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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF RIZATRIPTAN BENZOATE USING DIFFERENT SUPERDISINTEGRANTS

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ABSTRACT

The main objective of this study was to formulate and evaluate the Mouth dissolving tablets of Rizatriptan benzoate with superdisintegrants. In this investigation Mouth dissolving tablets of Rizatriptan benzoate were prepared using different superdisintegrants. A direct compression method was used to formulate mouth dissolving tablet of Rizatriptan benzoate. In study, different superdisintegrant were used such as croscarmellose sodium (CCS), sodium starch glycolate (SSG) and crospovidone (CPVP). The prepared tablets were evaluated for weight variation, drug content, hardness, disintegration time, wetting time, friability, in vitro dissolution study. The drug and excipients compatibility study was performed by FTIR and the study revealed that there was no interaction between drug and excipients. Formulation of crospovidone (5%) F4 shown less disintegration time of 15 seconds than other formulations . The in-vitro drug release of optimized formulation F4 was shown 99.29%.

KEYWORDS : *Rizatriptan benzoate, Wetgranulation, Mouth dissolving tablet, Superdisintegrants.*

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INTRODUCTION

The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. Oral dosage forms are more popular than other dosage forms because of Ease of administration, Accurate dosage, Self- medication, Pain avoidance, Patient compliance.[1] The most popular oral solid dosage forms are tablets and capsules. Tablets are widely accepted because of the convenience in terms of self-administration, compactness, and ease in manufacturing. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. Many elderly was difficulties in taking conventional dosage forms (tablets and capsules) because of their hand tremors and dysphagia. Swallowing problems are

also common in young individuals because of their under developed muscular and nervous system. Other groups, who may experience problems in swallowing solid dosage forms, are the mentally ill, the developmentally disabled, uncooperative patient and reduced liquid intake plans or nausea. Dysphagia is also associated with number of medical conditions including Stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy. In some cases such as motion sickness, sudden episode of allergic attack or coughing and an unavailability of water, the swallowing of tablet or capsules may become difficult.[2,3] Mouth dissolving tablets are also applicable when local action in the mouth is desirable such as local anaesthetic for toothaches, oral ulcers, cold sores, or teething.In order to assist these patients, several fast-dissolving drug delivery systems have been developed.[4]

"Mouth-dissolving tablets are those when put on tongue, disintegrates instantaneously, releasing the drug, which disperses or dissolves in the saliva". On placing mouth-dissolving tablets in the mouth, saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach & it may produce rapid onset of action. In such cases bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.[5]

Rizatriptan Benzoate is an antimigraine agent used in treatment of migraine associated with severe one- sided throbbing headache, which is followed by intense pain.[6] Hence to provide quick action there was a need to develop Mouth dissolving tablets. It is a 5-Hydroxy Tryptamine (1B/1D) [5HT (1B/1D)] receptor agonist. It is 10 times more potent than Sumatriptan, the traditional Anti-migraine drug. Rizatriptan Benzoate is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 45%. This is because of its poor absorption in lower gastrointestinal tract. It undergoes hepatic first pass metabolism and its elimination half-life is 2 to 3 hours.[7,8]

In the present study, an attempt was made to develop fast dissolving tablets of Rizatriptan benzoate so that patients suffering from migraine will get quick relief from headache. The objective of the present work is to develop mouth dissolving tablets of Rizatriptan Benzoate and to study the effect of superdisintegrant on the tablet properties.

MATERIALS AND METHODS

Rizatriptan benzoate was obtained as a gift sample from Alkem Laboratories Ltd., Taloja, Navi Mumbai. Sodium starch glycolate, Crospovidone, Crosscarmellose sodium, mannitol, microcrystalline cellulose, magnesium stearate, Aspartame were purchased from S.D. Fine chemicals Mumbai. All other chemicals & reagents were used of either pharmacoepial or analytical grade.

Preparation of Mouth dissolving tablets of Rizatriptan benzoate.

The critical parameters to formulate a mouth dissolving tablet are choice of superdisintegrant and optimization of concentration of super disintegrant. The main criteria for Mouth dissolving tablets is to disintegrate or dissolve rapidly in oral cavity within few seconds, without need of water and should have pleasant mouthfeel. The superdisintegrant (Crosscarmellose sodium, Crospovidone, Sodium starch glycolate) were used to formulate the tablets. Mouth dissolving tablets of Rizatriptan benzoate were prepared by direct compression method according to the formula given in Table no. 1

Rizatriptan Benzoate was weighed accurately and sifted through #40 mesh. Micro crystalline cellulose and Mannitol were weighed accurately sifted through #40 mesh separately and added individually to the above and mixed for 5 minutes. Aspartame and Mint were weighed accurately and passed through #40 mesh separately and added to the above mixture one after the other and for each addition the

mixture was blended thoroughly for 5 minutes. The Super disintegrants were weighed and sifted through #40 and added to the above mixture and blended for 5 minutes. Magnesium state & aerosil were weighed accurately and sifted through #60 and added to the above blend. The final blend was mixed thoroughly for 2-3 minutes in the poly bag and tablets was compressed using 8.5 mm round shaped punches on single punch tablet compression machine.

Table 1. Formulation of Mouth dissolving tablets of Rizatriptan benzoate

Ingredient	Quantity per tablet (mg)						
	F1	F2	F3	F4	F5	F6	F7
Rizatriptan benzoate	10(14.53)	10(14.53)	10(14.53)	10(14.53)	10(14.53)	10(14.53)	10(14.53)
Microcrystalline cellulose	100	100	100	100	100	100	100
Mannitol	57.47	57.47	57.47	57.47	57.47	57.47	57.47
Crosscarmellose sodium	5	10	15	2.5	-	2.5	-
Crospovidon	5	2.5	-	10	15	2.5	-
Sodium starch glycolate	5	2.5	-	2.5	-	10	15
Aspartame	5	5	5	5	5	5	5
Peppermint	1	1	1	1	1	1	1
Aerosil 200	4	4	4	4	4	4	4
Magnesium stearate	3	3	3	3	3	3	3
Total	200mg	200mg	200mg	200mg	200mg	200mg	200mg

Evaluation of precompression parameters [9,10]

1. Untapped Bulk Density

Powder weighing 10 g was placed into 100 ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and bulk density was calculated by the following equation:

$$\text{Untapped Bulk Density} = \frac{\text{Mass of bulk drug}}{\text{Volume of bulk drug}}$$

The experiment was done in triplicate.

2. Tapped Bulk Density

Powder weighing 10 g was placed into 100 ml measuring cylinder. The cylinder was then subjected to a fixed number of taps (~100 times) until the powder bed volume had reached the minimum level. The final volume was recorded and the tap density was calculated by the following equation:

$$\text{Tapped Bulk Density} = \frac{\text{Mass of bulk drug}}{\text{Volume of bulk drug on tapping}}$$

The experiment was done in triplicate.

3. Compressibility

Compressibility of the drug was found out using the following formula:

$$\% \text{ Compressibility} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

4. Hausner Ratio

Hausner of the drug was found out using the following formula:

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

5. Angle of repose

The angle of repose gives an indication of the flow ability of the substance. Funnel was adjusted such that the stem of the funnel lies 2 cm above the horizontal surface. The drug powder was allowed to flow from the funnel under the gravitational force till the apex of the pile just touched the stem of the funnel, so the height of the pile was taken as 2 cm. drawing a boundary along the circumference of the pile and taking the average of six diameters determined the diameter of the pile. These values of height and diameter were then substituted in the following equation:

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left(\frac{2h}{d}\right)$$

Where, h - Height of the pile and
d - Diameter of the pile.

Table no.2 Results of pre compression parameter

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner Ratio	Angle of repose (θ)
F1	0.470	0.581	18.79	1.23	30.22^0
F2	0.478	0.587	18.56	1.22	31.92^0
F3	0.467	0.569	17.92	1.21	28.61^0
F4	0.474	0.583	18.69	1.23	27.94^0
F5	0.479	0.587	18.39	1.22	32.61^0
F6	0.473	0.582	18.72	1.23	31.38^0
F7	0.475	0.573	17.10	1.20	29.86^0

Evaluation of postcompression parameters [11-13]

Weight variation: Randomly, twenty tablets were selected after direct compression but and the mean weight was determined. None of the tablets should deviate from the average weight by more than ±10%.

Friability: Friabillator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabillator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Wetting time: A piece of tissue paper folded twice was placed in Petri dish. A sample of final tablet was placed in Petri dish (10cm in diameter) containing 10ml simulated saliva pH (Phosphate buffer pH 6.8) at room temperature. The tablet was put on the paper and time required for the complete wetting of tablet was measured. The wetting time is that necessary for the complete wetting of the tablet.

Disintegrating Time: The disintegration test was carried out in an apparatus (Electro lab, Mumbai) 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 °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.

Dissolution study: Dissolution study was carried out by using USP Type II dissolution apparatus. The dissolution was carried out in 900 ml deaerated distilled water dissolution medium. 5ml sample where collected at 5, 10, 15, 20, 30 minutes time intervals and after proper dilution

they were analysed at 280nm against the blank solutions using Shimdzu UV/Visible double beam Spectrophotometer.

Drug content: Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of RZT was dissolved in 100 ml of distilled water, filtered, diluted suitably and analyzed for drug content at 280 nm using UV-Visible spectrophotometer.

Identification of Drug by IR : The IR spectrum of the pure Rizatriptan Benzoate sample recorded by FTIR spectrum is shown in Figure No.1. This was compared with standard functional group frequencies of Rizatriptan Benzoate. The pure rizatriptan benzoate exhibits characteristic peacks at 3410cm^{-1} (O-H stretching) 3120 cm^{-1}(aromatic secondary amine N-H stretching), 3010 cm^{-1}(aromatic C-H stretching), 1600cm^{-1}(C=O five member cyclic stretching), 1258 cm^{-1}(C-N aliphatic amine stretching)(Fig. 4). All these peaks have appeared in rizatriptan formulation (F7) at 3291 cm^{-1}(aromatic secondary amine N-H stretching), 2948cm^{-1}(aromatic C-H stretching), 1608cm^{-1}(C=O five member cyclic stretching), 1281cm^{-1}(C-N aliphatic amine stretching). This indicated that there was no interaction between the Rizatriptan benzoate and excipients.[14]

Fig.No.1.IR Spectra of Rizatriptan Benzoate

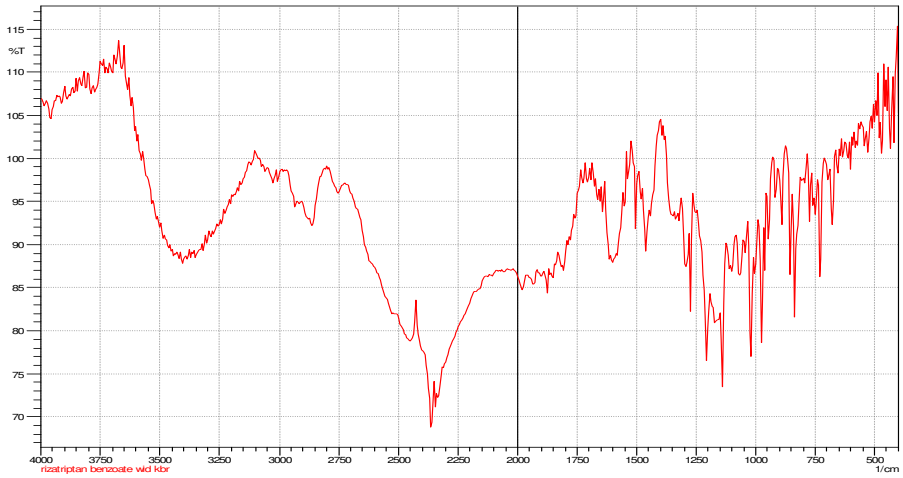


Fig.No.2.IR Spectra of Rizatriptan Benzoate MDT formulation (F7)

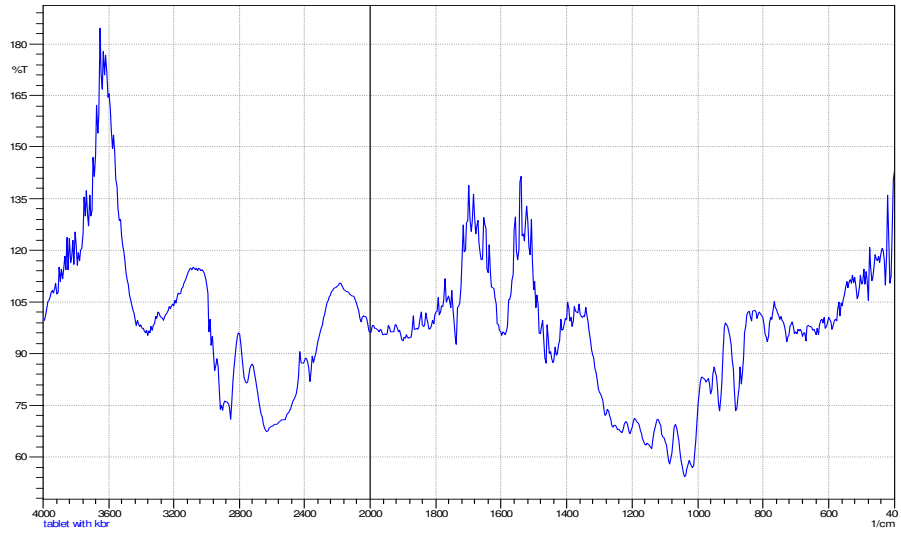


Table No.4. Result of post compression parameter study

Batch No.	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Wetting time (secs)	Disintegration time (secs)	Drug content (%) w/w
F1	3.03	3.8	0.132	40	20	99.29
F2	3.02	4.0	0.199	35	18	98.66
F3	3.01	3.7	0.231	42	23	96.46
F4	3.05	3.9	0.156	48	15	99.41
F5	3.06	4.1	0.213	39	19	98.31
F6	2.98	4.2	0.173	34	16	99.65
F7	3.01	4.0	0.153	41	21	95.32

Table No.5. In vitro dissolution profile data for F1 to F7 formulations

Time (hrs)	% Drug Release						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	36.89	38.94	39.65	42.36	40.35	40.65	40.54
10	54.28	56.32	59.78	58.95	53.61	52.39	56.92
15	75.64	82.53	83.64	84.26	85.27	79.39	78.65
20	85.34	89.26	90.25	92.25	90.25	88.94	89.35
30	93.21	94.32	96.28	99.27	95.23	94.83	96.45

Figure No.3 :In vitro dissolution Profile of Rizatriptan Benzoate Mouth Dissolving Tablet.

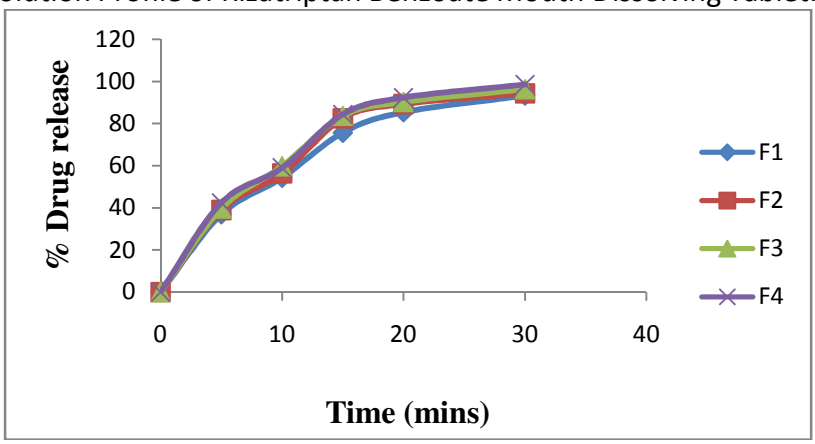
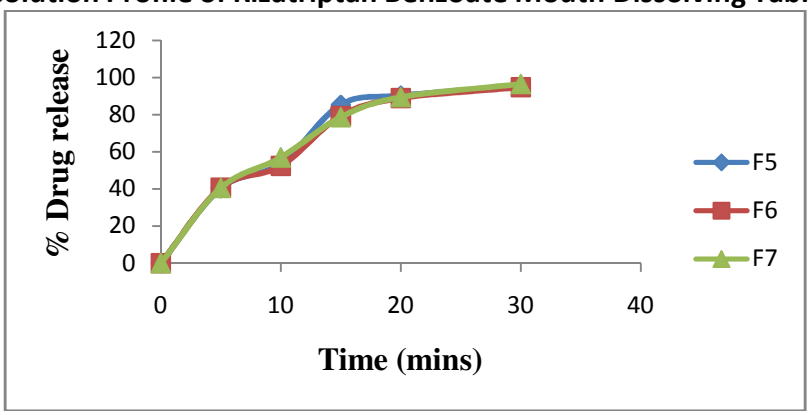


Figure No.4 :In vitro dissolution Profile of Rizatriptan Benzoate Mouth Dissolving Tablet.



RESULT AND DISCUSSION

In present study, Rizatriptan Benzoate Mouth dissolving tablet were prepared by using various superdisintegrants, e.g. Cross povidone. Crosscarmellose sodium, Sodium starch glycolate. Total seven batches of tablets, F1-F7 were prepared by wet granulation method using water as a binder.

Results of the precompression parameter evaluated were within prescribed limits and indicated good free flowing property which is described in table no.3.

The data obtained from all the post compression parameter evaluated are such as thickness, hardness, friability, weight variation, drug content, wetting time, and disintegration time are shown in table no.4 The hardness was found in the range of 3- 4.5kg/cm^2 in all the formulation indicating good mechanical strength having a capability to withstand physical and mechanical stress condition while handling and transportation. The data of FT-IR study showed no interaction between drug & excipients as shown in Figure 1&2.

All of the 7 formulations were having friability values less than one which meets with the IP limits. The tablets obtained had drug contents in the range of 98 to 100%. This is within the acceptable limit. All the tablets passed weight variation test as the % weight variation was within Pharmacopeial limit. The result of *in vitro* wetting time and disintegration time of the entire tablet were found to be within prescribed limit.

Overall all the formulation of Rizatriptan benzoate showed a good drug release but among all formulations F4 showed maximum drug release at the end of 30 mins.

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