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Formulation and Evaluation of Taste Masked Fast Disintegrating Tablets of Sumatriptan Succinate

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ABSTRACT

Sumatriptan Succinate is a potent and selective 5-hydroxytryptamine agonist. It is an effective agent in the treatment of migraine. Sumatriptan Succinate undergoes extensive first pass metabolism with an oral bioavailability of approximately 15%. Thus, formulating Sumatriptan Succinate into a fast disintegrating tablets form would provide fast relief by rapid onset of action, improved oral bioavailability. Sumatriptan Succinate is extremely bitter in taste. The present research deals with development of taste masked resinate of Sumatriptan Succinate using Kyron-T-114, Tulsion-335, Kyron T-154, Kyron T-159 in 1:1, 1:2, 1:3 ratio.The drug: ion exchange resin complex was prepared by batch technique. Among these resins, Tulsion-335(1:1) was selected for further studies because of percent complexation, drug release at salivary and gastric pH, assay of drug resin complex. Formation of complex was confirmed by FTIR, DSC and X-Ray diffraction study. The fast disintegrating tablets were prepared using microcrystalline cellulose (MCC) PH 102 as diluent along with different proportions of crospovidone (CP), croscarmellose sodium (CCM), and sodium starch glycolate (SSG) as super disintegrants. These fast disintegrating tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time (DT), and dissolution study. Study concluded that the fast disintegrating tablet formulation prepared with 4% crospovidone showed less disintegration time in comparison with other formulation. The stability studies were carried out for the optimized batch for three months and optimized batch was found to be stable.

INTRODUCTION

Oral drug delivery remains the preferred route for administration of various drugs [1]. But the most evident drawback of the oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients non compliance in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.[2] Recent advances in novel drug delivery system (NDDS) aimed to enhance safety and toxicity of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast disintegrating tablets.[3]

US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the "Orange Book," an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." European Pharmacopoeia described ODTs as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" and as tablets which should disintegrate within 3 minutes. Fast disintegrating tablets (FDTs) are also known as "fast dissolving," "mouth dissolving," "rapid dissolve," "quick disintegrating," "orally disintegrating," "rapimelt," "fast melts," "orodispersible," "melt in mouth," "quick dissolving," "porous tablets," "EFVDAS," or "effervescent drug absorption system".[4]

Migraine is chronic neurological disorder characterized by pulsating headache, usually restricted to one side. It is often associated with sensitivity to light and sound, flashes of light, vertigo, and loose motion. Sumatriptan Succinate is a potent and selective 5-hydroxytryptamine agonist. It is an effective agent in the treatment of migraine attack and cluster headaches. Sumatriptan Succinate undergoes extensive first pass metabolism with an oral bioavailability of approximately 15%.[5,6] Thus, formulating Sumatriptan Succinate into fast disintegrating tablets form would provide fast relief by rapid onset of action, improve the oral bioavailability.

Sumatriptan Succinate is extremely bitter in taste. So, there is need to mask the bitter taste of Sumatriptan Succinate. Taste masking of Sumatriptan Succinate can be done by using ion exchange resins. The purpose was to enhance patient compliance.

MATERIALS AND METHODS

Sumatriptan Succinate was received as a gift sample from Azakem Labs Pvt. Ltd. Hyderabad, Kyron T-114, Kyron T-154, Kyron T-159 were received as a gift sample from Corel Pharmaceuticals Ltd. (Gujarat), Tulsion 335 received as a gift sample from Thermax India Pvt. Ltd. Sodium starch glycolate (SSG), Crospovidone, Croscarmellose Sodium was purchased from Research Lab (Mumbai). Microcrystalline cellulose, Mannitol, Magnesium stearate, Aerosil, Sodium saccharin were of analytical grade.

1 Preparation of Drug: Resin Complex

1.1 Activation of Resin[7]

Changing the ionic form of IER might occasionally be required to convert a resin from one form to another if it does not have the desired counter ions.The conversion can be achieved by soaking the resins with acid or alkali solutions, respectively. After changing the ionic form, the resin is subjected to washing with distilled water until elute becomes neutral interaction and finally, is dried at 50°C. Accurately weighed resin, was placed on a filter paper in a funnel and then it was washed with double distilled water. For Acid- alkali activation, resin was treated with 1 N HCl and 1N NaOH (1 N HCl: 1N NaOH = 50:50). This activated resin was used for complexation process.

1.2 Preparation of Drug: Resin Complex[8,9]

Formulation of drug resin complex was done by the batch process. Kyron T-114, Tulsion-335 Kyron T- 154, Kyron T-159 were selected as ion exchange resins. Ion exchange resins (both strong and weak cation exchange resins) were weighed accurately. Each of the ion exchange resin was swelled by stirring in 25 ml of water for 30 min using a magnetic stirrer. After 30 min, the accurately weighed quantity of drug was added to slurry of resin during stirring. The resultant mixture of drug and ion exchange resin was stirred for 5 hours. Resinate thus formed was filtered, and the drug content was determined spectrometrically at 226.70 nm. The residue was washed with 10ml water and dried at 40°C. Solid complexes of each of the ion exchange resin with drug were prepared in various ratios.

2. Drug Release from Drug Resin complex

2.1. Simulated Salivary Fluid [10]

Solid drug: resin complex equivalent to 25 mg of drug was accurately weighed and added to 10 ml Simulated Salivary fluid pH 6.8 I.P. Aliquot was withdrawn after intervals of 1 min. The sample was filtered through Whatman filter paper. The absorbance was measured at 226.70 nm. Results for drug release from drug resin complex are given in **Table 4.**

2.2. Simulated Gastric Fluid [10]

Drug release from drug resin complex in Simulated Gastric fluid was determined using USP dissolution test apparatus II (Model: Disso TDT-08L Apparatus: Electrolab). Accurately weighed drug resin complex equivalent to 25 mg of Sumatriptan Succinate was added to 900 ml simulated gastric fluid for 30 minutes (50 rpm, 37ºC ± 5ºC). A 10-ml sample was withdrawn at the 5 min time interval and replacement was made each time with 10 ml of fresh dissolution medium. Each of the 10ml samples were filtered and analyzed from the standard curve of the drug in simulated gastric fluid at 226.70 nm. The reported values of percent drug release are shown in **Figure 1, 2, 3, 4 and 5.**

3. Assay of Drug: Resin Complexes [8]

A drug-resin complex equivalent to 25 mg of Sumatriptan Succinate was accurately weighed and in that 100 ml of 0.1N HCl was added to break the drug: resin complex. This was stirred on magnetic stirrer for 60 mins. Solution was filtered and 1 ml of the filtrate was diluted to 10 ml using 0.1N HCl and absorbance of this solution was measured at λ max 226.70 nm using 0.1N HCl as blank and content of Sumatriptan Succinate was estimated. The data obtained is shown in **Table 7.**

4. Characterization of drug resin complex

1. Fourier Transform Infra Red (FTIR) Study[11]

FTIR spectroscopic (FTIR 8400S Shimadzu spectrometer) studies were carried out by appropriately diluting the sample with dried potassium bromide (2mg sample in 200mg KBr) and acquiring IR spectrum in the range of 400-4,000 cm^{-1}. All three spectra were completely analyzed shown in **Figure 6.**

2. X-Ray Powder Diffraction (XRPD) Study [8, 12]

XRPD pattern of Sumatriptan Succinate, Tulsion-335and drug resin complex was taken by X ray diffractometer. Radiation generated from Copper source with wavelength of 20mA at 40 kV and the scanning rate employed was 1□ /min over the 8□ to 60□ □ diffraction angle (2□) range. The XRPD patterns of drug powder were recorded which is shown in **Figure 7.**

3. Differential Scanning Calorimetry (DSC) [11]

A Mettler Toledo (*SW920) Differential Scanning Calorimeter equipped with an in cooler and refrigerated cooling system was used to analyze the thermal behavior of Sumatriptan Succinate, Tulsion-335 and drug resin complex, DSC was carried out over a temperature range of 40-250^{o}C with a heating rate of 10^{o}C per min. in an inert environment of nitrogen gas. The data obtained is shown in **Table 8**. The DSC of Sumatriptan Succinate, Tulsion-335 and drug resin complex is shown in **figure 8**.

5. Formulation of Fast Disintegrating Tablets[13]

Fast disintegrating tablets were prepared by using solid drug: resin complex (1:1 ratio) of Sumatriptan succinate with Tulsion 335. The complex was taken equivalent to dose of drug. Nine different types of fast disintegrating tablets were formed using different types of super disintegrating agents. Complex of drug-resin earlier obtained were mixed/blended with super disintegrants (Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium), microcrystalline cellulose is used as diluent, mannitol is used as mouth feel enhancer, sodium saccharin as sweetener, vanilla dry as flavouring agent, talc as glidant and magnesium stearate as lubricant. All ingredients were passed through mesh # 60. Before compression hardness was adjusted. Drug-resin equivalent to 25mg of Sumatriptan Succinate was compressed into tablets (200 mg) using 8mm flat face punch set using a 23 station tablet press (RIMEK INDIA). The scheme for fast disintegrating tablet formulations using different ingredients is shown in **Table 1.**

Table 1: Scheme for Fast Disintegrating Tablets Formulations Using Different Ingredients

Ingredients	Quantity of Ingredients								
	Formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sumatriptan succinate: Tulsion T- 335complex (1:1 Ratio) Equivalent to 25mg	50	50	50	50	50	50	50	50	50
Crospovidone	4	6	8	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	4	6	8	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	4	6	8
Mannitol	40	40	40	40	40	40	40	40	40
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Sodium Sacharin	6	6	6	6	6	6	6	6	6
Vanilla Flavour	1	1	1	1	1	1	1	1	1
Microcrystalline Cellulose	95.5	93.5	91.5	95.5	93.5	91.5	95.5	93.5	91.5
Total (mg)	200	200	200	200	200	200	200	200	200

6. Evaluation of Powder Blend [13,14,15, 16, 17]

The prepared blend is evaluated by following tests.

□ □ Bulk density

□ □ Tapped density

□ □ Angle of repose

□ □ Hauser's ratio

□ □ Carr's index

1) Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (5gm) passed through standard sieve # 20 into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume.

Db = mass of powder**(**M)/ bulk volume of the powder**(**Vb)

2) Tapped Density (Dt)

Tapped density is ratio of mass of tablet blend to tapped volume of tablet blend. Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured. Then cylinder was allowed to 100 taps under its own weight onto a hard surface. The tapping was continued until no further change in height was noted.

Dt = mass of powder(M**)**/tapped volume of the powder (Vt)

3) Angle of Repose (θ)

The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The fixed funnel method employs a funnel that was secured with its tip at a given height (2cm), above the graph paper that was placed on a flat horizontal surface. Tablet blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel.

$$\tan(\theta) = h / r$$

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, (θ) is the angle of repose.

h is the height in cms

r is the radius in cms.

4) Carr's Index (or) % Compressibility

It indicates powder flow properties. It is expressed in percentage and is calculated using following equation:

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, Dt is the tapped density of the powder and

Db is the bulk density of the powder.

5) Hausner Ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density.

D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

7. Evaluation of Tablets

1. Weight Variation Test

Weight variation test was done by weighing 10 tablets individually, by using analytical balance. Calculating the average weight and comparing the individual tablet weight to the average weight.

The tablet passes the test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Average weight = Weight of 10 tablet/10

2. Tablet Thickness

The thickness was measured by placing tablet between two arms of the Vernier calipers. It was determined by checking five tablets from each formulation.

3. Tablet Hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force.A tablet was placed in the hardness tester(Pfizer) and load required to crush the tablet was measured. The hardness has influence on disintegration and dissolution time.

4. Tablet Friability

The friability of the tablets was measured in a Roche friabilator. Initial weight of 10 tablets is taken and these are placed in the Friabilator, which consists of a circular plastic chamber, divided into 2-3 compartments. The chamber rotating at 25 rpm for 4min and drops the tablets by a distance of 15 cm and gives 100 revolutions. After that, the tablets were weighed once again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

5. Content Uniformity

10 tablets were powdered and 25 mg drug equivalent powder dissolved in suitable media of 0.1N HCl. Volume of the solution made up to 100 ml by that media. Solution was filtered and diluted 100 times and analyzed using UV- spectrophotometer and further calculation was carried out to determine drug content in one tablet.

7) Wetting Time and Water Absorption Ratio

Wetting time of dosage form is related with the contact angle. Lower wetting time implies a quicker disintegration of the tablet. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper

surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, *R* can be the determined according to the following equation.

$$R = 100 (Wa-Wb) / Wb$$

8. *In-vitro* Disintegration Test

The test was carried out on 6 tablets using Tablet disintegration tester using 900 ml of 0.1 N HCl at 37 ± 0.5ºC as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured.

9. *In-vitro* Release Rate Study of Formulations

In-vitro dissolution of all fast disintegrating tablet i.e. formulation F1 to F9 of drug resin complex was carried out using USP dissolution rate test apparatus II (Model: Disso TDT-08L, Electro Lab) in simulated gastric fluid. 10 ml of the aliquot were withdrawn at different time interval of 5, 10, 15, 20, 25 & 30 min. and replacement was made each time with 10 ml of fresh dissolution medium. Each of the 10 ml sample was filtered through whatman filter paper. The absorbance was measured at 226.70 nm.The drug concentration in the sample was determined from the standard curve of the drug in simulated gastric fluid. The data is given in **Table 11 and Figure 9.**

9. Accelerated Stability Study of Optimized Batch[14]

The optimized formulation F6 was stored in aluminum capped clear glass vials and were subjected to a storage condition of 40°C±2˚C/ 75%±5% RH for 3 months in humidity chamber. The samples were withdrawn at time intervals of 0, 1, 2, 3 months and evaluated for hardness, friability, disintegration time, drug content and *in-vitro* dissolution study which is shown in **Table 12.** The data of dissolution of optimized batch F6 is shown in **Table 13.**

RESULTS AND DISCUSSION

1. Complexation of Sumatriptan Succinate with Ion Exchange Resins

Both the types of ion exchange resins i.e. strong and weak cation exchange resins were selected for the purpose of taste masking of Sumatriptan succinate. There is slight difference

in percent drug complexed with different ratios of drug: resin as well as slight difference in percent drug complexed with different types of resin used for complexation. Sumatriptan succinate showed complexation with Kyron T-114, Tulsion 335, Kyron T-154, Kyron T-159. The complexation of drug with different resins showed in **Table 2 and 3.**

Table 2: Percent drug complexed in various ratios of strong cation exchange resins

Ratio Drug: Resin (% w/w)	Percent drug complexed	
	Kyron T-159 (H^+)	Kyron T-154(Na^+)
1:1	99.69 ± 0.016	99.67± 0.045
1:2	99.74 ± 0.021	99.68 ±0.021
1:3	99.74 ± 0.024	99.69 ±0.012

Table 3: Percent drug complexed in various ratios of weak cation exchange resins

Ratio Drug: Resin (% w/w)	Percent drug complexed	
	Kyron T-114(H+)	Tulsion- 335 (H+)
1:1	99.73 ±0.012	99.75±0.032
1:2	99.74 ± 0.032	99.76±0.024
1:3	99.74± 0.016	99.76±0.020

Percent complexation of drug with different ratios of both strong cationic ion exchange resins showed that both strong cationic ion exchange resins had good complexation with Sumatriptan Succinate. Percent complexation of drug with different ratios of both weak cationic ion exchange resins showed that both the resins had good complexation with Sumatriptan Succinate. There is slight difference in percent drug complexed with different ratios of drug: resin as well as slight difference in percent drug complexed with different types of resin used for complexation.

2. Release rate study

2.1 Salivary pH

Any substance, which is soluble in saliva will interact with taste buds and can impart its taste. The reported values of percent drug release in simulated salivary fluid are shown in **table 4.**

Table 4: Percent drug release at salivary pH 6.8 after 60 sec

Ratio of Drug: Resin	Percent drug release in simulated salivary fluid		
	1:1	1:2	1:3
Drug: Tulsion- 335	0.105± 0.0028	0.069 ± 0.0044	0.053± 0.0033
Drug: KyronT-114	0.106±0.0032	0.069 ± 0.0044	0.052± 0.0032
Drug: Kyron T-159	0.103 ±0.0020	0.063 ± 0.0030	0.054 ± 0.0032
Kyron T-154(Na+)	0.106± 0.0032	0.064 ±0.0029	0.049 ±0.0024
Pure Drug	59.241±0.212		

It can be concluded that medium of dissolution at salivary pH (simulated salivary fluid pH 6.8) showed very slight difference in release at the end of 60 sec.

2.2 Gastric pH

The release rate of the drug from each of the ratio of the drug: resin (with Tulsion-335, Kyron T-114, Kyron T-159, Kyron T-154) complex was studied at the gastric pH in simulated gastric fluid to determine the amount of drug that would be released in the stomach after administration of formulation.

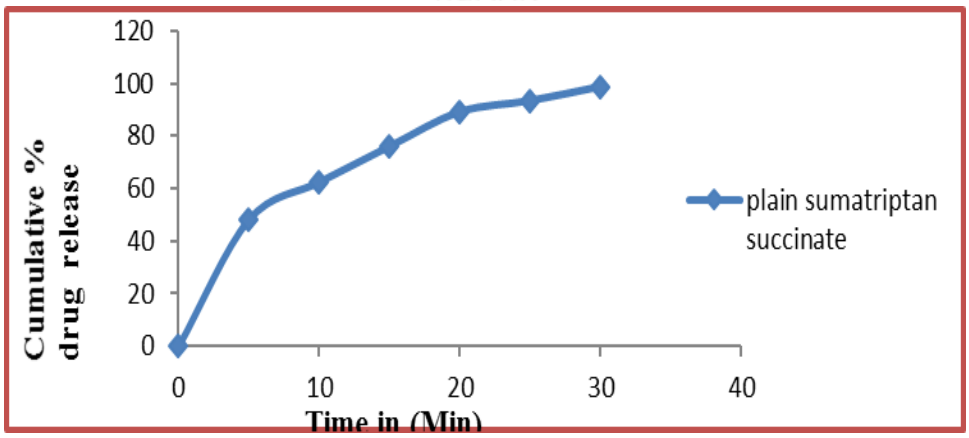


Fig. 1: Cumulative Percent Drug Release from Plain Sumatriptan Succinate at SGF.

Table 5: Percent Cumulative Drug Release from Complexes in Simulated Gastric fluid

Time (min)	Percent cumulative release of Sumatriptan Succinate					
	Sumatriptan Succinate: Kyron T-114			Sumatriptan Succinate: Tulsion 335		
	1:1	1:2	1:3	1:1	1:2	1:3
5	52.36±0.68	50.30±0.82	49.61±0.10	54.44±0.49	52.79±0.29	51.68±0.38
10	65.78±0.48	63.26±0.10	61.85±0.40	68.38±0.62	59.53±0.62	56.54±0.63
15	72.19±0.58	69.16±0.29	67.86±0.65	77.62±0.39	74.35±0.16	69.49±.0.74
20	80.23±0.44	73.56±0.97	74.27±1.42	87.69±0.53	84.72±0.41	80.79±0.34
25	89.18±0.33	87.78±0.54	85.49±0.25	92.95±0.26	91.72±0.54	85.77±0.75
30	94.49±0.37	91.66±0.17	89.55±0.15	98.11±0.33	94.21±0.33	90.25±0.72

Table 6: Percent Cumulative Drug Release from Complexes in Simulated Gastric fluid

Time (min)	Percent cumulative release of Sumatriptan Succinate					
	Sumatriptan Succinate: Kyron T-154			Sumatriptan Succinate: Kyron T-159		
	1:1	1:2	1:3	1:1	1:2	1:3
5	27.14±0.56	23.60±0.15	25.90±0.16	35.54±0.10	25.37±0.03	23.87±0.02
10	39.45±0.05	42.15±0.09	40.85±0.29	45.75±0.09	42.07±0.23	39.90±0.31
15	55.68±0.37	57.76±0.07	53.62±0.06	58.96±0.11	53.78±0.14	54.49±0.10
20	64.51±0.17	66.52±0.11	62.02±0.48	72.14±0.24	61.73±0.28	63.76±0.34
25	77.80±0.07	75.29±0.11	73.21±0.20	79.64±0.08	75.64±0.44	72.85±0.20
30	83.30±0.84	81.35±0.10	79.85±0.34	85.45±0.09	83.69±0.04	83.66±0.09

Type of resin and its ratio plays very important role in release of drug from complex. Strong resin Kyron T-159 and Kyron T-154 show release of drug more than 30 mins. While weak resin Tulsion 335 and Kyron T-114 releases the drug within 30 mins. This is because drug binds tightly with the strong resin and loosely with weak resins. So, weak resins Tulsion 335 and Kyron 114 were used for further study.

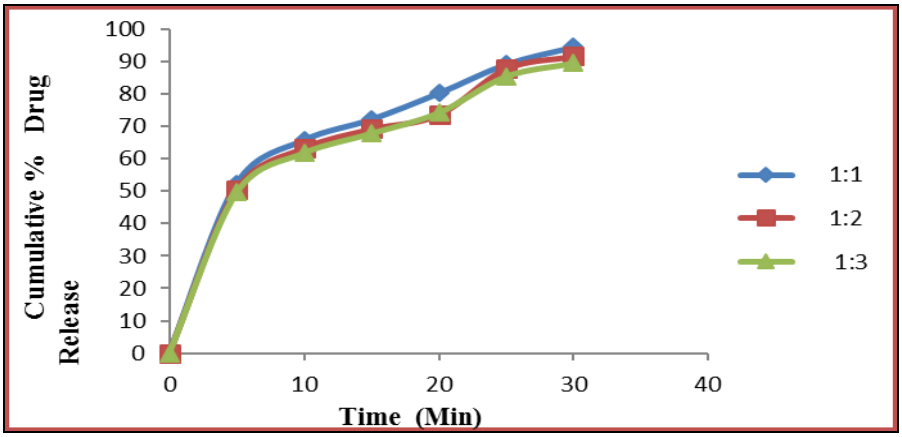


Fig. 2: Cumulative Percent Drug Release From Sumatriptan Succinate: Kyron T-114 at SGF

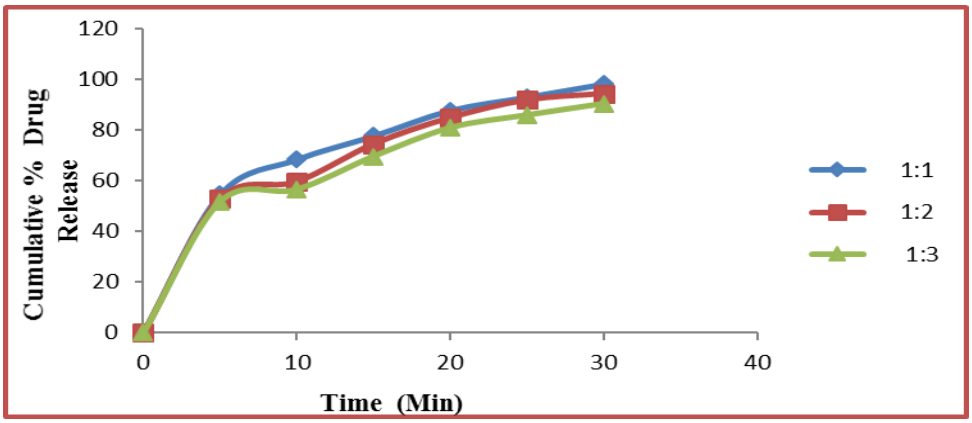


Fig. 3: Cumulative Percent Drug Release From Sumatriptan Succinate: Tulsion 335 at SGF.

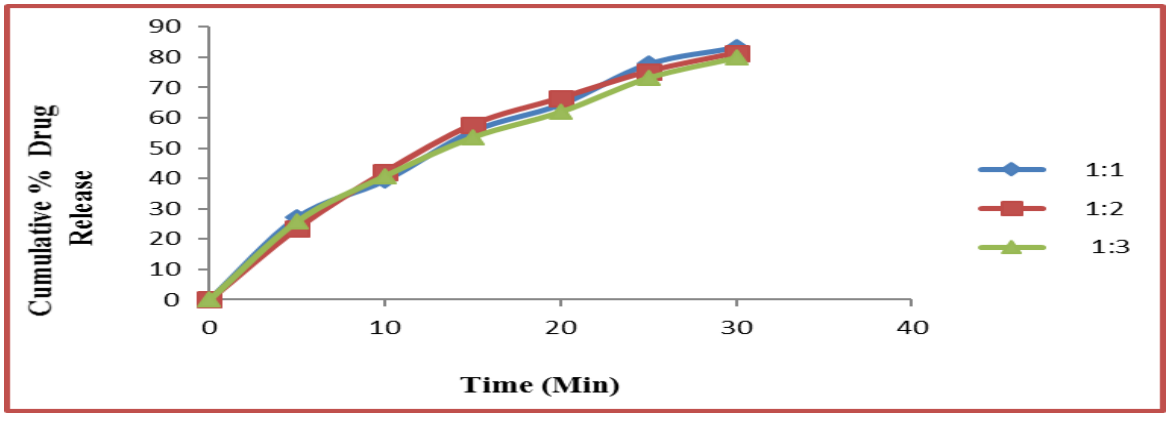


Fig. 4: Cumulative Percent Drug Release From Sumatriptan Succinate: Kyron 154 at SGF.

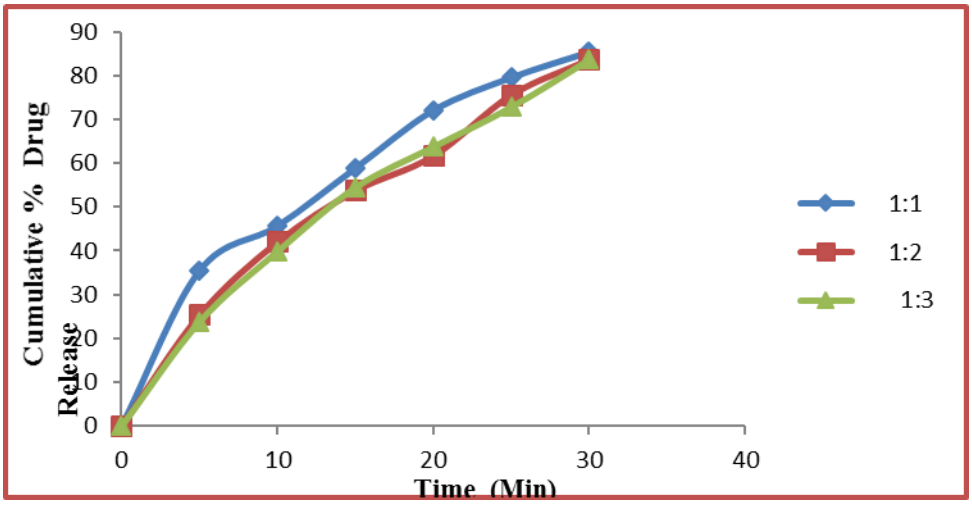


Fig. 5: Cumulative Percent Drug Release From Sumatriptan Succinate: Kyron 159 at SGF.

3. Assay of Drug: Resin Complexes

Both the samples of drug –resin complex (drug-KyronT-114, drug-Tulsion335) were assayed by UV- spectrophotometer at 226.70 nm for determination of percent drug content. The data obtained is shown in **Table 7**

Table 7: Percent Drug Content of Drug: Resin Complexes

Ratio of Drug: Resin (% w/w)	Percent drug content	
	Kyron T-114	**Tulsion 335**
1:1	98.41 ±0.35	99.43 ±0.49
1:2	97.52 ±0.52	98.74 ±0. 15
1:3	96.21 ±0.32	98.52 ±0.61

Both the complexes showed more than 95 % drug content but the ratio 1:1 of drug-Tulsion 335 complex showed 99.43 % drug content, so drug-Tulsion 335 complex (1:1) was finalized for further formulation study.

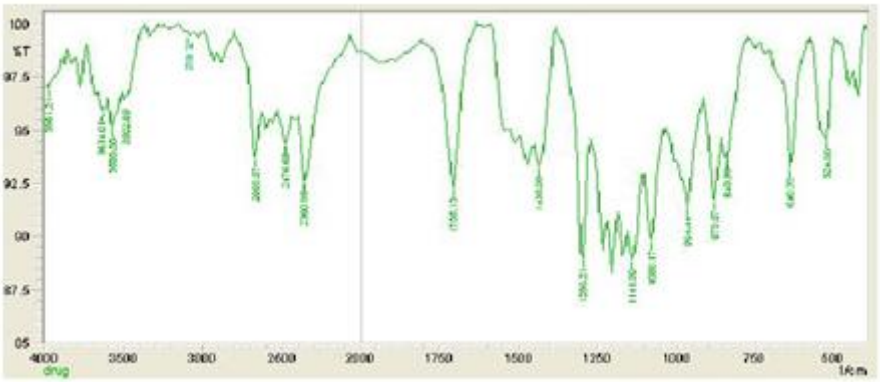
4. Characterization of Drug Resin Complex

1. Fourier Transform Infra Red (FTIR) Study:

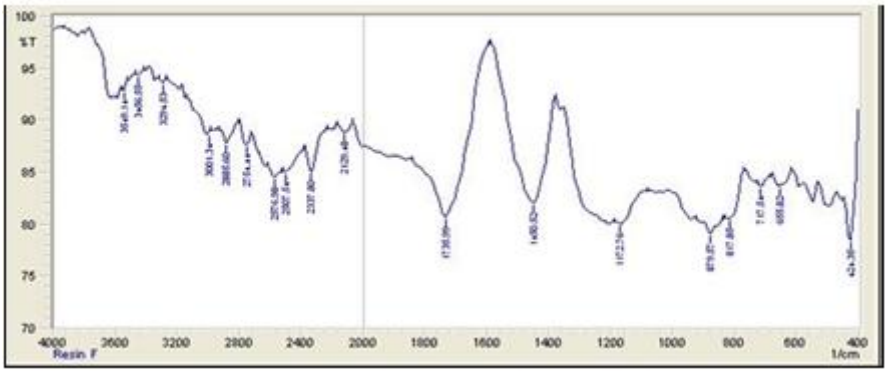
The FTIR spectrum of complex exhibit significant difference in the characteristic spectrum of the Sumatriptan Succinate, revealing modification of the drug environment. The spectrum of pure Sumatriptan Succinate showed characteristic peak at 1080 cm^{-1}, 1296.21cm^{-1}, 640cm^{-1}, 3109.35 cm^{-1}, 1705.13cm^{-1}, S=O Stretching, C-N Stretching, C-S Stretching, N-H Stretching, C=O Stretching respectively.The absence of Sumatriptan Succinate Peak i.e N-H Stretch at 3109.35cm-1, in DRC, confirms the complexation of drug with resin. The spectrum of Tulsion 335 showed distinct C=O stretch at 1735.99 cm^{-1} of the –COOH functional group of the resin, which was not seen in the spectrum of DRC. The functional groups involved in the complexation process were –COOH of Tulsion 335 along with the N-H of Sumatriptan Succinate. The absence of Sumatriptan Succinate peak in the spectrum of DRC indicated that the drug was completely embedded in the resin polymer matrix and thus the complexation was confirmed.The FTIR spectrums of resin Tulsion 335 & of Sumatriptan succinate:

Tulsion 335complex are shown in figure 6.

A. Sumatriptan Succinate



B. Tulsion-335



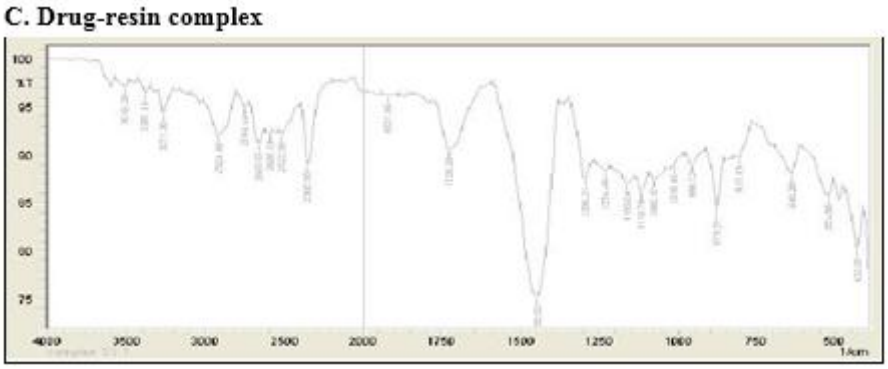


Fig. 6: A: FTIR spectrum of Sumatriptan Succinate. B: FTIR spectrum of Tulsion-335 C: FTIR spectrum of Drug Resin Complex.

2. XRPD Spectra

X-ray powder diffraction studies were performed to examine the crystallinity and provide further evidence of complex formation. The X-ray powder diffraction pattern confirms the crystalline nature of Sumatriptan Succinate that is evident from the number of sharp and intense diffraction peaks obtained for drug. The XRPD of resin showed diffused peaks. Only diffused peaks were observed in the diffraction pattern for complex regardless of presence of drug. According to the data from XRPD, the molecular state of pure drug was crystalline and that of the resin was amorphous. The molecular state of drug prepared as drug-resin complex was changed from crystalline to the amorphous.

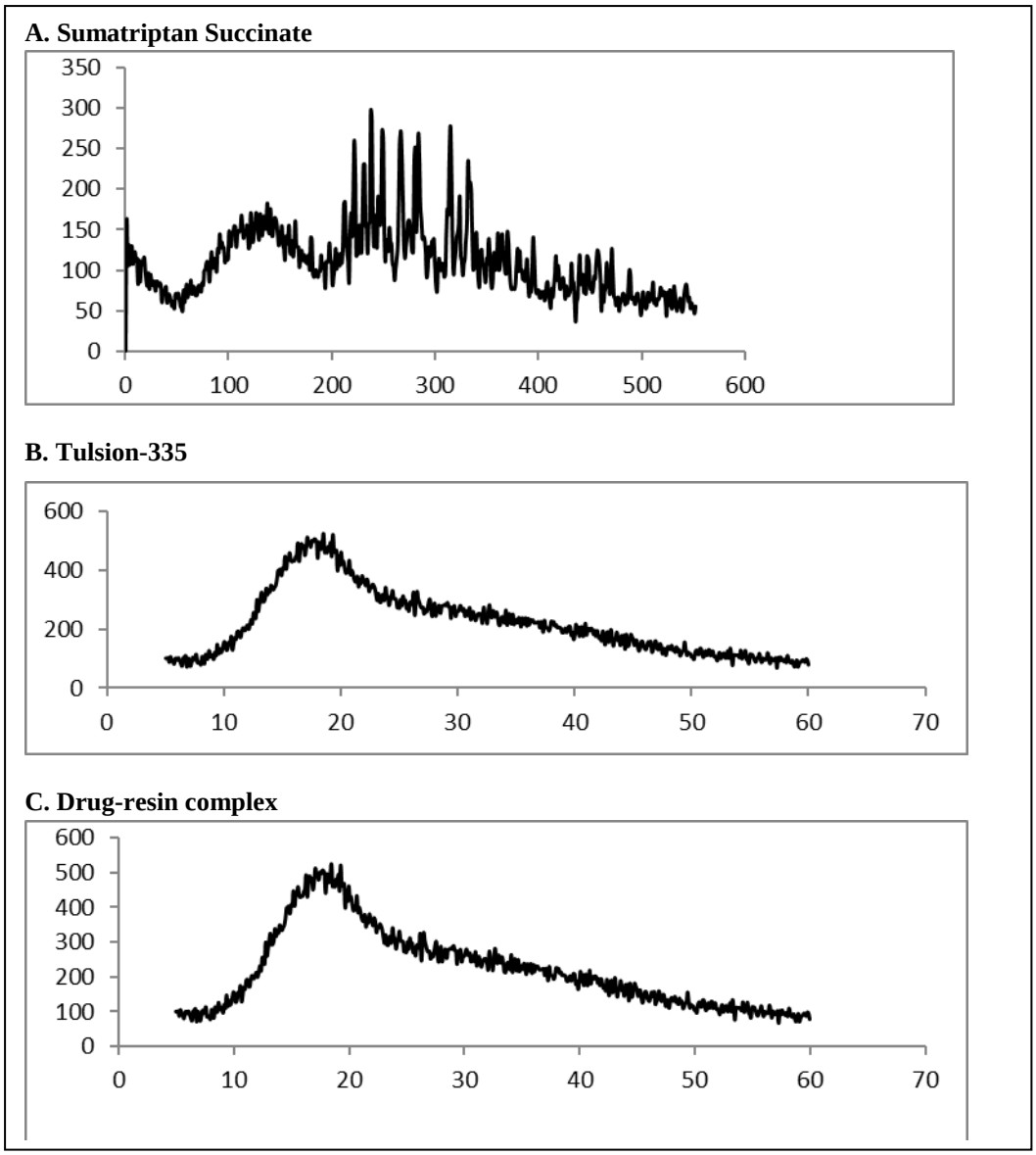


Fig. 7 A: XRD Curve of Drug (Sumatriptan Succinate). B: XRD Curve of Resin (Tulsion-335). C: XRD Curve of Drug resin complex.

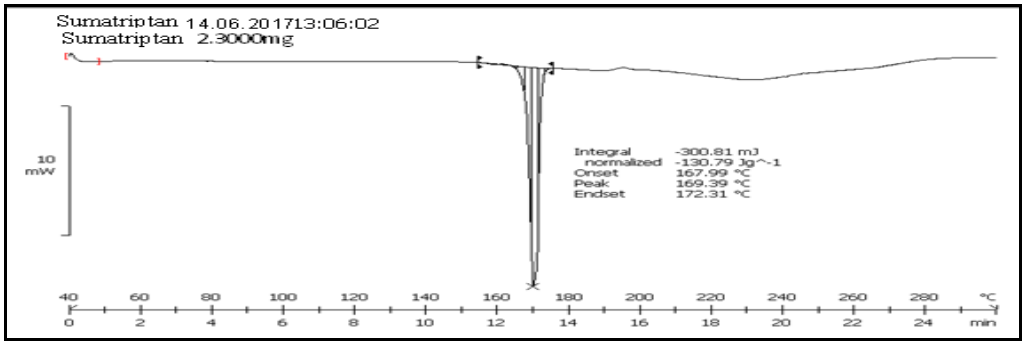
3. DSC Thermogram:

DSC Thermogram of pure drug shows sharp endothermic peak at 169.39^{0}C, indicating melting point of Sumatriptan succinate. In DSC curve of DRC total disappearance of drug melting temperature was occurred, which indicated that drug was completely embedded in resin: drug resin complex is shown in **Figure 8**.

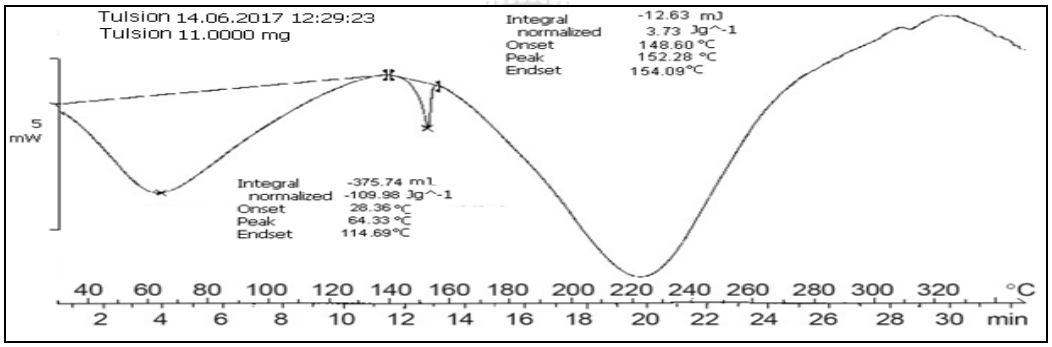
Table 8: DSC of Resin and Solid Drug: Resin Complexes

Sample	Endothermic Peak (ºC)
Sumatriptan Succinate (plain drug)	169.39°C
Tulsion 335	152.28°C
Drug – Resin complex	104.18°C

A. Sumatriptan succinate



B. Tulsion-335



C. Drug resin complex

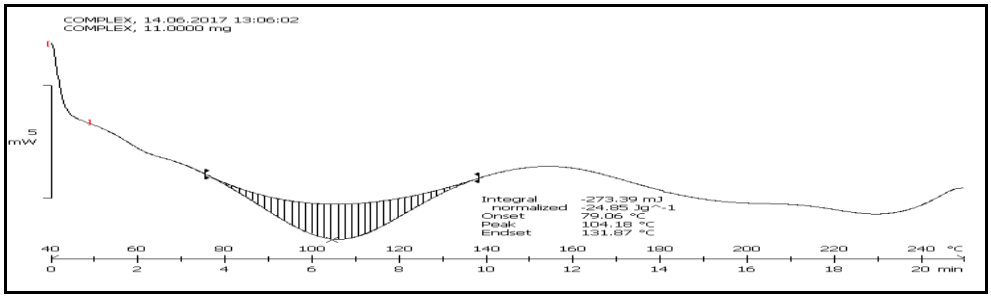


Fig. 8 A: DSC curve of drug (Sumatriptan Succinate). B: DSC curve of resin

B. (Tulsion-335) C: DSC curve of drug resin complex.

Evaluation of Powder Blend

The characterization of mixed blend was done for determination of mass-volume relationship parameters. The evaluation parameters like angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index are shown in **Table 9**

Table 9: Evaluation of Powder Blends of Sumatriptan Succinate: Tulsion 335

Formulations	Evaluation Parameters				
	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ^0)	Carr's Compressibility Index(%)	Hausner's Ratio (HR)
F1	0.417±0.005	0.496±0.005	28.38 ±0.085	15.97± 0.735	1.18±0.011
F2	0.401±0.001	0.452±0.006	27.47 ± 0.11	11.45 ±1.27	1.12±0.015
F3	0.439±0.006	0.488±0.007	26.1 ± 0.03	10 ± 1.36	1.10±0.015
F4	0.411±0.008	0.479±0.009	26.1 ± 0.03	12.79 ± 0.46	1.14±0.005
F5	0.433±0.003	0.493±0.002	27.02 ± 0.070	12.69 ± 0.90	1.14±0.01
F6	0.402±0.002	0.448±0.002	25.17 ± 0.035	10.39 ± 0.67	1.11±0.01
F7	0.424±0.002	0.482±0.007	27.92 ±0.10	11.94 ± 1.49	1.13±0.017
F8	0.436±0.002	0.483±0.002	24.22 ±0.07	10.26 ± 0.56	1.1 ±0.005
F9	0.422±0.004	0.473±0.005	27.92 ± 0.10	10.38 ± 0.92	1.11±0.011

Results are mean of three determinations

The preformulation parameters such as bulk density, tapped density, angle of repose, Hausner's ratio and compressibility index were analyzed. From the results of pre-compression studies of the batches F1-F9, it is concluded that powder mixture has good flow and compression property. Tablets were prepared by direct compression method.

10.9 Evaluation of Formulation:

The prepared tablets were evaluated for physicochemical parameters like hardness, disintegration time, wetting time, thickness, friability, drug content and weight variation and results are shown in **Table 10**

Table 10: Evaluation of Tablets of Sumatriptan Succinate: Tulsion 335

Formula-tions	Evaluation Parameters							
	Hardness (Kg/cm^2)	Thickness (MM)	Disintegration time (Sec)	Wetting time (Sec)	Friability (%W/W)	Drug Content (%W/W)	Weight Variation	Water Absorption Ratio
F1	3.0±0.17	3.9± 0.05	47.69± 0.63	34.62± 0.93	0.25± 0.041	97.2 ± 0.62	200±0.59	52±0.816
F2	3.1±0.20	4.0 ± 0.02	39.90± 1.22	30.88± 1.59	0.35± 0.073	98.7 ±0.23	198±0.63	56±0.942
F3	3.2±0.18	3.7± 0.07	34.87± 0.58	22.68± 0.63	0.26± 0.049	99.4 ±0.34	200±0.45	65±1.63
F4	3.0±0.15	3.8± 0.10	52.62± 0.44	39.59± 1.60	0.43± 0.098	97 ± 0.56	198±0.88	49±1.24
F5	3.2±0.16	3.9± 0.03	46.02± 0.62	33.31± 0.62	0.34± 0.11	97.4 ± 0.49	200±0.56	51±1.69
F6	3.1±0.22	3.9± 0.06	41.39± 0.82	29.33± 0.96	0.29± 0.069	99.8 ± 0.2	198±0.74	57±0.816
F7	3.2±0.24	3.8± 0.15	56.41± 1.11	42.76± 0.31	0.47± 0.080	97.2 ± 0.63	200±0.67	50±1.24
F8	3.0±0.22	3.9± 0.03	49.39± 0.89	37.33± 0.61	0.34± 0.11	98.4±0.56	199±0.77	56±0.471
F9	3.1±0.16	4.0 ± 0.01	44.62± 0.40	32.12± 1.73	0.44± 0.036	98.32±0.37	199±0.86	63±1.41

Results are mean of three determinations.

Tablet diameter and thickness was found to be uniform (3.7±0.07 - 4 ±0.02 mm). The measured average hardness of all the formulations met the limit (3.0±0.22-3.2 ± 0.24 Kg/cm^2). Disintegration test carried out on these tablets showed that there is fast disintegration of tablet within 1 min. which is less than official limit of FDT (3 min). Tablet containing crospovidone 4% showed better disintegration property. The % friability was

found to be less than 1% in all the batches, ensuring that the tablets were mechanically stable. Drug content estimation showed more than 90% of the drug present. All the tablets passed weight variation and all are in pharmacopoeial limit (7.5%). Water absorption ratio of F3 was high because crospovidone showed highest swelling property and low wetting time (i.e 22 sec). The results obtained in the *in-vitro* drug release for all formulations F1 to F9 are tabulated in **Table 11**. The cumulative percent release of formulations F1 to F9 in SGF is shown in **Figure 9.**

Table 11: Percent Cumulative Drug Release of Formulations F1 to F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	56.16 ±0.46	58.34 ±0.55	61.7 ±0.33	48.55 ±1.11	52.35 ±0.55	53.44 ±0.77	45.55 ±0.67	51.99 ±0.58	55.98 ±0.92
10	62.5 ±0.68	67.97 ±0.12	72.36 ±1.26	57.43 ±1.24	62.82 ±0.90	65.28 ±0.69	56.85 ±1.16	58.65 ±0.67	63.68 ±0.78
15	74.07 ±0.44	74.97 ±1.11	78.87 ±0.55	68.68 ±1.04	73.95 ±0.58	75.8 ±0.65	65.18 ±0.79	68.82 ±0.33	72.36 ±0.60
20	82.59 ±0.90	86.41 ±0.89	86.17 ±0.89	75.68 ±1.42	79.74 ±0.32	81.34 ±0.59	73.15 ±0.69	77.91 ±1.16	82.86 ±0.36
25	86.66 ±1.36	89.61 ±0.46	90.55 ±1.02	80.59 ±0.81	84.6 ±1.14	89.57 ±0.41	80.39 ±0.57	83.11 ±1.13	87.38 ±1.085
30	91.19 ±0.73	93.74 ±1.31	96.03 ±0.40	87.8 ±0.97	90.4 ±0.77	93.31 ±0.57	86.06 ±0.37	89.62 ±0.27	91.13 ±0.76

The reported values of percent drug release are average values of three readings.

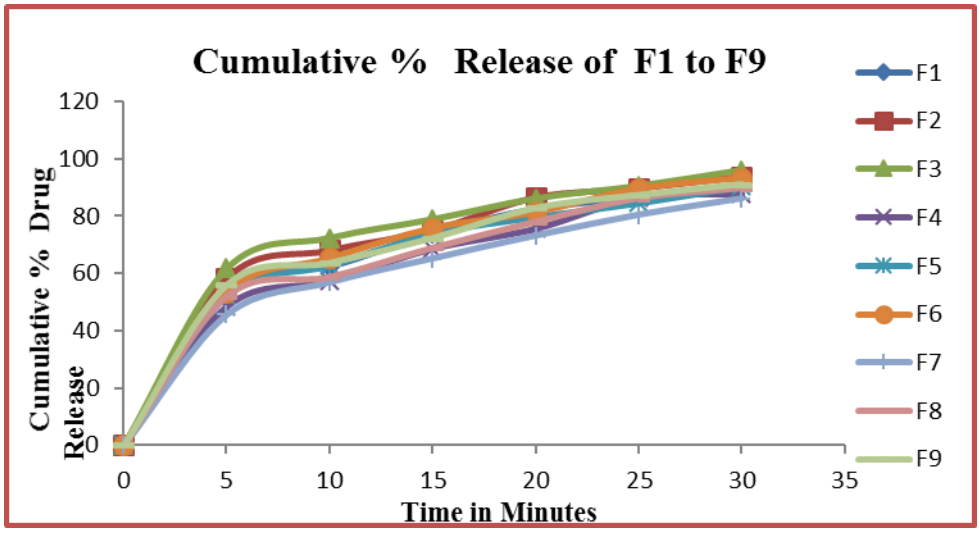


Fig. 9: *In-vitro* Drug Release Profile of Sumatriptan Succinate Tablets of F1to F9 Formulations.

From hardness, friability, disintegration time, wetting time and dissolution study at gastric pH using simulated gastric fluid. Formulation F3 was selected as the best formulation. Release of drug from formulation was similar to drug release from drug: Tulsion 335(1:1) complex.

10.10 Stability Study

Stability studies for the developed formulations were carried out as per ICH guideline by storing the selected formulations at 40°C/75% RH up to three months. The formulation F3 was selected for stability study on the basis of their high cumulative percentage drug release, results of *in-vitro* disintegration time, wetting time and in vitro dispersion studies. After each month tablet sample was analyzed for hardness, disintegration time, dissolution and drug content and results are shown in shown in T**able 12.** The data of dissolution of optimized batch F3 is shown in **Table 13**. **Figure 10** shows cumulative percent release of F3 Formulation. There was no significant difference in Disintegration time, Hardness, Friability, % drug content for optimized formulation. Formulation F3 was found to be stable after three months stability study.

Table 12: Stability Data for Optimized Formulation F3

Formulation	Parameters Evaluated	Initial	After one Month	After two Months	After three Months
F3	Disintegration time (sec)	34.87±0.58	34.94±0.33	36.87±0.39	36.16±0.55
	Hardness (kg/cm^2)	3.2 ±0.18	3.2±0.10	3.4±0.20	3.5±0.115
	% Drug Content	99.4± 0.34	99.16±0.39	98.11±0.53	97.04±0.60

Table 13: Dissolution Profile of Optimized Batch F3

Time (min)	Initial	After one Month	After two Months	After three months
0	0	0	0	0
5	61.7±0.33	60.25±0.89	59.92±0.46	59.7 ±1.30
10	72.36±1.26	71.43±0.89	69.43±0.68	69.44±1.13
15	78.87±0.55	75.64±0.91	75.64±0.79	74.19±0.27
20	86.17±0.89	85.09±0.65	85.64±0.52	84.79±0.28
25	90.55±1.02	90.56±0.38	90.09±1.14	89.16±0.69
30	96.03±0.40	95.25±0.55	94.09±0.31	94.38±0.71

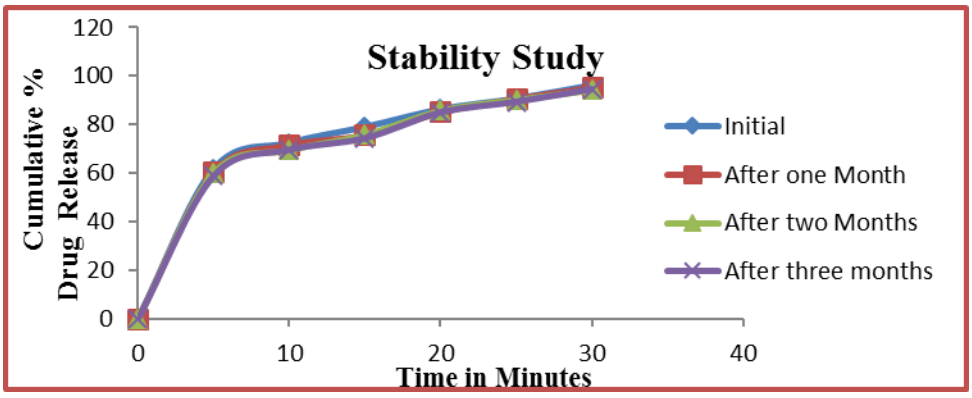


Fig. 10: Percent Cumulative Release from Sumatriptan Succinate: Tulsion 335 after Three Months.

The stability study showed that the formulation F3 was physically stable when stored at 40±2° C and 75±5 % RH for three months and there was no significant difference in dissolution for optimized formulation.

CONCLUSION

- Sumatriptan Succinate is a potent and selective 5- hydroxytryptamine agonist used medically as an antimigraine. Formulating Sumatriptan Succinate into a fast disintegrating tablets form to provide fast relief by rapid onset of action. Our aim was to prepare fast disintegrating tablets with quality consistent by using production friendly direct compression which avoids costly technology, equipment and lengthy manufacturing process. The process is simple and easy to demonstrate as observed from result batch manufactured.

- Sumatriptan Succinate is extremely bitter in taste, so there was need to mask the bitter taste. In the present work, attempt was made to use ion exchange resin as taste masking agent. The purpose was to enhance patient compliance. Kyron-114, Tulsion-335, Kyron-154 and Kyron-159 were used as ion exchange resin. It was mixed with the drug in different ratios & evaluated for the extent of complexation, release rate study.

- Results showed that there was slight difference in the percent drug complexed with different ratios of drug: resin as well as slight difference in percent drug complexed with different types of resins used for complexation.

- There was slight difference in the percent drug release in phosphate buffer pH 6.8 and simulated salivary fluid from different types and different ratios of DRC. But in simulated gastric fluid strong resin (i.e Kyron-154 and Kyron-159) showed release of drug in more than 30 min., while weak resin (i.e Kyron 114 and Tulsion 335) releases drug within 30 min. Kyron 114 and Tulsion 335 showed more drug release than other DRC. From this results, Kyron-114 and Tulsion-335 were selected for further study. In DRC assay, both the complexes of Kyron- 114 and Tulsion-335 showed more than 95% of drug content but the ratio of Drug: Tulsion-335 (1:1) complex show 99% of drug content. Sumatriptan Succinate: Tulsion-335(1:1) complex was selected on the basis of results of percent complexation, drug release at salivary and gastric pH and assay of DRC. Formation of complex was confirmed by FTIR, DSC and X-Ray diffraction.

- F1-F9 Batches were formulated by direct compression method. The formulations were prepared by incorporating varying composition of super disintegrants Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate and other excipients like Microcrystalline Cellulose, Magnesium Stearate, Aerosil, Mannitol, Sodium Saccharin, Vanilla Flavour.

- The pre-compression parameters such as bulk density, tapped density, angle of repose, Hausner's ratio and compressibility index were analyzed. From the results of pre-compression studies of the batches F1-F9, it is concluded that powder mixture has good flow and compression property. Tablets were prepared by direct compression method.

- Tablet diameter and thickness was found to be uniform (3.7±0.07 - 4 ±0.02 mm). The measured average hardness of all the formulations met the limit. (3.0±0.22-3.2 ± 0.24 Kg/cm^2). Disintegration test concluded on these tablets showed that there was fast disintegration of tablets within 1 min. which is less than official limit of FDT (3 min). Tablet containing crospovidone 4% show better disintegration property. The % friability is less than 1% in all the batches, ensuring that the tablets were mechanically stable. Drug content estimation shows more than 90% of the drug present. All the tablets passed weight variation and all were found in pharmacopoeial limit (7.5%). Water absorption ratio of F3 was high because crospovidone shows highest swelling property and low wetting time (i.e 22 sec).The *in-vitro* cumulative % drug release of F3 formulation was found to be high compare with other batches.

- From results of Hardness, Friability, Disintegration Time, Wetting Time, Dissolution study at gastric pH, "F3" formulation was selected as best formulation. Formulation F3 was selected further for stability study.

- Stability study was conducted for 3 months at 40°C / 75% R.H. There was no significant variation in the Disintegration Time, Hardness and *in-vitro* dissolution after 3 months of stability studies for optimized formulation F3 at 40°C / 75% R.H.

- In conclusion, the objective of taste masking, formulation development & evaluation of fast disintegrating tablets of Sumatriptan Succinate was achieved. The effective taste masking was achieved for Sumatriptan Succinate by preparation of complex using Tulsion-335 (1:1) ratio. The Sumatriptan Succinate: Tulsion-335(1:1) complex dissolved rapidly in stomach which show rapid onset of action.

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