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Optimization and Evaluation of Famotidine formulations for the treatment of Gastric Ulcer

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ABSTRACT

Aim of the present study was to optimize and evaluate Famotidine formulations, Floating tablet and in-situ gel. Low density HPMC E-15 LV, Carbopol- 934, Sodium bicarbonate and Citric acid were used for the formulation of floating tablet. For the formulation of in-situ gel Gellan gum, Calcium carbonate and Sodium citrate were used. Floating tablet and in-situ gel are compared for in-vitro evaluation for the batter treatment of Gastric Ulcer.

Key Words *- Floating in-situ Gel, Control Release, Floating tablet, Ulcer.*

INTRODUCTION

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. Amongst the extensive researchhas 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[1,2,3].

Famotidine is a histamine H_2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration, the dose is 40 mg daily by mouth at bedtime, for 4 to 8 weeks. In gastroesophageal reflux disease the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; where gastroesophageal reflux disease is associated with esophageal ulceration, the recommended dosage is 40 mg twice daily for a similar period[4,5].. For the short term, symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested.In the Zollinger-Ellision syndrome the initial dose by mouth is 20 mg every six hrs, increased as necessary; dose up to 80

mg daily have been employed [2,6]. Its low bioavailability (40-45%) and short biological half-life (2.5-4.0 hrs) following oral administration favours development of a sustained release formulation. Famotidine is fourth generation selective histamine H_2 blocker, several times more potent than ranitidine and particularly more potent than cimetidine. The active ingredient in Famotidine, USP is a histamine H2 receptor antagonist[3,7].

These *in situ* gelling systems consist of polymer that exhibit sol-to-gel phase transitions due to change in specific physicochemical parameters (pH, Temperature, ionic strength) in the environment. The sol-to-gel phase transition depending on the different methods employed and they are: pH-triggered system (eg.Cellulose acetate hydrogen phthalate latex), temperature dependent system (eg.Pluronics and tetronics) and ion activated system (eg.Gelrite)[8,9].

MATERIALS AND METHODS

Materials

Famotidine was obtained as gift sample fromDr. Reddy's Laboratory, Hyderabad.

Preparation and optimization of *in-situ* gel

Gellan gum solutions of concentrations 0.25 and 0.50 % (w/v) were prepared by adding the Gellan gum to ultra pure water containing 0.1%, 0.2% (w/v) sodium citrate and 0.01%, 0.02% (w/v) calcium carbonate and heating to 60 °C while stirring. Famotidine was then dissolved in 10 ml of 0.1N Hydrochloric acid solution (pH 1.2) and added in the resulting solution after cooling to below 40 °C. The solution was neutralized by 0.1N sodium hydroxide. A 1%, (w/v) control solution (for use in the *in-vitro* release experiments) was prepared by dissolving Famotidine in a 0.6% (w/v) aqueous solution of Gellan gum. A 1% (w/v) solution of Famotidine was prepared in ultra pure water. The resulting Gellan gum*in-situ* gel solution containing Famotidine was checked for viscosity and gelling property (Figure 1) and finally stored in amber color narrow mouth bottles until further use. In the preliminary trial batches GF-1 to GF-12 concentration of Calcium carbonate and Sodium citrate were kept constant at 0.02% and 0.2% w/v respectively. In factorial design batches G1 to G8 concentration of Gellan gum, Sodium citrate , Calcium carbonate was utilized to evaluate the responses.[8]

Preparation and optimization of *Floating tablet*

Floating tablet were prepared by Wet-granulation method. Famotidine (40 mg) was mixed with the specified quantities of HPMC E-15, Sodium bicarbonate, carbopol and citric acid by continuous mixing in a pestle mortar then 2% binder solution of PVP K-30 in isopropyl alcohol was added and stirred until IPA was evaporated to form a wet mass. Granules were obtained by passing through the sieve no 16. Granules were dried in oven at 30°C. The granules was passed though sieve no. 22. Then magnesium stearate and Talc was added in 1% w/w concentration then granules were compressed to form a tablet.

Evaluation

(i) Drug Release

Formulations were analysed for in vitro drug release,as the results showed that the gelling agent concentration is when increased the decrease in the rate and extent of drug release was observed and attributed to increase in density of the polymer matrix.

The release of the drug from in situ gel was characterized by initial phase of high release (Burst release) the remaining drug was released at a slow rate followed by a second phase of moderate release.The biphasic pattern of releaseis characteristic feature of matrix diffusion kinetics.[10]

The burst release was reduced with increasing concentration of Gellan gum. In absence of ca^{++} ion gelation is weak hence release rate was high. The drug release profile was compared between control formulations.

The drug release from the floating tablet was determined using USP 24 Dissolution apparatus 2 the formulation F8 showed the 92% release at 6 Hrs. in 0.1 N HCl.

Table No. 1 Formulation batches from F1 to F12 of Floating tablet

S. No.	Formulation Code	HPMC E-15 (mg)	Carbopol (mg)	$NaHCO_3$ (mg)	Citric acid (mg)
1	F1	20	10	10	20
2	F2	30	20	10	30
3	F3	30	40	20	30
4	F4	40	40	30	30
5	F5	80	40	30	50
6	F6	100	50	30	60
7	F7	140	80	40	60
8	F8	160	80	30	60
9	F9	85	40	30	50
10	F10	90	40	30	50
11	F11	95	40	30	50
12	F12	110	40	30	50

Table No. 2 Formulation batches from G1 to G8 of in-situ gel

Formulation Code	Concentration of Gellan Gum	Concentration of Calcium Chloride	Concentration of Sodium citrate
G1	0.25 %	0.02 %	0.1%
G2	0.50 %	0.02 %	0.2%
G3	0.25 %	0.01 %	0.1%
G4	0.50 %	0.02 %	0.1%
G5	0.25 %	0.02 %	0.2%
G6	0.50 %	0.01 %	0.1%
G7	0.50 %	0.01 %	0.2%
G8	0.25 %	0.01 %	0.2%

Table No. 3 % release of in-situ gel

Formulation Code	% release gel
G1	94.02
G2	72.83
G3	85.34
G4	79.88
G5	98.49
G6	74.84
G7	72.02
G8	88.29

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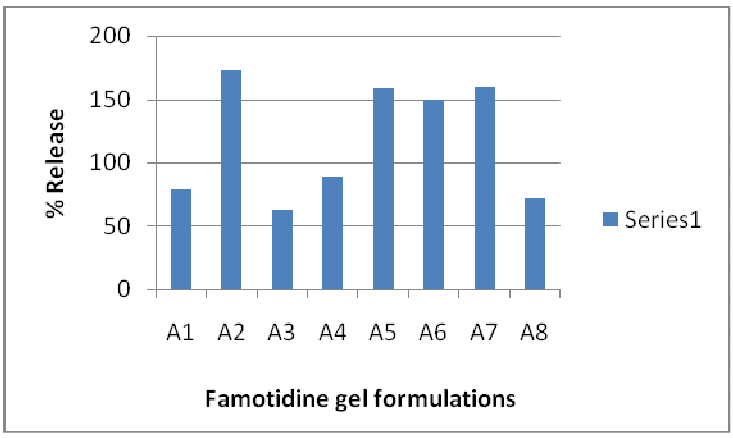

Figure No. 1 % release profile of Famotidine *in-situ* gel

Table No. 4 % release of Floating Tablet

Formulation Code	% release Tablet
F1	94.02
F2	72.83
F3	85.34
F4	79.88
F5	98.49
F6	74.84
F7	72.02
F8	95%
F9	83.02%
F10	56.80%
F11	73.06%
F12	83.02%

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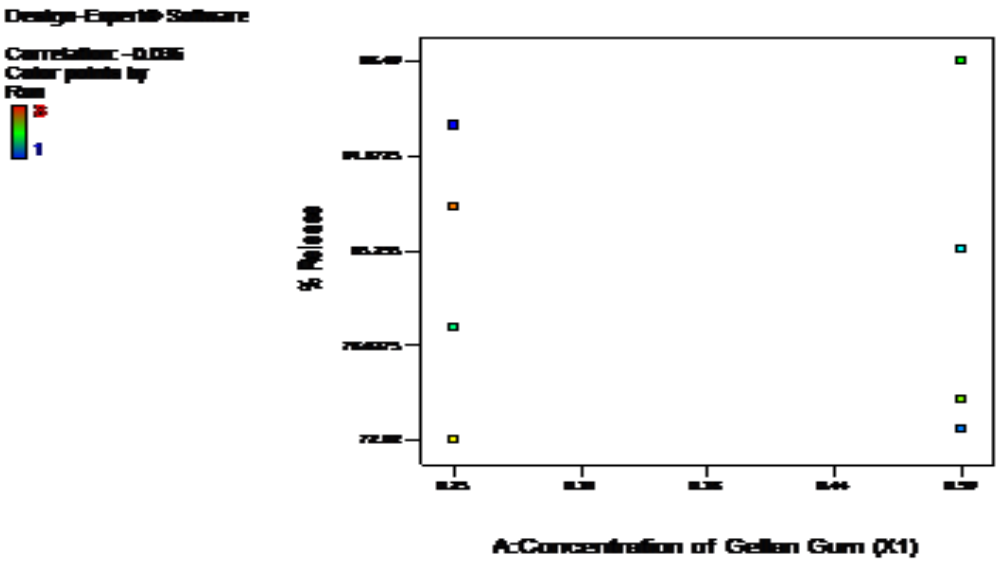

Figure No. 2 % Release of in-situ gel Formulation

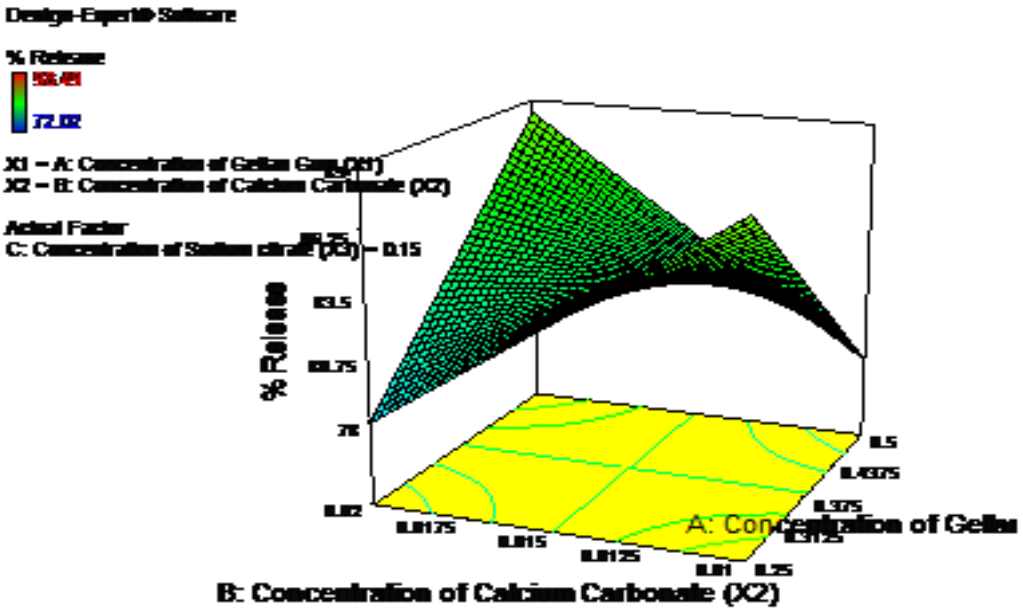

Figure No. 3 % Release of in-situ gel Formulation

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(ii) Measurement of Floating ability –

The formulations of Famotidine in-situ gel are Evaluated for Floating lag time and Floating time in 0.1 N HCl the results are shown in table. The Floating ability of the prepared formulations was evaluated in simulated Gastric Fluid. In the formulations cation induced gelation is occurred for the gelling of formulation in cation induced gelation the $Caco_3$ releases the Ca^{++} into the solution when the solution comes in contact with acidic media, The Ca^{++} forms a double helical junction with gelling agent and these double helical junction joint to form a complex that is gel. As the results showed that the optimum concentration of gelling agent with $CaCo_3$ provides the best gelling solution. If the concentration of gelling agent is low the gelation is not properly occurs and the resultant gel was loose in nature if the concentration is high the resultant gel become very tight or rigid in nature[9,11].

The Floating time of Floating tablets dependent on the Ratio of Calcium carbonate, Citric acid and HPMC if the concentration of HPMC is higher than the limit the floating time decreases and the ratio of Calcium carbonate and citric acid helps in floating by generating CO_2[9,12,13].

Table No. 5 Floating time of *in-situ g*el

Formulation	Floating time (in Hrs.)
G1	6
G2	10
G3	8
G4	8
G5	10
G6	7.5
G7	10
G8	9

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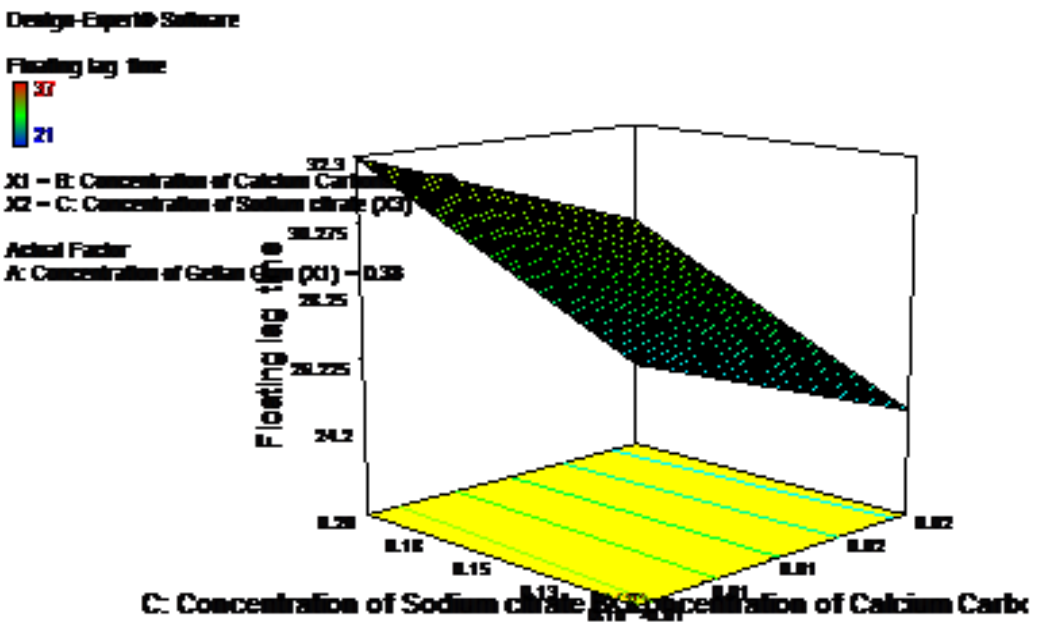

Figure No. 3 Floating time in gel formulation

Table No.6 Floating time in floating tablets

Formulation Code	**Floating time In min.**
F1	0
F2	0
F3	0
F4	20
F5	150
F6	325
F7	450
F8	480
F9	380
F10	320
F11	280
F12	220

CONCLUSION

The results revealed that Among the Dosage form of the Famotidine the floating tablet and in-situ gel the results revealed that the in-situ gel formulations are having batter results then Floating tablets. *in-situ* gel are more patient convenient in comparison to tablets .The in-situ gel are having results of floating time up to 8 Hrs and floating tablets up to 6 Hrs. the Formulation G8 of in-situ gel and F8 are the best formulations among the all prepared formulations. If the concentration of gelling agent is low the gelation is not properly occurs and the resultant gel was loose in nature if the concentration is high the resultant gel become very tight or rigid in nature[14]. When the concentration of $CaCo_3$ is less the viscosity of the formulation is also less and it forms a week gel which is removed easily from the stomach by peristaltic movement or having shorter gastric residence time. When the concentration of $CaCo_3$ is high the viscosity is increased and it forms a rigid gel with short gelation time or having good residence time.Result showed that the optimum concentration of Sodium alginate and $CaCo_3$ in adequate gel strength such vehicle will have a longer residence time and free flowing characteristics.

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