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FORMULATION AND EVALUATION OF ZOLMITRIPTAN ORALLY DISINTEGRATING TABLETS

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ABSTRACT

Zolmitriptan is a selective serotonin receptor agonist of the 1B and 1D subtypes, used in the acute treatment of migraine attacks and cluster headaches. The main objective of this research work is to formulate and evaluate oral disintegrating tablet of zolmitriptan with a view to enhance the patient compliance. Oral dispersible tablet of zolmitriptan were prepared by direct compression method after incorporating super disintigrants like cross povidone, IRP 88 and Ludiflash at different concentration (5%, 7.5% and 10%). Taste masking was done by ading flavoring agents. Precompression parameters such as bulk density, tapped density, compressibility index and hausner ratio were analyzed for prepared powder blend before compression. The prepared batches of tablets were evaluated for tablet weight variation, content uniformity, hardness, friability, In vitro disintegration and dissolution time. The flow properties of the powder blend was found to be within the limits showing good flow. Effects of super disintigrants on wetting time and in-vitro release also have been studied. Tablets containing cross povidone (10%) showed excellent in-vitro disintegration time and drug release. For better mouth sweetening agents and flavoring agents are added. FTIR & DSC results showed no evidence of interaction between the drug and excepients selected.

KEYWORDS: Cross povidone, migraine, oral disintegrating, zolmitriptan, super disintigrants.

INTRODUCTION

The oral route is considered as the most widely accepted route for drug administration because of its convenience of self administration and easy manufacturing.[1,2] But the drawback of the oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatrics.[1] It also applies to people who are ill in bed and to those active working patients who are busy or traveling and those who have no access to water.[2] Orally disintegrating tablets can also called as fast dissolving tablets, orodispersible tablets, mouth dissolving tablets, fast disintegrating tablets, porous tablets, quick disintegrating tablets, rapid dissolving tablets, and rapimelts. ODTs dissolve / disintegrate in the mouth in matter of seconds without water. Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action. Excellent mouths feel property can be produced by use of flavors and sweeteners help to change the perception of "medication as bitter pill" especially in pediatric population. ODTs have all the advantages of solid dosage forms and liquid dosage forms. They have Convenience of administration and accurate dosing compared to liquids.[3] Drugs when formulated as ODT, due its absorption in oral cavity the bioavailability of drugs can be increased. Pregastric absorption of saliva containing dispersed drugs avoids first pass metabolism effect.[4,5]

Zolmitriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors used for the acute treatment of adult migraine with or without auras. Zolmitriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists and has only a weak affinity for 5-HT1A, 5-HT5A, and 5-HT7 receptors and no significant affinity or pharmacological activity at 5-HT2, 5-HT3 or 5-HT4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1, dopamine2, muscarinic or benzodiazepine receptors. In addition it causes vasoconstriction. It binds with high affinity to human 5-HT1B and 5-HT1D receptors leading to cranial blood vessel constriction. The mean elimination half-life of zolmitriptan and of the active N-desmethyl metabolite is 3 hours. Mean absolute oral bioavailability is 40% and Food has no affect on the rate and extent of absorption.[6-10]

MATERIAL AND METHODS

Materials

Zolmitriptan was obtained as gift sample from Aurobindo laboratories, hyd, Cross povidone, IRP 88 and Ludiflash were obtained from Aveb chemicals, MCC was obtained from Dmv international, Aerosil was obtained from Aurobindo laboratories, hyd, Sweetener was obtained from Nutra sweet Ltd, india, Banana flavor was obtained from Bush boake allen Ltd, Talc was obtained from S.D. fine chemicals Pvt. Ltd., Mumbai, Magnesium stearate was obtained from Imedia pvt Ltd, mumbai.

Method

Formulation development of Zolmitriptan oral disintegrating tablets

The formulation development of Zolmitriptan tablets was initiated with using different super disintigrants such as cross povidone (Kollidon CL), Amberlite IRP 88, Ludiflash. MCC PH 200 was used as diluents, talc and aerosil were used as anti adherent and glident, magnesium stearate was used as lubricant. Complexation method was adopted to mask the bitter taste of the drug. The tablets were prepared at different concentrations such as 5%, 7.5% and 10% to the target tablet weight of 80 mg. The tablets were prepared by direct compression method using directly compressible microcrystalline cellulose (MCC PH 200). The drug and MCC were sifted through sieve no- 40, and then mixed thoroughly in a poly bag in the geometric ratio. Then the above mixed blend was pre lubricated with Aerosil and talc and finally lubricated with magnesium stearate. The tablets were compressed using 6 mm round flat faced punch.

Table No 1: Formulation composition of ODT tablets of Zolmitriptan.

Ingredients	Formulation codes										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Zolmitriptan	10	10	10	10	10	10	10	10	10	10	10
Cross Povidone	4	6	8	8	8	-	-	-	-	-	-
IRP 88	-	-	-	-	-	4	6	8	-	-	-
Ludiflash	-	-	-	-	-	-	-	-	4	6	8
Aspartame	-	-	-	2	4	4	4	4	4	4	4
Menthol	-	-	-	2	2	2	2	2	2	2	2
Orange flavor	-	-	-	1	1	1	1	1	1	1	1
MCC	60	58	56	51	49	53	51	49	53	51	49
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	80	80	80	80	80	80	80	80	80	80	80

Evaluation of ODT Tablets of Zolmitriptan

Precompression Parameters[11,12]

Angle of repose

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density and tapped density

Accurately weighed amount of powder was taken in a 50 ml capacity measuring cylinder and bulk volume was noted. It was tapped for 100 times on a plane hard wooden surface and tapped volume was estimated. Bulk density and Tapped density were calculated by using following formulas.

$$\text{Bullk Density} = \frac{\text{Weight (W)}}{\text{Volume(V1)}}$$

$$\text{Tapped Density} = \frac{\text{Weight (W)}}{\text{Volume(V2)}}$$

Carr's Compressibility index and Hausner ratio

Percent compressibility of powder mix was determined by Carr's compressibility index, and hausner ratio was calculated by using following formula.

$$\text{Carr's Index(CI)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner Ratio (HR)} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post Compression Parameters[13-15]

Weight variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight.

Hardness test

The hardness of the tablet was determined using Monsanto Hardness Tester.

Thickness

Thickness was measured by using digital Vernier calipers (Mitutoyo Corp, Japan) on 5 randomly selected tablets from each formulation.

Friability test

Six tablets from each batch were examined for friability using Roche Fribilator (Tropical Equipment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated.

%Friability = (Loss in weight/Initial weight) x 100

Wetting time

A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded.

Content uniformity test

Five tablets were weighed and powdered, 10 mg of equivalent of zolmitriptan was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 223 nm.

In vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24±0.50C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.

In vitro dissolution testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 500 ml of 0.1N Hcl was taken as the dissolution medium at 50 rpm and 370C±0.50C. Five millilitres of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 223 nm.

Characterization of Drug and Excipients[16]

Fourier transform infrared (FTIR)

FTIR studies are very helpful in the evaluation of drug– polymer interaction studies. If there is any incompatibility between the drugs and excipients, these can be predicted by changes in the functional peaks (characteristic wave numbers). Diffuse reflectance technique was used (400 to 4000 cm^{-1}), drug and various polymers were thoroughly mixed with 300 mg of potassium bromide, compressed and the spectrum was obtained by placing the thin pellet in the light path.

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The instrument is very versatile used to evaluate melting point, enthalpy changes and glass transition temperatures of drug with excipients and polymers. Entacapone was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 40 – 300ºC, heatingrate 10ºC/min, nitrogen atmosphere (20ml/min) and alumina as reference. Differential Scanning Calorimetry (DSC) was performed on pure drug, composition of the final formulation. DSC measurements were done on a Shimadzu DSC-60 and samples were heated at the rate of 10ºC min^{-1}. The samples were heated in an aluminium cup up to 300ºC.

RESULTS AND DISCUSSION

Pre compression properties of tablets prepared with cross povidone

The powdered blend of different formulations were evaluated for bulk properties like angle of repose, bulk density (BD), tapped density (TD), compressibility index, and Hausner's ratio. The angle of repose of the entire blend for all the formulations were found to be in the range 25. 64 ±1.04 to 26.78±1.03. Bulk and tapped densities are used for the measurement of Compressibility index and Hausner's ratio. The BD and TD ranged from 0.351±0.07 to 0.381±0.04 and 0.452±0.08 to 0.484±0.07 respectively. Compressibility index was found between 20.71±1.03 to 22.34±1.04. The Hausner 's ratio ranged from 1.26±0.07 to 1.28±0.05. The above results conclude that the powder blend showed good flow properties and were within the Pharmacopeial limits.

Post compression properties and dissolution profile of the tablets prepared with crosspovidone

Good physicochemical properties were observed for of the prepared tablets. The weight variation was observed within the range of 80 mg in all the batches.

Friability of the prepared tablets was below 0.81-0.88%. Hardness of the tablets was found in the range of 3.2 -3.6 Kg/cm^2 with a thickness in the range of 2.9 to 3.1 mm. The disintegration of the tablets with cross povidone was found in the range of 20-43 sec. As the concentration of the cross povidone increase the disintegration time was decreased. At lower concentration ie at 5% of crosspovidone the disintegration was found around 43 sec at 10% of cross povidone the disintegration was found around 32 sec. The wetting time was found to be in the range of 25 to 40secs.

The in vitro dissolution was performed on the prepared ODT tablets. The dissolution was performed in 500 ml of 0.1 N HCl. The dissolution of the tablets prepared with 5% of CP (F1) released 84% in 15 minutes and released the complete drug in 30 minutes. The dissolution of the tablets prepared with 7.5% of CP (F2) released 93% in 15 minutes. The dissolution of the tablets prepared with 10% of CP (F3) released 99% in 10 minutes. Based on the in vitro disintegration and dissolution, the tablets prepared with 10% of CP were used for further optimizations like taste and flavor.

The formulation F3 (10% fo CP) was incorporated with 2.5% and 5% of the aspartame and 2.5% of menthol separately. 1 mg of the orange flavor was added to each formulation. The physico chemical properties and in vitro dissolution were same as the basic formula. The tablets were subjected for taste evaluation with 6 healthy human volunteers with prior permission for the IHEC. The taste of F4 prepared with 2 mg was slightely bitter. The taste of F5 was found good. Menthol and orange flavor gave good taste and moth feel to the formulation.

Pre compression properties of the tablets prepared with IRP 88

The angle of repose of the entire blend for all the formulations were found to be in the range 26.30”±1.08 to 27.77±1.03. The BD and TD ranged from 0.346±0.07 to 0.389±0.03 and 0.441±0.05 to 0.499±0.08 respectively. Compressibility index was found between 21.54±1.08 to 22.63±1.05. The Hausner ‘s ratio ranged from 1.27±0.06 to 1.29±0.09. The above results

conclude that the powder blend showed good flow properties and were within the Pharmacopeial limits.

Post compression properties and dissolution profile of the tablets prepared with IRP 88

The weight variation was observed within the range (80 mg). Friability of the prepared tablets was below 0.62-0.73%. Hardness of the tablets was found in the range of 3.2 -3.6 Kg/cm^2 with a thickness in the range of 2.52 to 2.61 mm. The disintegration of the tablets with IRP 88 was found in the range of 25-45 sec. As the concentration of the disintegrant increase the disintegration time was decreased. The wetting time was found to be in the range of 30 to 50secs. The drug content was within the limits in all the three formulations.

The in vitro dissolution was performed on the prepared ODT tablets. The dissolution of the tablets with IRP 88 released 90% in F6, 96% in F7 and 99% in F8 of drug after 20 minutes. The taste of the tablets was found good.

Pre compression properties of the tablets prepared with ludiflash

The angle of repose of the entire blend for all the formulations were found to be in the range 25.46"±1.05 to 28.24±1.08. Bulk and tapped densities are used for the measurement of Compressibility index and Hausner's ratio. The BD and TD ranged from 0.333±0.04 to 0.385.03 and 0.423±0.06 to 0.494±0.04 respectively. Compressibility index was found between 21.27±1.07 to 23.24±1.06. The Hausner 's ratio ranged from 1.27±0.03 to 1.30±0.05. The above results conclude that the powder blend showed good flow properties and were within the Pharmacopeial limits.

Post compression properties and dissolution profile of the tablets prepared with ludiflash

The prepared tablets were evaluated for various physico chemical properties. The weight of the tablets was found 80 mg and assay of the tablets were with in the pharmacopoeia limits. The hardness of the tablets was found 3.1 to 3.3 kg/cm^2 form both the prepared formulations. The thickness of the tablets was found 2.54 and 2.58 mm. The friability of the prepared tablets was found 0.52 to 0.65% which was with in the range. The disintegration time of the prepared tablets with 5% of ludiflash was found around 73 sec, at 7.5% was found around 55 sec, at 10% was found around 40 sec. Low concentration of the ludiflash will not favour the disintegration. The drug content was found to be within the limits in all the three formulations. The wetting time was found to be in the range of 80 to 53secs.

In vitro dissolution of the prepared formulations was performed and the dissolution of 5% of ludiflash was found 87% of drug release in 15 minutes. The dissolution of the 7.5% of the ludiflash was found 93%. The release at 10% of ludiflash was found 96% in 15 minutes.

Table No 2: Pre compression parameters of ODT tablets of Zolmitriptan.

Parameters	Formulations codes								
	F1	F2	F3	F6	F7	F8	F9	F10	F11
Angle of repose	25.64± 1.04	25.80± 1.09	26.78± 1.03	26.30± 1.08	26.74± 1.06	27.77± 1.03	25.46± 1.05	27.28± 1.02	28.24± 1.08
Bulk density	0.356± 0.05	0.381 ±0.04	0.351± 0.07	0.346± 0.07	0.389± 0.03	0.376± 0.08	0.333± 0.04	0.385± 0.03	0.360± 0.05
Tapped density	0.449± 0.04	0.484 ±0.07	0.452± 0.08	0.441± 0.05	0.499± 0.08	0.486± 0.06	0.423± 0.06	0.494± 0.04	0.469± 0.08
Carr's index	20.71± 1.03	21.28± 1.06	22.34± 1.04	21.54± 1.08	22.04± 1.04	22.63± 1.05	21.27± 1.07	22.06± 1.03	23.24± 1.06
Hausner's ratio	1.26± 0.07	1.27± 0.04	1.28± 0.05	1.27± 0.06	1.28± 0.09	1.29± 0.09	1.27± 0.03	1.28± 0.07	1.30± 0.05

Table No 3: Post compression parameters and in vitro drug release profile of ODT tablets of Zolmitriptan.

Physico chemical properties	F1	F2	F3	F6	F7	F8	F9	F10	F11
Weight variation (mg)	80	80	80	80	80	81	80	80	81
Disintegration (sec)	43	32	20	45	34	25	73	55	40
Tablet hardness kg/cm^2	3.4	3.2	3.6	3.4	3.2	3.6	3.2	3.1	3.3
Tablet diameter (mm)	6	6	6	6	6	6	6	6	6
Thickness (mm)	2.9	3.1	3.0	2.61	2.55	2.52	2.58	2.57	2.54
Wetting time (sec)	40	35	25	50	37	30	80	72	53
Friability (%)	0.82	0.88	0.81	0.62	0.71	0.73	0.52	0.65	0.53
Drug Content (%)	97.22	98.11	99.17	98.11	97.72	97.89	99.11	98.12	99.19
In vitro dissolution									
Time in (min)	Cumulative % drug release								
0	0	0	0	0	0	0	0	0	0
5	66	74	90	65	72	80	67	76	84
10	77	86	97	75	81	89	78	83	90
15	84	93	99	80	90	95	87	93	96
20	93	97	99	90	96	99	91	98	99
30	99	99	99	99	99	99	96	99	99

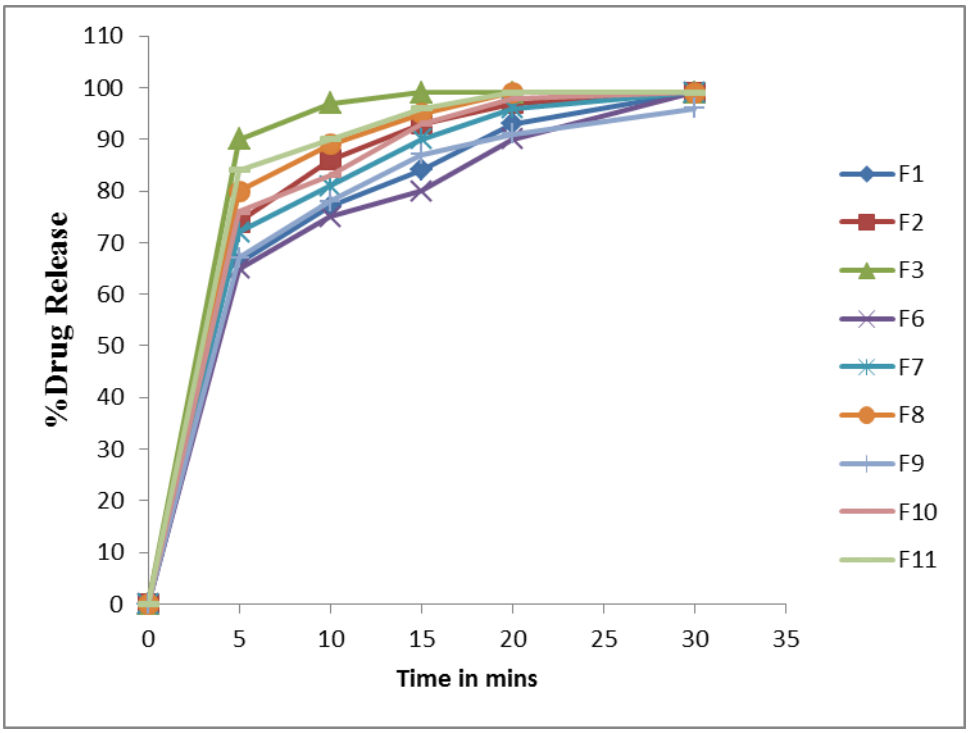

Fig. 1: In vitro dissolution of the prepared formulations.

DSC and FTIR study of the prepared formulations

The prepared tablets and films were characterized for DSC and FTIR. DSC of pure Zolmitriptan showed sharp endothermic peak at 141.0^{0}C, the DSC of physical mixture was found at 167.9 and the DSC of the drug resin complex was showed peaks at 99.85 and 210.63, these peaks are due to the Amberlit IRP 64. Similarly DSC of ODT-C(F-12) and ODF-C9F-14) showed broad peaks at almost similar melting points as described in the drug resin complex is clearly indicates the drug resin complex formation.

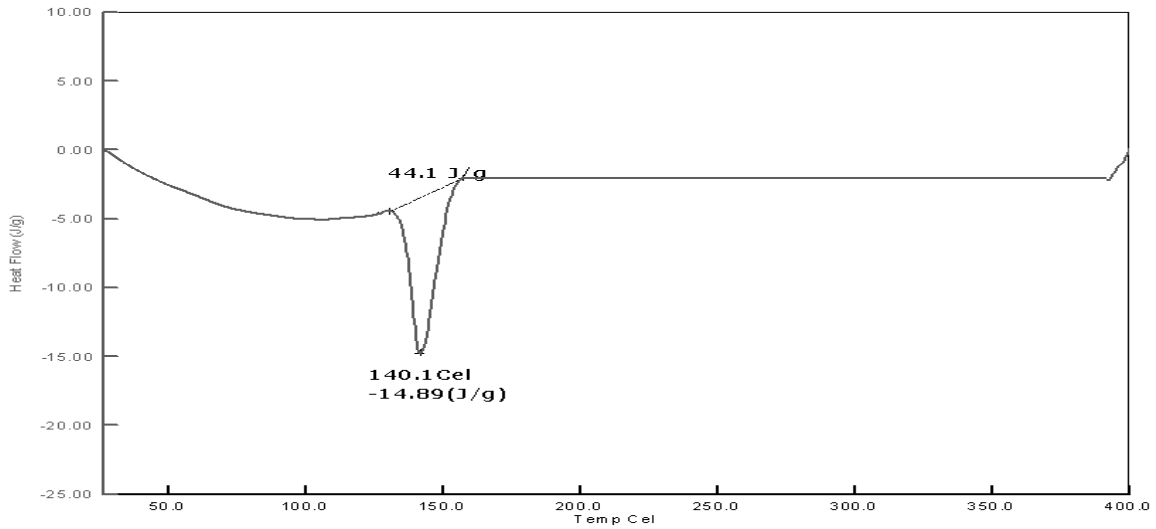

Fig. 2: DSC thermograph of the pure Zolmitriptan.

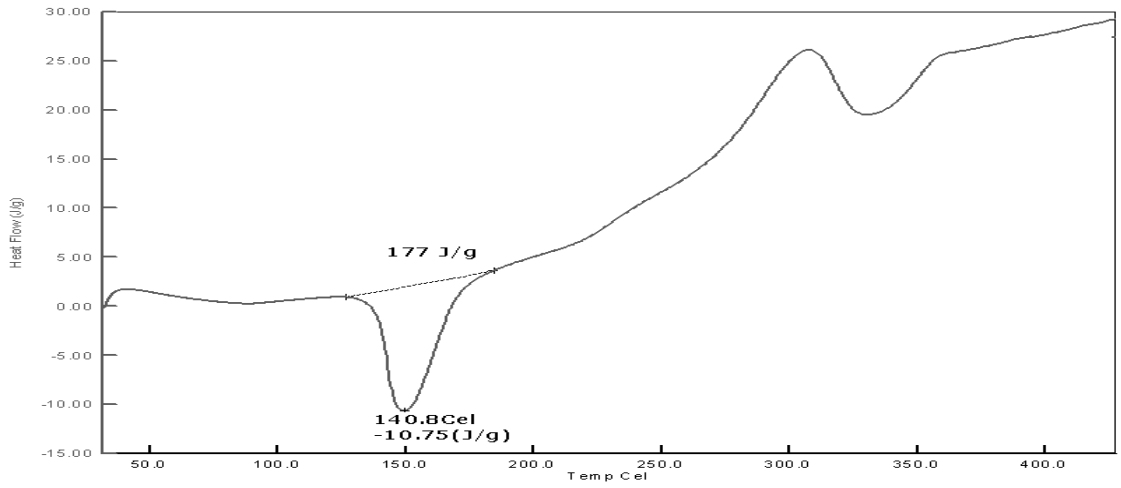

Fig. 3: DSC thermograph of the Zolmitriptan ODT prepared with Crosspovidone.

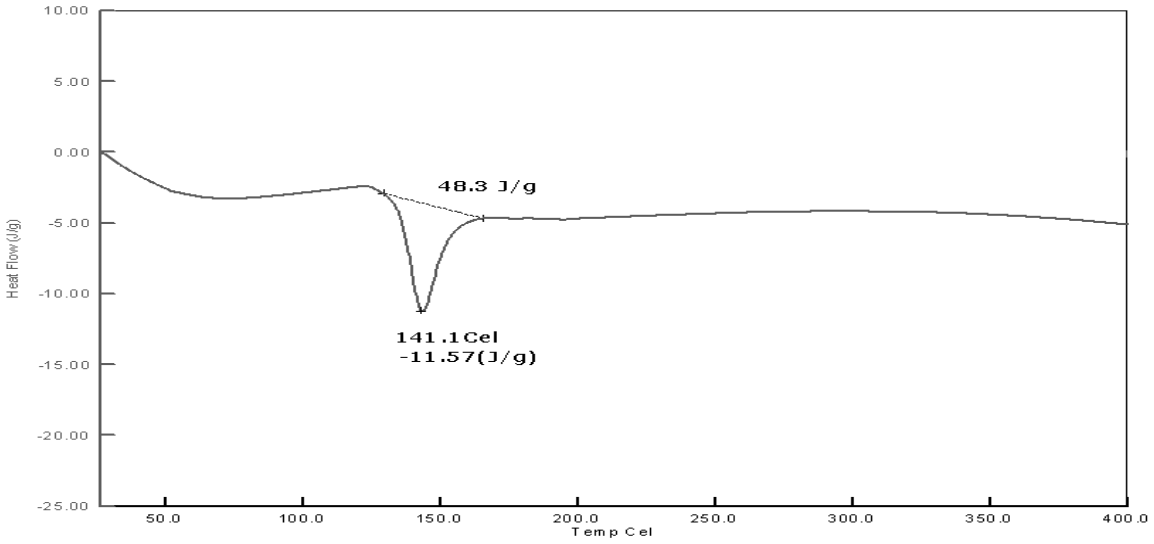

Fig. 4: DSC thermograph of the Zolmitriptan ODT prepared with IRP 88.

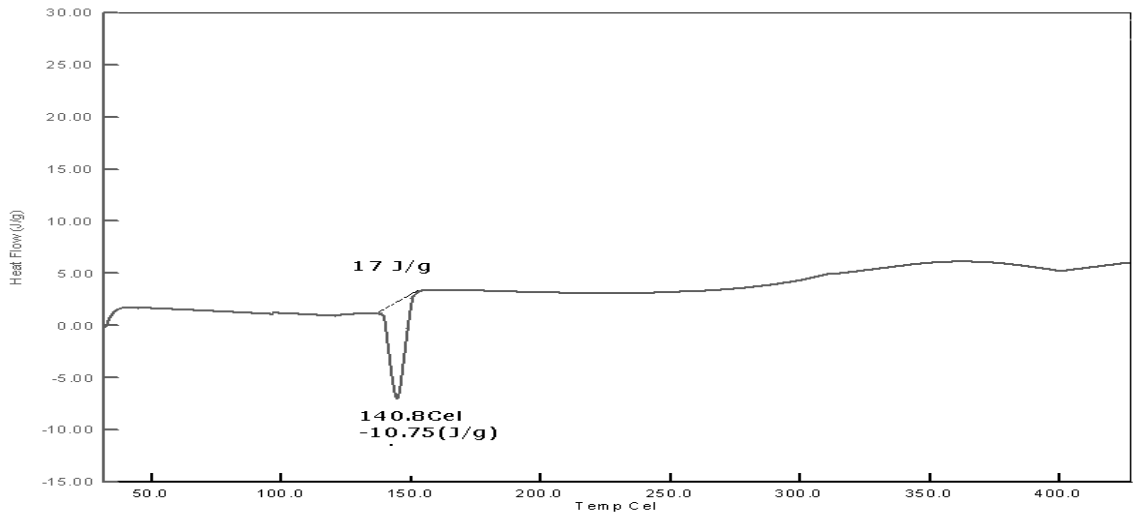

Fig. 5: DSC thermograph of the Zolmitriptan ODT prepared with Ludiflash.

Fourier Transforms Infrared Radiation measurement (FT-IR)

The FT-IR spectra acquired were taken from dried samples. A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm^{-1}, and 4 cm^{-1} resolution. The results were the means of 6 determinations. A quantity equivalent to 2 mg of pure drug and prepared formulation were selected separately.

The FTIR spectrum of the pure zolmitriptan and the formulation prepared with crospovidone, IRP 88 and Ludiflash was showed similar spectrum peak points clearly indicating the no drug polymer interaction.

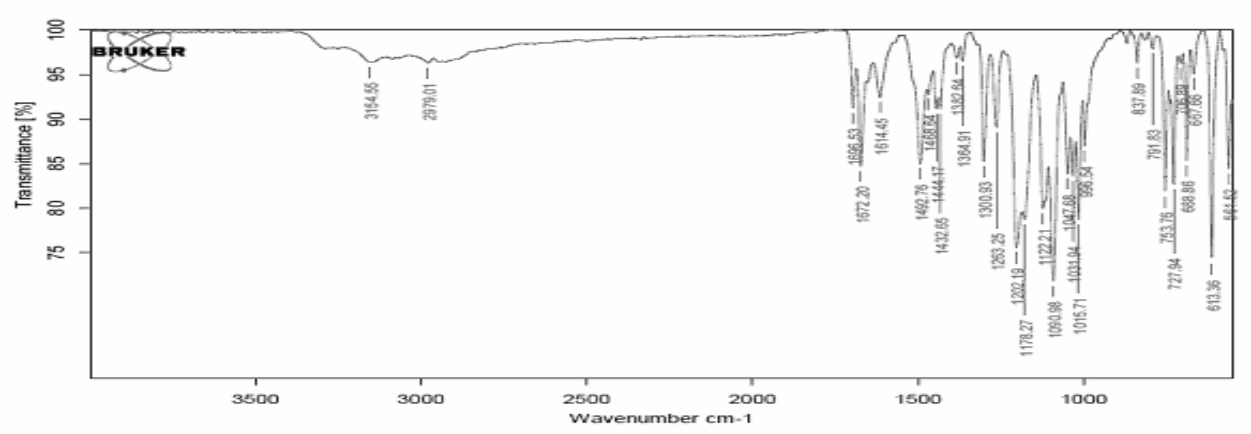

Fig. 6: FTIR spectra of the pure Zolmitriptan.

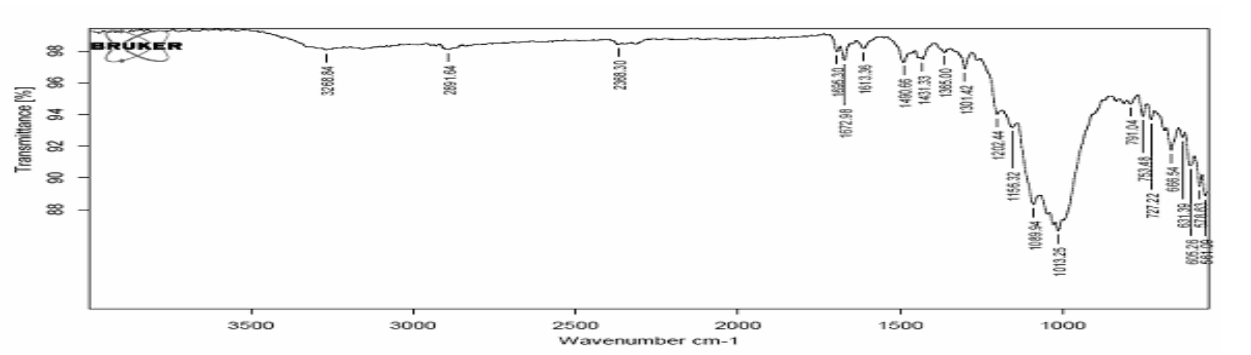

Fig. 7: FTIR spectra of the Zolmitriptan ODT prepared with Crosspovidone.

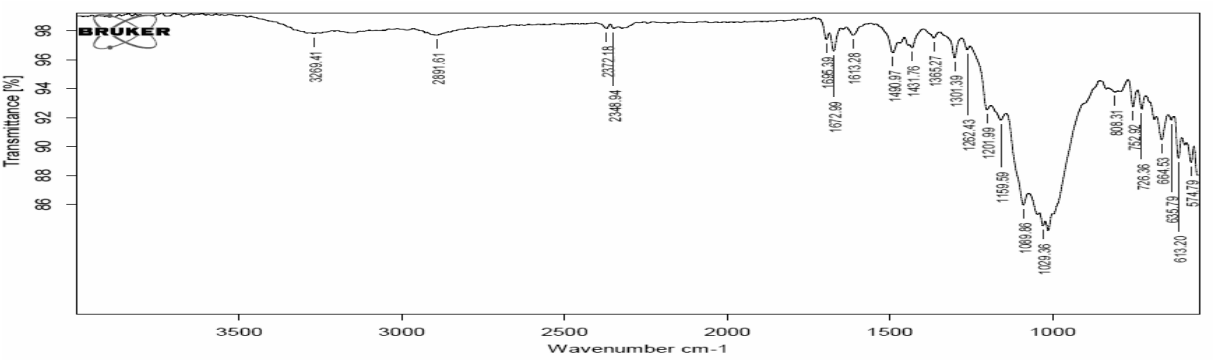

Fig. 8: FTIR spectra of the Zolmitriptan ODT prepared with IRP 88.

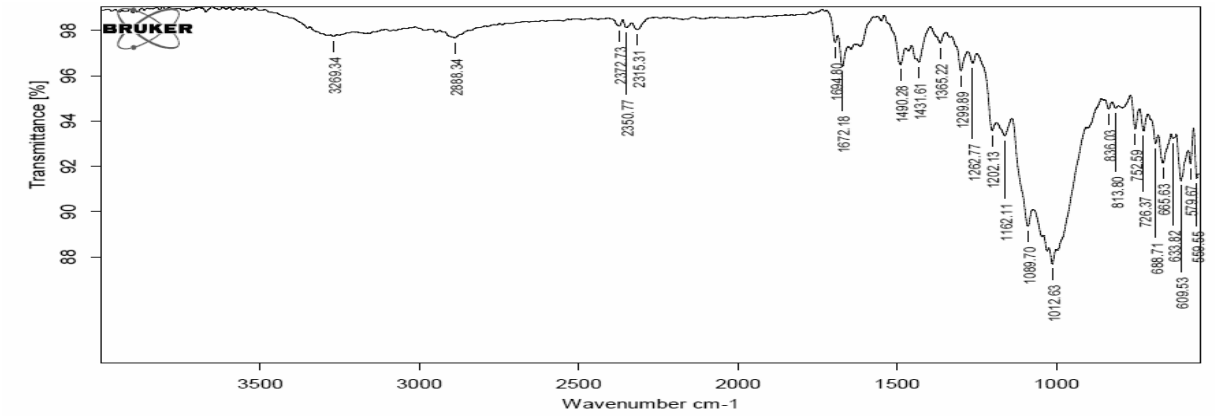

Fig. 9: FTIR spectra of the Zolmitriptan ODT prepared with IRP 88.

CONCLUSION

In this present work oral disintegrating tablets of zolmitriptan were designed with a view to enhance the patient compliance. oral disintegrating tablets of zolmitriptan were prepared by direct compression method after incorporating super disintigrants like cross povidone, IRP 88 and Ludiflash at different concentration (5, 7.5, 10%). The prepared batches of tablets were evaluated for tablet weight variation, content uniformity, hardness, friability, In vitro disintegration and dissolution time. The flow properties of the powder blend was found to be within the limits showing good flow. Effects of super disintigrants on wetting time and in-vitro release also have been studied. The weight of the tablets was found 80 mg and assay of the tablets were within the pharmacopoeia limits. The hardness of the tablets was found to be in the range of 3.1 to 3.6 kg/cm^2 in the prepared formulations. The thickness of the tablets was found in the range of 2.52 and 3.1 mm. The friability of the prepared tablets was found 0.52 to 0.88% which was within the range. The disintegration time of the prepared tablets was in the range of 73 sec to 20 sec. The wetting time was found to be in the range of 80 to 25secs. Tablet containing cross povidone (10%) showed excellent in-vitro disintegration time

and drug release. For better mouth sweetening agents and flavoring agents are added. FTIR & DSC results showed no evidence of interaction between the drug and excepients selected.

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