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Research Article

Box-Behnken design for development and evaluation of gastric floating tablets of thiamine HCl following a novel technique

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ABSTRACT

The objective of the present investigation is to develop and evaluate thermally sintered gastric floating tablets of thiamine using Box-Behnken design. The prepared floating tablets were evaluated for physicochemical properties, in vitro buoyancy characteristics and dissolution studies. Statistical optimization was done based on the results of t90, floating lag time and floating time. The optimum values of selected variables obtained from the Design Expert 12 software was 91.36 mg of carnauba wax, 14.63% w/w of sodium bicarbonate (to tablet weight), 40.17 °C of sintering temperature and 2.02 hours sintering exposure time. 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. Optimized formulation showed 124 seconds floating lag time and 12.25 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.

1. Introduction

Oral route of administration has gained lot of importance as it offers ease of administration, convenience, and patient compliance as primary benefits[1,2]. However, when the drugs are administered as conventional dosage forms, wide range of fluctuations in drug concentration in the blood stream and tissues are usually possible[3]. Oral controlled release system provides prolonged duration of drug release, better utilization of drug, continuous supply of drug, less side effects, and overall reduction in total dose. However, for drugs with absorption window in the stomach or upper GIT, gastro retentive drug delivery systems are preferred which work on the principle of prolonged gastric retention[4,5].

A controlled release gastro retentive drug delivery system is meant to release the drug slowly in a controlled manner which favours continuous absorption of drug in the upper gastrointestinal tract (GIT)[6-8]. Thereby they are known to offer better bioavailability for the drugs with specific absorption window in upper GIT with advantages in their pharmacokinetics and pharmacodynamics[9,10]. Further, gastro retentive systems are of different types and among them, floating drug delivery systems have gained their importance. Floating drug delivery systems float over the surface of the gastric fluid after certain lag time or immediately based on the type of system (effervescent or non-effervescent) resulting in gastric retention.

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”. 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[11].

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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 backbone1. Thiamine comes under the category of diet, food, nutrient, growth substrate and micronutrient[12,13].

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[14,15]. Thiamine melts and gets decomposed at 248 °C.

Box-Behnken design is an experimental design of response surface methodology that is popularly used for the statistical optimization of formulation.

The objective of the present investigation is to develop and evaluate thermally sintered gastric floating tablets of thiamine using Box-Behnken design. The prepared floating tablets were evaluated for physicochemical properties, in vitro buoyancy characteristics and dissolution studies. Statistical optimization was done based on the results of T_{90}, floating lag time and floating time.

2. Materials and Methods

Thiamine and carnauba wax were purchased from Pharma Train labs, Hyderabad. All other reagents and chemicals were 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	Carnauba wax		
		Low (-1)	Medium (0)	High (+1)
Formulation related				
X1	Drug-polymer ratio	1:0.6	1:0.8	1:1
X2	Weight of gas generating agent/tablet (% w/w)	5	10	15
Process related				
X3	Sintering temperature (°C)	40	50	60
X4	Sintering time (hours)	1	2	3

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.

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 formula is shown in **Table 3 and 4**. These are coded as unsintered tablets. These unsintered tablets were subjected to the 29 runs as shown in **Table 5** containing 100 of thiamine HCl.

Table 3: Formulae of thiamine HCl unsintered GFT using carnauba wax

Ingredient (mg)	TC1U	TC2U	TC6U	TC7U	TC11U
Thiamine HCl	100	100	100	100	100
Carnauba wax	60	60	60	80	80
Sodium bicarbonate	11	23.5	37.5	12.5	25.5
Microcrystalline cellulose	50	50	50	50	50
Magnesium stearate	2	2.5	2.5	2.5	2.5
Total weight (mg)	223	236	250	245	258

Table 4: Formulae of thiamine HCl unsintered GFT using carnauba wax

Ingredient (mg)	TC20U	TC24U	TC25U	TC29U
Thiamine HCl	100	100	100	100
Carnauba wax	80	100	100	100
Sodium bicarbonate	41	13	28	45
Microcrystalline cellulose	50	50	50	50
Magnesium stearate	3	3	3	3
Total weight (mg)	274	266	281	298

Table 5: Preparation of thiamine HCl sintered GFT using carnauba wax as per the predicted runs

Run No.	Formulation code	X1 (mg)	X2 (mg)	X3 (°C)	X4 (h)
1	TC1	60	11	50	2
2	TC2	60	23.5	50	1
3	TC3	60	23.5	50	3
4	TC4	60	23.5	40	2
5	TC5	60	23.5	60	2
6	TC6	60	37.5	50	2
7	TC7	80	12.5	40	2
8	TC8	80	12.5	60	2
9	TC9	80	12.5	50	1
10	TC10	80	12.5	50	3
11	TC11	80	25.5	40	1
12	TC12	80	25.5	60	1
13	TC13	80	25.5	40	3
14	TC14	80	25.5	60	3
15	TC15	80	25.5	50	2

16	TC16	80	25.5	50	2
17	TC17	80	25.5	50	2
18	TC18	80	25.5	50	2
19	TC19	80	25.5	50	2
20	TC20	80	41	40	2
21	TC21	80	41	60	2
22	TC22	80	41	50	1
23	TC23	80	41	50	3
24	TC24	100	13	50	2
25	TC25	100	28	50	1
26	TC26	100	28	50	3
27	TC27	100	28	40	2
28	TC28	100	28	60	2
29	TC29	100	45	50	2

Preparation of pre-compression blend

All the ingredients required for a batch of 300 tablets were passed through sieve #40 (aperture 425 µm, ASTM). Drug and polymer were geometrically mixed until a homogenous blend was achieved using poly bag. Gas generating agent was added to the above mixture and blended for another 5 minutes in that poly bag. Lubricant was finally added and blended for another 3 minutes.

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.

Preparation of GFTs of thiamine HCl

Tablet compression was done by using ten station RIMEK Minipress tablet compression machine following direct compression technique using 9 mm, flat and round punch.

Evaluation of GFTs of thiamine HCl

The prepared gastric floating tablets of thiamine HCl were evaluated for different post compression parameters like thickness and diameter, hardness, friability, uniformity of weight, drug content uniformity, 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 following UV spectrophotometric method by measuring the absorbance at 233 nm has been followed.

3. Results and Discussion

Pre-compression studies

The angle of repose of the powder blend was found to be in the range of 28.60°- 32.26° which indicated good to excellent flow property. The Carr's index values are in the range of 11.29 to 18.75 indicating the compressibility nature of powder blend whereas the Hausner's ratio values of all the formulations were in the range of 1.13 to 1.23 supporting the good flow of prepared powder blends. Hence direct compression method was used for compression of tablets. Results are shown in **Table 6**.

Table 6: Flow properties of GFT of thiamine prepared with carnauba wax formulation powder blends

Formu-lation	Angle of repose[a] (Ɵ)	Tapped density[a] (g/cm^3)	Bulk density[a] (g/cm^3)	Carr's index (%)	Hausner's ratio
TC1U	29.25±1.16	0.63±0.03	0.54±0.04	14.29	1.17
TC2U	30.11±0.98	0.66±0.02	0.56±0.03	15.15	1.18
TC6U	31.25±0.82	0.62±0.02	0.55±0.04	11.29	1.13
TC7U	29.03±1.06	0.62±0.02	0.53±0.04	14.52	1.17
TC11U	29.29±1.07	0.64±0.03	0.52±0.05	18.75	1.23
TC20U	28.60±1.14	0.63±0.05	0.53±0.02	15.87	1.19
TC24U	32.26±1.12	0.64±0.02	0.55±0.03	14.06	1.16
TC25U	30.96±0.96	0.66±0.01	0.55±0.03	16.67	1.20
TC29U	30.62±0.95	0.65±0.03	0.56±0.04	13.85	1.16

a: mean±s.d., n=3

Evaluation of GFTs of thiamine prepared with carnauba wax

The results showed a uniform thickness and diameter of prepared tablets. The measured hardness of tablets ranged between 3.9 to 5.4 kg/cm^2. This test ensures that prepared tablets have good handling characteristics. The friability values ranged between 0.37 to 0.63%. The % friability was found to be <1% ensuring that the tablets were mechanically stable. Based on the weight of the tablet, the allowed deviation is ±7.5%. 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 GFT of thiamine HCl prepared with carnauba wax 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 106 to 245 seconds whereas the floating time was found to be in the range of 4-15 hours.

Drug release from unsintered tablets prepared with carnauba wax has shown 100% within the range of 5-9 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. All the formulations, except TCU1, TC2U, TC6U, TC7U, TC20U and TC13 were found to follow zero order drug release kinetics. All the formulations 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.

Optimization and data analysis

The responses of sintered formulations of carnauba wax were fitted to linear, interaction and quadratic model using the Design Expert 12 software. Of the three models, linear model was suggested for the response T_{90} and floating time whereas quadratic model was suggested for floating lag time. Model parameters were used to construct models that describe the effect of independent variables on responses. Different batches of formulations within the experimental design were prepared to obtain floating tablets which were evaluated for their 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 107.76, 38.23 and 172.15, respectively, which indicated that the models are significant. The values of ''p-value'' less than 0.05 for all the responses indicated that the models are significant. Similarly, ''R^2'' value was also calculated for all responses and found to be nearer to ideal value (i.e., one), which indicated as a good model. In all the cases, ''Predicted R^2'' values are in reasonable agreement with the ''Adjusted R^2'' values. In all the cases, ''Adequate precision'' values are in the range 23.35 - 40.42, indicating an adequate signal that the model can be used to navigate the design space.

The optimum values of selected variables obtained from the Design Expert 12 software was 91.36 mg of carnauba wax, 14.63% w/w of sodium bicarbonate (to tablet weight), 40.17 °C of sintering temperature and 2.02 hours sintering exposure time as shown in **Table 7**. 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. Optimized formulation showed 124 seconds floating lag time and 12.5 hours of floating time. Obtained T90 was found to be 11.3 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 application of Response surface methodology (RSM) yielded the following regression equations which give an empirical relationship between the logarithmic values of t90, floating lag time and floating time. Test variables in coded units: (A: carnauba wax concentration, B: % w/w of sodium bicarbonate, C: sintering temperature, and D: sintering time)

T_{90} = 9.75 + 3.38 A + 0.4583 B + 0.6667 C + 1.06 D

Floating Lag Time = 179.80 - 43.00 A - 17.83 B + 6.58 C + 6.08 D + 6.50 AB - 4.00 AC - 5.00 AD + 0.0000 BC + 0.0000 BD - 0.2500 CD - 0.8583 A^2 - 9.86 B^2 - 5.73 C^2 - 4.73 D^2

Floating time = 9.50 + 4.08 A + 0.5417 B + 0.4167 C + 0.5417 D

Desirability plots are shown in **Figure 1** and overlay plot is shown in **Figure 2**.

Table 7: Formula of statistically optimized formulation, TC_{opt}

S.No.	Ingredient	Quantity (mg)
1	Thiamine	100
2	Carnauba wax	91.36
3	Sodium bicarbonate	42.64
4	Microcrystalline cellulose	50
5	Magnesium stearate	3
	Total	287

Sintering temperature: 40.17°C; Sintering time: 2.02 h

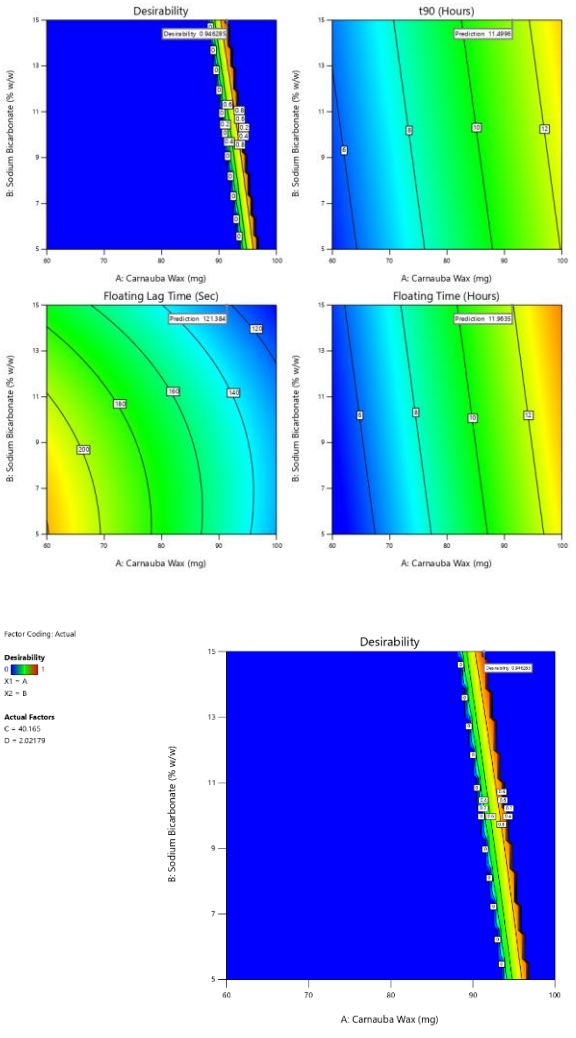

Fig. 1: Desirability plots for responses

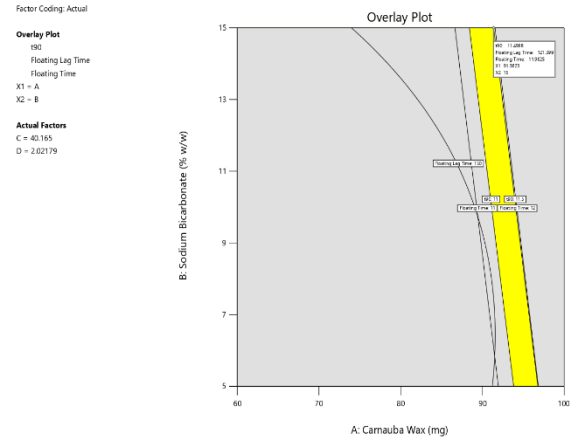

Fig. 2: Overlay plot for responses

Table 8: Comparison of predicted and observed responses of statistically optimized formulation, TC_{opt}

Response	Observed	Predicted	% Relative error
T_{90}	11.3	11.5	1.74%
Floating lag time	124	121.384	2.4%
Floating time	12.25	11.9635	2.39%

4. Conclusion

From the present investigation it can be concluded that Box-Behnken design is used to optimize the formulation of GFTs of thiamine HCl using carnauba wax as the rate controlling polymer and sodium bicarbonate as gas generating agent by following sintering technique.

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