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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and *In-vitro* evaluation of Gastroretentive Drug Delivery System of an Antiretroviral Agent

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ABSTRACT
Floating Matrix tablets of Zidovudine were developed to prolong gastric residence time and increase its bioavailability and sustained action. The present investigation was carried out to develop a gastric floating drug delivery system of Zidovudine to improve the efficacy of dosage form. For this 3^2 factorial design was employed to study the effect of independednt variables such as Low Density Polyethylene [LDPE] (X1), Glyceryl Behenate(X2) at three different levels those are -1, 0 and +1. Table 1 and 2 summarizes the nine experimental runs studies Buoyancy time (Y1) and time taken for 80 % drug release (T 80%; Y2) was taken as the response variables. The formulation with good floating time (24hrs) and the percent drug release (97.5) was selected as an Optimized Formulation.
Key words: *Antiretroviral agent, Zidovudine, Gastroretentive Drug Delivery.*

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INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine) [1]. *Floating Drug Delivery Systems* (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations [2].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 [3-4]. 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, 32 factorial designs were chosen. In this design amount of Low Density Polyethylene [LDPE] (X1), Glyceryl Behenate(X2) was selected as independent variable. The time required for 80% drug release to 80% (Y1) was selected as dependent variable. 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.

MATERIAL AND METHODS

Material:

Zidovudine was received as a gift sample from Cipla Ltd, India. Glyceryl Behenate were gift sample from Gattefosse Pvt., Ltd Mumbai, India. LDPE powder obtained from IPCL (Vadodara, India). Microcrystalline cellulose was purchased from S.D. Fine Chemicals, 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, LDPE, glyceryl behenate, microcrystalline cellulose, 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 11 mm flat face tooling on a tablet compression machine (Shakti Tab Press) [8, 9].

Table 1: Composition of tablet in preliminary study

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zidovudine	300	300	300	300	300	300	300	300	300
Glyceryl behenate	-	-	-	100	150	200	50	75	100
LDPE	100	150	200	-	-	-	50	75	100
Microcrystalline cellulose	130	80	30	130	80	30	130	80	30
Talc	10	10	10	10	10	10	10	10	10
Mg Stearate	10	10	10	10	10	10	10	10	10
Total	550	550	550	550	550	550	550	550	550

Experimental Design

In this design amount of Low Density Polyethylene [LDPE] (X1), Glyceryl Behenate(X2) was selected as independent variable. The time required for 80% drug release t 80% (Y1) was selected as dependent variable. 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.

EVALUATION

STUDY OF FLOATING PROPERTY

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.

IN-VITRO RELEASE STUDIES

In-vitro release study was carried out according to USP XXIII dissolution type II apparatus (Electro Lab TDT 008) using paddles. 0.1 N HCl solution was selected as a dissolution medium. The study was conducted by keeping 100 rpm paddle rotation at the temperature 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-1800)

STATISTICAL ANALYSIS

The Statistical analysis of the drug release data was done by multiple regression analysis using softwares Microsoft excels and Statplus 2008. Analysis of variance was performed using Biostateplus to evaluate contribution of factors. The response surface plots were generated using Table Curve 3D V4.

RESULT AND DISCUSSION

In the preliminary study, AZT tablets prepared using polymers Low density Polyethylene and Glyceryl Behenate as a low density polymers and release retardants. As the density of the tablet falls below 1, the tablet becomes buoyant. Six formulations were prepared by taking each polymers in increasing concentration with MCC, further Three formulations were prepared by taking both the polymers in combination with each other. The batches with combination were showed most desirable results.

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 10 to 18 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 Single and 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 12 to 22 hrs 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 91.5% and 98.81%. But formulations F8 (emerged as optimum), which contained intermediate polymer concentration in combination of Glyceryl Behenate and LDPE, 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 80% 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 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 $t_{80\%}$ for the 9 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 $t_{80\%}$ values are strongly dependent on the selected independent variables. The fitted equations relating the response $t_{80\%}$ are shown in Equation1.

$T_{80\%} = + 2.9394 - 2.2356\ _{X1} + 0.3814\ X_2 - 0.0187\ X_3$----------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 $t_{80\%}$ indicates validity of derived equations for dependent variables.

EFFECT OF FORMULATION VARIABLES ON RELEASE PROPERTIES

In the case of Y1 (t80% drug release), as the concentration of polymer (X1) is increased, the drug release decreased. Similar results were reported earlier: as the polymer concentration in the matrix increases, the release rate decreases. The relationship between variables was further elucidated using response surface plots. Figure 4. At low levels of X2, Y1 did not show any significant changes when X1 increased from the −1 level to the +1 level. But the same Y1 decreased from 98.39% to 89.98% when the total polymer content to drug ratio (X1) was increased and the polymer-to-polymer ratio (X2) 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 $t_{80\%}$ (Y1) is an only coefficient b1 was found to be significant, with an F value of 1.90 (P = 0.22). When the concentration of polymer (X1) values were increased, the $t_{80\%}$ values showed an increase in coefficient value of 0.34.

EFFECT OF FORMULATION VARIABLES ON FLOATING TIME

As the polymer concentration (X_1) increased, the floating time also increased. At a higher level of Polymer Combination (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 Polymer Combination (X_2), there was a significant increase in floating time from 6 to 14 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 (F7 and F9) 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.

Table 2: Results of preliminary study

Formulation Code	Floating Times (hrs)		
	LDPE	Glyceryl Behenate	LDPE+ Glyceryl Behenate
F1	5	-	-
F2	9	-	-
F3	13	-	-
F4	-	12	-
F5	-	16	-
F6	-	21	-
F7	-	-	22
F8	-	-	24
F9	-	-	24

Table 3: Formulation and t 50% drug release for Formulations (F1-F9) by Factorial Design

Formulations	**Coded Values**		**$T_{80\%}$ (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

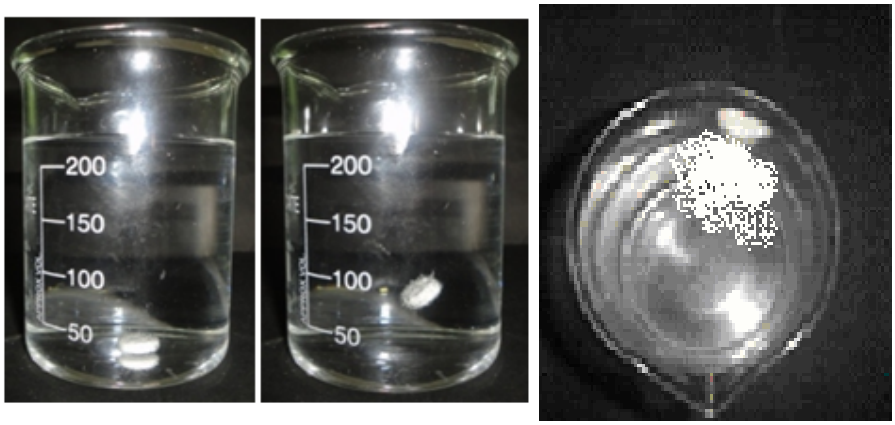
Table 3 Observed values and Predicted Values for check point formulations

Formulations	Observed values(hrs) $t_{80\%}$	Predicated values (hrs) $t_{80\%}$
C1	16.08	15.56
C2	17.2	17.08

Table 4 Analysis of Variance Table for Dependent Variables from Full Factorial Design*

Parameters	d.f	SS	MS	F	Significance F
For t80%					
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



At 0 hrs **At 24 hr**

Figure 1 *In-vitro* buoyancy of Optimum formulation (F8) of HPMC K4M

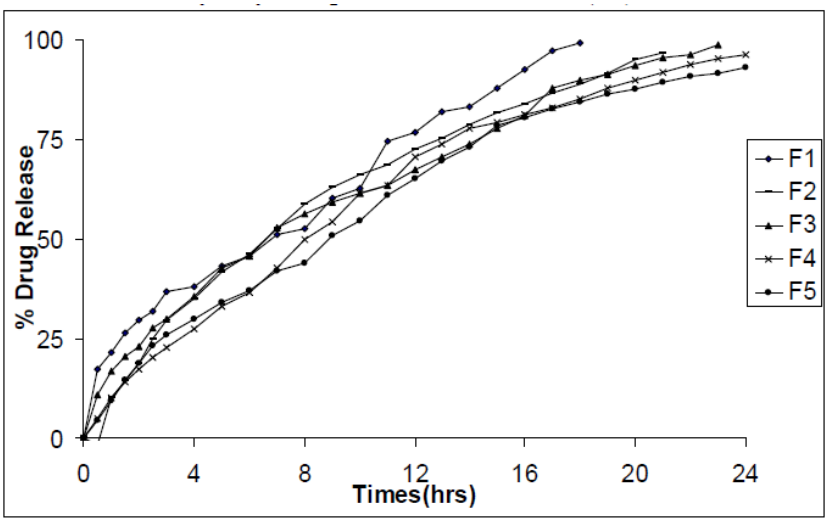


Figure 2. In vitro release profile of Zidovudine from formulations F1 to F5 (n = 3).

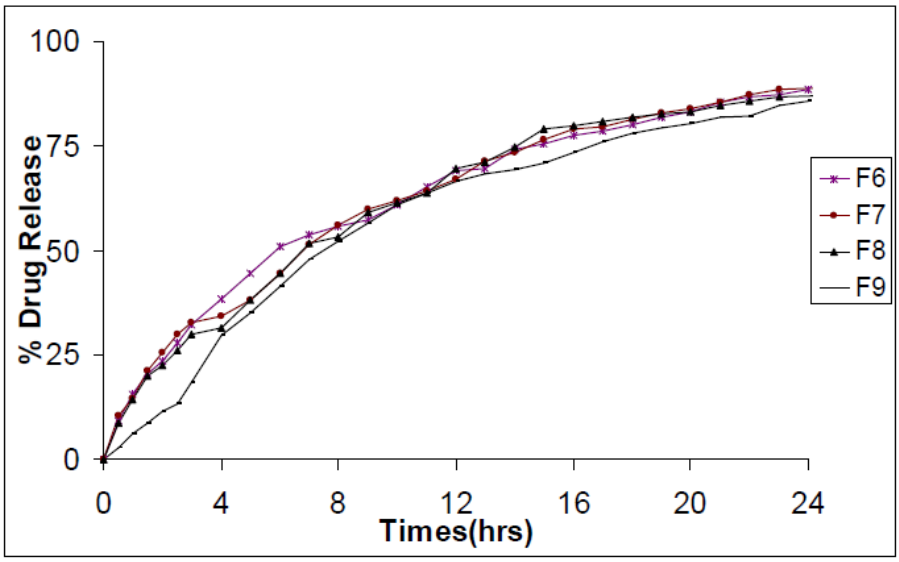


Figure 3. In vitro release profile of Zidovudine from formulations F6 to F9 (n = 3).

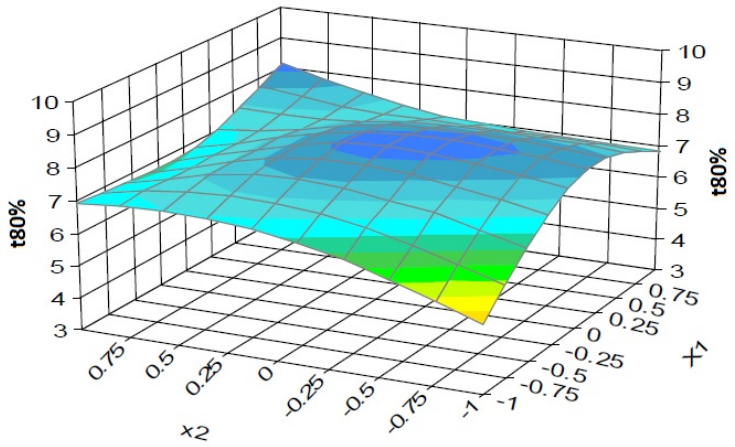


Figure 4: Response surface plot of chosen variables

CONCLUSION

The floating drug delivery is a promising approach to achieve in vitro buoyancy by using n Low density Polyethylene and Glyceryl Behenate as a low density polymers and release retardants. The 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.

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