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Research Article

Formulation and evaluation of sitagliptan floating tablets

M. Sambasiva rao, A. Sunil kumar reddy, A. Ashok Kumar

Professor & HOD OF Vijaya college of pharmacy, Munaganur (village), Hayathnagar (Mandal), Ranga redy (District), Pin-501511

Corresponding Author: A. Ashok Kumar

Email: ashok576@gmail.com

ABSTRCT

Gastro retentive dosage form using Guar gum was prepared to develop floating tablets of Sitagliptin that could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach. The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture. The post-compression parameters of all formulations were determined and the values were found to be satisfactory. From the drug content and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F9 i.e. the formulation containing guargum, Sodium bicarbonate, citric acid, micro crystalline cellulose and Magnesium stearate is the best formulation. As a result of this study it may be concluded that the floating tablets using a guar gum in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a sustained manner. The concept of formulating floating tablets of Sitagliptin offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

Keywords: Guar Gum, Sodium Bicarbonate, Citric acid

INTRODUCTION

Gastroretentive drug delivery systems

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.[5]

Floating systems or hydrodynamically 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.[6]

Comprehensive knowledge about GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc. is the key for the designing of oral controlled release dosage forms. The rate and

extent of drug absorption from different sites of GI tract and factors that govern the absorption further assist the design of dosage form.

Basic Gastrointestinal Tract Physiology

It is well recognized that stomach may be used as "depot" for sustained-release (SR) dosage forms, both in human and veterinary applications.[7] The stomach is anatomically divided into three parts: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump to accomplish gastric emptying. The process of gastric emptying occurs during fasting as well as fed states; however, the pattern of motility differs markedly in two states. In the fasted states, it is characterized by inter digestive series of electrical events, which cycle both through stomach and intestine every 2 to 3 hrs. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases:

Phase I (basal phase)

Lasts from 40 to 60 min with rare contractions. It is characterized by lack of any secretary and electrical activity and contractile motions.

Phase II (preburst phase)

Lasts for 20 to 40 min with intermittent action potential and contractions. Bile enters the duodenum during this phase, while the gastric mucous discharge occurs during the later part of phase I and throughout the phase III.

Phase III (burst phase)

Lasts for 10 to 20 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the "housekeeper wave".

Phase IV (transition period)

Lasts for 0 to 5 min and occurs between phase III and phase I.[8]

AIM AND OBJECTIVE

Aim

The aim of the present study is to formulate and evaluate Sitagliptin floating tablets.

The objective of the present study is given below:

1. To carry out compatibility studies for the possible drug/polymer interactions using FTIR spectral studies.
2. To develop sustained release floating (gastro-retentive) tablets.
3. To evaluate the formulated dosage forms.
4. Reduction in fluctuation in therapeutic level.
5. To increase in the gastric residence time.
6. To reduce chances of degradation of drug

METHODOLOGY

Preparation of calibration curve for sitagliptin

Standard curve in 0.1n HCL

Stock Sample Preparation

Accurately weighed 100 mg of drug was first dissolved in100 mL of 0.1N HCL in 100 mL of volumetric flask to make a concentration of 1000 µg/mL (primary stock solution). 5 mL of primary stock solution was pipetted out into 50 mL of volumetric flask and volume was adjusted with 0.1N HCL to make a concentration of 100µg/mL (secondary stock solution).

Sample Preparation

From the secondary stock solution pippetout 0.25,0.5,0.75,1,1.25 and 1.5 in to 10ml of volumetric flask and volume made up to with 0.1N HCL to give various concentrations such as5,10,15,20,25,30 µg/mL were prepared for calibration curve. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 288 nm.

Formulation of floating tablets of Sitagliptin by direct compression method

Floating tablets of Sitagliptin were prepared by direct compression method employing sodium bicarbonate as gas-generating agent and citric acid for supporting floating agent. HPMC, xanthum gum, guar gum were used as rate controlling polymers. The concentrations of the above

ingredients were optimized as shown in below table on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate retarding polymers and other excipients, except magnesium stearate, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for not more than 1 min (to ensure good lubrication.) About 350 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 16*8mm punche. The hardness of the tablets was adjusted at 7-8 kg/cm^2 using a Monsanto hardness tester.

RESULTS AND DISCUSSION

Table.1: Formulations of Sitagliptin Floating Tablets (in mg) by Direct compression

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
SITAGLIPTIN	100	100	100	100	100	100	100	100	100
HPMC	105	122.5	140	--	--	--	--	--	--
XANTHUM GUM	--	--	--	70	87.5	140	--	--	--
GUAR GUM	--	--	--	--	--	--	70	87.5	140
MCC	42	24.5	7	77	59.5	7	77	59.5	7
$NaHCo_3$	35	35	35	35	35	35	35	35	35
Citric acid	12	12	12	12	12	12	12	12	12
Mg. STEARATE	6	6	6	6	6	6	6	6	6
Total Weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Preparation of standard curve

Table no: 2 Calibration Curve Data of Sitagliptin

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2.5	0.046
5	0.088
7.5	0.124
10	0.161
12.5	0.203
15	0.246

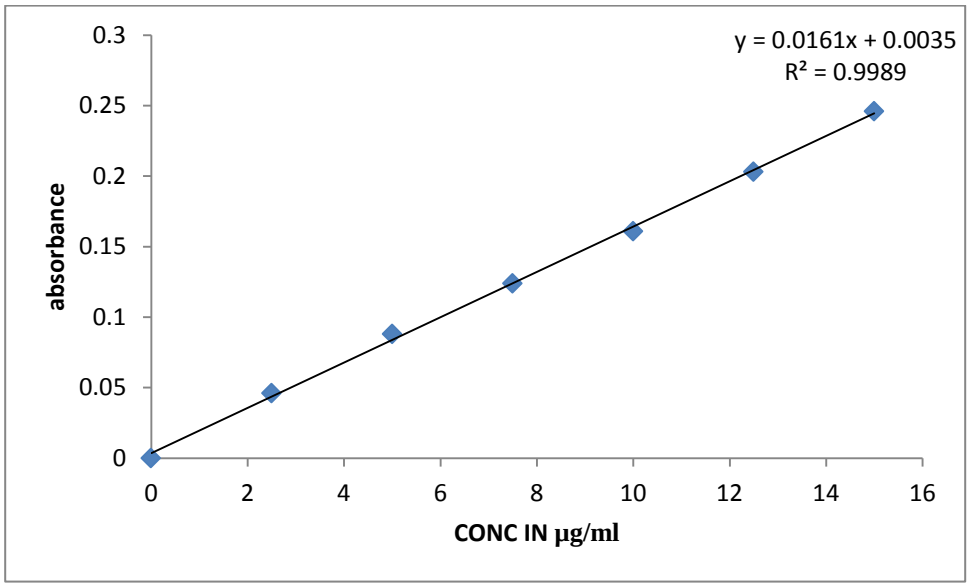

Fig :1 calibration cuve plot of Sitagliptin

Fourier transformer infrared spectroscopy

By correlating Sitagliptin peaks of pure drug spectrum with physical- mixtures of the optimized formulation it was found that the drug is compatible with the formulation components.

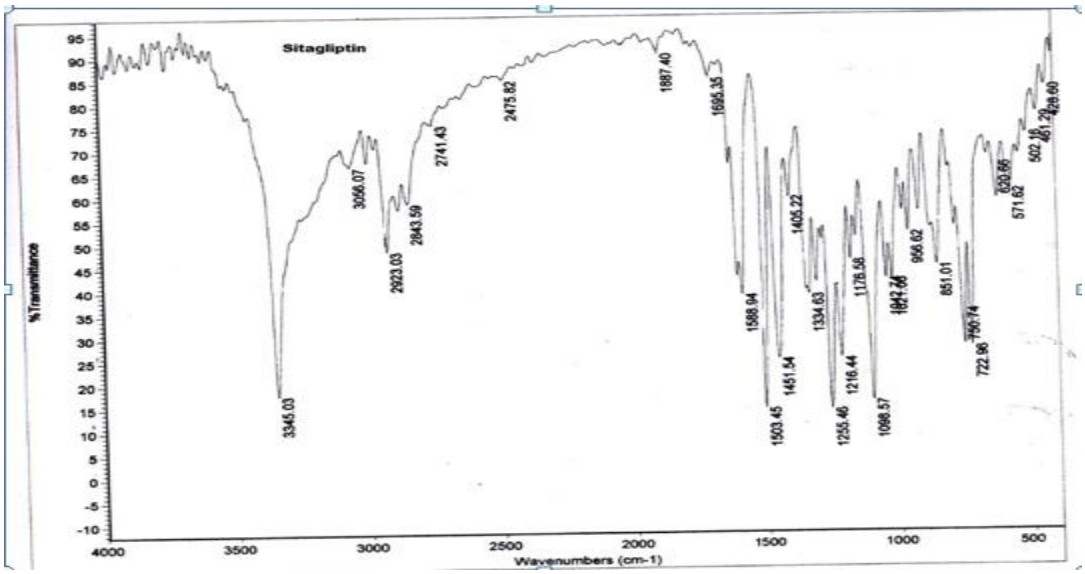

Fig No:2FTIR Spectra of Sitagliptin

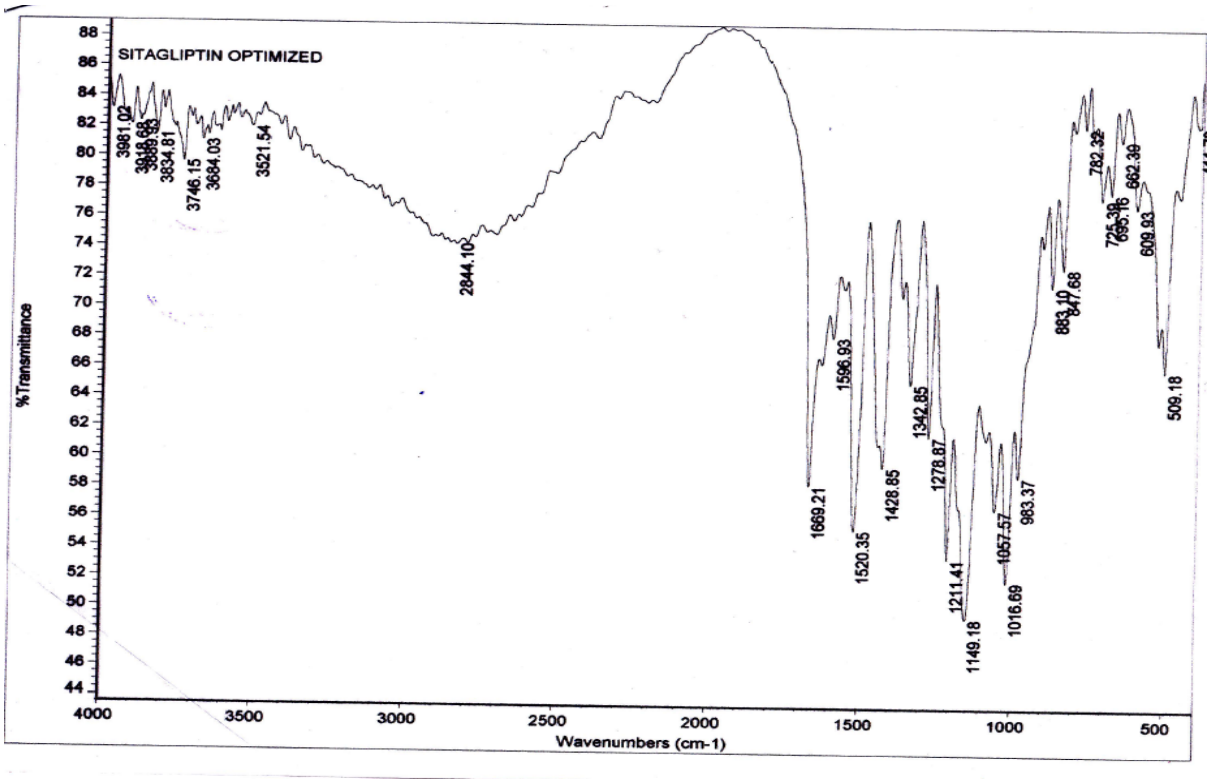

Fig No: 3FTIR Spectra of Sitagliptin optimized

Table no: 3PRE COMPRESSION PARAMETERS:

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)
F1	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06± 0.31
F2	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58± 0.15
F3	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44± 0.11
F4	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36± 0.13
F5	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	28.52± 0.19
F6	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	29.32± 0.19
F7	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09	29.69± 0.19
F8	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58± 0.15
F9	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36± 0.13

Sitagliptin floating tablets were prepared by direct compression method using 16*8mm punch, adjusting the hardness between 7-8 kg/cm^2. All the tablets white in color, round with smooth surfaces. All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have very good flow properties.

Table.:4 Data for post compression parameters of tablet formulations (F1-F9)

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	344±1.36	3.28±0.20	7.3±0.54	0.72±0.41
F2	348±2.02	3.33±0.22	7.5±0.75	0.37±0.42
F3	350±1.89	3.28±0.17	7.6±0.45	0.40±0.38
F4	347±1.99	3.16±0.05	7.9±0.25	0.46±0.36
F5	348±2.49	3.84±0.17	7.3 ±0.44	0.32±0.25
F6	347±1.99	3.92±0.25	7.6±0.31	0.30±0.17
F7	349±0.89	3.80±0.80	7.6±0.40	0.36±0.20
F8	350±1.88	3.82±0.20	7.5±0.55	0.31±0.25
F9	346±1.15	3.98±0.66	7.7±0.57	0.34±0.36

Table.:5 Data for post compression parameters of tablet formulations (F1-F9)

Formulation Code	Drug content (%)	Floating lag time	Swelling index (%)	Floating duration (hrs)
F1	98.78±0.24	46sec	32.12	6.3
F2	97.70±0.38	52sec	34.26	8.1
F3	99.51±0.32	59sec	36.01	9.2
F4	99.94±0.21	4min	34.95	8.3
F5	98.42±0.28	6min	37.23	10.1
F6	98.91±0.23	7min	38.18	11.0
F7	98.58±0.24	12sec	36.55	10.3
F8	99.26±0.44	28sec	37.75	11
F9	99.12±0.32	36sec	39.66	12

The tablets were evaluated for weight variation, thickness, hardness, friability, swelling index, floating lag time, floating duration, drug content and *in- vitro* drug release study. All the formulations passed the evaluation tests and showed comparable satisfactory results.

The thickness of all tablets was found to be in the range of 3.16-3.98 mm and hardness was found to be in the range of 7-8kg/cm^2 in all the formulations, the MCC and guar gum together showed good binding properties.

In all the formulations, the %friability was (0.31-0.72) below 1% as per USP.

The average weight was found to be 344-350 mg which will be within the given limits. Hence all

the tablets were found to show less weight variation.

The drug content of all formulations ranged from 97% to 99%, which is within the specified IP limits.

Swelling index was found to range from 30% to 40%, which shows that the formulations swell to a certain degree after coming in contact with the simulated gastric medium. Also the swelling index of tablets containing The results of formulations containing Guargum showed more values of swelling index than that of the ones containing xanthum and HPMC respectively because of the fact that the Guar gum showed good swelling properties in the later periods of time and that the CO_2 evolved by $NaHCO_3$ was entrapped by the fast hydrating polymer, thus maintaining the tablet integrity for longer periods of time, enhancing the floating duration time to be 12 hrs.

The floating lag time of the dosage forms made of guar gum and 10% of gas evolving agent were found to be satisfactory and were <1 min because guargum is a hydrophilic polymer and that it swells fast when it comes in contact with 1.2 pH acidic buffer. But the tablets made of HPMC, xanthum gum in increasing order of lag time showed lesser FLTs as its viscosity is less and that the polymer took even lesser time to form a matrix that could accommodate the evolved gas and also the entrapped gas bubbles during compression are more than that or the gas bubbles in matrices of guargum, a more viscous polymer. The tablets containing Guar gum alone showed longer FLT as the tablets tend to disintegrate due to the fast release of CO_2 gas. Guar gum were such that the gas released by the bicarbonate could facilitate the floating of the tablets, which was aided by the fast matrix forming polymer and highly viscous gel forming polymer (Guar gum) at the later stage of the drug dissolution, which is evident in the tablets showing a floating duration up to 12 hrs.

In vitro dissolution profile data of all the formulations

For gastroretentive formulations generally 0.1N HCL was used as dissolution medium and for present formulations 900ml 0.1N HCL as dissolution medium, USP Type 2 paddle apparatus, and 5ml samples were withdrawn for every time point.

Table: 6 Dissolution data of formulation F1-F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	31	28	26	21	18	16	20	16	13
2	40	35	33	35	33	32	35	32	28
3	52	46	45	42	41	38	42	40	36
4	73	65	59	55	52	50	55	52	50
5	85	77	72	69	65	63	67	66	62
6	98	85	83	83	74	76	76	73	68
8	-	95	91	94	83	80	88	82	75
10	-	-	94	-	97	90	99	94	89
12	-	-	-	-	-	92		95	97

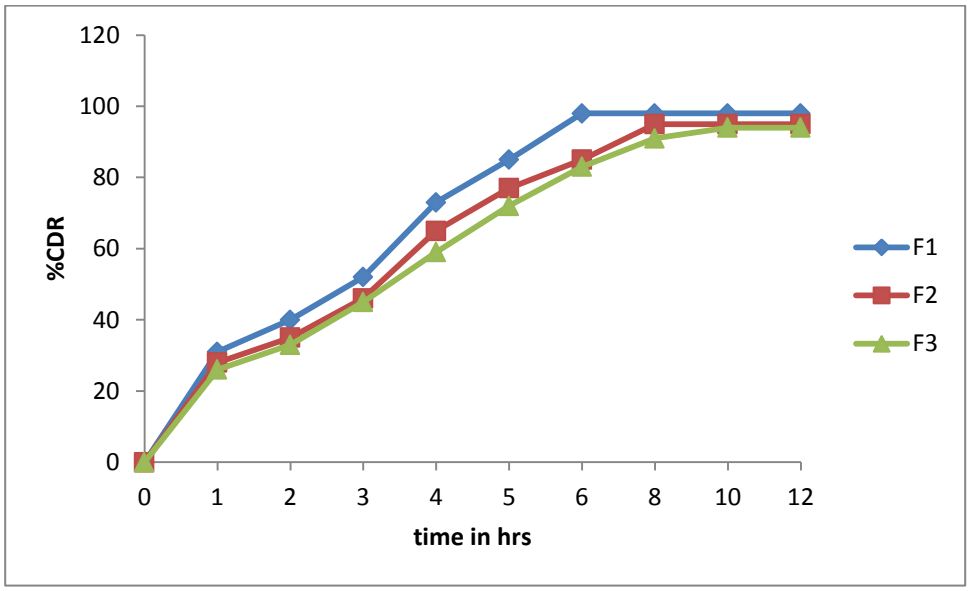

Fig no:4 Dissoulation graph for F1 – F3

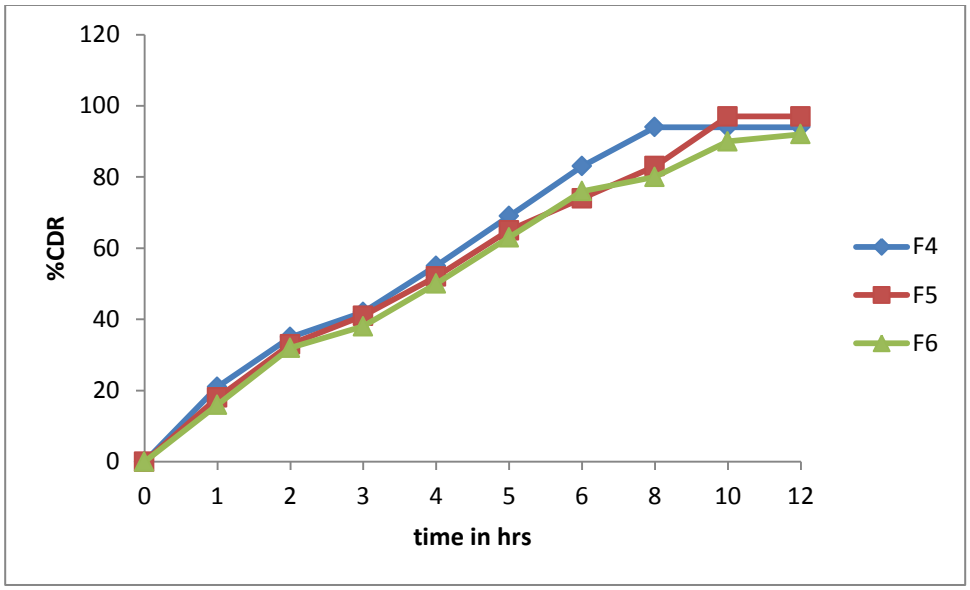

Fig no:5 Dissolution graphs for F4-F6

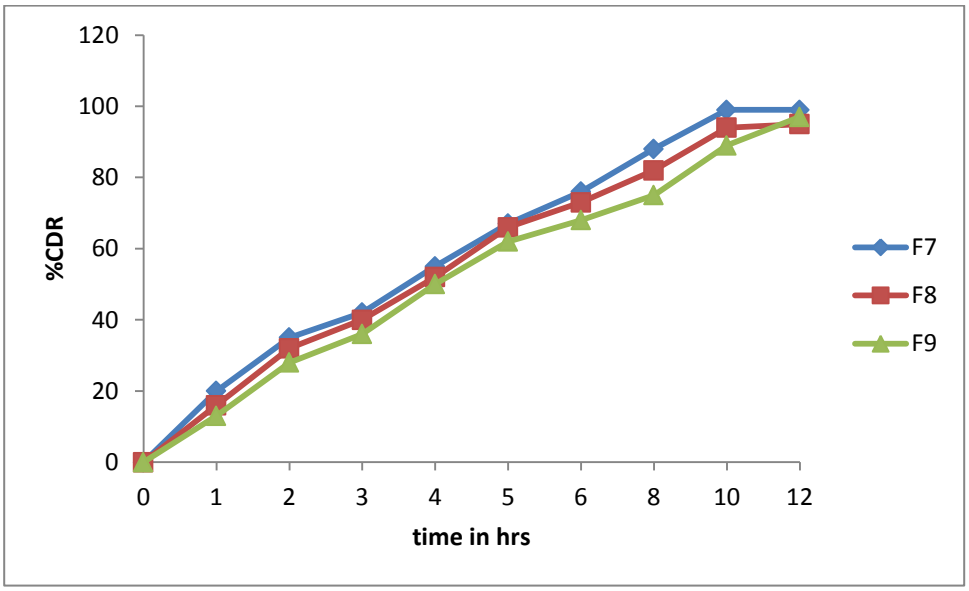

Fig no:6Dissolution graphs for F7-F9

The % Cumulative drug release of all the formulations F1, F2,F3, F5, F6 were not sustained the drug release for 12 hrs. F4, F7 and F8 formulations showed good integrity for 10 hrs. F9 formulation was optimised based on the floating behaviour. The optimized formulation F9 showed a %drug release of 97% for 12 hrs which shows greater release compare to all other formulation.

Kinetic modelling and mechanism of drug release

The results of kinetic equations applied to dissolution profiles of optimized batch F9 were determined as follows.

TABLE.7: Kinetic values obtained from different plots of F9 formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.971202304	-0.11465774	30.35961017	1.308499573
Intercept	11.14686825	2.115093439	-9.78941327	0.761137851
Correlation	0.972099715	-0.96315767	0.985702545	0.846467921
R 2	0.944977857	0.927672697	0.971609507	0.716507941

CONCLUSION

The post-compression parameters of all formulations were determined and the values were found to be satisfactory. From the drug content and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F9 i.e. the formulation containing guargum, Sodium bicarbonate, citric acid, micro crystalline cellulose and Magnesium stearate is the best formulation. As a result of this study it may be concluded that the floating tablets using a guar gum in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a sustained manner.

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