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Formulation and Evalution of Floating in Situ Gel of Pantoprazole Sodium

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ABSTRACT:-

Objective: The objective of the present investigation was to formulate, evaluate and optimize floating in situ gel of pantoprazole sodium.

Material and method: In situ gel formulations were prepared by using different concentrations of sodium alginate, calcium carbonate, sodium citrate and xanthan gum. pH triggered ionic gelation is the mechanism involved in the present study. All the formulations were subjected to various evaluation parameters.

Results: Formulation F8 containing0.04gm of Pantoprazole sodium, 2 gm of sodium alginate, 1 gm of CaCO3, 1 gm of xanthan gum and 0.25 gm sodium citrate was selected as optimized batch, floating time 44.33 sec and drug content 97.0%. The FTIR study revealed that there was no incompatibility. The optimized batch is passed the accelerated stability studies, nosignificant change in the Drug content. In-vivo study on Albino Wistar rats demonstrated significant anti-ulcer effect of Pantoprazole Sodium of the optimized formulation.

Conclusion: It was concluded that the hydrodynamically balanced oral In situ gel of Pantoprazole Sodium could be an effective dosage form which remains buoyant and sustain the drug release for 8 hrs.

Keywords: Pantoprazole Sodium,In situ gel, FTIR,Sodium alginate,Hydrodynamically balanced.

I. INTRODUCTION:-

Peptic ulcers are open craters or sores that develop in the inner lining (mucosa) of the stomach or the duodenum (the first section of the small intestine). A coating of mucus and other chemicals normally shield the stomach and duodenum from digesting themselves. When these protective mechanisms are disrupted, powerful digestive acids can erode into the lining of these organs and cause peptic ulcers. [(1)]

In situ is a Latin word which means in position. In situ gel formation of drug delivery systems can be defined as a liquid Formulation generating a solid or semisolid depot after administration. In-situ activated gel forming Systems are those which are when exposed to physiological conditions will shift to a gel phase. This new concept of producing a gel in situ was suggested for the first time in the early 1980s. Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or Non-covalent bond formation (physical cross-linking).[(2)]Floating drug delivery system is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. These delivery systems are desirable for drugs with anabsorption window in the stomach or in the upper small intestine. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. [(3)]

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).[(4)]

II. MATERIALS AND METHODS:-

Materials:

Pantoprazole Sodium is obtained as a generous gift sample from Pelltech Healthcare, Mumbai. Sodium Alginate, Calcium Carbonate andXanthan Gum from MeherChemie, Mumbai. Sodium Citrate from Varsha Pharma, Mumbai.

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Table No.01: Materials

Sr.No	Material	Property	Source
1.	Pantoprazole Sodium	API	Pelltech Healthcare, Mumbai.
2.	Sodium Alginate	Gelling Polymer	MeherChemie, Mumbai
3.	Calcium Carbonate	Cross Linking, Alkalizing Agent	MeherChemie, Mumbai
4.	Xanthan Gum	Rate Retarding Polymer	MeherChemie, Mumbai
5.	Sodium Citrate	Buffering, Neutralizing Agent	Varsha Pharma, Mumbai

Equipments:

Table No .02: Equipments

Sr.No	Equipment	Model No.	Make
1.	Magnetic Stirrer	Lms-28oe	Labtop
2.	Brookfield Viscometer	Model No. Cap-2000.	Middleboro Usa.
3.	UV-Spectrophotometer	UV-1800	Shimadzu Japan
4.	Digital Balance	Bl-22oh	Shimadzu Japan
5.	pH Meter	Pico+	Labindia
6.	Dissolution Apparatus	EDT – 08 LX	Electrolab
7.	FTIR	Specrum-2	Perkin Elmer

METHOD OF PREPARATION OF IN SITU GELLING SOLUTION: - [5]

Specified quantity of Pantoprazole sodium, calciumcarbonate, sodium citrate, different polymers such as sodium alginate and xanthan gum were weighed according to formula given in Table 1. The mixture of xanthan gum and Sodium alginate solution of different concentration were prepared in deionized Water containing 0.25% of sodium citrate. Low concentration of cations in solution was sufficient to hold the molecular chains together and inhibit hydration. Sodium alginate solution was heated to 70^0C with stirring. After cooling to below 40^0 C, different concentration of calcium carbonate and the drug were added and dispersed well with continuous stirring. The resulting sodium alginate and xanthan gum in-situ gelling solution containing Pantoprazole sodium was finally stored in amber colored bottles until further use.

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FORMULATION TABLE:-

Table No. 03: Formulation Details of Pantoprazole sodium of floating in situ gel

Sr.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	Pantoprazole sodium (mg)	400	400	400	400	400	404	400	400	400	400	400	400
2.	Sodium alginate (gm)	0.5	1	1.5	2	0.5	1	1.5	2	0.5	1	1.5	2
3.	Calcium carbonate (gm)	0.5	0.5	0.5	0.5	1	1	1	1	1	1	0.5	0.5
4.	Xanthan gum (gm)	0.5	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	1.5
5.	Sodium citrate (mg)	250	250	250	250	250	250	250	250	250	250	250	250
6.	Distilled water (upto100 ml)	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation Tests:-

Physical appearance and pH:[6]

Prepared sodium alginate in situ solutions of Ranitidine HCL are checked for their clarity and the time required for gel formation and type of gel formed. pH is measured using a calibrated digital pH meter at 27^0C. (See table no.5).

Viscosity of in situ Gelling Solutions:[7]

The viscosity of formulations was determined by a Brookfield viscometer DVIII (Brookfield, USA) using spindle number 2 with cup and bob setting at 50 rpm.

Floating Behavior:

The floating ability of the prepared formulations was evaluated in (0.1N HCl, pH 1.2) Solution. The floating time of the prepared formulation took to emerge on the medium surface (floating lag time) was found to be 60 sec. The time the formulation constantly floated on the dissolution medium surface (duration of floating) was evaluated to be 8 hrs resulting the formation of thick gel with good floating tendency.

Invitro gelation study:[8]

The in vitro gelling capacity of prepared formulations was measured by placing 5ml of the gelation solution (0.1 N HCl) in a 15 ml borosilicate glass test tube and maintained at 37 ± 1^0C temperature. 1 ml of formulation solution was added with the help of pipette. The formulation was transformed in such a way that places the pipette at the surface of the fluid in test tube and formulation was slowly released from the pipette. As the solution comes into contact with the gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of the solution was evaluated on the basis of stiffness of formed gel and time period for which formed gel remains as such.

Swelling index: [9]

Formed gel of 100mg was weighed accurately (W1) and placed in apetri dish containing 50ml of 0.1 N HCL. It was kept aside for 24 hrs. After 24 hrs gel was weighed (W2) and swelling index was calculated using the following formulae: (Ganapati et al., 2009).

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$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

Where,
W1 = Initial weight of gel (100mg)
W2 = Weight of gel after 24 hrs

Drug Content:[10]

10 ml of thesolution was added to 900 ml (0.1 N HCL,Ph 1.2) and the drug concentration was determined by using a UV-visible spectrophotometer a (Shimadzu UV 1700 Pharmazie) at 284 nm against a suitable blank solution.

In vitro Release Studies:[11]

An in vitro release study was carried out using dissolution test apparatus USP Type II (Paddle Method). The following procedure was followed throughout the study that is shown in (table 6,7) to determine the in vitro dissolution rate for the formulations. The release of Pantoprazole sodium from the formulations was determined using dissolution test apparatus USP Type II with a paddle stirrer at 50 rpm. The dissolution medium used 900 ml of (0.1 N HCL, pH 1.2) solution and temperature was maintained at 37± 0.2°C. 10 ml of the formulation were placed into a petri dish (4.5cm i.d.) which was kept in the dissolution vessel and 0.1 N HCl solution was carefully added to the vessel avoiding any disturbance of the petri dish.at each time interval, aprecisely measured sample of the dissolution medium was pipette out and replenished with fresh medium. Pantoprazole sodium concentration in the aliquot was determined spectrophotometrically.

Accelerated stability study of optimized formulation:[12]

Accelerated stability study was carried out for optimized formulation, to assess its stability as per ICH guidelines. The optimized formulation were kept in amber colored bottles and was placed in the accelerated stability chamber at elevated temperature and humidity of 400 c /75% RH and a control sample was placed at an ambient condition for a period of 1 month. Samplings were done at a predetermined time of initial 0,1,2,3, and 4, weeks interval respectively. At the end of study, samples were analyzed for the appearance, pH and drug content.

In-vivo study:[13-16]

Male / Female Wistar rats (200-250 gm each) utilized for in vivo experiment study. All the animal studies were conducted in accordance with the protocol approval by the institutional animal ethics committee. The ulcer protective efficiency of Pantoprazole sodium in situ gel was compared with plain Pantoprazole sodium solution dissolved in PBS (pH 7.4). the animals were divided into Five groups, each group containing five animals. The first group was treated as control and was fed with PBS (pH 7.4) by oral route. Second, third and fourth group was treated with immediate treatment of in situ gel, plain Pantoprazole sodium solution equivalent to 40 mg/kg) (Doi Y et al., 1999) and Pantoprazole sodium in situ gel, respectively.

One milliliter of 80% ethanol was used orally to induce gastric ulcer (Narayan s et al., 2004) after 5 hrs. the alcohol was given to dissolve the mucous coat of the stomach and so the condition was made to allow gastric acid to act on gastric walls. After 8 hrs, the animals were sacrificed (second group the animals were sacrificed after 20 min to observed whether gel is form or not) and stomachs were removed and dissected carefully to observe the ulcer protective function of Pantoprazole sodium in situ gel as compared to plain Pantoprazole sodium solution. The incised stomachs were first washed with running tap water and placed on the watch glass and examined for severity of ulceration. The ulcer index was determined using the formula: (Shay H et al., 1945; Kulkarni SK, 1999 and Ganguly AK, 1969) ulcer index = 10/X, Where X = total mucosal area/ total ulcerated area. The results of in vivo study are depicted in Table 9 and Figs. 8, 9.

III. RESULTS AND DISCUSSION:-

RESULTS:

A) λ max Determination ofPantoprazole sodium

The UV spectrum ofPantoprazole sodium in 0.1 N HClscanned in the range of 400-200 nm. The spectrum indicated that the observed λmax of Pantoprazole sodiumis 284 nm which is matched with pharmacopoeial value.

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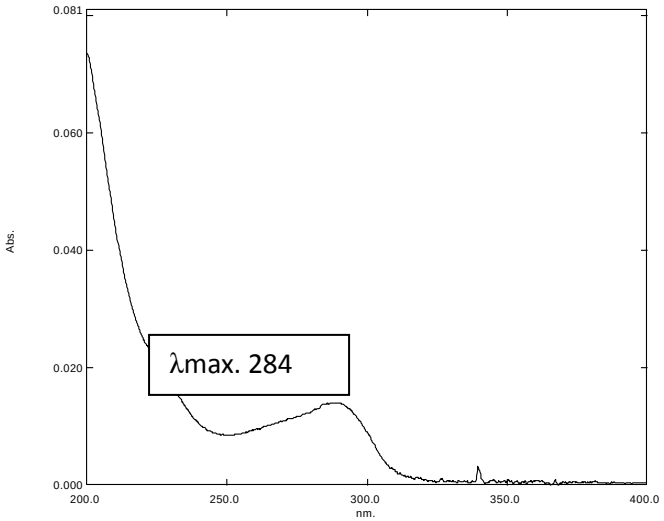

Fig. No. 01. UV Scan for Pantoprazole sodium at 284 nm in 0.1N HCl.

B) Preparation of standard calibration curve ofPantoprazole sodium.

Pantoprazole sodium showed maximum absorption at wavelength 284 nm in 0.001N HCl Standard curve was plotted by taking absorption of diluted stock solution (2, 4, 6, 8, and 10mg/ml,-) at wavelength 284 nm.

Table No.04: Standard calibration curve of Pantoprazole sodium

Sr.No.	Concentration µg/ml	Absorbance
0	0	0.000
1	2	0.052
2	4	0.091
3	6	0.141
4	8	0.182
5	10	0.234

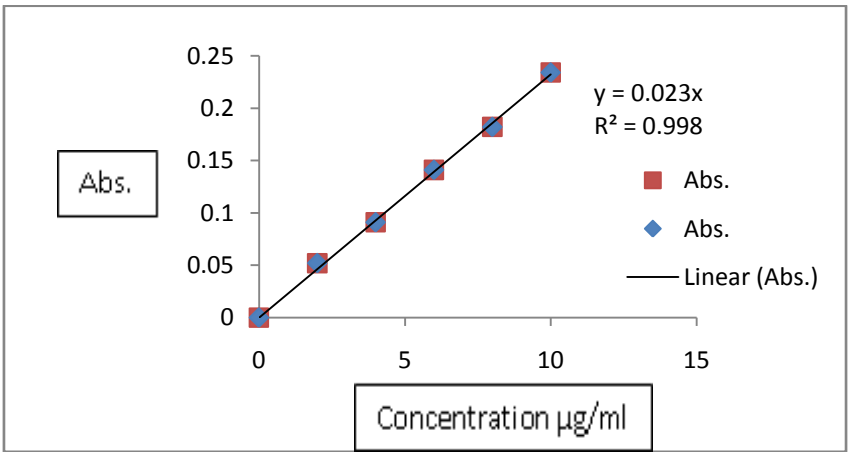

Fig No. 02: Standard calibration curve ofPantoprazole sodium in 0.1N HCl

FTIR Spectroscopy

Identification study was performed using FTIR spectrophotometer. The characteristic absorption peaks of pantoprazole sodium were obtained at different wave numbers. The peaks obtained in the spectra of pure drug correlates with the peaks of official spectrum of British Pharmacopeia which confirms the purity of drug.

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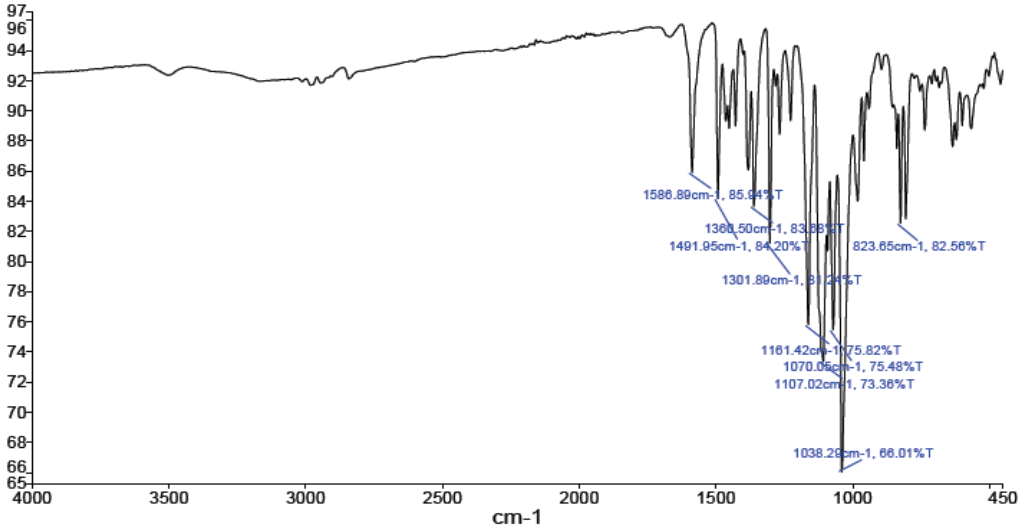

Fig. No. 03: FTIR spectra of Pantoprazole sodium

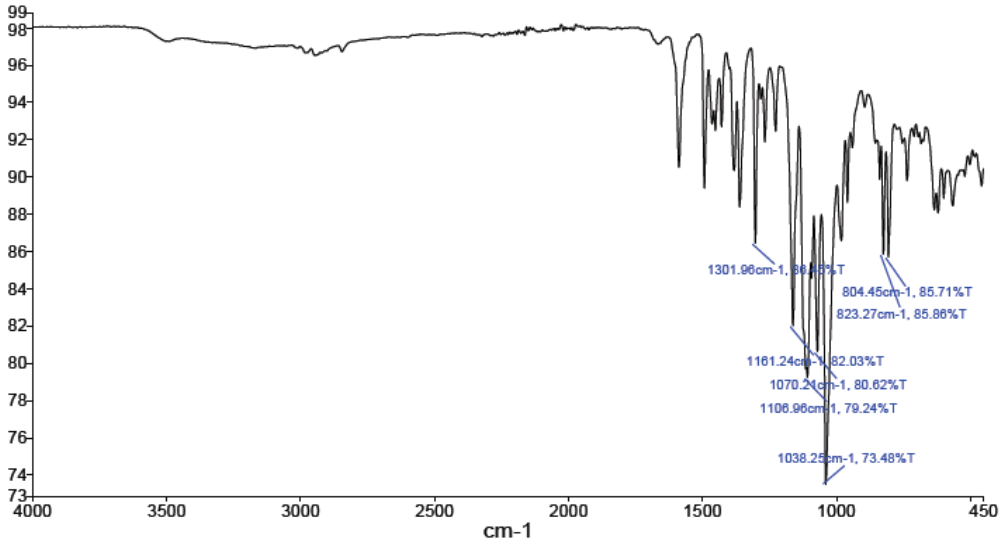

Fig.No.04.FTIR spectra of Sodium Alginate

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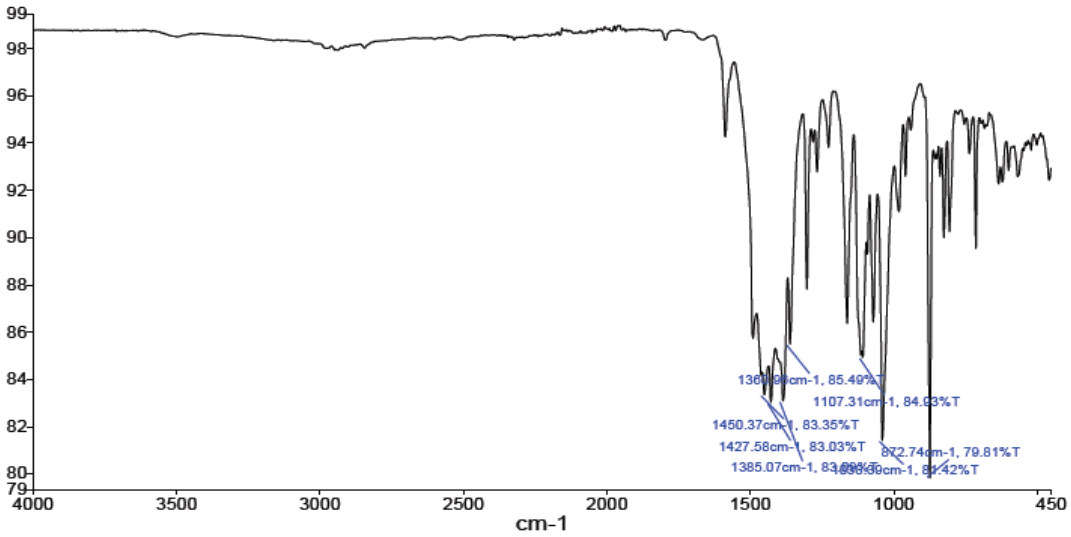

Fig.No.05.FTIR spectra of Calcium Carbonate

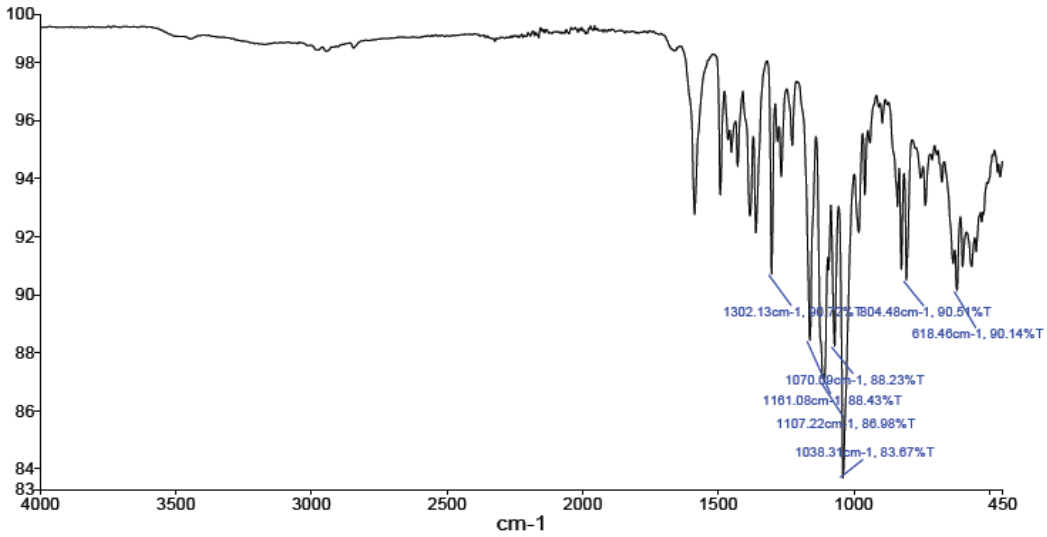

Fig.No.06.FTIR spectra of Sodium Citrate

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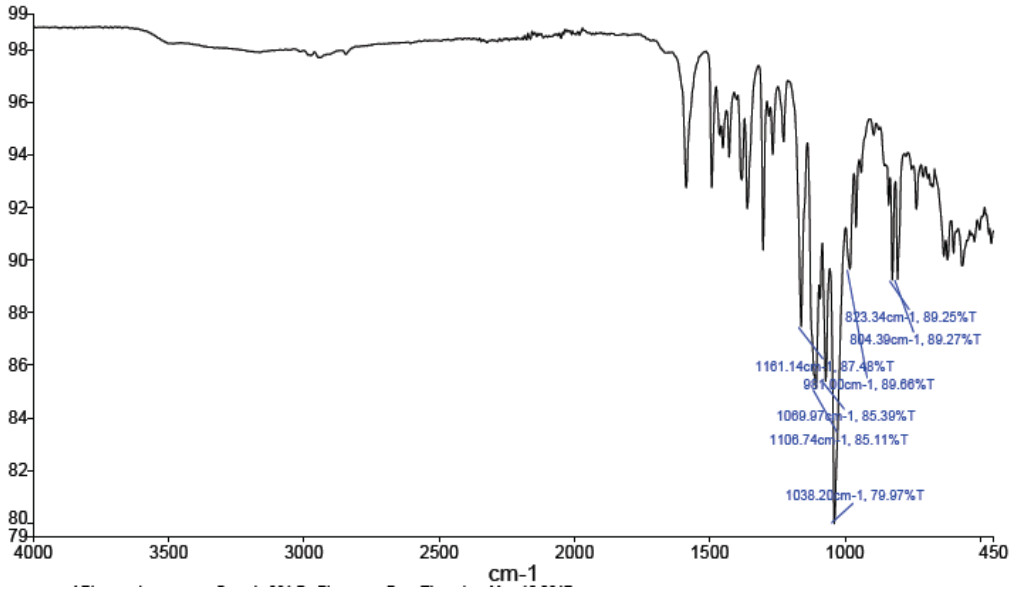

Fig.No.07.FTIR spectra of Xanthan gum

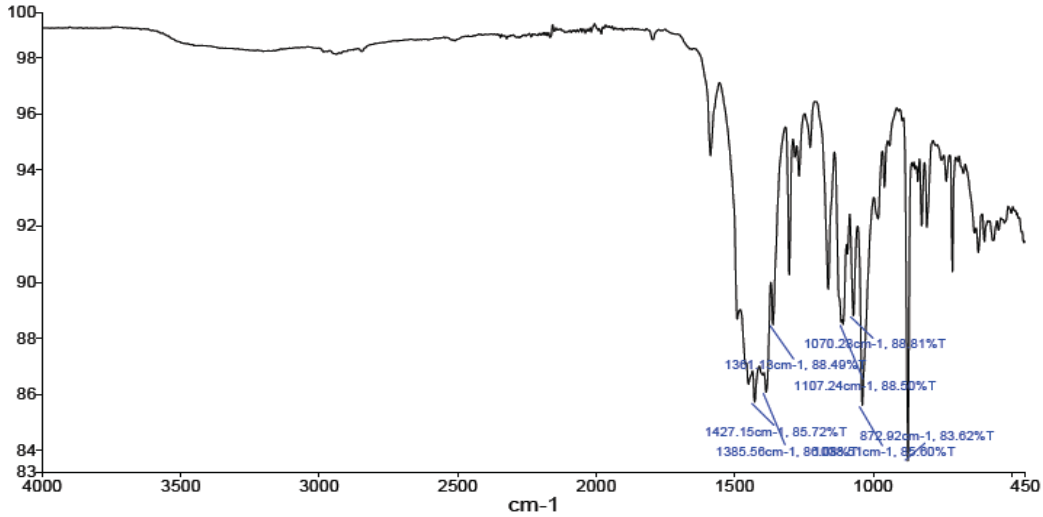

Fig.No.08.FTIR spectra of Optimized formulation batch F8

Evaluation Parameters

Table No. 05: Evaluation of Floating in- situ gel of Pantoprazole sodium.

Batch No.	Appearance	pH	Viscosity (cp)	Floating lag time (sec)	Floating time (hr)	In vitro gelation studies	Swelling Index (% at 8 hr.)	%Drug Content
F1	Milky White	6.80±0.10	167.3±2.51	28.66±1.52	>8	+	32.33±1.52	90.66±0.57
F2	Milky White	7.10±0.20	179.6±2.08	29.66±1.52	>8	+	36.0±1.0	93.0±1.0

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F3	Milky White	6.90±0.10	191.3±3.05	32.0±2.08	>8	++	39.0±2.0	93.66±1.52
F4	Milky White	7.20±0.20	202.6±2.51	33.33±2.08	>8	++	41.33±3.05	91.0±1.0
F5	Milky White	7.26±0.15	214.3±3.51	24.0±2.00	>8	+	46.0±2.0	94.66±0.57
F6	Milky White	6.96±0.20	229.2±2.51	37.33±1.52	>8	++	46.66±1.52	95.0±1.0
F7	Milky White	7.16±0.15	244.3±2.51	40.33±1.52	>8	+++	47.66±1.52	92.33±0.57
F8	Milky White	7.23±0.15	262.6±2.05	44.33±1.52	>8	+++	50.33±1.52	97.0±1.0
F9	Milky White	7.20±0.10	273.6±1.52	42.33±1.52	>8	+++	53.66±1.52	94.33±0.57
F10	Milky White	6.76±0.15	294.6±1.52	38.66±1.52	>8	+++	56.66±1.52	95.66±0.57
F11	Milky White	7.33±0.15	312.6±2.51	45.66±2.51	>8	+++	60.33±1.52	93.33±0.57
F12	Milky White	7.23±0.15	326.3±2.08	47.66±1.52	> 8	+++	60.33±2.08	95.33±0.57

All values are represented as mean ± standard deviation (n=3)

Table.no.9 shows the evaluation of formulation. Appearance was found mikywhite ,pH was found between 6.8 to 7.4, viscosity was found between 167 to 328 (cp),floating lag time was found between 28 to 48 (sec), floating time 8hr,In-vitro gelation study was found + Gel is formed, ++ Stiff gel is formed, +++ Very stiff gel is formed, Swelling index was found 31 to 62, Drug content was found 90 to 96.

Table No. 06:In vitro Dissolution Studies: In-vitro dissolution study of Pantoprazole sodium (F1-F6).

Time (hr)	**% Drug release**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0.000	0.000	0.000	0.000	0.000	0.000
0.5	2.429	0.475	0.475	1.452	0.990	0.475
1	11.225	10.245	12.199	9.270	8.290	7.315
2	17.099	17.096	18.075	17.096	16.115	15.138
3	22.003	24.930	26.887	23.956	24.9258	21.994
4	35.704	36.681	34.733	32.772	32.769	33.742
5	44.537	47.469	48.518	40.624	40621	43.549

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6	51.134	54.033	52.465	48.531	51.527	54.482
7	61.194	64.130	56.430	56.224	63.134	68.397
8	66.147	71.039	64.349	67.237	73.233	81.250

Table No. 07:In vitro Dissolution Studies: In-vitro dissolution study of Pantoprazole sodium (F7-F12).

Time (hr)	**% Drug release**					
	F7	**F8**	**F9**	**F10**	**F11**	**F12**
0	0.000	0.000	0.000	0.000	0.000	0.000
0.5	1.452	1.452	1.452	0.475	0.475	2.429
1	6.339	7.316	6.339	5.361	5.361	7.317
2	14.161	15.139	13.184	14.159	12.205	13.187
3	31.993	25.903	21.992	22.968	24.919	24.925
4	36.902	34.724	34.717	31.786	35.694	32.786
5	55.724	56.486	45.502	46.706	48.572	40.620
6	68.580	68.330	54.345	64.562	66.297	46.527
7	76.329	81.116	68.221	76.335	75.152	58.394
8	87.137	96.082	90.082	92.259	83.039	76.294

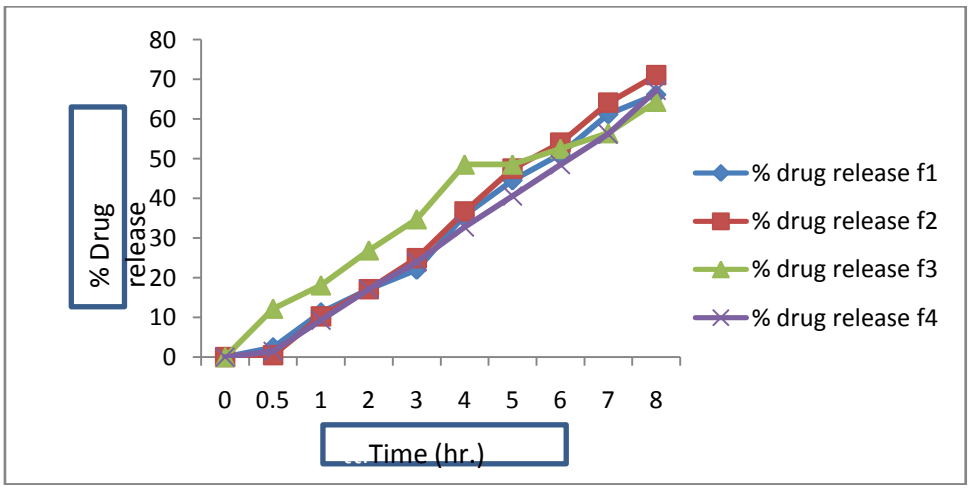

Fig.No. 09: In-vitro dissolution study/profile pantoprazole sodium of batches F1-F4

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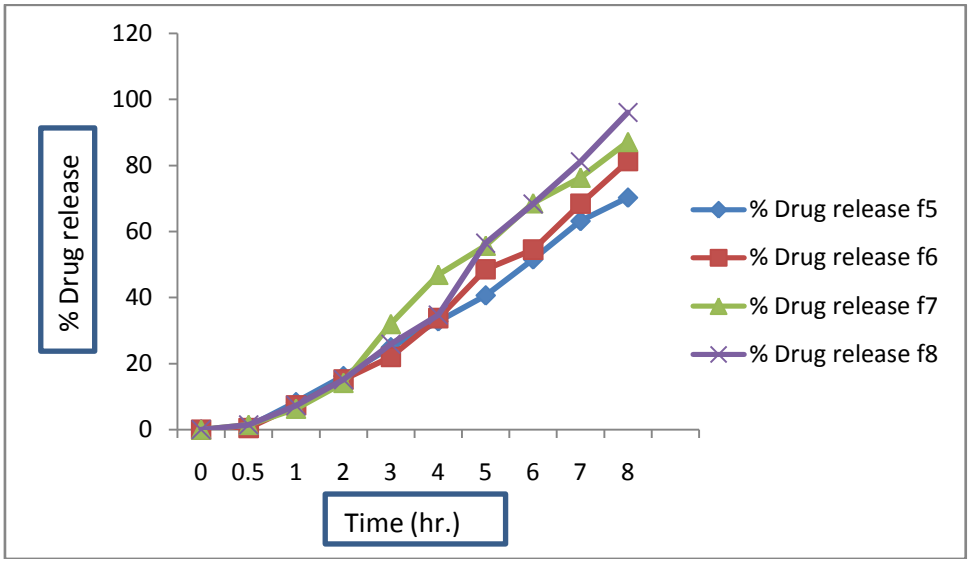

Fig.No. 10: In-vitro dissolution study/profile pantoprazole sodium of batches F5-F8

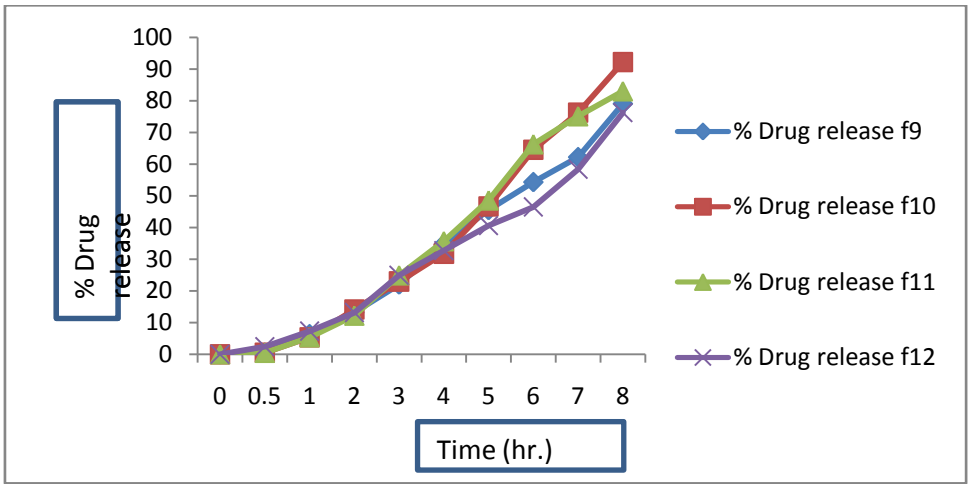

Fig. No. 11: In-vitro dissolution study/profile pantoprazole sodium of batches F9-F12

Accelerated stability study of optimized formulation:

In pantoprazole sodium preparations formulation F8 was to be stable during accelerated stability studies for Appearance, clarity, pH and % Drug content as shown in the Table 12. Finally it was observed that there was no change in Physical and Chemical properties as well as in drug release profile even after storage at 40^0 C and 75 % RH for 1 month.

Table No. 08: Results of accelerated stability study of optimized formulation F8:

Ambient Condition	Appearance & Clarity	pH	% Drug Content
Initial	No change	7.23	97.00
First week ambient	No change	7.15	96.50
40^0 C / 75 % RH	No change	7.15	96.50
Second week ambient	No change	7.19	95.30
40^0 C and 75 % RH	No change	7.19	95.30
Third week ambient	No change	7.32	97.68
40^0 C and 75 % RH	No change	7.32	97.68

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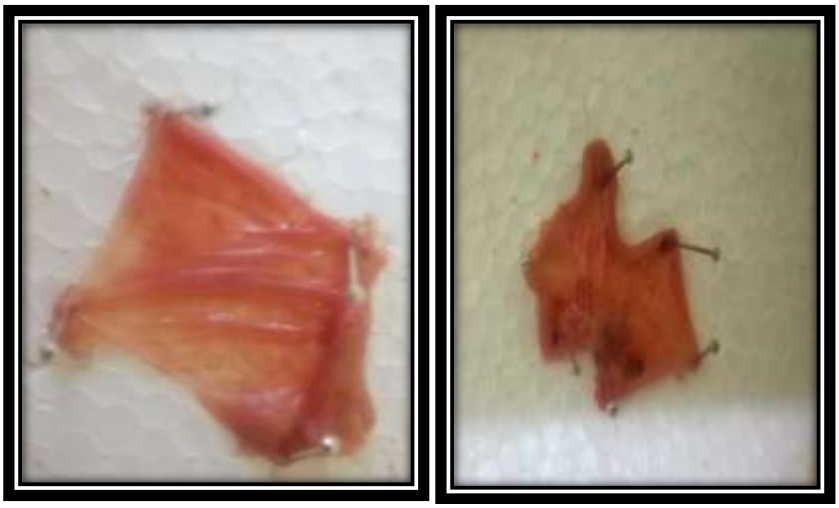
Result of In-vivo study:

The present in vivo investigations demonstrated that there was a marked difference in the reduction of ulcer index from the pantoprazole sodium in-situ gel (batch F8 drug content of 97.0% and the viscosity of 262.6±2.05cp) when compared with the plain pantoprazole sodium solution ($p< 0.05$). It was observed that the formulation under study not only decreased the ulcer index to a significant larger magnitude but also sustained this magnitude (table 9). In case of ethanol treated group, the ulcer index was found to be 2.145±0.06 (Fig 12a). In case of immediate gel formation group, the gel was formed but the ulcer was also identified to be 1.876±0.024 (Fig 12b). While in case of pantoprazole sodium in-situ gel, the ulcer index was found to be only 0.344±0.018 after 8 hrs of dosing (Fig 12d).However, for plain drug the ulcer index was found to be 0.400±0.08 after 8 hrs of dosing. The possible reason for this result may be the drug concentration in the body that was maintained for a longer duration in case of pantoprazole sodium in-situ gel as compared with that of plain pantoprazole sodium. The gel formation was checked in collected gastric juice of the rats and result showed immediately formation of gel in gastric juice of the rats.

Table No. 09: Effect of pantoprazole sodium in-situ gel on ulcer index

Treatment group	Ethanol treated	Immediate gel formation	Plain pantoprazole sodium	Pantoprazole sodium in situ gel	Control
Ulcer index	2.145±0.06	1.876±0.024	0.400±0.08	0.344±0.018	Not detectable



(A) (B)

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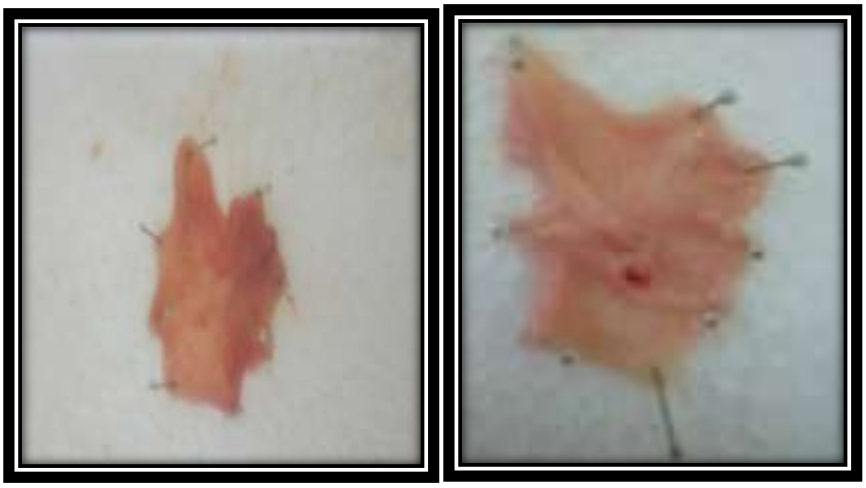

(C) (D)

Fig. No.12:(A) Ethanol treated group (B) Immediate gel formation group (C)Plain Pantoprazole sodium treated group (D) Pantoprazole sodium in situ gel treated group.

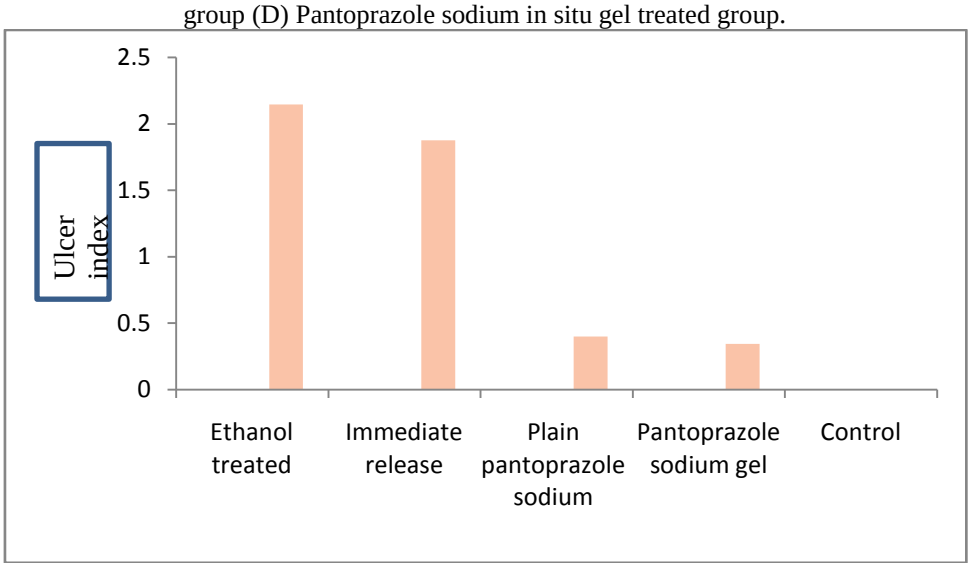

Fig. No.13: Ulcer index of alginate based in situ gel of pantoprazole sodium.

IV. CONCLUSION:-

Development of floating In-situ gel of Pantoprazole sodium drug delivery is a suitable drug delivery method to increase bioavailability and to provide prolonged release.floating In-situ gelformulation of FTIR studies concluded that there was no interaction between drug and excipients (sodium alginate, xanthan gum, calcium carbonate, sodium citrate).xanthan gumhas been used for extended drug release and Enhanced gastric retention times of the dosage form achieved a drug release in stomach.sodium alginate, calcium carbonate & sodium citrate used to gelling agent, gas generating agent & neutralizing agent respectively. Different formulations of floating In-situ gel of Pantoprazole sodium evaluation parameters results were observed F8 formulation was found to be the best formulation as it was provided slow release of Pantoprazole sodium over 8 hr and was considered as a good release (96.082).In vitro release rate studies showed that the maximum drug release was observed in F8 formulation up to 8 hours. in vivo study carried out by optimized formulations is F8 using Wistar rat & calculate the ulcer index.

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