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PREPARATION AND EVALUATION OF RIZATRIPTAN SUBLINGUAL TABLETS BY USING SUPERDISINTEGRANTS

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ABSTARCT
The present aim of study is to formulate and evaluate Sublingual tablets of Rizatriptan. Super disintegrating agents like Sodium starch glycolate, Gellan gum, and Croscarmellose sodium were employed has to increase the solubility and dissolution rate of the Rizatriptan drug molecule. Formulation of sublingual tablets was carried out by using direct compression method in 8 station rotary punching machine with a 6mm punch for all formulations. The mixture of nine formulations was passed Pre-compression and Post-compression parameters and they passed all the quality control parameters as per IP limits. The FTIR and DSC studies were analyzed for compatibility studies. The F4 formulation was considered as the optimized formulation as it shown maximum amount of release of drug was found to be 99.16% in 8 min. Gellan gum as a super disintegrant shown maximum drug release in the concentration of 10mg in F4 formulation.

KEYWORDS: Rizatriptan, Croscarmellose Sodium, Gellan Gum and Sodium Starch Glycolate.

1. INTRODUCTION
Sublingual administration of drugs shows the fast onset of action is carryout as compared to oral route. The retention time of sublingual medication is three to ten times greater than the oral route and is just passed by the hypodermic infusion method. Sublingual route has several advantages over the avoidance of first-pass metabolism, progressed patient compliance and ease of self-medication. This course has particular points of interest over the enteral and parenteral course of medication because of its high blood supply, the onset of action and improved bioavailability into the systemic circulation.[1] Various components like pH, molecular weight, and lipid solubility may exploit this technique. From these properties, a solvent medication may disperse too gradually through the mucosa to be dynamic. The sublingual glands are also considered as salivary glands which produce the mucin and helps in the fabrication of saliva, required for the breakdown of particles. These glands present in the lining of the oral cavity that is below the tongue. This also provides slippery that helps in chewing and swallowing the food. The amount of drug that reaches into the systemic circulation from the site of administration is directly proportional to membrane thickness. It is expressed in the following order Sublingual>buccal>gingival>palatal.[2]

Because of greater permeation and high blood supply, this release rapid onset of action and instant dosing regimen with less delivery period of drugs with the sublingual route. Sublingual means "under the tongue". It is considered to a method of placing drug via mouth so that the drug highly absorbed through blood vessels below the tongue more than digestive track. The sublingually administered drug pharmacologically activates in 1 – 2 minutes which is effectively impressed in this route. Some of the drugs which are administered through the sublingual route are Steroids, barbiturates, cardiovascular drugs, and enzymes. This administered drug directly reaches to nutritional benefits which avoid subject to gastric system and liver.[3]

1.1 Factors Affecting the Sublingual Absorption.[4,5]
1. Solubility in Salivary Secretion
2. Binding to Oral Mucosa
3. pH and pKa of The Saliva
4. Lipophilicity of Drug
5. Thickness of Oral Epithelium.

Rizatriptan is a selective 5-HT 1B/1D agonist receptors have week affinity towards 5-HT1A, 5-HT5A AND 5-HT7 receptors and there is no pharmacological activity for 5-HT2, 5-HT3 OR 5-HT4 receptor subtypes. It helps to relieve a headache, pain, and other migraine symptoms including nausea, vomiting, sensitivity to light/sound. The migraines can be easily treated to return your normal routine and decreases the pain medications.

And also it relieves the pain caused by certain nerves in the brain.[6]

2. MATERIALS AND METHOD

2.1 Materials: Rizatriptan is a gifted sample collected from Aurobindo Pharmaceutical Ltd., Hyderabad, Microcrystalline cellulose from Signet chemical corp, Sodium starch glycolate from Aurobindo Pharma Ltd., Hyderabad , Gellan gum from Aurobindo Pharma Ltd., Hyderabad, Croscarmellose sodium from Signet Chemical Corp, Magnesium stearate from S.D.Fine Chemicals Ltd, Talc from S.D. Fine Chemical Ltd.

2.2 Method: Preparation of sublingual tablets is done by using direct compression methods for nine formulations were prepared at different ratios.[7,8]

The mixture of all formulations were weighed and collected in a poly bag with different ratios with excipients. The powdered blend was compressed by using 8station with 6mm flat punch, B tooling rotary tablet machine. Each tablet contains 10 mg of Rizatriptan and other pharmaceutical ingredients. Total weight of the tablet is 150 mg. The composition of various formulations as shown in the table No. 1.

Table No. 1. Composition of F1 to F9 formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rizatriptan	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Croscarmellose Sodium	10mg	15mg	20mg	-	-	-	-	-	-
Gellan Gum	-	-	-	10mg	15mg	20mg	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	10mg	15mg	20mg
Magnesium Stearate	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Talc	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Mcc	124mg	119mg	114mg	124mg	119mg	114mg	124mg	119mg	114mg
Total Weight	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg

2.3 Evaluation Tests

2.3.1. Precompression parameters.[9,10]

Precompression parameters were studied before punching a tablet.

2.3.1.1 Bulk density

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk voume of the powder}}$$

It is measured in gm/ml.

2.3.1.2 Tapped density

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

It is measured in gm/ml.

2.3.1.3 Compressibility index

$$\text{carrs index\%} = \frac{\text{tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ x } 100$$

2.3.1.4 Hausner's Ratio

$$\text{Hausner Ratio} = \frac{\text{tapped density}}{\text{bulk density}} \text{ x } 100$$

2.3.1.5 Angle of Repose

The tangent angle of repose (θ) was calculated by an equation,

Tan θ = h/r

Angle of repose (θ) = tan-1(h/r)

Where,

h=height of the pile, r=radius of the pile, θ=angle of repose.

2.3.2 Drug- Excipient Compatibility Studies.[11,12]

2.3.2.1 FT-IR (Fourier Transform Infrared)

FT-IR study was carried out to find out the compatibility between the pure drug of Rizatriptan and polymers such as gellan gum, sodium starch glycolate, and crosscarmellose sodium. The prepared tablet powder was kept in the sample holder and scanned between the ranges of 4000cm^{-1} to 400cm^{-1}. The amount of Rizatriptan loaded into sublingual formulation was analyzed in FT-IR. The obtained spectra was compared and interpreted with the functional group peaks.

2.3.2.2 Differential Scanning Colorimetry

The molecular state of the drug and optimized formulation was analyzed. The sample was heated in hermetically aluminum pans between the ranges of 35°C-350°C at a constant rate of 10.0°C/min under a nitrogen purge at 20ml/min.

2.3.3 Post compression parameters.[13,14]

2.3.3.1 Weight variation

Variations in weight were tested in randomly selected 20 different tablets from every batch. Digital electronic balance (Citizen CTG-302, India) is used for measuring weight variations. Then individual tablets were weighed and compared with an average weight of tablets. Weight values were reported in mg.

2.3.3.2 Hardness

Place the tablet on the holder. Set the "0" on Monsanto tester scale. Press the tablet. The range of Monsanto hardness tester is "0 to 20" kg. When the tablet breaks read the pressure applied and cleans the holder. It is measured in kg/cm^2.

2.3.3.3 Thickness

The thickness of the 20 tablets was measured from each formulation. Digital Vernier caliper is used for this study and it gives accurate measurements and information about variation between tablets. It is measured in mm.

2.3.3.4 Friability (F)

Connect the main socket. Weigh the tablets before placing it in the friability apparatus. Place 10 tablets in friability test apparatus. Switch "ON" the mains. Take out tablets after 100 revolutions at 25rpm have completed. Switch "OFF" the mains. Clean a friability test apparatus with muslin cloth. Reweigh the tablets and friability percent was calculated using the following formula.

$$\%\text{Friability} = \frac{\text{Tablet weight before friability} - \text{Tablet weight after friability}}{\text{Tablet weight before friability}} \times 100$$

2.3.3.5 Wetting time[15]: The initial process in the disintegration of sublingual tablets involves water uptake and wetting of the tablet. So the determination of wetting time is also important. A Petri-dish containing 6 ml of the distilled water is taken and tissue paper folded twice is placed in it. The time required for the upper surface of the tablet to become complete wet is the wetting time.

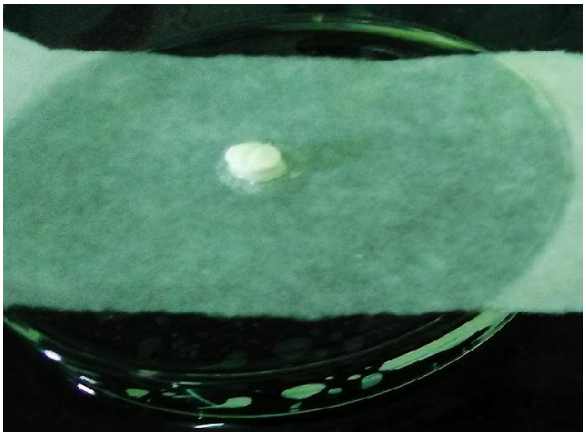

Figure No. 1. wetting time of sublingual tablet (F4).

2.3.3.6 Water absorption ratio.[15]

A pre weighed table (W_1) is taken and placed in a petridish contains 6ml of distilled water. After complete absorption of tablet weight of the wetting tablet was measured (W_2).Water absorption ratio R is calculated as

$R = W_2 - W_1/W_1 \times 100$

Where, W_1 = Weight of the tablet before immersing in water

W_2= Weight of the tablet after immersing in water.

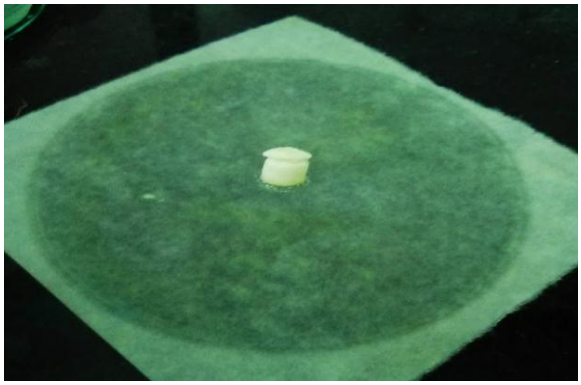

Figure No. 2. Water absorption ratio of sublingual tablet (F4).

2.3.4 *Invitro* dissolution studies.[16]

In-vitro drug release studies were carried out using a modified USP-II dissolution test apparatus (Lab India, DS-800). The dissolution medium was filled with phosphate buffer of pH 6.8 in each test tube containing 500ml buffered solution at a speed of 50rpm at 37°c. For every 1 minute samples of dissolution medium (5ml) were taken out and assayed for Rizatriptan by measuring the absorbance at 259nm. For all tests 5ml of test samples were collected and replaced with 5ml of phosphate buffer pH 6.8 at specific periods of time.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies

3.1.1 Spectrophotometric Studies

Standard Calibration curve of Rizatriptan

Table No. 2. Concentration and absorbance obtained for calibration curve of Rizatriptan in pH 6.8 phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 259 nm)
1	0	0±0
2	0.5	0.1599±0.0003
3	1	0.3079±0.0003
4	1.5	0.4507±0.0002
5	2	0.6029±0.0004
6	2.5	0.7349±0.0002

*All values are the mean of six readings± SD

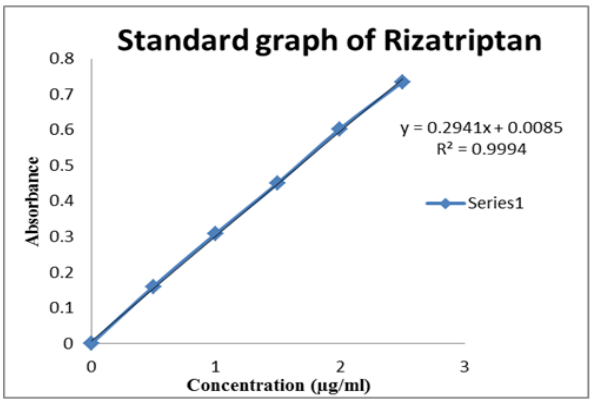

Figure No. 3. Standard graph of Rizatriptan in pH 6.8 phosphate buffer.

3.2. Compatibility Studies of Rizatriptan Sublingual Tablets

3.2.1. Fourier Transform Infrared Spectroscopy

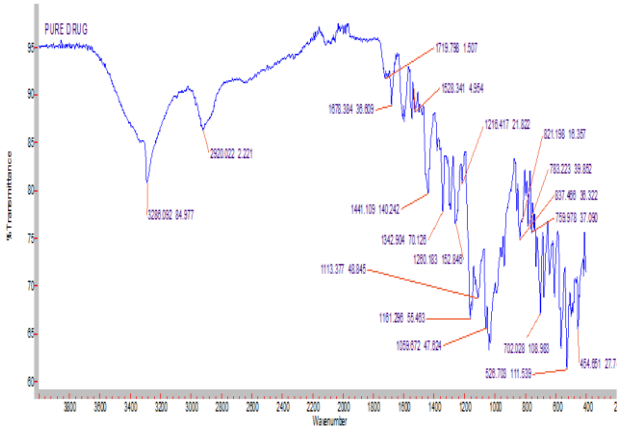

Figure No. 4. FTIR Spectrum of pure drug.

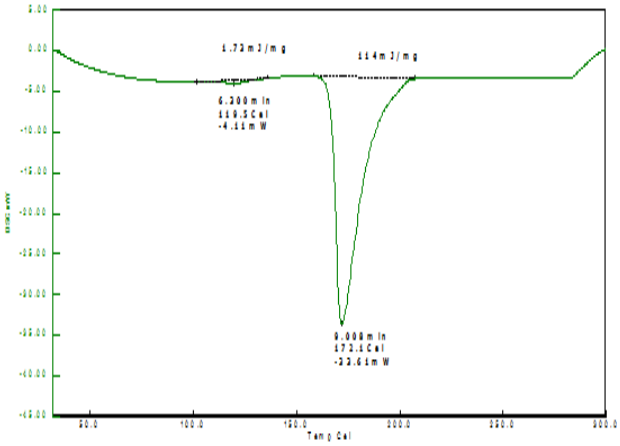

Figure No. 5. FTIR spectrum of optimized formulation.

Table No. 3. Frequency ranges of Rizatriptan (Pure drug) and Optimized formulation.

S. No.	Frequency of Pure Drug	Frequency of Optimized Drug	Frequency Range	Functional Group
1	3286.092	3282.477	3600-3200	Alcohol O-H stretch
2	1678.384	1678.966	1680-1600	C=C alkene
3	1528.341	1477.815	1600-1400	C=C aromatic
4	1441.109	1441.838	1480-1440	CH_2 bend
5	1342.904	1348.488	1400-1300	NO_2 stretch
6	1113.377	1112.543	1400-1000	C-F

The FT-IR of Rizatriptan exhibits reported peak values in the range of Pharmacopeial limit. The FT-IR of a mixture (Rizatriptan +excipients) exhibits the reported values within the FTIR frequency ranges. From the report of FTIR data, it was concluded that there is no interaction between Rizatriptan pure drug and mixture (Rizatriptan+excipients). As shown in table no.3.

3.2.2 Differential scanning colorimeter

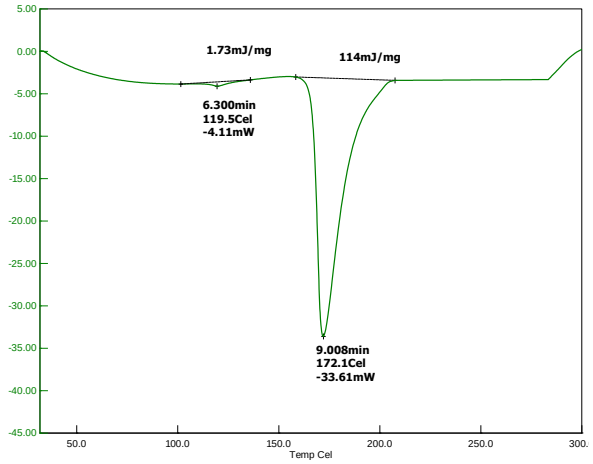

Figure. No. 6. Differential scanning colorimeter spectrum of Rizatriptan.

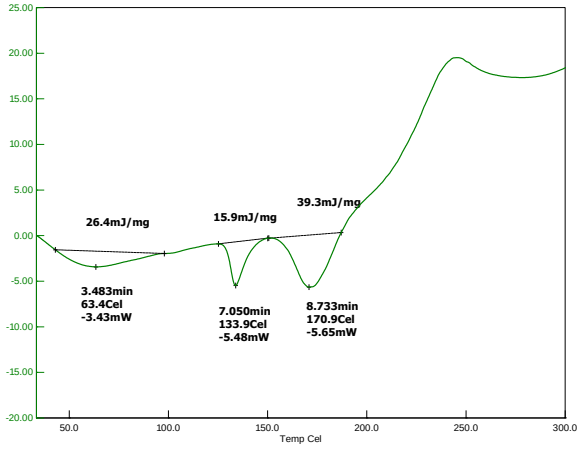

Figure. No. 7. DSC of optimized formulation (F4).

- Pure drug of Rizatriptan and optimized formulations (drug+excipients) of both thermogram show very high peak values. Pure drug melts at 172.1ºC and optimized formulation melts at 170.9ºC. DSC thermogram results showed that there is no change in the melting point of drug. Hence there was no compatibility between the pure drug and excipients.

3.3 Pre-compression parameters

Table No. 4. Pre-compression parameters.

Formulations	Bulk Density (gm/cm^2)*	Tap Density (gm/cm^2)*	Carr's Index (%)*	Hausner ratio*	Angle Of Repose(Ɵ)*
F_1	0.45±0.0264	0.55±0.0360	18.18±0.0458	1.22±0.0700	27.91±0.4373
F_2	0.47±0.0173	0.55±0.0482	14.54±0.0529	1.17±0.1062	28.23±0.5383
F_3	0.50±0.0300	0.58±0.0655	13.79±0.0300	1.16±0.0902	29.34±0.9651
F_4	0.46±0.0264	0.55±0.0400	16.36±0.0378	1.19±0.1108	26.71±1.0215
F_5	0.50±0.0458	0.58±0.0360	13.79±0.0416	1.16±0.0902	29.34±0.9888
F_6	0.47±0.0346	0.55±0.0346	14.54±0.0529	1.17±0.0820	28.23±0.8972
F_7	0.50±0.0435	0.58±0.0208	13.79±0.0100	1.16±0.0163	29.34±2.1704
F_8	0.41±0.0100	0.50±0.0264	18±0.180278	1.21±0.1202	26.78±1.4696
F_9	0.48±0.0360	0.57±0.0529	17±0.0500	1.19±0.0404	26.7±0.0600

*All values are the mean of three readings± SD

The data shown in Table 4. The values for angle of repose was found to be 25°-30°. The bulk and tapped density of all formulations were found in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blend was shown in the range of 13.79% to 18.18%. The Hausner's ratio falls in the range of 1.16 to 1.22. From the results, it was concluded that the powdered blend has good flow properties.

3.4 Post-compression parameters

Table. No. 5. Post compression Parameters.

Formulation code	Weight variation (mg)*	Hardness (kg/cm^2)*	Thickness (mm)*	Disintegration Time (sec)*	Friability (%)*
F1	150±1.6329	2.5±0.0816	2.34±0.9579	60±0..8164	0.43±0.0941
F2	152±4.3204	2.6±0.1414	2.24±0.0748	62±1.6329	0.34±0.1423
F3	149±2.1602	2.5±0.3265	2.29±0.0927	72±2.1602	0.49±0,0697
F4	151±4.966	2.6±0.1632	2.28±0.2141	69±0.8164	0.47±0.0668
F5	152±3.2659	2.3±0.2449	2.39±0.0941	70±0.4082	0.49±0.2624
F6	153±3.7416	2.7±0.3559	2.24±0.2785	62±1.6329	0.34±0.0848
F7	152±4.5460	2.5±0.1632	2.29±0,1930	70±0.8164	0.49±0.0535
F8	150±6.5319	2.6±0.4320	2.36±0.8309	67±2.4494	0.34±0.2135
F9	152±5.8878	2.5±0.2943	2.26±0.2039	67±2.0548	0.34±0.2006

*All values are the mean of six readings± SD

Table No. 6. Post compression parameters of Rizatriptan sublingual tablets.

Formulation Code	Wetting time(sec)*	Water absorption ratio (%)*	Assay (%)*
F1	1.03±0.00816	4.16±0.0326	97.23±0.8339
F2	1.04±0.01632	7.48±0.0902	98.55±0.4546
F3	1.15±0.02160	8.0±0.8164	98.16±0.8659
F4	1.29±0.00816	8.60±0.1632	99.24±0.8779
F5	1.50±0.01632	5.44±0.0588	98.16±0.3265
F6	1.59±0.02162	4.69±0.0294	98.55±0.9227
F7	1.05±0.00816	5.55±0.0216	98.16 ±0.6860
F8	1.02±0.01632	6.20±0.0432	99.25±0.2118
F9	1.08±0.03265	8.84±0.1423	99.25±0.1061

*All values are the mean of six readings ±SD

Weight variation test: Weight variation test for all formulations was checked and difference between the weight variation and percent deviation was checked for each tablet and were shown in table no 5. The average weight of tablet ranges from approximately 149 to 153mg. So, the permissible limit is ±10% (=100mg). It was concluded that tablet weights are within the Pharmacopeial limit.

Hardness test: The hardness for each batch of three

tablets was checked by using Monsanto hardness tester and the data's were shown in table no.5. The results confirmed that the hardness of tablets falls in the range of 2.5 to 2.7 kg/cm^2 which were IP limits.

Thickness: The Thickness of all formulations of three tablets was checked by using Vernier caliper and data's were shown in table no 5. The result has shown that the average thickness of tablet ranges between 2.24 to 2.39.

Friability: The percentage of friability for each batch was evaluated for tablets and data was shown in table no. 5.The Average friability of all formulations showed in the range of 0.34.to 0.49%. It indicates, the tablets have good mechanical resistance as per official requirement of IP.

***Invitro* disintegration time**: The tablet of each formulation was evaluated for *invitro* disintegration time. The data were shown in table no 5. The results showed in the range of 60 to 72 seconds.

Wetting time: The tablet of each formulation was evaluated for wetting time and the data was shown in table no 6. The average wetting time of all formulations ranges between 1.02 to 1.59 seconds.

Water absorption ratio: Tablets of each formulation were evaluated for water absorption ratio and the data was shown in Table no 6. The result showed that water absorption ratio lies in the range of 4.16 to 8.84%.

Assay: Assay studies were carried out for the prepared formulations and data's were shown in table 6. From assay studies, it was concluded that all formulations were showing the % drug content values in the range of 97.23 -99.25%.

***3.5 InVitro* Dissolution studies:** *Invitro* dissolution studies were carried out using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were performed for about 10 min.

Table no.7 *In-vitro* Dissolution studies of all Rizatriptan sublingual tablets

Time(min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
1	15.46±3.0496	10.83±1.1834	49.72 ± 0.7657	24.37±0.4030	31.73±0.9354	18.35±0.7266	28.45±0.9483	39.50±0.5115	12.51±0.4972
2	26.63±5.7052	26.72±4.5334	60.16± 0.7216	31.68±0.5921	34.56±0.9064	22.9±1.2083	35.28±0.7257	46.35±0.7505	26.38±1.2458
3	35.64±8.6661	36.16±0.7858	68.15±2.1475	49.37±0.6394	41.91±0.7968	38.71±1.2668	48.90±0.6963	56.28±0.7654	35.17±0.7970
4	40.38±4.0150	47.46±5.2198	72.56±0.7858	58.35±0.6491	62.48±1.124	50.16±0.8334	66.83±0.8573	69.71±0.8591	47.37±0.5848
5	46.44±6.98	58.57±1.5346	78.41±1.4697	74.37±0.7141	69.3±0.8258	64.32±1.3383	78.17±0.5463	76.26±0.8153	54.96±1.4012
6	53.64±1.9142	68.25±2.8884	83.27± 1.2947	88.18±1.3465	75.49±1.2706	76.42±0.1451	82.45±0.1643	80.14±1.3934	62.56±0.3080
7	69.82±8.4175	73.19±2.1485	87.45± 0.5242	94.65±0.7406	82.33±0.7826	80.14±0.8386	87.16±0.8659	85.26±0.3709	78.35±1.3684
8	80.56±17.968	90.16±2.4986	94.26± 0.4819	99.16±0.5953	89.65±0.6312	92.46±0.1000	92.18±0.7061	91.28±0.077	89.26±0.2698

3.5.1 *Invitro* dissolution Studies of all formulations.

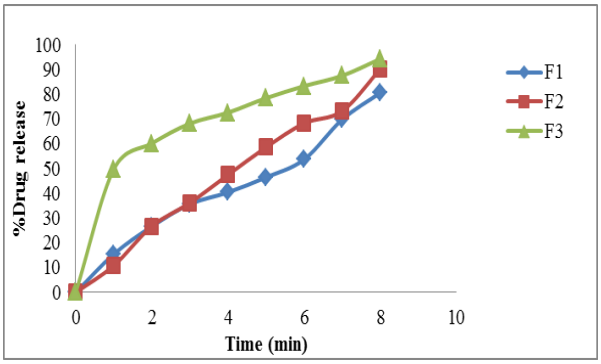

Figure No. 8 Dissolution profile of formulations prepared with Sodium starch glycollate as super disintegrate.

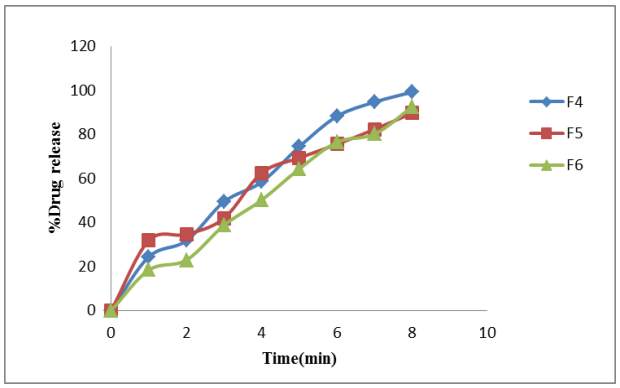

Figure no.9 Dissolution profile of formulations prepared with Gellan gum as super disintegrate.

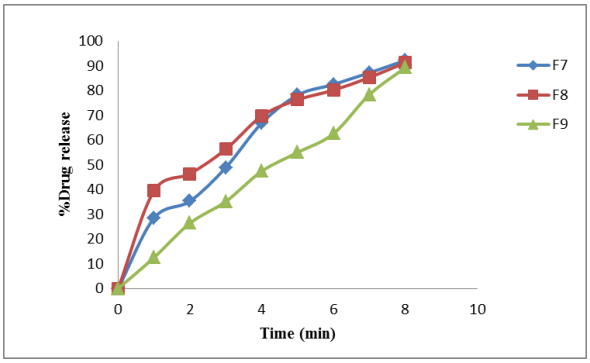

Figure. No. 10. Dissolution profile of formulations prepared with Croscarmellose sodium as super disintegrate.

From the table no.7 it was evident that the formulation prepared with super disintegrates, the gellan gum showed maximum percent of drug release in 8 min i.e. 99.16%. So, the principle of super disintegrate was found to be useful to produce Sublingual tablets. The F4 formulation was considered as optimized among all preparations.

4. CONCLUSION

In the recent work, an attempt has been made to develop Sublingual tablets of Rizatriptan. Sodium starch glycolate, Gellan gum, and Croscarmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of a selected drug molecule. Above all the formulations F4 formulation showed a maximum % drug release i.e., 99.16 % in 8 min hence it is considered as optimized formulation. The F4 formulation contains Gellan gum as super disintegrate in the concentration of 10 mg.

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