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Development and evaluation of gastroretentive floating tablets of Sumatriptan Succinate

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ABSTRACT

Sumatriptan is a medication used for the treatment of migrane headaches. It is a synthetic drug belonging to the triptan class. Structurally, it is an analog of the naturally occurring neuro-active alkaloids dimethyl tryptamine (DMT), bufotenine, and 5-methoxy-dimethyltryptamine, with an N-methyl sulfonamidomethyl- group at position C-5 on the indole ring. Various approaches have been developed to retain the dosage form in the stomach. Gastric floating drug delivery systems offer numerous advantages over other gastric retention systems. The GFDDS of sumatriptan succinate were developed in the form of tablets comprising of an effervescent agent. The prepared mini tablets were subjected to pre and post compressional parameters and the values were within the prescribed limits. The drug- excipient compatibility studies were performed using FTIR techniques. The effect of different formulation parameters such as concentrations of effervescent agent on floating properties and drug release kinetics were studied and the formulations were optimized. The concentration of the effervescent agent greatly influenced the floating lag time. From the results it can be concluded that F11 with HPMC K100M, and sodium bicarbonate as gas generating agent provides the 99.92 % of drug release up to 12hours. By increasing the concentration of the polymer, decreased dissolution rates were obtained for the all the polymers. The slow rate of polymer hydration and the presence of effervescent agent caused a burst release initially. Hence, all the GFDDS were formulated without addition of the loading dose. Although the release rate mainly depended on the proportion of the polymer, the entrapped gas within the hydrogel also influenced the rate of drug release from the GFDDS. By increasing the proportion of the effervescent agent, the porosity produced by the entrapped gas increased and dissolution rate was increased.

Keywords: mini tablets, dissolution rates, Sumatriptan.

INTRODUCTION

Introduction to controlled drug delivery system

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate.

Floating systems/ hydrodynamically balanced systems

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS')[1]. Floating systems or dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. After the release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Of these above mentioned approaches, floating drug delivery or

hydrodynamically balanced drug delivery systems are given much importance, because of their ease of preparation and reliable and reproducible gastric retentive action.

Gastric floating drug delivery systems (GFDDS)

Gastric floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolong period. The need for gastric retention dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems in which the problems associated with oral controlled release dosage forms could be rectified to a satisfactory extent for drugs having site-specific absorption at stomach or upper parts of small intestine.

Gastric Retention System

Gastric Retention System is a device, which resides in the confines of the stomach over a prolonged period of time (prolonging the residence time) for the purpose of providing a platform for controlled release of biologically active agents. The system releases the active agent to be absorbed or released from the stomach to be absorbed in the upper parts of the small intestine. In particular it allows for less frequent dosing of the active agent than with immediate release formulations or sustained release formulations that are not gastric retention dosage forms. In other applications the frequency of dosing may be the same, but the gastric retention dosage forms will beneficially alter the absorption profile of the active agent from that available with immediate release formulations. This may result in increased bioavailability of the active agent with reduced side effects.

Advantages of FDDS

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach eg:Antacids
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
4. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts.

Limitations of FDDS

1. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach for the drug delivery system to float therein and to work efficiently. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to mucous lining of the stomach wall. Alternatively, the dosage form may be administered with a glass full of water (200-250 ml).
2. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids. Drugs such as nifedipine, which is well absorbed along the entire G.I. tract and which undergoes significant first pass metabolism, may not be desirable candidate for GFDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of GFDDS for drugs that are irritant to gastric mucosa.

Approaches to GFDDS

The various buoyant preparations include hollow microspheres (‘microballoons’), granules, powders, capsules, tablets (pills), and laminated films. Based on the mechanism of buoyancy, two distinctly different technologies, i.e., non-effervescent and effervescent systems have been utilized in the development of GFDDS.

MATERIALS AND METHODS

Materials

Table 1: Materials used for the formulation development

S. No.	Ingredients
1	Sumatriptan succinate
2	HPMC 100 cps
3	Xanthan gum
4	Guar gum
5	Ethyl cellulose
6	Sodium bicarbonate
7	Citric acid
9	Starch
10	Magnesium stearate
11	Talc

Equipments

Table 2: Equipment used

S. No.	Name of the Equipment
1	8 Basket dissolution apparatus
2	Single stage tablet punching machine
3	U.V. Spectrophotometer
4	Analytical Balance
5	Friability Apparatus
6	Hardness tester
7	Tapped density tester

Formulation Development

Preparation of gastro retentive floating tablets

Floating tablets containing Sumatriptan succinate were prepared by wet granulation technique using variable concentrations of HPMCK100M, Xantham gum and guar gum, with gas generating agent such as sodium bicarbonate**.** Different tablet formulations were prepared by wet granulation technique. All the powders were passed through 60 mesh sieve. Magnesium stearate was finally added as glidant and lubricant. The blend was directly compressed (9mm). Each tablet contained 25 mg of sumatriptan succinate sodium and other pharmaceutical ingredients as listed in table at each section.

Table 3: Composition of Formulation table for Sumatriptan succinate

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Sumatriptan succinate	25	25	25	25	25	25	25	25	25	25	25	25
Xanthan gum	15	20	25	30	--	--	--	--	--	--	--	--
Guar gum	--	--	--	--	15	20	25	30	--	--	--	--
HPMC K 100 M					--	--	--	--	15	20	25	30
Sodium bi carbonate	10	10	10	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
MCC	91	86	81	76	91	86	82	76	91	86	81	76
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

Analytical method development

Preparation of standard solution for standard graph

100 mg of Sumatriptan succinate was dissolved in methanol in a 100 ml volumetric flask and the solution was made up to the mark with methano[14].

Procedure

The standard solution of Sumatriptan succinate was subsequently diluted with 0.1 N Hydrochloric acid to obtain a series of dilutions containing 2, 4, 6, 8 and 10μg of Sumatriptan succinate in 1 ml solution and the absorbance of these solutions was measured at 238nm in spectrophotometer (UV spectrophotometer) against corresponding blank. The concentration of Sumatriptan succinate and the corresponding absorbance values were given in Table.16. The calibration curve for the estimation of Sumatriptan succinate was constructed by plotting linear best fit between the concentration of Sumatriptan succinate and the corresponding mean absorbance values.

Evaluation of powder blend

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was 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.

Relationship between angle of repose and powder flow

S. No.	Angle of repose degrees	Flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	40 and above	Very Poor

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Compressibility index range

S.No.	% Compressibility index	Flow ability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair-passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V)

Porosity (%) =V_{bulk}-V/V_{bulk} x 10

RESULTS AND DISCUSSIONS

The effect of various formulation factors such as concentrations of cellulose polymers, different gums and effervescent agent on floating properties and drug release kinetics were studied to optimize the formulation. The floating lag time mainly depends up on the concentration of effervescent agent present in the matrix. In the present study sodium bicarbonate was used as effervescent agent, as it is cheap and safe

Table 4: Calibration curve of Sumatriptan succinate in 0.1N HCl

S. No	Concentration (µg/ml)	Absorbance at 229 nm
1.	0	0
2.	2	0.124
3	4	0.242
4.	6	0.323
5.	8	0.402
6.	10	0.539

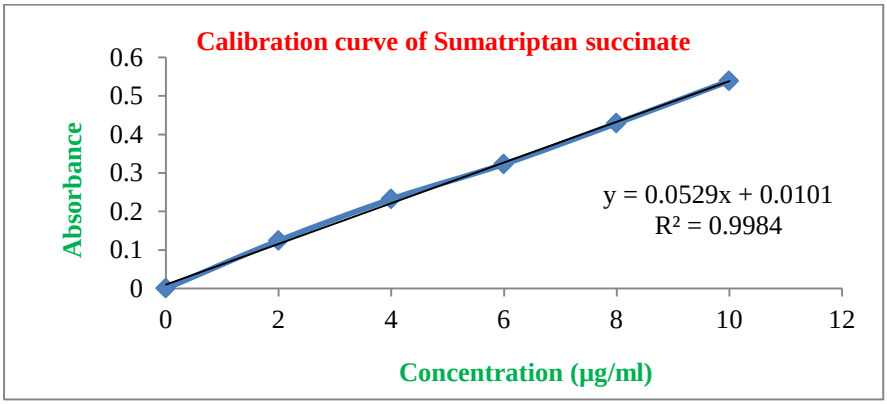

Fig 1: Standard plot of Sumatriptan succinate at 229 nm

Physical parameters of the prepared formulations

Table 5: Physical parameters of the precompression blend

Formulation	Compressibility Index	Angle of repose	Hausner ratio
F1	13.25±0.34	22.25±0.12	1.18±0.82
F2	18.59±0.12	21.16±0.31	1.38±0.54
F3	15.52±0.14	36.52±0.93	1.24±0.78
F4	17.86±0.25	28.56±0.34	1.18±0.56
F5	14.29±0.32	22.85±0.67	1.23±0.38
F6	17.84±0.54	21.43±0.89	1.16±0.32
F7	19.58±0.43	23.45±0.41	1.32±0.93
F8	15.56±0.61	22.47±0.62	1.16±0.26
F9	14.78±0.28	26.89±0.64	1.15±0.46
F10	17.42±0.32	27.45±0.15	1.27±0.62

F11	18.56±0.36	22.51±0.41	1.35±0.39
F12	14.28±0.53	21.85±0.62	1.26±0.20

Evaluation of post compression parameters

Table 6: Evaluation of post compression parameters

Batch No.	Average weight (mg)	Hardness (kg/cm^2)	Friability (%)	D.T (min)	Drug content (%)
F1	148.23±0.72	4.23±0.271	0.20	1.7	99.1
F2	149.62±0.56	4.61±0.268	0.12	1.5	99.7
F3	150.71±0.76	4.52±0.36	0.18	1.2	98.23
F4	149.25±1.42	4.73±0.361	0.16	1.5	99.62
F5	151.43.±0.96	4.76±0.213	0.13	2.4	97.27
F6	150.70±0.37	5.85±0.301	0.23	1.10	99.5
F7	148.52±0.18	4.88±0.310	0.20	1.4	101.4
F8	149.96±1.21	4.52±0.213	0.19	1.5	97.9
F9	150.95±1.32	4.36±0.403	0.20	1.3	98.8
F10	149.91±1.44	4.95±0.415	0.18	2.8	99.97
F11	151.84±1.51	4.11±0.353	0.18	1.4	99.2
F12	148.77±1.67	5.17±0.347	0.17	1.5	101.2

Table 7: Cumulative % release of formulations F9-F12

Time (hrs)	F9±SD	F10 ±SD	F11±SD	F12±SD
0.25	13.47±0.47	10.96±0.65	5.87±1.52	3.76±0.32
0.50	20.34±0.45	19.32±0.84	15.25±1.92	9.86±0.58
0.75	36.87±0.95	32.02±0.94	28.45±0.48	20.67±0.88
1	40.08±0.45	39.98±0.97	36.99±0.82	29.97±0.93
2	63.90±0.62	58.04±0.76	45.94±0.46	32.45±0.48
4	78.56±0.72	69.43±0.49	58.54±0.59	39.66±0.77
6	84.96±0.23	79.67±0.39	69.09±0.93	49.76±0.29
8	96.29±0.54	85.0±0.59	76.86±0.49	59.12±0.71
10	---	97.03±0.98	89.02±0.58	67.34±0.52
12	---	---	99.92±0.69	75.56± 0.95

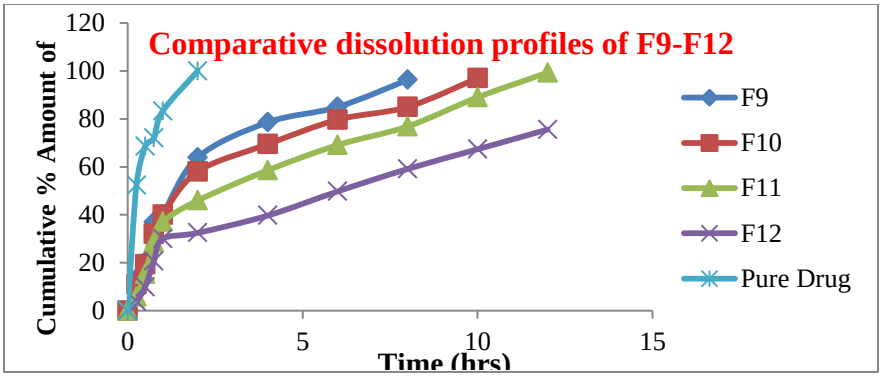

Fig 2: Comparative dissolution profiles of F9-F12

Drug release kinetics of prepared floating formulations

Table 8: Drug release kinetics of prepared floating formulations

	Correlation Co-efficient (r) value				Korsemeyer - Peppas	
Formulation	**Zero order**	**First order**	**Higuchi's**	**Erosion**	**r value**	**n value**
F1	0.744	0.983	0.596	0.733	0.984	0.353
F2	0.835	0.97	0.613	0.826	0.853	0.345
F3	0.863	0.936	0.615	0.855	0.954	0.441
F4	0.891	0.894	0.709	0.886	0.911	0.630
F5	0.703	0.946	0.638	0.698	0.441	0.558
F6	0.759	0.949	0.590	0.826	0.921	0.427
F7	0.899	0.952	0.694	0.893	0.973	0.549
F8	0.903	0.924	0.703	0.898	0.925	0.569
F9	0.840	0.967	0.671	0.834	0.943	0.556
F10	0.850	0.935	0.667	0.844	0.935	0.547
F11	**0.901**	**0.873**	**0.705**	**0.896**	**0.900**	**0.615**
F12	0.912	0.971	0.734	0.906	0.883	0.646
Pure Drug	0.84	0.730	0.700	0.921	0.986	0.311

The relative contributions of drug diffusion and matrix erosion to drug release were further confirmed by subjecting the dissolution data to Higuchi model and erosion model. It was found that diffusion (0.705) as well as erosion (0.896) governs the drug release from these formulations as indicated by r values.

Though the drug release is governed by diffusion as well as erosion, the contribution of drug matrix erosion is found to be slightly higher than that of diffusion as indicated by the higher r values of erosion model. It can be concluded that the drug release is predominately governed by erosion rather than diffusion. From this, it is clearly evident that the increase in the polymer content in the GFDDS decreased the dissolution rate of drug.

When the release data were analyzed as per peppas equation, the release exponent 'n' for F11 formulation was >0.5 to <1 with all the formulations indicating Non Fickian Diffusion as the release mechanism.

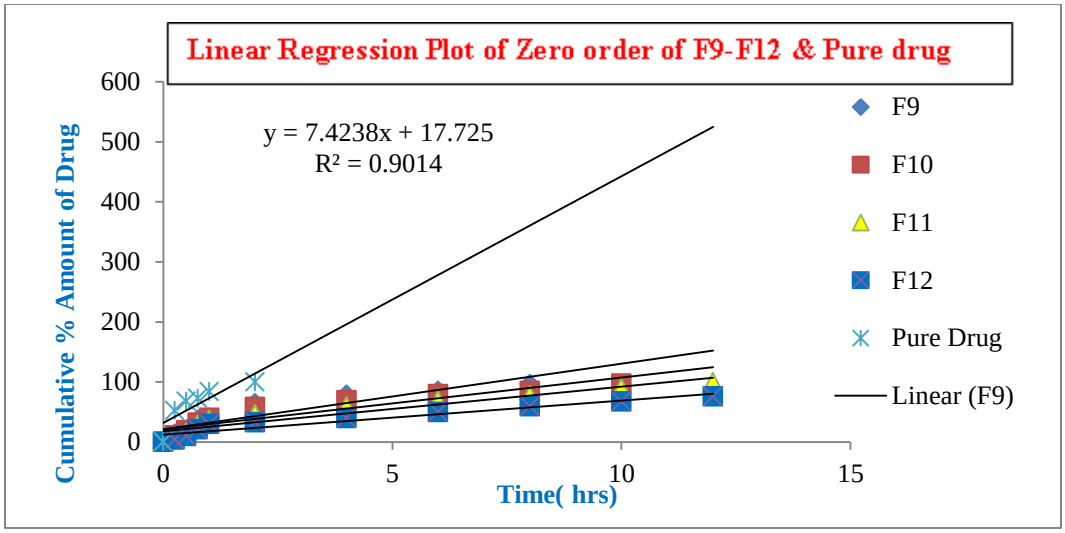

Fig 3: Linear regresion plots of Zero Order for F9-F12 &Pure Drug

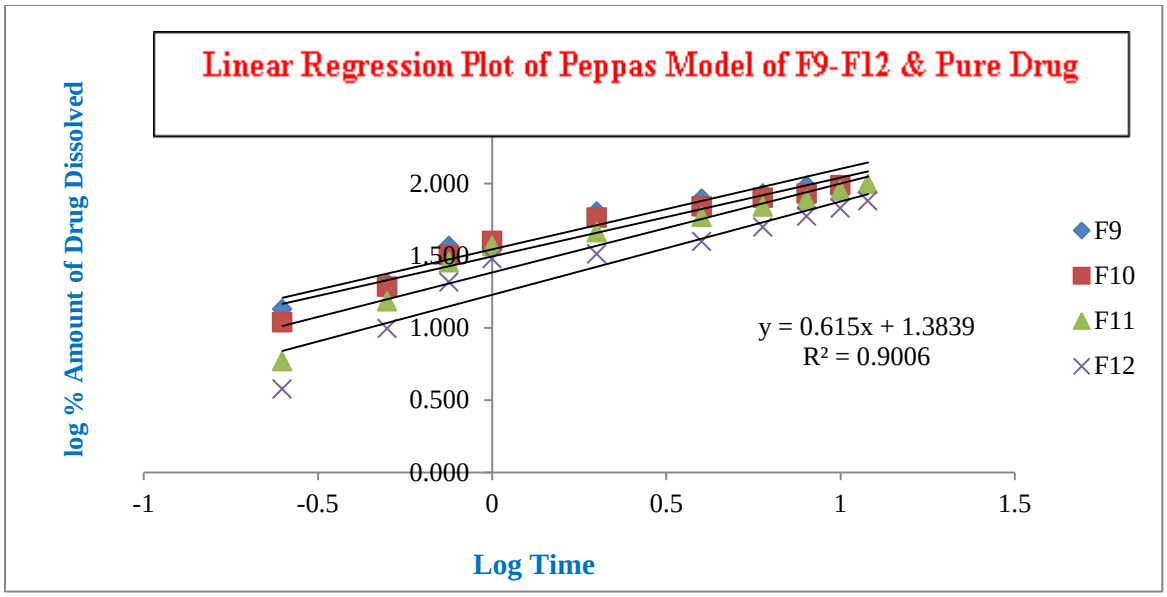

Fig 4: Linear regresion plots of Peppas model for F9- F12 & Pure Drug

Drug-polymer compatibility studies

IR spectroscopic studies

Sumatriptan succinate pure drug and sumatriptan succinate and polymer physical mixture, optimized tablet formulation were subjected to IR spectroscopic studies to check the compatability among them.

No prominent difference was observed in the IR peaks of Sumatriptan succinate + HPMC 100 K physical mixtures and optimized formulations upon comparison with the peaks of drug and polymer alone, which may considered that Sumatriptan succinate and HPMC K100M are compatible enough without any interactions.

IR Spectrum of Sumatriptan succinate pure drug

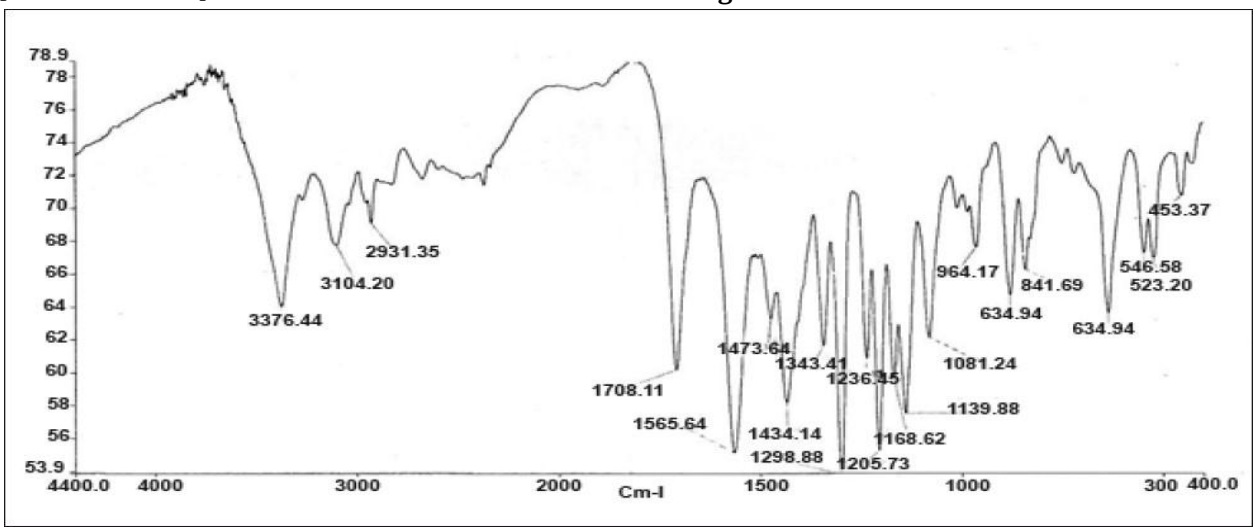

Fig 4: IR Spectrum of Sumatriptan succinate pure drug

SUMMARY AND CONCLUSION

The GFDDS of sumatriptan succinate prepared from HPMC remained intact and the compactness of the tablet was not affected during the *in vitro* dissolution test. It was found that the drug release from the GFDDS of sumatriptan succinate mainly depended upon the concentration of polymer present

in the GFDDS for all the twelve formulations. By increasing the concentration of the polymer, decreased dissolution rates were obtained for the all the polymers. The slow rate of polymer hydration and the presence of effervescent agent caused a burst release initially. Hence, all the GFDDS were formulated without addition of the loading dose. Although the release rate mainly depended on the proportion of the polymer, the entrapped gas within the hydrogel also influenced the rate of drug release from the GFDDS. By increasing the proportion of the effervescent agent, the porosity produced by the entrapped gas increased and dissolution rate was increased. The dissolution data were fitted to four popular release models such as zero-order, first-order, diffusion and erosion equations to determine the release mechanism. The correlation coefficients and the slope values from Higuchi plots indicated that the release mechanism followed diffusion and erosion with zero order kinetics. The results of the present study thus clearly indicated that GFDDS for sumatriptan succinate were successfully formulated by using different grades of hydrophilic polymers such as HPMC K100, xantham and guargum. From the results it can be concluded that F11 with HPMC K100M, and sodium bicarbonate as gas generating agent provides the 99.92 % of drug release up to 12hours.

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