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Formulation development and evaluation of orally disintegrating tablets rizatriptan benzoate

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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 eleven formulations for the present study were carried out. 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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Introduction

Oral Disintegrating Tablets (ODTs) [1,2] are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. The marketed drug of Rizatriptan is available under the brand name Maxalt-MLT25 in 5 mg and 10 mg strengths. Maxalt-MLT is prepared using freeze drying technique which is very cumbersome process and costly. Further the product obtained is very brittle which requires special attention during packing and removal from the pack. So, the aim of the present study is to develop better formulation of Rizatriptan that is having good stability using a cost effective process.

Rizatriptan Benzoate is an Anti migraine drug that is white to off white crystalline solid. Migraine [3,4] is a specific and common form of headache that has been known since antiquity. It is traditionally called as vascular headache due to the belief that it is due to abnormal changes in the blood vessel tone. The symptoms of a migraine may include throbbing or dull aching pain on one or both sides of the head nausea, vomiting, diarrhea, blurred vision or blind spots, anxious or restlessness, light headedness, tender scalp, cold hands and feet. The therapeutic activity of Rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT1B/1D receptors on the extra

cerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system thus causing vaso constriction and inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways and thus subsequent relief of migraine headache is seen.

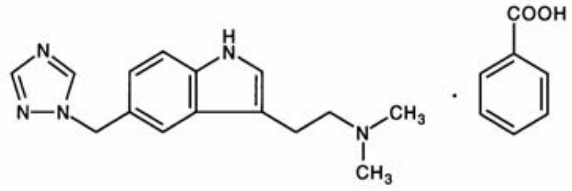

Figure 01: chemical structure of Rizatriptan Benzoate

Experimental work [5-6]

Materials and methods

Rizatriptan Benzoate USP , as a gift sample from Matrix laboratories Ltd, hyd. Lactose Spray Dried, Avicel ph 102 , Pearlitol SD 200 , Crosspovidone XL ,Cross carmellose sodiumSodium Starch Glycolate , Aspartame , Mint cream flavor , Magnesium stearate are purchased from Signet chemical corporation Mumbai. All other chemicals used were of analytical grade.

Methods

Preformulation study can divide in to two Subclasses.

1. API characterization,
2. Compatibility study

Manufacturing Process

Formulation of oral disintegrating tablets of Rizatriptan 5 mg and 10mg were carried out by direct compression technique.

Formulation Development For 5mg Tablets

Table 01: Formulation development for 5 mg tablets

S.NO	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Rizatriptan Benzoate	7.26	7.26	7.26	7.26	7.26	7.26	7.26	7.26	7.26	7.26	7.26
2	Spray dried Lactose	25.19	_	_	_	_	_	_	_	_	_	_
3	Avicel pH102	_	41.99	58.79	25.19	25.19	25.19	25.49	24.89	25.38	25.01	33.59
4	Pearlitol 200 SD	58.79	41.99	5.19	58.79	58.79	58.79	59.49	58.09	59.23	58.35	50.38
5	Cross povidone	5	5	5	5	_	_	4	6	5	5	5
6	Cross carmellose sodium	–	–	–	–	5	–	–	–	–	–	–
7	Sodium starch glycollate	–	–	–	–	–	5	–	–	–	–	–
8	Aspartame	2	2	2	2	2	2	2	2	2	2	2
9	Peppermint flavour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	0.62	1.87	1.25
	Total weight(mg)	100	100	100	100	100	100	100	100	100	100	100

Formulation Development For 10 mg Tablets

Table 02: Formulation development for 10 mg tablets

S.NO	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
2	Spray dried Lactose	50.39	–	–	–	–	–	–	–	–	–	–
3	Avicel pH102	_	83.98	117.57	50.39	50.39	50.39	50.99	49.79	50.76	50.01	50.39
4	Pearlitol 200SD	117.57	83.98	50.39	117.57	117.57	117.57	118.97	116.17	118.45	116.70	117.57
5	Cross povidone	10	10	10	10	_	_	8	12	10	10	10
6	Cross carmel-lose sodium	–	–	–	–	10	–	–	–	–	–	–
7	Sodium starch glycollate	–	–	–	–	–	10	–	–	–	–	–
8	Aspartame	4	4	4	4	4	4	4	4	4	4	4
9	Peppermint flavor	1	1	1	1	1	1	1	1	1	1	1
10	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	1.25	3.75	2.5
	Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200

1. **API Characterization**

Organoleptic evaluation
Loss on drying
Particle size analysis:
Angle of repose
Bulk density
Tapped density
Compressibility index
Hausner ratio
Solubility studies

Characterisation Of Rizatriptan Benzoate USP [7]

Characterisation Of Rizatriptan Benzoate Usp [7]

Table 03: Characterization of Rizatriptan benzoate

Test	Result	Specification
Description	Crystalline white powder.	Crystalline white to off white powder.
Solubility	Complies to the test	to be soluble in water and methanol
Bulk density (g/ml)	0.43	0.38-0.69
tapped density (g/ml)	0.82	0.74-0.93
Loss on drying (%)	0.12	NMT 0.5
Assay (%)	99.8	NLT 99.0& NMT 101.0
Residue on ignition	0.03	NMT 0.1

(%w/w)		
Benzoic acid (chemical)(%)	31.3	NLT 30.8&NMT 31.5
Particle size(microns)	30.4	NLT 50
Melting point(⁰C)	178	NLT 178&NMT 180

Solublity Studies

Table 04: Solubility studies of Rizatriptan benzoate

S.No.	Media	Solublity For 5mg Tablets (Mg/Ml)	Solublity For 10mg Tablets (Mg/Ml)
1	purified water	0.03	0.06
2	pH1.2 buffer	0.03	0.06
3	pH4.5 acetate buffer	0.03	0.06
4	pH6.8 phos-phate buffer	0.03	0.06

Results of Precompression Parameters

Table 05: Precompression results of blend

S.NO	Formu-lation Code	Bulk den-sity (g/ml)	Tapped den-sity (g/ml)	Carr's in-dex	Hausners ratio	Angle of re-pose (θ)
1	F1	0.58	0.79	26.58	1.36	25
2	F2	0.68	0.76	13.1	1.11	26
3	F3	0.67	0.78	12.8	1.16	28
4	F4	0.59	0.65	9.2	1.10	24
5	F5	0.62	0.70	11.4	1.12	27
6	F6	0.59	0.66	10.6	1.11	25
7	F7	0.63	0.71	11.2	1.12	27
8	F8	0.66	0.73	9.5	1.10	24
9	F9	0.66	0.74	10.8	1.12	32
10	F10	0.58	0.64	9.37	1.10	23
11	F11	0.60	0.66	9.0	1.10	23

Drug Excipient Compatiblity Studies Of Rizatriptan ODT's

Table 06: Drug Excipient compatibility studies

Ingredient	Ra-tio	Description	
		INITIAL	FI-NAL 40⁰ ± 2⁰C / 75% ±5 % RH(4 weeks)
Rizatriptan benzoate	1	white powder	No change
Spray dried Lactose	1	White powder	No change
Avicel Ph 102	1	white crystal-line pow-der	No change
Pearlitol 200 SD	1	white crystal-line pow-der	No change
Cross povidone	1	white crystal-line pow-der	No change
Cross carmellose sodium	1	white powder	No change
Sodium starch gly-collate	1	White powder	No change
Aspartame	1	white powder	No change
Peppermint flavor	1	white powder	No change
Magnesium stearate	1	white powder	No change
Rizatriptan benzo-ate+spray dried lac-tose	1:20	white powder	No change

Rizatriptan benzoate+avicel pH102	1:20	White crystalline powder	No change
Rizatriptan benzoate+ Pearlitol 200 SD	1:20	White crystalline powder	No change
Rizatriptan benzoate+cross povidone	1:2	White cryst powder	No change
Rizatriptan benzoate+cross carmellose sodium	1:2	White powder	No change
Rizatriptan benzoate+sodium starch glycollate	1:2	White powder	No change
Rizatriptan benzoate+aspartame	1:0.5	white powder	No change
Rizatriptan benzoate+peppermint flavor	1:0.5	White powder	No change
Rizatriptan benzoate+ magnesium stearate	1:0.5	White powder	No change

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 (W0) 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 tissuepaper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water absorption ratio (%) [10-11]

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 dissolution study [12-14]

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±0.5ºC 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.

Post Compression Parameters Of 5 Mg Tablets

Table 0 7: Physical parameters of 5 mg tablets

Formulation Code	Average weight (mg	Thickness (mm)	Hardness (kp)	Percentage Friability	Disintegration Time (sec)	Wetting time(sec)

	)			(%)		
F1	100.1	2.78	1.09	1.32	18	12
F2	100.2	3.12	2.01	0.19	19	11
F3	100.0	2.97	1.75	0.35	10	8
F4	100.0	2.83	1.73	0.38	9	6
F5	99.8	3.01	1.75	0.37	14	10
F6	100.1	2.88	1.76	0.36	18	11
F7	100.3	2.68	1.73	0.37	12	8
F8	100.0	2.79	1.73	0.38	9	6
F9	99.7	2.75	1.71	0.42	10	7
F10	99.9	2.81	1.76	0.34	11	7
F11	99.9	2.81	1.74	0.38	9	6

Post Compression Parameters Of 10 Mg Tablets

Table 08: Physical parameters of 10 mg tablets

Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kp)	Percentage Friability (%)	Disintegration Time (sec)	Wetting time(sec)
F1	199.23	2.97	1.12	1.29	22	14
F2	200.01	3.01	2.08	0.21	21	13
F3	200.03	2.89	1.77	0.36	12	9
F4	199.89	2.94	1.75	0.38	11	7
F5	200.01	3.01	1.78	0.43	15	12
F6	200.12	2.99	1.80	0.42	20	14
F7	199.98	3.03	1.76	0.40	14	9
F8	200.00	3.00	1.75	0.39	10	7
F9	200.02	3.01	1.74	0.39	12	7
F10	200.00	2.98	1.79	0.35	11	8
F11	200.00	2.95	1.74	0.34	11	7

Dissolution Studies For Rizatriptan ODT

Cumulative % drug release of 5 mg tablets

Table 09: Cumulative % drug release of 5 mg tablets

S.NO	TIME (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	0	0	0	0	0	0	0	0	0	0	0	0
2	5	88.9	89.3	90.0	89.8	89.2	88.9	89.5	89.9	89.5	89.8	90.0
3	10	95.2	95.9	96.2	97.1	96.8	96.3	96.8	97.3	97.1	97.2	97.5
4	15	98.8	99.1	99.6	100.2	99.6	99.3	99.8	100.1	99.9	100.0	100.1

Table 10: Cumulative% drug release of 10 mg tablets

Time (min)	MAXALT	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	2	2	2	2	2	2	2	2	2	2	2	2
5	0.99	1.103	1.021	1.004	0.995	1.004	1.029	1.012	1.008	1.012	1.004	1.008
10	0.612	0.740	0.59	0.612	0.431	0.491	0.591	0.505	0.414	0.477	0.447	0.380
15	-1	0	-0.09	-0.52	-	-0.698	-0.154	-1	-	-0.522	-1	-

Cumulative% drug release of 10 mg tablets

Table 10″ Cumulative% drug release of 10 mg tablets

S.No	Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	0	0	0	0	0	0	0	0	0	0	0	0
2	5	88.9	89.5	89.9	90.1	89.9	89.3	89.7	90.0	89.6	89.9	89.8
3	10	95.5	96.1	96.0	97.3	96.9	96.1	96.8	97.4	97.0	97.2	97.6
4	15	99.0	99.2	99.6	1001	99.8	99.3	99.9	1002	99.9	1000	1000.2

Log % drug remained of 5 mg tablet

Table 11: log% drug remained of 5 mg tablets

S.No	Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	0	0	0	0	0	0	0	0	0	0	0	0
2	5	88.9	89.5	89.9	90.1	89.9	89.3	89.7	90.0	89.6	89.9	89.8
3	10	95.5	96.1	96.0	97.3	96.9	96.1	96.8	97.4	97.0	97.2	97.6
4	15	99.0	99.2	99.6	1001	99.8	99.3	99.9	1002	99.9	1000	1000.2

Log % drug remained of 10 mg tablet

Table: 12 log % drug remained of 10 mg **tablets**

Time (Min)	MAXALT	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	2	2	2	2	2	2	2	2	2	2	2	2
5	0.995	1.11	1.02	0.995	1.008	1.0033	1.0045	1.0021	1.0112	1.0117	1.008	1
10	0.633	0.76	0.61	0.6025	0.4622	0.5055	0.5568	0.5055	0.4311	0.4622	0.4477	0.3977
15	-0.52	0.0799	-0.04	-0.2211	-	-0.3977	-0,1154	-0.69	-	-1	-	-

Results Of Stability Data For 5 Mg Tablets

Table 13: Stability study data for 5 mg tablets

Parameters Tested	Storage Conditions			
	INITIAL	$40^0C \pm 2^0C$ / 75% ±5% RH		
		1st Month	2nd Month	3rd Month
Description	White round tablets embossed with 5 on one side and plain on the other side.	No change	No change	No change
Average weight (mg)	100.56	100.54	100.56	100.59
Thickness (mm)	2.81	2.81	2.81	2.82
Hardness (kp)	1.74	1.74	1.74	1.75
% Friability	0.38	0.39	0.38	0.38
Disintegration time (sec)	9	9	9	10
Water content (%)	1.253	1.252	1.249	1.250

Results Of Stability Data For 10 Mg Tablets

Table 14: Stability study data for 10 mg tablets

Parameters Tested	Storage Conditions			
	INITIAL	$40^0C \pm 2^0C$ / 75% ±5% RH		
		1st Month	2nd Month	3rd Month
Description	White round tablets embossed with 10 on one side and plain on the other side.	No change	No change	No change
Average weight (mg)	200	201	201	202
Thickness (mm)	2.95	2.95	2.95	2.96
Hardness (kp)	1.74	1.74	1.73	1.74
% Friability	0.34	0.34	0.35	0.35
Disintegration time (sec)	10	11	10	10
Water content (%)	1.253	1.252	1.249	1.250

Summary and Conclusion

The purpose of the present study was to develop and characterize a generic product of RizatriptanOral disintegrating tablets of strength 5 mg and 10 mg; comparable to the brand product MAXALT-MLT(Merck. co. INC, USA).

To accomplish the objective, API characterization and reference product evaluation was carried out. The drug and excipients were subjected to preformulation studies which encompasses the "Drug-Excipient" compatibility. Direct compression technique was choosen to develop a finished pharmaceutical product of the envisaged form. Various formulation trials (F1-F11) were taken. In these trials, Drug: Excipient ratio was varied and the effect of Diluent, Superdisintegrant and lubricant on the performance of both blend as well as tablets was studied. Based on the results obtained it was concluded that the formulation F11, the reproducibility batch of F4 was finalized as the optimized formula. The final trial F11 was reproduced from formulation F4 to check various tablet parameters like Thickness (2.8-3.2)mm; Hardness (1.5-1.80)kp; Percentage Friability (<1%) and Disintegra-

tion time (<30 seconds), which were within the specified limits. The Dissolution and Assay results of F4 and F11 were good when compared with the reference product. Moisture uptake studies for the final batch F11 were performed at 43, 64 and 75% RH and there was a slight moisture uptake observed in tablets at 75% RH. The reproducibility batch F11 was loaded for long term and accelerated stability studies at 25 ± 2C/60±5% RH and 40±2C/75±5% RH respectively.. The results of stability data for 1st, 2nd month and 3rd months (40±2C/75±5% RH) were found to be good.

When subjected to accelerated stability studies the tablets were found to be stable. Thus, the work resulted in the development of a ODT of Rizatriptan comparable to inventors product.

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