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Evaluation of Novel Polymer in the Development of Floating *In situ* Gelling System

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Abstract

The objective of this work was to assess the new polymer obtained from natural source (*Helianthus annuus*) in the formation of floating *in situ* gel of Ranitidine HCl. Low Methoxy Pectin (LMP), calcium carbonate, sodium citrate, D-mannitol, methylparaben and propylparaben were utilized in developing floating *in situ* gelling formulations. The developed formulations were evaluated for various physicochemical properties like viscosity, floating lag time, and duration of floating, *in vitro* gelation and *in vitro* drug release. The 3^2 full factorial design was applied wherein concentration of LMP and calcium carbonate were considered as independent variables whereas floating lag time and drug release after 8 h (Q_8) were taken as dependent variables. All formulations (F1–F9) exhibited floating within 60 s and remained floated for around 24 h. All the formulations were pourable before coming in contact with gastric fluid. It was seen that floating lag time and cumulative percentage drug release was influenced by concentration of LMP and calcium carbonate. Formulation F5 showed optimum floating lag time (37 s) and drug release after 8 h (98.09%) amongst developed *in situ* gels. Thus it can be concluded that Ranitidine HCl can be formulated as floating *in situ* gel using LMP as a gelling polymer to sustain the drug release for 8 h.

Keywords: Ranitidine HCl; Oral drug delivery; Sustained release; Low methoxy pectin (LMP); *Helianthus annuus*

Abbreviations: LMP: Low Methoxy Pectin; DM: Degree of Methylation; HMP: High Methoxy Pectin; SGF: Simulated Gastric Fluid; RT: Room Temperature; RSM**:** Response Surface Methodology; MLRA: Multiple Linear Regression Analysis; ANOVA: Analysis of Variance; CV: Coefficient of Variance; PRESS: Predicted Residual Sum of Squares; DSC: Differential Scanning Calorimetry

Introduction

In situ gelling systems is getting favorable interest over the past few years. In recent years many patents for *in situ* gel forming systems and its use in various biomedical applications including drug delivery have been reported [1]. The growing interest in these delivery systems could be due to the numerous advantages shown by *in situ* **f**orming polymeric like ease of administration and reduced frequency of administration, improved patient compliance and comfort [2]. This drug delivery system can serve as an alternative to the for parental routes achieving systemic drug effects and for oral route wherein numerous drugs suffer from unacceptably low bioavailability and undergoes the hepatic first-pass metabolism, in particular of proteins and peptides. pH change, temperature modulation and ionic strength of the solution alone or in combination serves as stimuli for *in situ* gelation [3]. The polymers that undergo sol-gel transition are known as smart polymers and the set systems represent promising means of delivering the drugs. Natural and synthetic polymers were being investigated for controlled release formulations since ages and the advantages of using biodegradable polymers in clinical applications are evident. Till dat**e** *in situ* forming drug delivery systems has been developed using various natural and synthetic polymers [4].

Pectin's are bio-polymers consisting of D-galacturonic acid and galacturonic acid methyl ester residues and are being utilized as a gelling agent since ages [5]. Pectins have been classified based on their Degree of Methylation (DM) as High Methoxy Pectin (HMP) and Low Methoxy Pectin (LMP). Pectin's with DM higher than 50%, named as HMP and it forms gel after heating in sugar solutions at concentration higher than 55% and pH lower than 3.5. On the other hand, *in situ* gelation with a LMP (DM<50%) requires the presence of polyvalent ions [6]. In case of low sugar products like low-calorie jams and jellies, confectionery jelly products and other foods application LMP can be used as a gelling agent [3].

Ranitidine is a competitive, reversible inhibitor of the action of histamine at histamine H_2-receptors, including receptors on gastric cells with a minimal effect on H_1-receptors. It is most preferred drug for the treatment of active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease and erosive esophagitis and hence it was chosen as a model drug [7].

It is being documented that pectin has a complex structure and it completely depends upon its source and the extraction process. Pectin obtained from sunflower, shown to be also acetylated at some degree. Sunflower pectin, obtained from heads and stalks which remain in the field after seed removal, is naturally occurring LMP. The non-toxicity and the cheap production costs of pectin's make them of great interest in the formulation of controlled-release dosage [3] and hence in the present work we made an attempt to develop floating *in-situ* gelling system using LMP obtained from the heads of *Helianthus annuus,* as a novel gelling agent.

Experimental

Materials

Ranitidine hydrochloride was procured as gift sample from GlaxoSmithKline, Nasik, India. LMP obtained from head of *Helianthus*

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Factor	Level			Responses
	(-1)	0	(+1)	
Amount of polymer (w/v)	0.75	1	1.25	Drug release up to 8 h
Amount of calcium carbonate (w\v)	0.375	0.5	0.625	Floating lag time <60 s

Table 1: Experimental design.

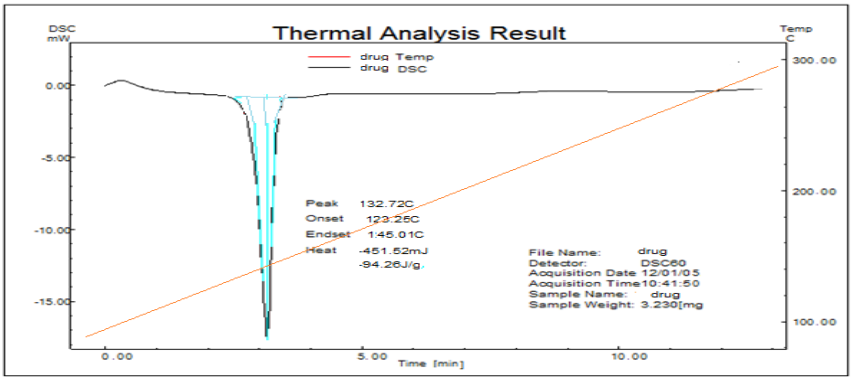

Figure 1: DSC analysis of Ranitidine hydrochloride.

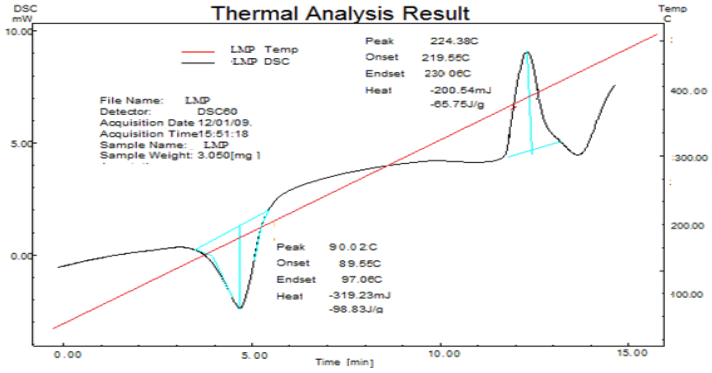

Figure 2: DSC analysis of low methoxy pectin.

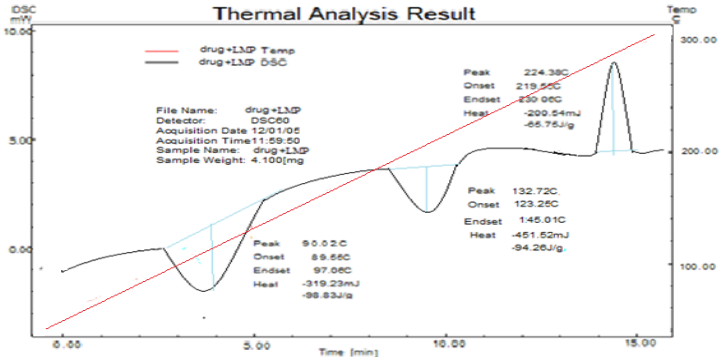

Figure 3: DSC analysis of drug and polymer mixture.

annuus was procured as gift sample from Krishna pectin, Jalgaon, India. Sodium citrate, calcium carbonate, D-Mannitol, methyl paraben, Propyl paraben were obtained from Loba chemie, Mumbai. All ingredients used in study are of analytical grade.

Optimization

Full factorial design was employed in the development of floating *in situ* gel. In the present investigation, according to 3^2 full factorial design the amount of LMP (X_1) and amount of calcium carbonate (X_2) were selected as independent variables whereas the floating lag time and percentage drug release at 8 h (Q_8), were selected as dependent variables. In this design, 2 factors were evaluated each at 3 different levels based on the results of trial batches and experimental bathes were prepared using possible 9 combinations (Table 1).

Methods

Drug excipient's compatibility study: The physicochemical compatibility study of the drug and polymer were tested by performing DSC analysis of pure drug (Ranitidine hydrochloride) and polymer (LMP). DSC curves of the samples were obtained with a Differential Scanning Calorimeter (Figures 1-3). 2-4 mg of samples was placed in aluminum pan and then crimped with an aluminum cover. Heating and cooling rates were 10 and 250°C. All measurements were performed over 50-400°C under a nitrogen purge at 50 $ml.min^{-1}$.

Preparation of *in situ* gelling solutions: LMP solution of varying concentrations was prepared in sodium citrate containing deionized water. LMP was firstly dispersed in chosen medium, heated up to 60°C with stirring and then cooled below to 40°C. The desired amount of calcium carbonate, drug and D-mannitol, methyl paraben and propyl paraben were added under continuous stirring to get uniform dispersion [8]. The formulation composition has been depicted in Table 2.

Measurement of viscosity of *in situ* gelling solutions: Brookfield viscometer (Brookfield Eng. Lab. Inc RVT-205449) spindle number 3 was used to determine the viscosities of the prepared solutions. The 100 ml samples were sheared at room temperature under shearing rate of 100 rpm/min [9]. Each formulation was evaluated for viscosity in triplicate.

***In vitro* gelation study:** 500 mL of simulated gastric fluid (SGF, pH 1.2) was taken in the beaker to which accurately measured 10 ml of developed solution was added with mild agitation that avoids breaking of formed gel. Gelling was observed visually by qualitative measurement [8]. Each sample was tested for *in vitro* gelation in triplicate.

***In vitro* floating study:** The floating ability of developed formulations was determined in a beaker using 500 ml of SGF (pH 1.2). Accurately measured 10 ml of *in situ* gelling solution was added to SGF with mild agitation. After adding solution to the beaker time taken for floating on surface (floating lag time) and total floating time were measured. Floating lag time and total floating time study was conducted in triplicate.

Determination of drug content: Accurately measured 10 ml of *in situ* gelling formulation was transferred to a volumetric flask. 70 ml of SGF was then added into the volumetric flask and content was shaken for 30 min, followed by 15 min sonication. Visually complete dispersion of contents was ensured and volume was then made up to 100 ml with SGF followed by filtration using whatman filter paper. 10 ml of sample was withdrawn from the resultant solution and diluted to 100 ml with SGF. The drug content was estimated spectrophotmeterically using double beam UV-Visible spectrophotometer (Jasco V-630) at the wavelength of 314 nm.

Measurement of *in vitro* drug release: The drug release estimation from the developed *in situ* gel preparations was carried out using slightly modified USP dissolution type II apparatus. The paddle stirring was set at a slow speed (50 rpm) in order to avoid the breaking of gelled formulation and to ensure the *in vivo* mild agitation conditions as well. 500 ml of SGF (pH 1.2) was the dissolution medium used and study temperature was maintained at 37 ± 2°C. 10 ml formulation was withdrawn every time using disposable syringe. The care was taken to wipe the needle head to remove excess formulations before extruding the withdrawn sample by depressing syringe plunger slowly into the petri-dish. The petri-dish containing 10 ml *in situ* gelling formulation was then kept in the dissolution vessel without much disturbance. At fixed time interval, a precisely measured sample of the dissolution medium was removed and replenished with pre-warmed (37 ± 2°C) fresh medium. Amount of the drug released from each formulation was estimated using UV Spectrophotometer at 314 nm (9). Drug release study was carried out in triplicate till 8 h.

Data analysis: To understand the method by which drug release takes place from every formulation, the drug release data was treated by the curve fitting method using PCP-Disso software. The full factorial design was carried out using the trial version of the DESIGN EXPERT® software version 8.0.4 (Stat-Ease Inc., Minneapolis, USA).

Stability study: The stability study for the optimized formulation was carried out following the study protocol intended for the global market in accordance with ICH guidelines. The samples were stored at accelerated stability conditions i.e., at temperature of 40 ± 2°C and humidity conditions of 75 ± 5% RH for three month to access their stability. After every 30 days, the samples were withdrawn and characterized for various physicochemical properties like viscosity, drug content, *in vitro* gelling study, floating lag time, total floating time and *in vitro* drug release study that can have bearing of accelerated condition of the study protocol.

Results and Discussion

In situ gel formulations present an interesting alternative for achieving systemic drug effects as that of parental routes for drugs which can be inconvenient to be given by oral route may be because of the extensive hepatic first-pass metabolism. Smart polymeric systems comprised of polymers that undergo sol-gel transition upon administration represent promising means of delivering these kinds of drugs. Various natural and synthetic polymers are used for formulation development of *in situ* forming drug delivery systems. Sunflower pectin, obtained from waste materials like heads and stalks after seed removal, is naturally occurring LMP. The non-toxicity and the low production costs of this pectin make them useful polymer for exploring into the development of controlled-release dosage form [3].

Name of ingredient	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranitidine HCl	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
LMP	0.75	0.75	0.75	1	1	1	1.25	1.25	1.25
Sodium citrate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium carbonate	0.375	0.5	0.625	0.375	0.5	0.625	0.375	0.5	0.625
D-Mannitol	2	2	2	2	2	2	2	2	2
Methyl paraben	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Deionized water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total volume–100 ml *All quantities in grams									

Table 2: Formulation of experimental batches.

Formulation code	Solution Viscosity (cps)	Gelling time (s)	Floating lag time (s)	Duration of floating (h)	Drug content (%)
F1	40	11 ± 0.1	42 ± 0.32	22.6 ± 0.54	95.7
F2	60	8 ± 0.23	45 ± 1.5	23.6 ± 0.54	94.6
F3	100	6 ± 0.16	37 ± 1.1	24	98.7
F4	90	9 ± 0.18	49 ± 2.3	23.6 ± 0.54	95.48
F5	115	6 ± 0.021	37 ± 1.4	24	99.63
F6	130	5 ± 0.036	32 ± 1.3	24	98.9
F7	150	8 ± 0.052	47 ± 3.1	24	98.73
F8	190	5 ± 0.096	31 ± 2.4	24	98.91
F9	210	4 ± 0.045	35 ± 1.8	24	99.27

Table 3: Evaluation of optimization batches.

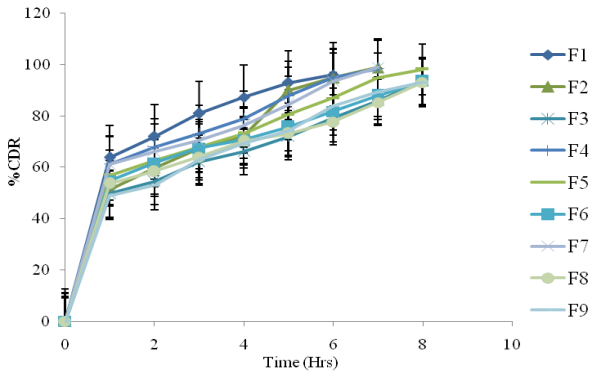

Figure 4: *In vitro* drug release study (F1-F9).

Evaluation of formulations

Optimum viscosity and excellent gelling capacity are the two main pre-requisites for *in situ* gelling systems. The optimum viscosity of the formulation will allow easy swallowing as a liquid, which then undergoes a rapid *in situ* sol-gel transition due to ionic interaction [8]. Moreover, *in situ* gel should preserve its gel strength for prolonged time to facilitate sustained release of drugs locally. The compositions of the developed formulations are depicted in Table 5. The developed formulations were found to meet all prerequisites to become excellent *in situ* gelling floating system that gelled and floated instantaneously in the pH conditions of the stomach. Sol to gel transformation of LMP occurs *in situ* as the calcium carbonate present in the formulation dissolves and releases carbon dioxide on reaction with gastric acid releasing the calcium ions which facilitate the formation of gel with floating characteristics. The released carbon dioxide is entrapped in the gel network of the formulation and giving buoyancy to the gel on the gastric contents [9].

Viscosity and gelling properties

Through the point of view of the proposed oral administration of developed formulation, rheological properties are of prime importance. A marked increase in viscosity was experienced with increasing LMP concentration of the solutions (Table 3). Increasing the calcium carbonate content in the formulation simultaneously increased the viscosity at all polymer concentrations studied. Since the calcium carbonate is present in the formulations as insoluble dispersion, an increase in its concentration proportionally increased the number of particles dispersed, thus contributing to increased viscosity (Table 3). Formulations F3, F6, F9 showed a marked increase in viscosity with increasing concentration of LMP and calcium carbonate. The gelation study was conducted using SGF (pH 1.2) and it was observed that all the formulations showed immediate gelation on making contact with SGF. Most of the formulations were gelled within 11 s and the gelling time ranged between 4-11 s (Table 3). The importance of presence of calcium carbonate for leading *in situ* gelation was evident from the fact that the formulation containing highest amount of calcium carbonate exhibited shortest gelation time whereas formulation containing small amount of calcium carbonate took longer time for gelation (Table 3). Formulation F3, F6, F9 showed a shortest gelation time, whereas formulation F1, F4, F7 showed a highest gelation time. This could be explained by the fact that calcium carbonate being present in the formulation as insoluble dispersion which becomes soluble in the acidic medium and release calcium ions, that cause gelation of LMP. In addition, the high polymer and calcium carbonate combinations demonstrated adequate gel strength when a pair of fine forceps pressed; indicating that they will withstand the shear forces likely to be encountered in the stomach. Thus, such vehicle will have longer residence time than oral solutions.

Floating properties

The floating ability of the prepared formulations was evaluated in SGF pH 1.2. The time taken by the formulation for buoyancy on the medium surface (floating lag time) and total time for which formulation constantly floated on the dissolution medium surface (duration of floating) were evaluated and are shown in Table 3. The calcium carbonate effervesced, releasing carbon dioxide and calcium ions. The released carbon dioxide is entrapped in the gel network producing buoyant formulation and then calcium ion reacted with LMP produced a cross linked three dimensional gel network that might restrict the further diffusion of carbon dioxide and drug molecules and has resulted in extended period of floating and drug release, respectively [10]. The floating ability of the formulation mainly depends on calcium carbonate and LMP concentrations. The calcium carbonate concentration is responsible for the increase in the amount of Ca^{++} and

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	63.87	51.3	49.6	56.8	61.1	54.6	61	53.7	49.5
2	71.75	59.7	54.4	62.7	67.8	61.6	66.1	58.3	52.9
3	81.3	67.1	62.1	67.8	72.9	67.4	70.4	63.9	62.9
4	87.25	72.1	66.1	73.1	78.7	70.6	76.3	70.1	69.1
5	92.94	89.9	71.9	80.5	87.8	75.6	84.4	73	74.08
6	95.94	94.8	79	86.9	94.1	81.6	93.4	77.6	83.9
7	-	98.7	85.9	94.7	98.4	87.9	98.8	85.2	89.2
8	-	-	93.6	98	-	93.5	-	93	93.7

Table 4: Cumulative % drug release.

Model	R^2	K-value
Zero order	0.634	14.9557
1st order	0.9475	-0.4133
Matrix	0.9564	36.9622
Peppas	**0.9683**	**53.3136**
Hix. Crowell	0.9461	-0.0906

Table 5: Model fitting of batch F5.

CO_2 that leads to reduction in floating lag time and increased duration of floating. Similarly, an increase in the polymer concentration resulted in decreased floating lag time and an increase in floating duration of the prepared systems. The best formulation (F5) containing (0.5%) calcium carbonate showed floating lag time 37 ± 3.1 s with duration of floating 24 h.

In vitro drug release

The drug release from floating *in situ* gel was analyzed by plotting the % Cumulative drug release against Time (h). The effect of polymer concentration on *in vitro* drug release from *in situ* gels is shown in Figure 4. Increase in polymer concentration leads to significant decrease in the rate and extent of drug release which could be attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length that has to be traversed by the drug molecules [11]. The release of drug from these gels was characterized by an initial phase of high release (burst effect). However, as gelation proceeds, the remaining drug was released at a slower rate followed by a second phase of moderate release this could be due to time required to conversion sol to gel. With the increase in polymer concentration the initial burst effect was found to be considerably reduced. The effect of calcium carbonate concentration on *in vitro* drug release from *in situ* gels is shown in Figure 4 which reveals that drug release was decreased with increasing the calcium carbonate concentration in formulations [9]. The *in vitro* drug release studies reveled that formulations F1 to F9 containing 0.75, 1 and 1.25% of novel polymer LMP respectively were able to sustained the drug release for up to 8 h. In all the formulations polymer concentration found to influence the release of the drug from the formulations.

The drug release data were fitted to different kinetic models and it was found to observe Korsmeyer–Peppas' kinetics. The Korsmeyer–Peppas equation [10] for drug release is given below:

$Mt=M1 ¼ Kt^n$

Where, $Mt=M_1$ is the fraction of drug released in time t, K is constant and n represents the release exponent indicative of mechanism of drug release. When n=0.5 means Fickian diffusion, 0.5>n<1.0 non-Fickian diffusion and n=1.0 super Case II transport. The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but there is also a relaxation of the polymer chains, which influences the drug release mechanism leading to non-Fickian or anomalous diffusion [12]. In the present study deviation from Fickian diffusion was observed could be attributed to the reason that the formulations during gelation usually imbibe a large amount of dissolution fluid leading to a swollen state of the gel. This even might have resulted in the polymeric chain relaxation resulting in non-Fickian mechanism of drug release. The model fitting for optimized formulations is presented in Tables 4 and 5.

Optimization data analysis

Widely practiced approach in the development and optimization of drug delivery devices is the Response Surface Methodology (RSM). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms. Based on the principle of design of experiments, the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation. Various computations for the current optimization study were performed using Design Expert software (Design Expert trial version 8.0.4; State-Ease Inc., Minneapolis, MN, USA). A two-factor three-level full factorial design was used for complete study of combination of natural polymer and effervescent agent. A 3^2 full factorial design was constructed where the amounts of LMP (X_1) and calcium carbonate (effervescent agent) (X_2) was selected as the independent variables i.e., factors. The levels of these factors were selected on the basis of initial studies and observations. All the other formulation aspects and processing variables were kept invariant throughout the study period. Polynomial models including interaction and quadratic terms were generated for the entire response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as $Y=B+B_1X_1+B_2X_2+B_3X_1X_2^2+B_4X_1^2X_2^2+B_5X_1^2X_2^2$.

Whereas, the B_0 is the arithmetic average of all the quantitative outcomes of nine runs and B_1 and B_2 are the coefficients computed from the observed experimental values of Y. X_1 and X_2 are the coded levels of independent variables. The interaction terms (X_1 and X_2) shows how the response values changes when the two factors are simultaneously changed. The polynomial equations can be used to draw conclusion after considering the magnitude coefficient and the mathematical sign that the coefficient carries. A high positive or negative value in the equation represent that by making a minor change in the setting of that factor one may obtain a significant change in the dependent variable. Statistical validity of the polynomials was established on the

Source	Sum of Squares	Df	Mean Square	F-Value	p-value Prob>F	Significance
Model	31.42	2	15.71	3.67	0.0909	S
A-Polymer Conc.	1.59	1	1.59	0.37	0.5643	NS
B- calcium carbonate Conc.	29.83	1	29.83	6.97	0.0385	S
Residual	25.67	6	4.28	-	-	-
Cor Total	57.1	8		-	-	-

Table 6: Analysis of variance for Y1 (Q_8).

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob>F	Significance
Model	212.83	2	106.42	4.86	0.0556	S
A-Polymer Conc.	20.17	1	20.17	0.92	-	-
B-Calcium Carbonate Conc.	192.67	1	192.67	8.8	-	-
Residual	131.39	6	21.9	-	-	-
Cor Total	344.22	8	-	-	-	-

Table 7: Analysis of variance for Y2.

No.	Concentration of LMP	Calcium Carbonate Concentration	%Drug release	Floating lag time in sec	Desirability
1	1	0.47	96.41	40	1

Table 8: Solutions for optimized batch.

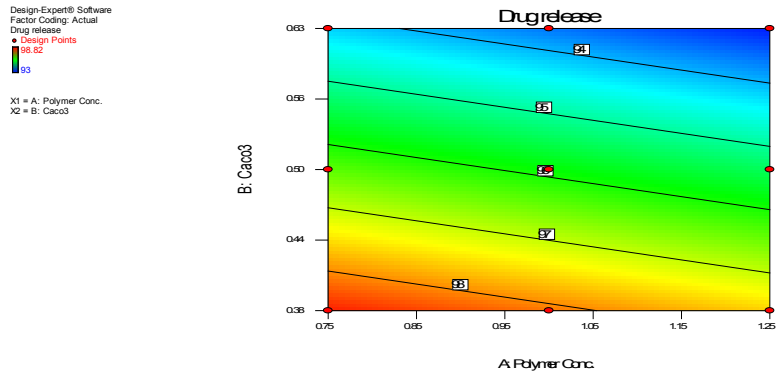

Figure 5: Contour plot of Q8 for floating *in situ* gel of Ranitidine hydrochloride.

basis of Analysis of Variance (ANOVA) provision in the Design Expert software. Level of significance was considered at $p<0.05$. The best-fitting mathematical model was selected based on the comparison of several statistical parameters, including the Coefficient of Variance (CV), the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2), and the Predicted Residual Sum of Squares (PRESS), provided by the software. PRESS indicates how well the model fits the data and for the chosen model, it should be small relative to the other models under consideration. The 3-D response surface graphs and the 2-D contour plots were also generated and are very useful to see interaction effects of the factors on responses.

Model assessments for the dependent variables

For Q_8 (drug release 8 h): Final Equation in Terms of Actual Factors

$$Q_8=+106.86033-2.06000 \times X_1-17.83867 \times X_2$$

The Model F-value of 3.67 implies there is a 9.09% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms are significant. In this case B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model (Table 6).

Floating lag time: Final equation in terms of actual factors: Floating lag time=+69.44444-7.33333 X_1-45.33333 X_2. The Model F-value of 4.86 implies there is a 5.56% chance that a "Model F-Value" this largecould occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant. If there are any insignificant model terms (not counting those required to support hierarchy), model reduction may mprove your model (Table 7).

Solutions for optimized batch

After analysis of both independent variables and dependent variables and setting the limits to achieve the set goal, Design expert software gave following solutions (Table 8).

Drug excipients compatibility studies

DSC study was used to check the compatibility between drug and polymer. Figure 3 shows the DSC curves of pure drug and polymer. A sharp endothermic peak of drug and LMP was obtained at 133°C and 224°C indicating melting point of drug (Ranitidine hydrochloride) and polymer (LMP). This indicated that there is no interaction between

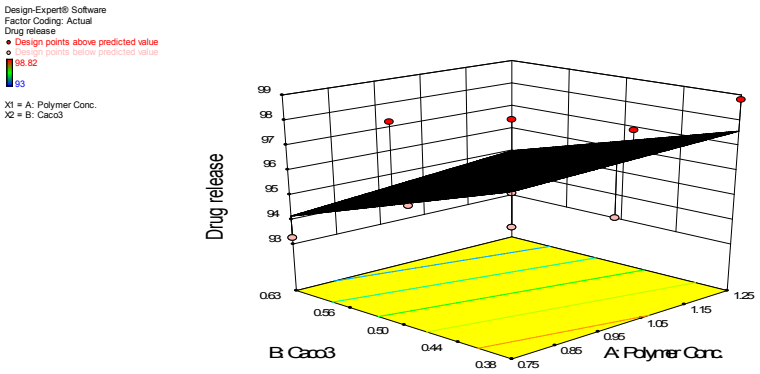

Figure 6: 3D response curve of Q8 floating *in situ* gel of Ranitidine hydrochloride.

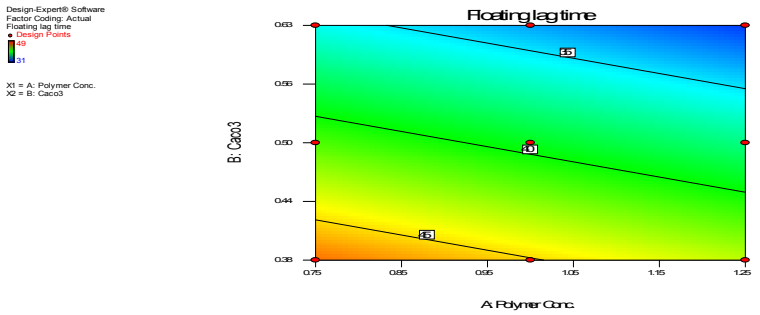

Figure 7: Contour plot of floating lag time for floating *in situ* gel of Ranitidine hydrochloride.

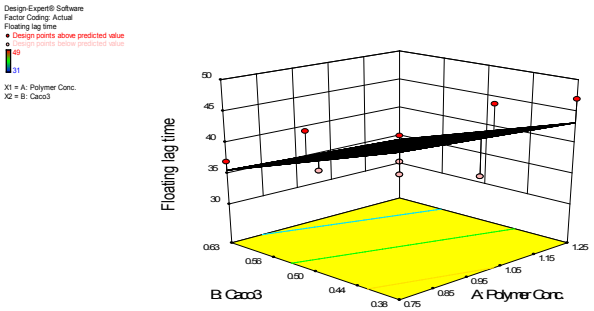

Figure 8: 3D response curve of floating lag time for floating *in situ* gel of Ranitidine hydrochloride.

drug and polymer used in the formulation i.e., the drug and polymer is compatible with each other.

Stability Studies

The stability studies were carried out for the optimized formulation. The optimized formulation did not show any significant change in drug content when kept at different conditions and periods. No significant differences in values of % drug release after 8 h observed during the stability studies. It indicates that irrespective of concentration of polymer, this formulation was able to retain its stability (Figures 5-8).

Conclusion

The formulated stable *in situ* gel for Ranitidine HCl was found to be easier and simpler to produce. It was found to have better floating efficacy and *in vitro* release profile characteristics. Hence it may represent as a new alternative, natural and cheaper formulation of Ranitidine HCl which may improve the patient compliance.

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