F4, F5 and F6 which shows drug release 88.15%, 95.99%, 99.17% respectively at the end of 15 min. Formulations F7, F8, F9 releases 72.36%, 85.82%, 90.72% respectively at the end of 15 minutes. This rapid dissolution might be due to fast breakdown of particles and rapid absorption of drug. The drug release was completely achieved in a shorter duration of time. In all the formulations the drug release within 15 minutes. High dissolution may occur due to faster breakdown.

In comparative study for the formulations F2, F3 and F6 drug releases 99.28%, 99.65% and 99.17% respectively at the end of 15 minutes and graphical representation is shown in Figure. Best optimized batch was F3 because of lesser disintegration time and highest percentage drug release at the end of 12 min among all the formulations.

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

Evaluation of pre-compression parameters of powder blend

Formulation	Bulk Density* (gm/cm^3)	Tapped density* (gm/cm^3)	Carr's index* (%)	Angle of Repose* (θ)	Hausner's ratio*
F 1	0.535±0.02	0.635±0.02	15.74±0.04	26.20±1.51	1.18±0.034
F2	0.521±0.07	0.615±0.01	15.28±0. 51	25.34±0.37	1.17±0.073
F3	0.513±0.01	0.605±0.03	15.20±0.65	24.45±0.52	1.17±0.033
F4	0.543±0.15	0.645±0.02	15.81±0.56	27.36±1.15	1.03±0.061
F5	0.522±0.02	0.632±0.01	17.40.±0.42	25.34±0.89	1.21±0.045
F6	0.534±0.13	0.641±0.02	16.69±0.09	26.74±1.13	1.20±0.034
F7	0.524±0.02	0.609±0.01	13.95±0.23	26.98±1.32	1.16±0.055
F8	0.531±0.03	0.625±0.02	15.04±0.45	25.15±1.15	1.17±0.029
F9	0.545±0.04	0.635±0.01	14.17±0.24	28.24±1.13	1.16±0.026

Evaluation of post compression parameters of Zolmitriptan Mouth dissolving tablet (I)

Formulation	Weight variation*	Thickness (mm)**	Hardness** Kg/cm^2	% Friability*	Drug content**
F1	102±0.43	3.37±0.20	3.5±0.10	0.56	99.65±1.40
F2	98±0.60	3.38±0.09	3.0±0.10	0.52	98.31±0.68
F3	98±0.42	3.27±0.13	3.0±0.14	0.47	99.50±1.31
F4	101±0.50	3.43±0.21	4.0±0.21	0.73	97.68±0.95
F5	99±0.61	3.27±0.17	3.6±0.15	0.49	98.56±1.42
F6	100±0.47	3.29±0.12	3.5±0.05	0.42	99.91±1.81
F7	100±1.42	3.25±0.20	4.0±0.21	0.67	99.05±1.16
F8	98±0.14	3.40±0.10	3.0±0.18	0.52	98.65±0.57
F9	101±1.14	3.30±0.25	3.0±0.10	0.72	98.41±1.33

***In vitro* dissolution study of Zolmitriptan MDT tablets**

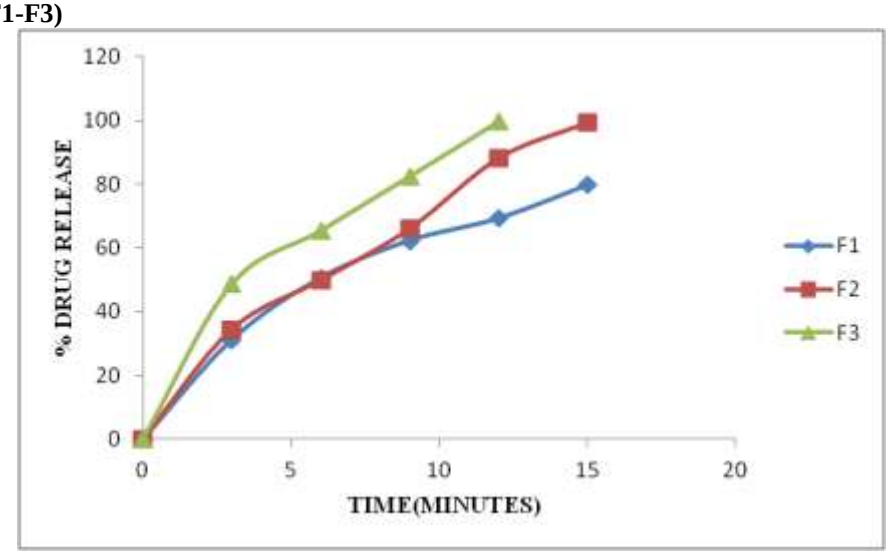
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	31.23	34.51	48.68	44.21	40.73	30.15	27.95	27.31	30.52
6	50.65	49.92	65.43	53.46	60.77	45.84	40.43	50.90	51.53
9	62.33	66.03	82.44	65.90	75.47	65.01	58.32	63.08	63.13
12	69.30	88.12	99.65	73.94	83.17	87.21	67.01	71.95	71.50
15	79.75	99.28		88.15	95.99	99.17	72.36	85.82	90.72

Invitro disintegration studies

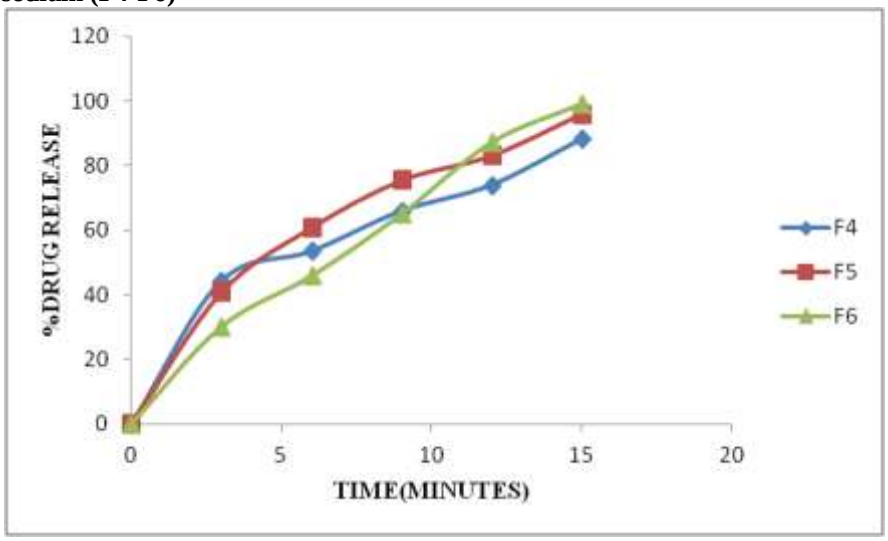
Formulation	Disintegration time (seconds)	Wetting time (seconds)	%Water absorption ratio
F1	16	17	80
F2	20	22	67
F3	28	41	71
F4	60	73	48

Formulation	Disintegration time (seconds)
F1	16
F2	20
F3	28
F4	60
F5	52
F6	34
F7	40
F8	39
F9	35

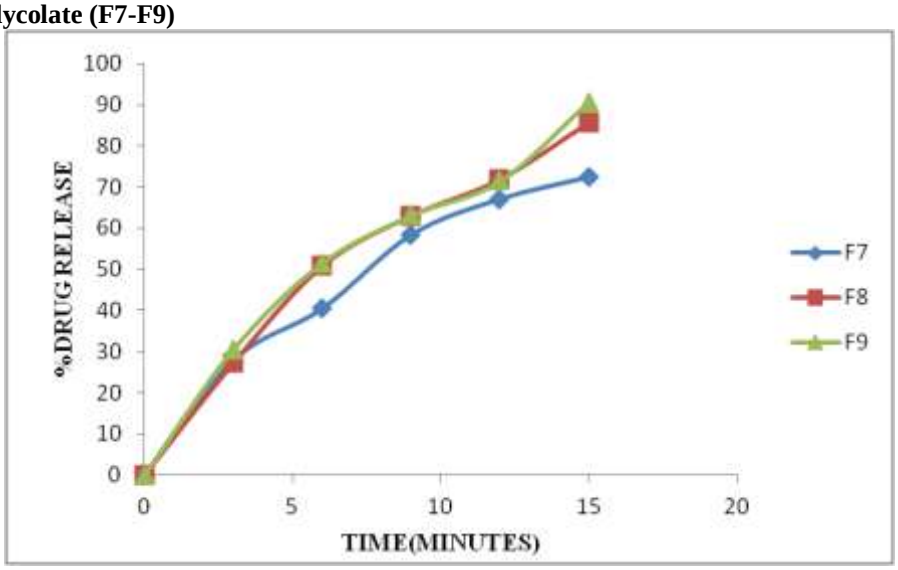
***In vitro* drug release of Zolmitriptan MDT tablets containing Crospovidone (F1-F3)**



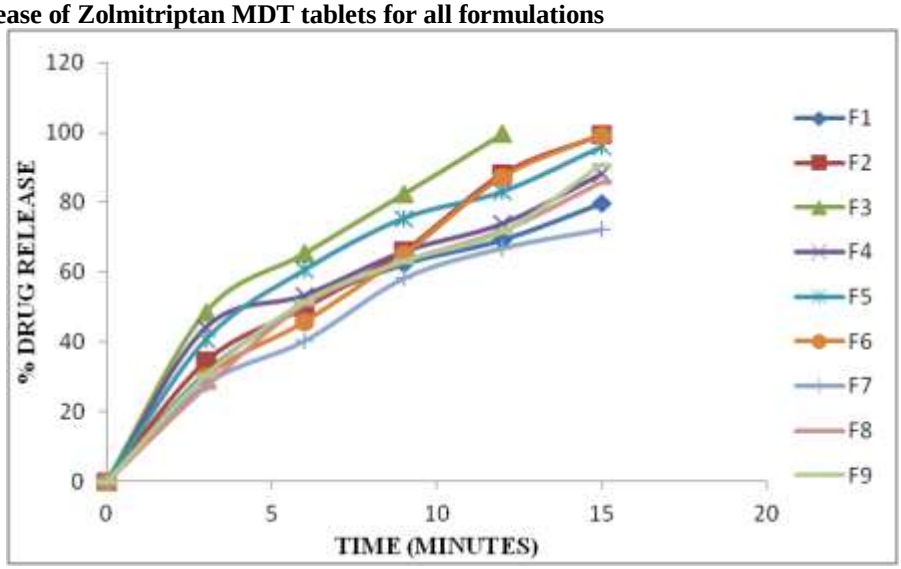
***In vitro* drug release of Zolmitriptan MDT tablets containing Croscaramellose sodium (F4-F6)**



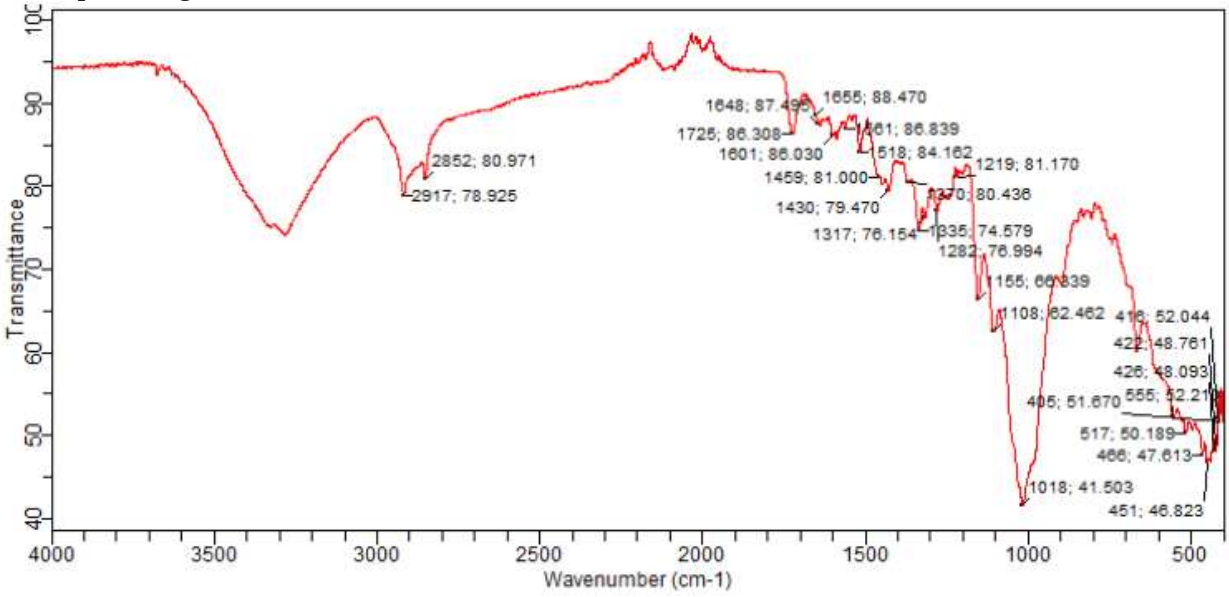
***In vitro* drug release of Zolmitriptan MDT tablets containing Sodium starch glycolate (F7-F9)**



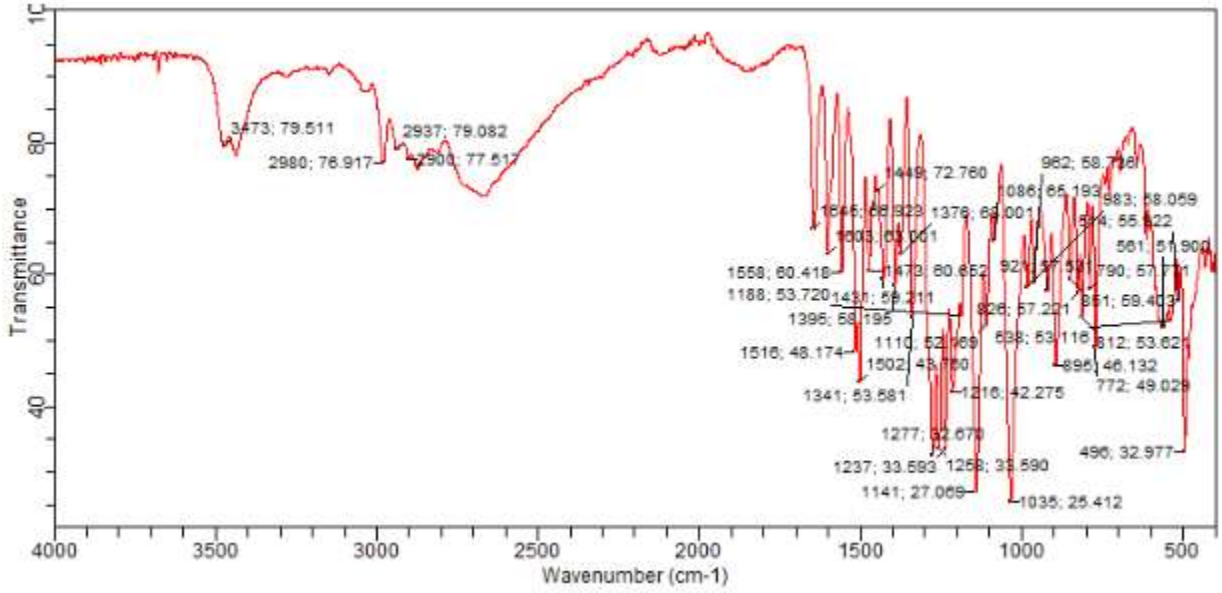
***In vitro* drug release of Zolmitriptan MDT tablets for all formulations**



FT-IR of pure drug



FTIR of optimised formula



CONCLUSION

In the present investigation, all formulations pre and post compression parameters were found to be within limits. The formulated tablets showed compliance for various physiochemical parameters viz. hardness, friability, weight variation, content uniformity and disintegration time. The drug content was within acceptable range which ensured dose uniformity in the formulation.

Preformulation studies of Zolmitriptan were performed; the FT-IR analysis revealed that the superdisintegrants and excipients used were compatible with Zolmitriptan Mouth dissolving tablets of Zolmitriptan is to be prepared by direct compression technique using superdisintegrants, namely crospovidone, sodium starch glycolate and croscarmellose sodium.

Amongst all the formulations, formulation containing crospovidone as superdisintgrants is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration compared to other superdisintegrants.

Apart from all the formulations, F3 formulation showed maximum drug release (99.65%) at the end of 12 min.

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