ORIGINAL ARTICLE

Factorial study on influence of gas generating agent and diluent on drug release kinetics of clopidogrel bisulfate floating tablets

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The purpose of present work was to formulate and characterize a floating drug delivery system for Clopidogrel bisulphate to improve bioavailability and to minimize the side-effects of the drug such as gastric bleeding and drug resistance development. Clopidogrel floating tablets were prepared by direct compression technique by the use of xanthan gum at different concentrations (20%, 25% and 30% w/w). Sodium bicarbonate (15% w/w) and microcrystalline cellulose (MCC) (30% w/w) were used as gas generating agent and diluent respectively. The effects of sodium bicarbonate and MCC on the drug release kinetics and floating properties were investigated. A 2^2 factorial design was applied systematically to optimized formulation. The percentage amount of sodium bicarbonate (X_1) and percentage amount of MCC (X_2) were selected as independent variables. The drug release rate constant (K) and time required for 85% drug dissolution (T85) was selected as dependent variables. Factorial design revealed that the percentage amount of sodium bicarbonate and MCC had insignificant effect on drug release kinetics (K,T85) within the chosen levels and a high level of sodium bicarbonate (X_1) and the low level of MCC (X_2) favor the preparation of clopidogrel floating tablets. All the Clopidogrel floating formulations followed first order kinetics, Higuchi drug release kinetics with diffusion as the dominant mechanism of drug release. As per Korsmeyer-Peppas equation, the release exponent "n" ranged 0.455-0.654 indicating that drug release from all the formulations was by non-fickian diffusion mechanism.

Key words: *Clopidogrel bisulfate, factorial study, floating tablets, release kinetics, variables*

INTRODUCTION

Controlled release drug delivery systems (CRDDS) are designed to enhance drug therapy and sustaining the duration of the action with or without targeted action. The CRDDS possessing ability of being retain in the stomach are called gastro-retentive drug delivery system and they are designed to prolong the gastric residence time after oral administration and controlling the release of drug. The controlled gastric retention of formulation may be achieved by the various approaches such as mucoadhesion, sedimentation, expansion, floatation and modified shape systems. Among the various approaches, floating drug delivery system (FDDS) promises to be a potential approach for gastric retention of drug.[1,2]

Clopidogrel is a thienopyridine class inhibitor of P2Y12 adenosine 5'-diphosphate (ADP) platelet receptors and used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel is a pro-drug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme. The active metabolite has an elimination half-life of about 7-8 h and acts by forming a disulfide bridge with the platelet ADP receptor. Following oral administration, it is well-absorbed with bioavailability of about only 50% due to poor water solubility. The main side effects of the drug are gastric bleeding and clopidogrel drug resistance during chronic treatment. Clopidogrel conventional formulations provides high concentrations of active metabolite immediately after

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dosing and 85% of drug after absorption is inactivated by esterases in blood and only 15% is available to undergo hepatic conversion to the active metabolite.[3]

A sustained release floating clopidogrel formulation may be desired for a number of reasons, such as improving the bioavailability and to minimize the side-effects of the drug such as gastric bleeding and to prevent development of drug resistance there by to improve patient compliance. Floating sustained release formulation retains the clopidogrel drug for several hours in gastric region where it has high solubility and improves the bioavailability. Although the formulation is floating on the gastric contents, the drug is released slowly at desired rate, which minimizes the exposure of high concentration of active metabolite thereby prevents the bleeding risks and clopidogrel resistance development.[4]

The objective of the study was to formulate and evaluate clopidogrel floating tablets for sustained release over a period of 8 h with increased bioavailability by the use of xanthan gum and to study the influence of the individual and combined effect of gas generating agent, Sodium bicarbonate (factor A) and diluent, Microcrystalline cellulose (MCC) (factor B) on drug release from clopidogrel bisulfate tablets were evaluated in a 2^2 factorial study.

MATERIALS AND METHODS

Materials

Clopidogrel bisulfate (gift samples from Dr. Reddy's Laboratories, Hyderabad), Xanthan gum, Sodium bicarbonate, MCC, Magnesium stearate, Talc (S. D. Fine Chemicals, Mumbai) and all other ingredients are of laboratory grade.

Drug-excipient compatibility studies[5]

Drug-excipient compatibility studies were performed for physical mixture of clopidogrel bisulfate with xanthan gum in the ratio 1:1. The physical mixture sample was subjected to Fourier transform infrared studies by employing KBr pellet method. Spectra of drug and xanthan gum was taken and analyzed for any major interaction.

Micromeritic properties[6]

The pure drug and formulation powder blend prepared before compression is evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

Optimisation of polymer concentration

Clopidogrel bisulfate floating tablets each containing 98 mg were prepared by direct compression method by effervescent approach. Xanthan gum was used as polymer and to optimize polymer concentration for desired sustained release property of 8 h drug release, varying concentrations 20%, 25%, 30% w/w were used as shown in the Table 1. Sodium bicarbonate at concentration 15% w/w was optimized as gas generating floating agent with 30% w/w MCC as diluent. The required quantities of drug, polymer and other ingredients were mixed and then compressed into tablets using multi station punching machine using 9 mm punch. The total weight of the tablet was not kept constant because that would require the use of additional amount of diluent for weight adjustment, which in turn may have caused variation in drug release profile.

Experimental factorial design

Factorial design was applied to best optimized xanthan gum (25% w/w) formulation to study the influence of gas generating agent, sodium bicarbonate and diluent, MCC on drug release. The 2^2 factorial design was selected to study the effect of two independent variables namely concentration of Sodium bicarbonate (factor A) and concentration of MCC (factor B) at two levels. The low and high levels for two variables were chosen and suitably coded as shown in Table 2. The drug release rate constant (K) and time required for 85% drug dissolution (T85) was selected as dependent variables.

Preparation of clopidogrel factorial formulations

Clopidogrel floating tablets were prepared by direct compression employing 25% w/w xanthan gum as release controlling polymer. Four formulations (Fo, Fa, Fb, Fab) were prepared as per the translation of the coded factor levels design as percentage of ingredients shown in Table 1. The required quantities of drug, xanthan gum, sodium bicarbonate and diluents were mixed well and then compressed into tablets on a multi station rotary tablet compression machine using 9 mm round flat punches. The total weight of the tablet was not kept constant while the amount of drug and concentration xanthan, magnesium stearate and talc were kept constant. The resulting data were fitted into Minitab 15 trail version software (Minitab Inc, Pennsylvania) and

Table 1: Composition of floating tablets of clopidogrel bisulfate

Ingredients (mg/tablet)	Xanthan formulations			Factorial formulations			
	F1	F2	F3	Fo	Fa	Fb	Fab
Clopidogrel bisulfate	98	98	98	98	98	98	98
Xanthan gum	60	88	126	65	88	88	137
Sodium bicarbonate	46	53	62	26	70	35	109
MCC	90	105	126	65	88	123	191
Magnesium stearate	3	3	4	3	3	3	5
Talc	3	3	4	3	3	3	5
Total weight	300	350	420	260	350	350	545

MCC: Microcrystalline cellulose

Table 2: 2^2 factorial design layout

Variable levels	Independent variable factors	
	A (% NaHCo3)	B (% MCC)
I (low) level	10	25
II (high) level	20	35

MCC: Microcrystalline cellulose

analyzed statistically using analysis of variance (ANOVA) of 2^2 factorial design.

Characterization of floating tablets

Tablet thickness

The thickness of ten tablets was determined using a Vernier calliper and the mean of these readings was taken as the mean tablet thickness.

Tablet weight uniformity

A total of 20 tablets were weighed individually, average weight was calculated and the individual tablet weights were compared with the average weight. The tablets meet the United States Pharmacopeia (USP) test if not more than two tablets are outside the percentage limit and if no tablets differs by more than two times the percentage limit.

Crushing strength

The crushing strengths of the tablets were determined individually with the Monsanto hardness tester. Three tablets were used and the mean crushing strength was calculated and expressed in kg/cm^2

Friability test

The friability of tablets was determined using Roche friabilator. Five tablets were initially weighed (W0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by the following equation.

$$\%F = (1 - W/W_0) \times 100 \quad (1)$$

% friability of tablets < 1% are considered acceptable.

Drug content[7]

A total of 10 tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of clopidogrel bisulfate was dissolved in 100 ml of 0.1 N hydrochloric acid (HCl). Then the solution was filtered, diluted suitably and analyzed using an ultra violet (UV) visible spectrophotometer at 270.5 nm.

In-vitro buoyancy studies[8]

The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the total floating time respectively.

In-vitro drug release studies[4]

Clopidogrel bisulfate drug release studies from different formulated tablets were performed by using USP type II apparatus in 900 ml of 0.1 N HCl as the dissolution medium, with a rpm of 50 and the bath was maintained at a temperature of 37 ± 0.5°C. Samples were withdrawn at regular intervals of time and these were replaced with equivalent volume of the fresh dissolution media. The withdrawn samples were analyzed after suitable dilutions at a wavelength of 270.5 nm using UV spectrophotometer. The cumulative percentage drug release was calculated using slope obtained from standard curve.

Kinetic modeling of drug release[9]

The dissolution data was fitted to popular release models such as zero-order, first-order, Higuchi and Peppa's-Korsemeyer equation models. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's-Korsemeyer equation.

Zero order release kinetics

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Qt = Q0 + K0t \quad (2)$$

Where Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K0 is the zero order release constant expressed in units of concentration/time.

First order release kinetics

The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log C0 - Kt/2.303 \quad (3)$$

Where C0 is the initial concentration of drug, k is the first order rate constant expressed in units of time-1 and t is the time.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time and can be expressed by the equation:

$$Q = K_H t^{1/2} \quad (4)$$

Where, K_H is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Korsmeyer-Peppas model

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsmeyer equation:

$$Mt/M\infty = K t^n \quad (5)$$

Where $Mt/M\infty$ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. In this model, the value of n characterizes the release mechanism of

drug. For the case of cylindrical tablets, $0.45 = n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxation) transport and $n > 0.89$ to super case II transport.

RESULTS AND DISCUSSION

The major objective of the study was to design and evaluate clopidogrel floating tablets for sustained release over a period of 8 h with increased bioavailability. Among the various approaches involved in the gastro retentive systems, effervescent floating approach was selected. For this purpose floating tablets were prepared by the use of xanthan gum at different concentrations (20%, 25% and 30% w/w). To study the influence of the individual and combined effect of gas generating agent, Sodium bicarbonate (factor A) and diluent, MCC (factor B) on drug release from clopidogrel bisulfate tablets formulated by xanthan gum were evaluated in a 2^2 - factorial study.

Drug polymer interaction was checked by comparing the infrared spectroscopy (IR) spectra of the physical mixture of drug with the polymer used with the IR spectrum of pure drug as shown in Figure 1a, clopidogrel bisulfate gives the peaks in IR spectrum nearby at 3106/cm^1 due to C-H stretching vibrations, 1749/cm^1 due to C = 0 stretching vibrations and the bands associated with C-0 stretching appeared at nearby 1156/cm^1. Characteristic unique absorption bands for clopidogrel bisulfate amorphous form 1 were also seen at 836 and 2983/cm^1. Figure 1b revealed the presence of peaks nearby at 3106/cm^1, 1749/cm^1, 1156/cm^1, 836/cm^1 and 2983/cm^1. Frequencies of functional groups and unique absorption bands of pure drug remained intact in physical mixture containing different polymers. Hence, there was no major interaction between the drug and excipients used in the study.

The micromeritic properties of pure drug of clopidogrel bisulfate showed excellent flow properties as it is observed from the values of Carr's index (10.39) and angle of repose (11.76). The flow properties of the formulation powder blend was also showed fair flow properties as it is observed from the values of Carr's index (23.6) and angle of repose (38.79). Hence clopidogrel bisulfate as such can be compressed to formulate the tablets by direct compression method. The micromeritic properties of drug and optimized bathes of xanthan formulation were shown in Table 3.

All the formulations were subjected to various quality control tests as per pharmacopoeial specifications. Post compression parameters such as weight variation, thickness, hardness and friability of all the formulations were shown in the Table 4. The hardness of all the batches was found to be in the range of 4-6 Kg/cm^2. The friability of all the formulations was found to be less than 1% and the drug content of the formulations was in between 97 and 103%. Hence all the clopidogrel floating tablets formulated by employing different concentrations of polymer and factorial formulations were of good quality and fulfilled the official specifications with regard to drug content, hardness and friability.

The formulations were subjected to *in-vitro* buoyancy studies and results were shown in the Table 5. All formulations floated in the buffer solution for more than 12 h except formulation F1, Fo and Fb which were floated for 12, 5 and 10 h respectively, which indicates the factorial formulations with low levels of sodium bicarbonate didn't shown desired floating characteristics. The FLT was observed to be less than 2 min for all the formulations.

All the formulations were subjected to *in-vitro* dissolution studies in 0.1N HCl (1.2-pH) and corresponding results were shown in Figure 2. The drug release extended from 5 to 12 h as the xanthan gum concentration varies from 20% to 30% respectively. The drug release was found to be more sustained (12 h) in the tablets with higher proportions of the xanthan gum. High initial drug release for the 1st h was

Table 3: Micromeritic properties of drug and optimized batch of clopidogrel blend with xanthan gum

Parameter	Pure drug	Formulation F2
Angle of repose	11.76±1.35	38.79±0.81
Bulk density (g/cc)	0.86±0.03	0.55±0.02
Tapped density (g/cc)	0.96±0.01	0.72±0.01
Carr's index (%)	10.39±0.16	23.6±0.4
Hausner's ratio	1.11±0.04	1.31±0.09

Each data represents mean±SD (n=3). SD: Standard deviation

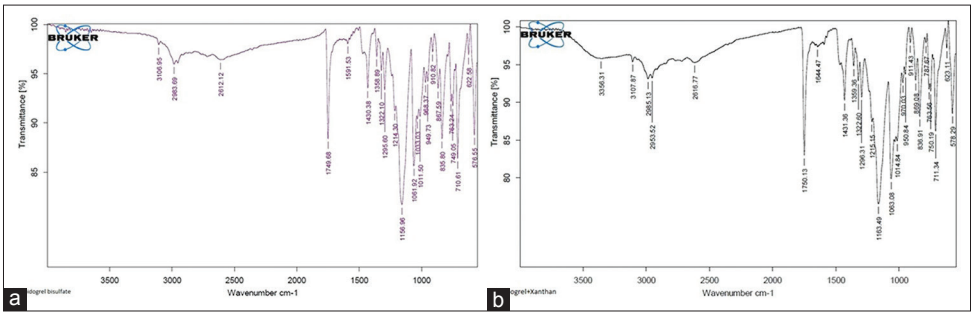

Figure 1: (a) Fourier transform infrared (FTIR) spectra of pure clopidogrel bisulfate drug. (b) FTIR spectra of physical mixture of clopidogrel bisulfate with xanthan gum

Table 4: Physical characteristics of clopidogrel floating tablets

Formulation code	Thickness (mm)	Average weight (mg)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F1	0.343±0.005	310.66±7.63	4.66±0.57	0.852	98.85
F2	0.403±0.005	315.66±7.63	5.33±0.28	0.721	102.31
F3	0.453±0.005	425.00±5.00	5.50±0.50	0.786	97.63
Fo	0.303±0.002	263.00±1.00	4.16±0.28	0.698	98.42
Fa	0.402±0.003	351.50±2.50	5.00±0.50	0.725	101.63
Fb	0.405±0.001	347.50±3.50	5.16±0.28	0.686	99.85
Fab	0.504±0.004	545.00±2.00	5.50±0.50	0.710	97.98

Each data represents mean±SD (n=3). SD: Standard deviation

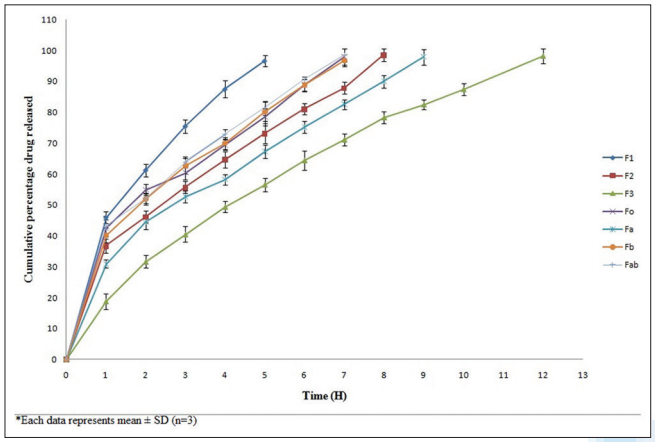

Figure 2: Cumulative percentage drug release profiles of clopidogrel tablets formulated with different concentrations of xanthan gum and factorial formulations

observed at low proportions of xanthan gum (20% w/w) may be due to insufficient amount of xanthan gum to maintain the tablet matrix integrity. Clopidogrel floating tablets formulated with xanthan gum at concentration 25% w/w with 15% w/w sodium bicarbonate and 30% w/w MCC (formulation F2) was the best formulation with desired *in-vitro* floating time (>12 h) and drug dissolution time (8 h).

The dissolution data were fitted to popular release kinetic equations. Analysis of the drug release data as per zero order and first order kinetic models indicating that all the formulations followed first order kinetics and different *in-vitro* dissolution parameters such as dissolution rate constant (K), time required for 50% drug dissolution (T50) and 90% drug dissolution (T90) were determined and presented in Table 6. Plots of percent release versus √ time (Higuchi plots) were found to be linear with $r^2 > 0.9941$ in all the formulations indicating diffusion as the release mechanism from all the clopidogrel floating tablets. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent "n" was in the range 0.455-0.654 indicating non-fickian diffusion as the release mechanism from all the clopidogrel floating tablets.

Factorial design

A 2^2 factorial design was applied to study the effect of the percentage amount of sodium bicarbonate and percentage amount of microcrystalline cellulose on the drug release

Table 5: *In-vitro* buoyancy data of clopidogrel floating tablets

Formulation code	FLT in s	TFT in h
F1	30±4	12±0.5
F2	55±3	16±0.25
F3	78±3	21±0.5
Fo	25±2	5±0.25
Fa	45±4	>12±0
Fb	55±2	10±0.75
Fab	60±3	>12±0

Each data represents mean±SD (n=3). FLT: Floating lag time, TFT: Total floating time, SD: Standard deviation

from floating clopidogrel tablets. The dependent variables chosen were the drug release rate constant (K) and time required for 85% drug dissolution (T85). A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1 \times_1 + b_2 \times_2 + b_{12} \times_1 X_2 \quad (6)$$

Where Y is the dependent variable, b0 is the arithmetic mean response of the 4 runs and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are changed simultaneously.

The drug release rate constant (K) and time required for 85% drug dissolution (T85) for the 4 formulations showed some variation. The responses of factorial design formulations were statistically analyzed by software Minitab 15 trail version (Minitab Inc, Pennsylvania) and the ANOVA results were shown in Table 7. The observed *P* values for the both the variables is greater than 0.05 and thus these results indicating that these selected two variables are not significantly influencing the dissolution rate constant (K) as well as time required for 85% drug dissolution (T85) within the chosen levels of the two variables. The fitted equations relating the responses K and T85 to the transformed factor are shown in following equations respectively.

Final polynomial equation in terms of coded factors for K:

$$K = 0.38795 - 0.01345X_1 + 0.03090X_2 + 0.04010X_1X_2 \quad (7)$$

Final polynomial equation in terms of coded factors for T85:

$$T85 = 5.0000 + 0.3000X_1 - 0.4500X_2 - 0.5500X_1X_2 \quad (8)$$

As per the polynomial equation and from the estimated coefficient values, the percentage concentration of sodium bicarbonate (X_1) has negative effect on drug release rate (K) and positive effect on time required for 85% drug dissolution (T85). The percentage concentration of MCC (X_2) has positive effect on drug release rate (K) and negative effect on time required for 85% drug dissolution (T85) whereas the combined interaction has positive effect on drug release rate (K) and negative effect on time required for 85% drug. Figure 3 shows pareto charts of effects for drug release rate (K) and time required for 85% drug dissolution (T85). Both the independent variables showed some effect on the dependent variables (K, T85) in which percent concentration of MCC (X_2) shown more effect than percent concentration of sodium bicarbonate (X_1). The combined effect of both the independent variables (X_1 X_2) is greater than the individual effects on dependent variables (K, T85); however, these effects were statistically insignificant within the chosen levels of the independent variables. Figures 4 shows counter

Table 7: ANOVA results

Source	df	Seq. SS	Adj. SS	Adj. MS	F	P
ANOVA for K						
Main effects	2	0.004543	0.004543	0.002271	0.35	0.766
Residual error	1	0.006432	0.006432	0.006432	-	-
Total	3	0.010975	-	-	-	-
ANOVA for T85						
Main effects	2	1.170	1.170	0.5850	0.48	0.713
Residual error	1	1.210	1.210	1.2100	-	-
Total	3	2.380	-	-	-	-

ANOVA: Analysis of variance

Table 6: Kinetic parameters of clopidogrel bisulfate floating tablets

Formulation code	Correlation coefficient (r^2)				Release kinetics			Exponential coefficient (*n*)
	Zero order	First order	Huguchi	Peppas	K (h^{-1})	T50% (h)	T85% (h)	
F1	0.9024	0.9677	0.9995	0.9988	0.5822	1.2	3.2	0.466
F2	0.8951	0.9185	0.9976	0.9929	0.3404	2.0	5.6	0.473
F3	0.9338	0.9457	0.9991	0.9901	0.2223	5.4	9.4	0.654
Fo	0.8650	0.9142	0.9941	0.9866	0.4106	1.7	4.6	0.478
Fa	0.9096	0.9109	0.9970	0.9964	0.3035	2.3	6.3	0.512
Fb	0.8797	0.9500	0.9982	0.9959	0.3922	1.8	4.8	0.455
Fab	08711	0.9181	0.9971	0.9912	0.4455	1.6	4.3	0.463

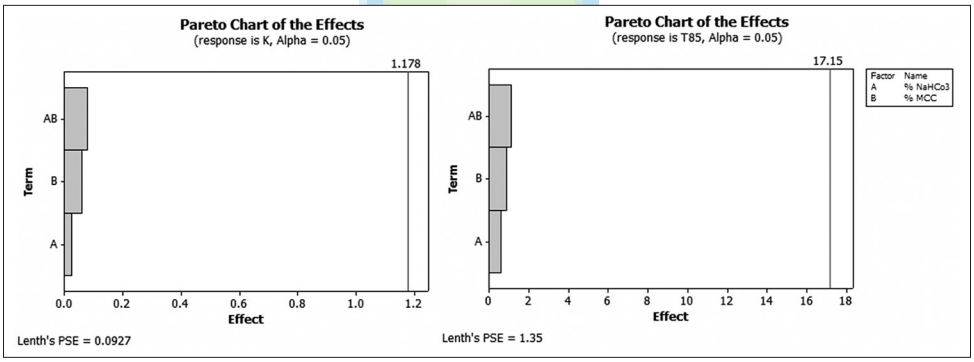

Figure 3: Pareto charts of estimated effects for K and T85

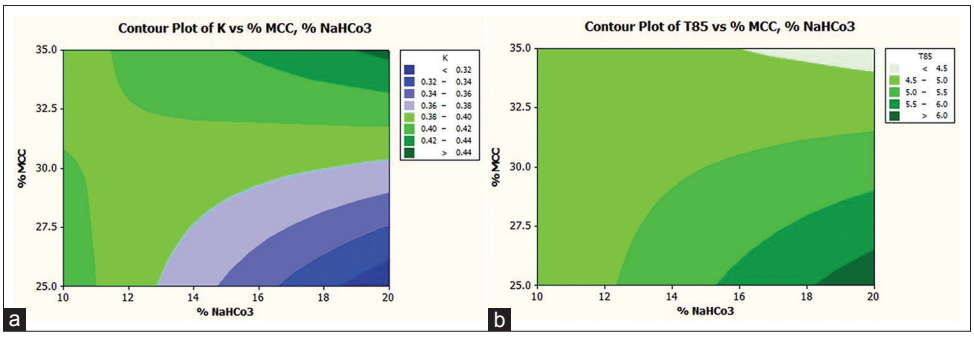

Figure 4: (a) Contour plot of K versus % sodium bicarbonate and microcrystalline cellulose. (b) Contour plot of T85 versus % sodium bicarbonate and microcrystalline cellulose

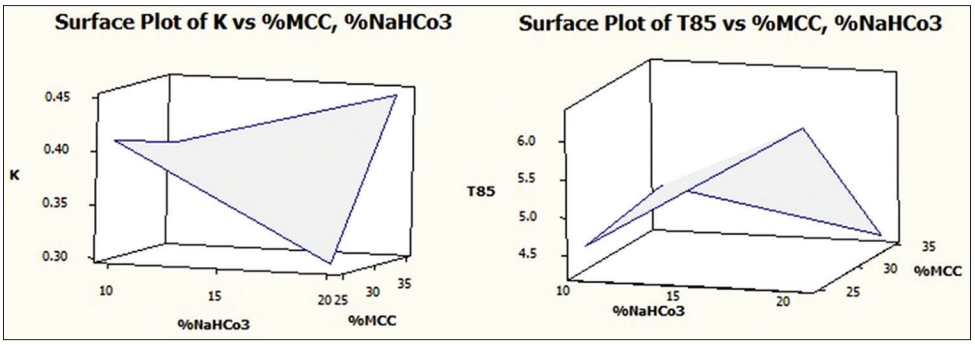

Figure 5: Response surface plots of percent sodium bicarbonate (X1) and percent microcrystalline cellulose (X2) versus K and T85

plots of percent amount of sodium bicarbonate (X_1) and percent amount of MCC (X_2) versus release rate (K) and time required for 85% drug dissolution (T85) respectively. The optimized concentrations of sodium bicarbonate and MCC for desired drug release profiles can be readily visualized form these contour plots. Figure 5 shows the plots of the percent amount of sodium bicarbonate (X_1) and percent amount of MCC (X_2) versus K and T85. These plots were drawn using Mini tab 15 trail software.

The data demonstrate that both independent variables X_1 and X_2 affect the drug release (K and T85), but not up to the significant level within the chosen levels of independent variables. It may also be concluded that the high level of percent amount of sodium bicarbonate (X_1) and the low level of percent amount of MCC (X_2) favors the preparation of gastroretensive sustained release clopidogrel bisulfate tablets.

CONCLUSION

FDDS are promising dosage forms for Clopidogrel which could be a better alternative to the conventional oral dosage forms in order to improve bioavailability by increasing the gastric retention time of the drug and to minimize the side effects. The effervescent based floating drug delivery is promising approach to achieve *in-vitro* buoyancy by using gel forming polymer xanthan gum and gas generating agent sodium bicarbonate. Clopidogrel bisulfate floating tablets prepared by employing xanthan at concentration 25% w/w with 15% w/w sodium bicarbonate and 30% w/w MCC (formulation F2) was the best formulation with desired *in-vitro* floating time and drug release. A systematic study using 2^2 factorial design revealed that the amount of sodium bicarbonate and MCC had insignificant effect on drug release kinetics (K, T85) within the chosen levels and the high level of percent amount of sodium bicarbonate (X_1) and the low level of percent amount of MCC (X_2) favors the preparation of gastroretensive sustained release clopidogrel bisulfate tablets.

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