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Research Article

Formulation and Evaluation of Rizatriptan Benzoate Orodispersible Tablets

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ABSTRACT

Oral disintegrating tablets have emerged as an alternative to the conventional oral dosage forms to improve the patient compliance. Due to problem in swallowing ability with age, the paediatric and geriatric patients complain of difficulty to take conventional solid dosage forms. The ODT's are solid dosage forms that dissolve or disintegrate rapidly in the oral cavity. This results in solution or suspension without the need of water. The main objective of this work is to formulate and evaluate Rizatriptan Benzoate ODT's using different concentration of super disintegrating agents like croscarmellose, Sodium Starch Glycolate (SSG), Crospovidone, Yellow potato starch. In this study uses different concentrations of diluents like Spry Dried Lactose, Avicel, Mannitol to optimize diluents concentration. After optimizing diluents concentration the study is continued by using different super disintegrating agents. Tablets were prepared by direct compression method and evaluated for hardness, thickness, friability, disintegration time, and percentage of drug release. The results indicated that formulation prepared with Crospovidone and Avicel: Mannitol (30:70) was found to be optimised which provides maximum drug release(100%) and minimum disintegration time (less than 10 second).

Key-words: Rizatriptan Benzoate, Oral disintegrating tablets, superdisintegrant, croscarmellose,Sodium Starch Glycolate, Crospovidone.

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INTRODUCTION

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. As a result children, bedridden patients and elderly patients have difficulty in swallowing these dosage forms. To overcome these drawback novel drug delivery systems like orally disintegrating tablets have been developed which disintegrate/dissolve/disperse in saliva within few seconds without water. United States of America Food and Drug Administration (USFDA) define ODT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue"[1].

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations. It provides the convenience of a tablet formulation, and also allowing the ease of swallowing provided by the liquid formulation[1]. The various technologies used to prepare ODT's include direct compression, sublimation, tablet moulding, spray drying, freeze drying and mass extrusion[2-4].

The new generation anti-migraine drug, 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[5]. Chemically it is 3-[2-(dimethylamino) ethyl]-5-(1H-1, 2, 4-triazol-1-ylmethyl) indoleonobenzoate. A 10mg dose of Rizatriptan benzoate is equipotent to a 100 mg of Sumatriptan, the traditional antimigraine drug. The bioavailability of Rizatriptan benzoate is about 45% which is superior to a poor 14-17% of Sumatriptan. On the basis of these considerations, in the present study it was proposed to formulate an oral delivery device, in the form of rapidly disintegrating tablets by using direct compression technology, with the aim of rapid disintegration and a complete drug release in a short period of time. The main effect and the interactions of disintegrants on dispersion time and drug release were studied.

MATERIALS AND METHODS:

Rizatriptan Benzoate was obtained as gift sample from Divis Laboratories Ltd. Vizag. Croscarmellose, Crospovidone and Sodium Starch Glycolate (SSG) where obtained from s.d fine chemicals. All chemicals used were of analytical grade.

PRE COMPRESSION PARAMETERS:

Bulk Density

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

Bulk density = weight of sample / Volume of packed

The experiment was repeated for three times.

Tapped Density

Granular powder weighing 10g was placed in 100ml measuring cylinder. The cylinder was then subjected for the fixed number of taps (≈100) until the powder bed has reached the minimum. The final volume was recorded and the tap density was calculated by the following equation.

True density = Mass of bulk sample / Volume of bulk drug on tapping

The experiment was repeated for three times.

Carr's Index

Carr's percent compressibility was calculated for granules prepared by using the equation

$$[\delta \text{ tap} - \delta \text{ bul} / \delta \text{ tap}] \times 100$$

Where,tap= Tapped density or True density bul = Bulk density.

Hausner ratio

Tapped density and bulk density were determined and the Hausner ratio was calculated by the following formula,

Hausner ratio = δ tap / δ bul

Where, δ tap= Tapped density or True density, δ bul = Bulk density.

Angle of repose

It is the maximum angle that can be obtained between the free standing surface of the granule heap and the horizontal plane. The angle of repose can be calculated by the following formula[6-8].

tanθ = h / r OR

θ= tan- h/r

Where, θ = Angle of repose, h = height of the pile, r = radius of plane surface occupy by the powder

Preparation of orally disintegrating tablets:

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. Sodium chloride, Glycine, Aspartame and Mint were weighed accurately and passed through #60 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 disintegrantCrospovidone was weighed and sifted through #40 and added to the above mixture and blended for 5 minutes. Magnesium sterate was weighed accurately and sifted through #40 and added to the above blend.The final blend was mixed thoroughly for 2-3 minutes in the poly bag and tablets were compressed using 7 mm round flat shaped punches.

Table1: Formulation Development

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Dizatriptan Benzoate	10	10	10	10	10	10	10
Lactose	50.47	_	_	_	_	_	-
Avicel PH 102	_	70	90	50.47	50.47	50.47	50.47
Mannitol	90	70	50.47	90	90	90	90
Crospovidone XL	10	10	10	10	—	_	-
Croscarmellose	_	_	_	_	10	_	-
Sodium starch glycolate	_	_	_	_	_	10	-
Yellow Potato Starch	_	_	_	_	_	_	10
STARCH							
Glycine	23	23.47	23	23	23	23	23
Sodium Chloride	5	5	5	5	5	5	5
Aspartame	4	4	4	4	4	4	4
Mint flavour	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200	200

EVALUATION OF TABLETS [9- 12]

Thickness:

Thickness was determined for twenty pre-weighed tablets of each batch using a digital venire scale (Mitutoyo- Digi) and the average thickness was determined in mm**.** The tablet thickness should be controlled within a ± 5% variation of a standard.

Hardness

Hardness or crushing strength is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a

compressible spring. The pointer moving along the gauze in the barrel at which the tablet fractures indicates the hardness of the tablet. Six tablets from each batch were taken randomly and their hardness was determined.

Friability
This test is performed to evaluate the ability of a tablet to withstand abrasion in packing, handling and transporting purpose. Twenty sample tablets were rotated at 25rpm for 4 minutes by a USP-type Roche friabilator, then reweighed after removal of fines and the percentage weight loss was calculated according to the following formula. The tablets were found to pass the friability test, if the percentage weight loss was found to be less than 1%.

% Friability= $(W_0-W)/W_0 \times 100$
Where W_0=initial weight of twenty tablets
W= weight of 20 tablets after 100 revolutions

Disintegrating Time
The disintegration test is 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. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 sec.

Dissolution study
Dissolution study was carried out by using USP Type II dissolution apparatus. The dissolution was carried out in pH 7.2 buffer solution as dissolution medium. 5ml sample where collected at 5, 10, 15,20,25,30 and 45 minutes time intervals and after proper dilution they were analyzed at 280nm against the blank pH 7.2 buffer solutions using an Eli co UV Double beam Spectrophotometer.

Stability studies[12]
The optimized formulation was subjected for stability studies at accelerated conditions of a temperature 400 C and a relative humidity of 75% and at 0,10,20 and 30 days for their physical appearance, hardness, disintegration time, drug content, friability, thickness and %drug release.

Results and discussion
Oral disintegrating tablets RizatriptanBenzoate,were prepared by direct compression method using Croscarmellose ,Crospovidone, Sodium Starch Glycolate (SSG) And Yellow Potato Starch as super disintegrants in different concentration. Seven formulations were prepared.The powder blend of seven formulations F1 to F7 was evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio, which showed the pre-compressed blend, has good flow property. The results are shown in [Table 2].
The values of different physical tests are given in [Table 3]. The tablets obtained had drug contents in the range of 98 to 100%. This is within the acceptable limit. Hardness of tablet was found in the range of 3.10 to 3.45 kg/cm^2. Friability was found to be below 1% which indicates good mechanical strength of the tablets. All the formulations found to have much faster wetting time when compared to the control with significant increase in the water absorption capacity. The disintegration time (DT) for the formulation prepared with Sodium Starch glycolate, Croscarmellose and crospovidone was found to be in the range of 10-14 second. Among all the formulations F4 were showing promising results as the DT was 10 second.

In-vitro drug release studies were performed with all formulations. The results are accordinglytabulated in [Table 4] [Fig 1, 2]. The percentage drug release for the formulation F4 was found 100% respectively at the end of 15 minutes. Formulation F4 prepared with crospovidone was found to be the optimized formulation than other formulations.

The optimized formulation F4 were selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation [Table 5].

Table: 2 Evaluation of Directly Compressible Blend

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)
F1	0.378	0.477	20-26	1.25	33.92°
F2	0.407	0.528	16.91	1.31	31.25°
F3	0.419	0.555	18.50	1.32	32.61°
F4	0.461	0.596	17.97	1.26	30.61°
F5	0.467	0.529	15.76	1.19	28.42°
F6	0.438	0.513	14.61	1.17	26.25°
F7	0.48	0.53	12.08	1.023	31°

Table: 3 Evaluations of Compressed Formulations

Formulation code	Average weight(mg)	Thickness (mm)	Hardness (Kp)	Percentage friability (%)	Disintegration time (sec)
F1	203.0	3.21	1.09	1.56	13
F2	197.6	3.10	1.30	0.69	14
F3	200.0	3.41	2.86	0.16	12
F4	198.4	3.45	1.75	0.35	11
F5	198.0	3.37	2.21	0.17	13
F6	200.2	3.16	2.92	0.12	10
F7	200.4	4.00	2.88	0.15	12

Table: 4 Cumulative percentage drug release of Rizatriptan Benzoate

Time(min)	F 1	F 2	F 3	F4	F5	F6	F7	Marketed product
0	0	0	0	0	0	0	0	0
5	85.3	84.4	85.2	85.5	87.6	88.5	81.4	90.4
10	89.1	92.4	94.6	90.6	92.9	98.71	90.88	97.6
15	93.2	95.5	98.6	96.3	98.0	101.4	96.2	100.9

Conclusion

On the basis of evolutionary result of precompression and post compression studies of all the formulation, we conclude that all the technological / evolutionary parameters of mouth dissolving tablet of Rizatriptan Benzoate with various superdisintegrants. Among that the crosspovidone is having the better disintegrating property.

Table 5: Accelerated Stability studies of the optimized batch at 40oC/75%RH

S.No	Parameters	Initial	15 days	30 days
1	Average weight of Tablet (mg)	200.2	200.3	200.3
2	Thickness (mm)	3.35	3.35	3.35
3	Hardness (kp)	3.2	3.3	3.3
4	Friability (%)	0.38	0.37	0.38
5	Disintegration time	10	10	9
6	Drug content (%)	101	102	101
7	%Drug release(at 15 sec)	102.3	100	100.2

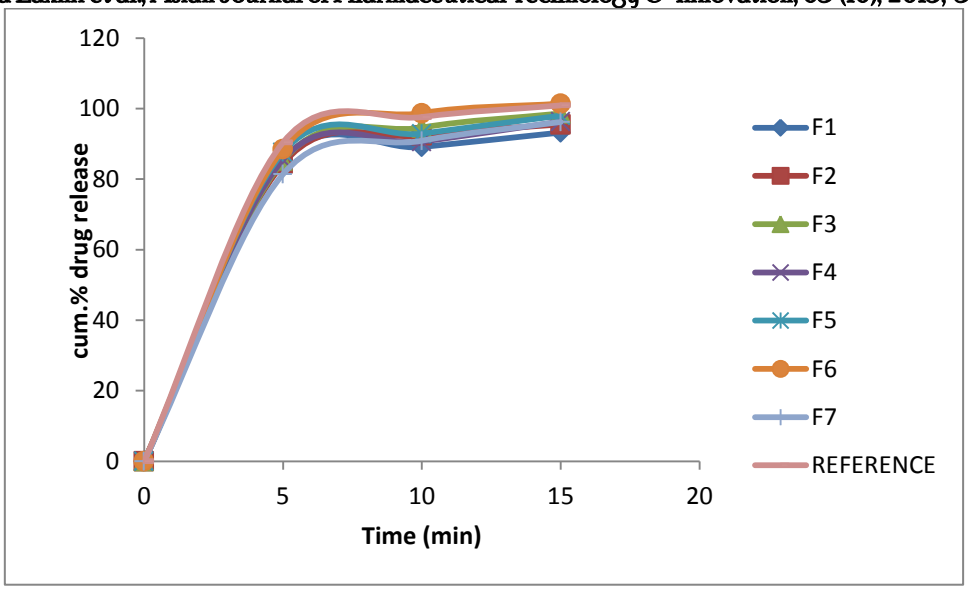

Figure: 1 Dissolution profile (F1-F6) along with marketed product

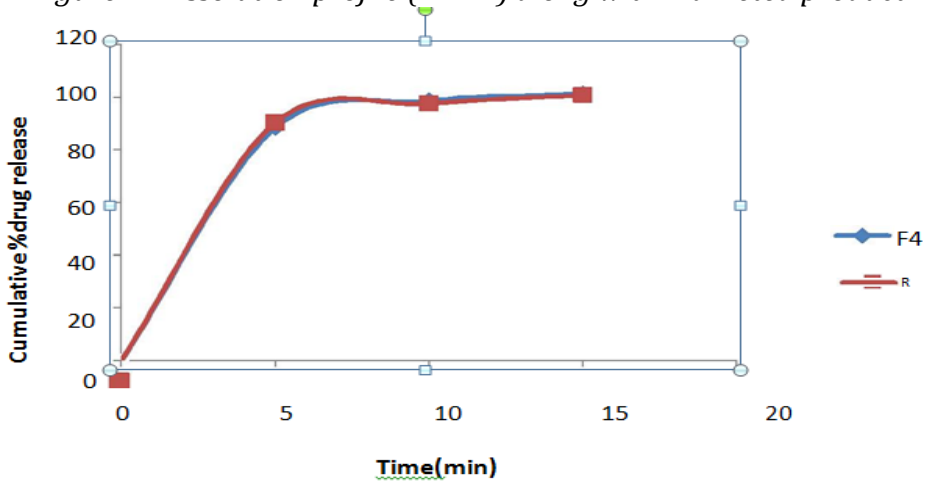

Figure: 2 Dissolution profile of F4 and Marketed product (R)

Figure: 2 Dissolution profile of F4 and Marketed product (R)

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