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FORMULATION,DEVELOPMENTAND EVALUATION OF FLOATING ORAL IN-SITU GEL CONTAINING IVABRADINE

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ABSTRACT:

Liquid Oral conventional dosage forms shows low bioavalability due to their rapid gastric transit time from the stomach. In this study novel approach used in the form of gastroretentive floating in - situ gel system have been developed to delivered drugs in a controlled manner. Liquid orals are low bioavailability because they are eliminated rapidly from the stomach. This problem overcome by development of oral insitu gels. Ivabradine oral in-situ gelling systems were prepared by using polymers like Guar gum, Xanthan gum, HPMC K15M, and Carbopol 940, Sodium citrate, Calcium carbonate and Sodium alginate. Total of twelve (F1 to F12) formulations were prepared and F12 was found to be the best formulation Carbopol 940. Drug and polymers was subjected for compatibility study using FTIR studies, which revealed that there was no interaction between drug and polymers. The prepared formulations were evaluated for drug content, floating lag time, total floating time, viscosity, gelling nature, visual appearance &invitro release studies were also performed. The invitrorelease studies of all the formulations among them F12 formulation containing carbopol 940 shows drug release of 98.42% by the end of 12hrs. The release kinetics of the optimized formulation was best fitted into Higuchi model (R^2 =0.991) and showed zero order (R^2 =0.994) drug release with super case transport mechanism.

KEYWORDS: Insitu – gel, floating drug delivery, gastroretentive drug delivery, ion sensitive polymer,Thermosensitive polymers.

INTRODUCTION :

The development of *in-situ* gelling systems has received considerable attention over the past few years. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles.These hydrogels are liquid at room temperature but undergo gelationwhen in contact with bodyfluidsorchangeinpH.Thesehave a characteristic property of temperature dependent,pHdependentand cation induced gelation. Compared to conventional controlledrelease formulations,*in-situ*forming drugdelivery systems possess potential advantageslike simplemanufacturing process, easeof administration,reducedfrequency of administration,improved patient complianceand comfort[1,2,3]*In-situ*gel formingdrug delivery isatype of mucoadhesivedrug delivery system.In contrasttovery stronggels,theycanbe easily applied inliquid form tothesiteof drugabsorption.Atthesiteof drug absorption they swell to forma stronggel thatiscapableofprolonging theresidence timeofthe activesubstance.Bothnatural and

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synthetic polymerscanbeusedforthe productionof*in-situ* gels.*In-situ*gel formation occurs due toone or combinationof differentstimulilike pH change,temperaturemodulationand ionic cross-linking[4,5,6]. So,*in-situ*gelsare administeredby oral[7],ocular[8], rectal[9], vaginal[10]injectable[11] and intra-peritoneal route[12] Recent advancesin*in-situ*gelshavemadeit possibletoexploit thechangesin physiological uniquenessindifferent regionsof theGI tractfor theimproved drugabsorptionaswell as patient's convenience andcompliance.

MATERIALS AND METHODS:

Materials

1.Solubility studies:

Solubility of Ivabradine was carried out in different solvents like 0.1N HCl, Water and 6.8 pH buffer. Saturated solutions were prepared by adding excess drug to the vehicles and Shaking on the shaker for 24hrs at 25^{o}C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Ivabradinewas determined spectrophotometricallyat 236nm.

2. Drug-excipient compatibility study:

a) Physical mixtures of drug and excipients were prepared by grinding specific ratios of drug and excipients in a mortar. Sample of 3-4 grams was loaded in a glass vial, covered with rubber stopper, sealed with aluminum cap and labeled properly. Samples were observed and color was recorded for initial evaluation and loaded into stability chambered at 40^{o}C temperature and 75% relative humidity for 30 days to study the Compatibility study. Samples were removed after 15 days and 30 days and observed for any change in the color.

b) FTIR spectroscopy:

The physical compatibility between the pure drug and polymers used in the research was tested by Infra Red (IR) spectroscopy. FTIR absorption spectra for pure drug and physical mixture were recorded in the range of 400-4000cm -1by KBr disc method using FTIR spectrophotometer.

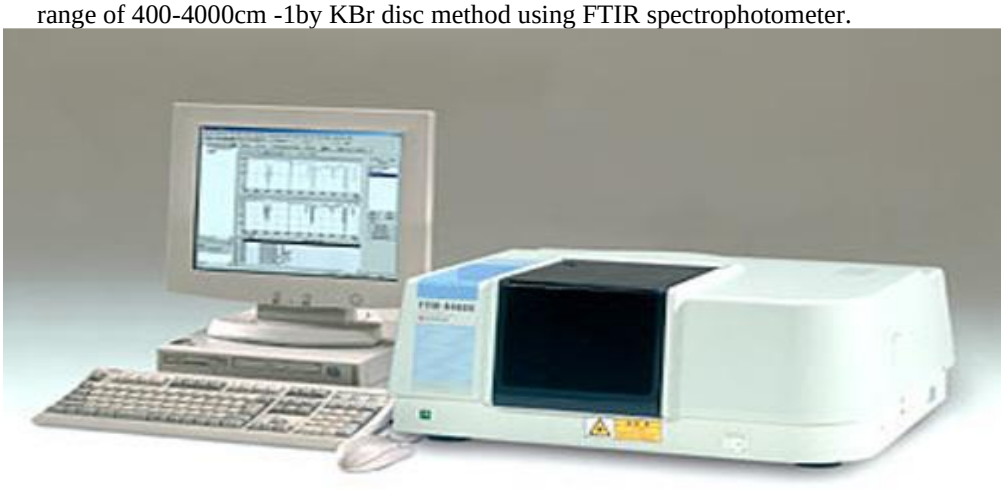

Fig.: Photography representation of instruments used for finding FTIR spectra.

2.1 Determination of Absorption maxima by UV spectrophotometer:

Solution of drug were prepared in 0.1N HCl and scanned in the range of 200 to 400 nm using T60 PG INSTRUMENTS UV spectrophotometer in order to determine the absorption maxima for analysis of dissolution samples.

2.2 Preparation of calibration curve of Ivabradine:

10 mg of Ivabradine was dissolved in 10 ml of 0.1N HCl by slight shaking (1000 µg/ml). 1ml of this solution was taken and made up to 10 ml with 0.1N HCl, which gives 100µg/ml concentration (Stock solution). From the stock solution Concentrations of 5,10,15,20,25 and 30 µg/min 0.1NHCl were prepared. The absorbance of diluted solutions was measured at 236nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated.

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3.3 Method of Preparation of *In-situ* Gel:

Floating *in-situ* gel formulations of Ivabradine were prepared using compositions given in Table. Take 100ml beaker, in that beaker take sodium alginate and add with polymer, then mix with 60ml distilled water, now heat the mixture at 60^{o}C till solution occurs using a heating magnetic stirrer. Take another 100ml beaker, in this add sodium citrate along with gas generating agent (calcium carbonate), and then mix with 30ml distilled water, heat the mixture at 60^{o}C till solution occurs. Now take another beaker, add 10ml hot water with drug, then three mixtures are mixed at 60^{o}C. After cooling this solution below 40^{o}C, keep the above mixture in mechanical stirring for 30 minutes, well to get the final preparation which was stored in amber colour bottles until further use.

Table: formulation table

Ingredients(g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ivabradine	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Sodium alginate	1	1	1	1	1	1	1	1	1	1	1	1
Calcium carbonate	0.25	0.75	0.75	0.25	0.25	0.75	0.25	0.75	0.75	0.25	0.75	0.75
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Xanthan gum	0.25	0.5	0.75	-	-	-	-	-	-	-	-	-
Guar gum	-	-	-	0.25	0.5	0.75	-	-	-	-	-	-
HPMC K15M	-	-	-	-	-	-	0.25	0.5	0.75	-	-	-
Carbopol 940	-	-	-	-	-	-	-	-	-	0.25	0.5	0.75
Water(ml)	100	100	100	100	100	100	100	100	100	100	100	100

3.4 Evaluation Parameters of Oral *in-situ* Gels:

3.4. 1. Visual Appearance and Clarity:

Visual appearance and Clarity was done under fluorescent light against a white and black back ground for presence of any particulate matter.

3.4.2 pH Measurement :

The pH of the prepared *in-situ* gelling system after addition of all the ingredients was measured using pH meter.

3.4.3 Determination of drug content:

Accurately 10 ml of formulation from different batches was measured and transferred to 100 ml volumetric flask. To this 50-70ml of 0.1 N HCl was added and sonicated for 30 min. Volume was adjusted to 100ml. Complete dispersion of contents was ensured visually and the dispersion was filtered using Whattman Filter Paper. From this solution, 10 ml of sample was withdrawn and diluted to 100mlwith 0.1 N HCl. Contents of Ivabradinewas measured at maximum absorbance at 236nmusing UV-Visible Spectrophotometer. [T60 PG INSTRUMENTS]

3.4.4 In vitro floating study:

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The in-vitro floating study was carried out by introducing 10 ml of formulation into a beaker containing 100 ml of 0.1N HCl, (pH 1.2) at 37°C without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on surface of the dissolution medium (duration of floating) were recorded.

3.4.5 In-vitro gelation study:

To evaluate the formulations for their in-vitro gelling capacity, accurately measured 10 ml of formulation was added to 100 ml of 0.1N hydrochloric acid (HCl, pH 1.2) at 37°C in a beaker with mild agitation that avoids breaking of formed gel. The in vitro gelling capacity was graded in three categories on the basis of stiffness of the formulation.

(+) Gels after few minutes, dispersed rapidly.
(++) Gelation immediate remains for few hours.
(+++) Gelation immediate remains for an extended period.

3.4.6 Measurement of viscosity of *in-situ* gelling system:

Viscosity of the dispersion was determined using a Brookfield digital viscometer (NDJ-5S Viscometer). The samples (10 ml) were sheared at a rate of 10 rpm/min using spindle number 2 at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 seconds.

3.4.7 In-Vitro Release Studies:

The drug release study was carried out using USP type II paddle type apparatus at 37 ± 0.5°C and at 50 rpm using 900 ml of 0.1 N HCl (pH 1.2). *in-situ* gel equivalent to 10 mg of ivabradine was used for the test. Sample solution (5 ml) was withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filter, diluted and suitably analyzed by UV spectrophotometric LABINDIA 8000 at 236 nm. Fresh dissolution medium was replaced immediately after withdrawal of the test sample to maintain sink condition. The dissolution studies were carried out for a period of 12 h.[21, 22] The dissolution data was analyzed by DD Solver TM software for mathematical modelling to predict the release kinetics.[23, 24]

RESULT:(Times New Roman front 11 **Bold Capital**)

Solubility Studies:

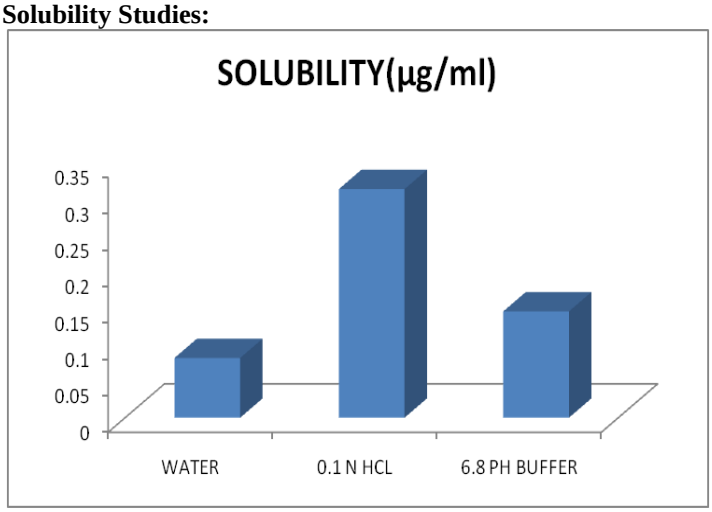

Fig: Solubility studies

FTIR studies:

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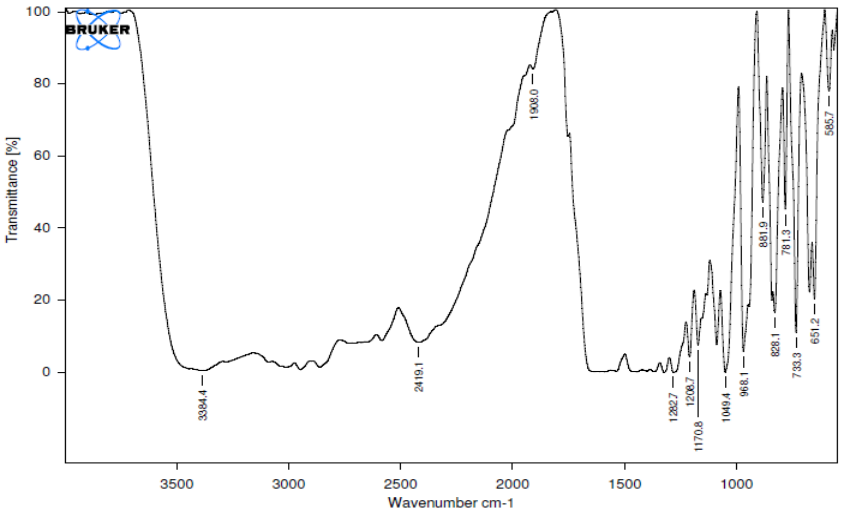
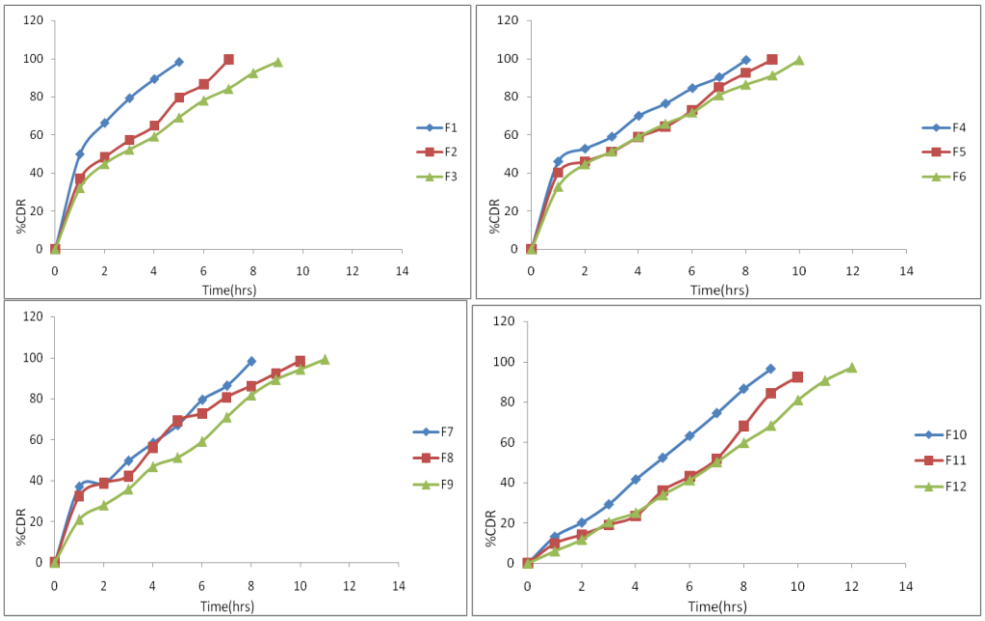
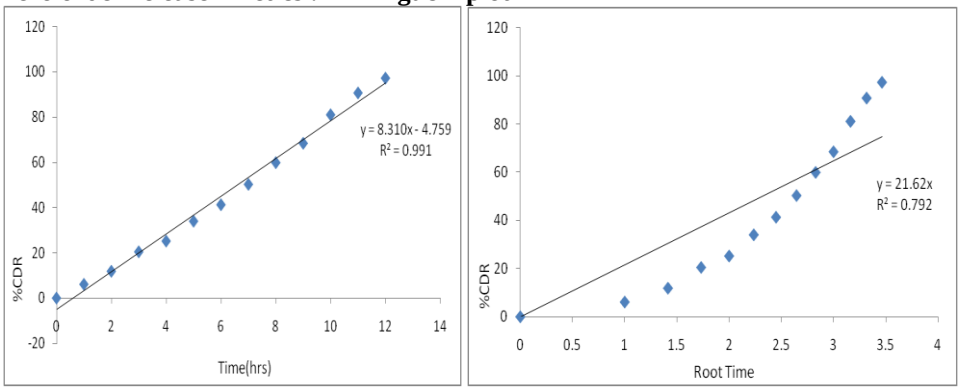


Figure 1.FTIR Spectra of optimized formulation.

Invitro dissolution profile graphs:



Zero order release kinetics : F12Higuchi plot



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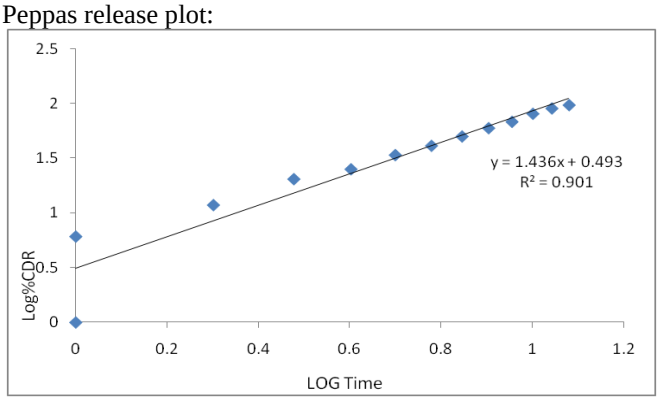
Peppas release plot:



DISCUSSION:

Ivabradine oral in-situ gelling systems were prepared by using polymers like Guar gum, Xanthan gum, HPMC K15M, and Carbopol 940, Sodium citrate, Calcium carbonate and Sodium alginate. Total of twelve (F1 to F12) formulations were prepared and F12 was found to be the best formulation Carbopol 940. Drug and polymers was subjected for compatibility study using FTIR studies, which revealed that there was no interaction between drug and polymers. The prepared formulations were evaluated for drug content, floating lag time, total floating time, viscosity, gelling nature, visual appearance &invitro release studies were also performed. The invitro release studies of all the formulations among them F12 formulation containing carbopol 940 shows drug release of 98.42% by the end of 12hrs. The release kinetics of the optimized formulation was best fitted into Higuchi model (R^2 =0.991) and showed zero order (R^2 =0.994) drug release with super case transport mechanism.

CONCLUSION:

The invitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppasequation.Optimized formulation F12 shows R^2 value 0.991. As its value nearer to the '1' it is conformed as it follows the Zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.The 'n' value is 1.436 for the optimisedformulation(F12) i.e., n value indicates super case transport mechanism.The release kinetics for the optimized formula are shown in table.

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