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Formulation and *In-vitro* evaluation of rizatriptan benzoate rapimelt tablets and oral thin films – A novel approach

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ABSTRACT

In view to enhance patient compliance an attempt has been made in the present work, Rizatriptan Benzoate Rapimelt tablets and Oral Thin Films (OTFs) were prepared by effervescence technique and solvent casting technique respectively. The motive of study is to provide a dosage form that can quickly disintegrate upon contact with the saliva. The excipients used in the preparation of Rapimelt tablets were effervescence agents (sodium bicarbonate & citric acid) along with superdisintegrants, such as Croscarmellose Sodium (2-4%), Crospovidone (2-4%), and Sodium Starch Glycolate (4-8%). The low viscosity hydrophilic polymer, HPMC E5 LV (1-5%) used in the preparation of Oral Thin Films. Sweetener and flavors were added to enhance the mouth feel in both dosage forms. The prepared tablets were evaluated for Thickness, Weight variation, Hardness, Friability, Assay, Content uniformity, *in- vitro* disintegration time, Simulated Wetting Time, and Dissolution. The Oral Thin Films were evaluated for physical appearance, thickness, folding endurance, assay, Content uniformity, *in- vitro* disintegration time, and dissolution. Based on the *in- vitro* disintegration time and dissolution results the best formulations were selected in each dosage form type (FT2 for Rapimelt Tablets &FF3 for Oral Thin Films).

Keywords: OTFs, HPMC E5 LV, Simulated Wetting Time, *in- vitro* Disintegration time.

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INTRODUCTION

The Rapimelt Tablets and Oral Thin Films come under class of fast disintegrating or dissolving oral delivery system [1]. These dosage forms disintegrate or dissolve in the saliva fluids of the oral cavity, releasing the drug and in-active ingredients. Most of the drug is swallowed with the saliva where subsequent absorption takes place in the Gastro Intestinal Tract [2]. Difficulty in swallowing (dysphasia) is common problem among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. An estimated 35% of the general population, additional 30-40% of elderly institutionalized patients and 18-22% of all persons in long-term care facilities. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets [3]. These dosage forms offer advantages such as disintegration without water, rapid onset of action, no chocking, pleasant taste. These advantages enables the market growth in this area, since first developed in 1970's as an alternative to tablets, capsules, syrups, and suspensions.

Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. In India 15 – 20% of people are suffering from migraine. Rizatriptan Benzoate is a potent selective 5-HT1B/1D receptor agonist, which was under triptan family used in the treatment of acute migraine attacks [4]. It is 10 times more potent than Sumatriptan, the traditional Anti-migraine drug. The quick onset of action is desired in the migraine and as it is not possible with conventional tablets, the concept of formulating Rapimelt tablets containing Rizatriptan Benzoate offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics.

MATERIALS AND METHODS

MATERIALS

Rizatriptan Benzoate is obtained from Aurobindo pharmaceuticals, (Hyderabad, India), Croscarmellose sodium (CCS), Crospovidone (CP), and Sodium Starch Glycolate (SSG) were received as gift samples from Concept pharmaceuticals, (Aurangabad, India), Aspartame and pineapple flavors were received as gift samples from GK Labs, (Acharapakkam, India), Microcrystalline Cellulose pH 102 (Avicel PH 102) was gift sample from Nickon Laboratories, (Puducherry, India), All other reagents and chemicals used were of analytical grade.

METHODS

DIFFERENTIAL SCANNING CALORIMETRY (DSC) [5]

The DSC analysis of pure drug, drug+ CCS, drug+ CP and drug+ SSG, drug+ HPMC E5LV were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer

interaction. The 2 mg samples were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºc at heating rate of 10ºc /min under nitrogen flow of 30ml/min

FORMULATION

FORMULATION OF RAPIMELT TABLETS [6]

The composition of different formulations of Rizatriptan Benzoate Rapimelt tablets is shown in Table 1(the concentrations of effervescence agents were optimized initially). All the ingredients were pre-sieved by using sieve no #44. The ingredients after shifting thoroughly mixed in a mortar and pestle for 15 minutes. The blend thus obtained was directly compressed (9 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmadabad, India). Each tablet contained 14.53 mg of Rizatriptan Benzoate.

Table 1: Composition of Rizatriptan Benzoate Rapimelt tablet

Ingredients*	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
CCS	3	6	-	-	-	-	3	-	3
CP	-	-	3	6	-	-	3	3	-
SSG	-	-	-	-	6	12	-	6	6
Sodium bicarbonate	15	30	15	30	15	30	22.5	22.5	22.5
Citric Acid	12	24	12	24	12	24	18	18	18
Mannitol	30	30	30	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3	3	3	3
Pineapple Flavor	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Microcrystalline Cellulose pH 102	68.72	38.72	68.72	38.72	65.72	32.72	52.22	52.22	52.22
Aerosil	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	150	150	150	150	150	150	150	150	150

*All quantities are in mg.

FORMULATION OF ORAL THIN FILMS [7]

BASE FILM SOLUTION

In this required quantity of HPMC E5LV was dispersed in measured quantity (3ml) of water followed by dissolving it by addition of remainder of cold water (2 ml).

DRUG SOLUTION

It involves the addition of all the ingredients expect for base film. Initially the drug is added in 5 ml of water. To this solution sweetener, sodium benzoate, citric acid was added with

continuous stirring. Then sweetener and flavor was added. At last the plasticizer PEG-400 was added to this homogenous solution.

To the base film solution the drug solution was added slowly with a care to eliminate air entrapment. This final preparation was casted on a Petri dish and dried in hot air oven at 50^0C until the film is completely dry, the films were then removed and cut as per the required size (2×2 cm) and stored. Different batches of formulations were prepared, the formulas of which are given in Table 2. Out of the different formulations the optimized two formulations were selected for further studies.

Table 2: Composition of Rizatriptan Oral Thin Films

Ingredients*	FF1	FF2	FF3	FF4	FF5
Rizatriptan Benzoate	230.9	230.9	230.9	230.9	230.9
HPMC E5LV	100	200	300	400	500
Aspartame	115	115	115	115	115
Citric Acid	70	70	70	70	70
Pineapple Flavor	50	50	50	50	50
Sodium Benzoate	50	50	50	50	50
PEG 400	0.5	0.5	0.5	0.5	0.5
Distilled Water	10	10	10	10	10

*All quantities are in mg, except PEG 400 and Distilled water (ml).

EVALUATION

EVALUATION OF RAPIMELT TABLETS

CHARACTERISATION OF MICROMERITICS OF POWDER BLENDS [8]:

The tablet blend was evaluated for their bulk density, tapped density, compressibility index, angle of repose and Hausner ratio. The tapping method was used to determine the bulk density, tapped density, percent compressibility index and Hausner ratio.

$$\text{Compressibility index} = [\rho_t - \rho_b / \rho_t] \times 100$$

$$\text{Hausner ratio} = \rho_t / \rho_b$$

Where ρ_t = tapped density

Pb = initial bulk density of tablet blend.

Angle of repose θ of the tablet blend measures the resistance to particle flow and was determined by fixed funnel method.

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EVALUATION OF POST COMPRESSION PARAMETERS

The prepared Rapimelt tablets were evaluated for Dimension (Diameter and Thickness) using 10 tablets (Vernier calipers), uniformity of weight using 20 tablets (Shimadzu BL-220H analytical balance), hardness using 6 tablets (Monsanto hardness tester), friability as specified in Indian Pharmacopoeia (Roche type friabilator) [9, 10].

ASSAY AND CONTENT UNIFORMITY [11]

For assay the drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 10 mg was added in 5-7 ml of 0.1N Sodium Hydroxide followed by sonication for 30 minutes. The solution was filtered through Whattman filter paper, the filtrate diluted suitably and the absorbance of resultant solution was measured by using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer at 227 nm using 0.1N as Sodium Hydroxide blank. For content uniformity 5 tablets were individually weighed and powdered. The powder equivalent to 10 mg was weighed and amount of Rizatriptan Benzoate in each formulation was determined by procedure said in assay.

IN-VITRO DISINTEGRATION [10]

For determination of in-vitro disintegration time six tablets were randomly selected from each formulation and the average time of six tablets to complete disintegration was reported as in-vitro disintegration time. The test was carried out by using United States Pharmacopeia (USP) disintegration test apparatus (Veego VTD-DV, Mumbai, India).

SIMULATED WETTING TIME [12]

The in-vitro Simulated Wetting Time (SWT) determined by dropping a tablet in 21 mm internal diameter cup containing 1.25 ml of Dye solution on a Whattman filter paper and the time for compete wetting of tablet was reported as SWT.

***IN- VITRO* RELEASE STUDIES** [10]

The release of Rizatriptan Benzoate from Rapimelt tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (2 ml) of the solution was withdrawn from the dissolution apparatus 2 minutes interval. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The samples were filtered through a Whattman filter and diluted to a suitable concentration with 0.1N hydrochloric acid.

Absorbance of these solutions was measured at 225.5 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The results were depicted in Figure 3.

EVALUATION OF ORAL THIN FILMS

THICKNESS [13]

All the batches were evaluated for thickness by using calibrated digital Vernier calipers. Five samples from all the batches was withdrawn and evaluated for thickness.

FOLDING ENDURANCE [13]

The folding endurance was measured manually for the prepared films. A strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

CONTENT UNIFORMITY [11, 13]

Total drug content per film was calculated by random sampling of the all batches. The same method said in evaluation of Rapimelt tablets was used.

IN-VITRO DISINTEGRATION [10]

For determination of in-vitro disintegration time six films were randomly selected from each formulation and the average time of six films to complete disintegration was reported as in-vitro disintegration time. The test was carried out by using United States Pharmacopeia (USP) disintegration test apparatus (Veego VTD-DV, Mumbai, India).

***IN- VITRO* RELEASE STUDIES** [14]

The release of Rizatriptan Benzoate from OTFs was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 1 (basket method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (2 ml) of the solution was withdrawn from the dissolution apparatus 2 minutes interval. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The samples were filtered through a Whattman filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 225.5 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The results were depicted in Figure 4.

ISSN: 0975-8585

RESULTS AND DISCUSSION

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Any possible drug polymer interaction can be studied by thermal analysis. Rizatriptan Benzoate exhibits a sharp endothermic peak at 186.91°C shown in Figure 1a, which corresponds to its melting point. The Rizatriptan Benzoate+ CCS exhibit a sharp endothermic peak at 184.42ºC, Rizatriptan Benzoate+ CP exhibit a sharp endothermic peak at 184.54ºC, Rizatriptan Benzoate+ SSG exhibit a sharp endothermic peak at 184.54ºC, and Rizatriptan Benzoate+ HPMC E5LV exhibit a sharp endothermic peak at 186.91ºC shown in Figure 1b, 1c, 1d and 1e respectively. Hence DSC study shows that there is no any drug polymer interaction.

Figure 1a: DSC thermal analysis of Rizatriptan Benzoate

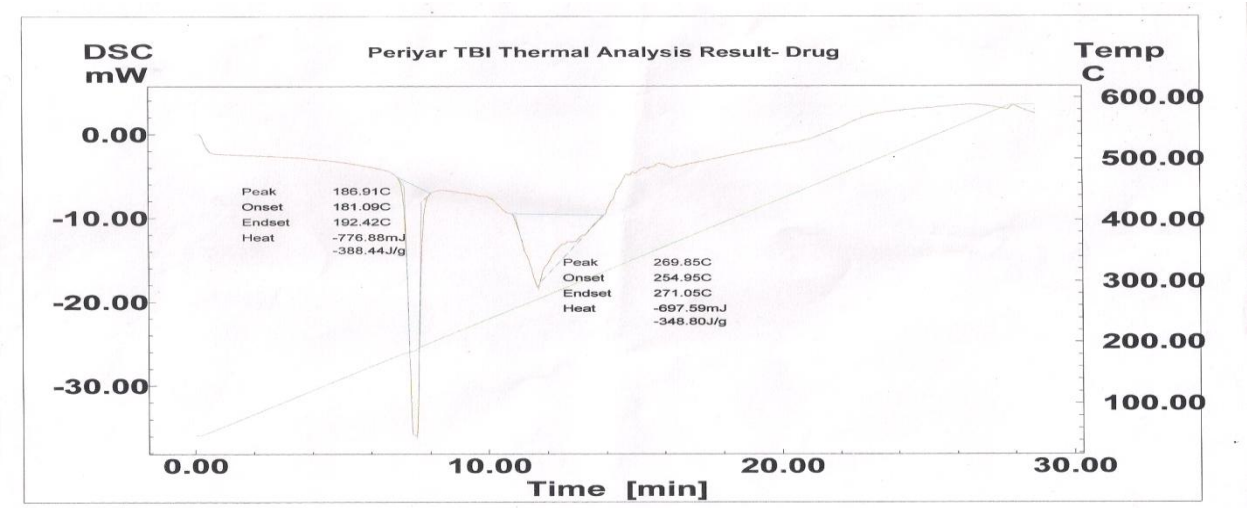


Figure 1b: DSC thermal analysis of Rizatriptan Benzoate+CCS

ISSN: 0975-8585

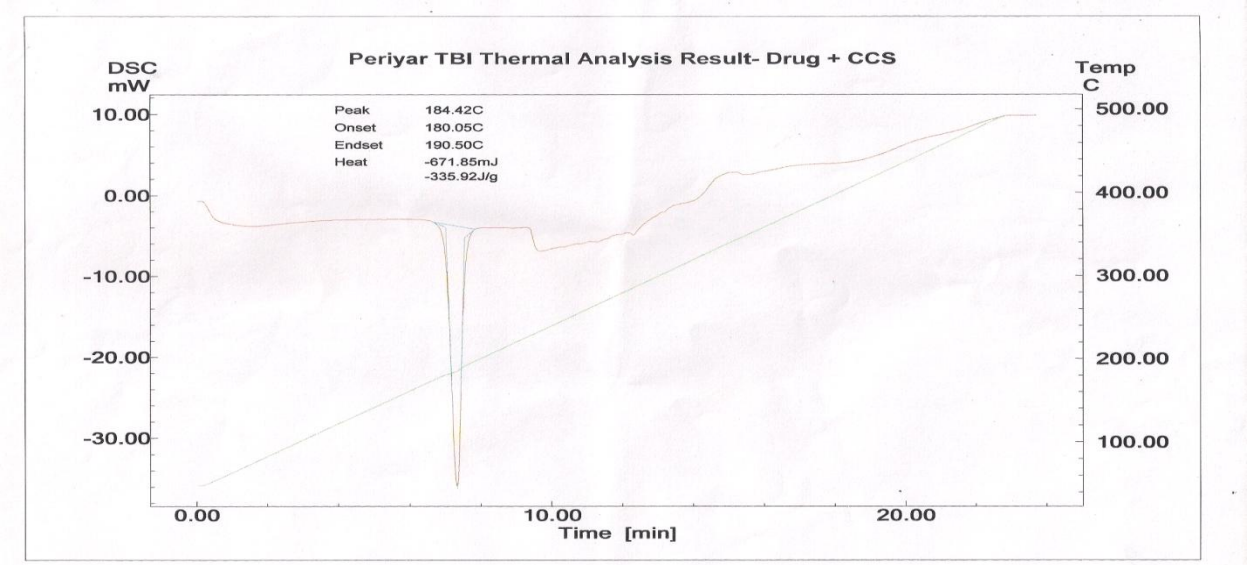


Figure 1c: DSC thermal analysis of Rizatriptan Benzoate+ CP

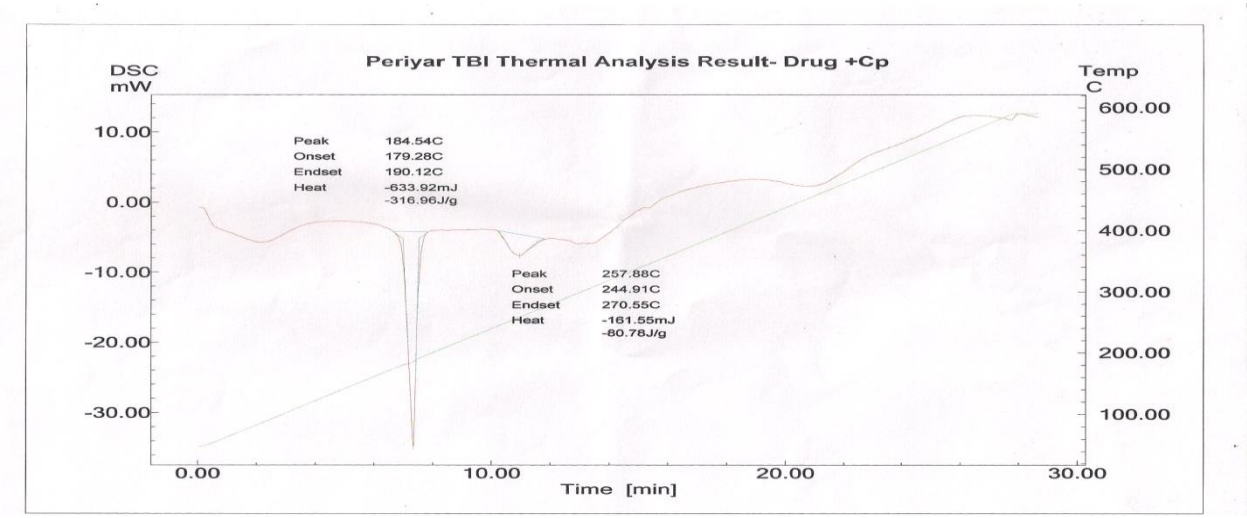


Figure 1d: DSC thermal analysis of Rizatriptan Benzoate+ SSG

ISSN: 0975-8585

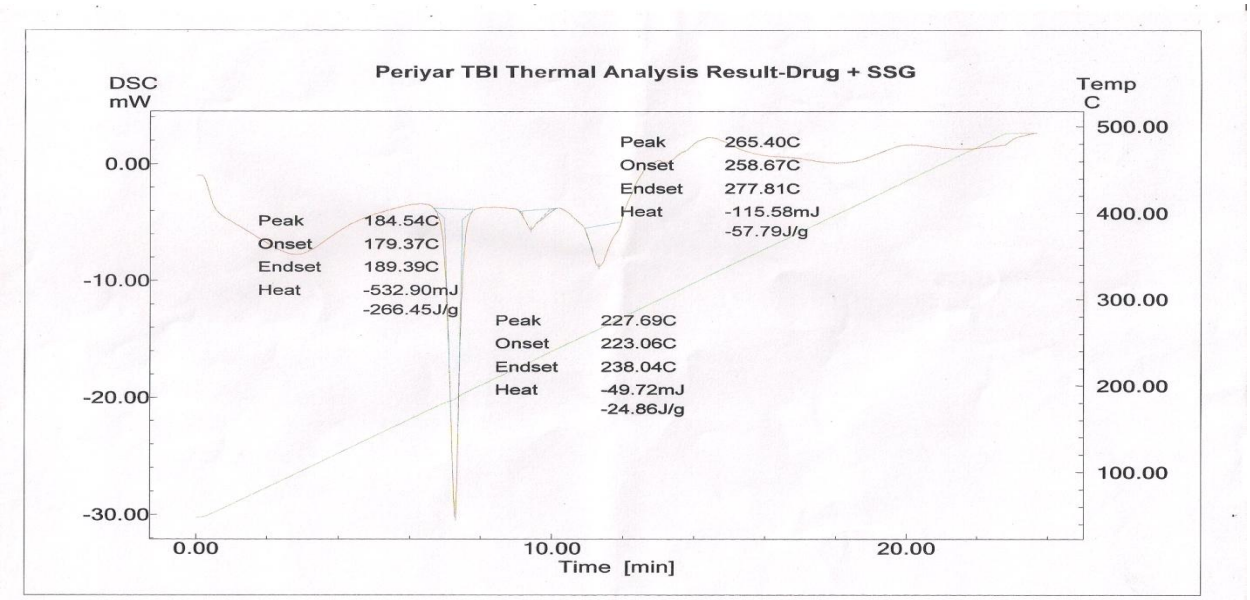
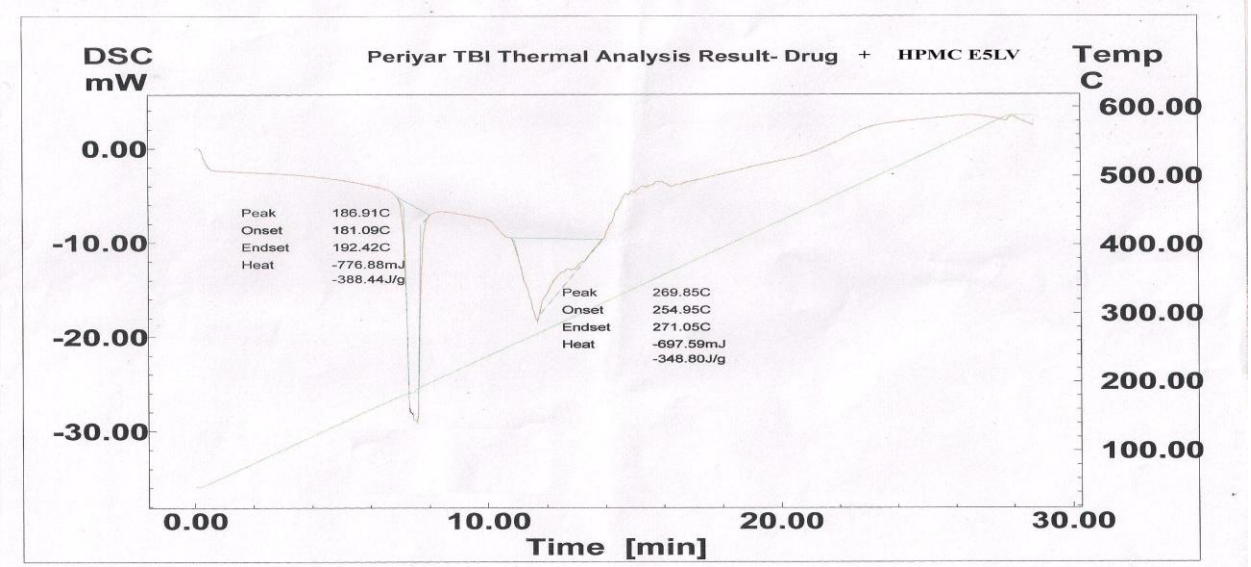


Figure 1e: DSC thermal analysis of Rizatriptan Benzoate+ HPMC E5LV



EVALUATION OF RAPIMELT TABLETS

CHARACTERIZATION OF MICROMERITICS POWDER BLENDS

The powders prepared for compression of Rapimelt tablets were evaluated for their flow properties, the results were shown in Table 3. Angle of repose for all formulations was

found to be lesser than 30º which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.532±0.0116 to 0.618±0.0001 gm/ml, the tapped density was in the range of 0.612±0.0001 to 0.722±0.0001 gm/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 13.04±0.005 to 16.67±0.005, the Hausner ratio was found to be in the range of 1.105±0.000 to 1.202±0.004, indicating compressibility of the tablet blend is good. These values indicate that the prepared powder blends exhibited good flow properties.

Table 3: Characterization of Micromeritics of Powder Blends

Formulation Code	Angle of repose (θ)*	Bulk density (gm/cm^3)*	Tapped density (gm/cm^3)*	Hausner Ratio*	Carr's Index*
FT1	29.17±0.51	0.532±0.011	0.612±0.003	1.51±0.02	13.12±1.95
FT2	28.31±0.19	0.618±0.000	0.722±0.000	1.16±0.00	14.28±0.00
FT3	29.53±0.03	0.538±0.000	0.641±0.001	1.19±0.00	16.00±0.01
FT4	30.08±0.04	0.578±0.001	0.693±0.002	1.12±0.01	16.67±0.00
FT5	30.18±0.12	0.583±0.000	0.699±0.001	1.20±0.00	16.67±0.00
FT6	27.24±1.09	0.590±0.000	0.689±0.000	1.16±0.00	14.28±0.01
FT7	29.42±0.08	0.538±0.001	0.615±0.001	1.14±0.01	12.49±0.00
FT8	29.22±0.46	0.573±0.001	0.659±0.001	1.11±0.06	13.04±0.00
FT9	28.47±0.07	0.571±0.001	0.657±0.000	1.15±0.00	13.04±0.01

*All the values are expressed as mean± SE, n=3.

EVALUATION OF POST COMPRESSION PARAMETERS

The Rapimelt Rizatriptan Benzoate tablets were off-white, smooth, flat shaped, and one side break line in appearance. The results of post compression parameters are shown in Table 4. The thickness of Rapimelt tablets was measured by Vernier caliper and was ranged between 2.092±0.010 to 2.096±0.008 mm. The weight variation for different formulations (FT1 to FT 9) was found to be lesser than 7.5%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the Rapimelt tablets was measured by Monsanto tester and was controlled between 2.25±0.27 to 2.58±0.37 kg/cm^2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The assay and content uniformity for FT1 to FT9 was found to be in between 97.51±0.50 to 98.82±0.26 and 13.59± 0.36 to 14.61± 0.37 mg of Rizatriptan Benzoate, it complies with official specifications.

ISSN: 0975-8585

Table 4: Physico-Chemical Characterization of Rizatriptan Benzoate Rapimelt Tablets

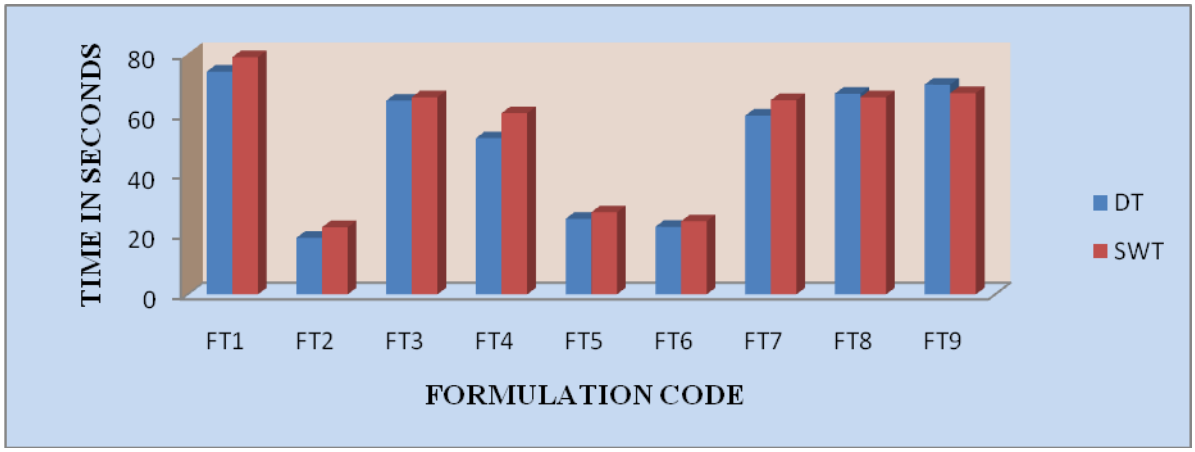
Code	Thickness (mm)#	Weight variation test (%)	Hardness (kg/cm^2)*	Friability (%)	Content uniformity (mg)*	Drug content (%)*
FT1	2.096±0.008	±1.614	2.25±0.27	0.243	14.03±0.06	98.30±0.76
FT2	2.096±0.008	±2.85	2.33±0.25	0.258	14.61±0.37	98.21±0.98
FT3	2.094±0.009	±2.552	2.33±0.25	0.212	13.81±0.29	98.00±1.40
FT4	2.092±0.013	±2.747	2.33±0.25	0.212	14.16±0.18	97.45±1.03
FT5	2.094±0.009	±2.625	2.25±0.27	0.196	14.14±0.16	98.08±0.92
FT6	2.096±0.008	±2.623	2.33±0.25	0.257	14.04±0.03	98.82±0.32
FT7	2.092±0.009	±2.788	2.50±0.31	0.167	13.87±0.20	97.74±0.65
FT8	2.094±0.009	±2.982	2.58±0.37	0.167	14.17±0.42	97.51±0.61
FT9	3.31±0.11	±2.607	2.50±0.31	0.167	13.59±0.36	98.13±0.73

*All the values are expressed as mean± SD, n=6; # All the values are expressed as mean± SD, n=10.

IN- VITRO DISINTEGRATION TIME AND SIMULATED WETTING TIME:

Among all the designed formulations, three formulations FT2, FT5, and FT6 were found to be promising and displayed an in-vitro disintegration time and SWT ranging from 18.83± 2.99 to 25.16± 3.81 seconds and 22.33± 0.57 to 27.33± 1.15 seconds respectively, which facilitates their faster dispersion in the mouth. Over all the formulations FT2 containing 4%w/w of CCS along with mixture of sodium bicarbonate 20% w/w and anhydrous citric acid 16% w/w was found to promising formulation. The results are shown in Figure 2.

Figure 2: Disintegration Time and Simulated Wetting Time of Rizatriptan Benzoate Rapimelt tablet (F1 to F9)

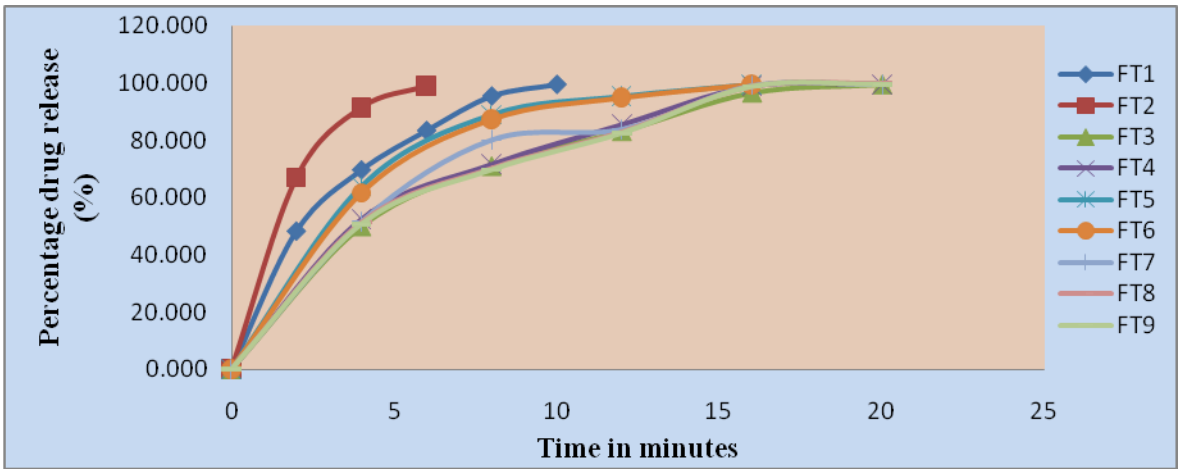


IN- VITRO RELEASE STUDY

In- vitro dissolution studies of all the formulations of Rapimelt tablets of Rizatriptan Benzoate were carried out in 0.1 N HCl. Rizatriptan Benzoate release was significantly faster from all the formulations compared to marketed conventional tablet formulation. Release rate

of Rizatriptan Benzoate from the formulation FT2 was found to be faster than other designed formulations. The results of in- vitro dissolution studies of all formulations were shown in Figure 3.

Figure 3: In- vitro drug release profile of Rizatriptan Benzoate Rapimelt tablet (F1 to F9)



EVALUATION OF ORAL THIN FILMS

Films prepared at 1% and 2% w/v concentrations of HPMC E5LV were very thin, brittle, and easily broken. HPMC E5LV 5% containing films were difficult to prepare as air entrapment was more. The films containing 3 and 4% w/v HPMC E5LV were separated easily, and clear. These formulations are selected for further evaluation.

THICKNESS

The both batches were evaluated for thickness using digital vernier calipers. The both batches were found to have thickness of 0.136±0.008 mm.

FOLDING ENDURANCE

The folding endurance was measured manually for the prepared films. A film was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. Table 5 shows the results for both the batches. Batch with higher amount of HPMC E5LV 4% scored higher folding endurance than the HPMC E5LV 3%.

CONTENT UNIFORMITY OF DRUG

Content uniformity was estimated for both the batches. The thin film was cut in 2cm×2cm area and the cut parts were evaluated for drug content using the prior mentioned UV

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method. All the batches were found satisfactory in uniformity of drug. All the films were found about 14.20 mg/cm2. Results are given in the Table 5.

Table 5: Evaluation of Oral Thin Films:

Code	Thickness (mm)#	Folding Endurance*	Content uniformity (mg) #	Disintegration Time (seconds)*
FF3	0.136±0.008	7±1.00	14.24±0.01	6.33±1.21
FF4	0.136±0.008	13.33±0.57	14.23±0.28	8.33±1.03

*All the values are expressed as mean± SD, n=3; # All the values are expressed as mean± SD, n=5. FF1, FF2, and FF5 were not selected for the evaluation.

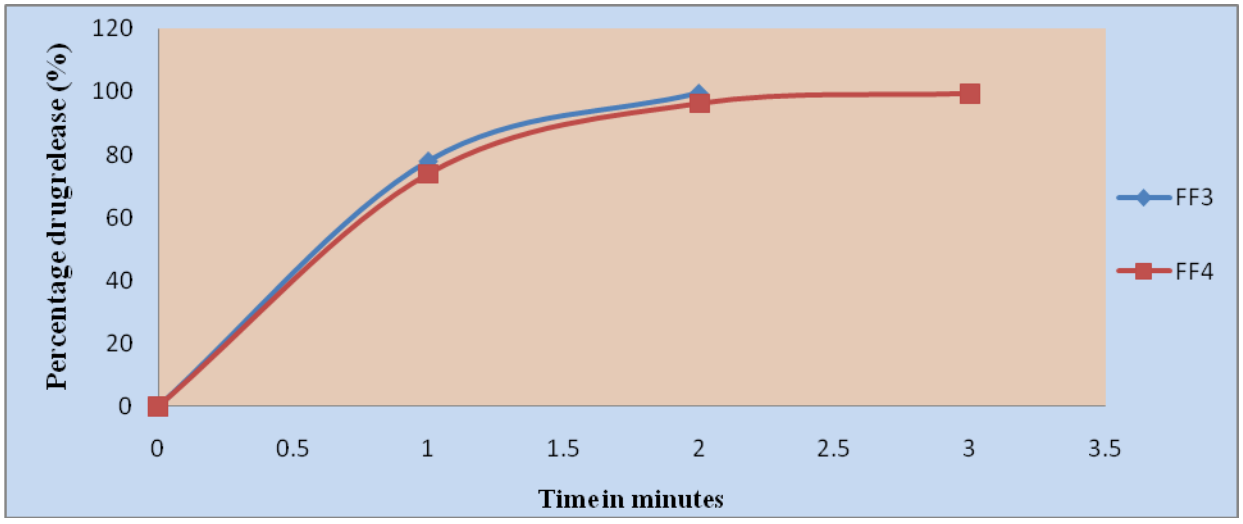
IN- VITRO DISINTEGRATION TIME

Disintegration test was performed for both the batches and both the batches found to disintegrating within 10 seconds. Batch with higher amount of polymer had comparatively high disintegration time as per results given in Table 5.

IN- VITRO RELEASE STUDY

In- vitro dissolution studies of all the formulations of OTFs of Rizatriptan Benzoate were carried out in 0.1 N HCl. Rizatriptan Benzoate release was significantly faster from both the formulations compared to Rapimelt tablets and marketed conventional tablet formulation. The results of in- vitro dissolution studies of all formulations were shown in Figure 4.

Figure 4: In- vitro drug release profile of Rizatriptan Benzoate Oral Thin Films



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CONCLUSION

A stable and effective Rapimelt tablets and Oral Thin Films of Rizatriptan Benzoate were formulated successfully. DSC studies showed compatibility of drug with functional excipients. Both the dosage forms were developed with the aim of immediate drug release to provide patients quick relief from suffering in an economic and industry feasible method. The Rapimelt tablet formulations shown faster disintegration (18.83± 2.99) and faster drug release rate (99.09± 0.63 in 5 minutes) but while compare to the Oral Thin Films (6.33± 1.21 & 99.59±0.21 in 2 minutes) it was somewhat slower. The patient compliance was more to OTFs than Rapimelt tablets. By considering these it was finally concluded Oral Thin Films of Rizatriptan were better dosage form than Rapimelt Tablets.

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