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Research Article

Sintering – An approach for the development of controlled release system of vitamin B1

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ABSTRACT

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat or by exposing to solvents. In the present investigation it was proposed to apply sintering in the development of controlled release system of vitamin B1 (thiamine HCl) following response surface methodology. Pre-compression and post compression parameters were evaluated and found the results within satisfactory limits. Ethylene vinyl acetate 15 was used as the release controlling polymer. Of the three models, quadratic model was suggested for all the responses T_{90}, floating lag time and floating time. The F value for the T_{90}, floating lag time and floating time responses was found to be 58.86, 77.08 and 26.58, respectively, which indicated that the models are significant. The optimum values of selected variables obtained from the Design Expert 12 software was 64.29 mg of EVA 15, 7.92% w/w of sodium bicarbonate (to tablet weight), 74.68 °C of sintering temperature and 1.99 hours sintering exposure time. Optimized formulation showed 103 seconds floating lag time and 12.2 hours of floating time. Obtained T_{90} was found to be 11.2 hours which followed zero order release kinetics with non-Fickian diffusion mechanism.

1. Introduction

Sintering is defined as "the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat or by exposing to solvents"[1-8]. Sintering means fusion of particles or formation of welded bonds among particles of polymer. In other words, sintering technique increases the cross linking across the particles in the polymer. There are limited reports where sintering technique was applied in the design of controlled drug delivery systems using different drugs and polymers. The use of sintering in the development of gastro retentive drug delivery systems has also been found to be a promising technique. However, there are only few reports on its applicability with few polymers.

Chemically thiamine belongs to a class of organic substances known as thiamines structurally characterized by 3-[(4-Amino-2-methyl-pyrimidin-5-yl)methyl]-4-methyl-thiazol-5-yl backbone[9]. Thiamine (Vitamin B1) comes under the category of diet, food, nutrient, growth substrate and micronutrient[10,11].

Thiamine is preferred in the cases of deficiency and is generally taken along with other B vitamins. It acts as cofactor in glucose metabolism. Thiamine plays a key role in conversion of carbohydrates and fats into energy. Thiamine is an essential vitamin for normal growth and development with proper functioning of heart, nervous and digestive systems. Thiamine melts and gets decomposed at 248 ºC. Thiamine is used in deficiency conditions like Beriberi, neuritis (inflammation of nerves) associated with pregnancy and pellagra. It is also used in digestive problems like ulcerative colitis, lack

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or poor appetite and diarrhoea. Thiamine is also preferred as immune booster for AIDS patients. Other indications include heart disease, diabetic pain, aging, alcoholism, cerebellar syndrome, sores, vision problems (cataract, glaucoma), motion sickness and for better athletic performance. Thiamine has also found advantage in kidney problems with diabetics and cervical cancer preventive measures. It is also indicated for Wernicke-Korsakov syndrome (encephalopathy), delirium, Korsakov's alcoholic psychosis, and peripheral neuritis.

In the preparation investigation gastric floating tablets (GFT) of thiamine HCl were prepared using thermal sintering technique. Box-Behnken design was used for optimizing the selected independent variables. Initial formulation and evaluation trials were made to assess the influence of drug-polymer ratio (1:0 to 1:2) and weight of gas generating agent/tablet. Based on the studies, the drug-polymer ratio and weight of sodium bicarbonate/tablet were identified and used for experimental design.

2. Materials and Methods

Thiamine HCl, EVA 15, sodium bicarbonate, microcrystalline cellulose and magnesium stearate are used of analytical grade. All other chemicals used are also of analytical grade.

Experimental design

Total four factors (two are formulation related and two are process related) at three levels were used to design the experiments for optimization. The formulation related independent variables are drug-polymer ratio and weight of gas generating agent/tablet (%w/w) and that of process related are sintering temperature and sintering time. Box-Behnken design was used for optimizing the independent variables selected. Responses namely T_{90} (time taken to release 90% drug), floating lag time (time taken for the tablet to float over the fluid surface) and floating time (duration for which the tablet floats on the surface of liquid) are taken as dependent variables. The independent variables and their levels are shown in **Table 1**.

Table 1: Independent variables and their levels used in Box-Behnken design

Code	Independent variable	EVA 15		
		Low (-1)	Medium (0)	High (+1)
X1	Drug-polymer ratio	1:0.4	1:0.6	1:0.8
X2	Weight of gas generating agent/tablet (% w/w) (sodium bicarbonate)	5	10	15
X3	Sintering temperature (°C)	60	70	80
X4	Sintering time (hours)	1.5	3	4.5

The critical values for achieving the desired response and the possible interaction effects of selected independent variables on responses were predicted by Design Expert software v12 and 29 runs including 5 replicates of center points were obtained as per Box-Behnken design for four independent variables at three levels as shown in **Table 2**.

Table 2: Experimental design codes for 4 factors at 3 levels

Standard run	X1	X2	X3	X4
1	-1	-1	0	0
2	-1	0	0	-1
3	-1	0	0	+1
4	-1	0	-1	0
5	-1	0	+1	0
6	-1	+1	0	0
7	0	-1	-1	0
8	0	-1	+1	0
9	0	-1	0	-1
10	0	-1	0	+1
11	0	0	-1	-1
12	0	0	+1	-1
13	0	0	-1	+1
14	0	0	+1	+1
15	0	0	0	0
16	0	0	0	0
17	0	0	0	0
18	0	0	0	0
19	0	0	0	0
20	0	+1	-1	0
21	0	+1	+1	0
22	0	+1	0	-1
23	0	+1	0	+1
24	+1	-1	0	0
25	+1	0	0	-1
26	+1	0	0	+1
27	+1	0	-1	0
28	+1	0	+1	0
29	+1	+1	0	0

Formulation of thiamine HCl GFT

A total of 9 formulations were predicted using the two formulation independent variables i.e., drug-polymer ratio and weight of gas generating agent/tablet (%w/w) as per Box-Behnken design. The formulae are shown in **Table 3 and 4** for tablets. These are coded as unsintered tablets. Initially these tablets were prepared and further subjected to process related independent variables i.e., sintering temperature and sintering time. These unsintered tablets were subjected to the 29 runs as shown in **Table 2** containing 100 of thiamine HCl.

Table 3: Formulae of thiamine HCl unsintered GFT using EVA 15

Ingredient	TE1 U	TE2 U	TE6 U	TE7 U	TE11 U
Thiamine HCl	100	100	100	100	100
EVA 15	40	40	40	60	60
Sodium bicarbonate	10	21	34	11	24
Microcrystalline cellulose	50	50	50	50	50
Magnesium stearate	2	2	2	2	2
Total weight (mg)	202	213	226	223	236

Table 4: Formulae of thiamine HCl unsintered GFT using EVA 15

Ingredient	TE20U	TE24U	TE25U	TE29U
Thiamine HCl	100	100	100	100
EVA 15	60	80	80	80
Sodium bicarbonate	37.5	12	26	41
Microcrystalline cellulose	50	50	50	50
Magnesium stearate	2.5	2.5	2.5	2.5
Total weight (mg)	250	244.5	258.5	273.5

Evaluation of flow properties of pre-compression blend

The flow properties of the pre-compression blend were determined by angle of repose, Carr's compressibility index and Hausner's ratio.

Evaluation of thiamine HCl GFT

The prepared thiamine HCl GFT were evaluated for different post compression parameters like thickness and diameter, hardness, friability, uniformity of weight, drug content, in vitro floating characteristics, and in vitro drug release.

In vitro drug release studies

In vitro drug release studies were carried out for the prepared formulations using USP type-II (paddle method) dissolution rate test apparatus Lab India DS-8000 using 900 mL of 0.1N HCl as dissolution medium maintained at a temperature of 37°C±0.5°C. The shaft rotation speed was maintained at 50 rpm. The study was performed for 12 hours and 5 mL samples were withdrawn at fixed time intervals using a syringe fitted with prefilter. 5 mL of fresh medium maintained at 37°C±0.5°C was used for replacement at every time interval by washing the particles back to dissolution medium adhered to prefilter. The samples collected were analysed for thiamine HCl content by measuring the absorbance at 235 nm after suitable dilutions wherever necessary against 0.1N HCl as blank. All the *in vitro* drug release studies were performed in triplicate and average values are reported.

3. Results and Discussion

Pre-compression studies

The drug and excipient powder blends were prepared as per the formulae given in Table 3.3 and 3.4 and evaluated for their flow characteristics angle of repose, Carr's index and Hausner's ratio. Bulk density and tapped density are estimated to get the necessary characteristics. The results are shown in Table 4.20. The angle of repose of the powder blend was found to be in the range of 25.36° - 31.25° which indicated good to excellent flow property. The Carr's index values are in the range of 10.81 to 19.74 indicating the compressibility nature of powder blend whereas the Hausner's ratio values of all the formulations were in the range of 1.12 to 1.25 supporting the good flow of prepared powder blends.

Post-compression studies

Results of the post compression studies conducted for the GFT of thiamine HCl prepared with EVA 15 showed a uniform thickness and diameter of prepared tablets. The measured hardness of tablets ranged between 4.2 to 5.1 kg/cm2. The friability values ranged between 0.41 to 0.63%. The results indicated that all the tablets passed weight variation test as the deviation in weight was within the Pharmacopoeial limits of ±7.5% of the average weight. The drug content of each individual preparation was found to be within the limits of 90 to 110% indicating that the test complies with the official compendia test for tablets. From the results, it was found that all the formulations shown floating lag time in the range of 61 to 153 seconds whereas the floating time was found to be in the range of 3.5-14 hours.

Drug release from unsintered tablets of thiamine HCl containing EVA 15 has shown 100% within the range of 5-8 hours whereas with the sintered tablets the drug release was extended in the range of 6-16 hours with varied drug-polymer ratio and sintering temperature and duration of heat treatment. Further the results are interpreted following statistical optimization as discussed in coming sections. All the formulations, except TE2U, and TE6U were found to follow zero order drug release kinetics. All the formulations except TE2U, TE6U, and TE20U, were found to follow diffusion mechanism based on the 'r' value. All the formulations were further found to follow non-Fickian diffusion mechanism of drug release.

Of the three models, quadratic model was suggested for all the responses T_{90}, floating lag time and floating time. The F value for the T_{90}, floating lag time and floating time responses was found to be 58.86, 77.08 and 26.58, respectively, which indicated that the models are significant. The optimum values of selected variables obtained from the Design Expert 12 software was 64.29 mg of EVA 15, 7.92% w/w of sodium bicarbonate (to tablet weight), 74.68 °C of sintering temperature and 1.99 hours sintering exposure time. Optimized formulation showed 134 seconds floating lag time and 12.5 hours of floating time. Obtained T_{90} was found to be 11.3 hours which followed zero order release kinetics with non-Fickian diffusion mechanism.

The application of RSM yielded the following regression equations which give an empirical relationship between the logarithmic values of T_{90}, floating lag time and floating time. Test variables in coded units: (A: Drug-polymer ratio EVA 15, B: weight of sodium bicarbonate/tablet (%w/w), C: sintering temperature, and D: sintering time)

T_{90} = 11.06 + 3.67 A + 0.2500 B + 0.9167 C + 0.7500 D - 0.1250 AB + 0.0000 AC + 0.1250 AD - 0.1250 BC + 0.2500 BD + 0.8750 CD - 1.36 A^2 - 0.3633 B^2 - 0.3633 C^2 - 0.6133 D^2

Floating lag time = 105.20 - 22.75 A - 20.75 B + 6.08 C + 3.58 D + 7.00 AB - 4.00 AC - 1.25 AD - 0.7500 BC + 0.0000 BD + 2.00 CD + 2.78 A^2 - 3.72 B^2 - 13.98 C^2 - 9.98 D^2

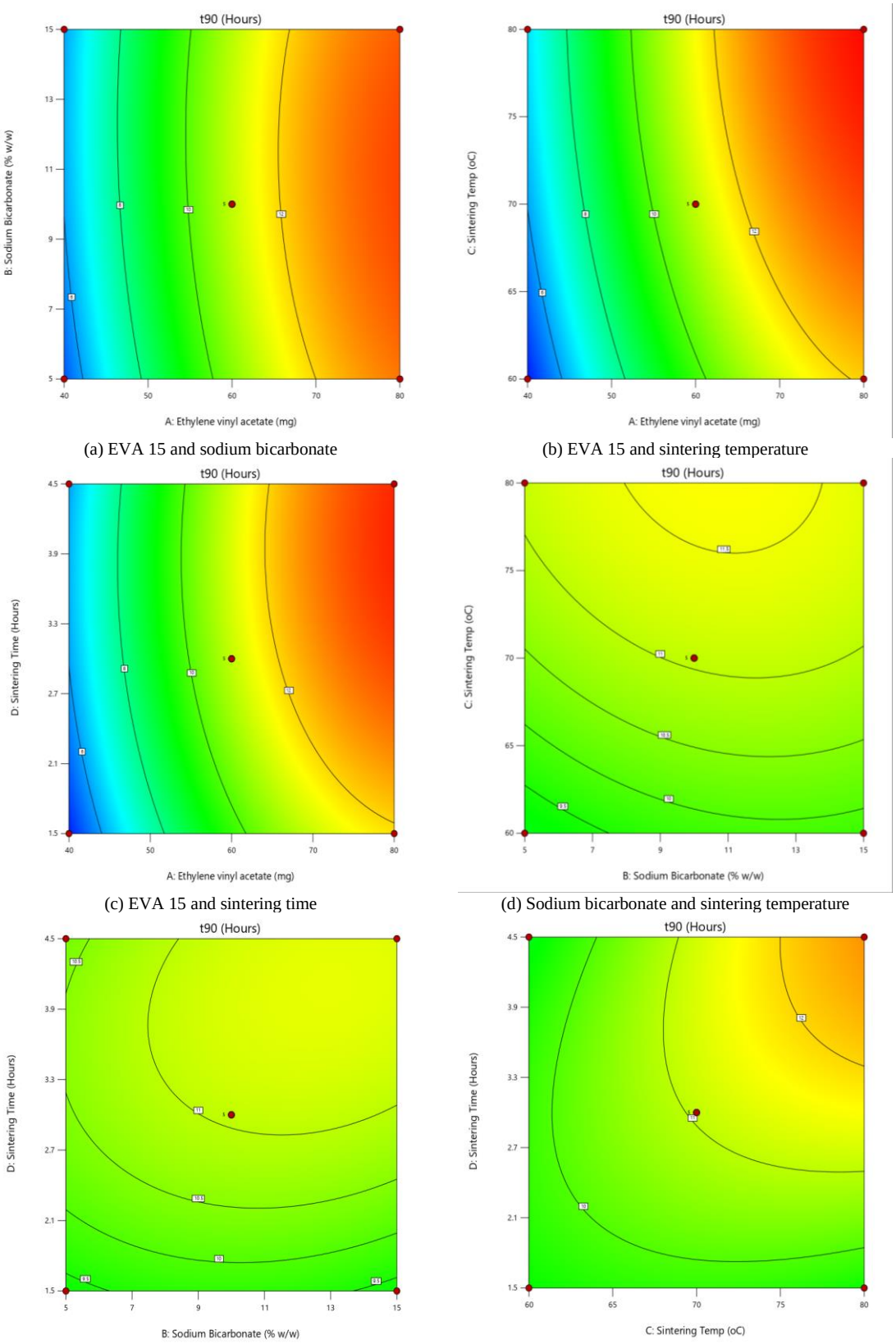
Floating time = 10.70 + 3.42 A + 0.2500 B + 1.04 C + 0.4583 D + 0.5000 AB - 0.2500 AC + 0.0000 AD - 0.2500 BC + 0.5000 BD + 0.6250 CD - 0.8708 A^2 - 0.6208 B^2 - 0.5583 C^2 - 0.5583 D^2

The contour plots and response surface plots for the responses of T_{90} formulation factors are shown in **Fig. 1 and 2** and the desirability plots are shown in **Fig. 3**. In response plots, the response surface is established as a function of two factors at a time, holding all other factors at fixed levels which is more helpful in understanding both the main and the interaction effects of these two factors.

Optimization

Optimized formulation was selected based on the criteria to attain the 90% drug release in between 11 to 12 hours, floating lag time at minimal and floating time should be 12 hours and these constrains are common for all the formulations. Various feasibility and grid searches were executed to establish the optimum formulation. The recommended concentrations of the independent variables were calculated by the Design Expert 12 software from the above techniques which indicated the highest desirability close to 1.0.

The optimum values of selected variables obtained from the Design Expert 12 software was 64.29 mg of EVA 15, 7.92% w/w of sodium bicarbonate (to tablet weight), 74.68 °C of sintering temperature and 1.99 hours sintering exposure time. The working formula for statistically optimized formulation (TE_{opt}) is presented in **Table 5**.



(a) EVA 15 and sodium bicarbonate

(b) EVA 15 and sintering temperature

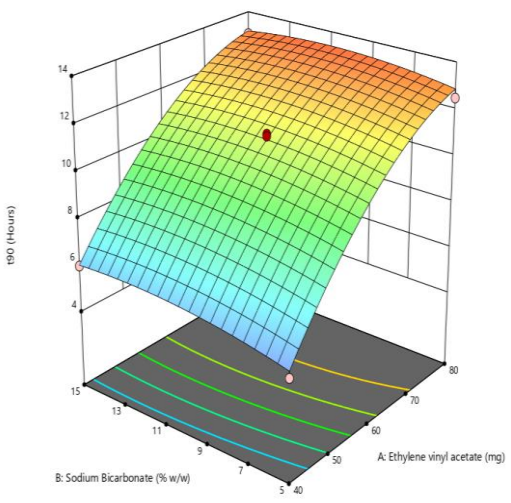
(c) EVA 15 and sintering time

(d) Sodium bicarbonate and sintering temperature

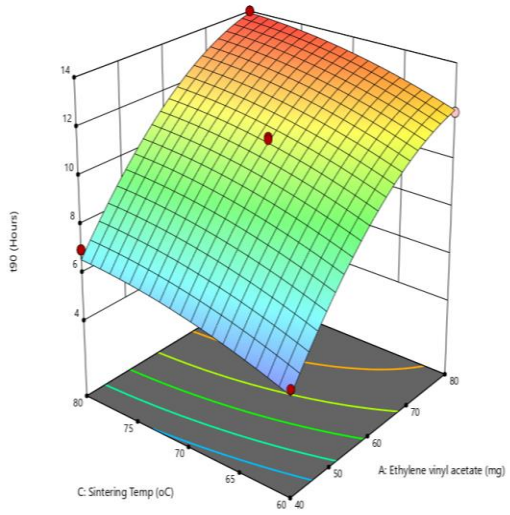
(e) Sodium bicarbonate and sintering time

(f) Sintering temperature and sintering time

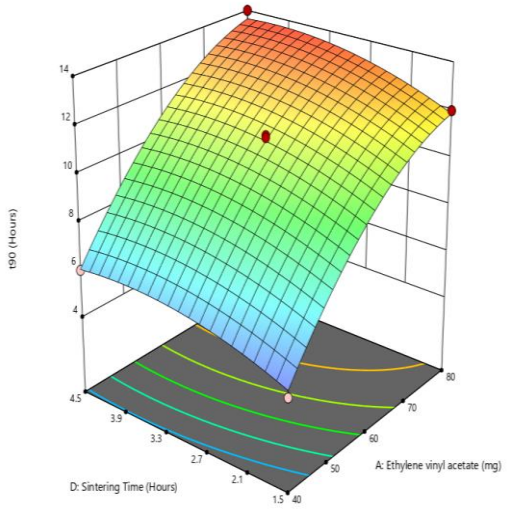
Fig. 1: Contour plots for the effect of various independent variables on T_{90} (Quadratic model)



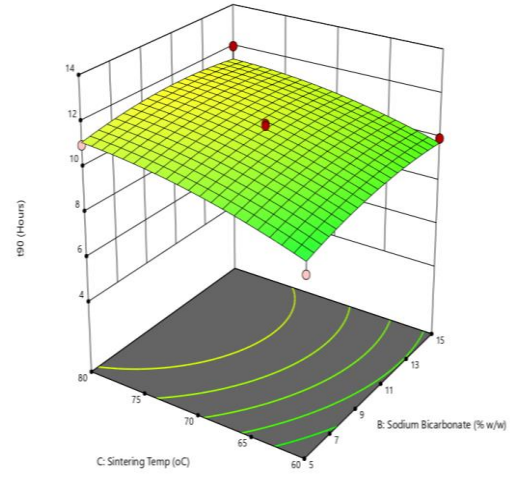
(a) EVA 15 and sodium bicarbonate



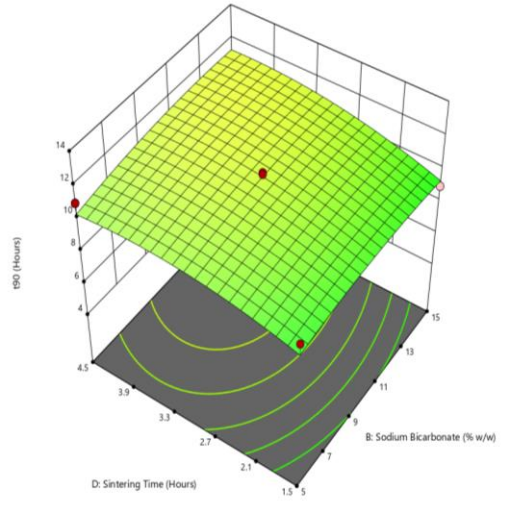
(b) EVA 15 and sintering temperature



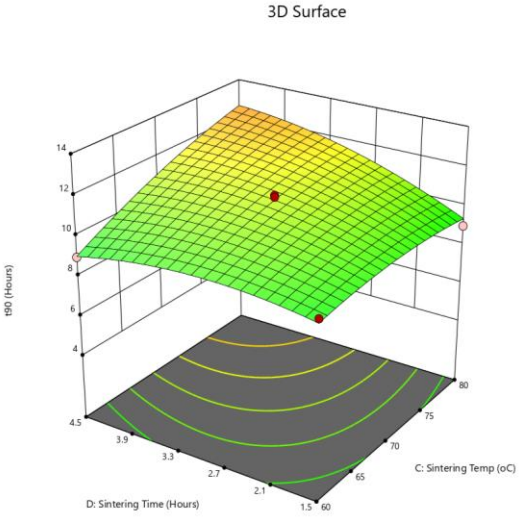
(c) EVA 15 and sintering time



(d) Sodium bicarbonate and sintering temperature



(e) Sodium bicarbonate and sintering time



(f) Sintering temperature and sintering time

Fig. 2: Response surface plots for the effect of various independent variables on T_{90} (Quadratic model)

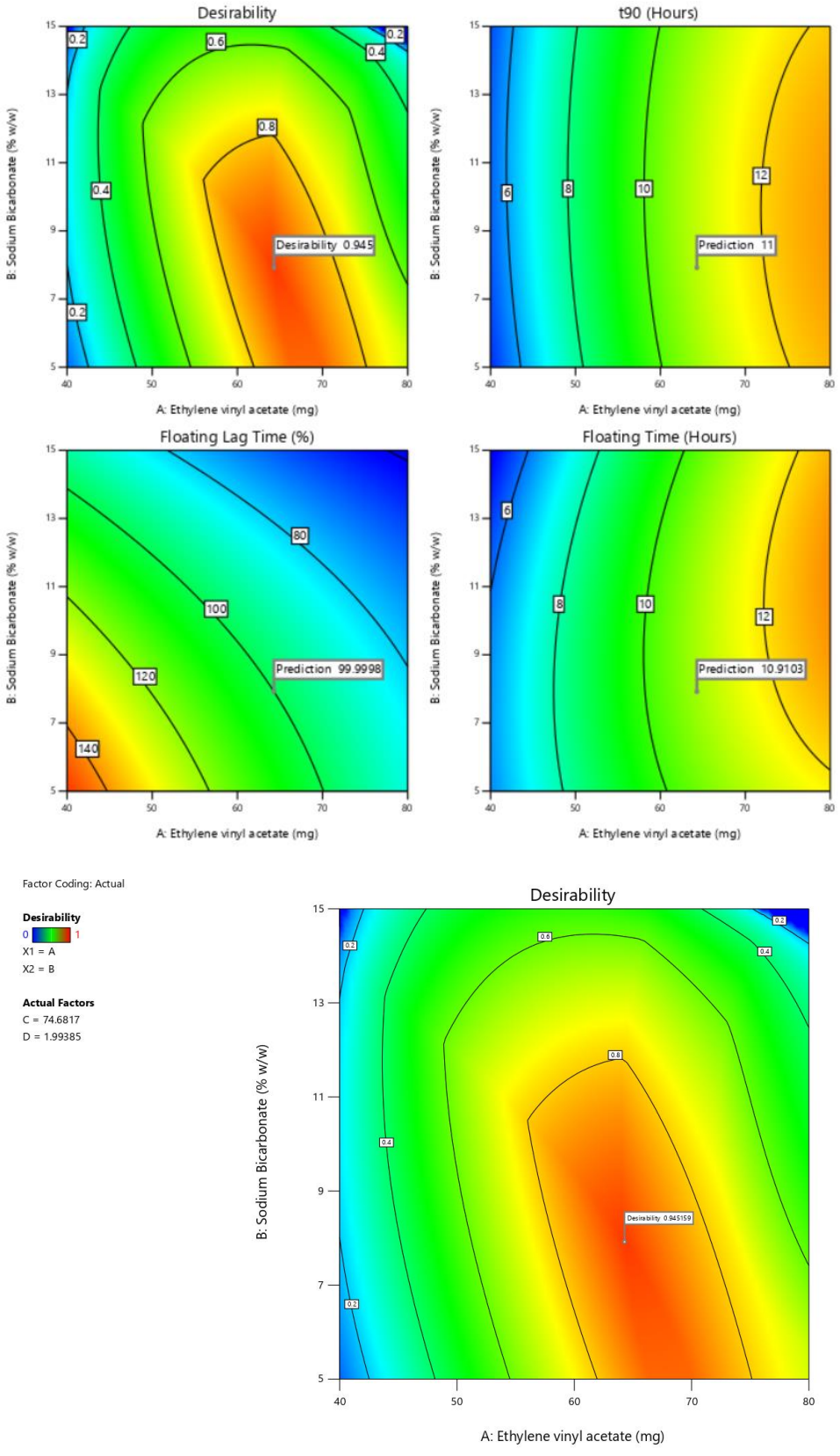


Fig. 3: Desirability plots for responses

Evaluation and validation of statistically optimized formulation

The statistically optimized formulation fulfilled all the criteria of physicochemical properties. In vitro dissolution studies were carried out for the optimized formulation for verification of the theoretical prediction. These experimental findings are in close agreement with the model predictions and are shown in **Table 6**.

Table 5: Formula of statistically optimized formulation, TE_{opt}

S.No.	Ingredient	Quantity (mg)
1	Thiamine	100
2	EVA 15	64.29
3	Sodium bicarbonate	18.71
4	Microcrystalline cellulose	50
5	Magnesium stearate	3
	Total	236

Sintering temperature: 74.68°C; Sintering time: 1.99 hours

Table 6: Comparison of predicted and observed responses of statistically optimized formulation, TE_{opt}

Response	Observed	Predicted	% Relative error
T_{90}	11.2	11	1.81%
Floating lag time	103	99.99	3.01%
Floating time	12.2	11.91	2.43%

Optimized formulation showed 103 seconds floating lag time and 12.2 hours of floating time.

Obtained T_{90} was found to be 11.2 hours which followed zero order release kinetics with non-Fickian diffusion mechanism.

The percentage of relative error between the predicted values and experimental values of each response was calculated and the values were found to be <5%. The experimental values are in agreement with the predicted values, which confirmed the predictability and validity of the model.

4. Conclusion

Gastric floating tablets of EVA 15 were developed and optimized to obtain 12 hours of drug release meeting all other tabletting characteristics and floating properties as per the objectives of present investigation using EVA 15 as polymer and following thermal sintering technique. Box-Behnken design was successfully applied for the optimization of formulation. Pre-compression and post-compression evaluation parameters revealed the quality characteristics of prepared formulation mixtures and tablets respectively are within acceptable criteria.

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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