

Formulation and Evaluation of Orodispersible Tablets of Rizatriptan Benzoate

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Abstract

The major intention of this research work is to formulate and evaluate the orodispersible tablets of Rizatriptan Benzoate for the management of Migraine. The tablets were prepared by using different excipients utilizing direct compression technique for the formulation of orodispersible tablets. Rizatriptan Benzoate was found to be soluble in water and thus water was used as dissolution medium. The powder blend of Rizatriptan Benzoate along with other excipients were subject for pre compression studies which showed good flow properties. The powder blends were compressed into tablets of 150 mg each using 10-station rotary tablet compression machine. The formulated tablets were subjected for post compression evaluation parameters. All the formulations passed the pharmacopoeial tests within the specified limits and the dissolution profiles were found to be satisfactory. The optimized formulation F6 containing banana powder showed a better drug release profile of 98.94 % at the end of 12 minutes with the disintegration time of 21 seconds.

Keywords: Rizatriptan Benzoate, Orodispersible Tablets, Banana powder.

1. Introduction

The route of drug administration prevails the bioavailability and the duration of the pharmacological effect. Among other routes, the enteral route of drug administration is found to be most common, convenient and economical route of administration. Apart from these, oral route manifests additional merits like possibility of self-medication, painless administration, increment in patient compliance and so on.[1] The predominant site for the drug absorption through oral route is generally small intestine which indicates that the amount of drug absorbed across the intestinal epithelium influences the bioavailability. Some major drawbacks include dysphagia, the insolubility of drugs at low pH level, inactivation of drug in the liver, irritation of gastrointestinal mucosa, variable absorption rates, etc.[2] Most of the orally administered dosage forms are intended to be swallowed which undergoes pre-systemic metabolism which implies that only a fraction of administered drug actually reaches the systemic circulation.[3] Geriatric and pediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablets when water is not available, in motion sickness and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. To overcome such hurdle, fast disintegrating tablets or

orodispersible tablets have transpired as a surrogate delivery system. Fast disintegrating tablets are not only preferable for people who have swallowing difficulties, but also are ideal for active people. [4-6] US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the “Orange Book,” an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.” European Pharmacopoeia described ODTs as “uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed” and as tablets which should disintegrate within 3 minutes.[7] Fast disintegrating tablets (FDTs) are also known as “fast dissolving,” “mouth dissolving,” “rapid dissolve,” “quick disintegrating,” “orally disintegrating,” “rapimelt,” “fast melts,” “orodispersible,” “melt in mouth,” “quick dissolving,” “porous tablets,” “EFVDAS,” or “effervescent drug absorption system.”[8]

1.1 Advantages of Orodispersible Tablets: [9, 10]

- ✓ No water and chewing needed, hence leads to the enhanced compliance.
- ✓ Ease of administration.
- ✓ No residue in the oral cavity after administration.
- ✓ Allow high drug loading.
- ✓ Rapid absorption and dissolution, offering a rapid onset of action.
- ✓ Advantageous over liquid dosage forms in terms of stability, administration as well as transportation.
- ✓ Avoids hepatic metabolism leading to the increment in the bioavailability.

1.2 Limitations of Orodispersible Tablets: [11]

- Low mechanical strength, so careful handling is required.
- Hygroscopic in nature, so packaging and storage should be highly considered.
- May leave unpalatable taste and grittiness if not formulated properly.

1.3 Criteria for selection of drug: [12]

- Low dose and no bitter taste.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially non-ionized at the oral cavity pH.
- Ability to permeate upper GIT and oral mucosal tissue.

Rizatriptan Benzoate, chemically 3- [2- (dimethylamino) ethyl]- 5 - (1 H 1, 2, 4- triazol – 1 -yl methyl) indole monobenzoate, is used for the treatment of acute migraine attack and is considered superior than other traditional triptans. It has a very fast onset of action within one hour of intake, providing immediate relief from migraine. [13]

In the present study the focus will be given in the fabrication of the orodispersible tablet or fast disintegrating tablets of Rizatriptan Benzoate with an intention of providing rapid relief for migraine sufferers so that they can resume their functional activities as quickly as possible. This system of drug delivery allows the general population to take their medications discretely wherever and whenever needed. The ODT of Rizatriptan Benzoate benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability as a dosage form of choice in the current market.

2. Materials and Methods

2.1 Materials

Rizatriptan benzoate was obtained from Hetero drug Limited, Vishakhapatnam, India as gift samples. All the other excipients, solvents, reagents and chemicals used were of either Pharmacopoeial or analytical grade.

2.2 Methods

2.2.1 Preparation of Natural Superdisintegrants

- i. Dehydrated Banana Powder: Unripe banana was purchased from the local market. Purchased bananas were peeled off and cut into small pieces. The pieces of bananas were allowed to dry under direct sunlight for 4-5 days. After complete dryness of banana, they were subjected for grinding. The obtained powder was then passed through sieve # 80 and stored in a desiccator. [14]
- ii. Mango peel pectin: Mango peel was obtained from the local market as a waste material which were thoroughly washed and shade dried for 24 hrs and additionally dried at 30-40°C. The dried peel were cut into pieces and grinded into powder form followed by sieving through sieve # 20 and stored. Pectin was extracted and isolated from the obtained mango peel powder which was used as a natural superdisintegrant. [15]

2.2.2 Pre-formulation Evaluation [16-20]

Pre-formulation study is the first step in the development of dosage form of a drug substance. It is defined as a phase of research and development, where the biopharmaceutical principles are applied to determine the physicochemical parameters of a new drug substance with a goal to design optimum drug delivery system.

- ❖ Identification of pure drug by FTIR Spectroscopy: The FTIR spectrum of the sample of the drug was compared with the standard FTIR spectra of the pure drug.
- ❖ Determination of Melting Point: Melting point of Rizatriptan Benzoate was determined by open capillary method.
- ❖ Solubility Analysis: Solubility analysis is carried out for Rizatriptan benzoate samples in various solvents. 30 mg pure drug was dissolved in 10ml of different solvents i.e. water, ethanol and methylene chloride solubility was determined.
- ❖ Preparation of Standard Calibration Curve: Accurately weighed 50mg of Rizatriptan Benzoate was dissolved with 0.1NaOH in 50ml volumetric flask. From this stock-I, 5ml was pipette in 50ml volumetric flask and volume was made with 0.1 NaOH to make second solution. From the second stock solution different aliquots were prepared in the range 5-25µg/ml. The standard curve was obtained by plotting absorbance vs concentration.
- ❖ Formulation of Orodispersible Tablets: Oral dispersible tablets each containing rizatriptan benzoate equivalent to 5 mg of Rizatriptan, were prepared by direct compression method. The ingredients were individually weighed and sifted through a 20# mesh. All the ingredients except magnesium stearate and the sweetening agent were uniformly blended followed by mixing of magnesium stearate and Aspartame. The tablet mixture was then compressed (8 mm diameter, concave punches) using a 10-station rotary tablet compression machine.

Name of Ingredients	Quantity (mg/tablet)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rizatriptan Benzoate	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27
Mango Peel Pectin	5	10	15	0	0	0	0	0	0
Dehydrated Banana Powder	0	0	0	5	10	15	0	0	0
Gellan Gum	0	0	0	0	0	0	5	10	15
Mannitol	40	40	40	40	40	40	40	40	40
Aspartame	3	3	3	3	3	3	3	3	3
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Starch	15	15	15	15	15	15	15	15	15
Microcrystalline Cellulose	67.73	62.73	57.73	68.73	64.73	60.73	68.73	64.73	60.73
Total in weight	150	150	150	150	150	150	150	150	150

Table 1: Formulation Table for Preparation of Orodispersible Tablets of Rizatriptan Benzoate. Defined bulk weight per tablet is 150 mg containing Rizatriptan Benzoate equivalent to 5 mg of Rizatriptan.

2.2.3 Pre-compression studies: [21-23]

In the pre-compression studies for tablets, various parameters are analyzed for prevent the possible defects in the formulation of tablets. Criteria like angle of repose, compressibility index, hausner’s ratio are measured to determine the flow properties of the powder blend, in addition, bulk density and tapped density are also ensured to be measured.

❖ Bulk Density: It is the ratio of weight of the powder by the bulk volume of the powder and is expressed in gm/cm³. The powder blend was weighed using the digital balance for each formulation and carefully poured into the 50 ml graduated cylinder. Without any compaction force, the unsettled volume of the powder was noted as bulk volume and calculated as:

$$\rho_{bulk} = \frac{M}{V_b}$$

Where,

ρ_{bulk} = bulk density

M = mass of the powder blend,

V_b = bulk volume

❖ Tapped Density: It is the ratio of the weight of the powder by the tapped density and is expressed in gm/cm³ as well. The graduated cylinder is subjected to tapping by placing it in the tap density apparatus and allowed to tap from a fixed height until no change in volume is observed. The tapped volume of the powder blend was noted and calculated as:

$$\rho_{tapped} = \frac{M}{V_t}$$

Where,

ρ_{tapped} = tapped density

M = mass of the powder blend,
 V_b = tapped volume

- ❖ Hausner’s Ratio: It is the ratio of tapped density to the bulk density and is a measure of flow ability of the powder and is calculated as:

$$\text{Hausner's Ratio} = \text{TD/BD}$$

Where,

TD = Tapped Density

BD = Bulk Density

- ❖ Compressibility Index: It correlated to the flowability of a powder or granular material. It is expressed in percentage. The higher the value the lower will the flow properties. It can be calculated as:

$$\text{Carr's Index} = \frac{\text{TBD}-\text{LBD}}{\text{TBD}} \times 100\%$$

Where,

TBD = Tapped Bulk Density

LBD = Loose Bulk Density

- ❖ Angle of Repose: Angle of repose can be defined as the possible greatest angle between the horizontal plane and surface of pile of powder. It was determined using the funnel method. It is expressed in degrees and can be calculated as:

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

where,

θ = Angle of Repose

h = height of the pile of powder

r = radius of the pile of powder

Flow Characteristics	Hausner’s Ratio	Carr’s Index	Angle of Repose
Excellent	1.00 – 1.11	01 – 10	25 – 30
Good	1.12 – 1.18	11 – 15	31 – 35
Fair	1.19 – 1.25	16 – 20	36 – 40
Passable	1.26 – 1.34	21 – 25	41 – 45
Poor	1.35 – 1.45	26 – 31	46 – 55
Very Poor	1.46 – 1.59	32 – 37	56 – 65
Extremely Poor	> 1.60	> 38	> 66

Table 2: Relationship between Hausner’s Ratio, Compressibility Index and Angle of Repose with the Flow properties.

2.2.4 Post-compression Studies: [24-26]

Post-compression studies are carried out after the formulation of the dosage forms. The post-compression study helps to assess the dosage forms’ physical, chemical and biological properties. All the nine formulations were subject to the following post-compression evaluation parameters.

- ❖ Shape and Appearance: The formulated tablets were visually observed and evaluated for its shape and appearance.

- ❖ **Weight Variation Test:** Weight variation of tablet was determined by analytical weighing balance. Twenty tablets were selected randomly from each batch and weighed individually. The average and standard deviation were then calculated. The specifications for weight variation and percentage deviation mentioned in Indian Pharmacopoeia are given in following table:

Average weight of tablets	Percentage deviation (%)
80 mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

Table 3: Limits for Weight Variation (IP)

- ❖ **Thickness:** Thicknesses of uncoated tablets were measured using a calibrated Vernier caliper. Three tablets of each formulation were picked randomly and dimensions were measured in mm along with mean and standard deviation.
- ❖ **Friability Test:** Roche Friabilator was used for friability test. Ten uncoated tablets from each formulation were weighed ($W_{initial}$) accurately, placed in the friabilator and was allowed to rotate at 25 rpm for a period of 4 min. After 100 rpm tablets were taken, dedusted and weighed again (W_{final}) and the percentage weight loss in tablet was determined using formula:

$$F = \frac{W (initial) - W (final)}{W (initial)} \times 100 \%$$

% friability of the tablets less than 1% is considered acceptable.

- ❖ **Hardness:** It is defined as the resistance of the applied force until the force breaks it. It is used to calculate the tensile strength of tablets to assess the manufacturability and compactibility of formulations. Hardness of uncoated tablets were determined using a Monsanto hardness tester. Three tablets were randomly picked from each batch and placed in the vertically holding edges of the anvil of the tester and screw was rotated until the tablet broke which showed hardness in kg/cm^2 .
- ❖ **In-vitro Disintegration test:** Disintegration test for uncoated tablets was carried by placing one tablet in each tube of the basket and top portion of each tube was closed with disc. The disintegrating apparatus was run using distilled water maintained at $37 \pm 2^\circ C$. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate from each formulation.
- ❖ **In-vitro drug release studies of tablets:** Drug release studies of each formulation were carried out using a USP type II dissolution apparatus (Apparatus 2, 50 rpm, $37^\circ C$) for 10 minutes in water (900 ml). The samples were withdrawn at time intervals 2, 4, 6, 8, 10 and 12 minutes and directly analyzed for Rizatriptan Benzoate content using UV spectrophotometer at 280 nm. Suitable volume of the dissolution media was added after each sample withdrawal to compensate loss.
- ❖ **Drug content uniformity:** 10 uncoated tablets from each formulation were crushed and powder equivalent to 10 mg Rizatriptan Benzoate was dissolved in 100 ml volumetric flask with water $100 \mu g/ml$ of the drug concentration was made. Then solution was filtered and further dilutes 1ml solution in 10 ml volumetric flask and diluted with water. The solution was analyzed UV

spectrophotometrically at 280 nm. The amount of Rizatriptan Benzoate was estimated by using standard calibration curve of the drug. Drug content was studied in triplets for each batch of formulation.

3. Results

3.1 FTIR Analysis: FTIR spectrum of sample was compared with the pure API. Moreover, drug and polymers used to prepare the formulations showed no unusual interactions.

3.2 Melting Point Determination: Melting point of the obtained API was determined by the capillary method which was found to be 179°C, which complied with the standard monograph, indicating the purity of the drug.

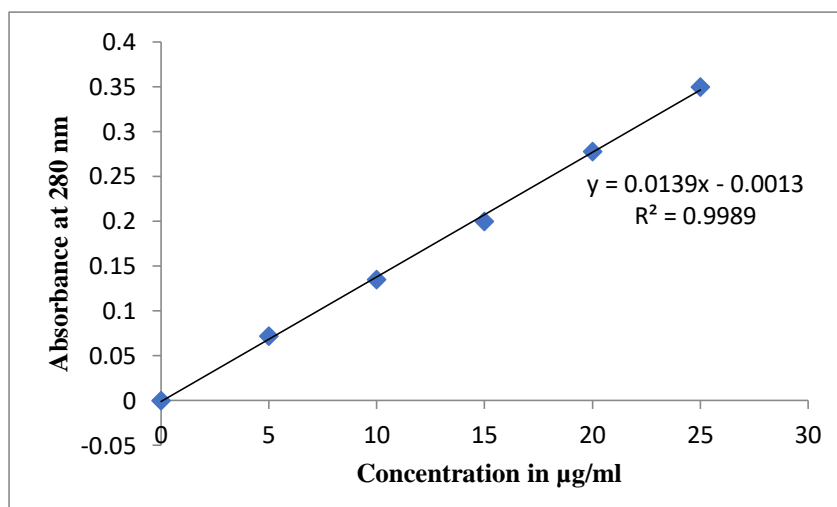
3.3 Solubility Analysis: Rizatriptan benzoate was found to be soluble in water, sparingly soluble in ethanol (96 percent) and slightly soluble in methylene chloride.

3.4 Standard Calibration Curve: Rizatriptan Benzoate obey the Beer’s law in concentration range of 5-25 µg/ml in 0.1 N NaOH with regression coefficient (R^2) of 0.998.

3.5

S.N.	Concentration	Absorbance
1	0	0
2	5	0.072±0.015
3	10	0.135±0.001
4	15	0.200±0.012
5	20	0.278±0.019
6	25	0.350±0.067

Table 4: Absorbance at 280 nm of various concentrations



Graph 1: Calibration Curve of Rizatriptan Benzoate at 280 nm

3.6 Preformulation studies:

Formulation Code	Bulk Density (gm/cm ³)	Tapped Density (gm/cm ³)	Hausner's Ratio	Carr's Index	Angle of Repose (°)
F1	0.313±0.005	0.369±0.008	1.17±0.011	15.17±0.08	28.70±1.21
F2	0.317±0.005	0.360±0.004	1.13±0.009	11.94±0.78	28.39±1.12
F3	0.310±0.003	0.359±0.003	1.15±0.007	13.64±0.07	29.60±1.09
F4	0.309±0.004	0.356±0.001	1.15±0.008	13.20±0.15	28.95±1.11
F5	0.309±0.012	0.360±0.005	1.16±0.004	14.16±0.05	28.07±1.56
F6	0.302±0.007	0.350±0.003	1.15±0.005	13.71±0.03	27.95±0.48
F7	0.305±0.020	0.358±0.002	1.17±0.015	14.80±0.09	29.35±0.05
F8	0.313±0.015	0.360±0.001	1.15±0.017	13.05±0.23	29.29±1.17
F9	0.302±0.001	0.340±0.002	1.12±0.002	11.20±0.16	29.89±1.07

Table 5: Data (mean ± standard deviation) of Preformation studies for each formulation

3.7 Post Compression Studies: The post compression studies were done for all the formulations and shown in the table 6.

- ❖ Shape and Appearance: The prepared tablets were white colored, round flat uncoated tablets having one side break line.
- ❖ Weight Variation Test: Prepared tablets of all formulations were evaluated for weight variation and standard deviations from the average weight were found to be within the prescribed pharmacopoeia limits of ±7.5%.
- ❖ Thickness: Thickness of the prepared tablets were within the limits.
- ❖ Friability Test: All the formulations passed the friability test and were below 1%.
- ❖ Hardness: The tablets were evaluated for the hardness test and found to be within limits between 3 to 4 kg/cm².
- ❖ In vitro disintegration test: The disintegration test for uncoated tablets were met by the developed formulations with the fastest being 21±0.2 seconds.
- ❖ Drug content: Drug content test was within the prescribed limit for the formulations ranging from 97.14±1.2 to 99.29±1.1.
- ❖ In vitro dissolution test: The formulations showed a satisfactory drug release within 12 minutes.

Formulation Code	Weight Variation (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm ²)	Disintegration Time (sec)	Drug Content (%)	% Drug Release
F1	151.20±0.7	2.65±0.03	0.22±0.2	3.5±0.2	41±0.7	98.41±1.5	93.12±0.001
F2	149.95±1.1	2.60±0.6	0.24±0.3	3.5±0.18	35±0.5	98.33±1.2	93.62±0.338
F3	152.32±0.4	2.70±0.1	0.21±0.2	3.5±0.2	32±1.3	97.52±1.3	94.71±0.217
F4	152.45±0.9	2.73±1.7	0.19±0.1	4.0±1.2	27±0.1	97.14±1.2	93.46±1.054
F5	151.36±0.6	2.65±0.04	0.21±0.8	3.5±0.18	24±0.12	98.86±1.5	95.17±1.35
F6	150.78±0.9	2.63±0.17	0.20±0.12	3.5±0.2	21±0.2	99.29±1.1	98.94±0.008
F7	151.95±2.0	2.67±0.9	0.21±0.2	4.0±0.3	83±1.6	98.71±1.4	82.94±1.64
F8	149.59±1.3	2.60±0.02	0.24±1.2	3.0±0.12	77±1.2	98.00±1.2	84.09±1.004

F9	151.29±1.0	2.64±0.7	0.21±0.3	3.5±0.8	64±0.5	98.43±0.5	90.57±0.027
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Table 6: Post compression parameters for various formulation codes.

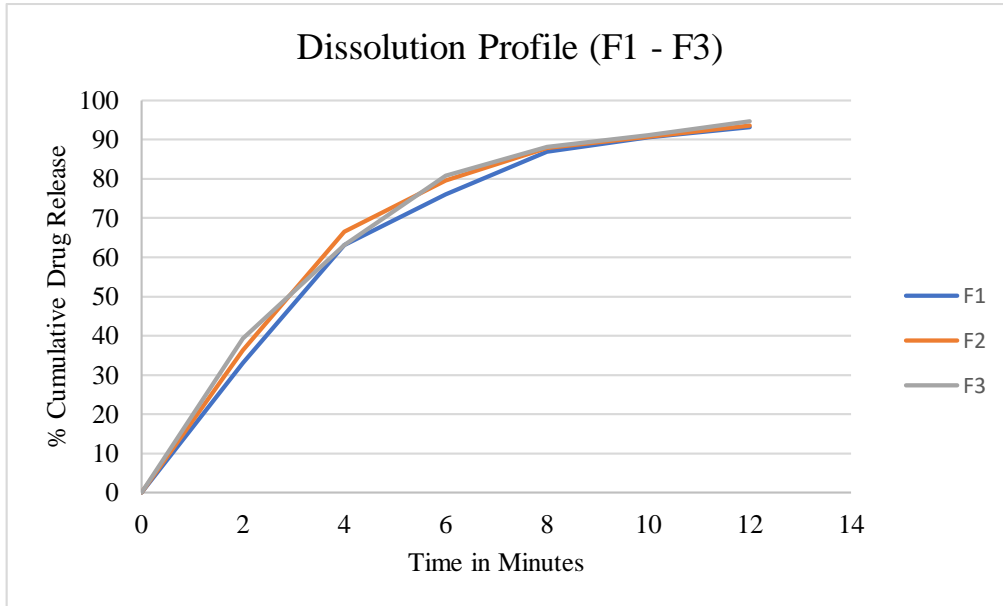
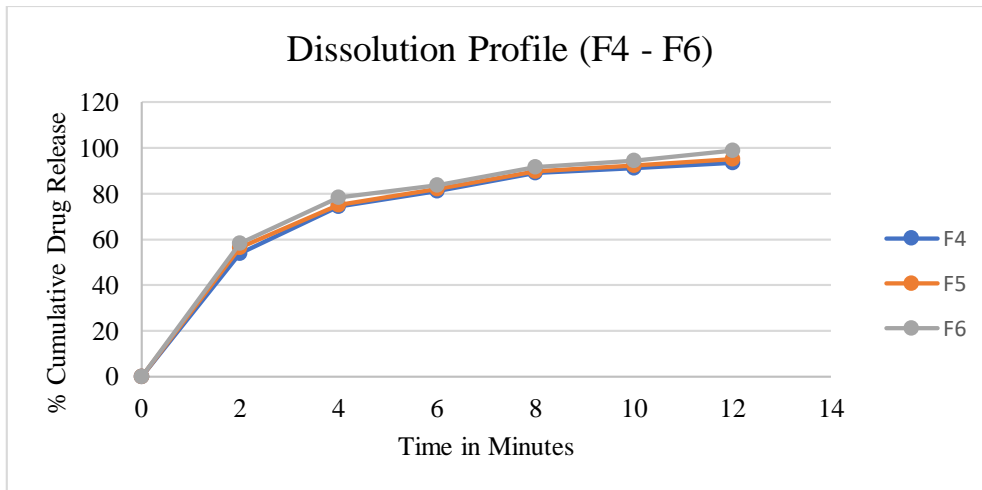
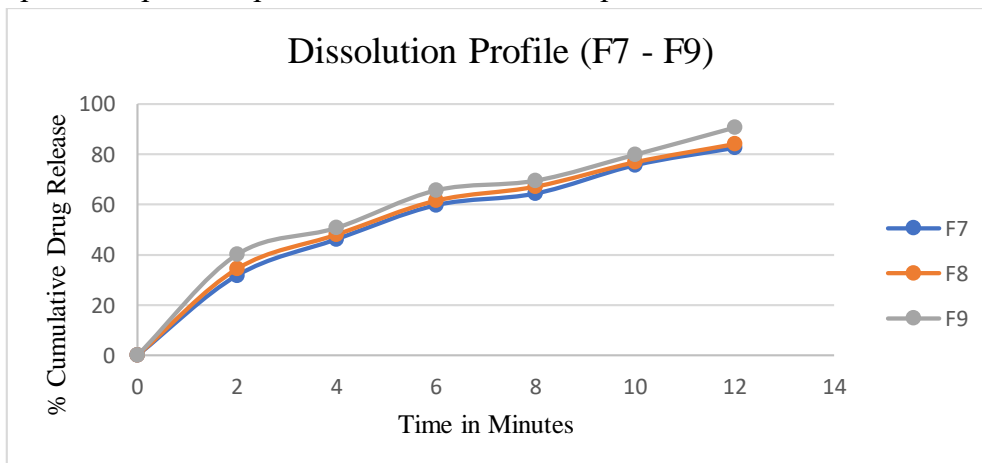


Chart 2: Graphical representation of dissolution profile of first three formulations



Graph 3: Graphical representation of dissolution profile of Formulation 4, 5 and 6.



Graph 4: Graphical representation of dissolution profile of Formulation 7, 8 and 9.

4. Conclusion

An effort was made for the formulation and evaluation of Orodispersible Tablets of Rizatriptan Benzoate using direct compression technique. Natural superdisintegrants were employed with an intention to increase the disintegration time so that the drug can readily go into solution form and gets absorbed. Dehydrated banana powder, mango peel pectin and gellan gum were used as natural superdisintegrants in the ratio of 1: 2: 3. The powder blends were evaluated for the pre-compression evaluation parameters which showed the expected result.

Altogether nine formulations were fabricated using 3^2 factorial designs. F1- F3 contained Mango peel pectin, F4-F6 were developed incorporating Dehydrated Banana powder and the last three formulations were fabricated with Gellan gum. The tablets were round flat white colored without any detectable defects. All the formulations were evaluated in triplicates for post-compression parameters and the result obtained was expressed as Mean \pm Standard Deviation. Furthermore, all the formulations depicted a satisfactory result. Among all the formulation F6 was considered as the optimized formulation as it has superior disintegration time of 21 ± 0.2 seconds meaning that the drug will be rapidly absorbed and showed a release of 98.94 ± 0.008 % at the end of 12 minutes.

For the future perspectives, stability studies and the IVIVC studies can be conducted for the deeper understanding of the current attempt made. All in all, the fabrication of orodispersible tablets of Rizatriptan Benzoate can reduce the unbearable pain of migraine and enhance the patient compliance. In addition, the combination of superdisintegrants might further accelerate the disintegration and release of the drug from the dosage form.

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