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Original Article

Formulation and Evaluation of Floating Oral *in situ* Gel of Liquorice Extract

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ABSTRACT

Background: The *in situ* gel, which after gelation floats in the stomach, is appropriate for sustaining drug release. Aqueous extract of liquorice used for the treatment of peptic ulcers and *Helicobacter pylori*, was used to create an *in situ* gel in the current research study for prolonged action. **Materials and Methods:** The aqueous extract of liquorice was subjected to phytochemical screening; pre-formulation studies such as extract compatibility with selected polymers. *In situ* gel containing liquorice extract, sodium alginate (Gelling Polymer), HPMC K100M (release retardant), Calcium Carbonate (Gas Generating Agent), Tri-Sodium Citrate and Methyl paraben were prepared by using pH induced ion gelation method and various parameters are evaluated. A factorial design was employed to evaluate the independent parameters i.e., sodium alginate and HPMC K100M, on dependent parameters such as lag time, viscosity and *in vitro* drug release at 9th hr of the formulation. **Results:** The pre-formulation studies showed compatibility between extract and excipient. The *in situ* formulation showed a pH ranges from 7.44 to 7.88, Viscosity 72.67 to 596.33 cps, lag time of 14.67 to 73 sec, Drug content 49.139 to 71.471% and remain buoyant in gastric environment for more than 12 hr. Concentration of HPMC K100M and Sodium Alginate decreases drug release due to the formation of rigid gel structure. Mechanism of drug release from formulations was Non Fickian super case-II, fitting into the Korsmeyer Peppas model. **Conclusion:** The optimized formulation was found to have a lag time of 28.67 sec, pH 7.69, viscosity 268 sec and drug release of 73.98% at end of 9th hr and found to be in acceptable range. Therefore, liquorice extract oral *in situ* solution can be a promising approach for prolonged and sustained effect for treating peptic ulcers.

Keywords: Liquorice extract, *in situ* gel, Peptic ulcer, Sustained release, Sodium Alginate, HPMC K100M, Gelling capacity, Floating ability.

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INTRODUCTION

The development of technology in the pharmaceutical sector has attracted a lot of interest in drug delivery systems in recent decades for administration of drugs through different routes, like parenteral, oral, topical, nasal, rectal, vaginal etc. Tablets and capsules are widely used solid dosage forms, however oral liquid formulations are increasingly in demand due to their convenience in drug administration as it is easily swallowed and accepted for geriatric and pediatric use.

Floating drug delivery system is an efficient method to increase residence time of drugs in stomach which have their absorption window in stomach. With low oral bioavailability, low-density systems are FDDS which float over gastric contents of stomach for extended period of time due to its adequate buoyancy, thereby providing controlled drug release. Drugs in this type of delivery system are absorbed from the upper part of the stomach. FDDS is useful for drugs which require local effect on the stomach. This can be achieved only if density of delivery system is lower than gastric fluid. However, the delivery system initially with high density settles down within the stomach, absorbs water, swells and decreases the density of the system and thereby floats. Floating can be rendered by either incorporating low-density excipients or by providing mechanism that leads to entrapment of air within the system. pH, ions and temperature are different parameters which induce gelation.[1,2]

Liquorice consists of dried peeled or unpeeled roots and stolon of Glycyrrhiza glabra Linn belonging to the family Fabaceae. It has been reported that liquorice is effective in treatment of peptic ulcers and glycyrrhizin has an anti-inflammatory and anti-ulcer effect. Liquorice can increase prostaglandins concentration in digestive system which promote mucus secretion from stomach and prolongs the life span of surface cells in stomach and has an antipepsin effect. It has also been reported that polysaccharides inhibit the adhesion of *Helicobacter pylori* to the gastric region

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and shows susceptibility to liquorice extract.[3,4] The current study aims at formulating *in situ* floating oral gel of liquorice root extract for sustaining the release of drug in gastric region and treat peptic ulcer.

MATERIALS AND METHODS

Materials

Liquorice root extract was provided as a gift sample from Sami-Sabinsa Group Ltd., Bangalore. Glycyrrhizic Acid was purchased from Otto Chemie Pvt. Ltd., Mumbai. Sodium alginate, methyl paraben was procured from Hi-Media Laboratories, Mumbai. HPMC K100M was procured from Kemphasol, Mumbai. Calcium carbonate was procured from SDFCL, Mumbai.

Method of preparation of *in situ* gel

Sodium alginate solution at different concentrations (0.5, 0.75, 1) % w/v were prepared in half volume of distilled water containing sodium citrate (0.5% w/v) and HPMC K100M (0.35, 0.5,0.75) % w/v was added to above solution with continuous stirring at 60°C using hotplate magnetic stirrer. After cooling below 40°C calcium carbonate (1%w/v) and Liquorice root extract (5%w/v) was added with other one third quantity of distilled water with continuous stirring. Methyl paraben (0.2%w/v) was finally added and volume was made upto 50 mL with distilled water.[5] Comparison of the formulation is shown in Table 1 and schematic representation for *in situ* gel was depicted in Figure 1.

Experimental design

A 3^2 full factorial design study was carried out to identify the amount of polymer required to achieve desired lag time, strength and drug release. Using 3^2 full factorial design, nine experimental formulation combinations were selected. The amount of sodium alginate and HPMC K100M are the two independent variables in the study design (X1 and X2 respectively) and dependent variables Y1, Y2, and Y3 are responses which corresponds to the percentage of drug release at the 9th hr, lag time, and viscosity of the formulation, respectively. Using Design Expert version 13 (Stat Ease) the experimental data was analyzed statistically and calculated the main effects. Optimized *in situ* gel generated from software based on results of interaction and effects of the formulation.[6,7]

Evaluation methods of *in situ* solution

Drug excipient compatibility studies

The interaction between the API and the polymer was analyzed using FTIR spectroscopy. To ensure the purity of the drug and interaction between drug and excipients in the formulation, the IR spectra of the drug obtained in its pure form and the formulation were compared.

Physical appearance

The prepared formulations were observed for appearance, colour and odour.

pH

The pH was determined using a previously calibrated digital pH meter. All pH measurements were taken in triplicates.[5]

In vitro gelling capacity

Test tube method was used to determine the gelling capacity of the formulation. To a test tube containing 10 mL gelling medium (0.1N HCl pH 1.2) 1 mL of the *in situ* gel was added. Time taken for sol to gel conversion was assessed visually. Based on the stiffness of gel and period of time it sustains its integrity, gelling capacity was categorized into 3 categories.[7]

Gel formed after few minutes, but disperses rapidly (+).

Immediate gelation which remains few hours (++).

Immediate gelation which remains for an extended period of time (+++).

Determination of viscosity

The viscosity was determined by Brookfield Viscometer using disc shape spindle at a speed of 50 rpm for 60 sec and triplicate readings were taken.[5]

Table 1: Composition of Liquorice Extract *in situ* gel Formulation.

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Liquorice Root Extract (mg)	2500	2500	2500	2500	2500	2500	2500	2500	2500
Sodium Alginate (mg)	250	250	250	375	375	375	500	500	500
HPMC K100M (mg)	175	250	325	175	250	325	175	250	325
Tri-Sodium Citrate (mg)	250	250	250	250	250	250	250	250	250
Calcium Carbonate (mg)	500	500	500	500	500	500	500	500	500
Methyl Paraben (mg)	100	100	100	100	100	100	100	100	100
Distilled Water Qs (mL)	50	50	50	50	50	50	50	50	50

In vitro buoyancy study

This study was performed in type II USP dissolution apparatus containing 0.1N HCl, 1.2 pH as dissolution medium at 37±0.5°C. The time taken for 10 mL of *in situ* gel to float in medium (floating lag time) and period of time formulation floats on surface of medium (duration of floating) was recorded.[7]

Drug content

10 mL of *in situ* gel (equivalent to 500 mg of drug) was added to 60 mL 0.1N HCl, pH 1.2, and shaken using a propeller for 15 min followed by sonication for 15 min, till gel is dispersed. The absorbance was recorded at 254 nm using UV spectrophotometer against blank solution.[5]

Measurement of density of gel

In situ of 10 mL formulation was poured into a beaker containing 30 mL of 0.1N HCl (pH 1.2) to convert into gel and HCl was drained. The gel was weighed and placed in a measuring cylinder and volume occupied is noted. Density of gel was calculated from following equation.[8]

$$\text{Density} = \frac{\text{MASS}}{\text{VOLUME}}$$

Water uptake studies

To perform this study 10 mL of the formulation added to 20 mL of 0.1N HCl (pH 1.2) to form a gel. Excess 0.1N HCl was drained and gel was weighed and initial weight was recorded. Further, 10 mL of distilled water was added to the gel. After every hr, water was removed and weighed the gel for 6 hr. The initial and final weight difference was calculated and recorded.[9]

$$\text{Water Uptake} = \frac{\text{Final Weight} - \text{Intial Weight}}{\text{Intial Weight}} \text{ X } 100$$

In vitro drug release

This study performed using USP Type 2 paddle type apparatus, at 50 rpm and it is required to maintain this speed to avoid breaking of gel. 10 mL of solution was added in dissolution basket containing 900 mL simulated gastric fluid (0.1N HCl, pH 1.2) maintained at 37±0.5°C and the drug release was carried out for upto 10 hr. 5 mL of sample was withdrawn at every specified time interval and replaced with same volume of the medium. The collected samples were filtered, suitably diluted and analyzed using UV Spectrophotometer at 254 nm.[10-12]

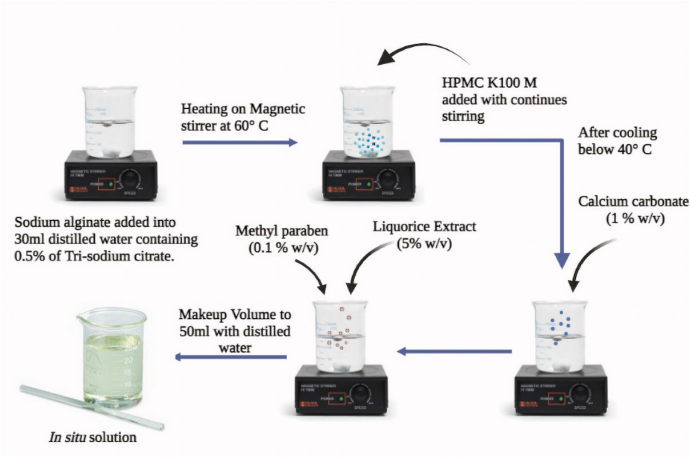

Figure 1: Preparation of *in situ* solution.

Drug release kinetic study

In vitro drug release data obtained from *in situ* gel was plotted into various mathematical models which predict release kinetics for various models like Zero order, First order, Higuchi model, Hixon Crowel and Korsmeyer Peppas model. Data analyzed using PCP Disso V3 Software to better understand order and mechanism of drug release. Best fit model was selected based on R^2 value.[13,14]

Stability study

It was carried out as per ICH guidelines. The optimized formulation was stored in amber coloured bottle and kept in a stability chamber at 40±2°C and 75±5% RH for 2 months. At every specified time interval samples are analyzed for any change in Viscosity, physical appearance, drug content, pH, lag time and *in vitro* dissolution profile.[15]

RESULTS AND DISCUSSION

FT-IR spectroscopy

Functional groups observed for Liquorice extract are OH 3267.55, CH^2 Assymetric stretching 2939.64, *C*=C stretching 1653.07, CH group bending 1393.63, OH bending (alcohol) 1349.26, *C*-O stretching (Primary alcohol) 1079.22, OH bend Carboxylic Acid 941.30 and almost similar peaks observed for physical mixture indicates no interaction between extract and mixture (Figure 2a and 2b).

DSC study

Thermograms of liquorice extract, physical mixture (Extract with Calcium Carbonate, Sodium Alginate, Sodium Citrate, HPMC K100M), and optimized *in situ* gel are illustrated in Figure 3a and 3b. The thermogram of the extract shows the endothermic peaks at 87.86°C and 177.89°C. The endothermic peak was observed at 189.62°C in physical mixture shows compatibility.

Physical appearance

The *in situ* gel formulations appeared as light to dark brown in color. In pH 1.2, the sol to gel transformation appeared as light yellow to brown color with a rigid structure.

pH

pH for all formulations was observed in the range of 7.44-7.88, which is regarded as an acceptable range for oral consumption

and is suitable for floating gel during its contact with Acidic pH. Results are shown in Table 2.

Drug content

The amount of drug in the formulations was determined using the drug content. For the optimal dose, uniform drug dispersion is required since the prepared formulations are liquids. The drug content ranges from 49.139±0.191% to 71.471±0.150% for all the formulations, as reported in Table 2.

In vitro gelling capacity

This study was carried out in 0.1N HCl at pH 1.2 and it was assessed on a scale between + and +++ as shown in Table 3. After coming into contact with the gelling medium, all formulations had undergone gelation immediately and persist more than 12 hr. This reveals that calcium ions form complex network along with polymer chains of Sodium Alginate, which results in the development of stiff gels. Gel stiffness is responsible for prolonged drug delivery since the drug molecules must pass through complex 3D polymer chain structure to reach physiological environment. The gelling capacity was depicted as in Figure 4.

Viscosity

Determination of viscosity of all the formulations revealed that there is a significant rise in the*in situ* gel viscosity, that the rheological properties changed as HPMC K100M concentration was increased. It was observed that viscosity of formulation increased proportionally as concentrations of sodium alginate and HPMC K100M increased. Viscosity was reported between 72.67 and 596.33 cps. Results revealed that all the formulations had viscosity within specified range which is shown in Table 2 and depicted in Figure 5.

Buoyancy studies

These studies are performed in 0.1N HCl, pH 1.2 medium and revealed that lag time ranges in between 14.67±0.471 sec to 64±0.816 sec and that floats over the surface of gastric region for more than 12 hr. Formulation becomes buoyant as a result of the CO_2 trapped in the gel network when it is introduced into the medium. Furthermore, a cross linked 3D gel network is formed as a result of the interaction between calcium ions and sodium alginate. This network swells and traps more CO_2. Entrapment of CO_2 in the network structure for extended time period caused flotation and buoyancy. Additionally, prolonged release

Table 2: pH, Viscosity and %Drug Content of Liquorice Extract of F1 to F9 Formulations.

Formulation Code	pH	Viscosity (cps)	Drug Content (%)	Water Uptake (%)
F1	7.44±0.036	72.67±0.471	49.139±0.191	30.07
F2	7.58±0.060	174.33±1.247	53.756±0.225	34.31
F3	7.64±0.032	313.67±0.943	56.380±0.268	36.68
F4	7.75±0.038	213.67±1.247	57.133±0.362	25.56
F5	7.67±0.056	236±0.816	61.556±0.209	32.82
F6	7.71±0.020	325.67±1.247	58.178±0.359	29.38
F7	7.75±0.102	442.33±0.943	71.471±0.150	26.50
F8	7.83±0.047	522.33±1.247	67.243±0.268	35.08
F9	7.88±0.056	596.33±0.471	70.061±0.225	39.39

Data expressed as Mean±SD (*n*=3).

Table 3: Floating lag time, Floating duration, Gelation time, Gelling capacity, Gel density of Liquorice Extract of F1 to F9 Formulations.

Formulation code	Floating lag time (Sec)	Floating duration (hr)	Gelation time (Sec)	Gelling capacity	Gel density (g/cm^3)
F1	14.67±0.471	>12	3.1±0.510	+++	0.596±0.010
F2	18.67±0.943	>12	3.53±0.330	+++	0.669±0.022
F3	21.33±1.247	>12	4.57±0.262	+++	0.832±0.015
F4	22±1.414	>12	4.37±0.249	+++	0.697±0.027
F5	24.33±1.247	>12	5.4±0.356	+++	0.712±0.034
F6	28.67±1.247	>12	7.3±0.374	+++	0.737±0.033
F7	54.34±0.471	>12	6.1±0.163	+++	0.773±0.029
F8	62.67±1.247	>12	7.3±0.374	+++	0.793±0.020
F9	64±0.816	>12	8.33±0.419	+++	0.842±0.027

Data expressed as Mean±SD (*n*=3)

pattern caused by the gel network, which delayed drug release, demonstrates that lag time is minimal for all formulations. Lag time and floating durations for *in situ* gel formulations are shown in Table 3.

Gel density

For a system to remain buoyant, density of system has to be less than gastric fluid (i.e., 1.004 g/cm^3) density. The densities of all formulations were found to be less than 1 g/cm^3 (Table 3) which results in floating for prolonged period of time. The density of formulation gradually increased along with the polymer concentration. Weight of the gel increased gradually due to

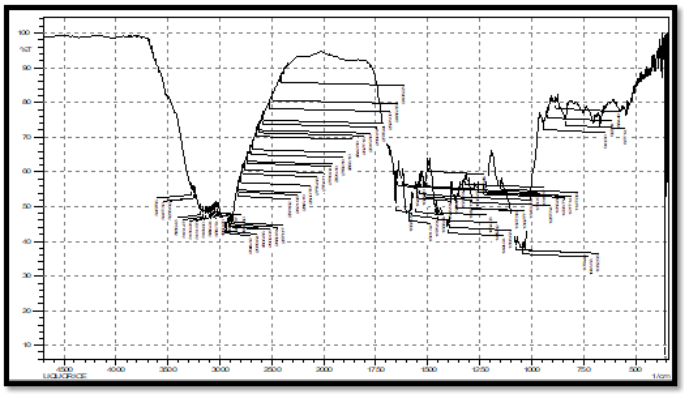

Figure 2a: FTIR Spectrum of Liquorice root extract.

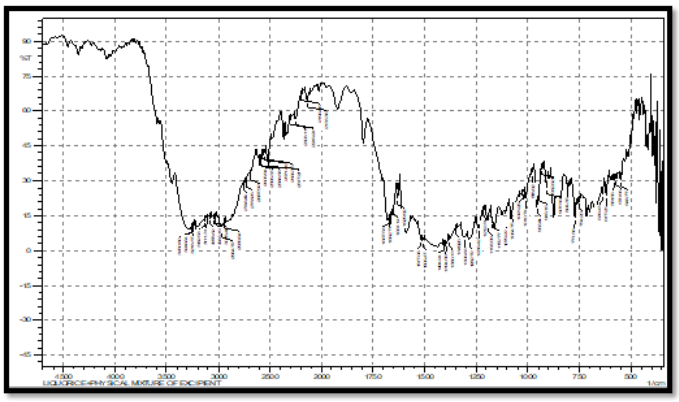

Figure 2b: FTIR Spectrum of Liquorice root extract and physical mixture of excipients.

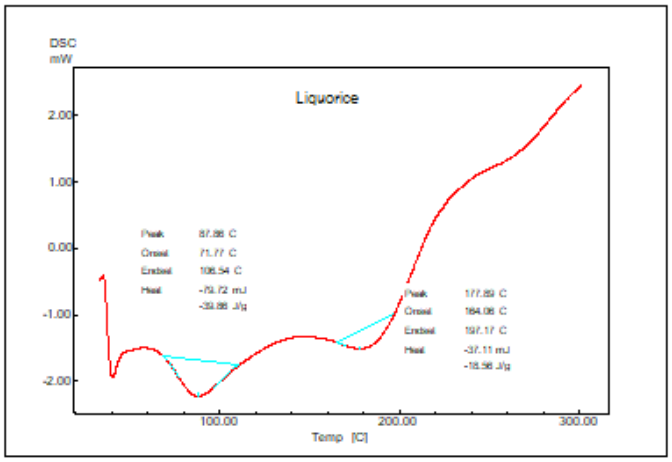

Figure 3a: DSC Thermogram of Liquorice root extract.

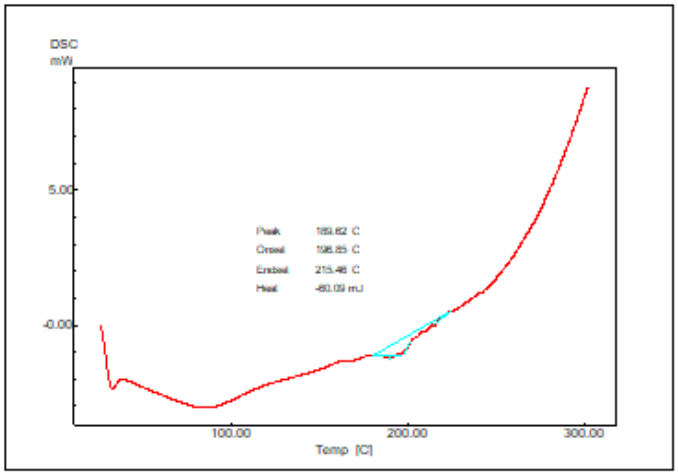

Figure 3b: DSC Thermogram of physical mixture of Liquorice root extract and along with other excipients.

Table 4: Drug Release Kinetic Profiles of Liquorice Extract *in situ* Formulations.

Formulation Code	Zero order	First order	Higuchi	Korsmeyer peppas		Hixson crowell	Best fit model
	R^2	R^2	R^2	R^2	n	R^2	
F1	0.9659	0.9625	0.8481	0.982	1.0941	0.9636	PEPPAS
F2	0.9726	0.9695	0.8581	0.9846	1.0815	0.9706	PEPPAS
F3	0.9654	0.9621	0.8459	0.9814	1.0915	0.9632	PEPPAS
F4	0.9652	0.962	0.8456	0.9806	1.1205	0.9631	PEPPAS
F5	0.9655	0.9624	0.8462	0.9808	1.0769	0.9634	PEPPAS
F6	0.9681	0.9646	0.8489	0.9826	1.0856	0.9658	PEPPAS
F7	0.9629	0.9594	0.8393	0.9854	1.1715	0.9606	PEPPAS
F8	0.9701	0.967	0.851	0.9818	1.1146	0.9681	PEPPAS
F9	0.9635	0.9599	0.8393	0.9782	1.1026	0.9611	PEPPAS

increase in absorption of water as concentration of polymer increases.

Water uptake studies

Drug release from polymer matrix is influenced by amount of water present in system. % water uptake for all formulations is given in Table 2. According to studies F9 showed highest water uptake of 39.39% compared to other formulations may be due to high capacity for swelling as polymer concentration rises, water absorption by gel also rises.

In vitro drug release

Effect of polymer concentration on release of drug determined through an *in vitro* study of prepared formulations. When concentration of polymer was increased, reduction in rate and amount of drug release was observed. This might be because the polymeric system density has increased, resulting in a longer diffusional path for molecules of drug. Additionally, HPMC K100M delays the drug release. All formulations showed drug release almost more than 80% by end of 10th hr except F9, which have highest concentration of polymer HPMC K100M. Due to high polymer concentration of gelling agent (Sodium Alginate) and release retardant (HPMC K100M), F9 has low drug release and F1 shows more than 90% of drug release in 9 hr because of low polymer concentration. The drug release data of all formulations illustrated in Figure 6 shows the drug release profile of % CDR vs Time (hr) for F1 to F9 formulation.

Drug release kinetics

Drug release mechanism was found by fitting multiple kinetic models to release data of all formulations. Based on kinetic equations goodness of fit was evaluated by using values of correlation coefficient (R). The R value was found to be higher for the Korsmeyer-Peppas model. The calculated R value for

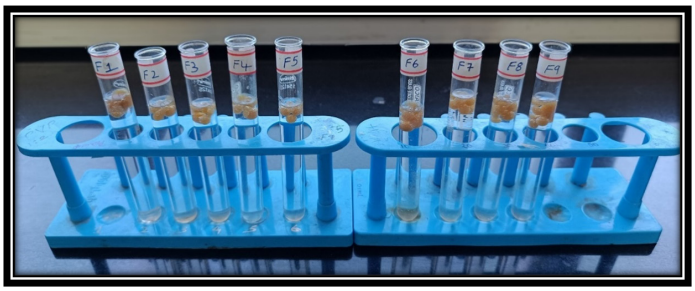

Figure 5: Effect of concentration of polymers in formulation on viscosity.

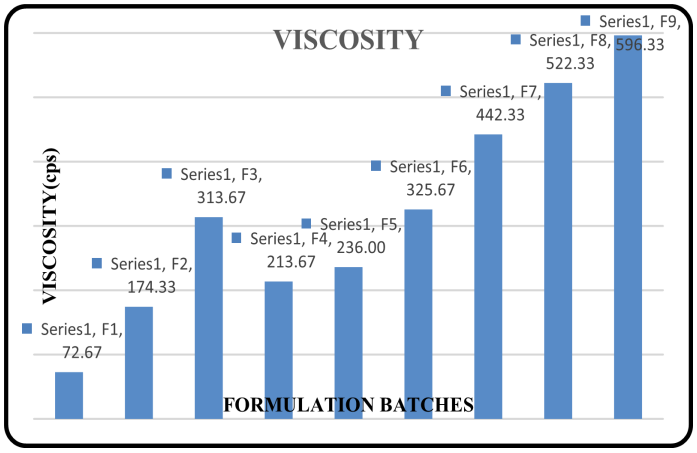

Figure 4: The gelling capacity of the F1 to F9 formulations.

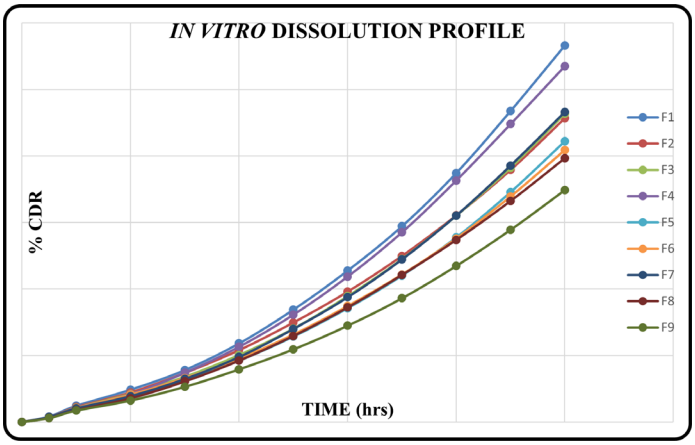

Figure 6: Drug Release Profile of % Cumulative drug release vs. Time (hr) for F1 to F9 Formulations.

Table 5: Stability Study of 3^2 Optimized *in situ* gel of Liquorice Extract.

Sl. No.	Observation	Before stability testing	During stability testing (40±2°C, 75±5% RH)	
			30 days	60 days
1	pH	7.69±0.816	7.72±0.024	7.75±0.029
2	Physical Appearance	Light to dark brown in color	Light to dark brown in color	Light to dark brown in color
3	Viscosity (cps)	268±0.816	269.33±1.247	271±1.633
4	Drug Content (%)	68.14±0.158	67.63±0.179	66.95±0.209
5	Drug Release (%)	73.981±0.54	72.217±0.548	71±1.992

Data expressed as Mean±SD (*n*=3).

Korsmeyer-Peppas was between the ranges of 0.9782 to 0.9854. According to the equation of Korsmeyer Peppas, the "*n*" (release exponent) value lies between 1.0769<*n*<1.1715, indicates it follows Non Fickian super case II transport mechanism and showed continuous release of drug for a prolonged period of time. Kinetic profile of drug release data is given in Table 4.

Statistical analysis

This study was carried by Design Expert V13 software. Significance of model is determined using the ANOVA, which was also used to estimate effect of independent factors on dependent variables. Polynomial equation demonstrated relationship between factors and responses, whereas coefficients of various terms represent relationship of nature and magnitude. According to ANOVA results, the probability value and F-value are significant. All responses have a difference less than 0.2, which indicates that the predicted R^2 value and the adjusted R^2 value are reasonably in close agreement. Ratio more than 4 regarded as desirable when assessing Adeq.precision, which measures the signal to noise ratio. The obtained ratio of 19.8248 for effect on viscosity, 38.1733 lag time effect and 12.985 for 9th hr drug release. From the results it was observed HPMC K 100M and Sodium alginate are found to have synergistic effect i.e., viscosity and lag time increases with increase in polymer concentration but retards drug release at 9th hr. Response surface plot and contour plot and describes the relation between factors and responses (Figure 7).

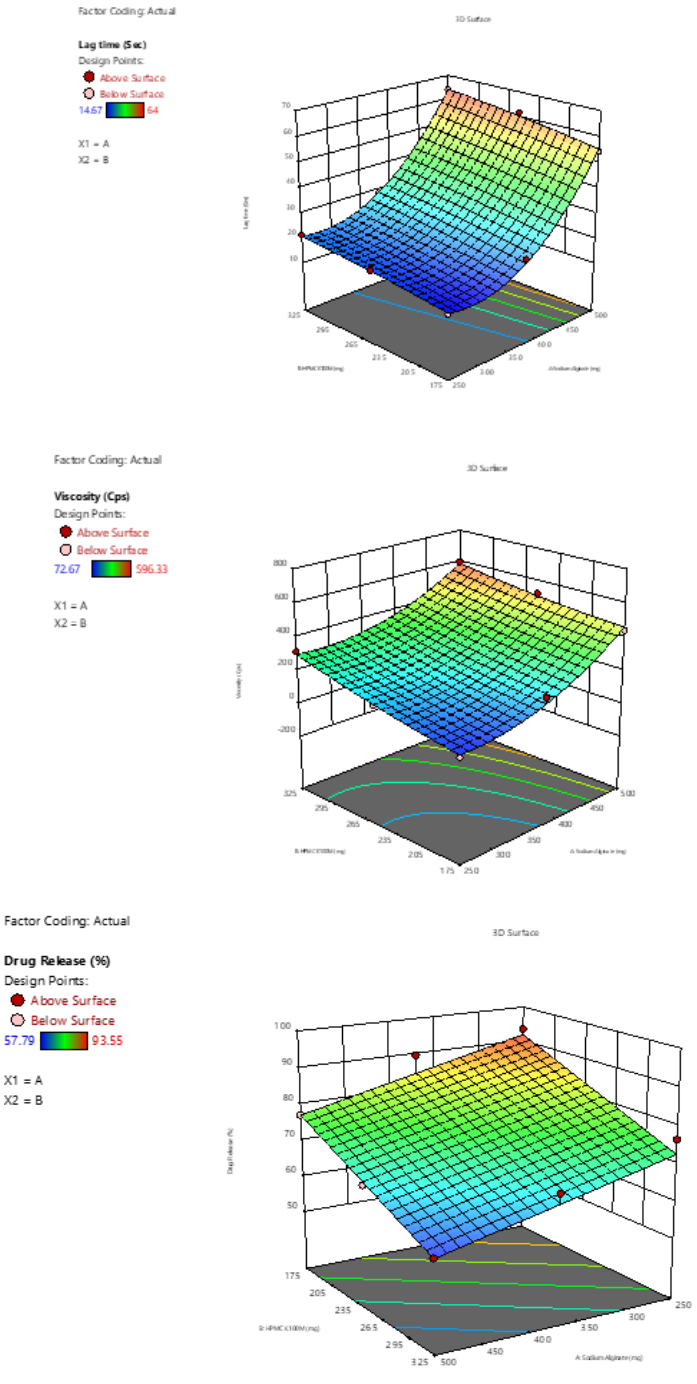

Figure 7: 3D graph representing the influence of HPMC K100M and sodium alginate on Lag time, Viscosity and Drug release at 9th hr.

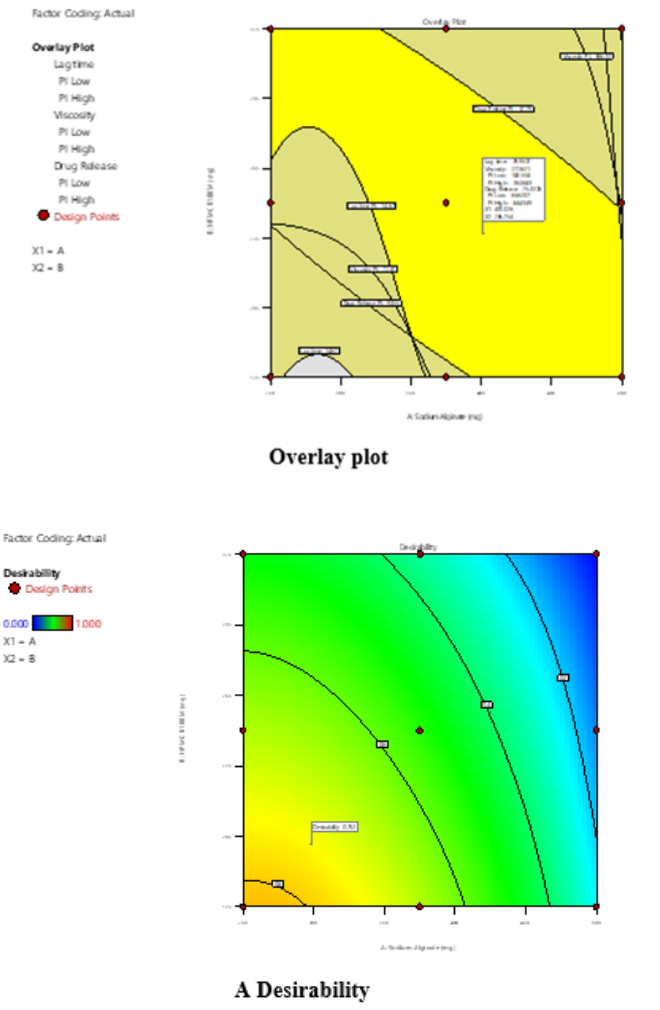

Figure 8: Optimization of *in situ* Formulation.

Optimization

Optimized formulation was developed using both numerical and graphical optimization method using desirability approach and overlay plot respectively (Figure 8). By setting constraints on each component an optimized formulation was developed to obtain desired response. Constraints are set to minimize viscosity and lag time, while maximize drug release at 9th hr. Design expert software recommended an optimized formula containing sodium alginate of 401.026 mg and 236.754 mg of HPMC K100M which had desirability of 0.817 based on constrains added. The values observed for lag time, viscosity and drug release at 9th hr (28.67±1.25 sec, 268±0.82 cps, 73.981±1.09%) are in close agreement with the predicted values (29.9517 sec, 272.621 cps, 75.0278%) within 5% of the relative error.

Stability studies

Stability study was performed for optimized formulation according to ICH guidelines. Samples were withdrawn at 30th and 60th day. No significant change is observed during stability testing for physical appearance, viscosity, pH, drug content and drug release as shown in the Table 5.

CONCLUSION

The current study has been successfully completed and formulated floating oral *in situ* gel of liquorice extract for treating peptic ulcer. From the experimental results it was concluded that all the pre-formulation studies was carried out, DSC and FT-IR studies reported there is no interaction between extract and polymer.

All characterization studies were performed and observed to be in the acceptable range for forming *in situ* gel. All formulations showed immediate gelation in 0.1N HCl, pH1. 2 and observed prolonged retention in the simulated Gastric Fluid. Optimized formulation was developed using numerical optimization method by imposing constraints on responses. At end of 9th hr, the optimized 3^2 full factorial design formulation showed the minimum lag time, viscosity and maximum drug release. Optimized formulation *in vitro* studies showed 73.98% drug release at 9th hr, which was achieved with minimum lag time.

It was observed all formulations show Korsmeyer-Peppas model and follows Non-Fickian Super Case II transport mechanism for prolonged period of time based on kinetic release data. Stability studies also performed as per ICH guidelines indicating optimized formulation was physically stable. Thus, it can be concluded that aqueous root extract of liquorice can be successfully formulated as floating drug delivery system.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RPM: Rotations Per Minute; **SEM:** Scanning Electron Microscopy; **HPMC:** Hydroxy propyl methyl cellulose; **Hr:** Hour mg: Microgram; **Ml:** mililittere.

SUMMARY

All characterization studies were performed and results were observed to be in the acceptable range for forming *in situ* gel. At end of 9th hour, the optimized formulation showed the minimum lag time, viscosity and maximum drug release, *in vitro* studies showed 73.98% drug release at 9th hour, which was achieved with minimum lag time. It was observed all formulations show Korsmeyer-Peppas model and follows Non Fickian Super Case II transport mechanism. Stability studies also performed as per ICH guidelines indicating optimized formulation was physically stable.

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