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FORMULATION AND EVALUATION OF ION SENSITIVE FLOATING *IN SITU* GEL OF PANTOPRAZOLE FOR GASTRO RETENTIVE DELIVERY

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ABSTRACT

The main aim of this study was to formulate and evaluate the performances off loating *In situ* gel pantoprazole. Polymers such as sodium alginate and gellangum were used as gelling agents. Sodium citrate and calcium chloride were used for cross linking, whereas calcium carbonate was used as a floating agent. FTIR studies confirmed compatibility between drugs and polymers. The pH of the formulations ranged form of 6.9-7.3, the drug content was found to be between 75.36% to 87.69%, floating lag time was less than 1 min, and floating duration was more than 12h. It was observed that the concentration of polymers increased gelling ability, viscosity, gel strength, and water absorption by the gel. *In vitro* drug release showed results in the range of 77.80% to 87.12%, at 12 h for all the formulations. The release of the drug was found to decrease with a rise in the concentration of the polymer. All the formulations followed Zero Order kinetics. The drug release mechanism followed the Higuchi diffusion model based on the values of the regression coefficient. Thus an oral *In situ* floating gelling systems of pantoprazole reduce dosing frequency and enhance the residence time of the drug in the stomach.

Keywords: *In situ*, Floating, Pantoprazole, Gelling capacity, Gastroretentive

Introduction

Among all the routes of administration, the oral route is the most preferred and predominant route for delivery. However, physiological variations such as gastric residence time and gastrointestinal transit variability act as a limiting factor in the overall transit of the dosage form. To overcome these limitations, attempts are made to develop a drug delivery system that remains in the stomach for prolonged as well as a predictable time. Gastro retentive dosage forms are formulations that serves the above purpose. The gastroretentive *in situ* gels are a unit system that enables sustained delivery of the drug at the absorption site (Pande *et al*., 2013) Pantoprazole is a proton pump inhibitor used for the treatment of gastric ulcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis (Chaniyra *et al*., 2013). The oral dosage formulations of pantoprazole are mainly available as a tablet and have disadvantages such as low bioavailability, repeated dosing regime, and limited biological half-life. resulting in poor patient compliance and increased risk of missing the dose. Thus there is a need to formulate a gastro retentive gel of pantoprazole which gives sustained drug release and also increases bioavailability (Kushal *et al*., 2013).

Materials and Methods

Materials

Pantoprazole was procured from Himalaya parenteral and formulation Pvt. Ltd Nepal. Sodium Citrate, Calcium carbonate, Concentrated Hydrochloric acid was obtained Loba Chemie Pvt. Ltd Mumbai. Sodium Alginate and Sodium saccharin was procured from Nice Chemicals Pvt. Ltd. Kochi. Gellan Gum and HPMC K100M were obtained from Yarrow Chem Products Mumbai and Deionised water from BN Laboratories Mangalore.

Methods

Preparation of pantoprazole incorporated *in situ* gelling solution

Different concentrations of polymers were done by adding the polymer to deionized water containing sodium citrate and stirred continuously with heating up to 90°C. To the polymer solution, then pantoprazole was dissolved with HPMC and calcium carbonate. Sucrose was added in 20 ml of distilled water along with preservative methyl and propylparaben and then added to the gelling solution with continuous stirring. The composition showed in table 1.

Table 1: Composition of various formulations of *in situ* gelling solution with drug after optimization

Ingredients (%w/v)	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Pantoprazole	1	1	1	1	1	1	1	1
Gellan gum	0.30	0.40	0.50	0.60	-	-	-	-
Sodium alginate	-	-	-	-	0.50	0.75	1.0	1.25
HPMC K100M	0.4	0.5	0.6	0.4	0.5	0.6	0.4	0.5
Calcium carbonate	1	1	1	1	1	1	1	1
Sodium citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Methyl paraben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Saccharin sodium	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Deionized water (ml)	100	100	100	100	100	100	100	100

Evaluation of *in situ* gelling solutions of pantoprazole

Determination of visual appearance

The general appearance is one of the most important characteristic features of the formulation. The developed formulations were visually checked for the appearance of the color, clarity, and consistency of the formulation (Panwar *et al*., 2014).

pH measurement

pH was determined using a digital pH meter at room temperature

***In vitro* gelation study**

5 ml of the gelation solution (0.1N HCl, pH 1.2) was poured into a 10 ml borosilicate glass test tube at 37±10C to assess the in vitro gelling potential. Then with the aid of a pipette1 ml of formulation solution was added., when the formulation is contacted with the gelation medium, it instantly converts into a stiff gel. Depending on the stiffness of gel and duration for which gel remains, the gelling capacity was evaluated. The *in vitro* gelling capacity was categorized as follows.

(+) Gels and disperses rapidly

(++) Immediate gelation and remains upto 12 h

(+++) Immediate gelation remains for more than 12 h (Parthiban *et al*., 2013).

Determination of viscosity

Viscosities of the formulations were determined using Brookfield Digital Viscometer RVDV- II+ Pro at 50 rpm using S21 Spindle. The viscosity measurement was done six times using a fresh sample each time, and average readings were noted (Pandya, 2013).

***In vitro* floating study**

Initially *In situ* gelling solution of 10 ml was incorporated into the dissolution vessel that contains 0.1N HCl, pH 1.2 as the dissolution medium at 37± 0.5 ºC. The timerequired for the gel to float on the surface of the medium and the period for which it continuously remained buoyant was determined (Patel, 2010).

Drug content

For drug content determination 100 ml of *in situ* solutions were taken in a volumetric flask to which 50ml of 0.1N HCl was added. The mixture was agitated for 30min followed by sonication for 15 min, filtered and suitably diluted, and analyzed using a UV Visible Spectrophotometer at 287 nm (Jayswal, 2010).

Measurement of water uptake by the gel

For this study, the *in situ* gel formed in 40 ml of 0.1N HCl, pH 1.2 was used. From each formulation, the gel was taken out and blotted out with a filter paper to remove the excess buffer. The initial weight of the gel was noted, and 10 ml of distilled water was added to this gel. The water was decanted after every 30 minutes, and the gel weight was determined. The difference in the initial and final weight was noted to measure the water uptake (Hallur *et al*., 2013).

Measurement of Density of the gel

The density of the floating solution was determined by using the water displacement method in method. 10 ml of *in situ* gelling solutions werepoured into a beaker having 50 ml of 0.1N HCl. The gel was transferred into a measuring cylinder and allowed to sediment. The volume of the gel was noted as well as the volume without gel. The difference between both was determined. The method was repeated for all the formulation (Parekh *et al*., 2013)

Measurement of gel strength

A sample of 30 g of the gel was taken in a 50 ml beaker. Then the 50 g weight was placed on the center of the surface of the gel, and it was allowed to penetrate the gel. The time taken by the 50 g weight to sink 5 cm through the prepared gel was noted for all the formulations. The same procedure was repeated six times for each fresh formulation and the average time was reported (Gulecha *et al*., 2012).

***In vitro* drug release study**

The drug release from the formulations was assessed using a USP dissolution test apparatus (type II), with a paddle stirrer at 50 rpm. The dissolution medium used was 500 ml of simulated gastric fluid at 37 ±0.5 ºC. 10 ml of the formulation was added into the dissolution vessel comprising the dissolution medium forming *in situ* gel., 5 ml of the sample was withdrawn and replaced with fresh medium at each time interval. The collected sample was filtered, suitably diluted and then subjected for analysis. The absorbance of the drug from the taken samples was measured at 287 nm using UV Spectrophotometer. The study was conducted in triplicates (Parthiban *et al*., 2013)

Kinetic analysis

Cumulative drug release at different time intervals was fitted to various models, and the correlation coefficient (R^2), and release constant were calculated.

***In vivo* fluorescence imaging studies**

Healthy mice of either sex were used for in vivo study. The mice were fasted for 24 hr before administration of the formulation but were allowed free access to water. 0.2-0.4 ml of the optimized formulation containing 70.94-94.6 mg sodium fluorescein calculated based on body weight was orally administered to the mice, and fluorescence images were recorded at 535 nm at 1hr time interval for 6-8 hours (Vipul *et al*., 2013).

Stability studies

Selected formulations were filled in a suitable glass container and well stoppered with cap. Then were stored at 4 ± 1 ºC and at ambient temperature for 8 weeks. These were evaluated periodically for visual appearance, pH, drug content and floating behaviour (Mahagen, 2014).

Results and Discussion

Preparation of in situ gelling solutions of pantoprazole

The pantoprazole incorporated *in situ* gelling solution as per the procedure specified in the methodology section. The eight formulations containing various combinations of polymer were prepared using sodium citrate as cross linking agent, calcium carbonate as floating agent the preservatives such as methyl and propyl paraben. All the *in situ* gel-forming formulations were of good appearance and easily pourable.

Evaluation of *in situ* gelling solutions of pantoprazole

Determination of visual appearance

The visual appearance of the formulation is an important parameter for oral delivery as it affects patient compliance. All the formulations were subjected to visual appearance. The results are depicted in Table 2 showed off white to a pale yellow colored solution. The solutions were free running and did not produce any gelation at room temperature.

Table 2: Appearance, pH, and gelling capacity of *in situ* gel-forming solution

Formulation code	Appearance	pH*	Gelling Capacity
FA1	Pale yellow	7.3 ± 0.15	++
FA2	Pale yellow	7.3 ± 0.09	++
FA3	Pale yellow	7.5 ± 0.12	++
FA4	Pale yellow	7.2 ± 0.02	++
FA5	Off white	7.1 ± 0.01	+++
FA6	Off white	6.9 ± 0.28	+++
FA7	Off white	7.2 ± 0.02	++
FA8	Off white	7.0 ± 0.021	++

pH

The pH was in the range of 6.9 to 7.5 as tabulated in Table 2. The obtained pH was in the orally acceptable range, and hence it didn't cause any irritation after administration.

***In vitro* gelation study**

Characteristics of the formulation gelation capacityare shown in Table 2. All the formulation had undergone sol to gel transition upon contact with gelation media. Sol to gel transformation occurred with the help of gel-forming polymers used like gellan gum and sodium alginate. The *in situ* released calcium ion from calcium chloride gets entrapped in polymeric chains, thereby causing cross-linking of polymer chains to form a gel matrix. Hence the stiff gel in a short time was formed by the formulation containing a low concentration of gellan gum and a high concentration of sodium alginate.

Viscosity

Results of the viscosity measurement of all formulations are tabulated in Table 3.5 and graphically represented in Fig 1. The order of obtained viscosity of the formulations are F1 – F8 are FA8 >FA7 > FA6 > FA5 > FA4 > FA3 > FA2 > FA1. An increase in viscosity with an increase in the concentration of polymer can be attributed to the increased cross-linking of the gelling polymer. The results showed a marked rise in viscosity with the increase in the concentration of gellan gum compared to the concentration of sodium alginate.

Table 3: Data of floating lag time, floating duration and percentage drug content estimation of *in situ* gel formulation

Formulation	Floating lag time (sec)	Floating duration (h)	Percentage Drug content(%)
F1	25 ± 0.8	12	81.0 ± 0.05
F2	22 ± 1.2	12	80.8 ± 0.09
F3	20 ± 0.9	12	82.0 ± 0.15
F4	18 ± 1.4	13	81.6 ± 0.20
F5	12 ± 0.5	14	87.0 ± 0.18
F6	10 ± 1.8	15	86.1 ± 0.09
F7	11 ± 1.4	15	85.0 ± 0.07
F8	15 ± 2.1	16	84.0 ± 0.15

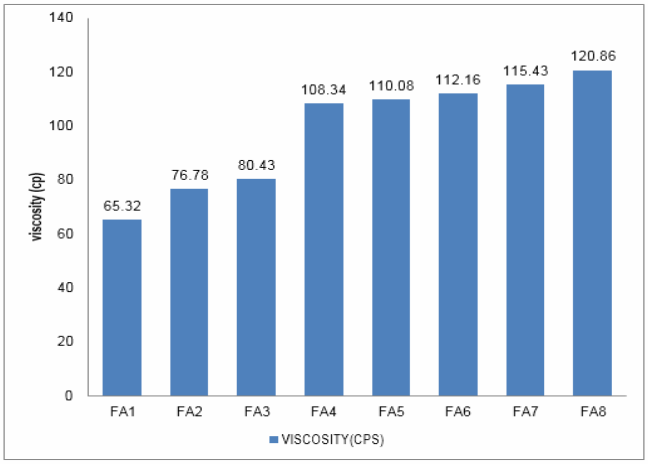

Fig. 1: Graphical representation of viscosity of *in situ* gel-forming solution

In vitro floating study

As shown in Table 3, the floating lag time of all the formulation was found to be lesser than 1 min, and the floating duration was more than 12 h. As the formulation came in contact with an acidic environment, gelation and cross linking of calcium ions took place, which in turn results in the gel. The released CO_2 gets entrapped in the gel matrix producing buoyant formulation. Then polymeric network restricts diffusion of carbon dioxide and drug molecules extending the floating duration and drug release respectively.

Drug content

In all the formulation the drug content was in the range of 80.80% to 87.0% which shows that drug is uniformly distributed in the formulation.

Water uptake by the gel

The water uptake of various formulations was shown in Table 4. The formulation FA5 has shown a better water uptake of 12.90% in comparison to other formulations within 2 h. The highest water uptake of FA5 may be due to the highest swelling capacity of polymer. as the polymer concentration increases, water uptake by gel also increased.

Table 4: Data of water uptake by the *in situ* gel formulation

Time (min)	% Water uptake by the gel*							
	F1	F2	F3	F4	F5	F6	F7	F8
30	2.67±0.08	3.25±0.21	4.10±0.3	4.25±0.2	5.21±0.23	5.33±0.31	5.57±0.12	6.25±0.08
60	2.98±0.14	3.89±0.07	4.56±0.2	4.68±0.1	6.45±0.16	7.24±0.24	8.25±0.31	8.67±0.27
90	3.02±0.09	4.21±0.11	5.02±0.2	5.40±0.1	10.02±0.16	10.18±0.22	10.29±0.13	10.45±0.11
120	4.21±0.21	5.12±0.23	5.78±0.2	6.10±0.2	12.90±0.26	12.08±0.09	12.34±0.08	12.42±0.07

Measurement of density of the gel

For *in situ* gel to float, the formulation must have a density less than or equal to gastric contents (~1.004 gcm^{-3}). The density of all the formulations (Table 5) was lesser than the above-specified value. Hence promotes the floating of *in situ* gel in the stomach.

Measurement of gel strength

Good gel strength was observed in all formulations which are very low as 12.6 sec for FA1 and higher values of 75.2 sec for FA5(table 5), which has a higher concentration of gellan gum. The excellent gel strength indicates that the ability of the formulation to withstand the peristaltic movement *in-vivo*.

Table 5 : Data for density and gel strength of formulated *in situ* gel

Formulation code	Density (g/ cm^3)	Gel strength (sec)
FA1	0.425 ± 0.24	12.6 ± 0.15
FA2	0.453 ± 0.09	24.0 ± 0.18
FA3	0.481 ± 0.18	31.0 ± 0.21
FA4	0.510 ± 0.15	36.6 ± 0.14
FA5	0.635 ± 0.11	71.5 ± 0.25
FA6	0.243 ± 0.19	72.6 ± 0.07
FA7	0.294 ± 0.07	75.2 ± 0.12
FA8	0.327 ± 0.09	78.52 ± 0.05

In vitro drug release study

From dissolution studies, it was confirmed that the release rate of the drug from in situ gel prepared from different gelling and matrix-forming polymers in different concentrations varied as follows With gellan gum FA5 > FA6 > FA7 > FA8 and with sodium alginate, FA1 > FA2 > FA3 > FA4. As shown in Fig 2, the cumulative percentage drug release from formulations FA1, FA2, FA3, and FA4 containing different concentrations of sodium alginate at 12 h was 81.23%, 79.12%, 80.44%, 77.74%, and 75.06% respectively. Fig 3 shows the cumulative drug release of FA5, FA6, FA7, and FA8 containing different concentrations of gellan gum at the end of 12 h was found to be 87.64%, 85.65% and 82.35%, 80.35%, respectively. The release decreased with an increase in gellangum and sodium alginate concentration. A significant decrease in drug release was observed with the increase in the polymer concentration. This can be attributed to the increase in the diffusional path length and density of the polymer matrix. The release pattern showed an initial burst release followed by moderate release. The burst effect helps to improve the pantoprazole concentration immediately after the oral administration of the formulation. The burst effect was reduced with an increase in polymer concentration. Among formulations FA1 to FA8,

FA5 showed the maximum and FA4 showed minimum drug release. On the basis of all the evaluated parameters of *in situ* gelling solution and *in situ* formed gel compared to all other formulation FA5 is considered as better which showed sustained drug release over a period of 12 h. Hence FA5 was subjected to the stability study.

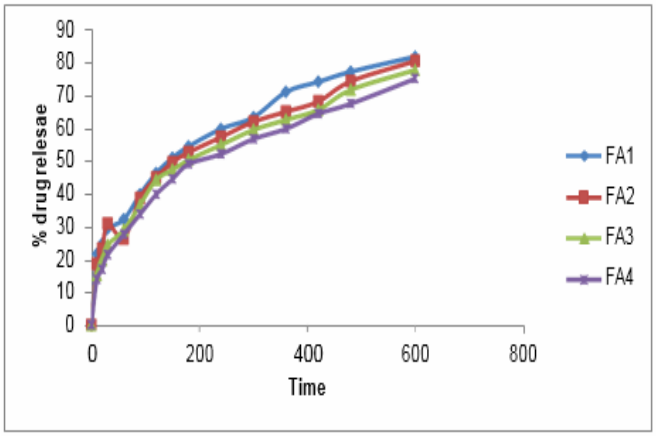

Fig. 2: *In vitro* release profile of pantoprazole *in situ* gels containing different concentration of sodium alginate

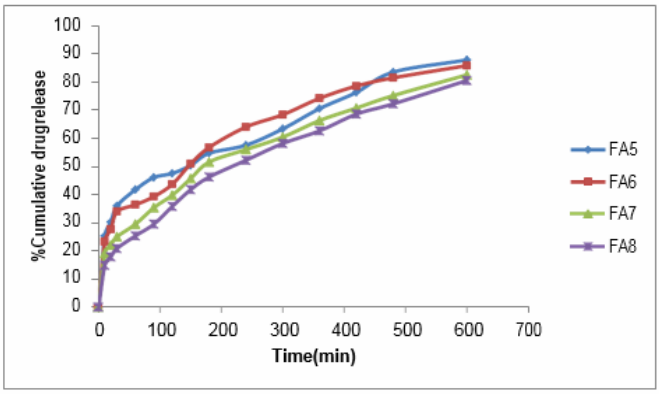

Fig. 3: In vitro release profile of pantoprazole *in situ* gels containing different concentration of gellan gum

Kinetic analysis

All the formulation in this study followed Higuchi"s model (Table 6), as the plots showed regression coefficients (R^2) of 0.9908 to 0.9974. This is indicated that the release process was diffusion controlled. In the above kinetic study, the "n" value obtained from Korsmeyer–Peppas model was between 0.34to 0.4289, suggested that the drug-releasing mechanism was Non-Fickian diffusion (anomalous transport).

Table 6: Data of drug release kinetics study of *in situ* gel

Formulation	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Korsemeyerpeppas model (R^2)	'n' Values for peppas model
FA1	0.9242	0.6189	0.9925	0.9785	0.3464
FA2	0.8972	0.607	0.9770	0.9670	0.3573
FA3	0.9044	0.6715	0.9971	0.9812	0.4003
FA4	0.9120	0.7241	0.9974	0.9881	0.4263
FA5	0.9008	0.5832	0.9887	0.9305	0.2825
FA6	0.9433	0.6182	0.9848	0.9681	0.3296
FA7	0.9536	0.7425	0.9908	0.9863	0.3713
FA8	0.9671	0.8305	0.9957	0.9917	0.4289

In vivo fluorescence imaging studies

The fluorescence images (Fig 4) taken after the administration of formulation FA5 show the gel's presence at 1, 2, 3, 4, 5, and 6 h. Even after 6h the presence of the gel in the stomach of the mice can be observed. This confirms that the *in situ* gelling formulation is successful in gastro retention beyond 6 h.

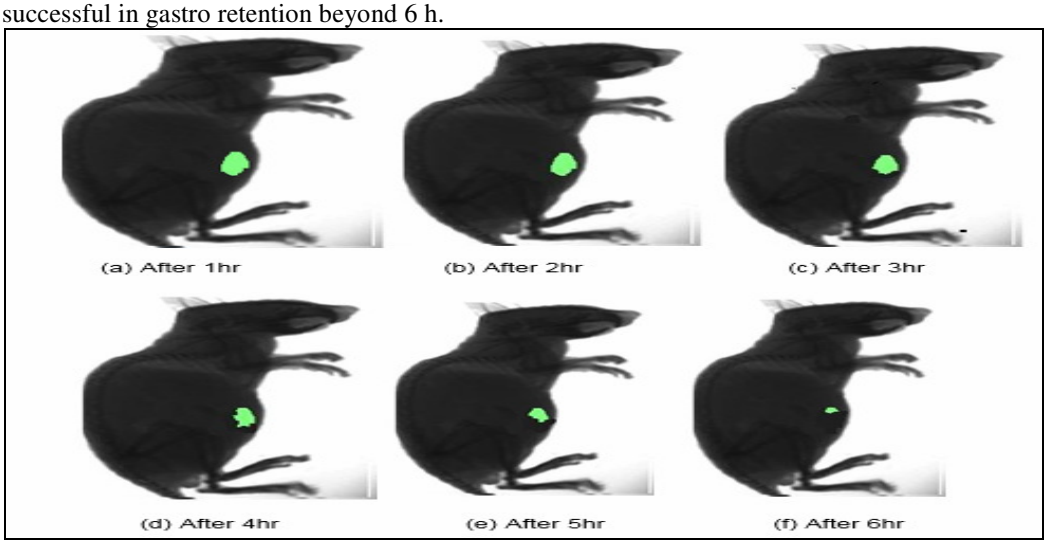

Fig. 4: Fluorescence images of the mice taken after administration of time FA5 at various time intervals

Stability studies

Based on the result obtained from the evaluated parameter FA5 was considered to be the better formulation compared to the other formulations as it showed good pH, low viscosity, good floating behavior, and sustained release of the drug. Therefore the selected formulation FA5 was subjected to stability studies under the conditions specified in the methodology, checked for changes in visual appearance, floating lag time, drug content, and drug release study. From the result obtained shown in Table 6, there was no marked differences in the appearance, floating behavior, drug content, and drug release from initial values, indicating that the formulations were stable for 8 weeks.

Conclusion

Formulations m*et a*l requirements to become an floating *in situ* gel system. The formulations instantaneously gelled and floated in the pH conditions of the stomach. Hence stomach specific *in situ* forming gel of pantoprazole was prepared as an effective formulation showing improved prolonged-release and gastro retention.

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