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Formulation Development and in Vitro Evaluation of Orally Disintegrating Tablets Containing Rizatriptan Benzoate.

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ABSTRACT

The present work aims to prepare and evaluate twelve different formulations of orally disintegrating tablets (ODT's) containing Rizatriptan benzoate using various superdisintegrants like SSG, Crospovidone and Croscarmellose sodium by direct compression method to enhance patient compliance. The tablets were evaluated for pre and post compression studies and found to be within the limits. Based on the disintegrating time and dissolution studies, formulation F11 prepared by using the super disintegrants SSG and Croscarmellose sodium in combination was found to be best formulation. The disintegration time was very less for optimized formulation F11 (18 sec), drug release was complete and very fast (within 18 minutes 99.9%) when compared with other prepared formulations. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. Stability studies were conducted for optimized formulation F11 and found to be stable which retained their original properties with minor differences. Oral disintegrating tablets are suitable dosage forms in disease conditions like migraine as these dosage forms are patient compliant as well as show rapid onset of action as they are quick dissolving dosage forms.

Key words: Rizatriptan benzoate, ODT's, SSG, Crospovidone, Croscarmellose sodium.

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INTRODUCTION

Many patients find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with the prescription which results in noncompliance and ineffective therapy. Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration to achieve better patient compliance. Rapidly disintegrating tablet are appreciated by significant segment of the population, particularly pediatric, geriatric, unconscious and bed-ridden patients who have difficulty swallowing conventional tablet and capsule [1]. To provide the patient with the most convenient mode of administration, there is need to develop a fast-disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without water, anywhere, anytime [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 characterised 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]. Rizatriptan benzoate is a potent and selective 5-hydroxytryptamine $_{1B/1D}$ receptor agonist and is considered more effective than the traditional triptans for the treatment of acute migraine attack [9]. The bioavailability of Rizatriptan benzoate is about 45% which is superior to a poor 14-17% of sumatriptan. It has a very fast onset of action within one hour of intake, providing immediate relief from migraine. Chemically it is 3-[2-(dimethylamino) ethyl]-5-(1H-1, 2, 4-triazol-1-ylmethyl) indole monobenzoate. A 10 mg dose of Rizatriptan benzoate is equipotent to a 100 mg of sumatriptan, the traditional antimigraine drug[10]. As migraine sufferers have markedly reduced functional ability, they would be benefited from acute treatment that helps them to resume their functional activities as quickly as possible.

MATERIALS AND METHODS

MAXALT-MLT 5mg was purchased from Merck & Co., Inc. Rizatriptan Benzoate was generous gift sample from Rubicon Labs Mumbai, 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.

Methods

Preparation of Oral Disintegrating 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, Crospovidone, 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 Strearate 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.

The composition of different Rizatriptan benzoate ODT's are shown in **Table 1**

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Table 1: Composition of Rizatriptan Benzoate oral disintegrating tablets

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Rizatriptan Benzoate	5	5	5	5	5	5	5	5	5	5	5	5
Sodium Starch Glycolate (SSG)	2	5					5	5			5	2
Crospovidone			2	5			5	2	5	5		
Croscarmellose Sodium					2	5			5	2	5	5
Lactose	98	97	98	97	98	97	90	93	90	93	90	93
Avicel 102(MCC)	20	20	20	20	20	20	20	20	20	20	20	20
Sorbitol	2	2	2	2	2	2	2	2	2	2	2	2
Peppermint	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight (mg)	130	130	130	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].

$$\text{Bulk density} = W/V_0 \text{ g/ml}$$

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.

$$\text{Tapped density} = W/V_f \text{ g/ml}$$

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

$$\% \text{ Compressibility} = [(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}] \text{ X } 100$$

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.

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

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

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.

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.

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.

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The percentage friability is expressed as the loss of weight and is calculated by the formula:

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

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^{0}C. 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 by using UV Visible spectroscopy at 226nm 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^{0}C. 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.

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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.

Stability studies

The stability of optimized formulation of Rizatriptan benzoate to assess their stability with respect to their hardness, friability, drug content and release characteristics after storing at 25°C/60% RH and 40°C/75% RH in properly closed HDPE bottles along with 1 g desiccant for 6 months [14].

RESULTS AND DISCUSSION

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

Table 2: Pre-compression Parameters of various Rizatriptan Benzoate formulations:

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ration	Angle of Repose (θ)
F_1	0.364	0.545	10.8	1.11	31.5
F_2	0.362	0.485	10.2	1.2	29.6
F_3	0.379	0.530	10.2	1.13	28.7
F_4	0.375	0.493	10.5	1.14	30.2
F_5	0.360	0.462	10.8	1.5	35.0
F_6	0.419	0.477	10.9	1.06	31.5
F_7	0.417	0.471	11.2	1.04	28.6
F_8	0.416	0.475	11.5	1.2	29.7
F_9	0.428	0.471	11.8	1.02	30.2
F_{10}	0.468	0.456	11.10	1.07	32.1
F_{11}	0.436	0.450	10	1.09	24.7
F_{12}	0.442	0.428	10.9	1.99	30.2

Evaluation of Rizatriptan Benzoate oral disintegrating tablets:

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 various prepared FDTs of Rizatriptan benzoate was found to be within the range of 18 to 35 seconds. The minimum disintegration time of 18

seconds was found for F11 prepared by using the combination of superdisintegrants sodium starch glycolate and Croscarmellose sodium. As the concentration of superdisintegrants in the formulations increased the disintegration time was found to decrease.

Table 3: Post compression Parameters of various Rizatriptan Benzoate formulations.

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability	Disintegration Time (sec)
F_1	130	3.72	3.8	0.10	34
F_2	129	3.68	3.6	0.12	26
F_3	128.9	3.75	4.0	0.14	34
F_4	130	3.76	3.8	0.63	27
F_5	128.6	3.69	4.0	0.15	35
F_6	130	3.69	3.9	0.52	26
F_7	129.8	3.70	3.6	0.10	25
F_8	130	3.65	3.7	0.90	30
F_9	130	3.56	3.9	0.13	24
F_{10}	130	3.74	4.0	0.17	26
F_{11}	130	3.70	3.9	0.13	18
F_{12}	130	3.69	3.5	0.16	29

Water Absorption Ratio:

Water absorption ratio will increase with increasing the concentration of superdisintegrants.

Formulations containing sodium starch glycolate shows greater water absorption ratio as compared to Crospovidone and Croscarmellose sodium. F1, F2, F7, F8, F9, F11 & F12 shown 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 F11 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 Rizatriptan benzoate present in respective formulation. The % drug release of 94.5, 99.8, 99.6, 99.0, 99.8, 98.8, 99.5, 99.6, 99.8, 99.0, 99.8, 99.2 was observed in formulations F1- F12 respectively at the end of 28 minutes and the results are tabulated in **Table 4** & graphical representation was observed in **Figure 1.** Among all the formulations F11 showed highest drug release i.e 99.98 within short time 18 minutes. Based on the post compression parameters, disintegration time and dissolution profile, F11 was found to be the best formulation prepared by using the combination of superdisintegrants sodium starch glycolate and Croscarmellose sodium. The % drug release of innovator product MAXALT-MLT 5mg (**Table 5** & **Figure 2**) was found to be 93%, when compared with optimized formulation F11 was 99.9% within 18 minutes.

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Table 4: In-Vitro Drug release profiles of different Rizatriptan benzoate Formulations

Time (min)	% Drug release											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
2	33	39	42	38	40	42	40	45	60	62	65	60
4	42	46	45	42	44	46	44	48	65	68	69	65
6	54	52	52	60	49	48	48	52	73	72	71	71.9
8	59	61	54	68	50	52	52	56	76	76	78	77
10	62	70.8	59	72	58	59	58	59	79	79	83.9	84.2
12	68	78	61	80	62	62	62	64	82	80	88.8	89
14	72	82	65	88	66	69	69	68	86	85	95	93
16	77	89	68	94	72	78.6	78.6	76	90	89	98	95
18	80.4	95.2	72	98.9	74	89	89	89	94	90	99.9	97
20	89.8	99.8	77	99.0	79	90	90.9	95	97	92		99.2
22	92	99.8	79.5		80	98	98.6	99.6	99.2	98.9		
24	94.5		80		82	98.8	99.5		99.8	99.0		
26			86		88							
28			99.6		99.8							
30												

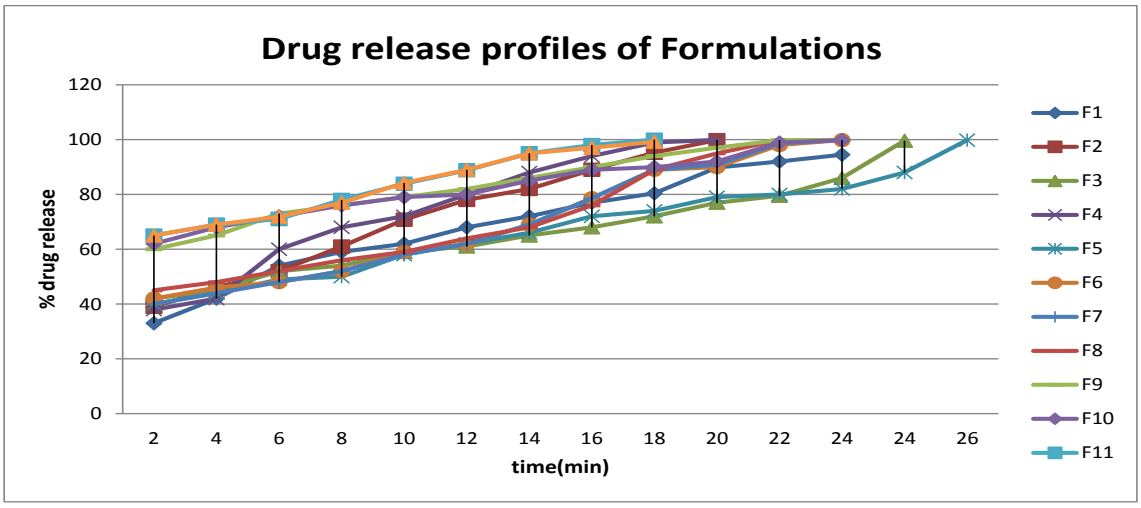

Figure 1: Drug release profiles of Rizatriptan different formulations

Table 5: Dissolution studies of reference product MAXALT-MLT 5mg

S. No	Time (min)	% Drug Release
1	0	0
2	2	54
3	4	62
4	6	69
5	8	74
6	10	78
7	12	80
8	14	86
9	16	90.7
10	18	93
11	20	97.9
12	24	99.6

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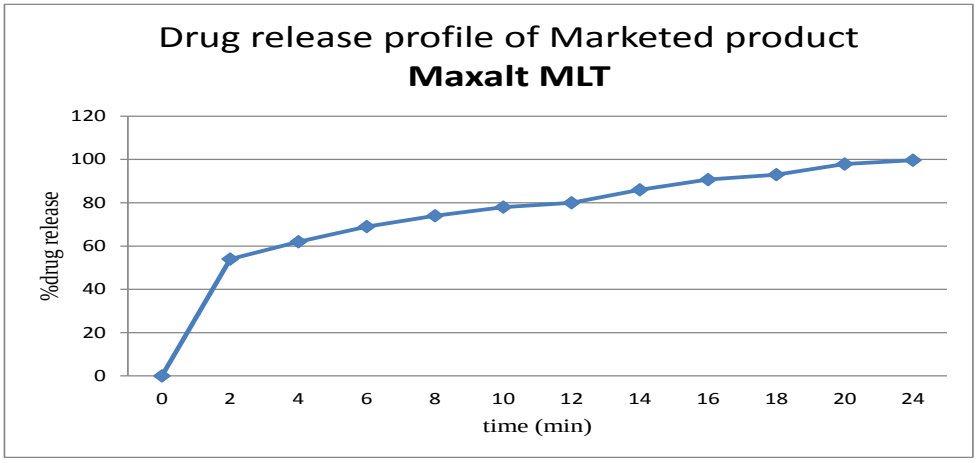

Figure 2: In Vitro Drug release profiles of reference product MAXALT-MLT 5mg

Drug-Excipient compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR spectra of the pure drug, Avicel pH 102, SSG and optimized formulations were shown **Figure 3, 4, 5 & 6** respectively. The FTIR spectrum of optimized formulation displayed the characteristic peaks of the drug. Thus there was no alteration in the characteristic peaks of Rizatriptan benzoate suggesting that there was no interaction takes place between the drug and polymers.

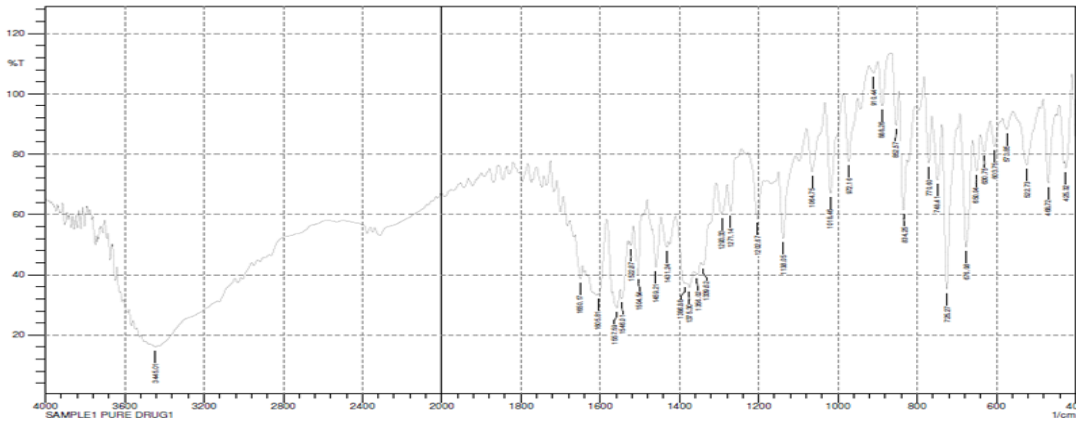

Figure 3: FTIR spectra of Rizatriptan Benzoate pure drug

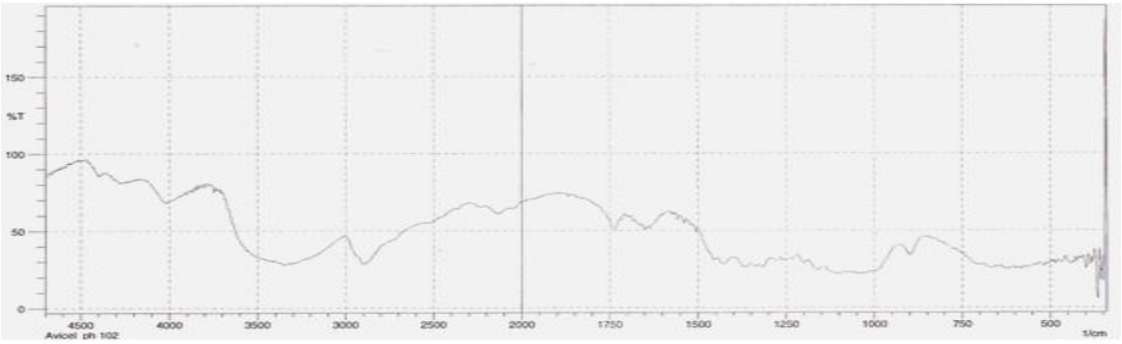

Figure 4: FTIR Spectra of Avicel pH 102

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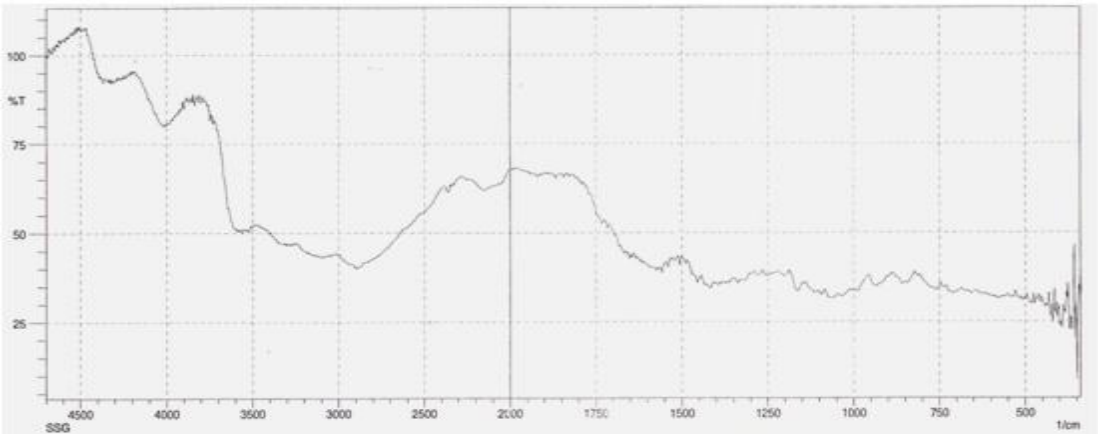

Figure 5: FTIR Spectra of SSG

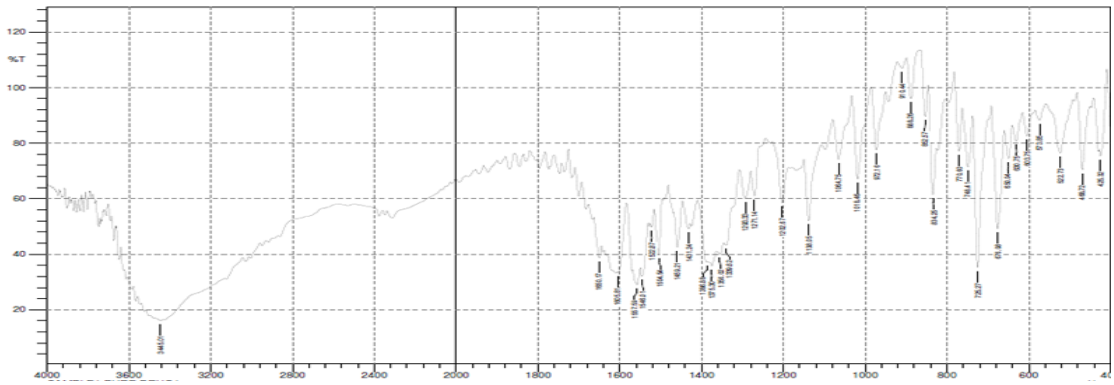

Figure 6: FTIR Spectra of optimized formulation F11

DSC Studies

The melting point of the drug Rizatriptan benzoate was 182.52^{0}C **(Figure 7**), SSG (Sodium Starch Glycolate) was 65.56^{0}C (**Figure 8**), CCS (Croscarmellose Sodium) was 60.33^{0}C (**Figure 9**), & the thermogram optimized formula (F11) was found to be 180.23^{0}C (**Figure 10**). It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

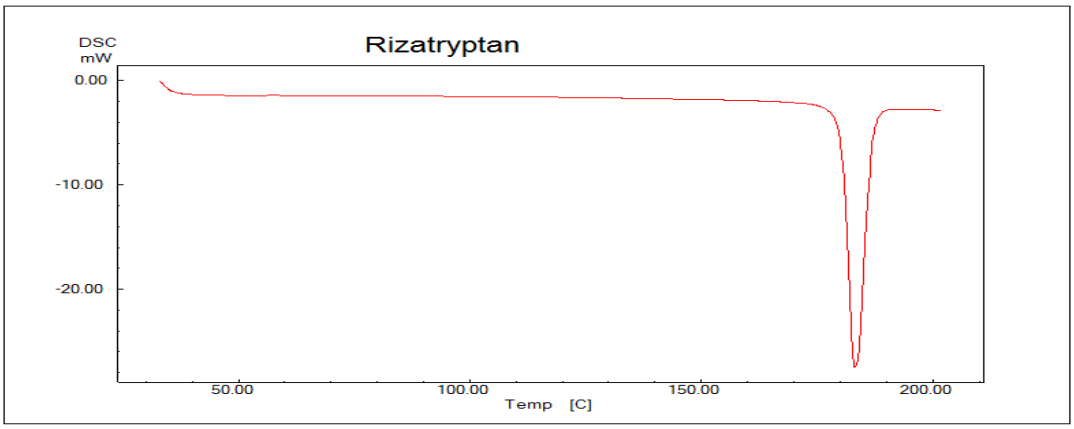

Figure 7: DSC thermogram of Rizatriptan benzoate pure drug

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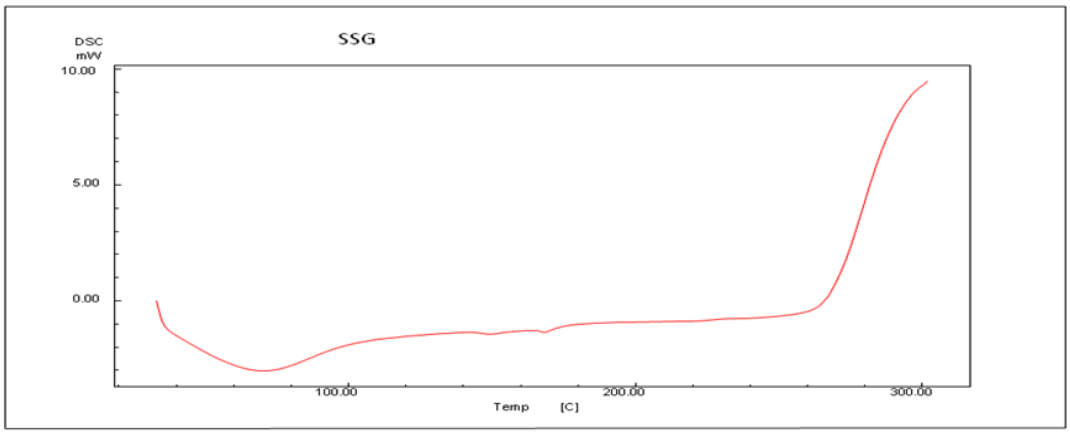

Figure 8: DSC thermogram of sodium starch glycolate

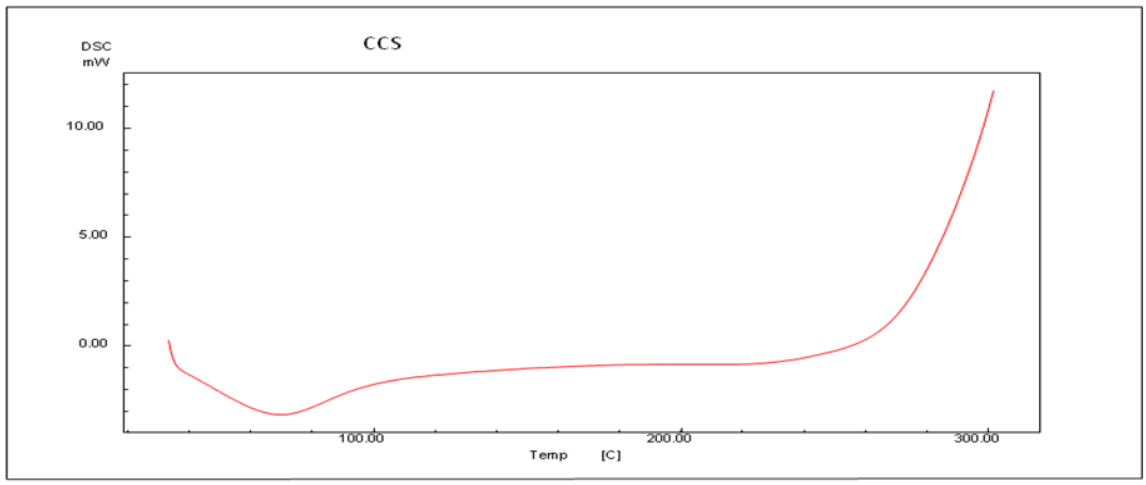

Figure 9: DSC thermogram of Croscarmellose sodium

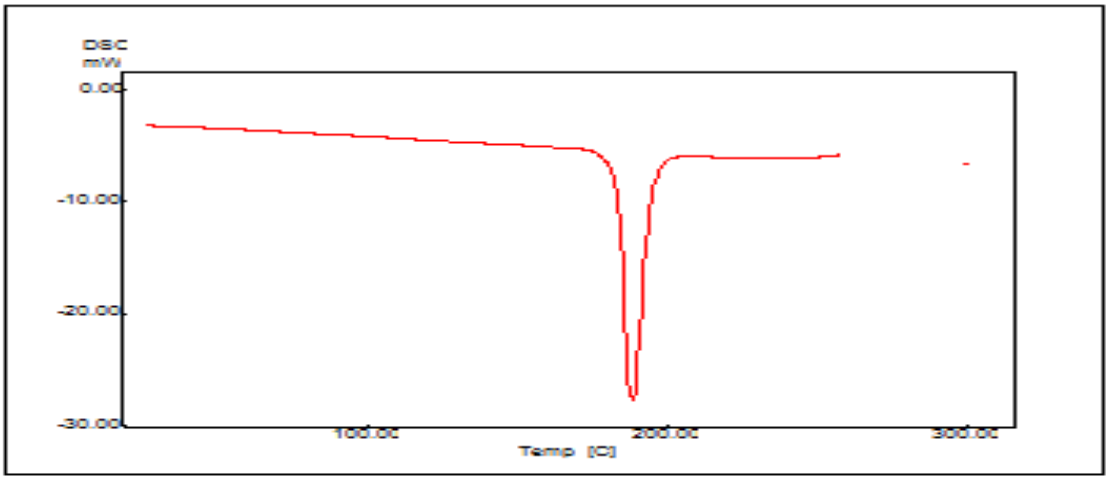

Figure 10: DSC thermogram of Rizatriptan benzoate optimized formulation (F11)

Stability Studies for optimized formulation (F11)

Optimized formulation (F11) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was

concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in **Table 6**.

Table 6: Physico-chemical characteristics of optimized formulation stored at 40±2ºC/75 ±5%RH

Retest Time For Optimized formulation	Friability (%)	Hardness (kg/cm^2)	Disintegration time (Sec)	*In-vitro* drug release profile (%)
0 days	0.13	3.9	18	99.9
30 days	0.15	4.0	20	99.1
60 days	0.18	4.1	21	98.6
120 days	0.20	4.1	22	97.5
180 days	0.23	4.2	23	95.05

SUMMARY AND CONCLUSION

Oral disintegrating tablets of Rizatriptan benzoate were prepared and evaluated using different super disintegrating agents like crospovidone, croscarmellose sodium and sodium starch glycolate. Twelve different formulations were prepared evaluated for their physical characteristics, hardness, thickness, weight variation, friability, wetting time, absorption ratio, disintegration time and found to be within the limits. The results suggest that the formulated ODT's of Rizatriptan benzoate exhibited good physical parameters and rapidly disintegrating without affecting the release profile. Based on the pre and post compression parameters, disintegrating time and dissolution studies F11 prepared by using the super disintegrants SSG and Croscarmellose sodium in combination was found to be best formulation. The disintegration time was very less for optimized formulation F11 (18 sec) and complete drug release was very fast (within 18 minutes 99.9%) when compared with other prepared formulations. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. Stability studies were conducted for optimized formulation, from the results it was concluded that, optimized formulation is stable and retained their original properties with minor differences. Oral disintegrating tablets are suitable dosage forms in disease conditions like migraine as these dosage forms are patient compliant as well as show rapid onset of action as they are quick dissolving dosage forms.

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