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FORMULATION AND *IN VITRO* EVALUATION OF GASTRO RETENTIVE SUPERPOROUS HYDROGEL TABLETS OF SUMATRIPTAN

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ABSTRACT

Superporous hydrogels (SPHs) are porous hydrophilic cross-linked structures with the facility of absorbing aqueous fluids. Initially hydrogels were developed as a novel drug delivery system for gastric retention devices. But they have the disadvantage that, they swells into aqueous fluids at slow rate (it takes several hours to attain equilibrium swelling), but many of the pharmaceutical applications need fast swelling property. Therefore Superporous hydrogels were developed, these systems have to immediately swell in the stomach and retain their consistency in the insensible stomach environment, while releasing the pharmaceutical active constituent. In the present study Superporous Hydrogel tablets of Sumatriptan were prepared by direct compression method. The directly compressed formulations exhibited better in-vitro drug release profiles. The formulation F10 prepared by direct compression containing chitosan, formaldehyde, sodium bicarbonate prepared by cross-linking technique exhibited good swelling index and maximum rate of drug release. Thus the formulated Superporous Hydrogel tablets of Sumatriptan offer a superior alternative over conventional marketed dosage forms in regards of controlled release of drug. FTIR studies combined with stability studies proved the integrity of the developed tablets.Therefore the prepared tablet shows improved bioavailability with increased drug release.

Key words: Hydrogels, Cross linkers, Sumatriptan, Chitosan, Swelling property.

INTRODUCTION

Hydrogels are polymeric materials with open porous structures with the ability to take in large quantities of water and solutes. They have attracted much interest because of their potential to find different application. Biocompatible polymer hydrogels are being used in the biomedicine, agriculture, food- processing industry and immobilization of enzymes [1-6]. Stimuli-responsive hydrogels are one of the more promising types of polymeric materials. The water uptake of such hydrogels depends on environmental conditions (pH, ionic strength, temperature, and electrical or magnetic field). Superporous hydrogels are three-dimensional networks of hydrophilic polymers that contain many pores which are hundreds of micrometres in diameter [7]. Because these hydrogels absorb a large volume of environmental fluids, which expand their volume considerably over a very short time, their sheer bulk hinders their transport to the next organ via the narrow pylorus. This unique swelling property allows them to be used as gastric retention carriers, providing sustained release through long residence in the stomach [8]. Polyelectrolytes are ideally suited for the preparation of pH-sensitive hydrogels [9].

Chitosan is a polyelectrolyte and is obtained from renewable resources. It is a linear, semi- rigid polysaccharide and is biodegradable, biocompatible and of relatively low toxicity; it is a copolymer of N-acetyl D-glucosamine and D-glucosamine [10]. Because chitosan has abundant amine groups within its polymer chain, it dissolves in acidic solution and forms a gel with dialdehydes such as glutaraldehyde and glyoxal. In low pH solution, chitosan hydrogels swell due to the presence of positive charges in the network [11,12]. A gastric retention device is a type of drug delivery system designed to enhance drug release efficiency by prolonging drug retention in the stomach. Generally, drugs administered orally are not adequately absorbed in the stomach due to the

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pulsatory force of the latter in an acidic environment which easily breaks up carrier structures [13].

Sumatriptan is a potent and selective 5-hydroxytryptamine agonist chemically it is 3-[2-(dimethyl amino) ethyl]-N-methyl-1H-indol-5-methanesulfonamide butane-1,4-dioate it is an effective agent in the treatment of acute migraine attack. It provides rapid symptoms relief up to 85-90% of migraine patient within two hours of treatment. It is white amorphous powder, freely soluble in water and is rapidly but incompletely absorbed following oral administration and undergoes first pass metabolism resulting in a low absolute bioavailability of 15%. The biological half-life of Sumatriptan is about 2.5 hr. [9,10]

In the present study an attempt has been made to develop and characterize Superporus hydrogel tablets Sumatriptan . On oral administration, it prolongs the gastric residence time, increases the drug bioavailability and sustained the action for a longer period of time.

MATERIALS AND METHODS

Sumatriptan, Chitosan Acetic acid, Formaldehyde were purchased from Spectrum pharma labs, Hyderabad. Sodium bicarbonate Mcc were purchased from S.D. Fine Chem. Limited, Mumbai, India Talc was purchased from Evonik Degussa India Pvt Ltd, Mumbai

Preparation of control release Superporous hydrogel tablets of Sumatriptan

Method

The main goal of this study was to prepare superporous hydrogel tablets of Sumatriptan by using direct compression method with chitosan and different polymers like Sodium bicarbonate, in different ratios in combination with microcrystalline cellulose.

Procedure for the preparation of superporous hydrogel tablets

The superporous hydrogel tablets of Sumatriptan was formulated by incorporating prepared polymers like chitosan and different polymers like Sodium bicarbonate, in different ratios in combination with microcrystalline cellulose. Furthermore microcrystalline cellulose was utilized as diluents whereas magnesium stearate functioned as glidant and lubricant respectively.

The ingredients except magnesium stearate were weighed accurately and transferred to a clean mortar and pestle. The powder blend was mixed for 5 minutes after which lubricated magnesium stearate to ensure complete mixing was added to the blend and the mixing was continued for another few minutes. After obtaining a uniform blend, it was passed through sieve no: 60 and was prepared for compression. Tablets containing Sumatriptan equivalent to 100mg were compressed by using suitable diameter, spherical tablet and adjusting thickness and hardness accordingly punches on a 16 station rotary compression machine. The content of each tablet is listed in Table.

The final tablets formulated would be evaluated for various post compression parameters. After assessing the individual effect of all the polymers on swelling nature and drug release an optimum range for both polymers was selected.

Evaluation of powder blends for precompression parameters (Angle of repose, Carr's index, Hausner's ratio etc.)

Drug excipient compatibility

FTIR spectroscopy The drug - excipients interaction were studied using Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA). An IR spectrum for the drug was recorded in a FTIR for pure drug and physical mixtue of pure drug and polymers with Potassium Bromide (KBr) pellets. The spectra were scanned over the 3600 to 400 cm-1 range.

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone, θ is the angle of repose.

Angle of repose values more than 40 indicates excellent, good poor flow properties. An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP model). The density apparatus was set for 100 tabs and after that the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formula.

$$\text{Bulk density} = W/V0$$

$$\text{Tapped density} = W/Vf$$

Where, W = weight of the powder; V0 = initial volume; Vf = final volume

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is.

$$CI = (TD - BD) \times 100/ TD$$

Where, TD is the tapped density and BD is the bulk density.

Hausner's ratio is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and as such could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Evaluation of Tablet (Post Compression Parameters)

Tablets are evaluated for its parameters like various quality control tests such as Tablet thickness and Diameter, Hardness, Friability, uniformity of weight and

content uniformity of drug and other specific evaluation tests for GRDDS like swelling studies & Release rate of drug.

Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers. The tablet thickness should be controlled within a ± 5% variation of a standard value. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. It is expressed in millimeters (mm).

Hardness

Tablet hardness has been defined as the force req uired breaking a tablet in adiametric Compression test. The hardness of the tablets was determined using pfizer hardness tester (cisco). Six tablets were picked randomly from each formulation for measurement. It is expressed in Kg/cm2. The force required to break the tablet is measured in kilograms/cm2 and a crushing strength of 4 kg/cm2 is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg/cm2; However, hypodermic and chewable tablets are usually much softer (3 kg/cm2) and some sustained release tablets are much harder (10 -20 kg/cm2).

Friability

The friability test was carried out to evaluate tablet surfaces and/or show evidence of lamination or capping when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020) and expressed in %. Ten tablets dedusted tablets were initially weighed [$W_{(initial)}$] and transferred to friabilator and are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were weighed again [$W_{(final)}$]. The friability (f) was calculated by the formula

$$f = \left[\frac{W_{(initial)} - W_{(final)}}{W_{(initial)}}\right] \times 100$$

Values of from 0.8-1.0% are regarded as the upper limit of acceptability.

Weight variation

Ten tablets were selected randomly from each batch were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

$$\%\ Deviation = \frac{individual - Averageweight}{Averageweight} \times 100$$

Drug content uniformity

The test is used to ensure that every tablet contains the amount of drug intended with little variation among tablets within a batch. From each batch of the formulation, 10 tablets were collected randomly and powered using a mortar and pestle. A quantity of the powder equivalent to the weight of one tablet (100mg drug) was transferred to a 100ml volumetric flask. The powder equivalent to 100mg drug was dissolved in 1.2 pH buffer and volume was made up to 100ml to give a concentration of 1000µg/ml. 1ml of this solution was taken and diluted to 10ml to give a concentration of 100µg/ml. The absorbance of the prepared solution was measured at 270 nm using UV Visible spectrophotometer (Lab India, UV-3200) and the drug concentration was determined from the standard calibration curve by using the regression equation.

$$\text{Concentration } (\mu g/ml) = \frac{\text{absorbance - intercept}}{\text{slope}}$$

$$\text{Drug content } (mg) = \text{concentration X dilution factor}$$

$$\%\ \text{Drug content} = \frac{\text{Drug content}}{\text{Labeled claim}} \text{ X } 100$$

The preparation passes the test if individual drug content is 85-115% of the average content.

Swelling studies

The dried superporous hydrogel (100 mg) was immersed in excess of the swelling medium (20 ml) at 37 ^{o}C. The swelling behavior of a dosage form was measured by studying its weight gain or water intake the dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{(W1 - W0) \times 100}{W0}$$

Wt= Weight of dosage form at time t.
W0 = Initial weight of dosage form

***In-vitro* Drug release studies**

In-vitro drug release of the samples was carried out using USP– type II dissolution apparatus (paddle type). The dissolution medium, 900 ml 0.1N Hcl solution, was placed into the dissolution flask maintaining the temperature of 37 $\pm$ 0.5^{o}C using 50 rpm. One Phenylephrine tablet was placed in each paddle of dissolution apparatus. The apparatus was allowed to run for 8 hours. Samples measuring 5 ml were withdrawn at regular intervals up to 8 hours using 5 ml syringe. The fresh dissolution medium (37^{o}C) was replaced every time with the same quantity (5ml) of dissolution medium. Collected samples were suitably diluted with 0.1N Hcl and analyzed at 270 nm using 0.1N Hcl as blank by using a double beam UV spectrophotometer (T60 UV-VISIBLE spectrophotometer). The cumulative percentage drug release was calculated. The graphs of time vs % release were plotted.

Details of parameters set:
Paddle rpm: 50rpm
Stirrer depth : 25mm
Dissolution media : 1.2 p^{H} buffer
Media volume : 900ml

Media temperature: 37±0.5ºC
Sampling intervals: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12.

To ascertain the order and mechanism of drug rel ease the in vitro release data was
subjected to various kinetic equations.

RESULT AND DISCUSSION

FTIR spectroscopy Compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of Pure drug and physical mixture of drug and polymers were studied. The characteristic absorption peaks were observed at 1076.57cm^{-1},1293.98 cm^{-1},1556 cm^{-1},1703cm^{-1},2934cm^{-1} for the pure Sumatriptan and absorption peaks were observed at 1080 cm^{-1} ,1295cm^{-1} ,1558 cm^{-1} ,1716 cm^{-1},2850 cm^{-1} for drug and polymer mixture show that how they were in official limits (±100 cm^{-1}) the drug is compatible with excepients (Fig 1 & Fig 2).

Inference

The angle of repose of different formulations was ≤ 28.23 which indicates that all the formulations have good flow property. So it was confirmed that the flow property of blends were free flowing. Among these formulations F10 has excellent flow property. The bulk density of blend was found between 0.408g/cm^3 to 0.491 g/cm^3.Tapped density was found between 0.467 g/cm^3 to 0.527 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 6.37-15.53. Among all formulations F10 was found to be best formulation based on carr's index property. Hausner's ratio was found to be 1.067-1.18 which reveals that the blends have good flow character. Among all formulations F10 was found to be best formulation.

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table 3.

Inference

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3 - 4 kg/cm^2. These hardness values shows F10 was found to best formulation. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The formulation F10 shows less variation among all formulations. Drug content uniformity of all tablets was in the range of 98.85±0.68-100.1±0.83 indicating good content uniformity in the all formulations. Among all these formulations F10 was found to be best formulation

WATER UPTAKE STUDY (SWELLING INDEX)

The swelling index was in range 40.00 ± 0.12 to 74.50 ± 0.20. F6 tablet formulation having higher swelling index. The reason for higher swelling index values appeared to act as channeling agent, thereby it allows more permeation of water into the gel layer and thereby it enhances the water retention property. This could be the reason for more moisture uptake by tablets from F4, F8 and F9, F10 and moisture uptake values are given in Table. No.4

Dissolution study of tablets

The formulation F1, F12 prepared with chitosan, Formaldehyde based showed tablet swelling in the range of 7±6min to 720±110 min respectively, The % drug releases Phenylephrine all the formulations were in the range of 100.8 to 94.5%,at the end of 10 hrs. The detailed *in-vitro* release data of all the formulations were given in Table 5.

Curve fitting analysis for F10 formulations

In-vitro drug release data of F10formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 6.

STABILITY STUDIES

The most promised formulations were selected stability studies. Three month stability studies were performed as per ICH guidelines at a temperature of 45^0 ± 10C over a period of three month on the promising SPH's tablet formulation F10.Sufficient number of tablets (10) were packed in aluminium packing and kept in stability chamber maintained at 45^0± 10C / 75 ± 5 % RH for 3 months. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and in-vitro floating studies were performed to determine the drug release profiles, the estimation of drug contents and data of dissolution and *in-vitro* dissolution studies are shown in table 7.

Table 1. Preparation superporous hydrogels different variation

Chitosan	2gr	2gr	2gr	2gr
Formaldehyde	0.06	0.12	0.18	0.24
Chitosan+ Acetic acid	5ml	5ml	5ml	5ml
Sodium bicarbonate	80mg	80mg	80mg	80mg
Chitosan	3gr	3gr	3gr	3gr
Formaldehyde	0.06	0.12	0.18	0.24
Chitosan+ Acetic acid	5ml	5ml	5ml	5ml
Sodium bicarbonate	80mg	80mg	80mg	80mg

Table 1. Formulations of Sumatriptan Tablets Prepared by Direct compression Method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug+Superporus Hydrogels	45	50	60	50	45	40	36	33	35	25	42	72
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Sodium Bicarbonate	8	8	8	8	8	8	8	8	8	8	8	8
Microcrystalline Cellulose	44	41	29	41	44	49	53	56	54	64	47	17
Total	100	100	100	100	100	100	100	100	100	100	100	100

All quantities in mg per tablet, F=formulation codes.

Table 2. Flow properties of tablet blend

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	0.436±0.01	0.492±0.015	27.24±0.30	11.47±1.97	1.128±0.02
F2	0.449±0.015	0.505±0.02	27.48±0.39	11.21±1.96	1.129±0.03
F3	0.491±0.015	0.58±0.01	28.98±0.68	11.88±3.97	1.137±0.05
F4	0.478±0.015	0.527±0.015	29.23±0.96	9.46±1.81	1.108±0.02
F5	0.432±0.02	0.499±0.03	26.37±0.73	12.68±2.25	1.148±0.03
F6	0.44±0.01	0.467±0.006	27.97±0.36	9.34±3.16	1.105±0.04
F7	0.451±0.025	0.538±0.025	28.23±0.29	15.53±1.19	1.186±0.02
F8	0.43±0.01	0.53±0.017	28.89±0.40	11.67±3.61	1.128±0.05
F9	0.419±0.01	0.459±0.025	26.19±0.34	8.71±2.84	1.095±0.04
F10	**0.485±0.015**	**0.518±0.032**	**25.76±0.63**	**6.37±1.11**	**1.067±0.01**
F11	0.430±0.02	0.49±0.01	26.95±0.46	12.24±2.48	1.138±0.03
F12	0.419±0.02	0.475±0.015	26.99±0.27	13.36±3.22	1.132±0.02

Table 3. Evaluation of Prepared Phenylephrine Superporous Hydrogel Tablets

Formulation	Weight variation	Thickness	Hardness	Friability	Drug content
F1	100±1.55	2.04 ±0.03	4.2±0.15	0.17±0.03	98.97±0.88
F2	99±0.94	2.08±0.02	4.2±0.25	0.14±0.02	100.1±0.83
F3	101±0.59	2.03±0.03	4.1±0.31	0.15±0.01	99.72±0.87
F4	100±1.81	2.06±0.05	4.2±0.21	0.31±0.02	100.8±0.64
F5	100±1.41	2.09±0.03	3.9±0.2	0.13±0.01	99.42±0.58
F6	101±1.57	2.07±0.04	3.8±0.26	0.24±0.02	99.98±0.8
F7	100±0.49	2.05±0.07	3.7±0.31	0.16±0.05	99.8±0.42
F8	100±1.46	2.08±0.02	4.3±0.25	0.14±0.03	99.9±0.5
F9	100±0.84	2.02±0.02	4.3±0.45	0.19±0.08	98.85±0.68
F10	99±0.2	2.04±0.02	4.4±0.41	0.23±0.02	99.97±0.87
F11	100±0.43	2.10±0.03	4.3±0.21	0.14±0.02	98.98±0.78
F12	100±1.23	2.06±0.03	3.8±0.15	0.26±0.01	100.1±0.74

Table 4. Swelling Index and Density of dried SPH's

Formulation	Swelling index
F1	47.35 ± 0.23
F2	58.00 ± 0.14
F3	40.00 ± 0.12
F4	68.60 ± 0.80
F5	52.75 ± 0.56

F6	74.50 ± 0.20
F7	48.80 ± 0.26
F8	69.40 ± 0.32
F9	71.50 ± 0.16
F10	70.40 ± 0.12
F11	49.70 ± 0.26
F12	52.60 ± 0.32

Table 5. Cumulative % drug release

Time(hrs)	Cumulative % drug release											
0	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	41.15	24.08	40.2	10.16	36.41	20.29	35.46	9.86	33.57	18.39	31.67	8.91
2	44.88	26.93	51.59	13.65	45.9	31.67	48.12	16.5	40.12	25.98	38.59	18.39
3	45.1	31.67	64.86	25.03	52.53	44.88	59.17	29.77	55.33	33.57	51.42	26.93
4	49.6	42.1	68.66	42.1	65.81	56.33	71.5	40.21	63.41	42.1	63.91	38.31
5	62.02	48.74	77.02	59.17	78.14	69.61	83.83	57.28	71.5	55.38	72.45	52.53
6	101.8	77.14	97.11	80.99	84.78	82.81	87.42	74.35	80.99	67.71	83.83	69.61
7		95.23		98.06	91.42	91.42	94.5	88.57	91.42	80.99	90.47	83.83
8					97.11	94.5	101.8	94.5	100.9	87.42	91.42	94.5
9								98.06		93	96.53	99.95
10										99.95		

Table 6. Curve fitting analysis for F10 formulations

Order of kinetics	Zero	First	Higuchi	Peppas
Regression values	0.982	0.922	0.937	0.715

Table 7. Drug Content Data Stability Formulation F10

Sl. No.	Trial No.	1st Day (%)	30th Day (%)	60th Day (%)	90th Day (%)
1.	I	99.99	99.81	99.75	99.73
2.	II	99.94	99.88	99.78	99.61
3.	III	99. 53	99.42	99.31	99. 23
4.	Mean	99.81	99.50	99.45	99.36

Fig 1. FT-IR Spectra of pure drug (Sumatriptan)

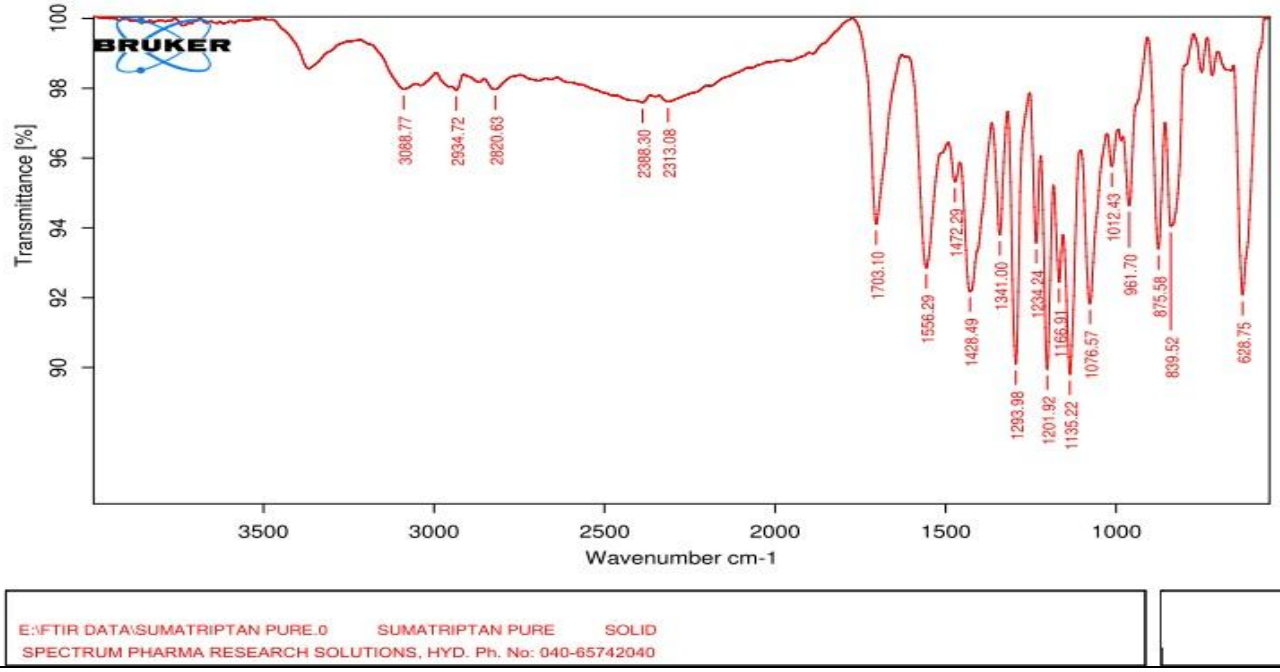


Fig 2. FT-IR Spectra of physical mixture of polymers and drug

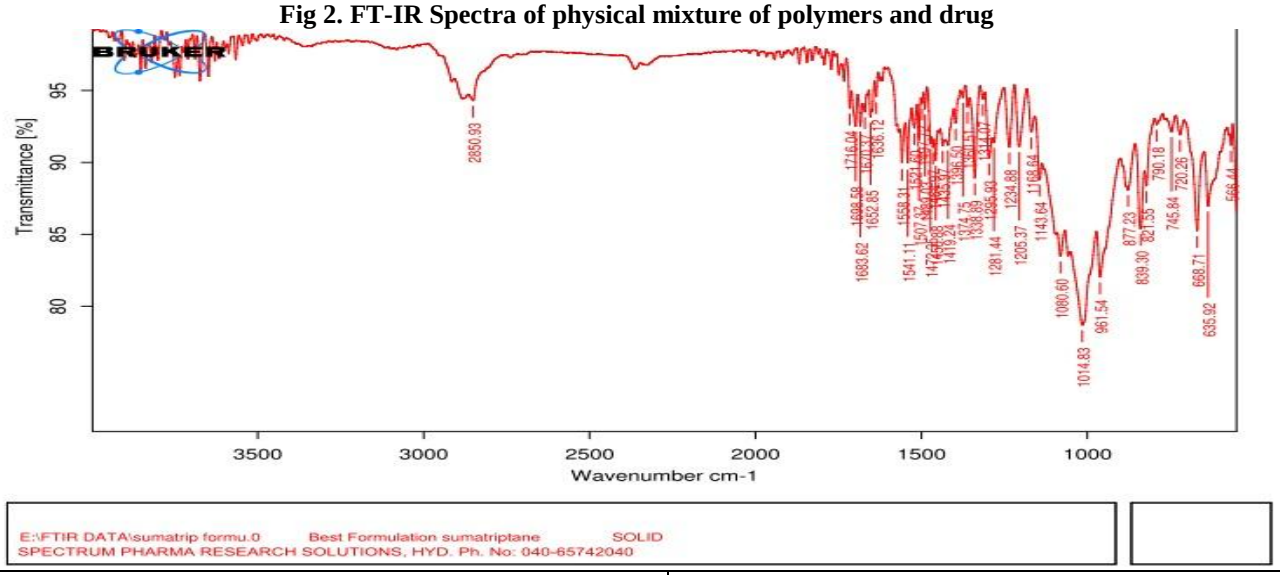


Fig 3. Cumulative %drug release (F1-F12.)

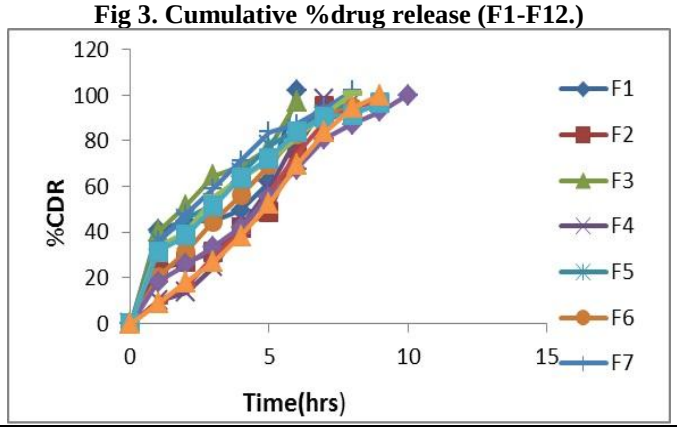


Fig 4. Cumulative percent drug released Vs Time plots (zero-order) of formulation of F10

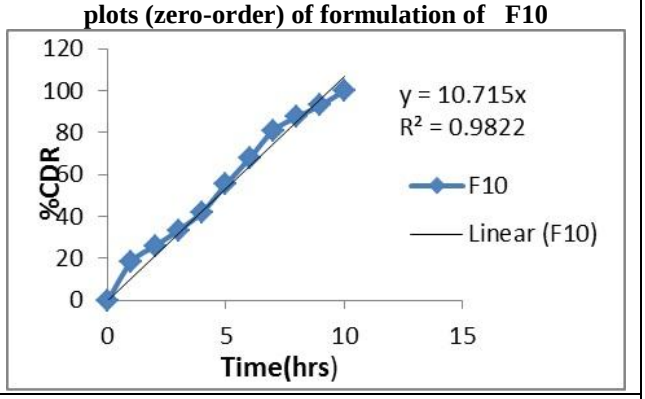


Fig 5. Log cumulative percent drug remaining vs Time plots (first order of formulation F10

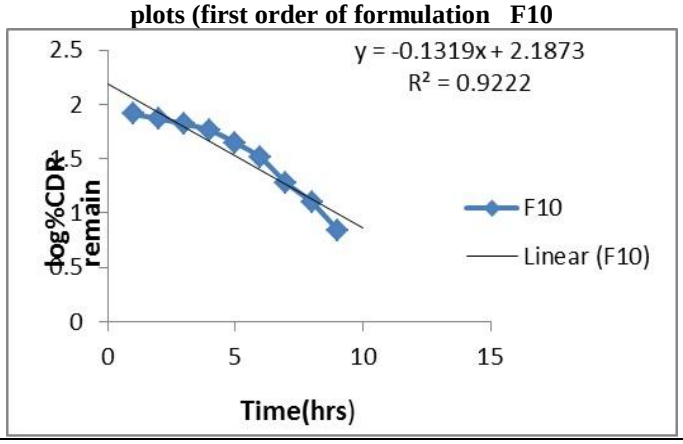


Fig 6. Cumulative percent drug released Vs Square root of time (Higuchi's plot) of formulation F10

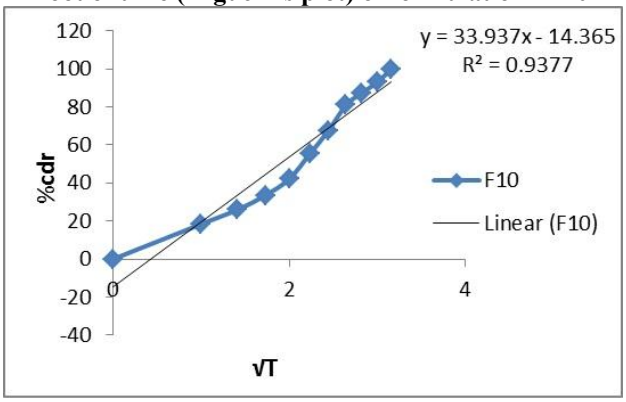
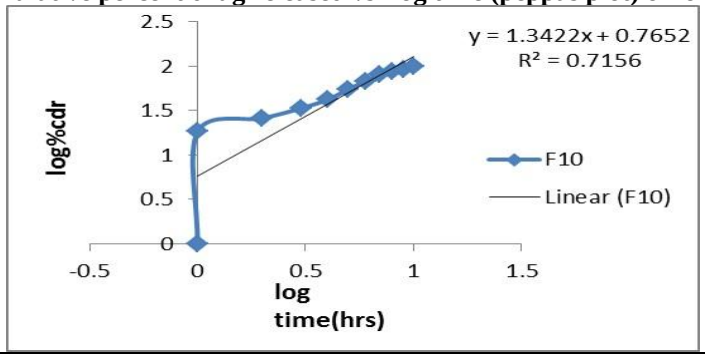


Fig 7. Log cumulative percent drug released vs Log time (peppas plot) of formulation F10



CONCLUSION

The formulation F10 prepared by direct compression containing chitosan, formaldehyde, sodium bicarbonate prepared by cross-linking technique exhibited good swelling index and maximum rate of drug release. So, this formulation was considered to be the optimized formulation. The prepared tablet formulations are evaluated for different precompressional and postcompressional parameters the results revealed that the all formulations shows good precompressional properties showing better flow ability, hardness is maintained in the range of 3.7-4.4kg/cm2 which provides good mechanical strength to the tablet. Other parameters like weight variation, friability, thickness, drug content are in the range of prescribed limits of IP. Thus the formulated Superporous Hydrogel tablets of Sumatriptan offer a superior alternative over conventional marketed dosage forms in regards of controlled release of drug. FTIR studies combined with stability studies proved the integrity of the developed tablets. Therefore the prepared tablet shows improved bioavailability with increased drug release.

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