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Original Article

COMPARATIVE STUDY ON EFFECT OF NATURAL AND SYNTHETIC SUPERDISINTEGRANTS IN THE FORMULATION OF RIZATRIPTAN BENZOATE ORAL DISPERSIBLE TABLETS

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ABSTRACT

Objective: In the present study, the effects of a natural superdisintegrant gellan gum, karya synthetic gum superdisintegrants like sodium starch glycolate, crospovidone and combination of natural and synthetic superdisintegrant were compared in the formulations of rizatriptan benzoate oral dispersible tablets.

Methods: This oral dispersible tablets were prepared by direct compression method and evaluated for weight variation, hardness, disintegration time, drug content, friability and dissolution. Drug compatibility with excipients was checked by FTIR studies. Stability study of the prepared tablets was done at 40±2°/75%±5% RH for a period of 1 mo.

Results: FTIR studies showed that no any chemical interaction between drugs and excipients. The *in vitro* drug release study revealed that formulation F9 combination of both crospovidone and karya gum was the most successful formulation and disintegrate time within 13 seconds and drug release within 10 min. The drug release from the best formulations followed first-order kinetics, which is concentration-dependent. Short terms stability studies of the tablet for three months showed non-significant drug loss.

Conclusion: The formulation containing a combination of natural and synthetic superdisintegrant was found to be the best results. Apart from fulfilling all official and other specifications, the tablets exhibited a higher rate of drug release.

Keywords: Orally dispersible tablets, Natural and synthetic superdisintegrants, Rizatriptan benzoate

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INTRODUCTION

Nowadays, or dispersible drug delivery systems are comprehensively used to expand bioavailability and patient compliance. Over the past three years, or dispersible tablets (ODTs) have gained considerable attention as a desired substitute to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. ODTs are solid dosage forms containing medicinal substances that disintegrate rapidly, usually within seconds, when placed on the tongue with or without the intake of water [1]. Usually, super disintegrants are added to a drug formulation to simplify the breakup or disintegration of tablet or capsule content into smaller particles that can dissolve more rapidly than in the absence of disintegrants. The faster the dissolution of the drug into the solution, the quicker is the absorption and onset of clinical effect. The bioavailability of certain drugs may increase due to the absorption of drugs in the oral cavity or also due to pregastric absorption of drug from saliva that pass down into the stomach [2]. Drug absorbed via "oral cavity" directly enters into systemic circulation by a jugular vein ensuring, a rapid onset of action, avoidance of the first-pass metabolism, and drug degradation in gastric region and enzymatic hydrolysis in the intestine. The various technologies used to prepare ODT's include direct compression, sublimation, tablet molding, spray drying, freeze-drying and mass extrusion [3].

The new generation anti-migraine drug, rizatriptan benzoate is a potent and selective 5-hydroxyl tryptamine receptor agonist and is considered more effective than the traditional triptans for the treatment of acute migraine attack. Chemically it is 3-[2-(dimethylamino) ethyl]-5-(1H-1, 2, 4-triazol-1-ylmethyl) indole monobenzoate. A 10 mg dose of rizatriptan benzoate is equipotent to a 100 mg of sumatriptan, the traditional ant migraine drug. The bioavailability of rizatriptan benzoate is about 45% which is superior to a poor 14-17% of sumatriptan [4].

The present study is to formulate rizatriptan oral dispersible tablets, by direct compression technique, using the various kinds of super disintegrants (Natural and Synthetic) along with studies of their role in tablet disintegration and dissolution, which are being used in the formulation to provide the safer and effective drug delivery with patient compliance.

MATERIALS AND METHODS

Rizatriptan Benzoate was obtained as a gift sample from Hetro Drug Ltd. Vishakahpatanam. Crospovidone, Sodium starch glycolate, Gellan gum, Karya gum and other excipients were obtained from Indian fine chemicals Mumbai. All other chemicals used were of analytical grade.

Formulation process

Oral dispersible tablets of Rizatriptan Benzoate were prepared by direct compression technique according to the formula given in table 1. The ingredients were sifted through a 20# mesh and then the required quantities weighed. All the ingredients except magnesium stearate and flavoring agents were uniformly blended. After mixing the drug and the excipients for 20 min, magnesium stearate and the flavoring agents were added and further mixed for an additional 2 min [5]. The tablet mixture was then compressed (8 mm diameter, concave punches) using a single punch tablet compression machine (Cadmach).

Preformulation studies

Calibration curve for rizatriptan benzoate

The standard calibration curve graph was obtained by preparing aliquots of standard solution of rizatriptan benzoate in 0.1 N HCl (pH 1.2) and the absorbance at 280 nm was measured after suitable dilution using UV/Visible spectrophotometer [6].

Drug-excipients compatibility studies

FT-IR spectroscopic study was performed to check the compatibility between drug, polymer and other excipients in the formulation. The FT-IR spectra of a drug alone and drug with polymers were obtained by KBr method and compared with the standard FT-IR spectrum of the pure drug.

Table 1: Formulation of an oral dispersible tablet of rizatriptan benzoate

Ingredients	Quantity (mg) present in each tablet											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rizatriptan Benzoate	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27
Sodiumstarch glycolate	7.5	10.5	13.5	—	—	—	—	—	—	7.5	10.5	13.5
Cross povidone	—	—	—	7.5	10.5	13.5	7.5	10.5	13.5	—	—	—
Gellan gum	—	—	—	—	—	—	—	—	—	7.5	10.5	13.5
Karya gum	—	—	—	—	—	—	7.5	10.5	13.5	—	—	—
Mannitol	18	18	18	18	18	18	18	18	18	18	18	18
Magnesium stearate	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42
Sodium Saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil 200	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Micro crystalline celulose101	113.56	110.56	107.56	113.56	110.56	107.56	106.06	100.06	94.06	106.06	100.06	94.06

Note: Defined bulk weight per tablet is 100 mg containing rizatriptan benzoate equivalent to 5 mg of rizatriptan.

Evaluation of pre-compression parameters

Bulk density

Bulk density (ρb) was determined by placing pre sieved drug excipients mixture into a graduated cylinder and measuring the volume (Vb) and weight (M) [7].

$$\rho b = M/Vb$$

Tapped density

The measuring cylinder containing a known quantity of blend was tapped for a fixed number of taps. Theminimum volume (Vt) occupied in the cylinder and theweight (M) of the drug excipients mixture was measured [8]. The tappeddensity (ρt) was calculated using the following formula.

$$\rho t = M/Vt$$

Angle of repose

Angle of repose (α) was determined using funnel method. The drug excipients mixture was poured through a funnel that can be raised vertically until a maximum cone height (*h*) was obtained. The radius of the pile (*r*) was measured and the angle of repose was calculated.

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

Carr's Index

Carr's Index or % compressibility is helpful to determine flow properties of powder mixtures, which is calculated as follows [8]:

$$C = (\rho t - \rho b)/\rho t \text{ X } 100$$

Where,

ρt - Tapped density

ρb - Untapped bulk density

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula.

$$\text{Hausner's ratio} = \rho t \backslash \rho b$$

Where,

ρt - Tapped density

ρb - Untapped bulk density

Post compression parameters

Weight variation test

Weight variation was determined by weighing 20 tablets individually; the average weight and percent variation of each tablet were calculated [9].

Hardness test

Hardness was determined using a Monsanto hardness tester. Three tablets were randomly picked from each batch and hardness is expressed in kg/cm^2. The mean and standard deviation were also calculated.

Thickness of tablets

The thicknesses of the tablets were determined by placing tablet between 2 arms of the Vernier Caliper. Five tablets were taken from each batch and average thickness values were calculated.

Friability of tablets

The friability of the tablets was determined for twenty tablets. Tablets were taken randomly from each batch. After weighing, the tablets were placed in the plastic chamber of the friability tester (Erweka tablets friability tester) for 100 revolutions [10]. The friability is evaluated by the following formula:

$$F = (W1-W2)/W1 \times 100$$

Where,

W1 is the weight of tablets before testing and

W2 is the weight of tablets after testing.

***In vitro* disintegration test**

Disintegration test was studied 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 water maintained at 37±2 °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 experiments were carried out in triplicate from each formulation [11].

Drug content uniformity

For the content uniformity test, ten tablets of each batch were weighed and powdered. Aliquot of this powder containing rizatriptan benzoate equivalent to 10 mg of rizatriptan was accurately weighed, suspended in approximately 100 ml of 0.1 N HCl and shaken for 15 min. Then the solution was filtered by using Whatmann filter paperand 5 ml of the filtrate was suitably diluted to 50 ml with the same buffer and analyzed spectrophotometrically at 280 nm. The amount of rizatriptan benzoate was estimated using the standard calibration curve of the drug. The study was carried out in triplicate for each batch of the formulation [6].

***In vitro* dissolution studies**

In vitro dissolution of rizatriptan benzoate oral dispersible tablets was carried out in USP dissolutiontest apparatus Type II (Labindia, Mumbai) employing a paddle stirrer at 50 rpm using 500 ml of 0.1 N HCl (pH 1.2) at 37±0.5 °C as dissolution medium. One tablet was used

in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 280 nm. The volume withdrawn at each time interval was replaced with 5 ml of fresh dissolution mediumto compensate loss. Cumulative percent of drug released was calculated and plotted against time [12]. The results are shown in fig. 1.

Stability studies

The selected formulation F9 was tested for its stability studies. Short-term stability studies were performed at temperature 40±2 °C over a period of 3 mo. five tablets were packed in amber coloured screw-capped bottles and kept in a stability chamber maintained at 40±2 °C. Samples were taken at 1 mo intervals for their drug content estimation, including physical parameters. At the end of 3 mo' period, the tablets were then evaluated for hardness, friability, *in vitro* disintegration time, wetting time, uniformity of content and assay [13].

RESULTS AND DISCUSSION

FTIR spectroscopic studies indicated that the drug is compatible with all the excipients. Oral dispersible tablets, each containing rizatriptan benzoate equivalent to 5 mg of rizatriptan, were prepared by direct compression method by using gellan gum, karya gum as natural superdisintegrant and sodium starch glycolate, crospovidoneas synthetic superdisintegrants in different ratios, either alone or in combination. Directly compressible excipients, microcrystalline cellulose and mannitol were used as diluents to enhance mouth feel. Aerosil was used as a glidant and magnesium stearate was acting as lubricant. A total of twelve formulations were designed and evaluated for the comparative study of synthetic and natural superdisintegrant (table 1).

Table 2 and table 3represents all the tablet precompression and post compression parameters evaluated. Bulkdensity was found to be between 0.302±0.001 and 0.317±0.005 gm/cm3 and tapped density between 0.370±0.002 and 0.370±0.002 gm/cm3 for all formulations. From density data carr's index was calculated and found to be between 11.20±0.16 and 15.17±0.08 %. Hausner's ratio was found below 1.17. Angle of repose was found to be in the range of 27.15±0.48 and 29.89±1.07°. All the formulation shows thegood blend properties for direct compression and hence tablets were prepared by using direct compression technology.

Table 2: Evaluation of pre-compression parameters

Formulation batch	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F1	0.317±0.005	0.360±0.004	11.94±0.78	1.13±0.009	28.39±1.12
F2	0.302±0.001	0.340±0.002	11.20±0.16	1.12±0.002	29.89±1.07
F3	0.314±0.007	0.366±0.001	14.20±0.04	1.16±0.012	28.30±1.19
F4	0.310±0.003	0.359±0.003	13.64±0.07	1.15±0.007	29.60±1.09
F5	0.316±0.012	0.363±0.002	12.94±0.16	1.14±0.003	28.61±0.08
F6	0.313±0.015	0.360±0.001	13.05±0.23	1.15±0.017	29.29±1.17
F7	0.305±0.020	0.358±0.002	14.80±0.09	1.17±0.015	29.35±0.05
F8	0.302±0.007	0.350±0.003	13.71±0.03	1.15±0.005	27.95±0.48
F9	0.315±0.014	0.370±0.002	14.86±0.02	1.17±0.006	28.52±1.38
F10	0.309±0.012	0.360±0.005	14.16±0.05	1.16±0.004	28.07±1.56
F11	0.313±0.005	0.369±0.008	15.17±0.08	1.17±0.011	28.70±1.21
F12	0.309±0.004	0.356±0.001	13.20±0.15	1.15±0.008	28.95±1.11

Note: All values are expressed as mean±SD. n=3.

The thickness of the prepared tablets was found to be in the range of 2.55±0.02 to 2.73±0.17 mm, while the weight of all the tablets was found to be in the range of 149.59±1.3 to 152.45±1.9 mg. Hardness of the tablets was found to be in the range of 3.0±0.12 to 4.0±0.3 kg/cm and percentage weight loss in the friability test was less than 1% in all the batches, which was an indication of good mechanical resistance of the tablets. The values of tablet hardness and percent friability indicated good handling property of the ODTs.

Drug content was found to be high (≥99.87%) in all the tablet formulations. The tablets containing synthetic and natural superdisintegrants in different ratio showed *in vitro* disintegration time in the following order, combination of Crospovidone and karaya gum>Crospovidone>gellan gum and combination of sodium starch glycolate>sodium starch glycolate. The tablets containing drug, crospovidone and karaya gum ratio1:1.5:1.5 combination showed faster disintegration (13 sec) than tablets containing drug and crospovidone alone ratio 1:3.

Table 3: Evaluation of post compression parameters

Formulation batch	Weight variation (mg) n=10	Hardness (kg/cm^2)	Thickness (mm)	Friability (%) n=10	Drug content (%)	Disintegration time (sec)
F1	151.20±0.7	3.5±0.2	2.65±0.03	0.22±0.2	98.43±1.2	90±0.4
F2	149.95±1.1	4.0±0.3	2.60±0.02	0.24±0.3	97.52±1.3	82±0.8
F3	152.32±0.4	3.5±0.2	2.70±0.12	0.21±0.2	98.43±1.5	70±0.2
F4	152.45±0.9	3.5±0.18	2.55±0.2	0.23±0.18	98.86±1.5	52±0.5
F5	151.36±0.6	3.0±0.12	2.60±0.8	0.20±0.12	99.29±1.1	35±0.5
F6	150.78±0.9	3.5±0.2	2.63±0.17	0.20±0.12	97.14±1.2	15±0.1
F7	151.95±2.0	3.5±0.18	2.60±0.3	0.23±0.18	98.00±1.2	48±1.2
F8	149.59±1.3	3.0±0.5	2.60±0.6	0.24±1.2	98.86±0.7	32±1.3
F9	151.29±1.0	3.0±0.1	2.73±1.7	0.21±0.8	99.87±0.2	13±0.2
F10	152.35±0.7	4.0±1.2	2.65±0.7	0.19±0.1	98.71±1.4	83±1.6
F11	151.34±1.4	3.5±1.0	2.67±0.9	0.21±0.2	98.43±0.5	77±1.2
F12	152.34±0.4	3.5±0.8	2.70±0.1	0.21±0.3	97.72.±0.9	64±0.5

Note: All values are expressed as mean±SD. n=3

The effect of superdisintegrants on the dissolution of rizatriptan from the ODTs tablets is shown as table 4. *In vitro* dissolution study on a best formulation (F9) exposed that more than 99.6% drug was released within 12 min and followed by formulation F6 crospovidone showed 96.25% within 12 min. From this dissolution, studies confirmed that the drug release increased to increase in the concentration of crospovidone.

Table 4: Cumulative drug release of the all formulation

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
2	27.40	32.34	34.34	50.14	56.17	55.77	53.72	56.41	60.35	28.44	32.62	45.00
4	33.04	38.26	39.54	62.26	61.28	81.45	66.30	64.02	79.10	32.40	39.34	52.48
6	38.46	43.46	43.80	68.42	69.52	85.22	74.80	72.009	81.24	36.04	42.88	59.50
8	42.12	49.22	48.00	71.28	76.96	88.87	82.35	80.37	84.78	42.16	49.36	64.22
10	46.06	53.70	52.36	78.60	88.09	94.14	86.08	88.97	94.53	48.82	50.10	68.30
12	53.64	58.92	58.48	81.66	91.70	96.25	91.29	92.59	99.69	52.26	58.32	72.38
14	59.22	62.54	62.12	93.18	93.76	--	93.37	96.23	--	58.98	60.42	78.66
16	63.46	68.36	68.52	95.26	97.39	--	95.46	--	--	62.32	67.84	80.25
18	69.46	72.82	73.48	95.78	--	--	--	--	--	69.18	71.44	84.46
20	71.82	79.57	79.86	97.87	--	--	--	--	--	70.15	78.62	89.58
22	77.23	87.91	80.81	--	--	--	--	--	--	78.30	83.47	93.17
24	83.34	88.40	89.13	--	--	--	--	--	--	83.48	89.99	98.07
26	89.21	93.62	92.76	--	--	--	--	--	--	89.11	90.74	--
28	92.43	98.62	96.42	--	--	--	--	--	--	92.69	92.81	--
30	97.95	--	--	--			--	--	--	96.29	98.47	--

From the stability studies, it was clear that the formulations were physically and chemically stable for three months. And there was no significant change in the physical parameters, drug content and *In vitro* dissolution release profiles (table 5).

Table 5: Stability study of formulation F9 at 40 °C/75% RH

Parameters	Results
Hardness (kg/cm^2)	3.0±0.21
Weight variation (mg)	151.03±0.09
Friability (%)	0.23±0.01
Thickness (mm)	2.72±0.01
Drug content (%)	99.56±0.19
Disintegration time (sec.)	13±0.02
Dissolution at 12 min (%)	98.99

CONCLUSION

From the present study, it can be concluded that a combination of natural and synthetic super disintegrates like *karaya gum and crospovidone* showed better disintegrating property than the most widely used synthetic super disintegrants like sodium starch glycolate and in the formulations of ODTs. These super disintegrating agents are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non-irritating, nontoxic in nature and biodegradable.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

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CONFLICT OF INTERESTS

Declared none

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