FORMULATION DESIGN AND CHARACTERIZATION OF ORALLY DISINTEGRATING TABLET OF RIZATRIPTAN USING DIFFERENT SUPERDISINTEGRANTS

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Abstract

Rizatriptan orodispersable teblets were created using the direct compression method with a variety of superdisintegrants, including sodium starch glycolate, crosspovidone and Ax-Di-sol with the appropriate subliming agent. Powder properties, wetting time, friability, *in-vitro* disintegration time, *in-vitro* dissolution profiles were assed for the produced formulations. Except for formula F1, which contains sodium starch glycolate, and formula F9, which is ma de using the direct compression method and crosspovidone, all of the created formulations sh owed satisfactory mechanical strength. The outcomes showed that the superdisintegrant crosspovidone containing tablets had a favourable dissolution profile and the quickest disintegration time. Using 6.5% crosspovidone as a superdisintegrant and a favourable dissolving profile with appropriate stability, the optimised formula F9 is created. The impact of formulation processing variables on tablet characteristics is revealed by this investigation. Rizatriptan (Formulation F9) orodispersible tablets have superior biopharmaceutical properties.

Keywords: Swelling, Porosity, Wettability, Deformation, Dry Granulation, Sublimation.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of accurate dosage, low cost of therapy, self-medication, non-invasive method, and ease of administration leading to high level of patient compliance[1]. Tablets and capsules constitute the foremost portion of oral dosage forms that are currently available in the market. However, traditional tablets and capsules administered with a glass of water may be inconvenient or unfeasible for some geriatric patients, because of changes in various physiological and neurological conditions associated with aging including dysphagia (difficulty in swallowing), hand tremors, hearing, memory, risk of choking in addition to change in taste and smell[2].

These solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally retarded, bed ridden, uncooperative, nauseated, or on reduced water intake have suffered difficulties of swallowing these dosage forms[2-5]. Moreover, patients travelling with little or no access to water, limit utility of orally administered conventional tablets or capsules. The disintegration time for ODTs generally ranges from several seconds to about a minute[6]. ODTs offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia[7] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications[8]. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. ODT products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia) [9]. These systems may offer superior profile with potential mucosal absorption thus increase the drug bioavailability.

Disintegrants are agents added to tablet (and some encapsulated) formulations to promote the breakup of the tablet (and capsule "slugs') into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10 % by weight relative to the total weight of the dosage unit[10].

MATERIALS AND METHODS

Materials

Rizatriptan was a gift sample from SMS Pharmaceuticals Ltd, Hyderabad. Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide samples were procured from Signet Pharmaceuticals, Hyderabad.

Methods

Sample preparation

The materials were weighed as per the formula and mixed well with the individual excipient(s) with API From the individual drug mixtures made, 2 g was placed in each vial.

The vials were closed with the stoppers. The vials were labeled with all the details. 3 vials were kept at each of the below mentioned intervals under study. 2gm of the active weighed into three vials (per interval) and placed this along with drug – excipient blends for study[11].

Sampling Schedules

Storage condition / Packing	Sampling intervals
Initial	Initial
40 ± 2 °C / 75 ± 5% RH Glass vial	2 weeks/ 4 weeks
60 °C	2 weeks
Room temperature	Control sample

Drug excipient compatibility studies

Fourier transform infrared spectroscopy (FT-IR) was carried out for following samples with Shimadzu FTIR model 8300 by taking the KBr disc.

Table 2: Formulation development of Rizatriptan oral disintegrating tablets

Rizatriptan	5	5	5	5	5	5	5	5	5
Supertab11SD	97	97	97	97	97	97	97	97	97
Avicel PH 102	19.6	18.3	17	19.6	18.3	17	19.6	18.3	17
Crospovidone	3.9	5.2	6.5	-	-	-	-	-	-
Ac-Di-Sol	-	-	-	3.9	5.2	6.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	3.9	5.2	6.5
Aspartame	2	2	2	2	2	2	2	2	2
Peppermint	1	1	1	1	1	1	1	1	1
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight (mg)	130	130	130	130	130	130	130	130	130

Process for F-1

- Rizatriptan, Supertab11SD, Avicel, Crospovidone, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.
- Mg stearate passed through #80 mesh which was added to the above blend and lubricated for 5 min in the poly bag
- From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Process for F-2 & F-3

In this trial concentration of Crospovidone increased gradually and evaluate parameters.

- Rizatriptan, Supertab11SD, Avicel, Crospovidone, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.
- Mg stearate passed through #80 mesh which was added to the above blend and lubricated for 5 min in the poly bag
- From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Process for F-4

In this trial Superdisintegrant Crospovidone was replaced by cross carmellose sodium initially low concentrations and evaluate parameters.

- Rizatriptan, Supertab11SD, Avicel, Croscarmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.
- Mg stearate passed through #80 mesh which was added to the above blend and lubricated for 5 min in the poly bag.
- From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Process for F-5 & F-6

In this trial concentration of Croscarmellose sodium increased gradually and evaluate parameters.

- Rizatriptan, Supertab11SD, Avicel, Croscarmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.
- Mg stearate passed through #80 mesh which was added to the above blend and lubricated for 5 min in te poly bag
- From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Process for F-7

In this trial Superdisintegrant was cross carmellose sodium replaced by Sodium starch glycolate initially low concentrations and evaluate parameters.

- Rizatriptan, Supertab11SD, Avicel, Croscarmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.
- Mg stearate passed through #80 mesh which was added to the above blend and lubricated for 5 min in the poly bag
- From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Process for F-8 & F-9

In this trial concentration of Sodium starch glycolate increased gradually and evaluate parameters.

- Rizatriptan, Supertab11SD, Avicel, Croscarmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.
- Mg stearate passed through #80 mesh which was added to the above blend and lubricated for 5 min in the poly bag
- From the final blend tablets[11-12] were compressed using 6.4 mm round flat shaped punches.

Pre-Compression Parameters

Angle of Repose

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose[13].

The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

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

h = Height of the pile

r = Radius of the pile

Post-Compression Parameters

Physical Appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour, embossing, debossing etc.

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickhness should be controlled within a ± 5% variation of a standard.

Weight Variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits[14].

Hardness Test

The crushing load which is the force required to break the tablet in the radial direction was measured using a Monsanto hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Percentage Friability

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.

If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets is tested.

The percentage friability[15] is expressed as the loss of weight and is calculated by the formula:

$\% \text{ Friability} = [(W_0 — W_f) / W_0] \times 100$

W_0 = Initial weight of tablets

W_f = Final weight of tablets

Disintegration Time

Disintegration time[16-17] is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus 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 ± 2^0C. 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 30seconds.

Percentage Water Content

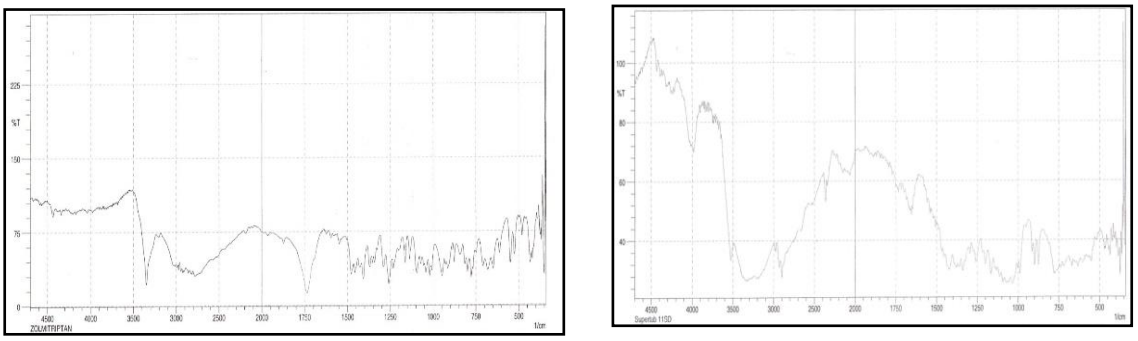
Karl Fischer reagent (sulphur dioxide and iodine dissolved in pyridine and methanol) is used to determine the water content of the tablets using Karl Fischer Titrator.

Dissolution Studies

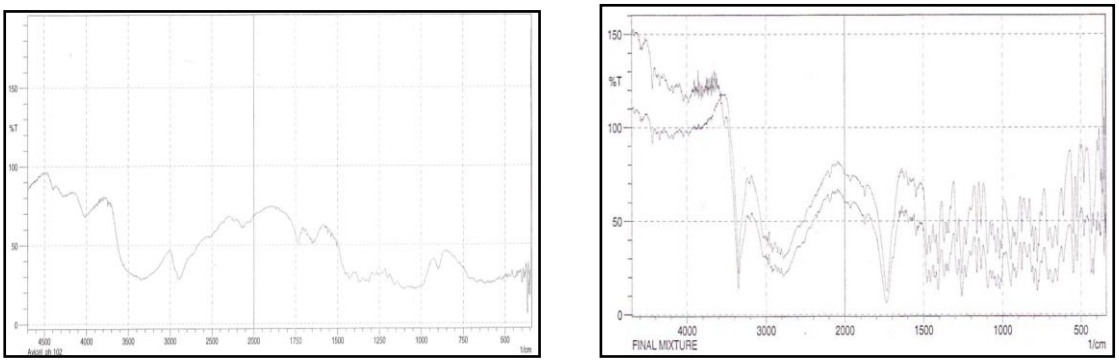
Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15, 20 30, min. 5 ml of fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions at 37^0C. Samples withdrawn were analyzed at 225 nm for the percentage of drug released[18-19].

RESULTS AND DISCUSSIONS



FTIR spectra of Rizatriptan, Sodium Starch Glycolate



FTIR spectra of Magnesium stearate, Final mixture

The FT-IR studies revealed that Rizatriptan is compatible with the excipients used in the formulation. There were no extra peaks observed in the IR spectrum. The IR absorption band in cm-1 of the drug and excipients was found to be similar. This established that the drug Rizatriptan and all the excipients used in the study showed no interaction and indicated that they were compatible with each other.

Table 3: Results of Precompression Parameters

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index	Hausner Ratio	Angle of repose(θ)	% LOD
F1	0.384	0.545	31.25	1.41	41.52	1.75
F2	0.362	0.485	25.36	1.33	40.61	1.80
F3	0.380	0.530	28.30	1.39	48.42	1.75
F4	0.371	0.493	24.74	1.32	37.41	1.50
F5	0.360	0.462	22.07	1.66	33.92	1.47
F6	0.419	0.477	12.26	1.14	24.28	1.37
F7	0.417	0.471	11.49	1.13	22.32	1.33
F8	0.416	0.475	12.44	1.13	25.54	1.20
F9	0.428	0.456	18.22	1.25	24.56	1.19

Precompression parameters were performed as per Pharmacopoeial Procedure. All the resultant values were within the limit. Angle of repose parameter was performed by using fixed funnel method. The percentage of Loss on Dry was within the standard limit. Carr's Index and Hausner's ration were performed and resultant values were within the limit. The flow properties for all prepared formulations [F1-F9] indicates excellent flow which was minimizing the weight variation for all formulations.

Table 4: Results of Post Compression Parameters

Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kp)	Percentage Friability (%)	Disintegration Time (sec)
F1	131.2	3.71	3.8	0.63	80
F2	130.6	3.65	4.2	1.22	71
F3	132.3	3.69	4.0	1.50	65
F4	131.8	3.68	4.3	0.78	59
F5	129.8	3.72	4.3	0.90	54
F6	129.6	3.66	4.4	1.75	50
F7	132.0	3.65	4.0	0.32	30
F8	130.5	3.72	.2	0.45	25
F9	130.2	3.70	4.0	0.68	21

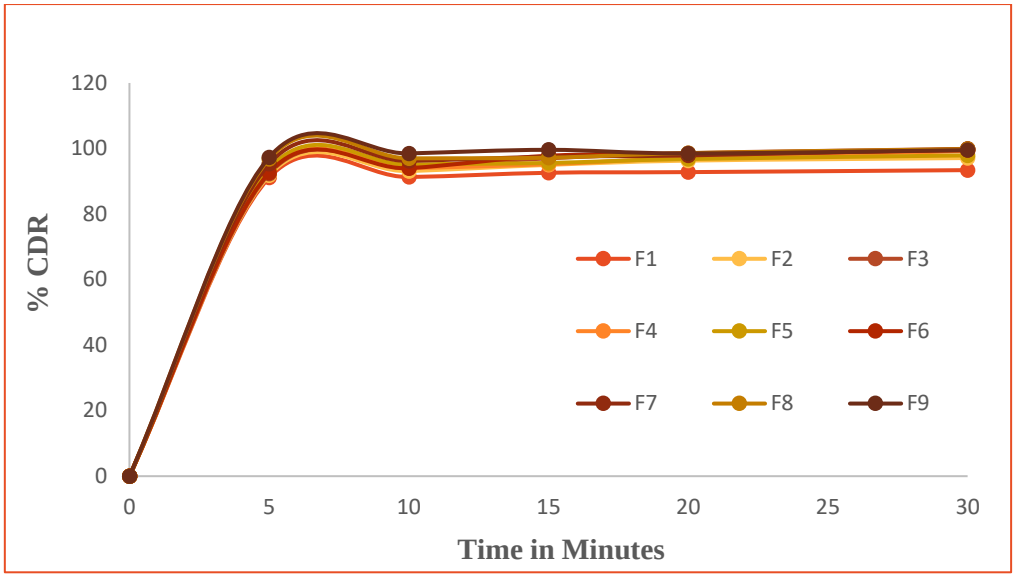


Figure 1. % Cumulative drug release of formulations [F1-F9]

Post Compression Parameter were conducted as per the Pharmacopoeial procedure. Weight variation for all prepared formulations within the limits which indicates no weight variation for formulations. Friability test was performed by using Roche Friabilator and all the resultant values were within 1%. The prepared formulations had sufficient strength to avoid breakage during packaging and transport of prepared tablets. Oral dispersable tablet has disintegration time less than/equal to 1 minutes as per pharmacopoeial standards. All the prepared formulation from F1-F9 shows within 1 minutes which indicates all formulations are oral dispersable tablets.

Moisture uptake studies (by weight gain method), Condition: 29%RH

Weight of petridish: 43.144 g

Weight of 10 tablets: 1.322 g (each tablet weight ≅ 130 mg)

Gross weight (weight of tablets + petridish):44.466g

Table 5: Moisture uptake observations at 35% RH

Time	Initial	1 hr	2 hr	4 hr	6 hr	8 hr	24 hr	48 hr	72 hr
Observed RH	35%	35%	38%	36%	38%	35%	35%	35%	38%
Observed temperature (^{0}C)	24.5^{0}C	24.5^{0}C	25^{0}C	25^{0}C	25^{0}C	25^{0}C	24.5^{0}C	25^{0}C	24.5^{0}C
Physical observation	No change	No change	No change	No change	No change	No change	No change	No change	No change
Observed weight (g)	1.322	1.322	1.322	1.322	1.322	1.322	1.320	1.321	1.322
Percentage moisture uptake	0%	0%	0%	0%	0%	0%	0.02%	0.01%	0%

Condition: 75%RH

Weight of petridish: 36.789 gm Weight of 10 tablets: 1.316 g (each tablet weight ≅130mg)

Gross weight (drug + petridish):38.105 g

Table 6: Moisture uptake observations at 75% RH

Time	Initial	1 hr	2 hr	4 hr	6 hr	8 hr	24 hr	48 hr	72 hr
Observed RH	75%	75%	75%	75%	75%	75%	75%	75%	75%
Observed temperature (^{0}C)	40^{0}C	40^{0}C	40^{0}C	40^{0}C	40^{0}C	40^{0}C	30^{0}C	40^{0}C	39^{0}C
Physical observation	No change	No change	No change	No change	No change	No change	No change	No change	No change
Observed weight(g)	1.316	1.708	1.320	1.323	1.329	1.339	1.340	1.339	1.321
Percentage moisture uptake	0%	0.56%	0.676%	0.89%	1.03%	1.11%	1.14%	1.108%	0.817%

Table 6: Stability study data

Parameters Tested	Storage Conditions		
	Initial	40^{0}C±2^{0}C / 75% ±5% RH	
		1st month	2nd month
Description	White coloured flat faced	No change	No change
Average weight (mg)	130.5	130.4	130.3
Thickness(mm)	3.79	3.80	3.81
Hardness (kp)	4.0	3.9	3.5
% Friability	0.51	NA	NA
Disintegration time (sec)	20	20	22

CONCLUSIONS

F1 was carried out using supertab 11SD as a diluent, crospovidone (3%) as Superdisintegrant & mg.stearate (1.15%).In this, disintegration time was very high. F2 was carried out using supertab 11SD as a diluent, crospovidone (4%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was very high with loss of friability. F3 was carried out using supertab 11SD as a diluent, crospovidone (5%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was high with loss of friability was very high. F4 was carried out using supertab 11SD as a diluent, Ac-di-sol (3%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was very high. F5 was carried out using supertab 11SD as a diluent, Ac-di-sol (4%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was very high with loss of friability. F6 was carried out using supertab 11SD as a diluent, Ac-di-sol (5%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was high with loss of friability was very high.

F7 was carried out using supertab 11SD as a diluent, Sodium starch glycolate (3%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was very high. F8 was carried out using supertab 11SD as a diluent, Sodium starch glycolate (4%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was good. F9 was

carried out using supertab 11SD as a diluent, Sodium starch glycolate (5%) as Superdisintegrant & mg.stearate (1.15%). In this trial disintegration time was good.

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