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FORMULATION DEVELOPMENT AND EVALUATION OF IVABRADINE HCL SUSTAINED RELEASE GASTRORETENTIVE FLOATING TABLETS

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ABSTRACT

The present study is an attempt to develop Gastro retentive floating tablets of Ivabradine HCL, with different polymers which releases a therapeutic amount of Ivabradine HCL to the proper site in the body and also to achieve and maintain the desired Ivabradine HCL concentration. The results of the drug-excipients compatibility by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients. The Precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. The final formulation showed acceptable flow properties. The post compression parameters like the thickness, hardness, friability, weight variation, content uniformity, FLT and TFT and *In vitro* release, were carried out and the values were found to be within IP limits. Optimized formula containing Guar gum (F12) showed better release compare to other formulations and it followed first order kinetics with super caseII transport mechanism.

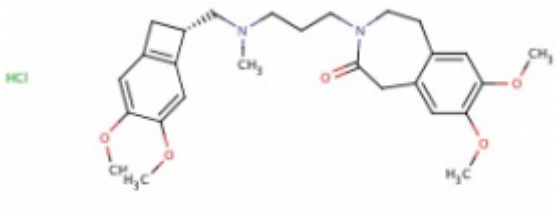
KEYWORDS: of Ivabradine HCL, Direct compression, guar gum, Gastro retentive floating tablets.

INTRODUCTION

The goal in designing sustained and controlled release is to reduce frequency of dosing or increase effectiveness of the drug by localization at site of action, reducing dose frequency, providing uniform drug delivery.[1] The current controlled release technology had made it possible to release drugs at a constant release rate for longer periods of time ranging from days to years. However, this benefit had not satisfied a variety of important drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, or (iv) exhibit low solubilities at high pH values. These limits promoted the development of gastroretentive drug delivery systems (GRDDS). Besides being able to continually and sustainably deliver drugs to the small intestine.

intestinal absorption window, the improvements provided from GRDDS include: achieving a greater and prolonged therapeutic effect and thus reducing the frequency of administration periods, providing a more effective treatment of local stomach disorders, and minimizing both lower-tract inactivation of the drug and drug effects on the lower intestinal flora Ivabradine is a novel heart rate lowering medicine for the symptomatic management of stable angina pectoralis and symptomatic chronic heart failure. Ivabradine, brand name Corlanor, was approved by the FDA in April 2015 for the treatment of chronic heart failure in patients with an ejection fraction of ≤35%, in sinus rhythm with resting heart rate ≥70 beats per minute, who are not on beta-blockers due to contraindications or already receiving maximum beta-blocker dose. Ivabradine acts by selectively inhibiting the "funny" channel pacemaker current (If) in the sinoatrial node in a dose-dependent fashion, resulting in a lower heart rate and thus more blood to flow to the myocardium. Although non-dihydropyridine calcium channel blockers and beta blockers also effectively lower heart rate, they exhibit adverse events due to their negative ionotropic effects. Therefore, as ivabradine is designed as a "pure" heart rate-lowering drug by selectively acting on the If channels, it may offer a more favorable side effect profile due to its lower likelihood of causing serious adverse effects.

Structure



EXPERIMENTAL WORK

Materials

Ivabradine HCL was purchased from Cadila pharmaceuticals, excipients like Guar gum, Karaya gum, ETHYL CELLULOSE, PVP K30, MCC, Sodium

bicarbonate, Mg-Stearate, Talc purchased from B.M.R. Chemicals, Hyderabad

Methodology

3.2 METHODS

3.2.1 Preformulation studies[48-50]

It is one of the important prerequisites in development of any drug delivery system. Preformulation studies of the drug were performed, which included melting point determination, solubility and compatibility studies.

a) Solubility studies

Solubility of Ivabradine HCL was determined in pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Ivabradine HCL in different beakers containing different solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 292 nm

b) Determination of melting point

Melting point of Ivabradine HCL was determined by capillary method. Fine powder of Ivabradine HCL was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermometer and placed in oil bath (light paraffin oil bath), The temperature at which it starts to melt was noted.

c) Determination of λmax of Ivabradine HCL using 0.1 N HCL

A solution of Ivabradine HCL containing the concentration of 10µg/ml was prepared in 0.1 N HCL and UV spectrum was taken. The solution was scanned in the range of 200-400nm.

- **Standard calibration curve of Ivabradine HCL using 0.1 N HCL**

Method

10 mg drug was taken accurately in 10ml volumetric flask. It was dissolved in 0.1N HCL to gives 1000 µg /ml. the standard stock solution stock solution was then serially diluted with 0.1 N HCL to get 5 to 30 µg/ml of Ivabradine HCL. The absorbance was measured against 0.1 N HCL as blank at 292 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

d) Compatibility Studies[51-52]

Compatibility studies were performed through FTIR spectroscopy. The IR spectrum of pure drug and physical mixture of drug and polymer was studied.

Spectral analysis of pure drug and physical mixture of drug and different excipients which were used for preparation of floating tablets was studied by FTIR. One milligram of sample was mixed with 100mg of dry powdered potassium bromide. The powdered mixture was taken in diffuse reflectance sampler and spectrum was recorded by scanning in the wavelength region of 4000cm^{-1} to 400cm^{-1} for 12 minutes. The resultant spectrum was compared for any spectral changes. They were obsevered in the presence of characteristics peaks in the respective funtional groups in the sample compounds.

COMPOSITION OF IVABRADINE HCL FLOATING TABLETS

Table: Composition of Ivabradine HCL floating tablets by Effervescent floating technique.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ivabradine HCL	5	5	5	5	5	5	5	5	5	5	5	5
ETHYL CELLULOSE	10	20	30	40	--	--	--	--	--	--	--	--
Karaya gum	--	--	--	--	10	20	30	40	--	--	--	--
Guar gum	--	--	--	--	--	--	--	--	10	20	30	40
NAHCO3	20	20	20	20	20	20	20	20	20	20	20	20
MCC	92	82	72	62	92	82	72	62	92	82	72	62
PVP K 30	15	15	15	15	15	15	15	15	15	15	15	15
Mg -stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total wt (mg)	150	150	150	150	150	150	150	150	150	150	150	150

All the quantities were in mg, Total weight is 150mg

Pre-compression evaluation [53- 56]

a)Angle of Repose

Angle of repose was determined by using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula.

$$\emptyset = \tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

b) Bulk density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (*Vb*) and weight of powder (*M*) was determined. The bulk density was calculated using the formula.

$$\rho b = \frac{m}{Vd}$$

c)Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (*ρt)* was calculated using the following formula

$$pt = \frac{m}{Vt}$$

d) Carr's compressibility index

The compressibility index of the granules was determined by Carr's compressibility index, which is calculated by using the following formula

$$I = \frac{Vo - Vt}{Vo} \times 100$$

e) Hausner 's ratio

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

$$\text{Haunser ratio} = \frac{pt}{pd}$$

Where ρt is tapped density and ρd is bulk density. Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25).

3.2.3 Preparation of Ivabradine HCL floating tablets By direct compression method

All ingredients were collected and weighed accurately. Ivabradine HCL with polymers were sifted and passed through sieve #60 and then the remaining excipients were rinsed over after pre blending all ingredients in mortar for 15minutes. The entire mixture was blended for 5minutes. Then magnesium stearate was added and blended again for 5-6 minutes, lubricated powder was compressed under 8mm punch of Remake tablet punching machine, Minipress - I 12 station D tooling. The composition of different formulations is shown in table(3.3).

3.2.4 Post-compression evaluation parameters for formulated tablets[58-61]

a. Weight variation

Six tablets from each formulation were selected at random and average weight was determined. Then the individual tablets were weighed and were compared with average weight.

b. Hardness

The hardness of the tablet from each formulation was determined using Pfizer hardness tester.

c. Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$\text{Friability (f)} = \left(1 - \frac{W_o}{W}\right) \times 100$$

Where, W0 is weight of the tablets before the test and W is the weight of the tablet after the test.

d. Thickness and diameter

The thickness and diameter of tablets was carried out using Digital caliper. six tablets were used for the above test from each batch and results were expressed in millimeter.

e. Drug content

Powder three tablet extraction was carried out using 0.1 N HCL. The concentration was determined spectrophotometrically against appropriate blank. Calculate the content of Ivabradine HCL specific absorbance at 292nm. As given in IP.

f. In-vitro buoyancy studies

The in vitro floating behavior of the tablets was studied by placing them in 100 ml beaker 100 ml of 0.1 N HCl (pH 1.2, 37^0C). The time, tablet required to emerge on the surface is floating lag time (FLT) or buoyancy lag time (BLT). And the time tablet constantly float on the surface of the medium is called total floating time (TFT).

g. Swelling study

The floating tablets were weighed individually (designated as W0) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C ± 1°C. At regular 1-hr time intervals until 12 hrs, the floating tablets were removed from beaker, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (Wt), and % swelling index (SI) was calculated using the following formula:

$$SI\ (\%) = (Wt - W0/\ W0).\ 100$$

Wt= Final weight

W0= initial weight

h. In-vitro dissolution studies

The release rate of Ivabradine HCL from floating tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The dissolution test was performed using 900ml of 0.1 N HCL, at 37 ± 0.5^0C and 50 rpm. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution medium, the samples were analyzed using uv spectroscopy at 292nm.

RELEASE KINETIC MODELS[61-62]

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models. The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism. In

order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release.

To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyers-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected.

- **Zero Order Kinetics:** This model describes the system where the release rate is independent of the concentration of the dissolved species.Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly assuming that area does not change and no equilibrium conditions are obtained can be represented by the following equation-

$$W_O - W_t = K\,t$$

Where, Wo = Initial amount of drug in pharmaceutical dosage form, Wt = Amount of drug in the dosage form at time t,K = Proportionality constant.

Dividing this equation by Wo and simplifying

$$ft = Kot$$

Where, *ft* = 1-(Wt/Wo) which represents the fraction of drug dissolved in time t,
Ko= Apparent dissolution rate constant or zero order release constant

The pharmaceutical dosage forms following this profile release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This following relation can in a simple way express this model

$$Qt = Qo + Kot$$

Where, Qt= Amount of drug dissolved in time t, Qo = Initial amount of drug in the solution and Ko = Zero order release constant.

- **First Order Kinetics:** The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

To study the first order release rate kinetics, the release rate data were fitted to the following equation.

$$\log Qt = \log Qo + K1t / 2.303$$

Where, Q_t = Amount of drug released in time t, Q_o = Initial amount of drug in the solution and K_1 = First order release constant.

The pharmaceutical dosage forms following this dissolution profile, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such a way that the amount of drug released by unit of time diminished.

- **Higuchi Model:** Higuchi developed several theoretical models to study the release of water soluble and low-soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is

$$f_t = K_H \times t_{1/2}$$

Where, f_t = Amount of drug released in time t and
K_H = Higuchi dissolution constant.
The equation describes the release from systems where solid is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

- **Korsemeyer-Peppas Model:** Korsemeyer et al. developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time. To study this model the release rate data is fitted to the following equation

$$Ft = M_t / M_\infty = K.\,t^n$$

Where, M_t / M_∞ = Fraction of drug release, K= Release constant, t = Drug release time and
n = Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.
This mathematical model has been used very frequently to describe the drug release from several different pharmaceutical modified release dosage forms.

The results obtained from in vitro drug release studies were plotted adopting four different mathematical models of data treatment as follows:

- % Cum. Drug Release v/s Time (Zero order rate kinetics).
- Log % Cum. Drug Retained v/s Time (First order rate kinetics).
- % Cum. Drug release was plotted against √T (root time). (Higuchi model)
- Log % Cum. Drug Release v/s Log Time (Korsmeyer-Peppas exponential equation).

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Solubility Studies

Solubility studies of Ivabradine HCL.

Solvent	Solubility(mg/ml)
0.1N HCL	0.68±2.03
6.8pH buffer	0.42±0.36
7.4pH buffer	0.39±0.48

From the Solubility studies it was observed that the Ivabradine HCL drug have more solubility in acidic buffer when compared to the alkaline buffers.

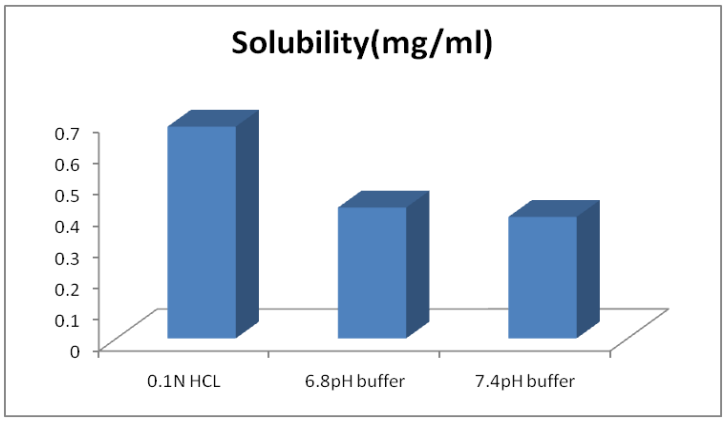


Fig: Solubility studies of Ivabradine HCL.

ESTIMATION OF IVABRADINE HCL BY UV SPECTROSCOPY

Determination of lambda max

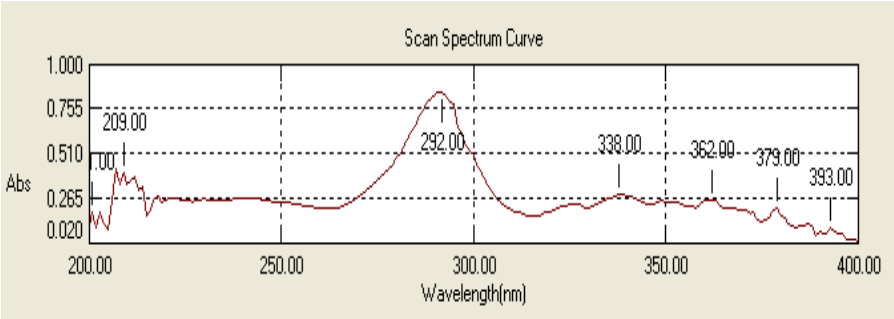


Fig. 4.1: Uv Spectrum Of Ivabradine HCL 292 nm.

UV Spectra of Ivabradine HCL at 25µg/ml concentration. Wavelength of maximum absorption in 0.1N HCL solution was found to be 292nm.

Calibration curve

Table: Absorbance data for the calibration curve of Ivabradine HCL in 0.1N HCL.

Concentration(µg/ml)	Absorbance
0	0
5	0.162
10	0.294
15	0.446
20	0.602
25	0.762
30	0.924

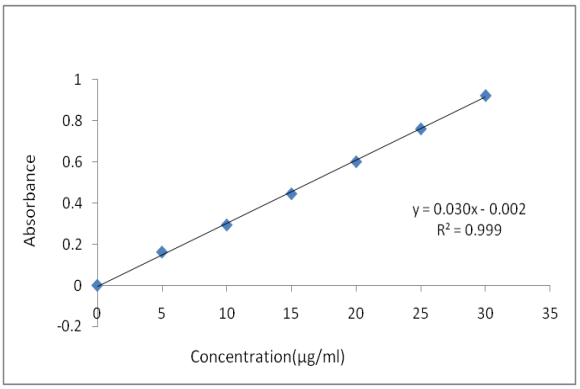


Fig. 4.2: Standard calibration curve of Ivabradine HCL in 0.1N HCl.

COMPATABILITY STUDIES

FTIR Spectroscopy

Identification of Ivabradine HCL

The IR spectrum of pure drug was found to be similar to the standard spectrum of Ivabradine HCL.

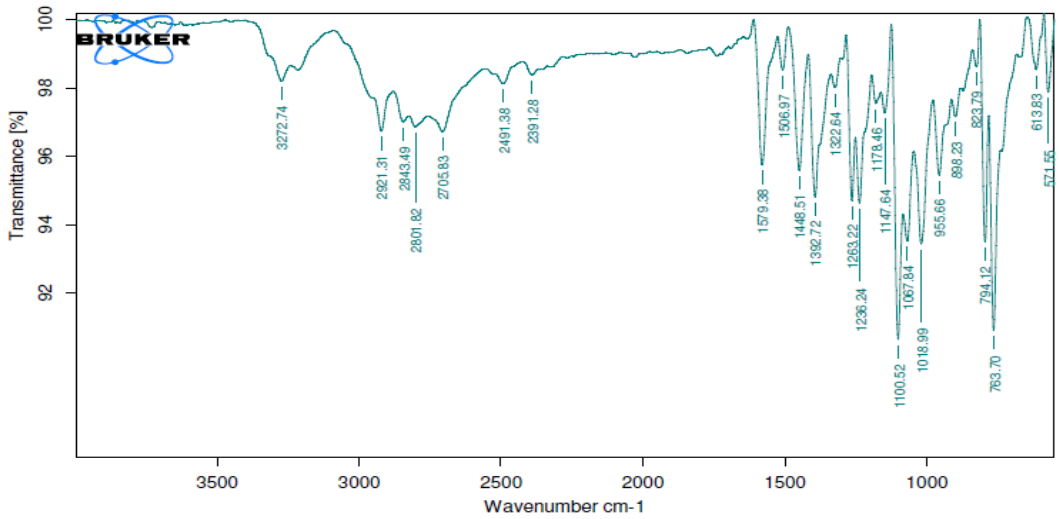


Fig. 4.3: FTIR spectra of Ivabradine HCL.

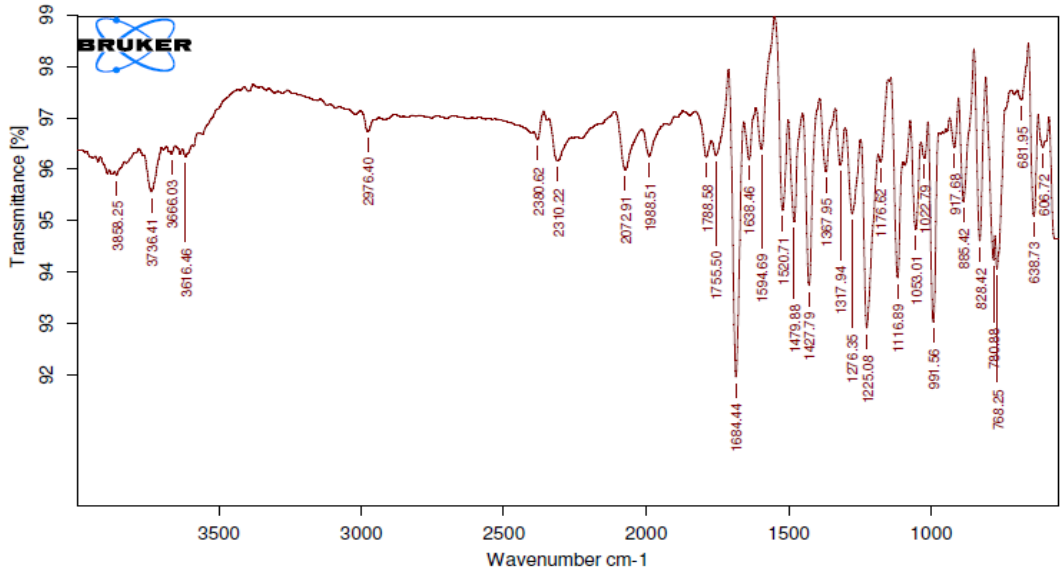


Fig. 4.4: FT-IR Spectra of Ivabradine HCL and Excipient.

PRE-COMPRESSION EVALUATION OF IVABRADINE HCL FLOATING TABLETS

Table 4.3: Pre-Compression Parameters Of Ivabradine Hcl Floating Tablets.

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tappeed Density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±0.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±0.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±2.08	1.14±0.05
F4	0.46±0.02	0.54±0.015	26.26±0.96	14.81±1.28	1.12±0.02
F5	0.52±0.6	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F6	0.49±0.2	0.58±0.006	29.26±0.36	15.51±0.96	1.18±0.05
F7	0.42±0.08	0.48±0.04	24.02±0.48	12.58±0.08	1.14±0.05
F8	0.52±0.12	0.60±0.03	30.68±0.73	13.33±0.86	1.17±0.04
F9	0.42±0.06	0.48±0.01	24.02±0.52	12.58±.08	1.14±1.05
F10	0.46±0.08	0.52±0.62	29.04±0.15	11.54±0.86	1.13±0.69
F11	0.42±0.46	0.51±0.32	29.53±0.02	17.65±0.24	1.21±0.42
F12	0.49±0.05	0.59±0.18	28.64±0.14	16.95±0.15	1.2±0.15

POST COMPRESSION EVALUATION OF IVABRADINE HCL FLOATING TABLETS

Table: 4.4Post-compression evaluation of Ivabradine HCL floating tablets.

Formulation Code	Avg.Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content(%)
F1	149.12±0.79	5.34±0.24	3.41±0.24	0.54±0.44	97.21±0.54
F2	148.97±0.22	5.12±0.68	3.69±0.89	0.41±0.16	95.64±1.26
F3	150.56±0.86	5.30±0.97	3.97±0.54	0.70±0.28	96.22±1.04
F4	151.56±0.47	5.20±0.58	3.55±0.22	0.54±0.14	94.12±0.58
F5	150.23±0.10	5.33±0.22	3.36±0.26	0.63±0.29	96.02±0.27
F6	149.78±0.22	5.45±0.48	3.64±0.87	0.70±0.27	98.54±0.59
F7	151.89±0.14	5.36±0.69	3.40±0.46	0.18±0.25	96.22±0.24
F8	149.55±0.18	6.55±0.48	3.39±0.48	0.35±0.49	97.26±0.87
F9	149.41±0.24	6.02±0.52	3.77±0.12	0.48±0.33	98.54±0.98
F10	148.52±0.19	6.24±0.75	3.05±0.75	0.52±0.36	96.51±0.28
F11	147.63±0.63	6.10±0.42	3.24±0.15	0.26±0.15	93.85±0.14
F12	148.21±0.24	6.04±0.36	3.56±0.32	0.75±0.02	92.48±0.15

4.4: In vitro floating buoyancy studies

Effervescent floating systems.

Formulation Code	Floating Lag Time(Secs)	Total Floating Time(hrs)
F1	31±1.04	5
F2	49±1.56	6
F3	62±2.84	8
F4	20±0.86	8
F5	14±0.57	4
F6	19±0.68	5
F7	16±0.98	7
F8	27±1.02	8
F9	30±0.55	6
F10	22.51±0.86	8
F11	39.45±0.42	10
F12	31.48±0.15	12

Table 4.5: Invitro floating buoyancy from F1 to F12.

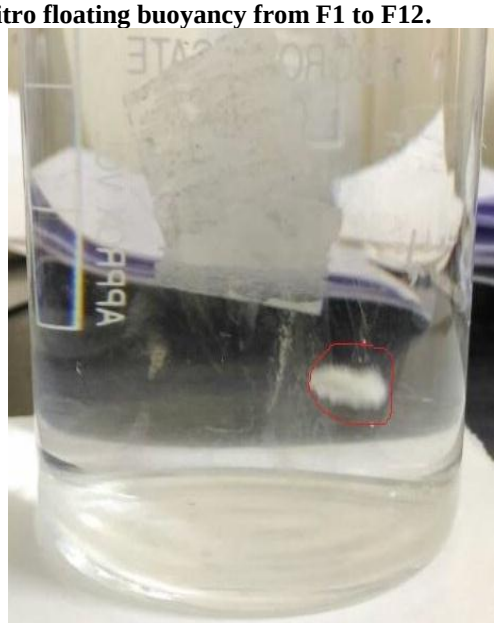


Fig. 4.5 FLT of F12 formulation.
FLT: Floating Lag Time

Fig:4.6 TFT of F12 formulation.
TFT:Total floating time

IN-VITRO DRUG RELEASE STUDIES

In-vitro drug release data of Ivabradine HCL floating tablets

Table: Vitro drug release data of Ivabradine HCL floating tablets of Batch F1 to F12.

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	38.37	21.92	19.53	14.89	45.31	35.67
2	52.92	36.07	35.24	24.61	62.89	49.59
3	67.47	50.81	49.63	39.52	79.63	55.93
4	76.1	61.23	53.42	46.95	85.04	73.46
5	86.4	66.5	65.04	59.04	96.53	83.4
6	99.23	82.08	76.45	65.49		92.35
7		98.18	85.34	79.31		96.26
8			96.42	89.62		
10				95.34		
12						
Time (hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	40.25	26.21	31.86	34.61	22.04	12.81
2	48.21	32.21	50.74	49.82	45.73	23.24
3	59.46	46.59	56.86	59.21	55.02	31.06
4	64.32	52.36	66.41	68.21	62.97	46.12
5	79.21	69.94	78.22	79.68	73.37	54.89
6	86.21	78.42	86.28	83.41	79.47	68.25
7	90.21	85.23	98.23	92.41	88.28	77.11
8	98.45	91.96		99.96	94.86	84.97
10		96.21			99.19	91.46
12						96.52

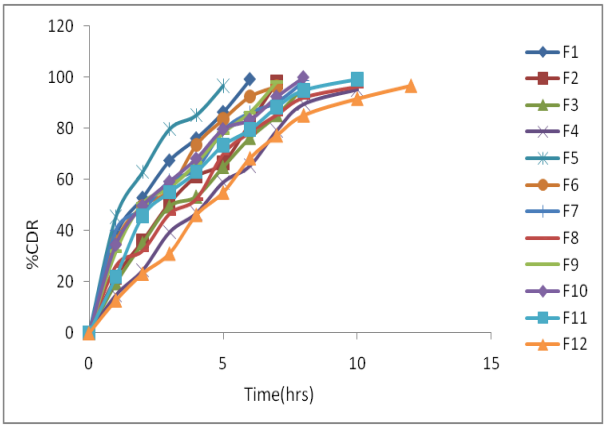


Fig: 4.8 *In-vitro* drug release profile of Ivabradine HCL floating tablets of batches F1 to F9.

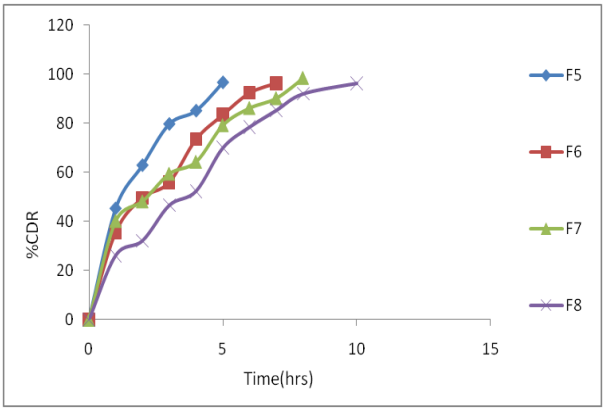


FIG. 4.10% CDR OF F5-F8.

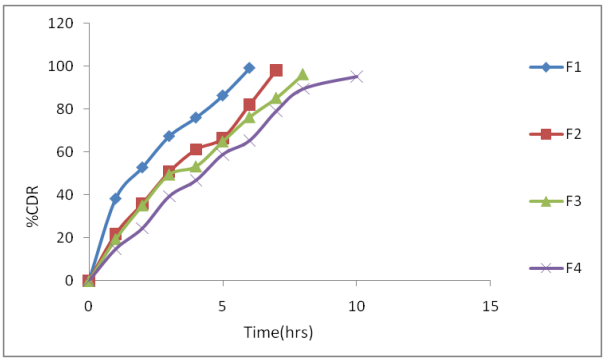


FIG. 4.9.%CDR OF F1-F4.

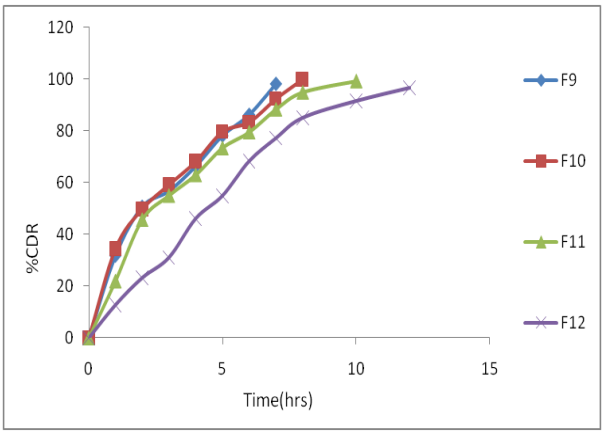


FIG.: 4.11% CDR OF F9-F12.

- From the in vitro dissolution studies it was observed that the F12 formulation containing GUAR GUM sustains the drug release upto indicating that the GUAR GUM (40mg) is the best concentration for formulating floating tablets of Ivabradine HCL. So F12 formulation was considered as the best formulation and drug release kinetics were performed for F12 formulation.

4.7 DRUG RELEASE KINETICS

ZERO ORDER

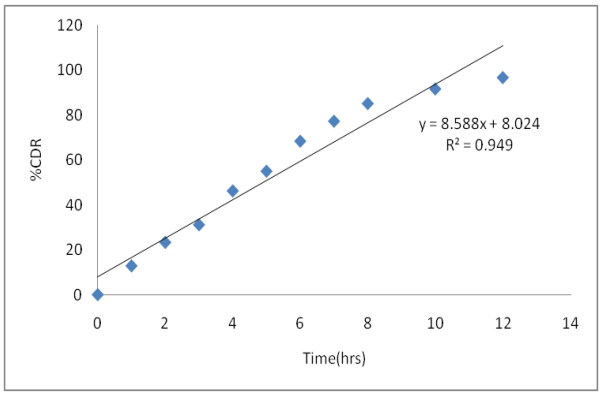


Fig 4.12:%CDR of F12.

FIRST ORDER

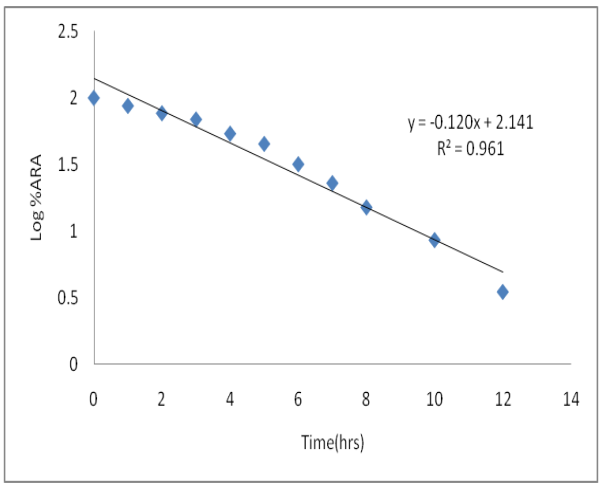


Fig. 4.13: Log% CDR of F12.

HIGUCHI PLOT

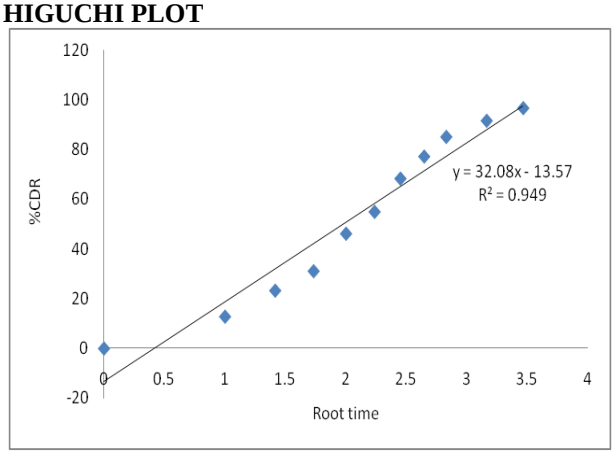


Fig. 4.14: %CDR of F12.

PEPPAS PLOT

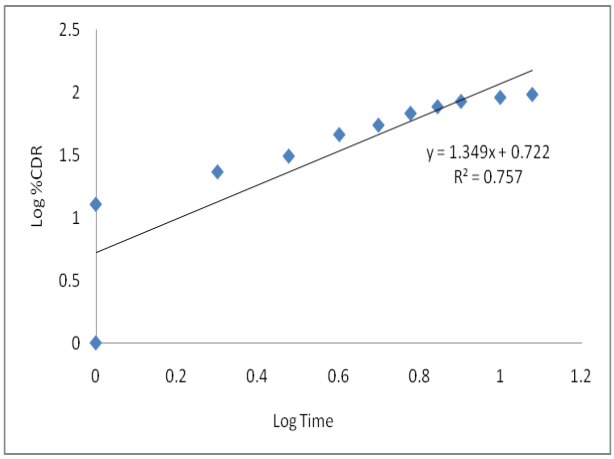


Fig. 4.15: Log%CDR of F12.

RELEASE KINETICS:(F12).

Regression Values(f12)	Zero Order	First Order	Higuchi Plot	Peppas Plot	N Value
R value	0.949	0.961	0.949	0.757	1.349

SUMMARY & CONCLUSION

The present study is an attempt to develop Gatro retentive floating tablets of Ivabradine HCL, with different polymers which releases a therapeutic amount of Ivabradine HCL to the proper site in the body and also to achieve and maintain the desired Ivabradine HCL concentration.

Direct compression method was used for formulation of floating tablets, also different types of polymers like Ethyl cellulose, Karaya gum, and Guar gum were studied. These polymers were widely used gel forming polymers. The release rate could effectively be modified by varying the "polymer" concentration. By using Guar gum they gave optimum FLT as well as long acting effect. It was found that the tablet formulation retarded the drug release for 12h as desired.

The results of the drug-excipients compatibility by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients. The Precompression parameters like bulk density, tapped

density, Carr's index and angle of repose were determined. The final formulation showed acceptable flow properties. The post compression parameters like the thickness, hardness, friability, weight variation, content uniformity, FLT and TFT and *In vitro* release, were carried out and the values were found to be within IP limits. Optimized formula containing Guar gum (F12) showed better release compare to other formulations and it followed first order kinetics with super caseII transport mechanism.

Thus it is summarized and concluded that Guar gum can be successfully used in formulation of Ivabradine HCL sustained release gastroretentive floating tablets.

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