Research Article

Formulation and Evaluation of Raft forming Gallic Acid Chewable Tablets for Peptic Ulcer

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ABSTRACT

Over past few decades, Peptic ulcer disease remains a common condition despite the numerous advancements in treatment. The objective of this research work was to formulate gastro retentive chewable tablet by raft approach using Gallic acid (Antioxidant, Cytoprotective, Anti-ulcerogenic agent) as drug candidate. Formulation also contained a raft forming agent along with alkalizing agents (Calcium carbonate and Sodium Bicarbonate). In preliminary screening, various raft forming agents (Natural as well as synthetic) were used but tablets containing Sodium alginate and pectin (2:1) were having maximum raft strength as compared to other agents. Raft strength was only affected by the amount of Raft forming agent, Calcium carbonate and Sodium Bicarbonate (alkalising agent). Tablets were prepared by wet granulation and evaluated for raft strength, acid neutralization capacity, weight variation, % drug content, thickness, hardness, friability and In vitro drug release. Experimental work: A Box Behnken design was used in present study for optimization. Amount of raft forming agent, amount of alkalising agents were selected as independent variables. Raft strength measurement, Acid neutralisation capacity, and %CDR at different time interval were selected as dependent variables. Raft strength, Acid neutralization capacity and In vitro drug release of all the experimental batches were found to be satisfactory. Result and Discussion: BB13 batch was optimized based on maximum raft strength, good acid neutralization capacity and better % drug release. Drug-excipients compatibility study showed no interaction between drug and excipients. Stability study of optimized formulation showed that tablets were stable in accelerated environmental condition. Conclusion: It was concluded that raft forming chewable tablet containing Gallic acid (Anti-oxidant, Cytoprotective, Anti-ulcerogenic agent) and alkalizing agents could be efficient in the treatment of peptic ulcer.

Keywords: Raft forming chewable tablet, Gallic Acid, Box-Behnken Design, Peptic ulcer.

INTRODUCTION

A peptic ulcer is a sore in the lining of stomach and duodenum. The two most common types of ulcers are called "gastric ulcer" and "duodenum ulcer". Peptic ulcers are found to be an imbalance between aggressive factors such as hydrochloric acid (HCL), pepsin, refluxed bile, leukotrienes, reactive oxygen species and defensive factors, which include the functions of mucus bicarbonate barrier, prostaglandins, mucosal blood flow, cell renewal and migration, non enzymatic and enzymatic antioxidants and some growth factors. H. Pylori infection and use of non steroidal anti inflammatory drugs are the predominant causes of peptic ulcers. Also a number of factors are implicated in pathogenesis of gastric ulcer, among which major factors involved are bacterial infection, certain medications, chemicals (HCL/ethanol), gastric cancer and minor factors are stress, smoking, spicy food, and nutritional deficiencies. The idea behind treating ulcers is to lower the amount of acid that your stomach makes, to neutralize the acid that made and to protect injured area so it protect the injured area so it can have time to heal.

Oral delivery of the drug is the more suitable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations but has a drawback of non-site specificity and short gastric resident time. In order to overcome the drawbacks of conventional oral drug delivery systems, much technical advancement have led to the development of gastro retentive drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits. Gastro retentive drug delivery system is facing many challenges which can be overcome by upcoming newly emerging approach i.e. raft forming system.

Among other systems, the raft forming system has been well preferred as it is for achieving a prolonged and predictable drug delivery profile in the GI tract. This system is capable of releasing a drug in a sustained manner affording relatively constant plasma profiles. It is developed to provide symptom relief by forming a physical barrier on top of the stomach contents in the form of a neutral floating raft. Rafts were cohesive, buoyant, voluminous, and resistant to reflux and durable under conditions of movement (resilient).The goal for designing this system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, decreasing the dose required or providing uniform drug delivery.

The mechanism involved in the raft formation is that this raft floats on gastric fluids because of low bulk density created by the formation of CO_2. The system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system

less dense and float on the gastric fluids. A raft forming formulation requires sodium or potassium bicarbonate. Calcium carbonate can be used as a alkalizing agent as well as raft strengthening agent. Various polymers have been used. Alginic acid, alginates, pectin are most widely used raft forming agents. Other polysaccharides such as carrageenan, isapgol, locust bean gum, guar gum, Xanthan gum are also being used. [1-5]

All recent treatments available for peptic ulcer either have one or more problems like side effects, costly or painful. Hence the objective of the present investigation was to formulate and evaluate raft forming chewable tablets containing Gallic acid has Anti ulcerogenic, cytoprotective and anti oxidant action that gives protection to mucosal layer, neutralizes acid and removal of free radicals. [6-10]

MATERIALS AND METHODS

Materials

Gallic acid was purchased from Sisco Research laboratory Pvt. Ltd. Maharastra, India. Sodium Alginate was purchased from Krishna chemical Industry, Gujarat, India. Pectin was purchased from Suvidhinath Lab, Gujarat, India. All other excipients used to prepare chewable tablets were of standard pharmaceutical grade and all chemical reagents were Analytical grade. [12]

Methods

Preparation of Raft forming chewable tablets

Weigh accurately drug, polymer and other ingredients separately. All the ingredients except binder and lubricant were mixed thoroughly. PVP K30 was dissolved in sufficient quantity of solvent and added to powder mixture to prepare dump wet mass. The prepared wet mass was passed through 22 # sieve. Granules were allowed to dry in hot air oven and then resifted through 40 # sieve. Granules were collected and other ingredients were added and lubricated. Granules Batches were prepared according to described in table 1 which was on the bases of selection for raft forming agent and alkalizing agent 1 containing Magnesium Oxide, alkalizing agent 2 containing sodium bicarbonate and selection for diluents and binders.[11]

Table 1: Polymer screening

Ingredients	Amount for 1000mg tablets					
	A1	A2	A3	A4	A5	A6
Gallic Acid	250	250	250	250	250	250
Sodium Alginate	200					
Pectin		200				
Guar Gum			200			
Xanthan Gum				200		
Cabopol 934					200	
Sodium Alginate+ Pectin (2:1)						200+100
Sodium Bicarbonate	50	50	50	50	50	50
Calcium carbonate	125	125	125	125	125	125
Mannitol	290	290	290	290	290	175
PVP K30	50	50	50	50	50	50
Talc	20	20	20	20	20	20
Magnesium Stearate	10	10	10	10	10	10
Propyl Hydroxy Benzoate	5	5	5	5	5	5
Raft strength	++ (Degrade above 1.7 pH)	++	+	+	Not formed	+++
Acid Neutralization capacity	5.9	4.1	5.4	4.3	5.1	6.3

+++: Good, ++: Average, +: Poor

From the preliminary study of granules

From the preliminary study of granules as a polymer screening two properties namely raft strength and acid neutralization capacity was evaluated as described in table 1. Both tests are performed which is described as in evaluation parameters.

Drug-Excipients Compatibility Study

Drug excipients interaction play important role in the release of drug from formulation. Fourier transform infrared spectroscopy (FTIR) has been used to study the physical and chemical interaction between drug and excipients. The FTIR spectra of Gallic acid mixture of Gallic acid with other excipients were recorded using an FTIR instrument (FTIR – 8400S; Shimadzu). [13]

Optimization by Box Behnken Statistical Design

Box Behnken design was preferred as choice of experimental design considering its requirement of fewer numbers of experimental runs for three independent variables than full factorial design. A Box Behnken Design was adopted to optimize the formulation variables. Amount of raft forming agent, alkalizing agent and amount of calcium carbonate as independent variables have significant influence on raft strength, acid neutralization capacity and drug release as a dependent variables**.** RSM option of Design expert® software (version 11.0, stat-Ease Inc., Minneapolis, MN) was employed to perform optimization of developed for raft forming chewable tablet composition. This design performed by selecting most suitable batch from preliminary study PB21 which is optimized by box Behnken design. Coding variables are described in Table 2. The formulation layout of experimental batches is shown in Table 3. Tablets of all the batches were evaluated for weight variation, hardness, drug content, friability, raft strength, acid neutralization capacity and drug release. The polynomial equation can be used to draw conclusions after considering the magnitude of the coefficient and mathematical sign it carries (i.e. positive or negative). Data were analysed using regression by design expert. [14, 15, 16]

Table 2: Coding Variables

Variables	Low(-1 level)	Medium(0)	High (1 level)
X1	300	200	100
X2	40	50	60
X3	75	137.5	200

Evaluation of raft forming chewable tablets

Weight variation

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10%.

Tablet hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

Friability

Friability is the measure of tablet strength. Roche friabilator was used. Required no. of tablets as per specification were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined. That lose <0.5 to 1%of their weight are considered acceptable.

Uniformity of content

Weight twenty tablets and finely powder. Powder equivalent to 250 mg of Gallic acid was dissolve in 100 ml 0.1 N HCl. Solution was filter through whatman paper no. 1. Further 10 ml solution diluted up to 100ml 0.1 N HCl and absorbance is measured at 273 nm by using UV spectroscopy Shimadzu 1601. The amount of Gallic acid was calculated by using the equation of calibration curve.

Raft strength measurement by in house method

Different types of manual and automatic methods are used for raft strength measurement. Here, the raft strength of the preliminary trial batches was determined by a modified balance method. In which powder of tablets equivalent to unit dose was transferred to 150 ml of 0.1 N HCl and maintained at 37°C in a 250 ml glass beaker in one pan on the balance and another side same amount of solvent except powder was taken. The raft was allowed to form around an L-shaped wire probe (diameter: 1 mm) held upright in the beaker throughout the whole period (30 min) of raft development. After 30 min of raft development, the probe was pulled vertically up through the raft at a rate of 30 mm/min. The ml required to pull the wire probe up through the raft was recorded.

Acid Neutralization Capacity

Granules (Pre compression) or a tablet powder equivalent to unit dose (In post compression) was transferred to a 250 ml beaker; 50 ml of water was added to it and was mixed on a magnetic stirrer for 1 min. A 30‑ml volume of 0.1 N HCl was added with continuous stirring on the magnetic stirrer for 10 min after addition of the acid. Stirring was discontinued and the gum base was removed using a long needle without delay. The needle was promptly rinsed with 20 ml of water, and the washing was collected in the beaker; stirring was resumed for 5 min. Titration began immediately. Excess HCl was titrated against 0.5N sodium hydroxide to attain a stable pH of 3.5. The number of mEq of acid consumed by the tablet tested was calculated by the following formula-

Total mEq = (30 * N HCl) - (V NaOH * N NaOH)

Where, N HCl=Normality of HCl; V NaOH =Volume of NaOH required; and N NaOH =Normality of NaOH.

Table 3: Compositions of Experimental Batches (BB1-BB13)

Ingredients (mg)	BB1	BB2	BB3	BB4	BB5	BB6	BB7	BB8	BB9	BB10	BB11	BB12	BB13
Gallic Acid	250	250	250	250	250	250	250	250	250	250	250	250	250
Sodium Alginate+Pectin (2:1)	100	300	100	300	100	300	100	300	200	200	200	200	200
Sodium Bicarbonate	40	40	60	60	50	50	50	50	40	60	40	60	50
Calcium Carbonate	137.5	137.5	137.5	137.5	75	75	200	200	75	75	200	200	137.5
Mannitol	387.5	187.5	367.5	167.5	440	240	400	200	350	330	225	205	277.5
PVPK30 (In water)	50	50	50	50	50	50	50	50	50	50	50	50	50
Talc	20	20	20	20	20	20	20	20	20	20	20	20	20
Mg Stearate	10	10	10	10	10	10	10	10	10	10	10	10	10
PropylHydroxy Benzoate	5	5	5	5	5	5	5	5	5	5	5	5	5
Total (mg)	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**

Dissolution studies

The release rate of Gallic acid from raft chewable tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5 °C and 50 rpm. Aliquot 10 ml volume was withdrawn from the dissolution apparatus at every 1 hour, and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release was determined from the calibration curve. [17, 18, 19, 20]

RESULTS AND DISCUSSION

Results of Preliminary screening

Selection of Raft strength & Acid Neutralization capacity-: Different excipients were used for selection of accurate formulation to make raft forming chewable tablet. In which Batch A6 showed good raft strength. It contained Sodium alginate and pectin which controlled the drug release and formed good raft compared to other polymers. Sodium alginate has shown to form rafts over a narrow pH range of 1 to 1.4. At higher pH more than 1.7 it did not form good raft. Adding pectin with sodium alginate was selected which showed goof raft strength. Results of different polymers were described in table 1. Sodium carbonate showed better acid neutralization capacity in stomach environment.

Different batches of granules were formulated using PVP K30 in which PVP K30 in water showed better binding capacity and good sustained release than other solvents. So, PVP K30 in water was selected for the preparation of Raft forming chewable tablets. Diluent plays an important role in increasing the bulk of the final formulation; it does not have any significant role in flow properties of granules or any other characteristics. Gallic acid has compatibility with Mannitol and also improves palatability. So, Mannitol was selected for the preparation of Raft forming chewable tablet of Gallic acid. A6 batch has shown good property so it was selected for experimental design.

Evaluation of Experimental Design Batches (BB1-BB13)

The experimental design batches were evaluated for various parameters by the methods described in methodology section. Carr's index for all the batches ranges from 10.00-16.27 Hausner's ratios for all the batches were found to be between 1.11-1.23. Values for angle of repose were in the range of 16.6-19.9. It was concluded that all the batches were having good flow characteristics. Acid neutralization capacity must be at least 5.0 mEq. All the bathes were having acid neutralization capacity above that limit. So results for acid neutralization capacity are satisfactory. Batch BB13 was having maximum raft strength of 4.5 gm with optimum acid neutralization capacity 6.80. Initially load was increased with time, it showed maximum load when raft was broken and then it decreased sharply. The maximum raft strength observed at the breaking (rupture) point of the raft was found to be 4.5 gm. BB13 Showed sustained release as described in table 7.

Table 4: Evaluation Parameters of Experimental Batches

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Angle of Repose(θ)	Hausner's ratio
BB1	0.36±0.01	0.42±0.02	14.28±0.5	18.2±0.03	1.16±0.01
BB2	0.35±0.01	0.43±0.03	14.63±0.5	18.6±0.04	1.22±0.02
BB3	0.34±0.03	0.39±0.02	12.82±0.2	16.6±0.05	1.14±0.01
BB4	0.38±0.02	0.44±0.01	13.63±0.2	17.2±0.02	1.15±0.02
BB5	0.35±0.04	0.41±0.05	14.63±0.2	17.6±0.03	1.17±0.03
BB6	0.36±0.02	0.40±0.04	10.00±0.5	18.8±0.05	1.11±0.04
BB7	0.37±0.01	0.42±0.03	11.90±0.8	19.9±0.03	1.13±0.02
BB8	0.35±0.05	0.42±0.08	16.66±0.05	15.6±0.05	1.23±0.02
BB9	0.34±0.02	0.40±0.05	15.00±0.06	17.6±0.03	1.08±0.03
BB10	0.37±0.04	0.44±0.05	15.90±0.06	18.5±0.02	1.18±0.05
BB11	0.38±0.05	0.45±0.02	15.55±0.05	16.5±0.02	1.18±0.04
BB12	0.34±0.02	0.39±0.03	12.82±0.06	17.8±0.01	1.14±0.05
BB13	**0.36±0.03**	**0.43±0.04**	**16.27±0.08**	**18.1±0.02**	**1.19±0.08**

* All values are means ±SD (n=3)

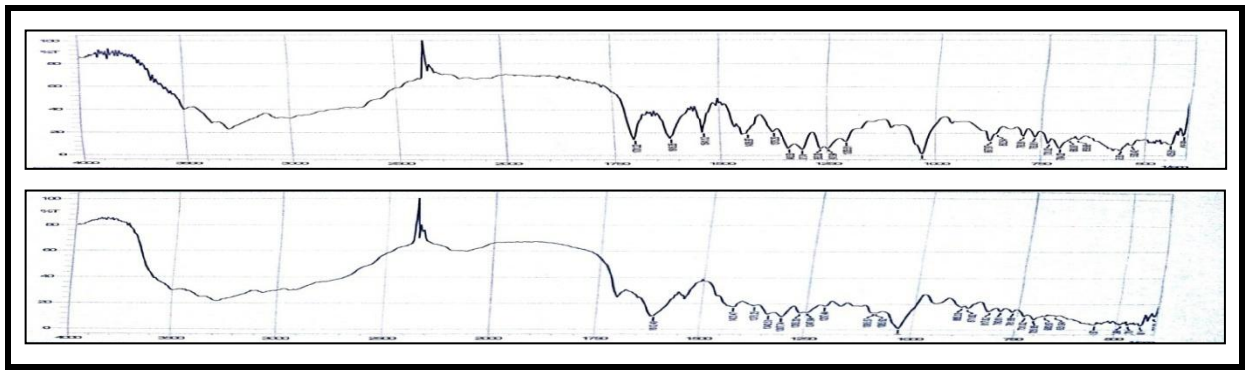

Figure 1: Fourier Transform infrared spectra of a) Gallic acid and b) Physical mixture of batch BB13 formulation.

Table 5: Results of Characterization of Raft forming tablets

Batch No.	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	%Drug Content	Friability (%)
BB1	994.46±0.66	4.91±0.34	4.25±3.00	99.11±0.01	0.52±0.02
BB2	993.52±0.94	5.11±0.14	4.27±0.01	99.24±0.09	0.65±0.09
BB3	994.85±1.85	5.00±0.07	4.30±0.02	98.75±0.34	0.58±0.04
BB4	992.22±0.94	5.23±0.16	4.29±0.01	98.53±0.15	0.45±0.09
BB5	993.55±0.13	5.31±0.05	4.33±0.02	99.62±0.77	0.72±0.19
BB6	993.36±0.57	4.85±0.32	4.28±0.03	98.39±0.86	0.81±0.06
BB7	992.55±0.31	5.21±0.25	4.41±0.09	99.21±0.57	0.61±0.05
BB8	992.69±0.25	5.15±0.21	4.35±0.02	99.24±0.52	0.53±0.21
BB9	993.21±0.21	5.18±0.35	4.38±0.05	98.78±0.062	0.48±0.05
BB10	994.51±0.15	4.98±0.25	4.21±0.04	99.11±0.65	0.58±0.06
BB11	993.78±0.16	4.95±0.21	4.25±0.06	98.56±0.05	0.62±0.08
BB12	992.52±0.14	5.55±0.15	4.11±0.08	99.85±0.21	0.63±0.05
BB13	**993.56±0.41**	**5.45±0.26**	**4.25±0.05**	**98.35±0.35**	**0.58±0.04**

* All values are means ±SD (n=3)

Table 6: Results of Raft strength and Acid Neutralization capacity

Batch	Raft strength (gm)	Acid neutralisation capacity (mEq)
BB1	3.81±1.27	5.21±0.01
BB2	5.36±0.21	7.17±1.48
BB3	3.65±0.14	5.82±1.47
BB4	5.42±0.49	5.88±0.19
BB5	3.70±0.42	5.32±0.57
BB6	5.01±0.84	5.29±0.59
BB7	3.56±0.52	5.41±0.77
BB8	5.60±0.56	5.36±0.25
BB9	3.98±0.62	5.10±0.56
BB10	4.00±0.23	5.75±0.69
BB11	4.19±0.45	5.19±0.58
BB12	4.25±0.66	5.92±0.62
BB13	**4.50±0.86**	**6.80±1.12**

* All values are means ±SD (n=3)

Table 7: Results of *In-Vitro* Drug Release of Raft forming Tablets

Time (Hour)	BB1	BB2	BB3	BB4	BB5	BB6	BB7
0	0±00	0±00	0±00	0±00	0±00	0±00	0±00
1	46.55±1.02	48.65±1.05	56.55±2.14	48.55±1.03	52.25±2.00	52.55±3.01	47.55±1.25
2	53.35±0.05	56.21±1.23	61.22±3.25	58.65±2.53	60.56±1.23	68.22±1.23	59.91±1.63
4	59.61±2.53	58.66±1.63	68.25±0.06	65.48±3.56	65.85±1.05	72.55±2.30	68.11±1.68
6	63.67±2.65	67.22±2.89	75.65±0.09	78.55±1.25	71.22±1.25	78.55±0.06	75.12±2.63
8	85.52±0.05	88.55±3.01	89.22±0.05	82.11±1.16	86.55±0.06	85.12±1.23	87.55±2.42
12	93.88±0.09	91.51±0.05	93.98±0.02	91.85±0.06	94.11±0.08	90.55±0.06	92.08±0.04
Time (Hour)	**BB8**	**BB9**	**BB10**	**BB11**	**BB12**	**BB13**	
0	0±00	0±00	0±00	0±00	0±00	**0±00**	
1	43.59±0.05	52.64±1.25	40.52±1.68	48.69±2.36	45.23±1.78	**53.85±3.55**	
2	57.35±0.06	57.29±2.36	48.26±2.36	58.66±1.25	58.59±1.66	**67.58±0.06**	
4	59.68±1.25	61.68±0.05	59.23±0.05	65.49±1.63	65.84±1.36	**73.39±0.05**	
6	70.68±2.36	67.26±1.45	69.64±0.26	78.56±1.98	71.29±1.57	**79.55±1.36**	
8	86.51±1.65	83.58±1.95	81.29±0.03	88.16±1.55	76.57±0.07	**82.12±2.45**	
12	91.88±0.06	88.87±0.02	89.12±0.01	87.51±0.06	87.39±0.02	**85.21±0.08**	

* All values are means ±SD (n=3)

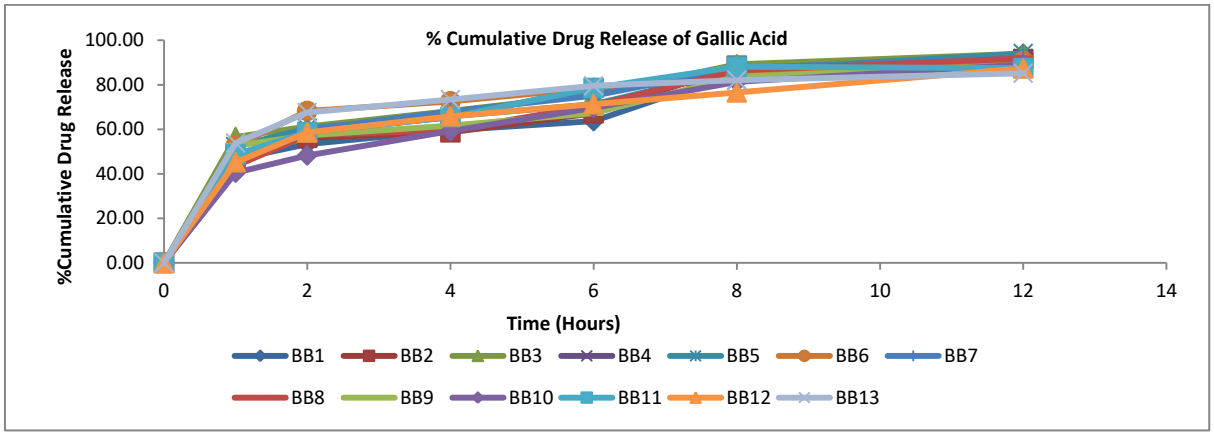

Figure 2: % Cumulative Drug Release of Gallic acid Formulations BB1-BB13

Table 8: Analysis of experimental design

Regression	DF	SS	MS	F value	P value	R^2
Raft strength (R1)						
FM	9	6.29	0.69	501.95	0.0001	0.9993
Acid Neutralizing capacity (R2)						
FM	9	2.69	0.2985	303.52	0.0003	0.9989
% Cumulative Drug Release (R3)						
FM	9	94.02	10.45	39.45	0.0058	0.9916

FM: Full model, DF: Degree of Freedom, SS: Sum of square, MS: Mean Square

The Model F-value of 501.95 implies the model is **significant**. P-values less than 0.0500 indicate model terms are **significant**. Final equation in terms of actual components,

Raft strength- +4.50 , X1* - +0.8337, X2*- +0.063, X3*- +0.1100

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 62.12 indicates an adequate signal. From that it was concluded that amount of sodium alginate increases raft strength increases

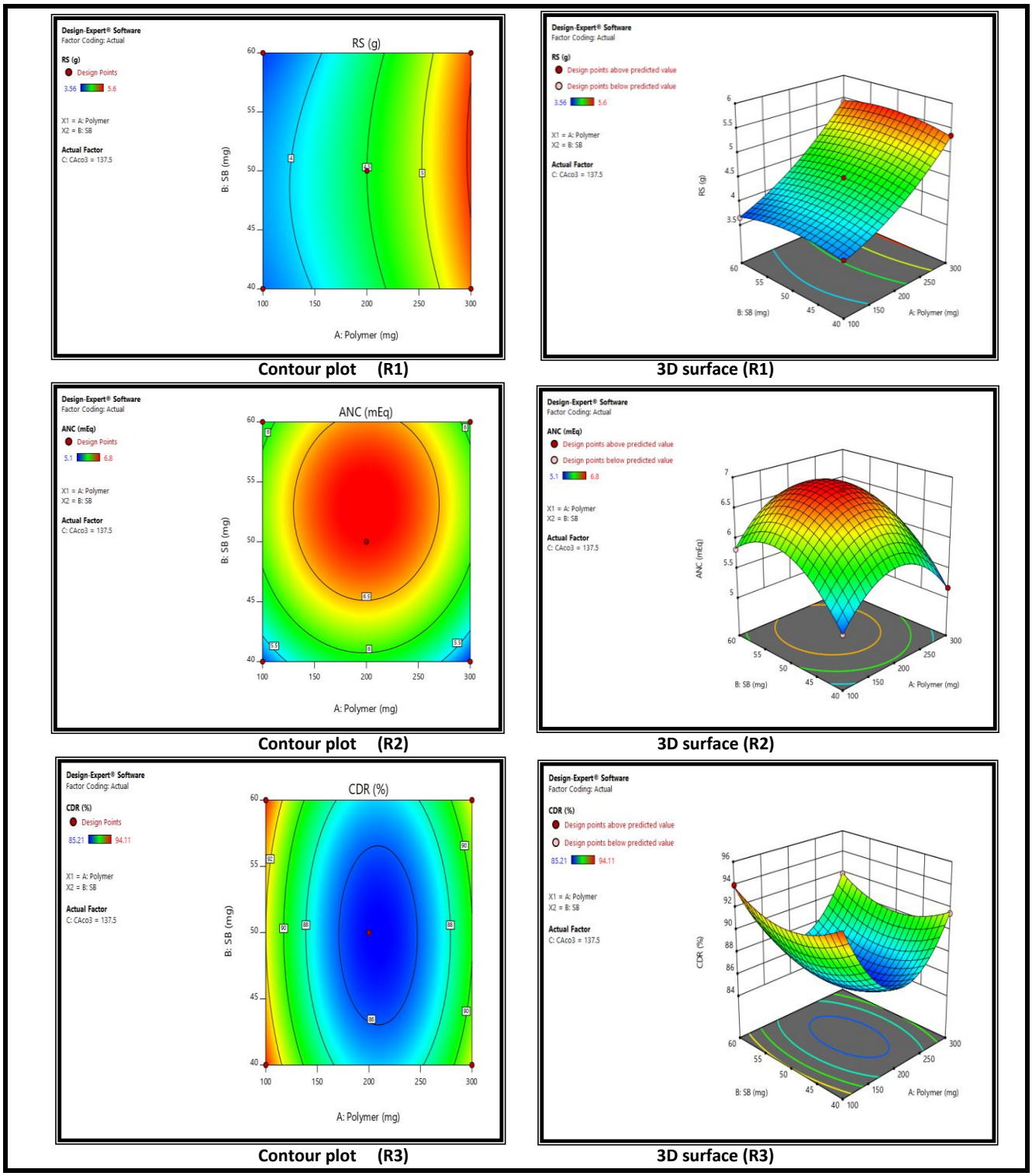

Figure 3: Contour plots and 3D surface plot for dependent responses (R1-R3)

The Model F-value of 302.52 implies the model is significant. P-values less than 0.0500 indicate model terms are significant. Final equation in terms of actual components,

Acid Neutralizing capacity - +6.80, X1- + 0.02, X2- +0.5918, X3 - +0.0516

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 61.084 indicates an adequate signal. From that it was concluded that as sodium bicarbonate increases acid neutralization capacity increases.

The Model F-value of 39.45 implies the model is significant. P-values less than 0.0500 indicate model terms are significant. Final equation in terms of actual components,

% Cumulative Drug Release - +85.21, X1 = -0.2623, X2= -1.81, X3= -0.1102

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 20.586 indicates an adequate signal. From that it was concluded that as Sodium alginate and Calcium carbonate concentration increases % cumulative drug release decreases it means that good sustained release formulation obtained.

CONCLUSIONS

A conclusion can be drawn that Gallic acid raft forming tablet was prepared using raft forming agents like sodium alginate and pectin. The raft floating was successfully achieved using sodium bicarbonate and calcium carbonate. The evaluation parameters like raft strength, Acid Neutralization capacity and drug release were showing satisfactory results. For the selection of optimized batch point prediction option of software utilized 13 trial formulations prepared according to Box-Behnken design. The optimized composition of present formulation was selected by software. It was found that formulation BB13 with the polymer combination of Sodium alginate and Pectin at 2:1 ratio (A) 200 mg, Sodium Bicarbonate (B) 50 mg, Calcium carbonate (C) 137.5 mg fulfilled the criteria of an optimum formulation. Optimized formulation produced Raft strength (Y1) 4.5 g, Acid Neutralization capacity (Y2) 6.80 mEq, % Cumulative Dug release (Y3) 85.21%. Thus it can be said that the novel raft forming tablet of Gallic acid as Anti ulcerative, cytoprotective and antioxidant can be used in treatment of peptic ulcer which is common problem of many patients.

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