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PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.1, No.4, pp 1678-1684, Oct-Dec 2009

GASTRORETENTIVE DRUG DELIVERY SYSTEM OF AN ANTIRETROVIRAL AGENT

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ABSTRACT: Zidovudine is a novel compound used in the treatment of HIV. The purpose of this study was to develop a Gastroretentive tablet of Zidovudine to enhance its bioavaibility and sustained action. In 3^2 factorial design, amount of HPMC K4M (X_1) and gas generating agents (X_2) were selected as independent variable. The time required for 50% drug release $t_{50\%}$ (Y_1) was selected as dependent variable. The derived polynomial equations for $t_{50\%}$were verified by two check point formulations. The results of factorial design showed thatfactor X_1 and X_2 significantly affect the studied dependent variables. The formulationwith good floating time (24hrs) and the percent drug release (98.05) emerged as optimal.
Key words: Gastroretentive Drug Delivery, Antiretroviral agent, Zidovudine

INTRODUCTION

Acquired Immuno Deficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation. In reality AIDS is not a disease but a collection of seventy or more conditions which result from the damage done to the immune system and other parts of the body as a result of infection by HIV[1]. It is crucial for the success of AIDS therapy to maintain the systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment. There are a number of
drugs that have been considered as to be anti HIV. The drugs like Zidovudine appears most promising because it crosses the blood brain barrier and can be taken orally and in treaties they do not cause serious side effects [2, 3]Zidovudine (AZT) is the first approved compound for the treatment of AIDS; however the main limitation to therapeutic effectiveness of AZT is its dose-dependent toxicity, short biological half-life and poor bioavailability[4]. This limitation can be overcome by formulating gastroretentive drug delivery systems which retained in the stomach and help in continuously releasing the drug, thus ensuring optimal bioavailability[5-7]The objective of this study was to develop a gastric floating drug delivery system (GFDDS) containing Zidovudine. To achieve the objective, 3^2 factorial design were chosen. In this design amount of HPMC K4M (X_1) and gas generating agents (X2) were selected as independent variable. The time required for 50% drug release $t_{50\%}$ (Y_1) was selected as dependent variable. The derived polynomial equations for $t_{50\%}$ were verified by check point formulations. Regression analysis was performed to identify the best formulation and to validate the model by comparing the experimental results with the theoretical values of the responses.

MATERIALS AND METHODS

Zidovudine was received as a gift sample from Cipla Ltd, India. HPMC K4 M was kindly supplied by Colorcon Asia Pvt Ltd. (Goa, India). Microcrystalline cellulose, Sodium bicarbonate and Citric acid anhydrous (here after referred as citric acid), Magnesium stearate and talc were purchased from Qualigens fine chemicals, Mumbai, India. All other ingredients were of laboratory grade.

PRELIMINARY TRIALS: PREPARATION OF ZIDOVUDINE FLOATING TABLETS

The formulations were fabricated using direct compression method (Table 1). Required quantities of Zidovudine, HPMC K4 M/guar gum/Xanthan gum, Microcrystalline cellulose, Sodium bicarbonate and Citric acid were passed through sieve
No.40 separately. The drug was mixed with the polymer and other ingredients for 10 minutes. The powder blend was then lubricated with magnesium stearate (presifted through40#), talc (2%w/w). Then the powder blend was compressed into tablet using 12.5mm flat face tooling on a tablet compression machine (Rimek minis press) [8,9].

Table 1: Composition of tablet in preliminary study

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Zidovudine	300	300	300	300	300	300	300	300
HPMC K4M	20	40	60	80	100	120	140	160
Guar Gum	25	50	75	100	–	–	–	–
Xanthan Gum	–	–	–	–	25	50	75	100

EXPERIMENTAL DESIGN

In the studies, 9 formulations with different drug polymer ratios were formulated based on 3^2 factorial design (Table 3). The design includes 2 factors evaluated each at 3 levels. The amounts of HPMC K4 M (X_1) and amount of Mixture of gas generating agents(X_2) were selected as independent variable. The time required for $t_{50\%}$ (Y_1) was selected as dependent variable[10]

EVALUATION

A) STUDY OF FLOATING PROPERTY

The floating behavior was determined by the method described by Rosa et al.[11] The floating lag time and the total floating duration was determined by placing the tablets in a

100 ml flask containing pH 1.2 solutions. The time required for dosage form to emerge on surface of the medium is called total floating lag time. The duration of time by which the dosage forms constantly emerge on surface of the medium called is total floating time.

B) IN-VITRO RELEASE STUDIES[12]

In-vitro release study was carried out according to USP XXIII dissolution type II apparatus (Electro Lab.DTD – 06P) using paddles. 0.1 N HCl solution was selected as adissolution medium. The study was conducted by keeping 100 rpm paddle rotation at thetemperature of 37 ± 0.5 0C. The samples were withdrawn at predetermined time interval and same volume of fresh medium was replaced. The withdrawn samples were suitably diluted and the amount of drug release was estimated using UV spectrophotometer (Shimadzu-1700)

C) STATISTICAL ANALYSIS

The Statistical analysis of the drug release data was done by multiple regression analysis using softwares Microsoft excel and Statplus2008. Analysis of variance was performed using Biostateplus to evaluate contribution of factors. The response surface plotswere generated using Table Curve 3D V4.

RESULT AND DISCUSSION

PRELIMINARY STUDY

In the preliminary study, AZT tablets prepared using polymers such as HPMC K4 M, guargum and xanthan gum. The mixture of sodium bicarbonate and citric acid was added as a gas-generating agent which generated CO_2 in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1,the tablet becomes buoyant. Whitehead et al have demonstrated good correlation between in vitro and in vivo buoyancy of floating dosage forms[13]. Batches containing guar gum and xanthan gum, failed to form a matrix system with sufficient strength, while tablets produced with HPMC K4 M have good matrix strength and used for further study. The results, shown in (Table 2)

IN-VITRO DRUG RELEASE STUDY

Release profiles from the 9 formulations of 3^2 factorial designs are shown in Figure 2 and Figure 3.In vitro drug release study for all the factorial design formulations was carried out in 0.1 N HCl for 24 hrs. The formulation F1, F2, F3 showed gastric floating time in the range of 15 to21 hrs and the percent drug release was observed between 98.70% and 99.28%. Hence this formulation did not follow the principle of floating for the desire period of time because of the lowest polymer concentration, which could not control the release for longer period possibly because of the poor strength of the matrix. The formulations F4, F5, F6 float in the range of 22 to 24hrs and percent drug release was observed between 88.39 and 96.27%.The formulations F7, F8, F9 float for more than 24hrs and percent drug release was observed between 85.65 and 89.81%. But formulationsF4 (emerged as optimum), which contained a high polymer concentration, were able to keep their integrity and therefore showed good control of the drug dissolution process, with a desired slower release rate for a longer period of time.

DEVELOPED AND VALIDATION OF POLYNOMIAL EQUATION

The dependent variables chosen for the study was, time required for 50% drug release. The fitting of an empirical polynomial equation to the experimental result facilitates the optimization procedure. The general polynomial equation is as follows:

$Y = B_0 + B_1X_1 + B_2 X_2 + B_3 X_3 + + B_{12} X_1X_2 + B_{13}X_1X_3 + B_{23}X_2X_3$ ---

Where Y is the response.

Where X_1, X_2, X_3 are the levels (concentration) of the 1, 2, 3 factor.

B_1, B_2, B_3, B_{12}, B_{13}, B_{23}, are the polynomial coefficient

B_0 is the intercept (which represents the response when the level of all factors is Low) i.e.arithmetic mean response of the 9 runs).Xi(X_1, X_2, X_1X_2, $X_{12}$and X_{22}), which represents the average result of changing 1 factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_{12}andX_{22}) are included to investigate nonlinearity. The $t_{50\%}$ for the9 batches (F1-F9) showed a wide variation the responses of formulation prepared by 3^2 factorial designs are indicated in Table 1. The data clearly indicate that the $t_{50\%}$ values are strongly dependent on the selected independent variables. The fitted equations relating the response $t_{50\%}$ are shown in Equation 1.

$t_{50\%} = + 2.9394 - 2.2356_{X1} + 0.3814 X_2 - 0.0187 X_3$----------Equation 1

Validity of the above equations was verified by designing two check point formulations

(C1 and C2).The dissolution parameters predicted from the equations derived and those

observed from experimental results are summarized Table 4. The closeness of predicated

and observed values for $t_{50\%}$ indicates validity of derived equations for dependent variables.

EFFECT OF FORMULATION VARIABLES ON RELEASE PROPERTIES

In the case of Y_1 ($t_{50\%}$ drug release), as the concentration of polymer (X_1) is increased, thedrug release decreased. Similar results were reported earlier: as the polymer concentration in the matrix increases, the release rate decreases.[14] The relationship between variables was further elucidated using response surface plots. Figure 4. At low levels of X_2, Y_1 did not show any significant changes when X_1 increased from the –1 level to the +1 level. But the same Y_1 decreased from 98.39% to 89.98% when the total polymer content-to-drug ratio (X_1) was increased and the polymer-to-polymer ratio (X_2) was kept at the highest level. This finding was due to the increased strength of the gel layer; the drug diffusion was controlled by the penetration of liquid through the gel layer.

The ANOVA analysis for $t_{50\%}$ (Y_1) is shown in Table 5 only coefficient b1 was found to be significant, with an F value of 1.90 (P = 0.22). When the concentration of polymer (X_1) values were increased, the $t_{50\%}$ values showed an increase in coefficient value of 0.34 (Table 5), which may have been due to slower water uptake (the water diffusion and

release rate also slowed).As the variables X_1 and X_2 increased, the diffusion coefficient also increased, which may have been due to the fact that increased polymer loading increased the strength and viscosity of the gel layer, which in turn delayed the water diffusion into the core of the tablet, leading to uniform drug release. Such behavior may be closely related to the porosity and tortuosity of the gel barrier. Because of the high viscous gel layer, more resistance to erosion was observed and these matrices could maintain the integrity of the tablet for up to 24hours.

EFFECT OF FORMULATION VARIABLES ON FLOATING TIME

As the polymer concentration (X_1) increased, the floating time also increased. At a higher level of gas generating agents (X_2), the floating time increased from 10.33 hours to 22.20 hours when polymer concentration (X_1) was increased from 0 to +1. At a lower level of gas generating agents (X_2), there was a significant increase in floating time from 8 to 16 hours, when X_1 was increased from –1 to 0. For all the formulations, the time required for the tablets to go from the bottom to the top of a beaker containing pH 1.2 at 37°C ± 1°C was found to be less than 20 minutes. Once the tablets (F4 and F5) came up to the surface, they remained buoyant for up to 24 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced because of disintegration and erosion. In fact, the floating time (buoyancy) of the tablets is governed by both the swelling (hydration) of the hydrocolloid particles on the tablets' surface when the tablets come in contact with the gastric fluid, which in turn results in an increase in the bulk volume; and the presence of the internal voids in the dry center of the tablet (porosity). These 2 factors are essential for the tablet to acquire a bulk density of less than 1 and remain buoyant on the gastric fluid.[15] The figure 1 shows the floating behavior of optimum formulation.

CONCLUSIONS

The floating drug delivery is a promising approach to achieve in vitro buoyancy by using

gel-forming polymer HPMC K4M and gas-generating agent using systematic study of 3^2

full-factorial design the desired dissolution profile could be achieved. The optimized formulation gives the best result in terms of the floating duration (24hours) and drug release. This dosage form holds promised for further in vivo studies, which can be extrapolated for the development of other delivery systems

Table 2: Results of preliminary study

Formulation Code	Floating Times (hrs)		
	HPMC K4M	Guar Gum	Xanthan Gum
F1	2-3	Not floating	-
F2	5-6	1	-
F3	13	2-3	-
F4	16	5-6	-
F5	18	-	Not floating
F6	20	-	Not floating
F7	22	-	2-3
F8	24	-	5-6

Table 3: Formulation and t50% drug release for Formulations (F1-F9) by Factorial Design

Formulations	Coded Values		$t_{50\%}$ (hrs)
Code	X_1	X_2	
F1	-1	-1	3.45
F2	-1	0	5.26
F3	-1	1	7.33
F4	0	-1	6. 21
F5	0	0	7. 50
F6	0	1	7.24
F7	1	-1	7.35
F8	1	0	8. 03
F9	1	1	8.44

Table 3(b) coded values of the variables

Coded Values	Actual Values in mg	
	X_1	X_2
-1	60	10
0	120	25
1	180	40

Table 4 Observed values and Predicted Values for check point formulations

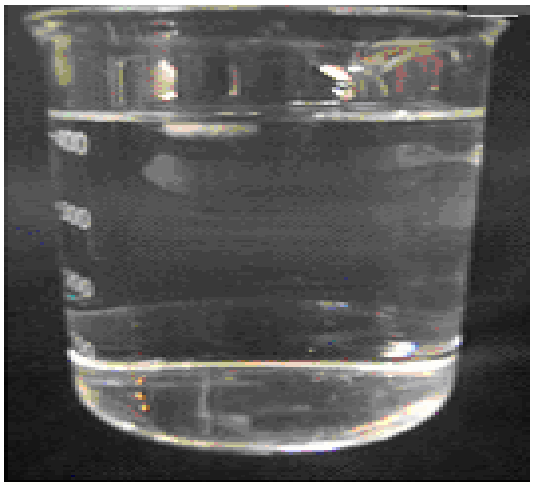
Formulations	Observed values(hrs) $t_{50\%}$	Predicated values (hrs) $t_{50\%}$
C1	6.08	5.56
C2	7.2	7.08

Table 5 Analysis of Variance Table for Dependent Variables from Full Factorial Design*

Parameters	d.f	SS	MS	F	Significance F
For t50%					
Regression	2	2.61	1.30	1.90	0.22
Residual	6	4.1	.68		
Total	8	6.72			

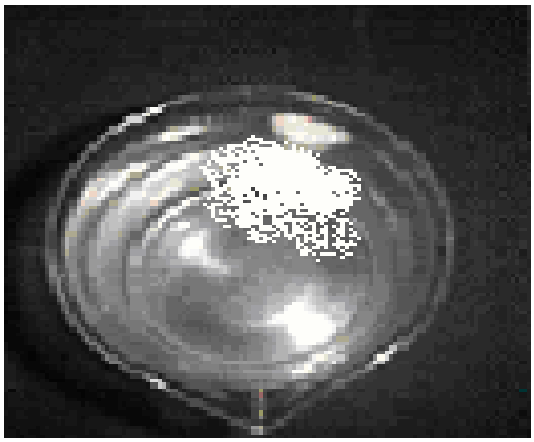
*Probe > F less than 0.5 indicate model terms are significant.

a) F4 at 0 second,



b) F4 at 12 hrs

C) At 18 hrs



D) At 24 hrs

Figure 1 In-vitro buoyancy of Optimum formulation (F4) of HPMC K4M

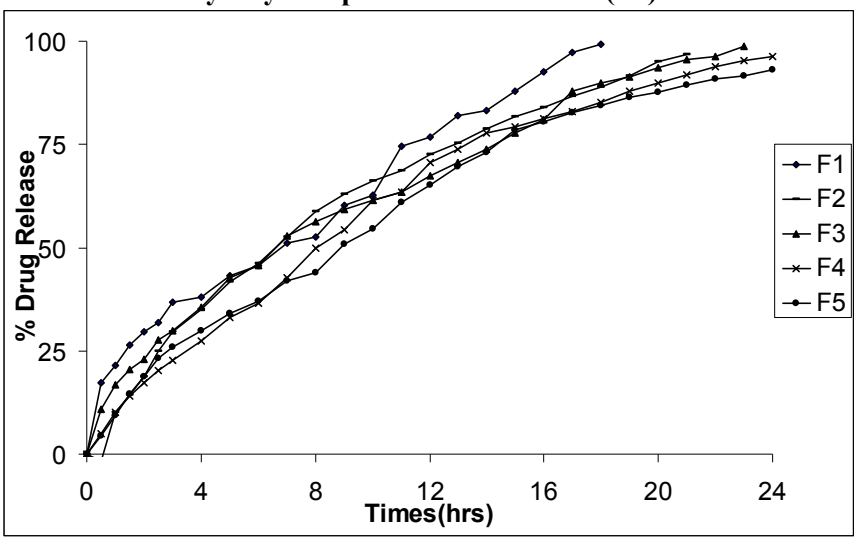


Figure 2. In vitro release profile of Zidovudine from formulations F1 to F5 (n = 3).

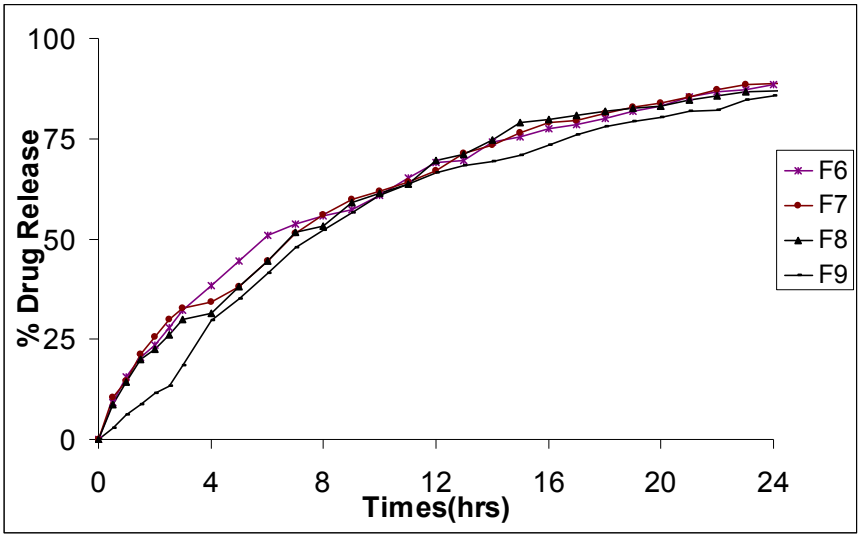


Figure 3. In vitro release profile of Zidovudine from formulations F6 to F9 (n = 3).

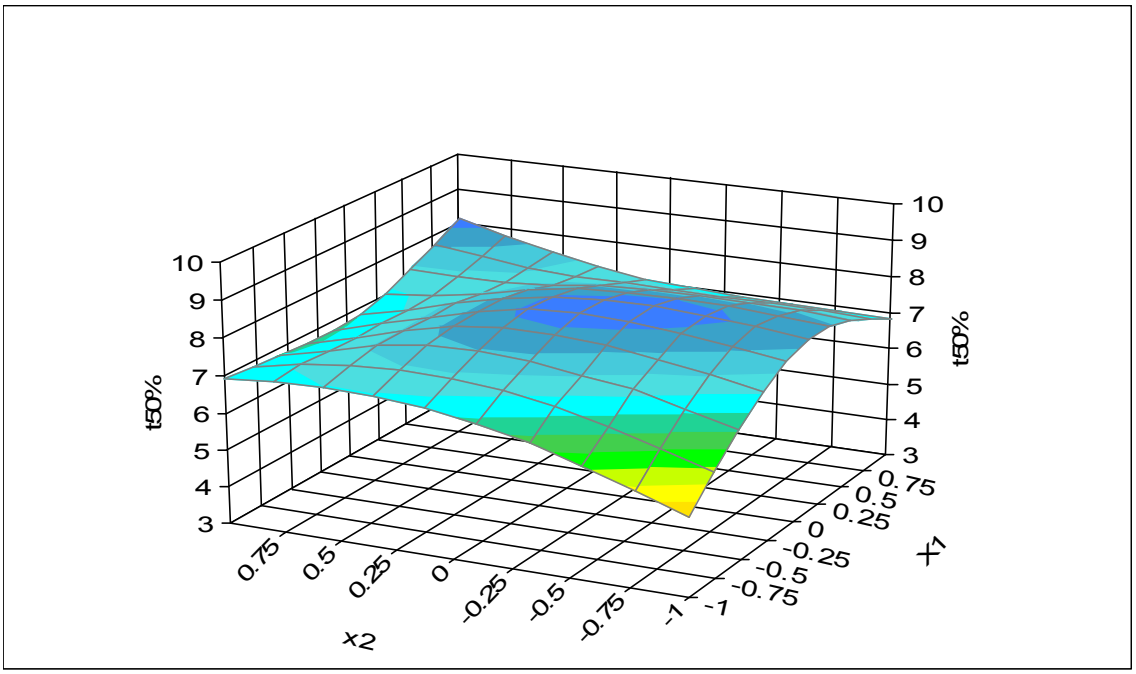


Figure 4. Response Surface plot of the chosen Variables

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