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Formulation and evaluation of Rizatriptan Benzoate Orally Disintegrating Tablets

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Abstract
Formulation research is oriented towards safety, efficacy and quick onset of action of existing drug molecule through novel concepts of drug delivery. Orally disintegrating tablets of Rizatriptan benzoate were prepared by direct compression method to provide faster relief from pain to migraine sufferers. About twelve formulations for the present study were carried out based on 2 level 2 factor full factorial design for each set of superdisintegrants. Croscarmellose sodium, Crospovidone and Sodium starch glycolate (SSG) were used as superdisintegrants, while microcrystalline cellulose was used as diluent. The prepared batches of tablets were evaluated for weight variation, hardness, friability, wetting time, *invitro* dispersion time, drug content and *invitro* dissolution studies. The formulation containing combination of Croscarmellose sodium and Sodium starch glycolate showed rapid *invitro* dispersion time as compared to other formulations. The optimized formulation dispersed in 8 seconds. It also showed a higher water absorption ratio and 99.58% of drug is released within 2 minutes.

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Key words:
Orally disintegrating tablets, Superdisintegrants, Rizatriptan benzoate, Factorial design technique, Direct compression.

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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 this 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-hydroxy tryptamine $_{1B/1D}$ 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) indole onobenzoate. 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. In this study, effort has been made to prepare different formulations based on 2^2 full factorial design for each set of super disintegrants at their two levels viz., higher and lower concentrations. The main effect and the interactions of disintegrants on dispersion time and drug release were studied.

MATERIALS AND METHODS:

Rizatriptan Benzoate was obtained as a gift sample from Matrix laboratories Ltd, hyd. Crospovidone, Croscarmellose sodium, Sodium starch glycolate and other excipients were obtained as a gift sample from Orchid laboratories, Chennai. All other chemicals used were of analytical grade.

Formulation Designing

2^n factorial design technique [6] was used for formulation designing. In this "2" is factor i.e. combination of two super disintegrants at a time and "n" indicates level i.e. higher and lower concentration (table1). Twelve formulations were designed. Sodium starch glycolate [7] was used in concentration of 2 % & 8 %, crospovidone 2 % & 4 % and croscarmellose sodium 1 % & 3 %. Microcrystalline cellulose [7] was used as diluents, which is also a super disintegrant. Each formulation was composed of drug and excipients in various proportions as shown in table 2.

Preparation of Mixed Blend of Drug and Excipients

All ingredients were passed through 40# mesh and then the required quantities were weighed, uniformly blended and compressed using a single punch tablet compression machine.

Table 1: Formulation Designing:

Formulation no.	SSG	Crospovidone
1	-	-
2	+	-
3	-	+
4	+	+
	Cross Povidone	Cross Carmellose
5	-	-
6	-	+
7	+	-
8	+	+
	SSG	Cross Carmellose
9	-	-
10	+	+
11	+	-
12	+	+

Here "+" sign indicates high concentration and "-" sign indicates low concentration.

Table 2: Formulation of Rizatriptan Benzoate Orally Disintegrating Tablets by Direct compression method

Sl No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Rizatriptan Benzoate	10	10	10	10	10	10	10	10	10	10	10	10
2	Sodium starch glycolate	2	8	2	8	–	–	–	–	2	2	8	8
3	Cross povidone	2	2	4	4	2	2	4	4	–	–	–	–
4	Crosscarmellose sodium	–	–	–	–	1	3	1	3	1	3	1	3
5	Mannitol	10	10	10	10	10	10	10	10	10	10	10	10
6	Aerosil	1	1	1	1	1	1	1	1	1	1	1	1
7	Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
9	Flavours	2	2	2	2	2	2	2	2	2	2	2	2
10	MCC	69.5	63.5	67.5	61.5	70.5	68.5	68.5	66.5	70.5	68.5	64.5	62.5
Tablet wt(mg)		100	100	100	100	100	100	100	100	100	100	100	100

Evaluation Parameters of Orally Disintegrating Tablets

Weight variation test [8]

Weight variation test was done by weighing 20 tablets individually, by using analytical balance. Calculating the average weight and comparing the individual tablet weight to the average weight.

Tablet thickness [8]

The thickness was measured by placing tablet between two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness [8]

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability [8]

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (Wo) are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

Wetting time [9]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water- containing Eosin, a water soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water absorption ratio (%) [10]

A piece of tissue paper folded twice was placed in a small petridish (Internal Diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following equation.

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where, Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after water absorption.

***In vitro* disintegration test** [6]

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37°C ± 2°C was used as a disintegration media and the time in seconds taken for complete disintegration of the

tablet with no palable mass remaining in the apparatus was measured.

***In vitro* dispersion time** [11]

Tablet was added to 10 ml of phosphate buffe r solution (pH 6.8) at 37 ± 0.5°C. Time required for complete dispersion of a tablet was measured.

***In-vitro* dissolution study** [12]

The release rate of Rizatriptan benzoate from orally disintegrating tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl pH 1.2 as a dissolution medium, at 37±0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 3, 4, 5, 10, 20 and 30 min. The samples were filtered through a 0.45 membrane filter. Absorbance of these solutions was measured at 280 nm using a Shimadzu UV-1700 UV/VIS spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Twelve formulations were designed, using higher and lower level of super disintegrants and employing combination of two super disintegrants and employing combination of two super disintegrants at a time (Table 1). Crospovidone, croscarmellose sodium and sodium starch glycolate were used as super disintegrants while microcrystalline cellulose was used as diluents, which is a superdisintegrant. For each designed formulation, blend of drug and excipients were prepared and evaluated for precompression parameters. The results indicate good flow properties of the blend.

Tablets were prepared by direct compression technique. As the material was free flowing, tablets of all formulations were obtained of uniform weight due to uniform die fill, complied with pharmacopoeia limits. Hardness of tablets of formulations is kept within 3-4 kg /cm^2. Friability of the formulations were below 1.0% was an indication of good mechanical resistance of tablets. When assayed Drug content was found to be 95-105% which is within acceptable limits.

Table 3: Evaluation of directly compressible orally disintegrating tablets

S. l	Test	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Wt.variation (%)	4.00	3.50	4.00	4.50	3.00	3.50	4.00	5.00	4.50	3.50	3.0	3.0
2	Hardness (kg/cm2)	3.5	3.4	3.5	3.5	3.2	3.4	3.60	3.5	3.4	3.4	3.6	3.6
3	Friability(%)	0.45	0.42	0.4	0.35	0.5	0.4	0.45	0.35	0.35	0.5	0.4	0.4
4	Thickness(mm)	Cxvfdgdffa 3.23	3.14	3.20	3.19	3.15	3.20	3.23	3.15	3.21	3.23	3.22	3.1
5	Wetting time (s)	30	20	18	18	25	15	25	10	20	23	17	15
6	Water absorption ratio(%)	70.2	73.1	79.4	84.9	71.4	75.6	86.3	92.3	82.4	90.4	86.4	92.9
7	Disintegration time(s)	45	23	21	18	58	32	17	13	22	11	14	11
8	*Invitro* dispersion time(s)	40	20	18	18	55	30	15	10	20	8	10	8
9	Assay	98.2	98.5	98.3	99.2	98.5	99.4	98.9	100	99.8	99.5	99.6	99.4

Water absorption ratio which is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water, was calculated and was in the range of 70 to 93%. For all designed formulations amount of drug released after 5th was above 95%, while about conventional marketed tablet require about 30 minutes for the same amount of drug to be released. *Invitro*

dispersion time was 8 to 20 seconds for formulations containing combination of sodium starch glycolate and croscarmellose sodium. Amount of drug released after *invitro* dispersion of tablet was determined.

High level of crospovidone increase in concentration of sodium starch glycolate had no effect on dispersion time on ODT. Nevertheless at low level of crospovidone increase in concentration of sodium starch glycolate had a negative effect, decreases the dispersion time. When a combination of crospovidone and croscarmellose sodium was tried we identified that they had an interaction between them as evident from figure 3. ODT containing 3% croscarmellose sodium and 4% crospovidone showed the lowest dispersion time (10s). croscarmellose sodium, when tried in combination with sodium starch glycolate showed a negative effect on *invitro* dispersion time at lower levels of sodium starch glycolate and only a slight effect at higher levels of sodium starch glycolate.

Formulation (F12) containing (3%) croscarmellose sodium and (8%) sodium starch glycolate showed the lowest *invitro* dispersion time of 8s. Among all the twelve formulations, confirming it to be the optimum combination of super disintegrants. The same formulation showed short wetting time and larger water absorption ratio.

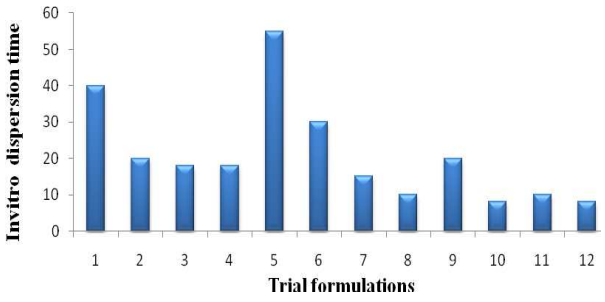

Figure: 1 *Invitro* dispersion time of all formulations

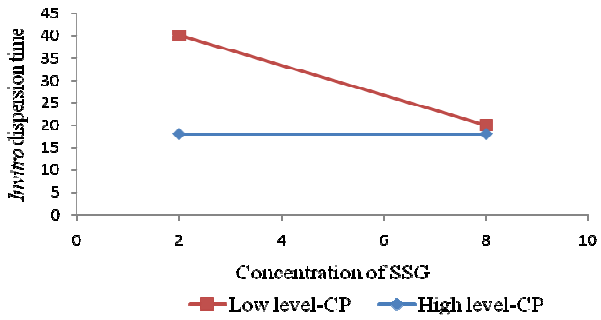

Figure 2: Combination of Sodium starch glycolate & Crospovidone at high & low level

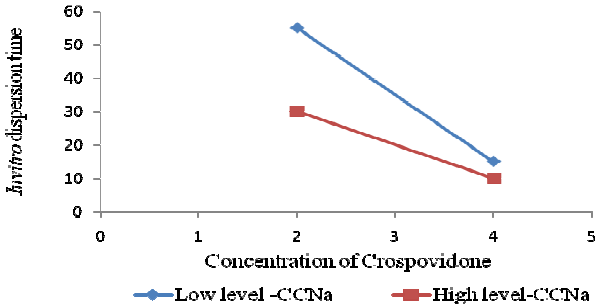

Figure 3: Combination of Croscarmellose sodium & Crospovidone at high & low levels

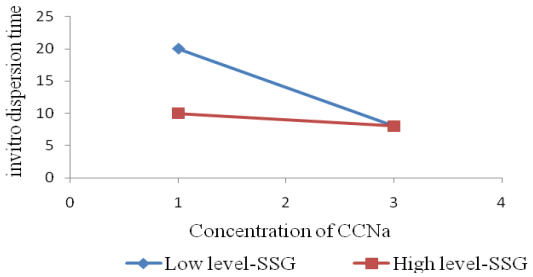

Figure 4: Combination of Croscarmellose sodium & Sodium starch glycolate at high & low level.

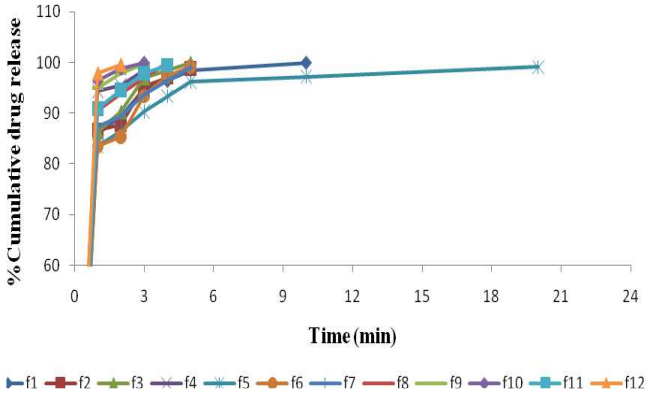

Fig: 5 Cumulative drug releases of all formulations

Table 4: Cumulative drug release of all formulations

S. No	Time (min)	ODT1	ODT2	ODT3	ODT4	ODT5	ODT6	ODT7	ODT8	ODT9	ODT10	ODT 11	ODT 12
1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	85.86	86.65	86.32	94.42	83.43	83.50	87.30	90.46	94.89	96.46	90.87	97.85
3	2	89.49	87.78	90.3	95.46	86.40	85.36	89.40	93.89	97.93	98.84	94.60	99.58
4	3	94.71	95.24	96.9	98.42	90.30	93.39	93.60	96.98	99.78	99.95	97.89	--
5	4	96.4	97.04	98.46	--	93.34	97.30	96.46	99.87	--	--	99.43	--
6	5	98.52	98.85	99.9	--	96.22	99.23	98.97	--	--	--	--	--
7	10	99.98	--	--	--	97.24	--	--	--	--	--	--	--
8	20	--	--	--	--	99.12	--	--	--	--	--	--	--
9	30	--	--	--	--	--	--	--	--	----	--	--	--

CONCLUSION:

The goal of the present investigation was to identify the optimum combination of superdisintegrants for the development of orally disintegrating tablets of Rizatriptan benzoate. Three superdisintegrants viz., crospovidone, croscarmellose sodium and sodium starch glycolate were tried. 2^2 full factorial design was used for a set of two superdisintegrants and totally twelve formulations were made by direct compression method and evaluated for their hardness, friability and the key parameters like *invitro* dispersion time, wetting time and water absortion ratio. Factorial design had facilitated the study and helped in understanding the interaction between superdisintegrants when used in combinations. 3%croscarmellose sodium and 8% sodium starch glyocolate (F12) was identified as the optimum combination of super disintegrants based on *invitro* dispersion time, wetting time and water absorption ratio.

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