ORIGINAL ARTICLE

Enrichment of anti-ulcer activity of monoammonium glycerrhizin and *Aloe vera* gel powder through a novel drug delivery system

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Usual treatment for *Helicobacter pylori*-induced peptic ulcer includes a 14-day "triple therapy" of two antibiotics and a proton pump inhibitor. However, the current therapy has side-effects like stomach upset, non-compliance, incomplete absorption of drug and antibiotic resistance. To overcome these limitations, there is a need to suggest an alternative therapy. The best possible alternative is to deliver herbal constituents. The purpose of the present study was to optimize the efficacy of herbal constituents by applying the concept of a novel drug delivery system. The present investigation is designed to deliver and retain two herbal constituents in the stomach for better action against gastric ulcers. The objective was to develop a bilayer floating tablet of monoammonium glycerrhizin and *Aloe vera* gel powder through rational combination of excipients to give the lowest possible lag time with maximum drug release in 7 h. Formulation OF2 containing hydroxy propyl methyl cellulose E5, crospovidone and effervescent agents in the ratio 1:2 gave 98% drug release with desired floating properties. Pharmacodynamic studies in rats showed that the combination of monoammonium glycerrhizin and *Aloe vera* gave 99% ulcer inhibition in comparison with 51% ulcer inhibition in the group administered with monoammonium glycerrhizin alone. X-ray studies in rabbits proved the gastroretention of the tablet for more than 6 h. This suggests relevance of NDDS in delivery of herbal constituents in the treatment of gastric ulcer.

Key words: *Aloe vera, floating tablet, gastric ulcer, monoammonium glycerrhizin, pharmacodynamic studies*

INTRODUCTION

Usual treatment for *Helicobacter pylori*-induced peptic ulcer includes a 14-day "triple therapy" of two antibiotics and a proton pump inhibitor. However, the current therapy has side-effects like stomach upset, nausea, non-compliance, incomplete absorption of drug and antibiotic resistance. To overcome these limitations in the existing therapy, there is a need to suggest an alternative therapy. The best possible alternative is to deliver herbal constituents.[1]

In the alternative system of medicine, Ayurveda drug delivery of herbal constituents is through conventional dosage forms and as polyherbal formulations. As a result, drug efficacy cannot be optimized to the maximum extent.

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The purpose of the present study was to optimize the efficacy of herbal constituents by applying the concept of a novel drug delivery system (NDDS).[2]

The present investigation is designed to deliver and retain two herbal constituents in the stomach for better action against gastric ulcers caused by *H. pylori.* For this purpose, two isolated herbal constituents - glycyrrhizin and *Aloe vera* powder- were selected.

Glycyrrhizin is a triterpene saponin isolated from liquorice.The monoammonium salt of glycyrrhizin was selected due to its high acid solubility. Monoammonium glycyrrhizin is a yellow to buff colored powder with a sweet taste, is odorless and has a melting range of

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DOI: 10.4103/0973-8398.143932

209-212°C. It has high solubility in acidic pH and is slightly soluble in water. It is known for its anti-inflammatory, anti-bacterial and anti-ulcer activities. This glycyrrhizin gets converted to aglycone glycyrrhetic acid by bacteria present in the stomach, and this glycyrrhetic acid is responsible for the various effects of liquorice. The anti-ulcer activity of liquorice is found to be due to an increase in the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach. It also extends the life span of the surface cells in the stomach and has an anti-pepsin effect.[3,4] It has also been reported that *H.pylori* shows susceptibility to liquorice extract.[5]

Aloe vera gel showed inhibition of gastric acid secretions by direct interaction with the acid-producing cells or possible interaction with H_2 receptors on the parietal cells.The antiulcer activity is due to its anti-inflammatory, cytoprotective, healing and mucus-stimulatory effects.[6] The gastroprotective activity of *Aloe vera* at lower concentrations is due to the presence of lectins. Lectins are proteins/glycoproteins capable of binding to carbohydrate moieties.[7]

The objective was to develop a bilayer floating tablet for monoammonium glycerrhizin and *Aloe vera* gel powder through rational combination of excipients to give the lowest possible lag time with maximum drug release in the period of 7 h.

MATERIALS AND METHODS

Monoammonium glycerrhizin in the powder form with 95% purity was purchased from Yucca Enterprises, Mumbai, India. *Aloe vera* gel powder of pharmaceutical grade and hydroxy propyl methyl cellulose (HPMC) wereobtained as a gift sample from Maple Biotech, Pune, India and Colorcon Asia Pvt. Ltd., Goa, India respectively. All other chemicals and reagents used were of analytical grade.

Animals

Experimental procedures in this investigation were carried out using healthy Wistar albino male rats weighing approximately 200-250 g and New Zealand albino male rabbits weighing 1.5-2 kg. All these procedures were reviewed and approved by the Institutional Animal Ethics Committee (IAEC) constituted under the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA) (Protocol Approval No. IAEC/2012-13/39 dated 28/12/12).

Method

Preliminary batches for selection of HPMC grade

Preliminary batches for selection of HPMC grade were prepared as per the composition shown in Table 1. Formulations F1, F2, F3, F4 and F5 represent various grades of HPMC, *viz*. HPMC K4M, K15M, K100M, E5 and E15, respectively.

Table 1: Composition of the preliminary batches

Ingredient (mg per tablet)	F1	F2	F3	F4	F5
First layer					
Monoammonium glycerrhizin	204	204	204	204	204
HPMC	100	100	100	100	100
$NaHCO_3$	60	60	60	60	60
Citric acid	30	30	30	30	30
Avicel PH (102)	18	18	18	18	18
Magnesium stearate	3	3	3	3	3
Talc	2	2	2	2	2
Second layer					
Aloe vera gel powder	32	32	32	32	32
Avicel PH (102)	12	12	12	12	12
Talc	2	2	2	2	2
Color	q.s.	q.s.	q.s.	q.s.	q.s.
Total	463	463	463	463	463

HPMC: Hydroxy propyl methyl cellulose

Preparation of bilayer floating tablets

Monoammonium glycerrhizin, sodium bicarbonate ($NaHCO_3$), citric acid, Avicel PH 102 and HPMC were passed through # 40 and mixed in a planetary mixer (Gem Machinery Company, Mumbai, India) for 5 min. Magnesium stearate and talc were added to the above mixture and mixing was further continued. The final mixture was compressed on a multistation rotary tableting machine (Gem Machinery Company, India) at low pressure using a 9 mm punch. This formed the first layer of the bilayer tablet. *Aloe vera* gel powder previously mixed with Avicel PH 102 and talc was added on this first layer and compressed at high pressure to obtain a bilayer tablet.

Statistical optimization

To optimize the drug release from the tablets, a 3^2 full factorial design was applied. In this optimization technique, two factors were evaluated each at three levels and experiments were performed using all possible nine combinations.[8] In this research work, superdisintegrant crospovidone and HPMC E5 were selected as independent variables. Drug release was selected as the dependent variable [Table 2].

Evaluation of floating tablets

The prepared tablets were tested for hardness, thickness, weight variation, friability, content uniformity, floating lag time, total floating time, drug release studies and pharmacodynamic studies.

Content uniformity

Twenty tablets were crushed and powder equivalent to the weight of one tablet was dissolved in 0.1N hydrochloric acid. Further, suitable dilutions were made and absorbance was measured at 254 nm wavelength using a UV spectrophotometer (Model: 1800, Shimadzu, Japan).

Table 2: Optimization batches

Ingredient (mg per tablet)	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
First layer									
Monoammonium glycerrhizin	204	204	204	204	204	204	204	204	204
HPMC E5	10	10	10	20	20	20	30	30	30
$NaHCO_3$	60	60	60	60	60	60	60	60	60
Citric acid	30	30	30	30	30	30	30	30	30
Crospovidone	20	25	30	20	25	30	20	25	30
Avicel PH (102)	18	18	18	18	18	18	18	18	18
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Lactose	30	25	20	20	15	10	10	05	-
Second layer									
Aloe vera gel powder	32	32	32	32	32	32	32	32	32
Avicel PH (102)	12	12	12	12	12	12	12	12	12
Talc	2	2	2	2	2	2	2	2	2
Color	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	423	423	423	423	423	423	423	423	423

HPMC: Hydroxy propyl methyl cellulose

Floating lag time, total floating time determination and drug release studies

Floating lag time and total floating time were determined in a USP dissolution apparatus II (Electrolab, TDT-08L, Mumbai, India) simultaneously with drug release studies using 900 mL 0.1N hydrochloric acid maintained at 37 ± 0.5ºC and at 50 rpm. The time required for the tablet to rise to the surface and float was determined as the floating lag time. The total time for which the tablet floated in the dissolution medium, including the floating lag time, was recorded as the total floating time.[2] For drug release studies, 10 mL of the sample was withdrawn at 10, 20, 30, 60,120,180, 240, 300, 360 and 420 min and was replaced with an equal volume of dissolution medium. After suitable dilution, the amount of drug released was estimated by a UV spectrophotometric method at 254 nm.

Pharmacodynamic studies

A pharmacodynamic study for the duration of 1 day was carried out for the optimized formulation by the pylorus ligation-induced ulcer model. Five groups of Wistar rats (six in each group) were used for the study. Animals were fasted for 24 h before pylorus ligation but were allowed to have free access to water. Suspensions of clarithromycin, monoammonium glycerrhizin and bilayer tablet were prepared by mixing with 5% gum acacia. Clarithromycin was used as one of the groups as it is a part of the current triple therapy practiced for treating gastric ulcers caused by *H.pylori*.[1] The following groups of animals were considered for the study:

Group I : Normal control
Group II : Gastric ulcer control (vehicle solution without drug)
Group III: Standard clarithromycin (20 mg/kg)
Group IV: Pure monoammonium glycerrhizin (200mg/kg)
Group V : Bilayer tablet suspension of monoammonium glycerrhizin and *Aloe vera* (200 mg/kg and 5 mg/kg, respectively).

Thirty minutes after oral dosing, Wistar rats were anesthetized with ketamine (45 mg/kg) and pylorus was ligated. The stomach was then closed by interrupted sutures. After 5 h of ligation, all animals were sacrificed and their stomachs were removed, cut along the greater curvature and observed for ulcer. The numbers of ulcers were counted using a magnifying glass. The following arbitrary scoring system was used to grade the prevalence and severity of lesions: (i) Score 0 = no ulcer, (ii) score 10 = denuded epithelium, (iii) score 20 = petechial and flank hemorrhages, (iv) score 30 = one or two ulcers and (v) score 40 = multiple ulcers.The ulcer index (UI) and percent inhibition of ulceration were determined using the following formulae.[9]

$$UI = U_N + U_S + U_P \times 10^{-1} \quad (1)$$

where, U_N is the average of number of ulcers per animal, U_s is the mean severity of ulcer score and U_p is the percentage of animals with ulcer prevalence.

$$\% \text{ Inhibition of ulceration} = \frac{(\text{Ulcer index control} - \text{Ulcer index test}) \times 100}{\text{(Ulcer index control)}} \quad (2)$$

Histopathological evaluation

The stomach samples of all groups were preserved in 10% buffered formalin and processed for routine paraffin block preparation and stained with hematoxylin and eosin. Samples were examined under the microscope for histopathological changes such as degeneration, hemorrhage, edematous appearance, erosion and necrosis and compared with the histopathology of rat stomach of normal control.

In vivo experimental results were expressed as mean ± S.E.M. Data wereanalyzed by analysis of

variance (ANOVA) followed by Tukey's multiple comparison test, with the level of significance set at $P = 0.05$. All the *in vivo* experimental results were expressed as mean ± S.E.M. of six parallel measurements. $P < 0.05$ were considered significant.[10]

In vivo X-ray studies

To view the *in vivo* gastric retention and floating behavior of the tablet, X-ray studies were performed in rabbits. Inclusion of barium sulfate in the tablet was essential to make the tablet visible in the X-ray. For this purpose, half the drug was replaced with barium sulfate while keeping the other ingredients constant. After overnight fasting, three New Zealand albino rabbits were given low-calorie food and water. One hour later, the tablet was administered orally with 15 mL water. X-ray images were taken at 1, 4 and 6 h. One image of the empty stomach was also taken as control before administration of the tablet. The X-ray parameters were kept constant throughout the study.[11]

RESULTS

Evaluation of physical parameters

Results for weight variation were found to be within the limits prescribed by the Indian Pharmacopoeia (IP). Friability test of all formulations was also found to be within the USP limit, signifying enough resistance to the mechanical shock and abrasion. Hardness of the tablet was found to be between 6 and 7 kg/cm^2. Drug content uniformity for monoammonium glycerrhizin was found to be within the IP limits [Table 3].

Floating lag time and total floating time determination

Bilayer floating tablets were prepared with the aim of having maximum drug release in 7 h and with bare minimum floating lag time and good matrix integrity. Table 4 shows the results for floating lag time, total floating time and matrix integrity for formulations F1 to F5. The value of the floating lag time varied from 6 to 21 s. The total floating time ranged from 8 to 10 h.

Drug release studies

All the formulations showed drug release over a period of 7 h. It was observed that formulation F3 containing HPMC K100M showed the least release of 20% whereas formulation F4 containing HPMC E5 showed a better release of 60% [Table 5 and Figure 1]. This suggested a need to improve drug release through application of an optimization technique. Because F4 gave comparatively better drug release than the other formulations, it was decided to perform optimization on F4.

Statistical optimization

In the optimization technique used in this investigation, the effect of HPMC E5 and crospovidone was studied on drug release from the tablet using a 3^2 factorial design. The results of optimization for formulations OF1 to OF9 are shown in Tables 6 and 7 and Figures 2 and 3. Increasing the amount of crospovidone and lowering the amount of HPMC E5 increased the drug release significantly.

Table 4: Floating lag time, total floating time and matrix integrity of the preliminary formulations

Formulation code	Floating lag time (s)	Total floating time	Matrix integrity
F1	10±0.08	Upto 8 h	$^{++}$
F2	15±0.2	Upto 9 h	$^{++}$
F3	21±0.01	Upto 10 h	$^{+++}$
F4	6±0.1	Upto 8 h	$^{++}$
F5	12±0.05	Upto 9 h	$^{+++}$

Mean±S.D. (n=6), $^{+}$Fair, $^{++}$Good, $^{+++}$Excellent

Table 5: Drug release of the preliminary batches

Formulation code	Drug release (%)
F1	45±0.4
F2	36±0.6
F3	20±0.2
F4	61±0.4
F5	51±0.3

Mean±S.D. (n=6)

Table 6: Results of statistical optimization

Batch	HPMC E5 (X_1)	Crospovidone (X_2)	% drug release
OF1	−1	−1	90.27
OF2	−1	0	98.15
OF3	−1	+1	Tablet burst
OF4	0	−1	83.98
OF5	0	0	87.28
OF6	0	+1	89.37
OF7	+1	−1	78.17
OF8	+1	0	80.54
OF9	+1	+1	82.26

HPMC: Hydroxy propyl methyl cellulose

Table 3: Physical parameters of the preliminary formulations

Batch code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Uniformity of weight (mg)	Uniformity of content (%)
F1	5±0.05	6±0.01	0.06±0.02	422.9±0.1	99.6±0.1
F2	5±0.03	7±0.05	0.02±0.05	423.5±0.3	98.4±0.5
F3	5±0.02	6±0.02	0.07±0.07	423.0±0.6	99.2±0.8
F4	5±0.07	6±0.03	0.05±0.03	423.6±0.5	98.6±0.6
F5	5±0.06	6±0.06	0.06±0.02	422.4±0.8	98.1±0.1

Mean±S.D. (n=6)

Pharmacodynamicstudies

In vivo study in rats was carried out to confirm the effect of ammonium glycerrhizin and *Aloe vera* in combination for ulcer therapy and parameters estimated were UI and percent inhibition of ulceration. Results of Group II showed ulcers while results of Groups III, IV and V showed reduction in ulceration after 5 h of the treatment [Figure 4]. The values of UI and percent inhibition of ulceration are given in Table 8. The UI of GroupsII, III, IV and V were 14.6 ± 0.34, 8.7 ± 0.13, 5.13 ± 0.26 and 0.017 ± 0.11, respectively [Figure 5]. The percentinhibition of ulceration of Groups III, IV and V were 39.8 ± 0.16, 51.0 ± 0.5 and 99.0 ± 0.43%, respectively [Figure 6].

Histopathological evaluation

Histopathological studies for the ulcer control group showeddisruption in intact mucosa with inflammatory cells when compared with thenormal rat stomach [Figure 7I]). However, animals treated with clarithromycin showed almost normal pattern [Figure 7 III]. In case of pure monoammonium glycyrrhizin-treated animals, superficial ulcers were observed in the microphotographs [Figure 7 IV]. Optimized formulation shows significant reduction in ulceration [Figure 7 V].

***In vivo* X-ray studies**

Figure 8 shows the images of barium sulfate-labeled floating tablet in Albino rabbits. It was observed that the tablet remained afloat in the stomach for 6 h.

DISCUSSION

Liquorice is known for its anti-ulcer activity. However, studies have concluded that there is poor absorption of main triterpene saponin glycyrrhizin as such in both rats and humans. Further, it is seen that this glycyrrhizin gets converted to aglycone glycyrrhetic acid by bacteria present in the stomach, and this glycyrrhetic acid is responsible for the various effects of liquorice. This suggests the suitability of the gastroretentive dosage form of liquorice. The

Table 7: Analysis of variance for the measured responses

Parameters	Degree of freedom	Sum of squares	Mean sum of square	Fisher's ratio	*P*
Drug release %					
Regression	5	4840.51	968.16	1.44	0.4058

Table 8: Effect of treatment on pylorus ligation-induced gastric ulcer in rats

Treatment	Dose (mg/kg)	Ulcer index	% inhibition of ulceration
Ulcer control	-	14.6±0.34***	-
Standard clarithromycin	25 (p.o.)	8.7±0.13***	39.8±0.16***
Monoammonium glycerrhizin	200 (p.o.)	5.13±0.26***	51±0.5***
Monoammonium glycerrhizin +*Aloe vera* gel powder	200+5 (p.o.)	0.017±0.11***	99±0.43***

Values are represented as mean±S.E.M., *n*=6 in each group, ****P*<0.001 for ulcer control (one-way ANOVA followed by Tukey's multiple comparison test)

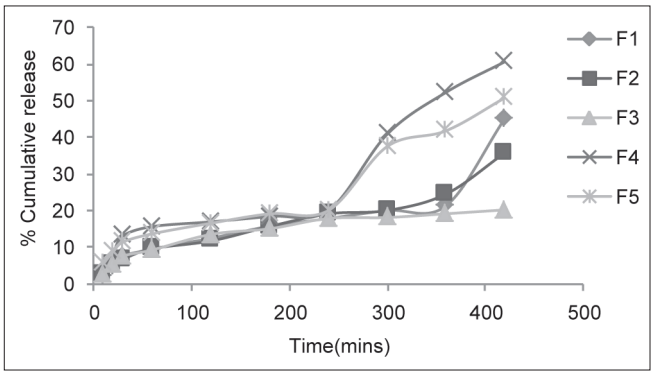

Figure 1: *In vitro* release profile of formulations F1 to F5 (mean ± S.D., *n*=6)

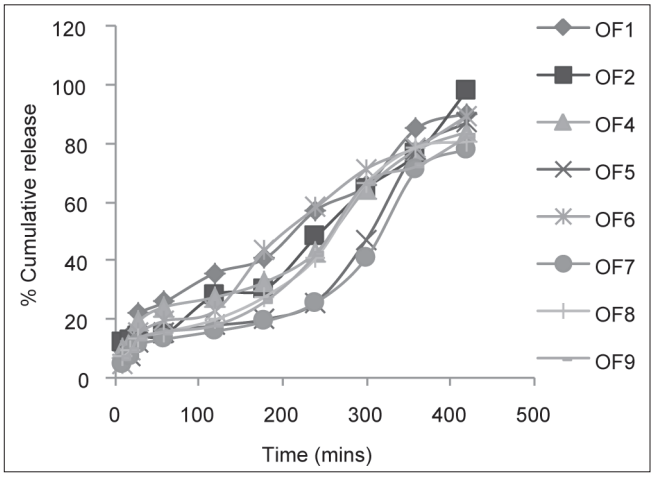

Figure 2: *In vitro* release profile of formulations OF1 to OF9 (mean ± S.D., *n*=6)

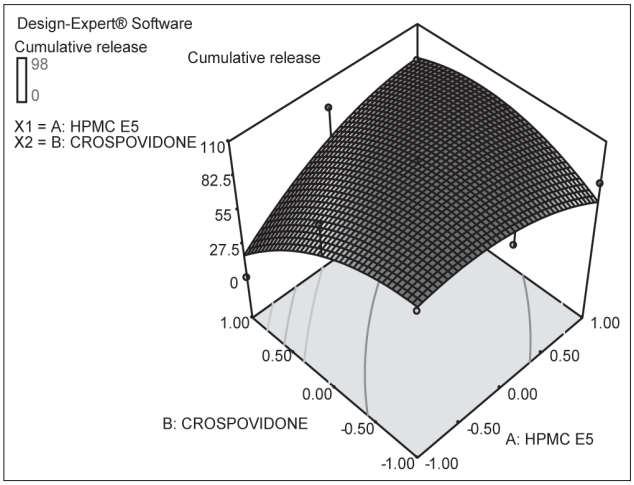

Figure 3: Surface plots for the effect of drug release

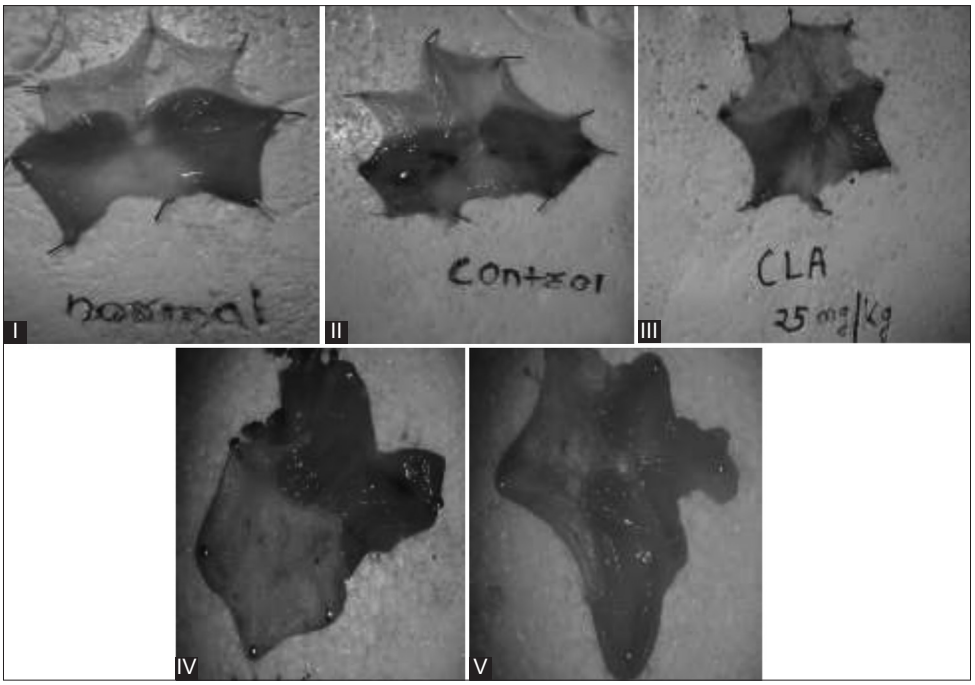

Figure 4: Photographs of rat stomach showing ulcerated area: (I) Normal control, (II) ulcer control, (III) treated with clarithromycin, (IV) treated with monoammonium glycerrhizinand (V) treated with optimized formulation

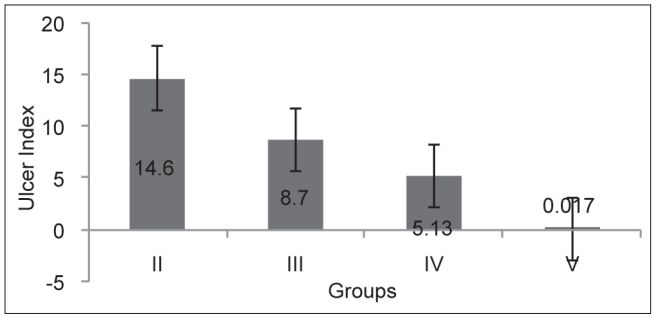

Figure 5: Graph of ulcer index in different groups

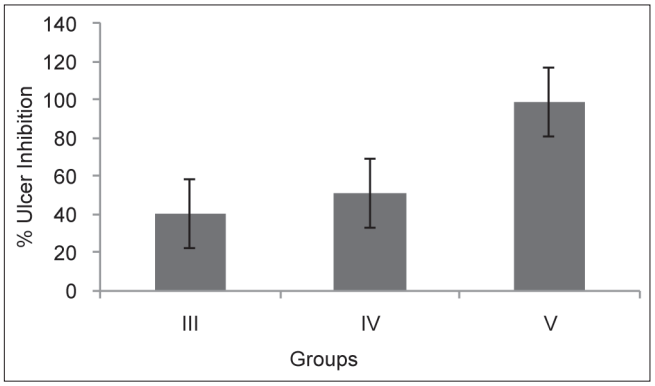

Figure 6: Graph of percentinhibition of ulceration in different treatment groups

monoammonium salt form of glycyrrhizin was considered for the present investigation because of its increased solubility in the acidic pH of the stomach. The anti-ulcer activity of liquorice is found due to an increase in the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach. It has also been reported that *H. pylori* shows susceptibility to liquorice extract.[3-6]

Use of *Aloe vera* gel powder will additionally benefit in curing gastric ulcers due to its mucoprotective and healing effects.[7]

Floating lag time and total floating time determination of preliminary batches

When the preliminary formulations F1 to F5 were subjected to floating lag time and total floating time determination, it was observed that the grade of HPMC influenced both the parameters, withigher viscosity series of HPMC (K-series) gels to a higherextent on contact with water. This results in trapping of carbon dioxide generated from the reaction between sodium bicarbonate in the formulation and hydrochloric acid in the stomach in the swollen network, giving a floating lag time in the range of 10-21s. As a result of this trapped carbon dioxide, the total floating time of the formulations was also found to prolong upto10 h. Extensive gelling of high-viscosity grades HPMC imparts excellent matrix integrity to the tablet.When the E-series of HPMC were tried, it was found that HPMC E15 gave comparable results to the K-series of HPMC for the above parameters.HPMC E5 being a low-viscosity grade polymer gels to a lesser extent and thusdoes not trap carbon dioxide to a great degree.[12,13] This results in immediate floating of the tablet. Swelling of HPMC E5 provided good matrix integrity with sufficient total floating time.

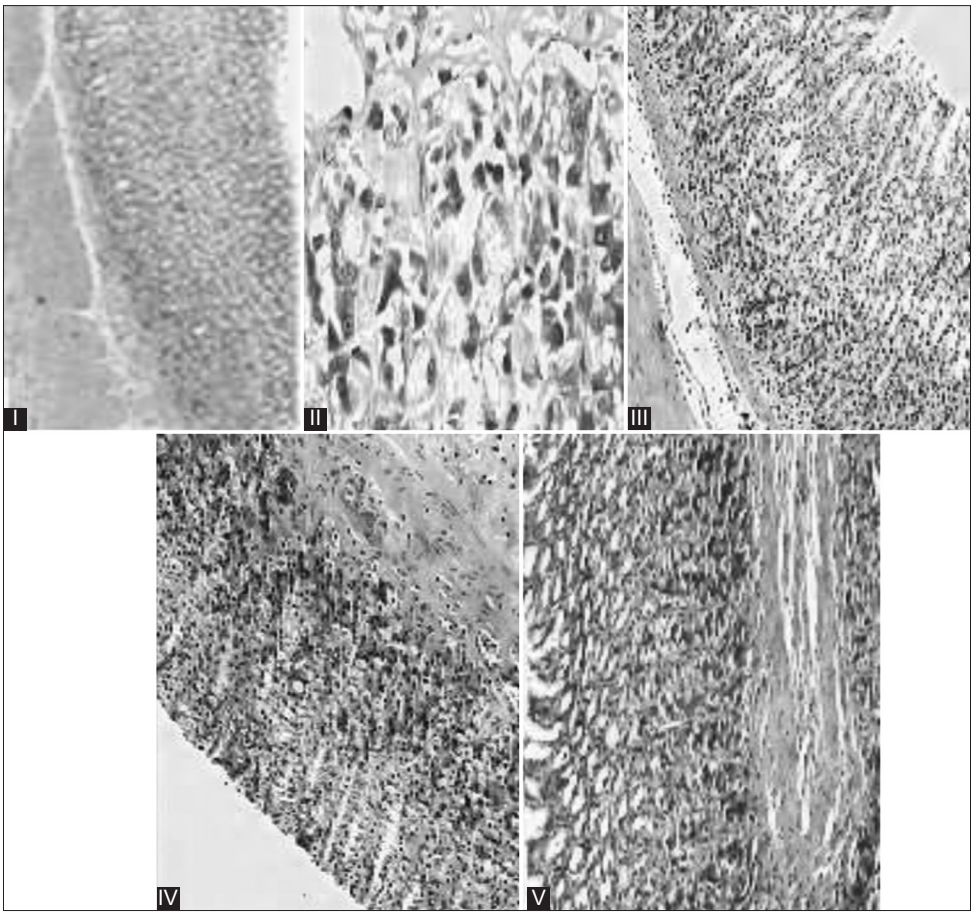

Figure 7: Histopathological studies of rat stomach: (I) Normal control, (II) ulcer control, (III) treated withclarithromycin, (IV) treated with monoammonium giycerrhizin and (V) treated with optimized formulation

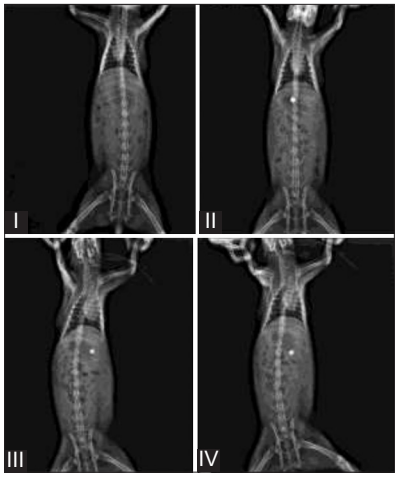

Figure 8: *In vivo* X-ray images of albino rabbits taken at different time periods: (I) Empty stomach, (II) 1 h, (III) 4 hand (IV) 6 h

Drug release studies

There exists a direct relationship between grade of HPMC and drug release from the tablets. With increase in viscosity grade, the average molecular weight of the polymer increases, resulting in an increased polymeric entanglement. This reduces the mobility of the polymer chain, reducing diffusion and retarding drug release from the tablet.[13] Drug release for formulation OF3 could not be obtained as the tablet burst immediately on being added to the dissolution medium.This could be a result of lowest concentration of HPMC E5 and highest concentration of super disintegrant crospovidone in the formulation. The results of drug release studies justify the need of optimization in this investigation.Becausethe formulation F4 containing HPMC E5 showed comparatively higher release of 61%, it was decided to continue optimization using HPMC E5.

Statistical optimization

In the optimization technique applied, the level of crospovidone and HPMC E5 were selected as independent variables and their response on drug release was studied as the dependent variable. A statistical model established to evaluate the responses for the present technique is

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2 \quad (3)$$

In this equation, Y is the dependent variable, β_0 is the arithmetic mean of nineresponses and β_i isthe estimated coefficient of factor Xi. X_1 and X_2 represent the average result of changing one factor at a time from its low to high value.

The interaction terms $X_1 X_2$ show how the response changes when two factors are changed simultaneously and also to check the non-linearity. Mathematical relationship for the response variables is as below:

$$\text{Drug release} = +98.41 + 8.80^{*}A - 13.32^{*}B + 23.52^{*}A^{*}B - 14.87A^2 - 18.12B^2 \quad (4)$$

Response surface plots were used to study the effect of two factors on the responses one at a time. Figure 3 shows the direct relationship between the amount of crospovidone, HPMC E5 and drug release from the tablet.

Addition of a superdisintegrant like crospovidone showed an increase in the dissolution rate of the tablet. This increase is due to lack of any interaction between the drug and the superdisintegrant. Absence of interaction is the attribute of the non-ionic nature of crospovidone.[14]

In the present investigation, estimation of *Aloe vera* was not carried out as it is added in the formulation to impart local effect at the ulcer site.

***In vivo* studies**

From the results of animal studies and histopathological evaluation, it was found that pure monoammonium glycyrrhizin gave 51% ulcer inhibition. When combined with *Aloe vera* gel powder in the form of a bilayer tablet, this value increased to 99%, indicating better activity against gastric ulcers.

***In vivo* X-ray studies**

From the results of this study, it was proven that the dosage form developed has gastroretention properties *in vivo*. Retention of the tablet in the stomach for 6 h ensures complete drug absorption.

CONCLUSION

In the present work, formulation OF2 containing HPMC E5, crospovidone and effervescent agents in the ratio 1:2 gave better drug release and floating properties in comparison withthe other formulations. *In vivo* studies showed that the combination of monoammonium glycyrrhizin and *Aloe vera* gel powder gave noteworthypercentulcer inhibition and retention in the stomach. Thus, this approach can be a promising practice in the treatment of gastric ulcer.

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How to cite this article: Ranade AN, Ranpise NS, Ramesh C. Enrichment of anti-ulcer activity of monoammonium glycerrhizin and *Aloe vera* gel powder through a novel drug delivery system. Asian J Pharm 2014;8:222-9.

Source of Support: Nil. **Conflict of Interest:** None declared.