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Formulation development and evaluation of oral floating *insitu* gel of Ilaprazole

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ABSTRACT

The development of in situ gel systems has received considerable attention over the past few years. In the past few years, increasing number of in situ gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. In the present research work Oral Floating Gel of Ilaprazole was formulated using Sodium Alginate, HPMC K100M, Eudragir RSPO, Ethyl cellulose, Rosin. In the optimized batch Sodium Alginate 2% and Ethyl cellulose 2% (1:1) ratio gave gastric retention of drug Ilaprazole for 12 hours. Invivo study was performed by providing the formulation to rabbit and then X-ray were taken for the confirmation of formation of gel in stomach and floating of dosage form for 12 hrs. And it was found to be floating for 12 hrs. From formulation and evaluation studies of oral floating insitu gel it was observed that gas forming agent sodium bicarbonate and calcium carbonate 2% each (1:1) proportion gives floating of gel for >12 hrs.

Keywords: Oral floating, Insitu Gel, Ilaprazole, Buoyancy enhancer.

INTRODUCTION

***In situ* Gel[1,2]**

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. Amongst the extensive research has been carried in designing of polymeric drug delivery systems. The development of *in situ* gel systems has received considerable attention over the past few years. In the past few years, increasing number of *in situ* gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. This interest has been sparked by the advantages shown by *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. *In situ* gel formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes, which can be inconvenient or oral route, which can result in unacceptably low bioavailability and passes the hepatic first-pass metabolism, in particular of proteins and peptides. The In-situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes.

***IN SITU* FORMATION BASED ON PHYSICAL MECHANISM:[3]**

a) Swelling and Diffusion:

Stomach floating *in situ* gel systems, since they exhibit the tendency to remain extended at the pyloric sphincter. Swelling of polymer happen after absorption of water causes formation of gel certain biodegradable lipid substance such as myverol (glycerol mono-oleate) forms *in situ* gel under such phenomenon. Swelling is maintained by the degree of cross-linking between the polymeric chains on coming in contact with gastric fluid, the polymer absorbs water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-linkers in the hydrophilic polymer network. Solution of polymer such as N – methyl pyrrolidone (NMP) involves diffusion of solvent from Polymer solution into surrounding tissue and results in solidification of polymer matrix. These cross links minimize the dissolution of the polymer and hence maintain the physical integrity of the dosage form.

IN SITU GELLING BASED ON CHEMICAL STIMULI:[3]

a) Ionic crosslinking:

Certain ion ph sensitive polysaccharides such as carrageenan, Gellan gum (Gelrite®), Pectin, Sodium Alginate undergo phase transition In presence of various ions such as Ca+2, Mg+2, Na+**.** For e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca2+ due to the interaction with guluronic acid block in alginate chain.

Enzymatic cross linking:

Certain natural enzymes which operate efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation *in situ*.

Temperature dependant *in situ* gelling:

In this approach, temperature dependent phase transition from less viscous solution to relatively high viscosity gel is seen. Polymer-polymer interaction occurs to form a solvated Change in temperature causes sudden change in the solubility of polymer within system, macromolecule of hydrophobic nature. Temperature sensitive polymers are the most studied class for producing the *in situ* gel characteristics, e.g. Polyacrylic acid, polyacrylamide etc. Before administration these are present in liquid form, transfer in to gel at body temperature. These *in situ* gel are liquid at room temperature (20^oC-25^oC) and after exposure to body fluid goes in gelation phase (35^oC-37^oC), due to an increase in temperature this approach exploits temperature-induced phase transition. Some polymers undergo sudden changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST). At the LCST, hydrogen bonding between the polymer and water becomes adverse, compared to polymer–polymer and water–water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature. A positive temperature- sensitive *in situ* has an upper critical solution temperature (UCST), such insitu gel contracts upon cooling below the UCST. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAM) or poly (acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling.

Principle of *in situ* gel formation[4]

Formulation of gastroretentive *in situ* gel system involves the use of gelling agent which can form a stable sol containing the dispersed drug and other excipients. The gelling of this sol system is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. The formulation adopted is a sodium alginate solution containing calcium carbonate (as a source of Ca2+) and sodium citrate, which complexes the free Ca2+ ions and releases them only in the acidic environment of the stomach. Sodium alginate acts as a gelling agent. The free Ca2+ ions gets entrapped in polymeric chains of sodium alginate thereby causing cross linking of polymer chains to form matrix structure. This gelation involve the formation of double helical junction zones followed by re aggregation of the double helical segments to form a three- dimentional network by complexation with cations and hydrogen bonding with water.

$$\text{Sodium citrate} + \text{Ca. Carbonate}(Ca^{2+}) \longrightarrow \text{Ca.citrate complex} \xrightarrow[\text{environment}]{\text{acidic}} (Ca^{2+}) + COO^-$$

In this way, the formulation remains in liquid form until it reaches the stomach, where gelation of sodium alginate is instantaneous.

The drug Ilaprazole was used in formulation. Ilaprazole is proton pump Inhibitor which is used in Hyper acidity and in the treatment of duodenal ulcer.

Advantages of ilaprazole

- With its longest gastric pH maintenance (pH exceeded 4) Ilaprazole shows the most efficient therapeutic advantage and the highest GERD cure rate among existing PPIs.
- Has a longer half-life and greater acid suppression and low dose than omeprazole.
- It has lesser drug interaction due to no metabolism dependence to CYP2C19 and low affinity to CYP isoenzyme.
- Alleviation of night time heartburn.
- Ilaprazole is more effective than Lansoprazole for healing severe C/D grades of GERD.
- Ilaprazole has 1.5-2 times higher therapeutic gain than esomeprazole by baseline therapy index comparison.
- Ilaprazole has the Rapid onset time & High Activation.[5-8]

MATERIALS AND METHODS

2.1 Material:
Drug : Ilaprazole. Polymers: Sodium Alginate, HPMC K100M, Eudragir RSPO, Ethyl cellulose, Rosin. Excipients: Sodium Bicarbonate, calcium carbonate, Calcium chloride, Sodium citrate etc.

2.2 Method:
The formulations was prepared as given in table no 1 by heating polymer at 60^0C in deionized water with continuous stirring. After cooling below 40^0C, gas forming agent Calcium Carbonate, Cross linking agent Calcium Chloride, Buoyancy enhancer Sodium Bicarbonate, and drug (Ilaprazole) was added with continuous stirring. Finally Sodium Citrate was added to maintain fluidity of formulation.

Table No 1: Formulation of Oral Floating *in situ* Gel of Ilaprazole (weights in %)

Name of ingredients	Formulation Code											
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12
Ilaprazole (mg)	10	10	10	10	10	10	10	10	10	10	10	10
Sodium alginate	-	-	-	-	3	1	3	1	0.4	3.6	2	2
HPMC K 100M	0.5	0.5	-	-	-	-	-	-	-	-	-	-
Rosin	-	-	2	2	-	-	-	-	-	-	-	-
Eudragit RSPO	2	-	2	-	-	-	1	3	-	0.4	2	-
Ethyl cellulose	-	2	-	2	1	3	1	-	3.6	-	-	2
Calcium carbonate	2	2	2	2	2	2	2	2	2	2	2	2
Calcium chloride	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 bicarbonate	2	2	2	2	2	2	2	2	2	2	2	2
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
Flavoring agent	qs	qs	qs	qs	Qs	qs	Qs	qs	qs	qs	qs	Qs
Distilled water (up to ml)	100	100	100	100	100	100	100	100	100	100	100	100

1. EVALUATION OF FORMULATION:
3.1 Characterization of Oral *In situ* Gel of Ilaprazole:
a) Appearance[9]: The developed formulations were inspected visually for clarity of sol by observing in white and black background.

b) pH measurement[9]: The pH of the each formulation was determined by using pH meter. The pH meter was first calibrated using solutions of pH 4 and pH 7.

c) Measurement of viscosity[10]: The viscosity of formulations was determined by a Brookfield viscometer DV-III (Brookfield, USA).

d) Gelling time[10]: It was graded in three categories on the basis of gelation time and time period for which the formed gel remains as it is a) gel after few minutes, b)dispersed rapidly, c) gelation immediate, remain for 12hr. Gelation immediate, remain for more than 12hr.

e) Floating lag time[11]: In this test 10ml of *in situ* formulation was added into the 900ml dissolution vessel containing 0.1N HCl at 37^0C. It is the time the formulation took to emerge on surface of dissolution medium is referred as floating lag time.

f) Floating duration[11]: In this test 10ml of *in situ* formulation was added into the 900ml dissolution vessel containing 0.1N HCl at 37^0C. The time that formulation took to remain constantly floating on surface of dissolution medium is referred as duration of floating.

g) Drug content estimation[11]: The prepared *in situ* gel formulations were analyzed for drug content by transferring 1 ml of formulation in 100 ml volumetric flask and add 50 ml of 0.1N HCl with pH 1.2 with continuous shaking. Final volume was adjusted upto 100 ml with the help of 0.1N HCl of pH 1.2 and filtered the solution. Drug concentration in filtrated solution was determined spectrophotometrically at respective wavelength of drug using UV-Visible spectrophotometer (Shimadzu 1800, Japan).

h)Drug Interaction Studies (Compatibility Studies)[17]:
It's important to check any kind of interaction between drug candidate and polymer. The polymers which are to be incorporated into formulation should be compatible with the drug. This compatibility study or interaction study was done using Fourier transformed infrared spectroscopy.

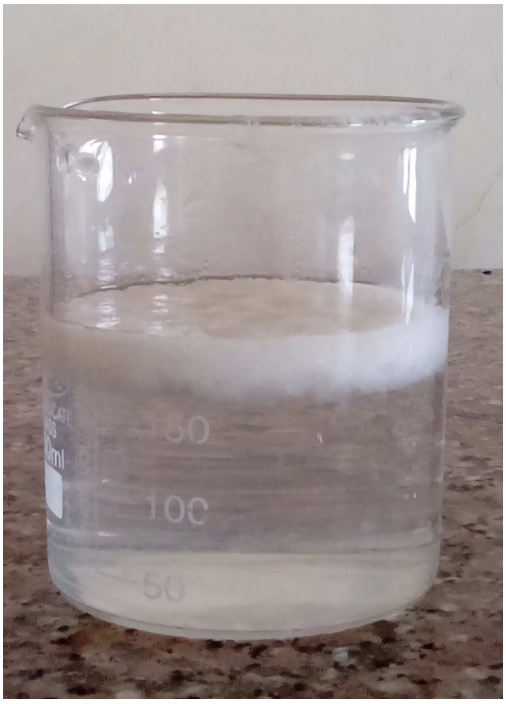


Figure No1 : Showing Gelation of *In situ* Gel formulation

IR spectra of pure Ilaprazole and polymers viz. Sodium Alginate, Ethyl cellulose, were taken separately. Then to know if there is any interaction between drug and polymer, IR spectra of Ilaprazole and other polymers were taken in combination. (figure no 2,3,4,5 , Table No 3,4,5,6)

3.2) In vitro dissolution study[12] :An in vitro release study was carried out using dissolution test apparatus USP Type II (Paddle Method). Volume of dissolution media was 900 ml, of Hydrochloric acid buffer solution of pH 1.2, temperature $37^0C \pm 0.2^0C$, RPM was 50. 1Ml of sample was removed each hour and it was diluted to 10 ml with 0.1 N HCl at 305 nm. And 1 ml of sample was replaced in dissolution media to maintain sink condition.

3.3) In vivo studies :[13]
An in vivo release study was carried out in healthy rabbits. Using oral feeding tube and syring gels (Ilaprazole) was feeded to rabbits and X rays were taken of rabbit abdomen to check the floating ability of gel formulation.

For this barium sulphate (15%) loaded oral floating insitu gel were prepared, Healthy rabbit weighing approximately 2.3 Kg was used to assess *in vivo* floating behavior. Ethical clearance for the handling of experimental animals was obtained from the institutional animal ethical committee (IAEC) of the institute. The animal was fasted for 12 hrs. The rabbit was made to swallow barium sulphate loaded insitu gel with water. During the experiment, rabbit was not allowed to eat but water was provided. At predetermined time intervals, (empty stomach, immediate after feed, after 1 hour of feed and after 8 hr of feed) the radiograph of abdomen was taken using an X-ray machine.

3.4) Drug Kinetic study:[14]
The release data obtained from various batches were studied with respect to effect of drug: polymer ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of optimized batches was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas, models to ascertain the kinetic modeling of drug release.

3.5) Statistical Analysis:[15]
It comes under Planned versus posteriori (unplanned) comparisons in ANNOVA. Bonferroni method is often used to control the alpha level for multiple comparisons for an over all level of alpha, the level is set at α/k for each test, while k is the number of comparisons planned. For the planned data comparisons at an overall level of 0.05 it show there is significant difference or non significant different in the data.

In this study the Bonferroni method was applied to dissolution study to check there was significant difference or non significant difference in release of drug in formulated formulations.

3.6) Stability testing:[16]

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The ICH Guidelines have established that long term stability testing should be done at 250C/60% RH; stress testing should be done at 400C/75%RH for 6 months. If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e. 300C/65%RH.

RESULTS AND DISCUSSION

4.1 Characterization of Oral *In situ* Gel of Ilaprazole:

For the Characterization of oral *in situ* gel of Ilaprazole pH, viscosity, Gelling time, Floating lag time, Floating duration and Content uniformity tests were performed and the results were as follows:

Table no 2: Showing various characterization of oral *In situ* gel of Ilaprazole:

Formulation code	pH	Viscosity in cps	Gelling time (sec)	Floating lag time (sec)	Floating Duration in hr	Drug content (%)
I1	9.5	8.97	3-5	4-5	> 12	97.13 ±0.51
I2	9.2	8.87	4-5	3-4	> 12	98.88 ±0.57
I3	9.4	8.83	4-5	3-4	> 12	97.23 ±0.81
I4	9.5	9.06	3-4	4-5	> 12	99.00 ±0.63
I5	9.6	9.12	3-5	2-3	> 12	99.04 ±0.71
I6	9.3	9.33	3-5	2-3	> 12	98.90 ±0.89
I7	9.8	9.48	4-5	1-2	> 12	99.5 ±0.49
I8	9.7	9.38	3-4	1-2	> 12	97.66 ±0.51
I9	10.2	9.44	2-4	Immediate	> 12	100.12 ±0.24
I10	10.5	9.53	3-4	Immediate	> 12	98.66 ±0.43
I11	10.2	9.44	4-5	3-4	> 12	98.86 ±0.37
I12	10.4	9.58	Immediate	Immediate	> 12	99.00 ±0.57

N=3

a) Appearance: All the prepared batches was found to be clear in appearance.

b) pH: The pH was measured of each of the polymer formulation based *in situ* solution using a calibrated digital pH meter at 27^0C. The pH of all the prepared batches was found in the range of 9.2 to 10.5. The optimized batch I12 showed pH 10.4. (as given in table no 2)

c) Viscosity: The viscosity of all formulations was determined by a Brookfield viscometer DV-III (Brookfield, USA) using spindle number 62 with cup and bob setting at 100 rpm. All the prepared formulations showed viscosity in the range of 8.83 to 9.58 cps. The optimized batch I12 show viscosity of 9.58 cps. (as given in table no 2)

d) Gelling time: The gelling capacity of prepared formulations was observed by visual examination. All the prepared batches show gelling time from 4-5 second to immediate after entering in 0.1 N HCl. The optimized batch I12 showed immediate gelling after getting in contact with 0.1 N HCl and remain in the form of gel for more than 12 hours. (as per given in table no 2)

e) Floating lag time: Floating lag time of all the prepared formulations was observed by visual examination. All the prepared formulations show Floating lag time from 4-5 seconds to immediate. And the optimized batch I12 show immediate floating after entering in 0.1 N HCl and show floating for more than 12 hrs. (as per given in table no 2)

f) Floating Duration: All prepared formulation show floating duration more than 12 hours. (as per given in table 2)

g) Drug Content Uniformity: All the prepared formulations show drug content uniformity in the range of 97.13% to 100.12 % . The values are acceptable as per Indian pharmacopeia standards. (as per given in table no 2)

h) Drug Interaction Studies (Compatibility Studies)

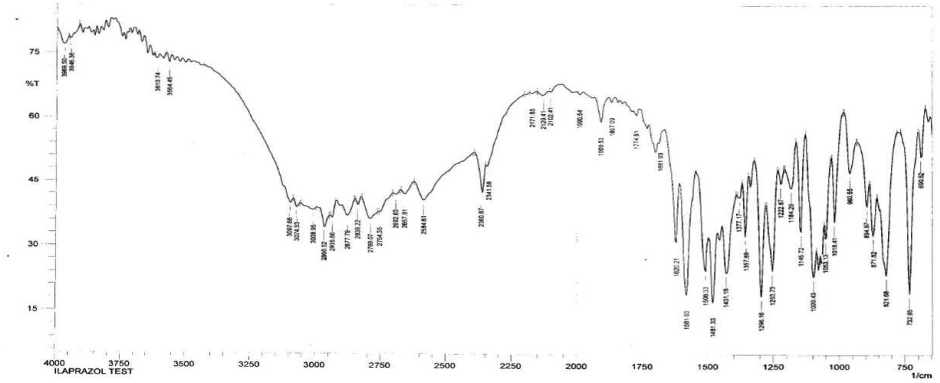


Figure No 2 : IR of Ilaprazole

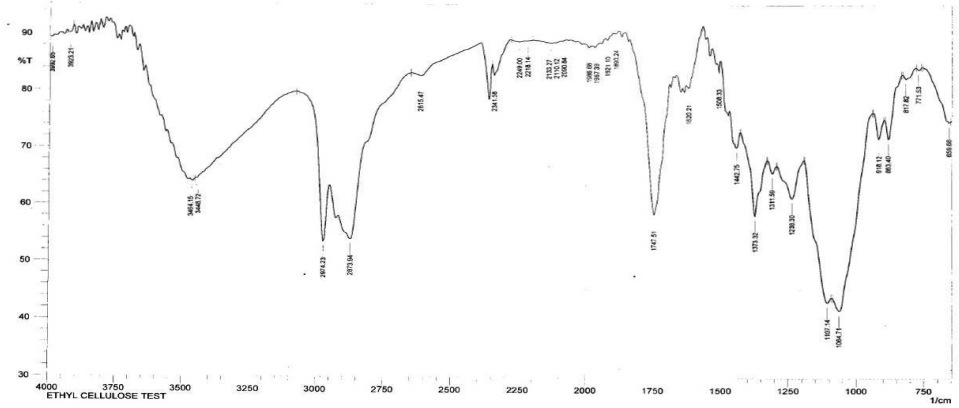


Figure No 3 : IR of Ethyl Cellulose

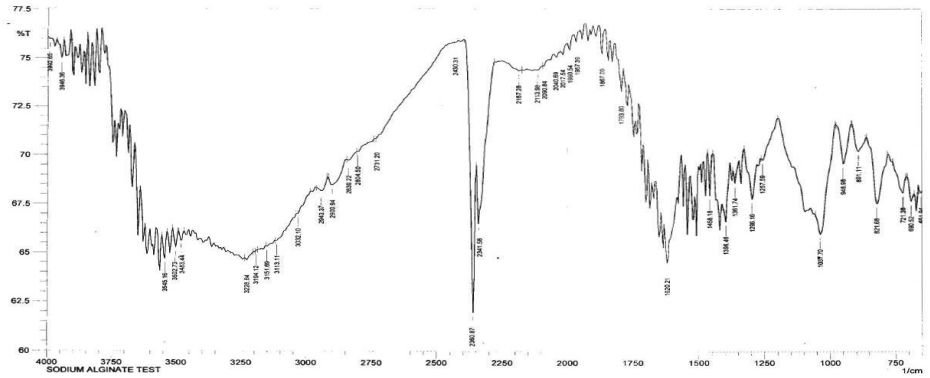


Figure No 4 : IR of Sodium Alginate

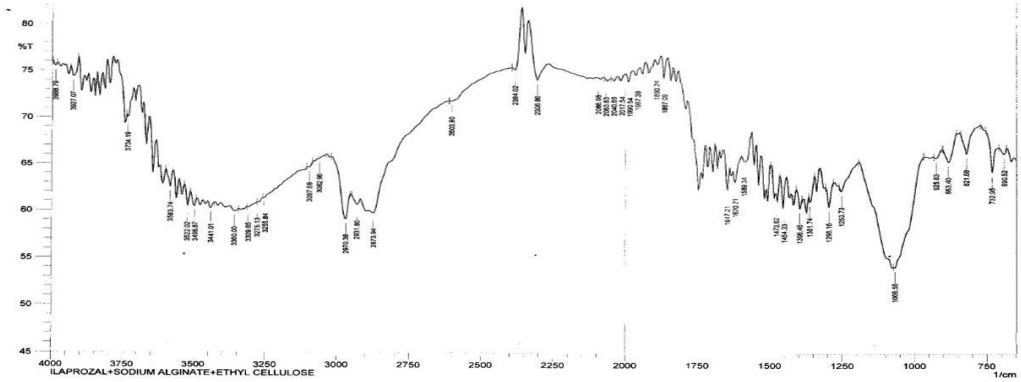


Figure No5 : IR of Ilaprazole + Sodium Alginate +Ethyl Cellulose

Table of Peaks:

Table No 3: Principle peaks and chemical groups present in IR spectrum of pure ILAPRAZOLE drug

Sr. no	Functional group	Peak values (cm^{-1})
1	NH Stretching	3564.45
2	=C-H Stretching	3074
3	-C-H Stretching	2900
4	S=O Stretching	2360
5	C=C Aromatic ring	1681
6	C-O Stretching	1000.43

Table No 4 : Principle peaks and chemical groups present in IR spectrum of Sodium Alginate

Sr. no	Functional group	Peak values (cm^{-1})
1	-OH Stretching	3545
2	-C-H Stretching	2943.27
3	-C=O Stretching	1620
4	C-O Stretching	1037.70

Table No 5 : Principle peaks and chemical groups present in IR spectrum of plane Ethyl cellulose

Sr. no	Functional group	Peak values (cm^{-1})
1	C-H	2974.23
2	C-O	1107.14 1064.71

Table No 6 : Principle peaks and chemical groups present in IR spectrum of Ilaprazole, Sodium Alginate and Ethyl cellulose

Sr no	Functional groups in Ilaprazole	Peaks values (cm^{-1}) in Ilaprazole	Peaks values (cm^{-1}) in Sodium Alginate	Peaks values (cm^{-1}) in Ethyl Cellulose	Peaks values (cm^{-1}) in Constitution Combination	Interpretation
1	NH aromatic Stretching	3564.45	-	-	3583.74	No Interaction
2	=C-H aliphatic Stretching	3074	-	-	3062	No Interaction
3	-C-H Stretching	2900	2943.47	2974.23	2970.38	No Interaction
4	S=O Stretching	2360 1909	-	-	2306.86 1990	No Interaction
5	C=C Aromatic ring	1681	-	-	1647	No Interaction

Interpretation:
There was no drug interaction in drug and polymers since the peaks of pure drug and polymers retains in combination.

4.2 Invito Dissolution Study for Oral Floating Insitu Gel of Ilaprazole:
Insitu gel forming polymeric formulations are the drug delivery system that are in sol or suspension form before administration in body, but once administered, undergo gelation *in situ*, to form gel. Insitu gel forming system have been widely investigated as vehicle for sustain drug delivery system.

➢ The main prerequisite of insitu gelling system were optimum viscosity, gelling time, floating lag time and floating duration. The formulation should have an optimum viscosity that will allow easy swallowing as a liquid, which then undergoes a rapid sol–gel transition due to ionic interaction. On this basis various formulations were tried to formulate and evaluate as various natural as well as synthetic polymers in the combination of Natural: Natural , Natural: Synthetic, Synthetic : Synthetic were used in different ratio.

➢ Different formulations were developed with various polymers like guar gum, xanthan gum, pectin, various grads of carbapol like carbapol 934, carbapol 940, carbapol 971, various grades of eudragits like Eudragit L100, Eudragit S 100, various grades of HPMC like HPMC K4 M, K15 m, etc. but these polymers in different proportion fails to sustain the drug release for 12 hours, they show burst release within 2-3 hours so they fails to show gastric retention.

➢ The formulated batch I1 (HPMC K100 M 0.5% : Eudragit RSPO 2%) show invitro release for 4 hours, batch I2 (HPMC K100 M 0.5% : Ethyl cellulose 2%) show invitro release for 4 hours, batch I3 (Rosin 2% : Eudragit RSPO 2%) show in vitro release for 3 hours, batch I4 (Rosin 2% : Ethyl cellulose 2%) show in vitro release for 5 hours, batch I5 (Sodium Alginate 3% : Ethyl Cellulose 1%) show in vitro release for 8 hours, batch I6 (Sodium Alginate 1% : Ethyl Cellulose 3%) show in vitro release for 10 hours, batch I7 (Sodium Alginate 3% : Eudragit RSPO 1%) show in vitro release for 9 hours, batch I8 (Sodium Alginate 1% : Eudragit RSPO 3%) show in vitro release for 6 hours, batch I9 (Sodium Alginate 0.4% : Ethyl Cellulose 3.6%) show in vitro release for 6 hours, batch I10 (Sodium

Alginate 3.6% : Ethyl Cellulose 0.4%) show in vitro release for 5 hours. All these formulations did not give the release of the drug for 12 hours it can because interaction between these polymers did not form strong matrix gel formation to retard the release of drug for 12 hour to show gastric retention. As in the batch I1 –I4 though sustain release, viscosity increasing polymers etc were used but insitu gelling polymer was not used. In the other batches use of sodium alginate as Insitu gelling polymer and gelling polymer was used but concentration of sodium alginate with different polymers were not sufficient to retard the release of drug for 12 hours.

➢ In the batch I11 (Sodium Alginate 2% : Eudragit RSPO 2%) show in vitro release for 12 hours. Though it show release for 12 hours it gave floating lag time as 4-5 sec and floating duration 3-4 sec, than optimized batch, optimized batch show floating lag time immediate and floating time immediate. It also show significant different than optimized batch so this batch did not optimized.

➢ The batch I12 (Sodium Alginate 2% : Ethyl cellulose 2%) in the ratio 1:1 gave in vitro drug release for 12 hours (98.06 ±0.98), as the matrix formation between sodium alginate and ethyl cellulose was strong to retard the drug release. It floats immediately and also gets converted into gel immediately after incorporation in 0.1 N HCl. It's floating duration was found to be more than 12 hrs. on these basis it has showed gastric retention. Kinetically this batch follow Korsmeyr-pappas model.

➢ On the basis of pre requisition insitu gelling system i.e. optimum viscosity, gelling time, floating lag time and floating duration the batch I12 was optimized.

Table No 7: Showing % Invitro Drug Release of Oral Floating Insitu Gel of Ilaprazole:

Time (in hr)	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	56.61 ±0.86	53.96 ±0.73	63.39 ±0.95	48.75 ±1.02	27.39 ±0.96	22.94 ±1.03	24.46 ±1.01	44.19 ±0.79	45.72 ±0.84	51.79 ±0.99	33.57 ±0.92	21.41 ±0.82
2	69.17 ±0.72	67.11 ±0.65	81.85 ±0.69	56.04 ±0.89	33.60 ±0.86	29.09 ±0.86	30.56 ±0..77	54.88 ±0.91	59.44 ±0.99	60.96 ±0.76	41.20 ±0.97	27.52 ±0.79
3	89.89 ±0.91	83.1 ±0.71	93.06 ±0.75	73.16 ±0.69	39.71 ±0.78	39.70 ±0.66	38.18 ±0.75	62.53 ±086	64.05 ±0.79	73.17 ±0.77	47.32 ±0.88	38.18 ±0.99
4	95.18 ±0.82	97.23 ±0.94		82.36 ±0.90	48.86 ±0.88	50.37 ±0.85	47.34 ±0.73	71.71 ±0.85	73.24 ±0.92	82.36 ±0.91	53.45 ±0.77	45.81 ±.0.65
5				91.56 ±1.0	59.55 ±0.93	56.5 ±0.70	53.46 ±0.84	80.9 ±0.90	85.46 ±0.89	93.08 ±0.95	62.62 ±0.90	51.94 ±0.83
6					67.2 ±0.87	64.16 ±0.96	64.15 ±0.89	90.1 ±1.54	91.23 ±0.69		67.24 ±0.82	59.59 ±0.82
7					79.43 ±1.01	71.82 ±0.98	70.30 ±0.69				76.42 ±0.83	68.76 ±0.76
8					91.66 ±0.81	79.49 ±0.77	82.52 ±0.70				81.06 ±0.67	77.95 ±0.95
9						85.65 ±0.99	94.76 ±0.80				85.71 ±0.78	82.59 ±0.62
10						93.34 ±0.92					90.36 ±0.68	87.24 ±0.78
11											93.05 ±0.89	90.37 ±0.97
12											96.64 ±0.88	98.06 ±0.98

Where N=3

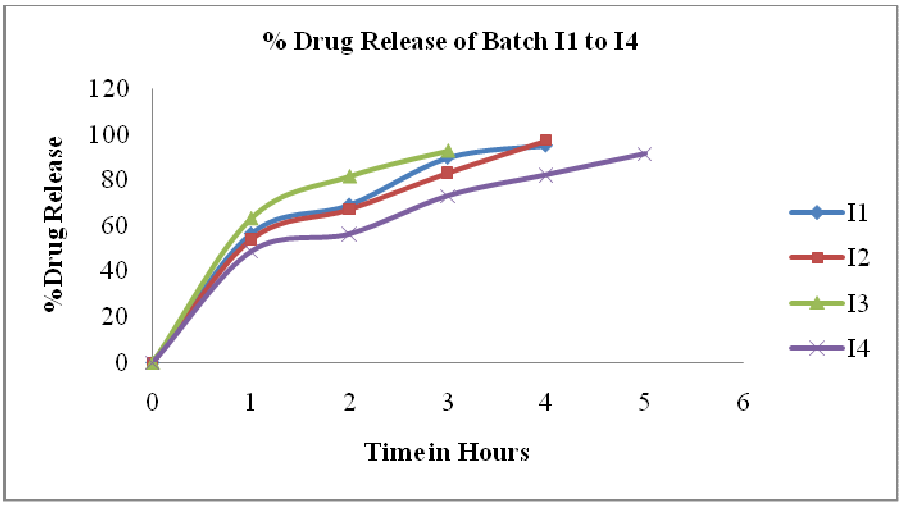


Figure No 6: % In vitro drug release dissolution of Batches I1 to I4

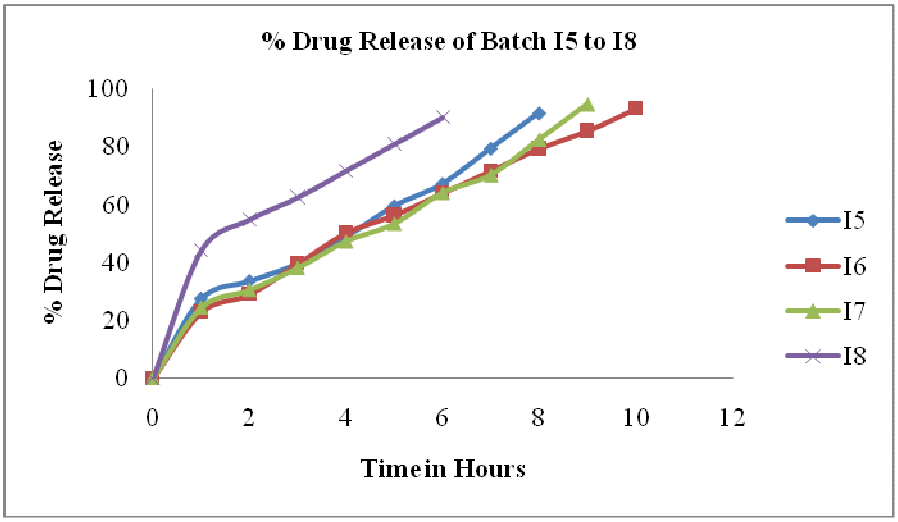


Figure No 7 : % In vitro drug release of Batches I5 to I8

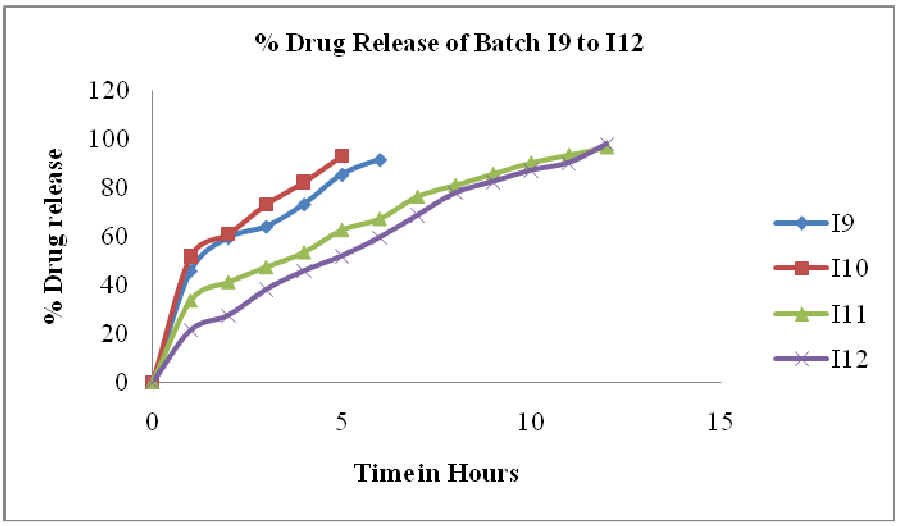
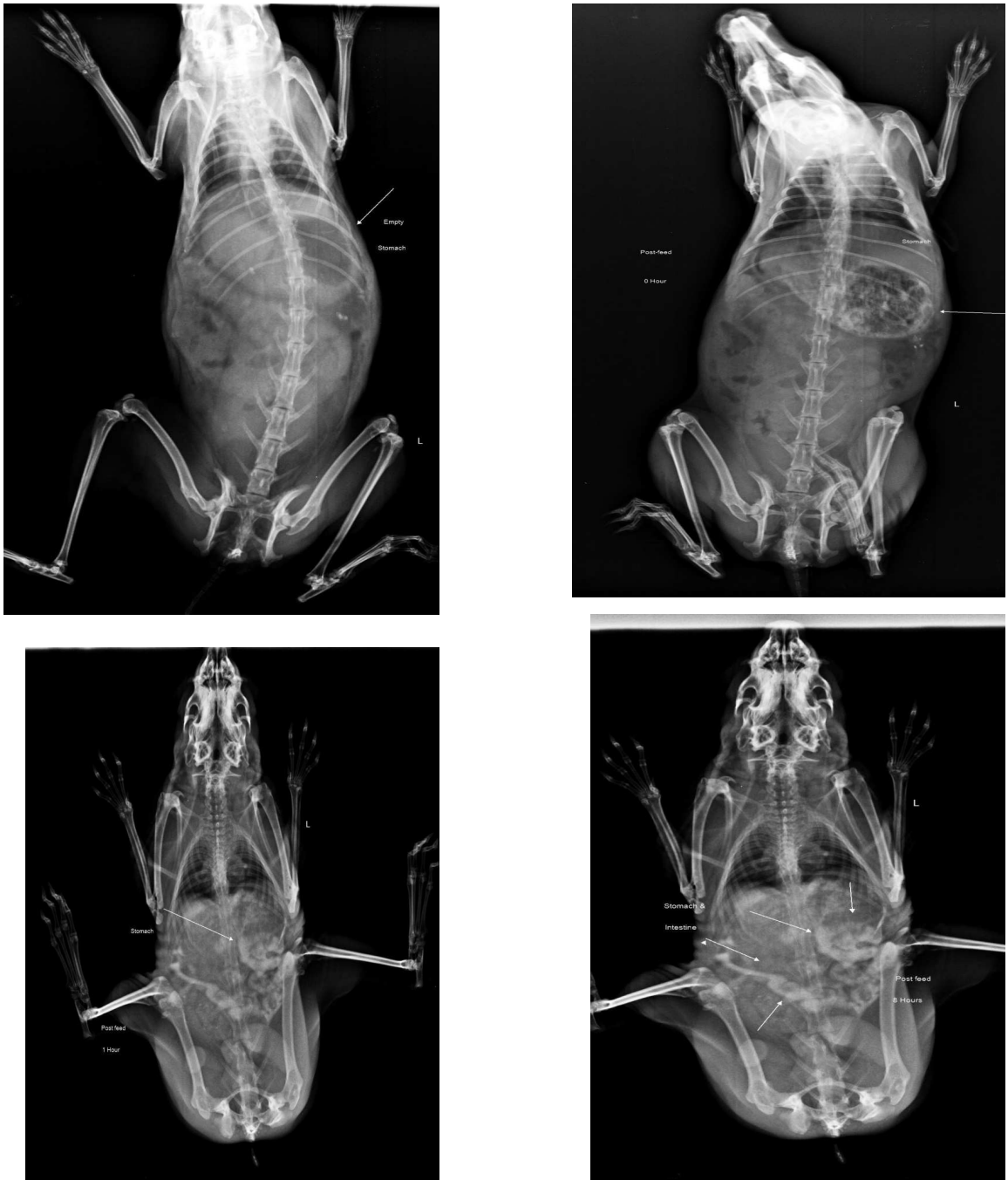


Figure No 8 : % In vitro drug release of batches I9 tp I12

4.3 In vivo studies : An in vivo release study was carried out in healthy rabbits. Using oral feeding tube and needle gel of Ilaprazole was feeded to rabbits and X rays were taken of rabbit abdomen to check the floating ability of gel

formulation. The X rays were taken as a) X ray of empty stomach b) X ray immediate after feeding of gel c) X ray after 1 Hr. of feeding of gel d) X ray after 8 Hr of feed. It was found that the oral floating insitu gel was float immediately after feeding to rabbit and it was found to be floating in the stomach more than 6 hours. The following Xray shows a) the Xray of empty stomach, b) show Xray immediate after feeding of gel to rabbit, c) Xray after 1 hour of feding d) Xray after 8 hour of feeding. Images are as follows:

(a) And (b)



(C)and (d)

Figure 9: Invivo Study of oral floating Insitu gel of Ilaprazole

Optimization:

In the present study various natural as well as synthetic polymers in the combination of Natural: Natural , Natural: Synthetic, Synthetic : Synthetic were used in different ratio. But in the formulated batches I 1 to I 10 did not gave invitro release for 12 hours. In batch I11 though it float for 12 hours it gave floating lag time as 4-5 sec and floating duration 3-4 sec, than optimized batch show floating lag time immediate and floating time immediate. It also show

significant different than optimized batch so this batch did not optimized. The formulate batch I12 (Sodium Alginate 2% : Ethyl cellulose 2%) in the ratio 1:1 gave in vitro drug release for 12 hours(98.06±0.98). It can be because sodium alginate is gel formulating agent and use mostly in Insitu gel formulation and ethyl cellulose use to increase the viscosity of sol that form strong gel matrix formulation in 0.1 N HCl. It floats immediately also gets converted in gel immediately after incorporation in 0.1 N HCl. It also floating duration was found to be more than 12 hrs. Also it was found stable in 6 months of accelerated stability study. So batch I12 was optimized.

4.4 Kinetic Studies:

The release data obtained from various batches was studied with respect to effect of drug: polymer ratio, diluents ratio. Dissolution data of drug from prepared *in situ* gel at different time periods was plotted as cumulative % drug release v/s time. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. It was found that the optimized batch I12 follow Korsmeyr-pappas model.

The drug release kinetics from all the batches were calculated, which was illustrated as follows-

Table No 8 : Kinetic study of Oral Floating Insitu gel of Ilaprazole

Batch	Zero order	First order	Matrix	Peppas	Hixon crowell	Best Model fit
I1	0.852	0.942	0.979	0.964	0.945	Peppas
I2	0.895	0.957	0.964	0.98	0.905	Peppas
I3	0.895	0.953	0.979	0.98	0.907	Peppas
I4	0.894	0.949	0.97	0.98	0.908	Peppas
I5	0.882	0.922	0.984	0.962	0.921	Peppas
I6	0.888	0.972	0.982	0.962	0.911	Peppas
I7	0.892	0.943	0.971	0.979	0.909	Peppas
I8	0.898	0.87	0.976	0.958	0.902	Peppas
I9	0.884	0.937	0.982	0.972	0.919	Peppas
I10	0.897	0.921	0.935	0.981	0.887	Peppas
I11	0.895	0.913	0.961	0.97	0.902	Peppas
I12	0.896	0.822	0.965	0.954	0.901	**Peppas**

4.5 Stastical Analysis:

In this study the Bonferroni method was applied to dissolution study to check there was significant difference or non significant difference in release of drug in formulated formulations. The optimized batch show significant difference from all the other formulated batches the description is given in table no 33.

Table No 9 : Statistical Analysis of Dissolution parameters of Oral Floating Insitu gel of Ilaprazole :

Sr. No	Between batches	t-test	P-value (<0.05)	Significance
1	I12 vs I1	3.801	0.0191	S
2	I12 vs I2	3.754	0.0199	S
3	I12 vs I3	2.920	0.0156	S
4	I12 vs I4	4.733	0.0052	S
5	I12 vs I5	4.329	0.0025	S
6	I12 vs I6	5.214	0.0004	S
7	I12 vs I7	2.853	0.0190	S
8	I12 vs I8	5.805	0.0011	S
9	I12 vs I9	5.723	0.0012	S
10	I12 vs I10	4.854	0.0047	S
11	I12 vs I11	4.739	0.0005	S

4.6 Stability Study:

Stability studies were carried out as per ICH guidelines. The optimized formulation I12 was exposed to accelerated stability conditions as 40°C±2°C 75%RH±5% RH for the period of 6 months. In between the stability studies the formulation was removed at 3 month and 6 month to check all the evaluation tests as pH, viscosity, gelling time, floating lag time, floating time, Floating duration, Dissolution studies etc. During the stability studies, the product was exposed to normal conditions of temperature and humidity. The optimized batch was found to be stable for all the evaluation tests in this time period of stability testing.

Table No 10: Various characteristics of oral floating *In situ* gel of Ilaprazole after stability study

Stability Duration	pH	Viscosity in cps	Gelling time (sec)	Floating lag time (sec)	Floating Duration in hr	Drug content (%)
Zero month	10.4	9.58	2-3	Immediate	> 12	99.00 ±0.57
After 3 Month	10.3	9.58	2-3	Immediate	> 12	99.00 ±0.52
After 6 Month	10.3	9.58	2-3	Immediate	> 12	99.00±0.0.55

Table No 11: % Drug Release of oral floating *In situ* gel of Ilaprazole after stability study

Time (in hr)	ZERO MONTH	3 MONTH	6 MONTH
0	0	0	0
1	21.41 ± 0.82	19.9 ± 0.99	18.39 ± 0.73
2	27.52 ± 0.79	26 ± 0.69	24.84 ±0.81
3	38.18 ± 0.99	36.66 ± 0.78	34.41 ± 0.72
4	45.81 ± 0.65	44.2 ± 1.05	41.8 ± 0.93
5	51.94 ± 0.83	50.49 ± 0.83	47.89 ± 0.79
6	59.59 ± 0.82	58 ± 0.94	56.45 ± 0.96
7	68.76 ± 0.76	67.24 ± 0.88	65.17 ± 0.76
8	77.95 ± 0.95	76.2 ± 0.71	74.9 ± 0.79
9	82.59 ± 0.62	81.06 ± 0.91	79.05 ±0.95
10	87.24 ± 0.78	85.17 ± 0.77	83.81 ± 0.83
11	90.37 ± 0.97	88.48 ± 0.72	87.3 ± 0.65
12	98.06 ± 0.98	96.53 ± 0.95	95.01± 0.87

N=3

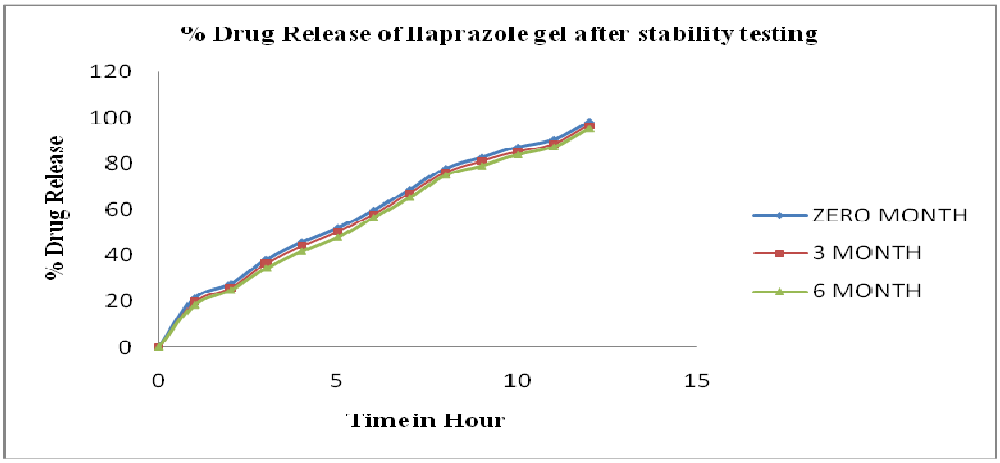


Figure No 10: % Drug release of Oral floating Insitu gel of Ilaprazole after stability study

Table No 12: Kinetic study of oral floating Insitu gel of Ilaprazole after stability study

Time / Model	Zero order	First order	Matrix	Peppas	Hixon crowell	Best Model fit
ZERO MONTH	0.896	0.822	0.965	0.954	0.901	**Peppas**
3 MONTH	0.9681	0.9377	0.9789	0.9950	0.9860	**Peppas**
6 MONTH	0.9730	0.9527	0.9750	0.9953	0.9892	**Peppas**

5) SUMMARY:

In the present study various natural as well as synthetic polymers in the combination of Natural: Natural , Natural: Synthetic, Synthetic : Synthetic were used in different ratio. But in the formulated batches I 1 to I 10 did not gave invitro release for 12 hours. In batch I11 though it float for 12 hours it gave floating lag time as 4-5 sec and floating duration 3-4 sec, than optimized batch show floating lag time immediate and floating time immediate. It also show significant different than optimized batch so this batch did not optimized. In optimized batch Sodium alginate 2% and Ethyl cellulose 2% gives the retarding result for 12 hrs. The optimized batch show floating of insitu gel of Ilaprazole for more than 8 hours. The batch was found to be stable for 6 months in accelerated stability study. In Kinetic study the optimized batch follows peppas model.

CONCLUSION

⇨From formulation and evaluation studies of oral floating insitu gel it was concluded that gas forming agent sodium bicarbonate and calcium carbonate 2% each (1:1) proportion gives floating of gel for >12 hrs.
⇨Sodium Alginate 2% and Ethyl cellulose 2% (1:1) ratio gave gastric retention of drug Ilaprazole for 12 hours.
⇨Invivo study was performed by providing the formulation to rabbit and then X-ray were taken for the confirmation of formation of gel in stomach and floating of dosage form for 12 hrs. And it was found to be floating for more than 12 hrs.
⇨The batch was found to be stable for 6 months in accelerated stability study.

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