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Research Article

FORMULARION AND EVALUATION OF ORODISPERSIBLE TABLETS OF RIZATRIPTAN BENZOATE

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ABSTRACT

The present investigation was carried out to develop Orodispersible tablet dosage form of class III drug, Rizatriptan Benzoate. The Tablets were prepared by using different excipients. Drug–Excipient compatibility study of Rizatriptan Benzoate with different categories of excipients was carried out and the result shows impurity level with some drug and excipient combination increases and also slight changes in appearance, all were compatible with Rizatriptan benzoate. The pH dependent solubility study carried out and shows solubility of Rizatriptan Benzoate was more in pH 4.5, i.e. 89.68 mg/ml Therefore, water was used as dissolution medium. The flow properties of pure drug shows poor flow. So, it was decided to overcome this problem API mix well with diluent which was done by Direct compression technique using Aerosil as glident to import good flow as well as compressibility. In the initial trials drug content uniformity found outside limit but, after that each trials drug contents ranging from 98% - 101.2% which is within the range of 92.5 – 105% for Rizatriptan. It indicates uniform distribution of drug in the tablets of each formulation. The Rizatriptan Benzoate Orodispersible Tablets were subjected to *in vitro* drug release studies in water for 30 min. The drug release studies carried out all trials dissolution profile of 3 trials i.e. Trail - 02, Trial - 05, Trial - 13 matches with innovator in water medium. Only Trial – 13 matches with three media with innovator. trial – 13 shows F2 – value 87.60 in water medium and when it subjected to pH 4.5 acetate buffer and D.M. Water media it shows F2 – values 89.68 respectively. This value indications trial – 13 shows good release profile in all media. So it was chosen as final formulation. Exposure studies were carried out of selected trial and result shows similar behavior between our trial and innovator in different conditions. The stability studies of final trial was done for 3 months by packing in HDPE container. All parameters of formulation including physical parameters, impurity profile, content uniformity or dissolution profile were within specification limit. So it indicates optimized formulation were stable. Worst case study for final formulation was performing to optimize the critical stages during the formulation process. In this case dry mixing, lubrication of compression force were considered as critical stages which may cause problem if the set parameters vary so. By considering that thing out final formulation be optimized by varying different parameters in there critical stages. Dry mixing challenge did by using 3 big batches of change in different mixing time i.e. 10min, 20 min and 30 min in 5.0 liter Blender at 25°C/55% RH condition. It is found in al three conditions after taking samples from different location in blender that at 10 min mixing was not very satisfactory that which required 20 min and 30 min mixing time shows satisfactory content uniformity of drug so, our dry mixing time was 30min. In compression force challenge study at three different compression forces was done. The dissolution profiles for all three conditions were found to be satisfactory.

Keywords: Rizatriptan Benzoate, Orodispersible tablet.

INTRODUCTION

Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc, are disintegrating and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within less than 60 seconds tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition.
Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

i. As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients. 1-4
ii. No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.
iii. Easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients)
iv. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. 5
v. Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.
vi. Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased. 6-8
vii. Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.9

MATERIALS AND METHODS

MATERIALS

Rizatriptan benzoate was obtained from Alkem Research centre, India as gift samples. All the other excipients, solvents, reagents and chemicals used were of either Pharamcopoeial or analytical grade

Preformulation Studies

Preformulation testing is the first step in the development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.
The overall objective of Preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produce.
Preformulation study can divided into two subclasses:

Compatibility study

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Active pharmaceutical ingredient (API) characterization

Organoleptic evaluation

These are preliminary characteristics of any substance, which is useful in identification of specific material. Physical properties of API like Color, Taste, odour.

Loss on drying

0.5g of sample of Rizatriptan Benzoate was accurately weighed and the powder was kept in a Mettler Toledo apparatus for 5 min. at 105ºC and the moisture content was calculated.

Solubility Analysis

A semi quantitative determination of solubility can be made by adding a solute in small incremental amounts to fixed volume of solvents whose pH ranging from 1.2 to 7.4 including distilled water. After

each addition, the system is vigorously shaken and examined usually for any undissolved particles. When some solute remains undissolved the total amount added up to that point serves as a good and rapid estimate of solid.

Table 1: Trials 01 to 04 for rizatriptan benzoate tablet 10 mg by wet granulation

Sr. No.	Ingredients	Trial No			
		Trial-01	Trial-02	Trial-03	Trial-04
Intragranular		**Quantity Per Tablet (mg)**			
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53
2	Pearlitol SD200	42.47	142.47	62.97	75.97
3	Calcium Silicate	---	---	---	8.9
4	Kollidone CL	3.0	3.0	20	20
5	Lycatab C	---	---	19	19
6	Aspartame	4.0	4.0	---	---
7	Water	q.s	q.s	q.s	q.s
Extragranular					
8	Avicel pH 102	25	25	25	25
9	Pearlitol SD200	100	---	---	---
10	Kollidone CL	3	3	20	20
11	Calcium Silicate	---	---	---	8.5
12	Aspartame	4	4	5.5	5.5
13	Peppermint	1	1	1	1
14	Magnesium Stearate	3	3	2	2
Tablet Weight (mg)		200	200	200	200

Table 2: Trials 05 to 08 for rizatriptan benzoate tablet 10 mg by wet granulation

Sr. No.	Ingredients	Trial no.			
		Trial-05	**Trial-06**	**Trial-07**	**Trial-08**
Intragranular		**Quantity Per Tablet (mg)**			
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53
2	Pearlitol SD200	93.47	93.47	72.65	15.0
3	Sodium chloride	---	---	1.75	1.75
4	Calcium Silicate	4.25	---	---	---
5	Kollidone CL	30	30	15	---
6	Glycine	---	4.25	---	---
7	Water	**q.s**	**q.s**	**q.s**	**q.s**
Extragranular					
8	Avicel pH 102	25	25	---	11
9	Pearlitol SD200	---	---	61.205	42.47
10	Kollidone CL	20	20	15	---
11	Glycine	---	4.25	2.5	2.5
12	Calcium Silicate	4.25	---	---	---
13	Citric Acid	---	---	1.75	1.75
14	Ac-di-sol	---	---	7.50	7.50
15	Aspartame	5.5	5.5	2	2
16	Peppermint	1	1	0.50	0.50
17	Magnesium Stearate	2	2	1	1
Tablet Weight (mg)		200	200	200	100

Table 3: Trials 09 to 14 for rizatriptan benzoate tablet 10 mg by wet granulation

Sr. No.	Ingredients	Trial No.					
		Trial-09	Trial-10	Trial-11	Trial-12	Trial-13	Trial-14
Intragranular		Quantity Per Tablet (mg)					
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53
2	Avicel pH102	118.47	25.6	25.6	---	25.6	---
3	Pearlitol SD200	54	147.41	156.41	68.47	133.44	68.47
4	Sodium chloride	---	---	---	2.5	2	1.75
5	Glycine	---	---	---	2.5	2.45	2.50
6	Aspartame	10	10	---	2	5	2
7	Citric Acid	---	---	---	---	---	1.75
8	Trisodium citrate	---	---	---	2.5	---	---
9	Ac-di-sol	---	---	---	6	10	7.50
10	Aerosil	---	---	---	---	3.52	---
11	Peppermint	1	---	1	0.5	1	0.50
12	Magnesium Stearate	2	3	3	1	3	1
Tablet Weight (mg)		200	200	200	100	200	100

API Calculation

Rizatriptan (mg/Tab)
14.53mg Rizatriptan Benzoate~10mg Rizatriptan
Strength * 100*100*/Assay (100- Water Content)
= 14.53*100*100/99.8(100-0.29)
=14.57mg

Evaluation of Tablet

Pre-compression Parameters

- Loss on drying. (Dry mix and final blend)
- Density analysis.
- Compressibility Index and Hauser's ratio.
- Sieve analysis.
- Angle of repose.

These parameters are determined using the same procedure as described previously in preformulation study.

Exposure Study

Exposure study was done for finding the degradation pathways of drug formulation by exposing formulation to stress conditions like 80°C temperature for 2 days & in Autoclave for 15 min. at 121°C after these tests formulation was compared with Innovator formulation which was also kept in same conditions. If any measurable difference seen then that formulation, was rejected otherwise selected.

Stability Study

Stability study was done by exposing the formulation to different conditions including stress conditions of temperature & pressure. Generally stability study was done at 40°C/75%RH (for 1,2,3,6 months), 30°C/75%RH (for 1,2,3,6,9,12,24 months), 2-8°C (1,2,3,6,9,12,24 months). After that study was over formulation was checked for its physical & chemical parameters, if all parameters were present within the specification limit then that formulation was selected.

Worst Case Study

Worst case study was done for optimizing the final process of formulation by changing different processing variables which seems to be critical. In our formulation, dry mixing time, granulation time, compression force was selected as critical steps.

Dry mixing Challenge

For this study we took 3 batches of big size i.e. 5000 tablets. Each batch was subject to dry mixing in Rapid Mixing Granulator at impeller speed 150 RPM for 5min, 10min & 15min. respectively. After mixing take out samples of dry mix material at 10 different positions & test these samples for content uniformity. Batch which shows less weight variation in ascending order of time of mixing was selected. Environmental condition should be same for all 3 batches during study was going on.

Granulation Challenge

For this study we take 3 batches of big size i.e. 5000 tablets. Each batch was subject to granulation in Rapid Mixing Granulator with impeller at speed 150 RPM for 3min, 5min & 10min. respectively & with chopper at speed 2500 RPM for 3 min, 7min, 11min respectively. After granulation their all micromeritics, in process as well as dissolution test was done for all three batches. Batch which shows good flow property, physical stability & better drug release profile was selected. Environmental condition should be same for all 3 batches during study was going on.

Compression Force Challenge

In this study same batch was subjected to different compression forces at same machine speed & same environmental conditions. Take tablet batches with hardness 25-35N, 35-45N & 45-55N. All the in process parameters & dissolution profile were checked. Batch which shows good dissolution profile was selected.

EXPERIMENTAL OBSERVATIONS

Table 4: pH Dependant Solubility Study of API (Rizatriptan Benzoate)

Medium	Solubility (mg/ml)
Purified Water	43.13
0.1 N Hcl	21.98
0.01 N Hcl	46.17
0.001 N Hcl	42.75
pH 4.5 acetate buffer	51.24
pH 5.5 Phosphate buffer	45.55
pH 6.8 Phosphate buffer	44.48
pH 7.4 Phosphate buffer	43.75

Table 5: Powder Flow Characterization of API (Rizatriptan Benzoate)

Parameters	Observations
Angle of Repose	Not Detected
Bulk Density	0.44g/ml
Tapped Density	0.67g/ml
Hauser's ratio	1.522
Compressibility Index	34.32%
LOD	-1.52%

Table 6: US food & Drug Administration approve by Dissolution method for the Rizatriptan Benzoate Orodispersible tablet{Orolly disintegration}

US Apparatus	II (paddle)
Speed	R.P.Ms 50
Medium	Water (deaerated)
Volume	900ml
Sampling times(minutes)	5,10,15&30

Table 7: Pre Compression Parameters of All Trials 01 to 14

Trial No.	Loss on drying (%w/w)		Bulk density (gm/ml)	Tap density (gm/ml)	Carr's index (%)	Hauser's ratio
	Dried Granules	Final blend				
Trial-1	1.96	2.12	0.47	0.61	22.95	1.29
Trial-2	0.90	2.24	0.42	0.53	20.75	1.26
Trial-3	2.43	5.18	0.47	0.59	20.33	1.26
Trial-4	0.83	6.09	0.47	0.58	18.97	1.23
Trial-5	2.0	4.12	0.41	0.51	19.60	1.24
Trial-6	2.10	4.91	0.46	0.55	16.36	1.19
Trial-7	0.96	1.27	0.48	0.61	21.31	1.27
Trial-8	1.19	2.46	0.48	0.59	20	1.25
Trial-9	1.92	4.12	0.40	0.55	26.53	1.38
Trial-10	1.19	3.18	0.52	0.64	16.13	1.17
Trial-11	1.99	2.98	0.45	0.62	26.15	1.37
Trial-12	1.83	2.73	0.48	0.64	31.80	1.46
Trial-13	1.99	2.45	0.43	0.56	21.31	1.30
Trial-14	1.99	2.66	0.50	0.69	27.53	1.38

Table 8: Post Compression Parameters of All Trials 01 to 14

Trial No.	Average wt.(mg)	Thickness (mm)	Hardness (N)	Disintegration time(sec.)	Assay (% w/w)
Trial-1	197-203	3.43-3.50	49-68	22-32	87.76
Trial-2	198-202	3.46-3.51	49-57	26-30	98.62
Trial-3	198-205	3.62-3.75	29-52	25-29	98.7
Trial-4	195-2044	2.97-3.46	45-61	14-18	99.40
Trial-5	197-204	3.06-3.43	43-56	16-23	98.70
Trial-6	197-206	3.17-322	43-55	18-23	89.21
Trial-7	197-205	3.69-3.73	28-37	28-37	88.54
Trial-8	196-205	3.64-3.69	29-42	28-39	99.15
Trial-9	200-204	3.37-3.45	40-58	12-15	99.48
Trial-10	199-203	3.27-3.41	48-57	70-102	98.55
Trial-11	199-203	3.46-3.60	44-55	45-65	97.56
Trial-12	196-204	2.60-2.69	30-46	18-30	98.43
Trial-13	200-203	3.68-3.85	35-46	21-28	99.24
Trial-14	97-104	2.49-2.58	40-69	20-33	99.33

Table 9: Dissolution Profile of Different Trials in Water of trials 01 to 04

Time Point	Formulation				
	Innovator	Trial-1	Trial-2	Trial-3	Trial-4
0	0	0	0	0	0
5	87.6	84.2	88.2	63.4	86.4
10	94.2	88.7	95.2	65.6	89.7
15	95.4	89.6	96.1	67	90.8
20	97.3	89.5	96.8	67.8	91.2
30	97.5	89.5	97	68.4	91
F2	**NA**	**61.59**	**96.41**	**29.59**	**66.75**

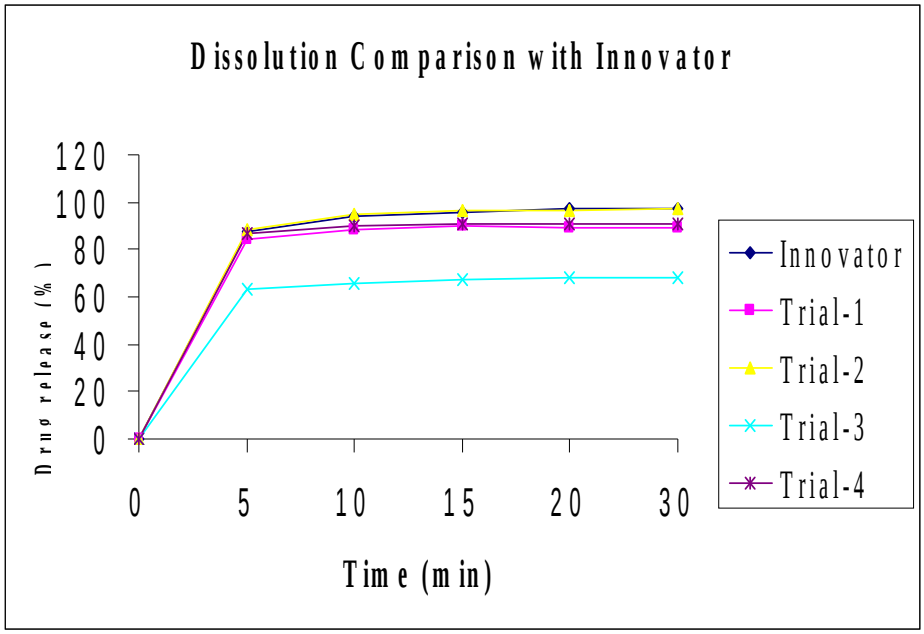

Fig. 1: Dissolution Profile of Different Trial 01 to 04 with innovator

Table 10: Dissolution Profile of Different Trials in Water of trials 05 to 08

Time Point	Formulation				
	Innovator	Trial-5	Trial-6	Trial-7	Trial-8
0	0	0	0	0	0
5	87.6	88.1	80.7	60	65
10	94.2	94.9	89.6	73.7	76.5
15	95.4	96.6	91.5	78.2	79.6
20	97.3	96.6	92.3	80.8	83.3
30	97.5	96.4	92.2	82.9	85.8
F2	**NA**	**94.58**	**65.57**	**37.1**	**40.7**

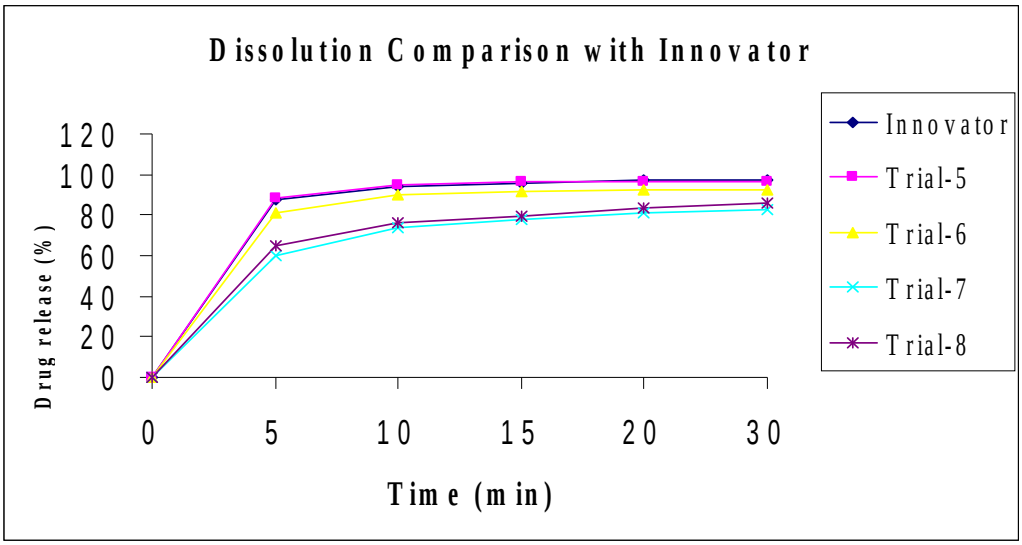

Fig. 2: Dissolution Profile of Different Trial 05 to 08 with innovator.

Table 11: Dissolution Profile of Different Trials in Water of trials 09 to 12

Time Point	Formulation				
	Innovator	Trial-9	Trial-10	Trial-11	Trial-12
0	0	0	0	0	0
5	87.6	82.4	90.9	92.5	63.9
10	94.2	89.5	92.8	93.6	73.7
15	95.4	91.6	93.5	92.8	77.5
20	97.3	91.6	93.9	93.1	80.7
30	97.5	93.4	93.8	93.5	82.1
F2	**NA**	**67.58**	**77.49**	**73.21**	**37.95**

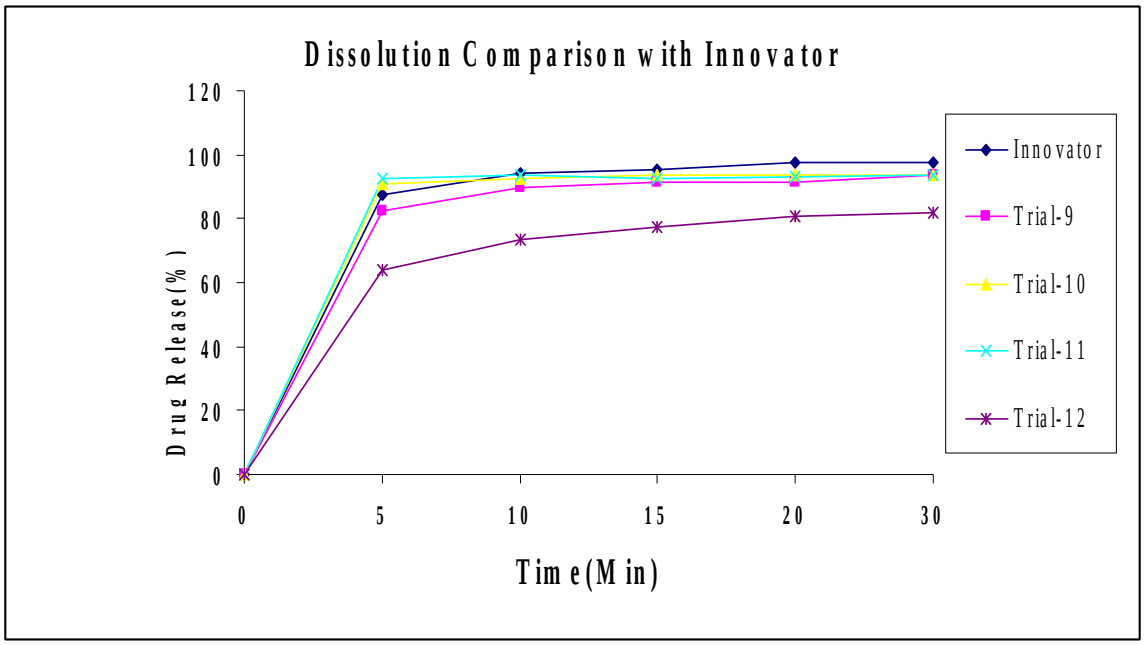

Fig. 3: Dissolution Profile of Different Trial 09 to 12 with innovator

Table 12: Dissolution Profile of Different Trials in Water of trials 13 to 14

Time Point	Formulation		
	Innovator	Trial-13	Trial-14
0	0	0	0
5	87.6	85.5	67.8
10	94.2	92	77.2
15	95.4	93.9	81.1
20	97.3	96.2	82.5
30	97.5	97.8	83.3
F2	**NA**	**87.6**	**41.5**

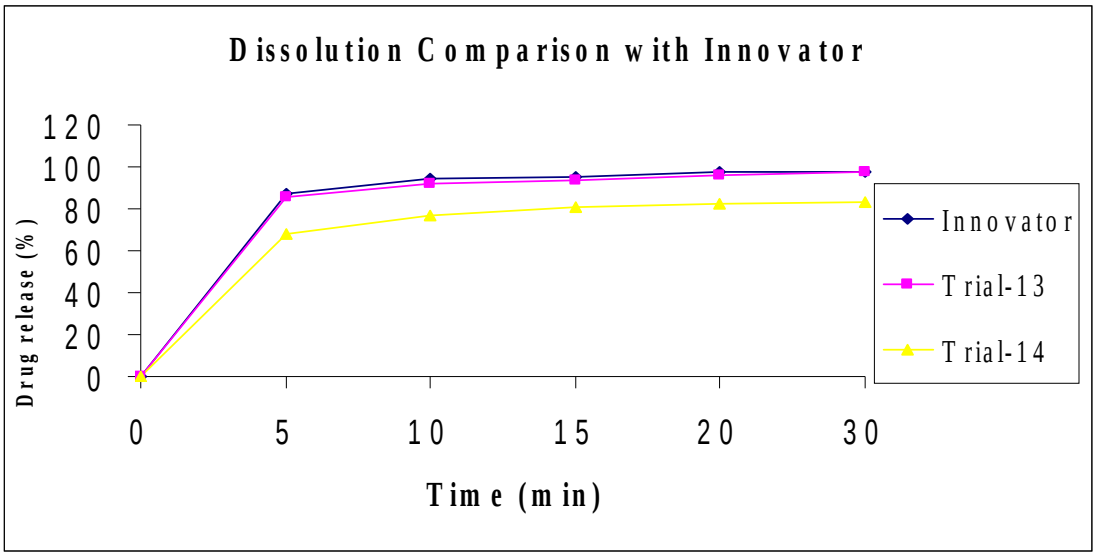

Fig. 4: Dissolution Profile of Different Trial 13 to 14 with innovator

Table 13: Dissolution Profile of Different Trials in 0.1 N HCl of trials 05, 09, 12 and 13

Time Point	Formulation				
	Innovator	Trial-5	Trial-9	Trial-12	Trial-13
0	0	0	0	0	0
5	91.5	82.4	84.2	88.7	96.8
10	97.8	83.3	87.3	89.5	98.3
15	98.6	82.9	89.2	89.1	98.9
20	98.5	84.5	90.4	89.3	98.4
30	99.1	93.2	91.3	89.2	99.4
F2	**NA**	**47.2**	**54.84**	**55.68**	**81**

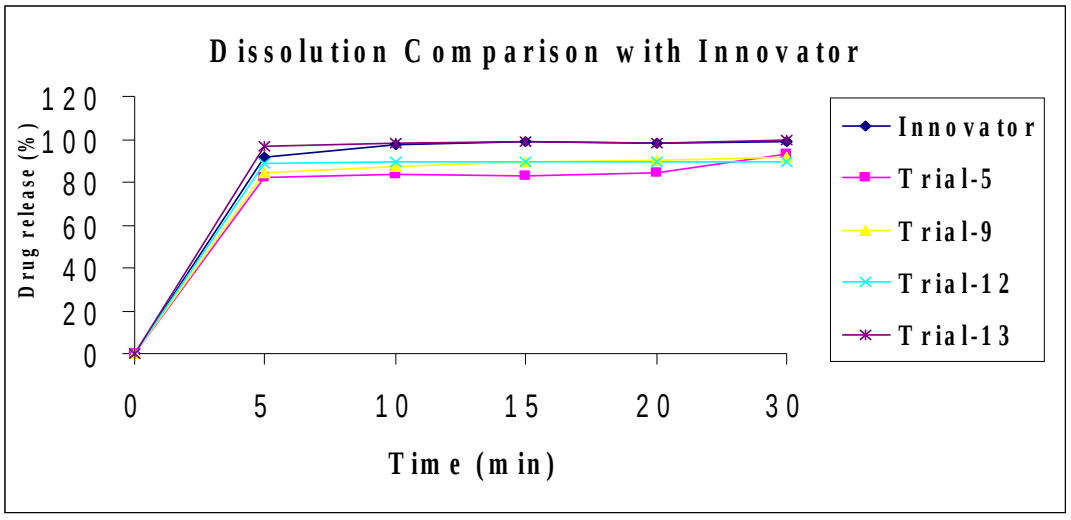

Fig. 5: Dissolution Profile in 0.1 N HCl of Different Trial 05, 09, 12 and 13 with innovator

Table 14: Dissolution Profile in pH 4.5 acetate Buffer of Different Trial 13 to 14 with innovator

Time Point	Formulation				
	Innovator	Trial-5	Trial-9	Trial-12	Trial-13
0	0	0	0	0	0
5	95	51.4	84	93.2	93.7
10	100	62	87.3	95.5	97.9
15	99.6	62.4	88.8	95.7	98.5
20	99.4	62.4	89.3	95.8	98.9
30	99.8	62.8	90.8	96.2	98.4
F2	**NA**	**22.62**	**50.22**	**73.23**	**89.68**

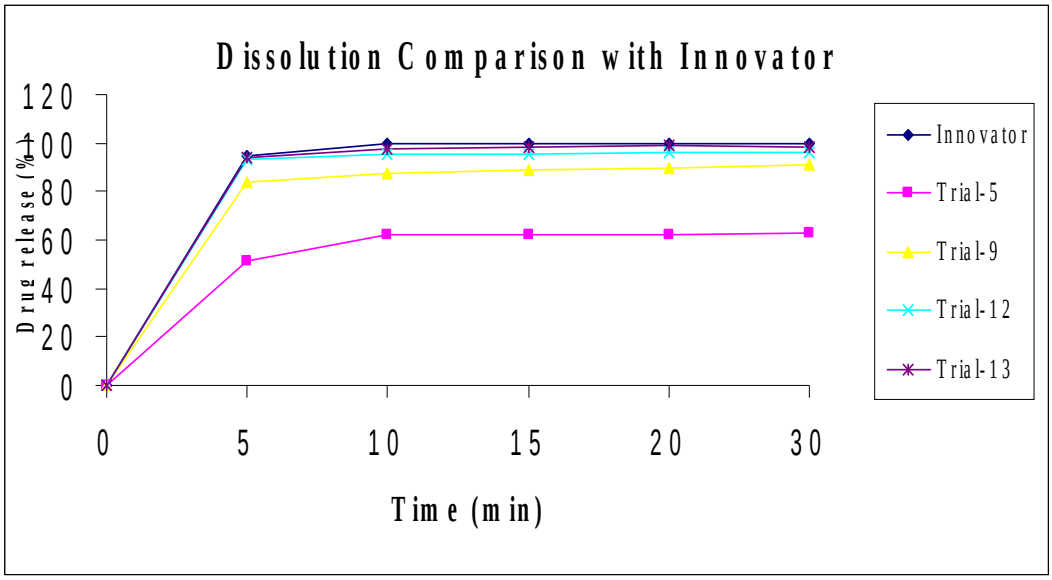

Fig. 6: Dissolution Profile in pH 4.5 acetate Buffer of Different Trial 05, 09, 12 and 13 with innovator

Table 15: Dissolution Profile in pH 6.8 phosphate Buffer of Different Trial 13 to 14 with innovator

Time Point	Formulation				
	Innovator	Trial-5	Trial-9	Trial-12	Trial-13
0	0	0	0	0	0
5	96.6	74	77	91.2	99.9
10	98.6	81.8	82	93.5	102.8
15	98.3	82.9	83.9	93.5	103.6
20	98	84.8	85.6	92.9	104.7
30	98.4	83.9	87.1	93.2	105.3
F2	**NA**	**40.64**	**42.89**	**66.02**	**64.69**

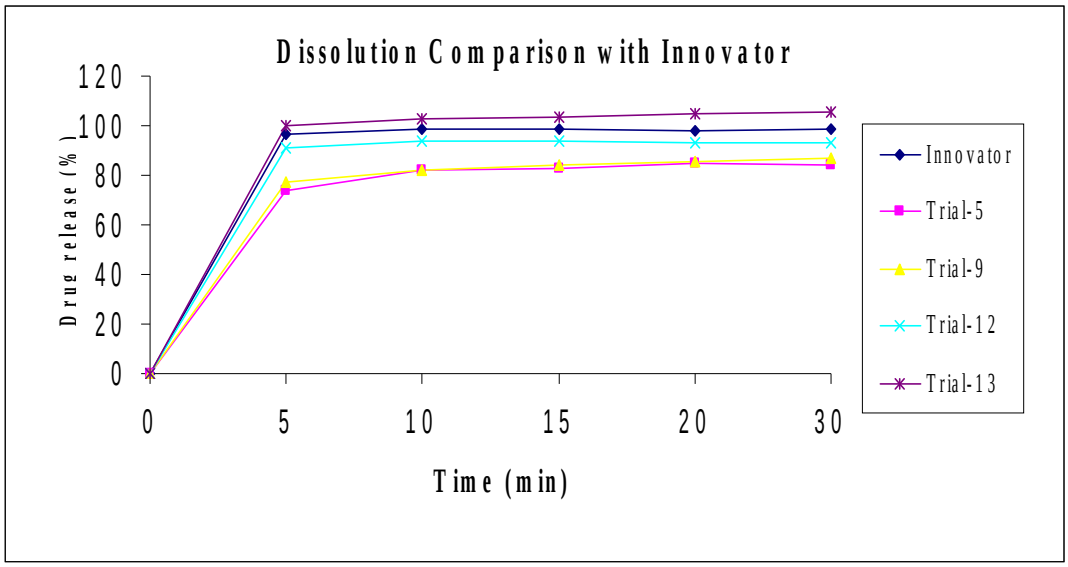

Fig. 7: Dissolution Profile in pH 4.5 acetate Buffer of Different Trial 05, 09, 12 and 13 with innovator

Table 16: Exposure Study of Final Trial-13

Storage condition→	Room Temperature		80°C		Autoclave	
Period →	Initial		2 Days (open)		At 121°C for 15 min	
Formulations →	Innovator	Trial13	Innovator	Trial 13	Innovator	Trial 13
Parameters↓	Observations					
Physical Appearance	Whitish yellow	White	Whitish yellow	White	Whitish yellow	White
Hardness (N)	Very Soft	35-45	Very Soft	45-55	Not Applicable	
LOD (%)	NA	2.45	NA	1.88	NA	3.10
D.T. (sec.)	2-5	21-28	2-5	29-32	Not Applicable	
Assay (%)	99.13	99.24	99.80	99.37	99.81	99.56
Dissolution (at 30 min.)	97.5	97.8	NA	NA	Not Applicable	
Total Impurity (%)	0.244	0.139	1.067	1.086	0.846	0.748

Table 17: Stability Observations of Trials 13

Storage condition→	Room Temperature		40°C/75%RH						Specifications
Period→	Initial		1 Month		2 Months		3 Months		
Formulations →	Innovator	Final Trial	Innovator	Final trial	Innovator	Final trial	Innovator	Final trial	
Parameters↓	Observations								
Physical Appearance	Whitish yellow	White	White	White	White	White	White	White	No change should observed
Hardness (N)	Very Soft	35-46	NA	32-39	NA	37-42	NA	38-43	NLT 50 N
LOD (%)	NA	2.45	NA	2.76	NA	2.98	NA	3.05	NMT 4.0%
D.T. (min.)	2-5	21-28	2-5	20-25	2-5	21-27	2-5	18-22	NMT 60 sec.
Assay (%)	99.13	100.2	98.5	99.64	99.9	99.5	98.6	98.15	90-110%
Dissolution (at 15 min)	95.4	93.9	--	91.3	---	90.1	---	91.1	NLT Q 80% in 15 min.

Table No. 18: Stability Dissolution Results for Trial 13

Time Point (min) ↓	Condition				
	Initial	40°C/75%RH			
		15days(o)	1 Month	2 Months	3 months
0	0	0	0	0	0
5	85.5	80.2	87.2	88.7	87.6
10	92	81.7	89.7	90.7	90.4
15	93.9	84.5	91.3	90.1	91.1
20	96.2	89.3	93.7	94.8	93.7
30	97.8	92.5	96.7	95.9	92.7

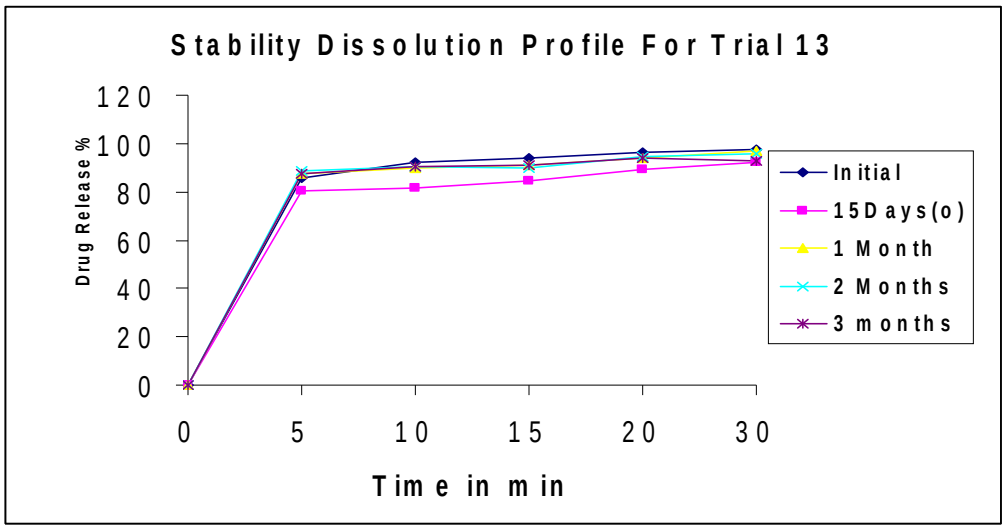

Fig. 8: Stability Dissolution Results for Trial 13

Table 19: Worst Case Study of Final Formulation

Critical Steps	Justification	Challenge	Parameters
Mixing	Dry mixing impacts: Content Uniformity	Samples from 10 different location	Content Uniformity
Lubrication	Lubrication impacts: Drug Release & Physical Parameters of tablet	3min, 5min, 7min	Drug Release
Compression	Hardness Impacts: Physical Parameters & Drug Release	25-35N, 35-45N, 45-55N	Friability, D.T, Drug Release, Thickness

Table 20: Dry Mixing Challenge of Trials A, B and C

Stage	Parameter	10min	20min	30min
Blending	Trial no.	A	B	C
	Batch Size (Tablets)	5000	5000	5000
	Blender (capacity)	5.0 L	5.0 L	5.0 L
Environmental Conditions		25°C/55%RH	25°C/55%RH	25°C/55%RH
Content Uniformity at Different Location (%)				
Upper Left		97.5	90.4	98.2
Upper Right		100.6	92.8	99.3
Upper Middle		99.6	95.6	101.3
Middle Left		98.6	104.6	98.7
Middle Right		93.5	108.8	97.9
Middle		103.8	99.9	99.9
Lower Left		100.2	95.7	100.1
Lower Right		96.8	91.7	101.5
Lower Middle		99.9	104.1	98.2
Composite Sample		99.8	102.4	100.3

Table 21: Process Challenge of Trials A, B and C

Parameters	Parameter		3min	5min	7min
Lubrication	Trial no.		A	B	C
	Batch Size (tabs)		5000	5000	5000
	Blender (capacity)		5.0 L	5.0 L	5.0 L
Environmental Conditions			25ºC/55%RH	25ºC/55%RH	25ºC/55%RH
Micrometrics of lubricated granule	TD gm/ml		0.58	0.58	0.52
	BD gm/ml		0.44	0.45	0.41
	CI		24.50%	22.42%	21.15%
	HR		1.31	1.28	1.2
	LOD		2.0	2.3	2.7
Sieve Analysis% Retained	40 #		0		
	60 #		17.5		
	80 #		15.2		
	100 #		16.4		
	BASE		50.9		
Compression Parameters	Weight Variation		0.90%	0.50%	0.60%
	Thickness		3.75-3.85mm	3.75-3.86mm	3.76-3.89mm
	Hardness (N)		35-47N	30-45N	35-45N
	Friability (100rtn's)		0.019%	0.02%	0.02%
	D.T (min.)		25-30 sec	20-26 sec	22-28sec
DR Profile Innovator Vs Trial at Water, 50RPM,Paddle,900ml volume	*Minutes*	*Innovator*			
	5	87.6	72.9	85.7	85.2
	10	94.2	80.1	93.1	91.2
	15	95.4	87.25	94.4	93.2
	20	97.3	94.3	96.2	96.8
	30	97.5	96.1	97.4	97.8
F2 Value			**52.00**	**91.57**	**84.10**

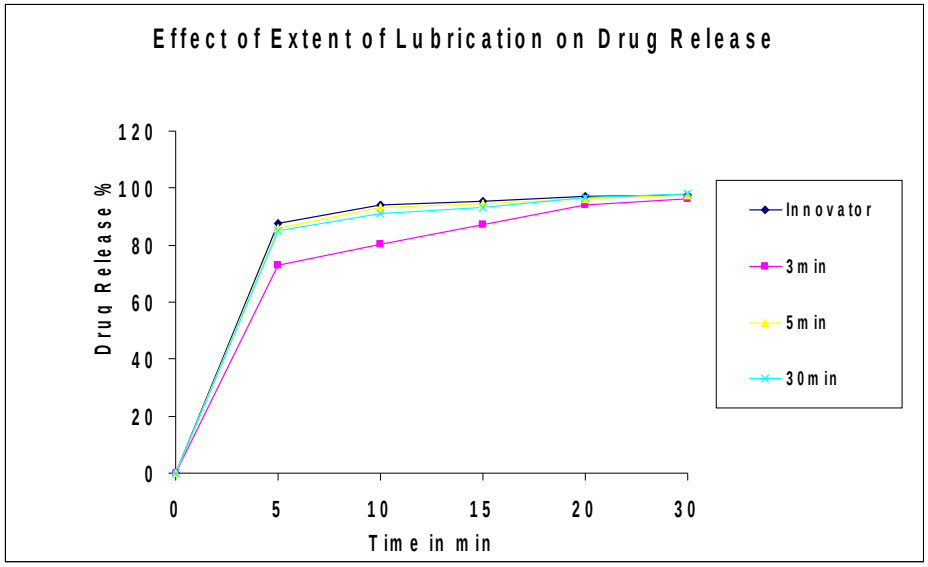

Fig. 9: Results for effect of Lubrication on Dissolution

Table 22: Compression Challenge (Hardness)

Parameter		Low	Optimum	High
Trial no.		A	B	C
Machine Speed		18 rpm	18 rpm	18 rpm
Environmental Conditions		25ºC/55%RH	25ºC/55%RH	25ºC/55%RH
Hardness (N)		25-35N	35-45N	50-60N
Appearance		OK	OK	OK
Weight Variation		1.50%	-1.625% to +4.0%	-1.125% to +4.5%
Thickness (mm)		3.55-3.85mm	3.40-3.54mm	3.30-3.41mm
Friability (100rtn's)		0.02%	0.02%	0.01%
DT (min)		20-25 sec	25-30 sec	50-60 sec
Dissolution Profile of All 3 Conditions				
Time Point (Min)	***Cumulative % Drug Release***			
	Innovator	*Low*	*Optimum*	*High*
5	85.6	85	80	60
10	94.1	92	88	74
15	96.7	98	94	87
30	99.8	100	98	95
F2 Value		**89.52**	**67.06**	**38.25**

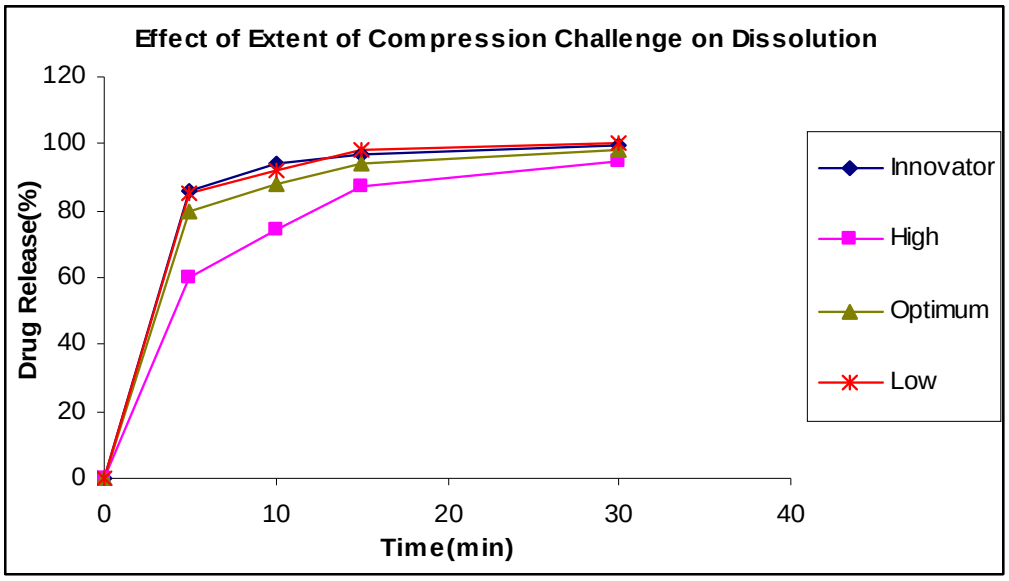

Fig. 10: Results for effect of Hardness on Dissolution

RESULT AND DISCUSSION

Preformulation Study

The present investigation was carried out to develop Orodispersible tablet dosage form of class III drug, Rizatriptan Benzoate. The Tablets were prepared by using different excipients.

Compatibility Study

Drug–Excipient compatibility study of Rizatriptan Benzoate with different categories of excipients was carried out. The study was carried out at different conditions of temperature and humidity like 40°C/75%RH, 2–8°C, room temperature & found their physical appearance, impurity level and water content after 2 week, 4 weeks and compare with initial value.

The result shows impurity level with some drug and excipient combination increases and also slight changes in appearance, all were compatible with Rizatriptan benzoate. Excipients were considered compatible only if the total impurities do not exceed 2–times the impurities of initial.

API Characterization Study

pH Dependent Solubility Study

pH of Rizatriptan Benzoate in 10% solution (water) found to slightly acidic. The pH dependent solubility study carried out by wing different pH buffer solution rangingb water, pH 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Study shows solubility of Rizatriptan Benzoate was more in pH 4.5, i.e. 89.68 mg/ml Therefore, water was used as dissolution medium (It is also official in FDA).

Powder Flow Properties

The flow properties of pure drug were carried out and the results indicate that drug shows poor flow. So, it was decided to overcome this problem API mix well with diluent which was done by Direct compression technique wing Aerosil as glident to import good flow as well as compressibility.

Evaluation of Formulation Parameters

Evaluation was divided in mainly

- Pre compression Parameters and
- Post compression Parameters.

This includes Loss on Drying of dried granules and final blend, bulk density, tapped density, Carr's Index, Houser's Ratio and sieve analysis in pre compression parameters and average weight, thickness, hardness, disintegration time and friability in post compression parameters.

Pre Compression Parameters

Loss on Drying (LOD) - As calculated, theoretical moisture content of drug and excipient which was 3.00%w/w, LOD of Dry mix maintained in that level NMT ± 1% variation by drying at 105°C and optimize drying time for achieve LOD in particular limit.

Powder Flow Characteristics

Initially some flow problem arises in Wet compression method granules blend shows poor flow which causes weight variation, problem in content uniformity, But direct Granulation Method shows good flow properties of powder and final blend.

- Bulk density in the range 0.41 – 0.5 gm/ml
- Tapped density in the range 0.50-0.65 gm/ml,
- Carr's Index ranging 19-25% and
- Hauser's ration in the range 1.2-1.4shows the good flow characteristics.

Sieve Analysis

Sieve Analysis by Mechanical shaker shows there was good blend of fines which result in good flow and reduces weight variation problems.

Post Compression Parameters

- **Weight Variation**
  Initially in same trails, weight variation observed, but in final trial tablet ranging 195-205 mg (Target wt – 200mg/Tablet) for 10 mg tablet formulation, which is less than 5% indicates that the variation in the weight of the tablets is within standard official limits.
- **Thickness Evaluation**
  Thickness of tablets was observed by Vernier Caliper. Thickness of Tablet was show any measurable Complete sent
- **Hardness Test**
  Hardness of the tablet was measured in 'Newton' unit in digital harness tester The hardness of tablets found to be uniform within range 30 N to 55 N
- **Disintegration Test**
  Disintegration test was carried out in Electro lab (ED-2AL). Disintegration time for 6 tablets found to be 20 – 30 sec indicating that disintegration time within the specification limit.
- **Friability Test**
  The friability was carried out by using Roche Friabilator. The percentage friability of tablet was ranging 0.1% - 0.5%. They are less than the standard limit of 1% indicates that the prepared tablets are mechanically stable.

Drug Content Uniformity
In the initial trials drug content uniformity found outside limit but, after that each trials drug contents ranging from 98% - 101.2% which is within the range of 92.5 – 105% for Rizatriptan. It indicates uniform distribution of drug in the tablets of each formulation.

***In-Vitro* Drug Release Studies**
The Rizatriptan Benzoate Orodispersible Tablets were subjected to in vitro drug release studies in water for 30 min. The drug release studies carried out in dissolution test apparatus using 900 ml of dissolution medium, maintained at 37°C ± 0.5°C
Among all trials dissolution profile of 3 trials i.e. Trail - 02, Trial - 05, Trial - 13 matches with innovator in water medium. Only Trial – 13 matches with a;; three media with innovator. Thus, Trial - 13 was finalized.

F_2 Value
Similarity factor (F2) was calculated between innovator formulation and our formulation. Similarity factor value in the range of 50-100 indicates that there is Similarity in the release profile of the formulations.
Among all Trials, Trial 5 shows highest F2 value 94.58 in water medium, but when it subjected to D.M. 0.1 n HCl medium it shows F2 – Value 47.2 which was less Than 50 – 80, it was not chosen. On the other hand trial – 13 shows F2 – value 87.60 in water medium and when it subjected to pH 4.5 acetate buffer and D.M. Water media it shows F2 – values 89.68 respectively. This value indications trial – 13 shows good release profile in all media. So it was chosen as final formulation.

Formula Development 10 mg Formulation
After selecting final formulation of Rizatriptan Benzoate Orodispersible Tablet 10 mg.

Exposure Study
Exposure studies were carried out of selected trial. In exposure study, our trial and innovator formulation was subjected to different environmental stress conditions like 80° for 2 days and in autoclave at 121°C for 15 min. The result shows similar behavior between our trial and innovator in different conditions.

Stability Study
The stability studies of final trial was done for 3 months by packing in HDPE container in humidity chamber (40°C/75% RM)
The result given in table for 1 month, 2 months, 3 months show. All parameters of formulation including physical parameters, impurity profile, content uniformity or dissolution profile were within specification limit. So it indicates optimized formulation were stable.

Worst Case Study
Worst case study for final formulation was performing to optimize the critical stages during the formulation process. In this case dry mixing, lubrication of compression force were considered as critical stages which may cause problem if the set parameters vary so. By considering that thing out final formulation be optimized by varying different parameters in there critical stages.

Dry Mixing Challenge
Dry mixing challenge did by using 3 big batches of change in different mixing time i.e. 10min, 20 min and 30 min in 5.0 liter Blender at 25°C/55% RH condition. It is found in al three conditions after taking samples from different location in blender that at 10 min mixing was not very satisfactory that which required 20 min and 30 min mixing time shows satisfactory content uniformity of drug so, our dry mixing time was 30min.

Compression Force Challenge
In compression force challenge study at three different compression forces. Their higher and lower extreme level was selected by considering good physical appearance at constant machine speed 18 rpm.
The dissolution profiles for all three conditions were found to be satisfactory. So, compression force was show any measurable effect. F_2 – Value found to be 38.25, 67.06 and 89.52 for high, optimum and low respectively. So, by completing worst case study we optimized the final process of formulating.
These low rpm speerd steps formulation and development study of Rizatriptan Benzoate orodispersible tablet was successfully accomplished and results were found also satisfactory.

CONCLUSION

Before going to preformulation a detailed literature review was carried out to know about the innovator i.e. type of dosage form available in the market, its dimensions, shape and size, excipients used and all other physical parameters. The patent status of the drug is thoroughly monitored. Preformulation study and drug excipient compatibility study was done initially and the results obtained directed the way to method of formulation. With the data obtained from Literature review, Preformulation and drug excipient compatibility study, prototype formulation trials were started for the highest dose of Rizatriptan Benzoate (10 mg) and optimized to get the final formula. Rizatriptan Benzoate has very poor flow property so dry granulation and direct compression method was avoided. Granules were evaluated for tests such as LOD, Bulk density, Tapped density, Compressibility index and Hausner ratio and sieve analysis before compression. tablets were tested for weight variation, thickness, hardness, friability, and dissolution. In vitro dissolutions were performed and F1 and F2 values were calculated. Dissolution profile of final trial batch was matched perfectly with innovator and F2 value was found to be excellent. Also tability result of final trial batch was found to be excellent. Worst case study for final formulation was performing to optimize the critical stages during the formulation process. In this case dry mixing, lubrication of compression force and results were found satisfactory.

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