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Formulation and Evaluation of Orally Disintegrating Tablets of Zolmitriptan Using Direct Compression Method

D.V.R.N.Bhikshapathi*[1], M. Shyamala Devi[1], V.V.Rajesham[1], B. Rajkamal[2]
1. Vijaya College of Pharmacy, Hayath nagar, Hyderabad, A.P, India.
2. Ganga Pharmacy College, Das Nagar, Borgaon (K), Nizamabad, A.P, India.

ABSTRACT

The present study was an attempt to prepare and evaluate Zolmitriptan 9 different oral disintegrating tablets using superdisintegrants like SSG, Crospovidone and Croscarmellose sodium. Formulations were evaluated for their micromeretic properties and post compression studies and found to be within the limits. Based on the disintegrating time and dissolution studies F9 was found to be best formulation. It was found that the sodium starch glycolate is much more effective than the other super disintegrating agents in the preparation of Zolmitriptan oral disintegrating tablets. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation.

Keywords: Zolmitriptan, ODT's, SSG, Crospovidone, Croscarmellose sodium.

*Corresponding Author Email: dbpathi@yahoo.com
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INTRODUCTION

Despite tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, noninvasive method, and ease of administration leading to high level of patient compliance.[1] The most popular dosage forms are conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is "dysphagia" or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence, patients do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy[2].Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance[3].FDTs are prepared by various techniques, mainly direct compression, lyophilization and moulding. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies[4]. Migraine is a chronic, episodic, neurological disorder, which usually begins in childhood, adolescence or early adult life, characterized by unilateral headache often accompanied by nausea and vomiting[5,] gastrointestinal disturbance and extreme sensitivity to light and sound[6]**.** It affects 10-20% of the population during the most productive periods of their working lives, women are affected up to four times more often than men[7] Clinically, migraine is characterized by recurrent attacks of headache and various combinations of symptoms related to the gastrointestinal and autonomic nervous system. Migraine greatly affects quality of life. WHO ranks migraine among the world's most disabling medical illness[8].Zolmitriptan is a selective serotonin 5-HT1B/1D receptor agonist used for the treatment of migraine with or without aura[9] .The half-life of the Zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism, the absolute oral bioavailability is about 40-50%[10].

MATERIALS AND METHOD

Zomig-ZMT (5mg) was purchased from AstraZeneca Pharmaceuticals, Chennai. Zolmitriptan was generous gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium and MCC were obtained from Rubicon Research Pvt. Ltd., Mumbai. All other polymers and solvents used were of analytical grade.

Preparation of oral dispersible tablets by direct compression method

Step I: Dispensing: Carryout the dispensing of the active pharmaceutical ingredient and excipients in dispensing booth as per manufacturing formula.

Step II: Sifting: Sift API, Spertab11SD, Avicel pH 102, Crosspovidone, Croscarmellose Sodium, Sodium starch glycolate, Aspartame, through #40.

Step III: Mixing: Transfer the sifted material of Step II into a virgin polybag and mix it well.

Step IV: Lubrication: Sift Magnesium Stearate through #80 and transfer the Lubricating material i.e. magnesium stearate into the blend of Step III and blend for 5 minutes.

Step V: Compression**:** Compress the lubricated material of step IV in 16 station Compression machine using 6.4 mm Flat punches.

Table 1: Composition of Zolmitriptan Oral Disintegrating Tablets

S. No.	Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1	Zolmitriptan	5	5	5	5	5	5	5	5	5
2	Lactose	97	97	97	97	97	97	97	97	97
3	Avicel 102	19.6	18.3	17	19.6	18.3	17	19.6	18.3	17
4	Crospovidone	3.9	5.2	6.5	-	-	-	-	-	-
5	Croscarmellose Sodium	-	-	-	3.9	5.2	6.5	-	-	-
6	Sodium Starch Glycolate	-	-	-	-	-	-	3.9	5.2	6.5
7	Aspartame	2	2	2	2	2	2	2	2	2
8	Peppermint	1	1	1	1	1	1	1	1	1
9	Mg Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Total weight of the tablet (mg)	130	130	130	130	130	130	130	130	130

Pre formulation Studies

Preformulation studies like Angle of Repose, Bulk density, Tapped density, Compressibility Index and Hausner's ratio were calculated.

Angle of Repose

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose. The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula[11].

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

Where h = Height of the pile

r = Radius of the pile

Bulk Density

Bulk density is used as a measure to describe packing materials or granules. Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated[12] .

Bulk density = W/V_0 g/ml

W= Mass of the blend

V_0 =Untapped volume

Tapped Density

Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

Tapped density=W/V_f g/ml

W= Mass of the blend

V_f = Tapped volume

Compressibility Index

It is measured by tapped density apparatus for 500 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula[13] .

$$\% \text{ Compressibility} = [(V_0 - V_f) / V_0] \text{ X } 100$$

OR

% Compressibility = [(Tapped density – Bulk density) / Tapped density] X 100

Hausner ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powders is called Hausner's ratio.

Hausner's ratio= Tapped density / Bulk density

Loss on drying

The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (1.5g) was determined by using electronic LOD (helium lamp) apparatus at 105°C.

EVALUATION PARAMETERS

Physical appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour, embossing, debossing etc.

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickness should be controlled within a ± 5% variation of a standard.

Weight variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits

Hardness test

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Percentage friability

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping. If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Electrolab Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets is being tested. The percentage friability is expressed as the loss of weight and is calculated by the formula:

% Friability = $[(W_0—W_f) / W_0] \times 100$

W_0 = Initial weight of tablets, W_f = Final weight of tablets

Disintegration time

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37 ± 2^0C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh # 10 was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30seconds.

Dissolution studies

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under

specified conditions. The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15, 20 30, min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters

Dissolution Apparatus :USP Apparatus Type II (Paddle)

Dissolution Medium :0.1N Hydrochloric acid

Volume :500 ml

Temperature :37±2° C

Rpm : 50

Sampling Intervals (min):5, 10, 15, 20, 30 mins.

Water absorption ratio (r)

The weight of the tablet prior to placement in the petridish was noted (W_b) using a Shimadzu digital balance. The wetted tablet was removed and reweighed (W_a). Water absorption ratio, R, was then determined according to the following equation.

$$R = 100 \times (W_a - W_b) / W_b$$

Where W_b = Weight of tablet before water absorption

W_a = Weight of tablet after water absorption.

Wetting time

Five circular tissue papers were placed in a petridish of 10cm diameter. Ten millimeters of water was added to the petridish. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25^0C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch.

Drug Excipient Compatability Studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method and Differential Scanning Colorimetry (DSC) method.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The DSC thermograms were recorded for pure drug, different superdisintegrants and optimized formulation. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

RESULTS AND DISCUSSION

Micromeritic properties of the powder blend of oral disintegrating tablets of Zolmitriptan

The powdered blends were evaluated for Bulk density, Tapped density, Carr's index, Hausner ratio, Angle of repose and Loss on drying. The results of powder blend of oral disintegrating tablets were found to be within the limits, (Table 2), which shows good flow properties of the powdered blend.

Table 2: Pre-compression Parameters of various Zolmitriptan formulations

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index	Hausner Ratio	Angle of repose(θ)	%LOD
F1	0.384±0.23	0.545±0.11	31.25±0.25	1.41±0.22	41.52±0.45	1.75±0.21
F2	0.362±0.29	0.485±0.25	25.36±0.12	1.33±0.52	40.61±0.25	1.80±0.23
F3	0.380±0.45	0.530±0.52	28.30±0.25	1.39±0.25	48.42±0.14	1.75±0.25
F4	0.371±0.56	0.493±0.35	24.74±0.55	1.32±0.21	37.41±0.25	1.50±0.52
F5	0.360±0.25	0.462±0.55	22.07±0.65	1.66±0.55	33.92±0.56	1.47±0.12
F6	0.419±0.69	0.477±0.25	12.26±0.41	1.14±0.58	24.28±0.58	1.37±0.25
F7	0.417±0.55	0.471±0.45	11.49±0.12	1.13±0.45	22.32±0.25	1.33±0.52
F8	0.416±0.89	0.475±0.12	12.44±0.22	1.13±0.54	25.54±0.56	1.20±0.12
F9	0.428±0.21	0.456±0.22	18.22±0.12	1.25±0.21	24.56±0.32	1.19±0.32

All values were expressed as mean ± SD; number of trials (n) =3

Table 3: Post compression Parameters of various Zolmitriptan formulations

Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kp)	Percentage Friability (%)	Disintegration Time (sec)
F1	131.2±0.32	3.71±0.029	3.8±0.089	0.63±0.32	45±0.98
F2	130.6±0.23	3.65±0.025	4.2±0.054	1.22±0.23	42±0.88
F3	132.3±0.21	3.69±0.055	4.0±0.024	1.50±0.52	40±0.98
F4	131.8±0.24	3.68±0.054	4.3±0.065	0.78±0.23	39±0.87
F5	129.8±0.21	3.72±0.089	4.3±0.025	0.90±0.52	36±0.58
F6	129.6±0.52	3.66±0.086	4.4±0.025	1.75±0.54	35±0.88
F7	132.0±0.12	3.65±0.029	4.0±0.025	0.32±0.21	30±0.84
F8	130.5±0.25	3.72±0.048	4.2±0.052	0.45±0.12	26±0.88
F9	130.2±0.12	3.70±0.024	4.0±0.052	0.68±0.21	20±0.85

All values were expressed as mean ± SD; number of trials (n) =3

The prepared tablets were evaluated for different physico-chemical properties like weight variation, hardness, thickness, friability and disintegration time and the results are within the limits which depicted in Table 3. Disintegration time is very important for FDTs which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of prepared FDTs was in the range of 20 to 45 seconds and the order was SSG < Croscarmellose sodium < Crospovidone. As the concentration of superdisintegrants in the formulations increased the disintegration time was found to decrease.

Water Absorption Ratio

Water absorption ratio increase with increasing the concentrations of disintegrating agents, Formulations containing sodium starch glycolate shows greater water absorption ratio as compared to Crospovidone and Ac-Di-Sol. F7, F8 and F9 shows water absorption ratios ranges between 72 to 78%.

Wetting Time

The wetting time was rapid in sodium starch glycolate followed by Crospovidone and Ac-Di-Sol. The concentration of disintegrates increased, time taken for wetting was reduced. It was observed that wetting time of tablets was in the range of 18-35 sec. The optimized formulation F9 with Sodium starch glycolate shows wetting time of 18 sec.

In vitro drug release studies

Cumulative % drug release was calculated on the basis of mean Zolmitriptan present in respective formulation. The drug release of 93%, 95% & 96% was observed in formulation F1, F2 and F3 respectively at the end of 30 minutes. On the other hand in formulations F4, F5and F6 the drug releases was 97%, 98.1% and98.6% respectively at the end of 30 minutes and in formulations F7, F8 and F9 the drug releases 98%, 98% and 99% respectively at the end of 30 minutes. The rapid dissolution In Formulations F7, F8 and F9 might be due to fast break down of particles and rapid absorption of drug. The optimized formulation F9 shown highest drug release (99.8%) at the end of 30 min when compared with innovator product Zomig-ZMT i.e 97.4%. The results are summarized in Table 4.

Table 4: Percentage drug release of Zolmitriptan oral disintegrating tablets F1-F9 with Innovator product Zomig-ZMT 5mg.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	Zomig - ZMT (5mg)
0	0	0	0	0	0	0	0	0	0	0
5	91.1±0.025	91.8±0.05	92.3±0.064	92.8±0.075	93.2±0.087	96.6±0.056	95.3±0.085	96.8±0.085	97.3±0.045	88.1±0.087
10	91.3±0.083	93.1±0.08	94.5±0.084	94±0.054	95.1±0.056	97.0±0.087	96.2±0.058	97.0±0.065	98.5±0.085	92.2±0.058
15	92.6±0.057	95±0.055	97.0±0.046	95.2±0.058	96.8±0.056	97.8±0.078	97.5±0.078	98.2±0.071	99.1±0.041	95.4±0.056
20	92.8±0.063	96.3±0.05	97.2±0.044	97.1±0.085	98.0±0.054	98.2±0.078	97.9±0.074	98.6±0.074	99.6±0.074	96.8±0.078
30	93.4±0.068	95.1±0.04	96.7±0.014	97.9±0.052	98.1±0.085	98.6±0.045	98.4±0.045	98.9±0.024	99.8±0.047	97.4±0.046

All Values Were Expressed As Mean ± SD: Number of Trials (n) =3

Drug-Excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

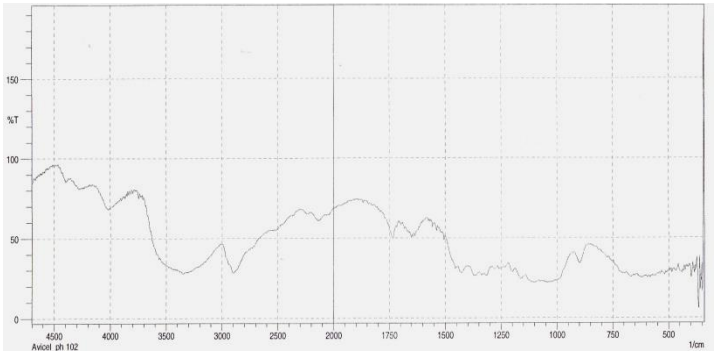

Figure 1: FTIR spectra of Zolmitriptan pure drug

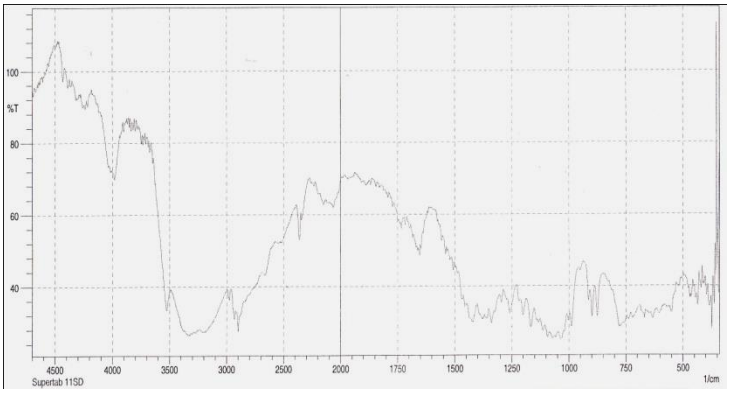

Figure 2: FTIR Spectra of Avicel pH 102

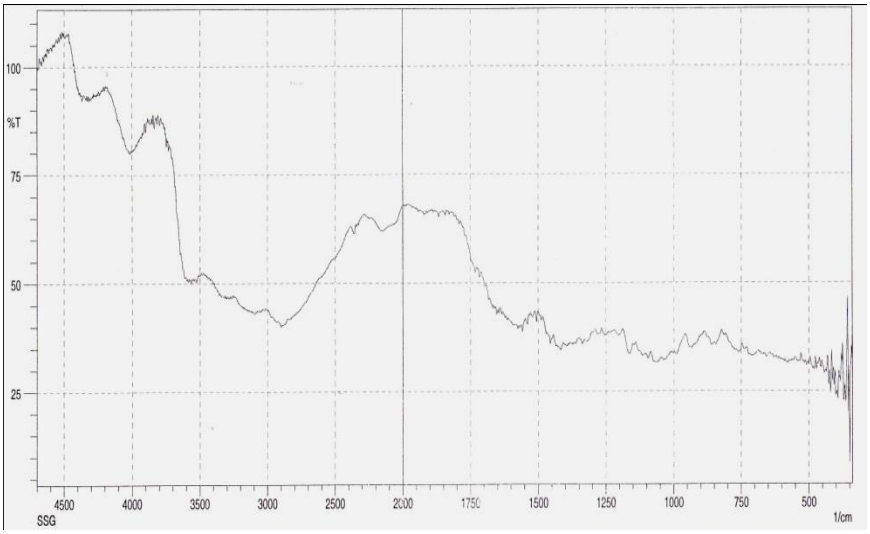

Figure 3: FTIR Spectra of SuperTab 11SD

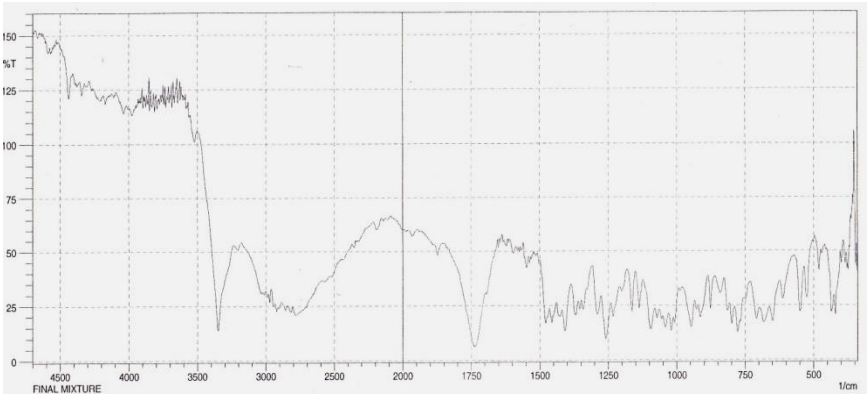

Figure 4: FTIR Spectra of SSG

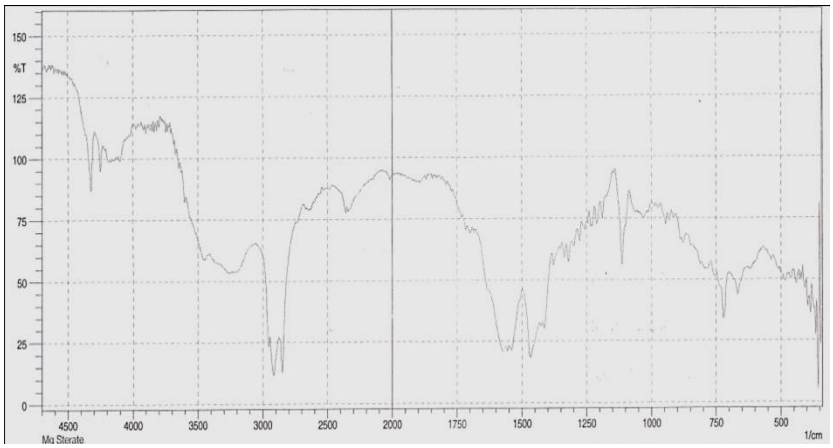

Figure 5: FTIR Spectra of Mg Stearate

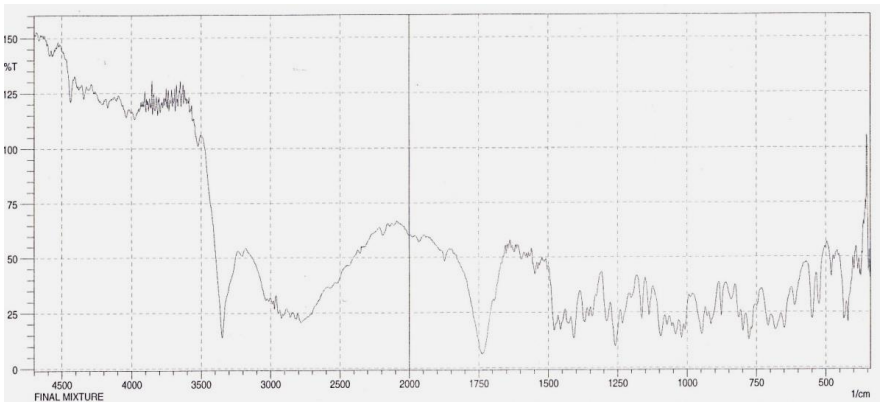

Figure 6: FTIR Spectra of optimized formulation F9

Table 5: FTIR Study of Final Mixture

Compound	Functional Group	Bond shows peak	Wave number cm^{-1}	Assignment
Final Mixture	Indol	N–H	3500 cm^{-1}	N–H stretching
	Alkenes	C=C	3250cm^{-1}	C=C stretching
	Aliphatic compound	C–H	2980 cm^{-1}	Methyl symmetric C–H stretching
	Secondary amine	C–N	1615 cm^{-1}	C–N stretching

Table 6: FTIR Study of Zolmitriptan

Compound	Functional Group	Bond shows peak	Wave number cm^{-1}	Assignment
Zolmitriptan (API)	Indole	N–H	3500 cm^{-1}	N–H stretching
	Alkenes	C=C	3250cm^{-1}	C=C stretching
	Aliphatic compound	C–H	2980 cm^{-1}	Methyl symmetric C–H stretching
	Secondary amine	C–N	1615 cm^{-1}	C–N stretching

The FT-IR studies revealed that zolmitriptan is compatible with the excipients used in the formulation. There were no extra peaks observed in the IR spectrum. This established that the drug zolmitriptan and all the excipients used in the study showed no interaction and indicated that they were compatible with each other (Table 5 & 6). The FTIR spectrum of Zolmitriptan pure durg, Avicel pH 102, Super tab 11SD, SSG, Mg Stearate and optimized formulations were shown in Figure 1-6 respectively.

DSC Studies

DSC thermograms revealed that there is no considerable change observed in melting endotherm of Zolmitriptan pure drug (136.52) (Figure 7) and drug in optimized formulation (135.22) (Figure 8). It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

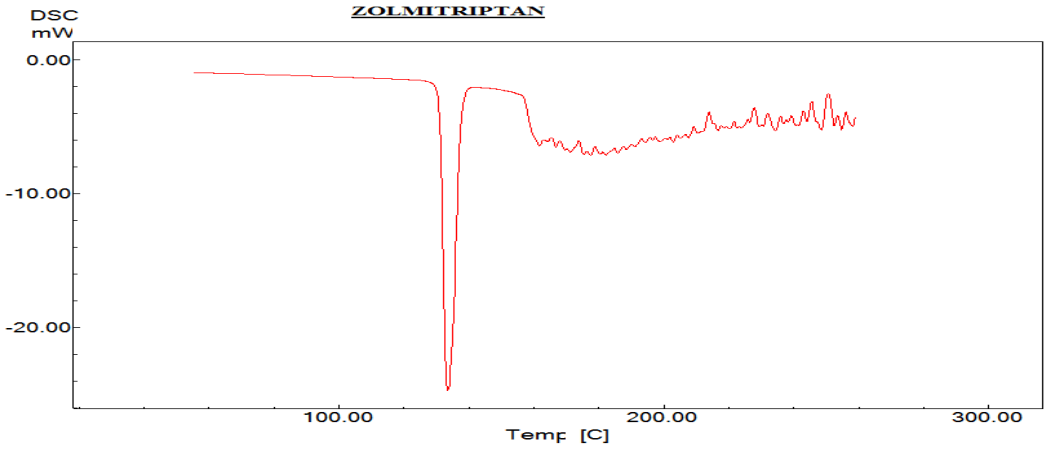

Figure 7. DSC thermogram of Zolmitriptan pure drug

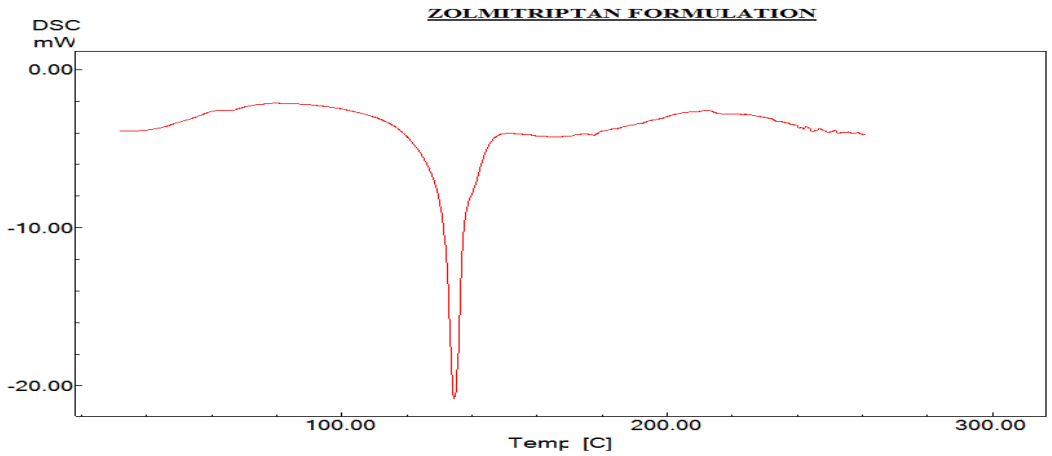

Figure 8. DSC thermogram of Zolmitriptan optimized formulation (F9)

CONCLUSION

Oral disintegrating tablets of Zolmitriptan using different super disintegrating agents like crospovidone, croscarmellose sodium and sodium starch glycolate were prepared and evaluated. Formulations were evaluated for their physical characteristics, hardness, thickness, weight variation, friability, wetting time and absorption ratio and disintegration time and found to be within the limits. Based on the pre and post compression parameters, disintegrating time and dissolution studies F9 was found to be best formulation. It was found that the sodium starch glycolate is much more effective than the other super disintegrating agents in the preparation of Zolmitriptan ODT. The optimized formulation F9 shown highest drug release at the end of 30 min when compared with innovator product Zomig-ZMT. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation.

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