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Original Article

Formulation and Evaluation of Fast Disintegrating Sublingual Tablets of Rizatriptin Using Different Superdisintegrants

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ABSTRACT

The aim of present study was to design and evaluate fast disintegrating sublingual tablets of Rizatriptan using different super-disintegrants. Migraine is a common type of headache that may occur with symptoms such as nausea, vomiting or sensitivity to light. In many people, a throbbing pain is felt only on one side of the head. The oral dispersible dosage forms are less effective as they undergoes first pass metabolism. Compared with ODT, the onset of action produced by sublingual tablets is faster. Rizatriptan is one of the widely used drugs for the treatment of migraine. The objective of the present study was to develop fast disintegrating sublingual tablets of Rizatriptan using different superdisintegrants like croscarmellose sodium, crospovidone and L-HPC in different concentrations. The tablets were evaluated for pre compression and post compression parameters. Among all the formulations, F3 was selected as best formulation and stability studies of the prepared tablets (F3) were performed at certain conditions as per ICH guidelines.

Keywords: sublingual tablets, rizatriptan, super disintegrants, direct compression

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility and most importantly, patient compliance [1]. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules [2]. Dysphagia is associated with many medical conditions, including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy [3]. The most common complaint is tablet size, followed by surface form and taste. The problem of swallowing tablets is more evident in geriatric and pediatrics patients, as well as travelling patients who may not have ready access to water [4, 5]. These studies show an urgent need for a new dosage form like FDDS that make tablets disintegrate in the mouth without chewing or additional water intake and thus improve patient compliance [6]. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance [7]. One such a novel technology includes oral fast-dispersing dosage forms which are also known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets [8]. Pharmaceutical marketing is one reason for the increase in available fast-dissolving or disintegrating products. As a drug entity reaches the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A dosage form allows the manufacturer to extend the market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen [9].

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through sublingual blood vessels bypass the hepatic first pass metabolic process. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action [10, 11]. The sublingual administration of the drug means placement of drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into reticulated vein which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein and braclocephalic vein and then drained into systemic circulation [12]. The aim

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of present study was to prepare and evaluate rizatriptan sublingual tablets using direct compression method.

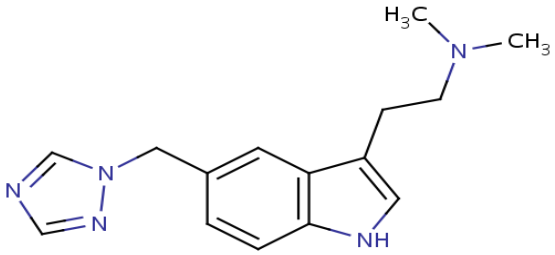

Fig. No. 1: Structure of Rizatriptan

MATERIALS AND METHODS

Materials: All the samples were commercially obtained. Rizatriptan (Taj Phramaceuticals Limited, India), Crospovidone (Jiaozuo Yuanhai Fine Chemicals, Japan), Croscarmellose sodium (Amish drugs and chemicals, Ahmedabad), low substituted hydroxyl propyl cellulose (Shin-etsu chemicals co Ltd, Japan), mannitol (Merk, India), aspartame (S.D. fine chemicals, Mumbai), magnesium stearate (Harish Chemicals Pvt Ltd, Ahmedabad), potassium dihydrogen ortho phosphate (Qualigens Fine Chemicals Pvt Ltd, Mumbai), sodium hydroxide pellets (Qualigens Fine Chemicals Pvt Ltd, Mumbai), hydrochloric acid (Qualigens Fine Chemicals Pvt Ltd, Mumbai), KBr IR grade (Qualigens Fine Chemicals Pvt Ltd, Mumbai).

Drug excipient compatibility studies

FTIR Spectroscopy: Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic pressure at 10tons pressure. It was scanned from 4000-400cm^{-1} in FTIR spectrophotometer. The IR Spectrum of physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Preparation of sublingual tablets by direct compression method: The fast disintegrating sublingual tablets of Rizatriptan (5mg) were prepared through direct compression method. According to the composition, various steps (Sieving, Dry mixing, Lubrication & Compression) involved in the tablet production by direct compression method were orchestrated below:

- **Sieving:** The active ingredient was passed through the sieve #40 followed by other ingredients through the same sieve.
- **Dry Mixing:** All the ingredients (Including the active ingredient) were taken in poly bag and mixed for 5mins to ensure uniform mixing of the ingredients with the drug.
- **Lubrication:** The Magnesium Stearate mixed with the powder mixture in a poly bag for 5mins to get a uniform blend.
- **Compression:** Finally, the powder mixture was compressed into tablets using 7mm Flat shaped punches in single rotary tablet compression machines at the weight of 100mg each.

Table 1: Composition of Rizatriptan fast disintigratting sublingual tablets

Ingredients	Quantity for tablet (mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Rizatriptan	5	5	5	5	5	5	5	5	5	5
Crospovidone	3	4	5	-	-	-	-	-	-	3
Croscamellose sodium	-	-	-	3	4	5	-	-	-	3
L-HPC	-	-	-	-	-	-	3	4	5	-
Mannitol	89	88	87	89	88	87	89	88	87	86
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

EVALUATION OF POWDER MIXTURE

Bulk density: Weighed quantity of powder was transferred into a 50 ml measuring cylinder without tapping. During transfer the volume occupied by powder was measured. It is expressed in gm/ml. Bulk density was measured by using formula.

$$P = m/V_o$$

Where
P = Bulk density
V_o = Untapped volume
m = mass of the blend

Tapped density: Weighed quantity of powder was taken into graduated cylinder, volume occupied by powder was noted down. Then cylinder was subjected to 500 taps in tapped density tester.

$$P_t = m/V_i$$

Where,
P_t = Tapped density
V_i = Tapped volume
m = Mass of the blend

Angle of repose: The powder blend was assessed for its flow property by determining the angle of repose. The angle of repose was measured by allowing the powder to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height. The height of the heap was measured and then circumference of the base of heap was drawn on graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

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

Where
θ = angle of repose
h = height of the heap
r = radius of the base of the heap

Carr's Index: After determining the bulk density the powder was then tapped mechanically for 100 times till a constant volume called tapped bulk volume was obtained. Using bulk density and tapped density, the percentage compressibility of the powder was determined, which is given as carr's compressibility index.

Carr's compressibility index (%) = Tapped density-bulk density/ tapped density
Bulk density = mass of powder/ untapped volume of packing
Tapped density = mass of powder/ tapped volume of packing

Hausner's Ratio: It was determined by the ratio of tapped density and bulk density [13]

$$\text{Hausner's ratio} = V_o/V_i$$

Where
V_o = Bulk density
V_i = Tapped density

Table 2: Limits for flow properties of powder

S.NO	Type of flow	Angle of Repose	Carr's Index	Hausner's Ratio
1	Excellent	25-30	10	1-1.11
2	Good	31-35s	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.54
7	Very very poor	>66	>38	>1.60

EVALUATION OF SUBLINGUAL TABLETS

The formulated tablets were evaluated for the following parameters.

General appearance: The formulated tablets were assessed for their general appearance and observations were made for shape, colour, texture, and odour.

Thickness: The thickness of the formulated Rizatriptan fast disintegrating sublingual tablets was measured by using digital vernier calipers.

Uniformity of weight: 20 tablets were selected and were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 200mg tablets and none by more than double that percentage [14].

Hardness test: Hardness of the tablet was determined using the Pfizer hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force [15].

Friability test: 20 previously weighed tablets were placed in the apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula [16]

Percentage friability = [(Initial weight-Average weight) / (Initial weight)] X 100

Disintegration test: Tablet disintegration study was performed in disintegration apparatus. One tablet in each of the six tubes in the basket were placed and the basket rack was positioned in a one litre beaker of water, at 37°C±2°C. The machine was operated until the tablets were completely disintegrated.

Drug content: For the content uniformity test, 10 tablets were weighed and puverized to a fine powder, a quantity of powder equivalent to 5mg of rizatriptan was transferred into a 10ml standard flask and the volume was made with mobile phase. Further 10ml of the above solution was diluted to 10ml with mobile phase.

Wetting time: The tablet wetting time was measured by placing the tablet at the centre of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with pH 6.8 phosphate buffer, excess buffer was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stop watch.

Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of buffer pH 6.8. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$$R = 100 \times W_a - W_b / W_a$$

Where, W_a = Weight of tablet after water absorption

W_b = Weight of tablet before water absorption

***In vitro* dissolution studies:** *In vitro* Dissolution Studies of fast disintegrating sublingual tablets was determined with the help of USP dissolution apparatus type II. The fast disintegrating tablet was placed in dissolution flask which contains 900 ml 6.8 pH phosphate buffer as dissolution medium. The flask was maintained at $37^0 \pm 0.5^0$C by a constant temperature bath. The motor was adjusted to turn at the specified speed (50 rpm) and sample of the fluid are withdrawn at intervals of 2, 4, 6, 8 and 10 minutes respectively to determine the amount of drug in the solution [17].

Stability studies of the tablet: Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously. Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess their physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance of drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light enabling recommended storage conditions, re-test periods and shelf- lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of the accelerated stability studies are adapted.

Method: The selective aluminium packed formulations were stored at 25°C/60%RH and 40°C/75%RH for 12 weeks and evaluated for their physical appearance and drug content at specified interval of time. The formulations were further scanned to observe any possible spectral changes. And also in vitro dissolution studies were performed.

RESULTS AND DISCUSSION

Drug –Polymer compatibility studies by FTIR:

The FTIR spectra of Rizatriptan, Crospovidone, L-HPC, Croscamellose Sodium and the combination of drug and polymers showed no significant interaction between drug and polymer. Hence the drug and the polymer are compatible with one another.

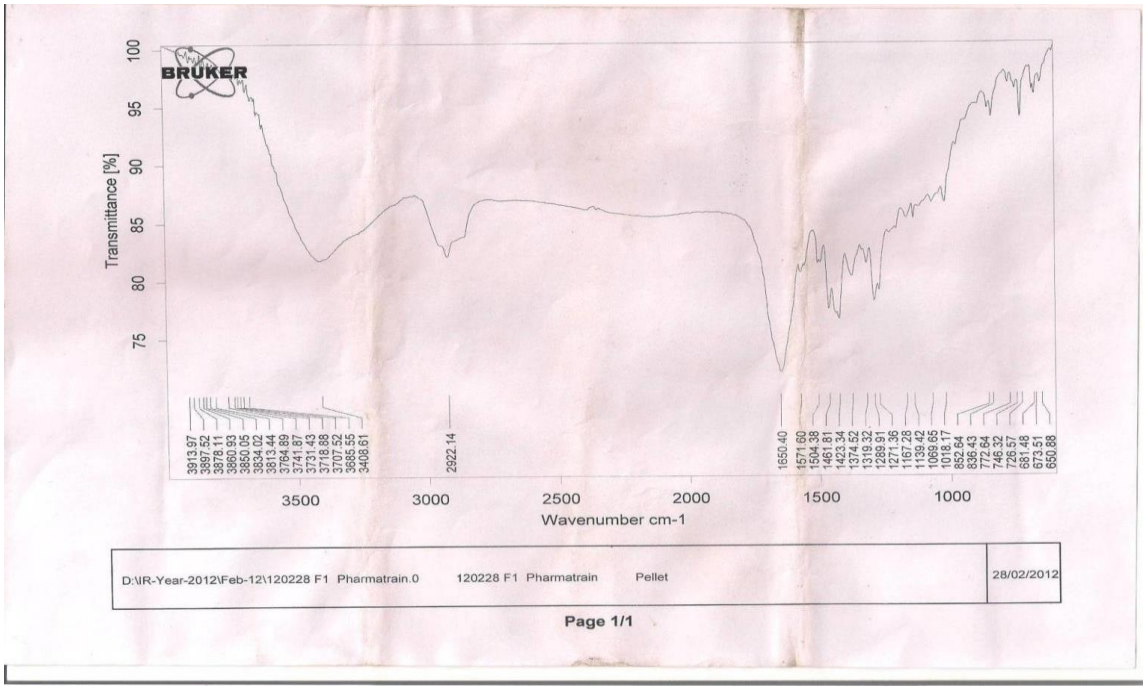

Fig No.2: FTIR spectrum of Rizatriptan

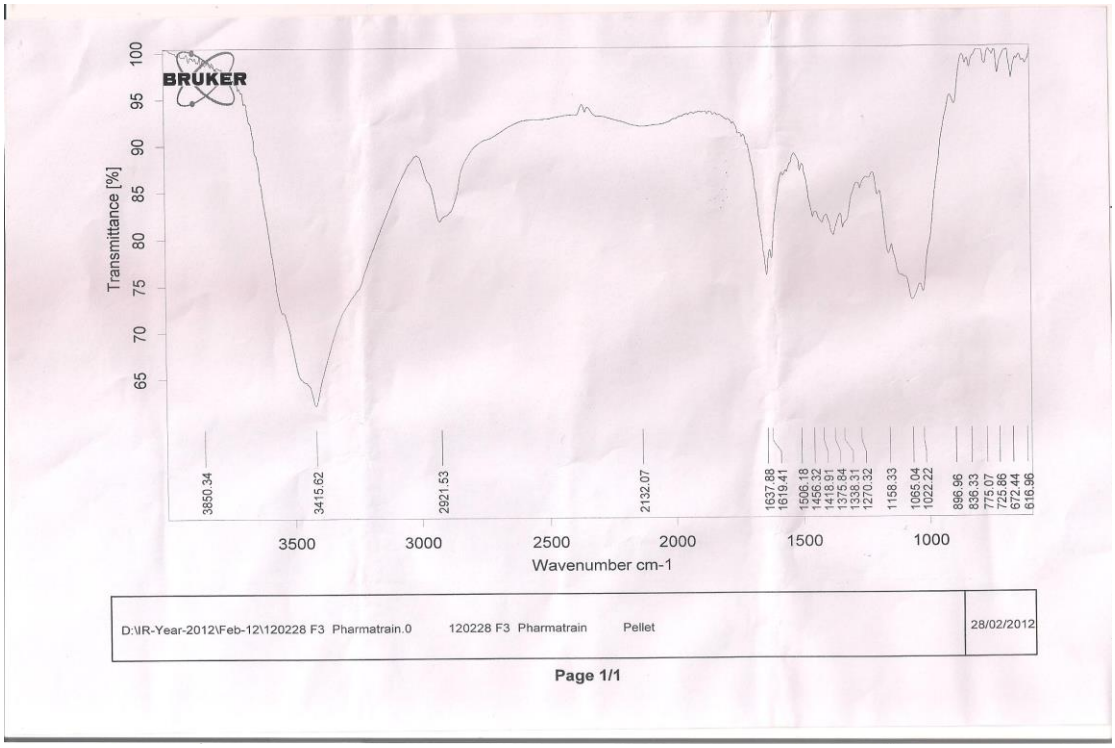

Fig. No. 3: FTIR Spectrum of Rizatriptan+ Crospovidone

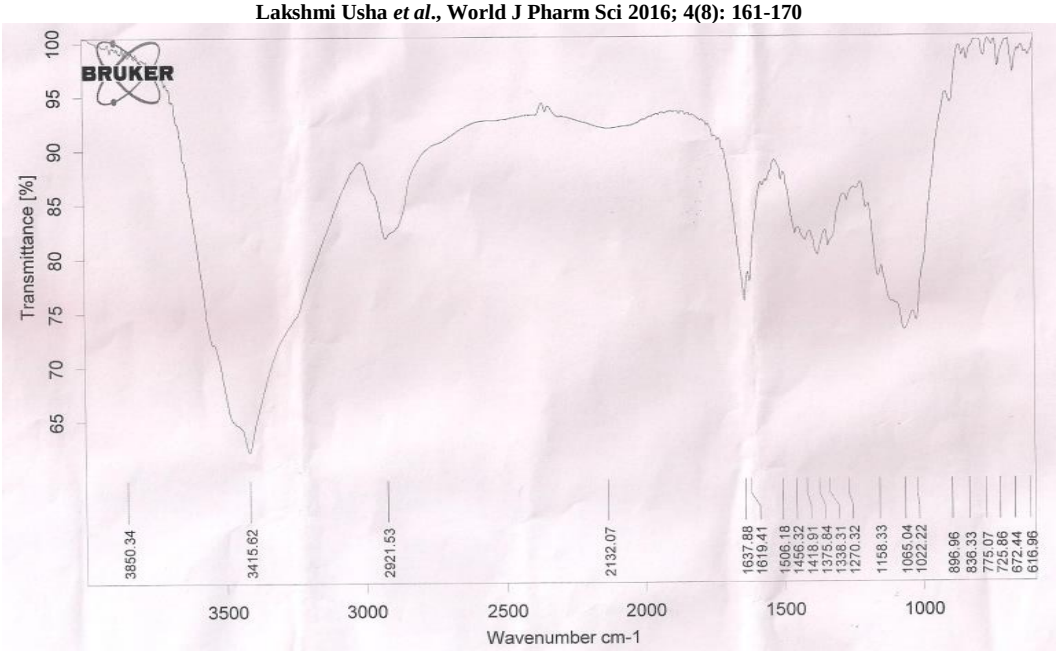

Fig. No. 4: FTIR Spectrum of Rizatriptan + Croscamellose sodium

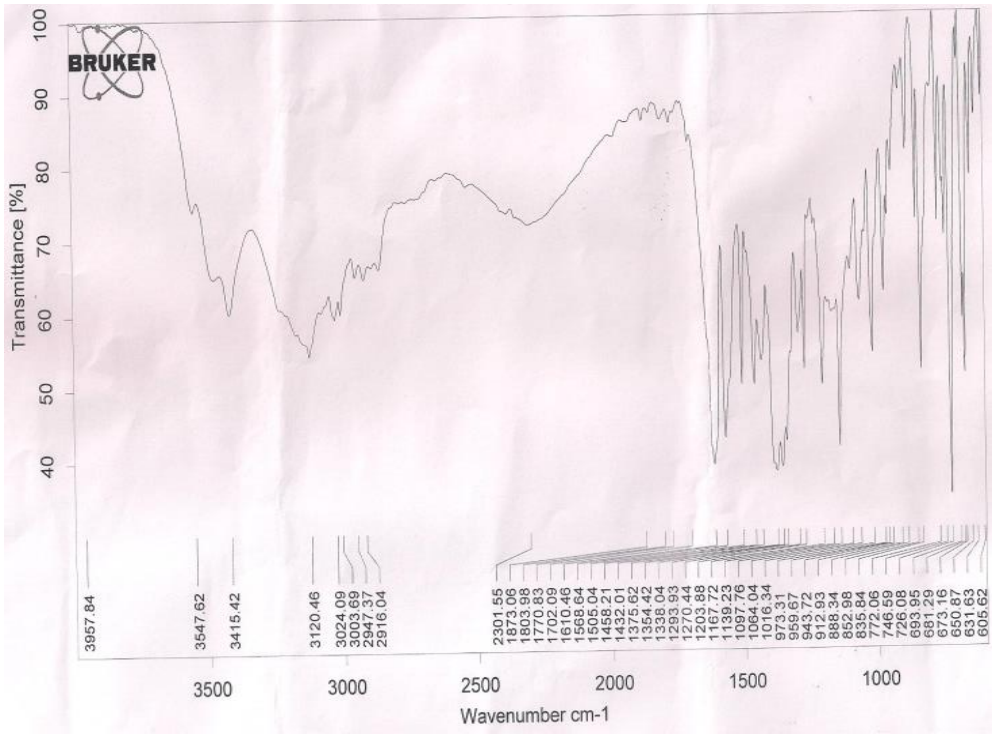

Fig. No. 5: FTIR Spectrum of Rizatriptan + L-HPC

Flow properties: The powder substances of drug and other excipients used for the formulation of Rizatriptan Fast disintegrating Sublingual tablets were evaluated for derived and flow properties include bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio before carry out the formulations. Angle of repose of the powder mixture prepared for tablet preparation ranged from 29.9°- 32.3° and was within the pharmacopeial limits. The bulk density and tapped density of the powder mixture were within the limits and the values are 0.22-0.27 g/cm^3 and 0.24-0.29 g/cm^3 respectively. The compressibility index was calculated for the powder mixture and was within the range of 10.45-14.21%. The Hausner's ratio was calculated and the range of the ratio is 1.11-1.15. If the ratio value is closer to one then the powder mixture has good flow property. The values of blend parameters evaluated within the prescribed limits and shows good free flow property.

Table 3: Results of Derived properties

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.27±0.01	0.25±0.015	32.3±0.2	10.45±1.97	1.14±0.02
F2	0.25±0.015	0.24±0.02	32.1±0.2	11.23±1.96	1.13±0.03
F3	0.26±0.015	0.26±0.01	31.5± 0.12	11.49±3.97	1.13±0.05
F4	0.25±0.015	0.29±0.015	30.43±0.14	12.02±1.81	1.15±0.02
F5	0.23±0.02	0.27±0.03	30.01±0.11	11.87±2.25	1.13±0.03
F6	0.24±0.01	0.27±0.006	30.05±0.13	11.38±3.16	1.13±0.04
F7	0.23±0.025	0.27±0.025	29.9 ±0.15	10.46±1.19	1.12±0.02
F8	0.22±0.01	0.26±0.017	30.98±0.11	10.59±3.61	1.12±0.05
F9	0.24±0.01	0.28±0.025	32.17±0.14	10.87±2.84	1.11±0.04
F10	0.22±0.015	0.26±0.032	31.78±0.12	14.21±1.11	1.15±0.01

Hardness test: The hardness of tablets of each batch ranged between 2.4 to 3.1 kg/cm^2. This ensures good handling characteristics for all batches.

Friability Test: The Percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight Variation Test: All the formulated (F1 to F10) tablets passed weight variation test as the % weight variation was within the standard pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Table 4: Results of post compression parameters

Formulation Code	Average weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	101.4	2.8	2.8	0.25
F2	101.67	2.7	2.79	0.21
F3	100.13	2.8	2.84	0.26
F4	101.9	2.9	2.91	0.22
F5	101.7	2.7	2.84	0.24
F6	101.6	2.5	2.67	0.23
F7	101.63	3.1	2.79	0.21
F8	99.96	2.9	2.81	0.23
F9	101.56	2.9	2.77	0.24
F10	100.34	2.4	2.86	0.22

Drug content: In order to estimate the amount of drug in each tablet for the therapeutic activity of Rizatriptan, the prepared tablets were evaluated for drug content as triplicate and the drug content was found to be in the range between 98.34 to 102.1%. The observed results indicate reproducible with minimum intra-batch variability.

Wetting Time: The wetting time for all the formulations lies between 7.2 to 15.1 sec.

***In vitro* drug release studies:** All the formulations of prepared fast disintegrating sublingual tablets of Rizatriptan were subjected to *in vitro* release studies and these studies were carried out using dissolution media of Phosphate buffer 6.8 pH. However the formulation was prepared by direct compression method with Crospovidone 3mg and the drug release profile in pH 6.8 buffer up to 10mins dissolution time period were ranged between 56.18 to 81.96%. The percentage of super disintegrant in F1 is 3% and the % drug release at 2min is 56.18%.

Stability Studies: Stability studies were carried out as per ICH guidelines for F3 batch of this product for three months. Stability studies were performed for formulation F-3, optimized formulation. There is no change in physical appearance and there is slight increase in friability, hardness and assay. The dissolution profile of the optimized batch at 25°C±2ºC/60% ± 5% RH and 40°C±2ºC/75% ± 5% RH was calculated and observed that there is slight decrease in the percentage of drug released.

Conclusion: Various physico-chemical parameters were tested for the formulation and it showed that all the results were within the specified values. From the release study and mathematical models it was concluded that the novel formulation can bypass the first pass metabolism and produce a quicker onset of action.

Table 5: Results of post compression parameters

Formulation Code	Water Absorption Ratio(%)	Drug Content (%)	Wetting Time (Sec)	Disintegration Time (Sec)
F1	27.18	99.91	12.3	15
F2	31.24	99.20	11.4	14
F3	34.17	99.54	9.3	12
F4	32.14	98.34	15.1	17
F5	29.38	101.11	12.5	14
F6	34.37	99.5	10.4	13
F7	40.24	102.1	14.5	18
F8	36.28	98.99	13.1	15
F9	38.34	99.32	11.4	14
F10	42.18	100.27	7.2	11

Table 6: *In vitro* release profile of Rizatriptan sublingual tablets

Time in mins	% Drug Release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
2	56.18	61.27	68.32	52.78	57.26	65.37	51.51	58.42	64.39	72.46
4	62.24	69.46	74.43	59.24	62.47	72.14	57.34	63.21	69.43	79.31
6	69.72	74.34	82.69	65.46	69.43	79.42	62.64	69.48	76.79	86.44
8	74.47	81.12	89.42	77.18	76.27	88.65	68.27	76.82	85.87	92.18
10	81.96	90.46	98.79	78.34	87.38	95.9	77.38	85.87	92.54	99.34

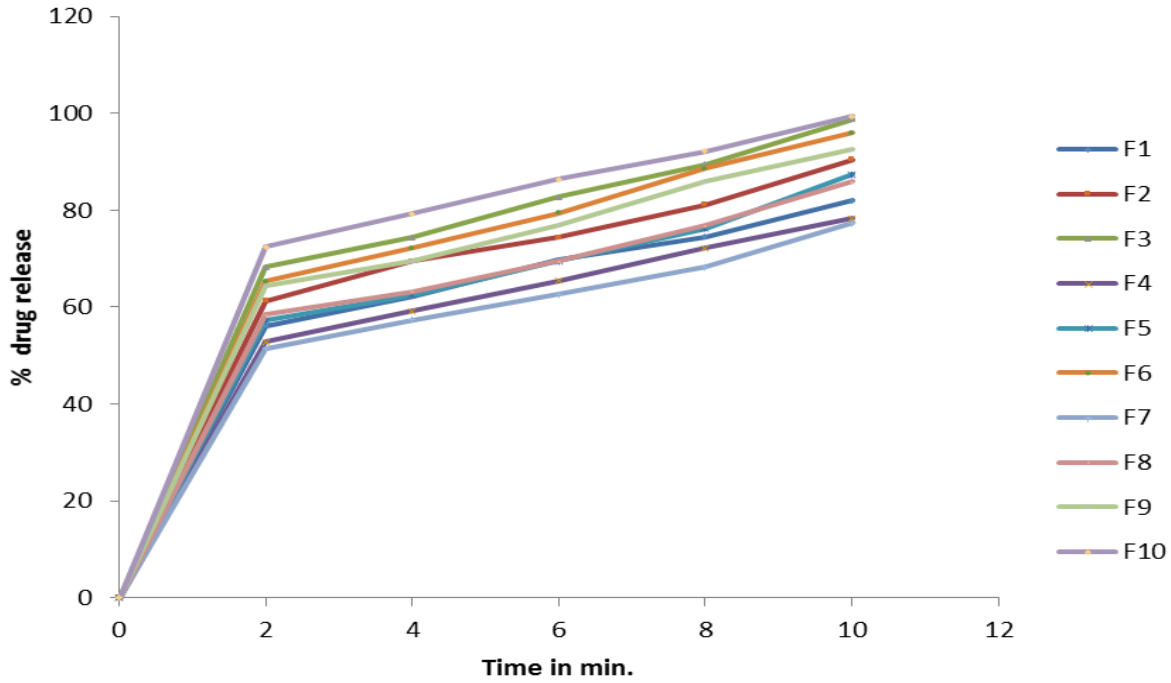

Fig No. 6: Drug release profile of all formulations

Table 7: Stability studies

S.No	Parameters	Stability conditions at	
		25°C 60%RH	40°C 75% RH
1	Physical appearance	No change	No change
2	Friability	0.26%	0.263%
3	Hardness	2.8 kg/cm^2	2.9 Kg /cm^2
4	Assay	99.54%	99.55%

Table 8: Evaluation parameter values at different temperature conditions
Drug release profile for Formulation F3

Time in min	% drug release at 25°C±2ºC/60%± 5%RH	% drug release at 40°C±2ºC/75% ±5%RH
0	0	0
1	68.34	68.35
2	74.47	74.47
3	82.68	82.68
4	89.47	89.45
5	98.82	98.81

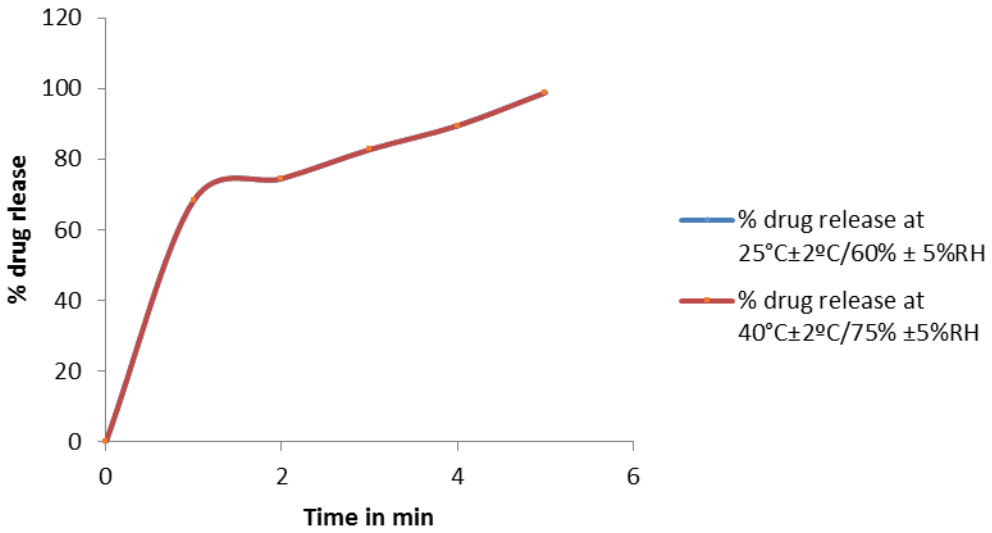

Fig No. 7: **Dissolution profile of optimized batch F3 at 25°C±2ºC/60% ± 5% RH And at 40°C±2ºC/60% ± 5% RH**

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