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Research Article

Formulation, optimization and *in vivo* studies of oral controlled release tablets of Zidovudine

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ABSTRACT

The main aim of this research work was to develop a controlled release tablet of Zidovudine (AZT) by simplex lat---tice design. For this purpose three rate controlling polymers were studied i.e HPC, HPMC k100 and guar gum. Tab---lets were prepared following direct compression. The pre-compression and post-compression parameters were studied and were found to be within the limits of pharmacopoeia. The results of release profile suggested that the thick, viscous gel around the tablet contributed for controlled release. Statistical analysis was performed and found that, an appropriate amount of ternary blend of HPC, HPMC k100 and guar gum was crucial in controlling the release of AZT. Further formula optimization was done by using numerical optimization technique and the results suggested that the formula developed was reproducible. The results of *in vivo* studies showed that a C_{max} of 3.36 ± 0.84 (µcg/ml) was achieved in 4hr. The half-life and mean residence time were found to be 6.26 ± 0.65hr and 11.30 ± 0.75 hr respectively indicating a prolonged release of Zidovudine.

Keywords: Simplex lattice design; rate controlling polymers; numerical optimization; Cmax; half-life

INTRODUCTION

Oral drug administration is known to be the most pop---ular route for drug delivery due to the gastrointestinal physiology offers more flexibility in dosage form design than other routes (Chen X et al., 2010). Controlled re---lease (CR) drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time (Nair AB et al., 2010). Hydrophillic ma---trix systems are among the most commonly used re---sources for oral controlled drug delivery as they can reproduce a desirable drug profile at most cost effec---tively (Prajapati GB and Patel RK., 2010). Drug delivery has been at the focus of pharmaceutical research due to its many benefits over conventional dosage. Hence, oral controlled release matrix tablets are widely used in the formulation (Raja NA et al., 2012).

Zidovudine (AZT) belongs to the drug class nucleoside reverse transcriptase inhibitors (NRTIs), used to treat infection of human immunodeficiency virus (HIV). NRTIs work by blocking HIV reverse transcriptase, an HIV enzyme (AIDSinfo). This prevents HIV from replicat---ing, and lowers the amount of HIV in the blood. AZT are administered multiple times a day depending on the dose (300 mg twice daily or 200 mg thrice daily) due to its short half-life ($t_{1/2}$=0.5 to 3 h) (Anthony SF et al., 2001, Blum MR et al., 1998) . Conventional formu---lations of AZT are known to cause many serious ad---verse drug reactions due to the accumulation of drug in the plasma (Brinkman K, 1998 and Moyle G, 2000) to its increased frequency of dose (Chariot P et al., 1999); which also leads to poor compliance (Re M C et al., 2003) and increase the cost of the treatment (Richman D et al., 1987). Hence CR of AZT once daily formulation can overcome these problems. Hence this research work was aimed to develop a controlled release tablet of Zidovudine by simplex lattice design.

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MATERIALS AND METHODS

Materials

Zidovudine was received as a gift sample from M/s Hetero Drugs Ltd., Hyderabad, India. Hydroxypropyl methyl cellulose (HPMC) (METHOCEL™) K100M and Hydroxypropyl Cellulose (HPC) procured from Colorcon Asia Pvt. Ltd., Goa, India. Other materials, including Magnesium stearate (LobaChemie Pvt. Ltd., Mumbai, India), Aerosil (SD Fine-Chem Ltd, Mumbai, India), Talc (Nice Chemicals (P) Ltd., Kochi, India), Gaur gum (GG) (Loba chemi. Pvt. Ltd., Mumbai) and Lactose DC (Sig--- ma-Aldrich Co. LLC., Bangalore, India) was purchased from a commercial source. All other chemicals used in the study were of analytical grade.

Drug excipients compatibility study

Sample of pure drug, physical mixture of excipients with drug and polymers in 1:1 ratio was placed in an accelerated stability condition of 40 ± 2^0C and 75 ± 5% RH for a period of 3 months. At the end of 3 months, samples were evaluated for drug excipient compatibility by using differential scanning colorimeter (DSC) (Pyris-1, Perkin-Elmer, USA).

Experimental design

A Simplex Lattice Design (SLD) was adapted to optimize the formulation variables of AZT (Karaman S et al., 2011, Mandlik SK et al., 2012). In this design, 3 factors were evaluated by changing their concentrations simultaneously and keeping total concentration constant. The simplex lattice design for a 3-component (A, B and C) system is represented by an equilateral triangle in 2-dimensional space (Figure 1) (Patel et al., 2007, Prajapati et al., 2009, Rajamma AJ et al., 2012).

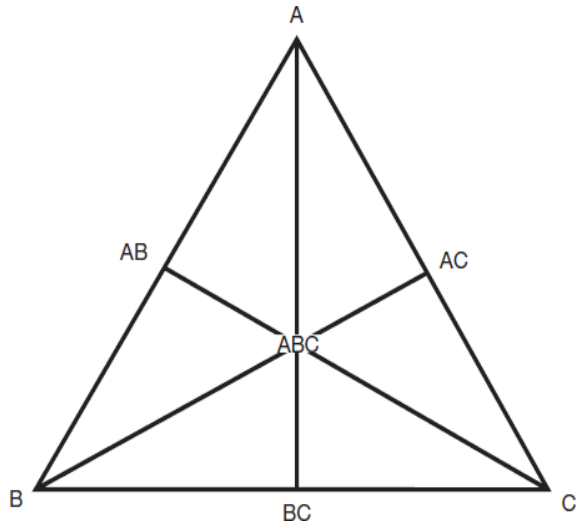

Figure 1: Simplex Lattice Design

The design layout is shown in the Table 1. Twelve batches (F1-F12) of tablet formulations were prepared, one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the 2 ingredients. The center point represents a formulation containing one third of each ingredient.

Independent variables

X_1 = Amount of HPC (50mg to 100mg)

X_2 = Amount of HPMC K 100 (50mg to 100mg)

X_2 = Amount of Guar gum (GG) (50mg to 100mg)

Dependent variables (Responses values)

Y_1 = Percentage drug release at 1hr

Y_2 = Percentage drug release at 8 hr

Y_3 = Diffusion Coefficient (n)

Y_4 = Time required for 50% of the drug release in hr ($T_{50\%}$)

The response values obtained were analyzed using multiple regression analysis to find out their relationship with the factors used. The design layout is shown in the Table 1 as per simplex lattice design.

Preparation of CR matrix tablets

The tablets were prepared by direct compression method. The different stages involved in the process which includes, weighing and sieving**,** mixing and tablet compression. First stage, all the materials were passed through sieve no. 60 and weighed accurately as per the formulae. In the second stage, Zidovudine (AZT) (300 mg), Polymers (HPMC/HPC/GG), Mg. stearate, Talc, Aerosil and directly compressible Lactose were mixed thoroughly by kalweka mixer (M/S. Karnavati Engineering Limited., Gujarat, India) to get uniform mix. Third stage involving direct compression technique; the final blend obtained from above was compressed in 16 sta---

Table 1: Design Summary

Formulation code	Type	X_1	X_2	X_3	Y_1 (%)	Y_2 (%)	Y_3 (h)	Y_4 (n)
Z1	Vertex	1	0	0	23.35	71.06	4.64	0.52
Z2	CentEdge	0.5	0.5	0	20.21	59.32	5.28	0.42
Z3	CentEdge	0.5	0	0.5	33.33	66.09	4.63	0.35
Z4	Vertex	0	1	0	28.37	66.36	4.9	0.41
Z5	CentEdge	0	0.5	0.5	24.13	69.41	4.97	0.53
Z6	Vertex	0	0	1	25.71	62.12	5.71	0.43
Z7	AxialCB	0.6667	0.1667	0.1667	21.76	57.26	6.3	0.44
Z8	AxialCB	0.1667	0.6667	0.1667	21.23	58.75	6.58	0.47
Z9	AxialCB	0.1667	0.1667	0.6667	26.01	59.88	6.36	0.43
Z10	Center	0.3333	0.3333	0.3333	22.78	55.28	7.02	0.43
Z11	Vertex	1	0	0	22.34	70.65	4.61	0.52
Z12	Vertex	0	0	1	24.74	60.42	5.52	0.43

tion tablet compressing machine (Rimek, Karnavati Engineering Pvt. Ltd., Ahmedabad, India), using B-tooling 12mm standard biconcave punch. The tablets were compressed by maintaining a constant hardness of 13±0.5 kg/cm^3.

Characterization of pre-compression mixture

Prior to compression, the mixture was evaluated for their characteristic parameters (USP, 2007). Angle of repose was determined by funnel method; Bulk density (BD) was determined by using a measuring cylinder and tapped density (TD) was determined by Tap Density Tester (ETD-1020, Electrolab, India). Carr's index (CI) was calculated using the following equation (1),

$$CI = (TD - BD) \times 100 / TD \quad \text{..... (1)}$$

Characterization of tablets

The properties of the compressed matrix tablets, such as hardness, friability and weight variation were determined as per United States Pharmacopoeia specifications (USP, 2011). The drug content of 06 randomly selected CR matrix tablets from each batch was determined by using UV double beam spectrophotometer (UV-1601, Shimadzu Co., Japan). Friability was determined using friability testing apparatus (Electrolab, India). Weight variation of tablets was determined as per official procedure for randomly selected 20 tablets by using an electronic balance (Denver APX-100, Arvada, Colorado).

***In vitro* dissolution studies**

The drug release profile of the formulated tablets was studied using USP dissolution apparatus II (TDT-06T, Electrolab, India) at 37^{0}C ± 1^{0}C using 900ml of pH 1.2 buffer for the first 2 hr, followed by pH 7.4 buffer till the end of dissolution studies. The paddle rotation speed was set to 75rpm. Aliquot samples were withdrawn at every 1 hr and after suitable dilutions the samples were analyzed spectrophotometrically 266nm. The volume of the sample withdrawn each time was replaced with the same volume of the respective buffer solutions. The studies were carried out in triplicate and mean values plotted versus time with standard error of mean, indicating the reproducibility of the results. The release data were fitted to various mathematical models for describing the release mechanism from tablets; such as Korsmeyer-Peppas model (Korsmeyer RW et al., 1983), Zero-order model (Lee PI, 1984), and Higuchi release model (Higuchi T, 1963). All curve fitting, simulation and plotting were carried out by using commercially available software (SigmaPlot® version 9, Systat Software, Inc.).

Statistical analysis

The effect of formulation variables on the response variables was statistically evaluated by applying one way ANOVA at 0.05 levels using a commercially available software, including package design of experiments® 6.05 (Stat Ease, USA). The design was evaluated by linear mixture model, which bears the equation (2);

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1 X_2 + b_5 X_2 X_3 + b_5 X_1 X_2 X_3 \quad \text{..... (2)}$$

Where Y is the response variable, b_0 the constant and b_1, b_2, b_3 … b_5 is the regression coefficient. X_1 and X_2 stand for the main effect; X_1X_2 are the interaction terms and show how the response changes when two factors are simultaneously changed. Whereas $X_1 X_2 X_3$ show how the response changes when three factors are simultaneously changed.

Stability studies

Stability studies were conducted on the optimized formulation. The optimized formulation was packed in a screw capped amber colored glass container. The containers were exposed to 40°C ± 2°C/ 75% ± 5% RH as per ICH guidelines for 6 months. Sampling was done at predetermined time intervals and evaluated for various physico-chemical parameters viz., appearance, drug content and hardness. *In vitro* drug release studies were also performed at the end of stability studies. To confirm the similarity of drug release profiles before and after stability studies, a model-independent statistical tool for comparison of dissolution profile *"similarity factor"* (f_2) was used by the equation (3) (Costa P and Sousa Lobo JM, 2001).

$$f_2 = 50 \cdot \log\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} * 100\} \quad \text{.. (3)}$$

***In vivo* pharmacokinetic studies**

The i*n vivo* pharmacokinetic studies were carried out using six male New Zealand white rabbits, weighing 2.5-3.2kg after obtaining approval from the institutional animal ethics committee. Animals were housed in a 12-hr light-dark, constant temperature environment prior to the study. All rabbits were fasted for one day before the experiment and water was supplied *ad libitum*. The optimal CR matrix tablet of AZT (containing 150mg of AZT) was orally administered with small amount of water. At pre-determined time intervals, 1ml of blood was collected from a marginal ear vein into heparinized plastic tubes. Blood samples collected were centrifuged at 2000rpm for 10 min and stored at --- 20^{o}C till further use. The concentration of the drug was determined by a standard HPLC method with minor modifications (Matta MK et al., 2012). The pharmaco--- kinetic parameters were computed by using plasma concentration time profile data utilizing a commercially available software Kinetica@ 2000 Version 3 (InnaPhase Corp., USA).

RESULTS AND DISCUSSION

Drug excipient compatibility studies

The DSC thermogram of AZT shows a sharp endothermic peak at 124 ^{0}C, where as physical mixtures of drug

with polymers exhibited an endothermic peaks ranging from 122.87 to 124 ^{0}C (Figure 2) which is correspond---ing to the melting point of the drug, thus indicating no interaction between the drug-polymers used for this study.

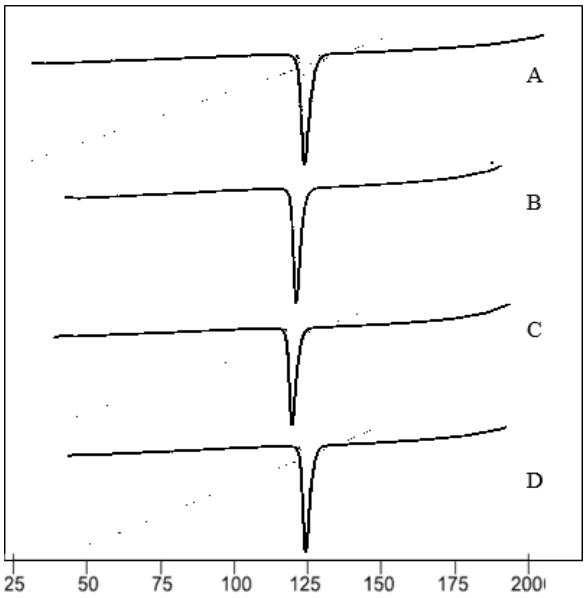

Figure 2: DSC thermogram of AZT (A) physical mixture of AZT with GG (B), physical mixture of AZT with HPMC (C) physical mixture of AZT with HPC (D)

Properties of pre-compression mixture

The properties of pre-compression mixtures were evaluated for all the batches. The angle of repose val---ues ranged between 19.43 ± 0.70 to 22.57 ± 0.36. The results indicate good flow properties. The cars index measures the propensity of a powder to consolidate when undergoing vibration, shipping and handling. The result ranges from 5.71 ± 0.82 to 13.79 ± 1.86 %, which indicate good flow properties.

Evaluation of tablets

The tablets of different batches showed a uniform thickness of 5.47 ± 0.02 to 5.70 ± 0.02 mm and hard---ness of 12.53 ± 0.24 to 13.25 ± 0.18 kg/cm^2. The as---sayed content of the drug in various formulations var---ied between 93.11 to 102.14 %. The average percent---age weight deviations for 20 tablets were found to be less than 5% and friability was found to be less than 1%. Thus, all the physical parameters were found to be within the permissible limits of the USP.

Release profile

Figure 3 and 4 illustrates the release profiles of twelve formulations prepared by following Simplex Lattice Design. In the first hour of dissolution studies, the axial points exhibited the release profile ranging from 21.23 to 26.01 %, vertex points exhibited 22.34 to 28.37 % and centre point formulation showed 22.78%.

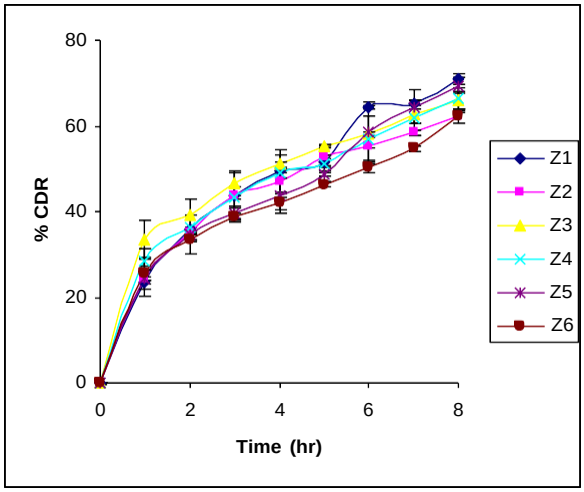

Figure 3: Dissolution profile of Zidovudine from for---mulation Z1-Z6

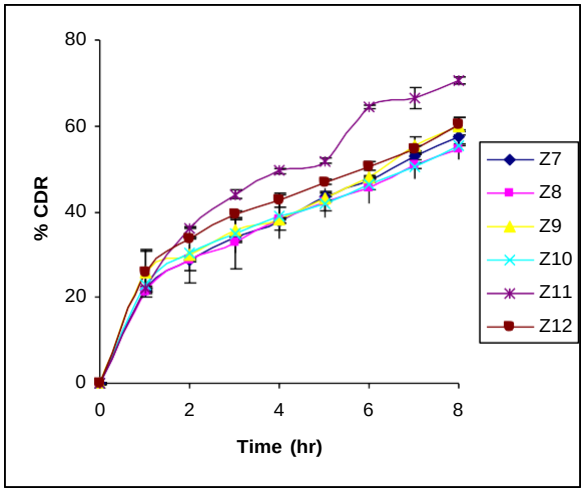

Figure 4: Dissolution profile of Zidovudine from for---mulation Z7-Z12

Formulations containing HPC or HPMC K100 or GG alone as rate controlling polymer exhibited release of 70 to 71 %, 66.36 and 60 to 62% respectively at the end of 8th hr of dissolution studies. Such a variation in release profiles may be attributed due to hydrating property of the polymers used. But in case formula---tions containing all the three polymers at same con---centration exhibited least release profile of 55.28% at the end of 8th hr of dissolution studies. This behavior may be due to the formation of thick gel around the tablet contributed by all the three studied polymers. Thus the results of release studies suggest that if all the three studied polymers were included at appropriate amount, then the release from the dosage form can be controlled for a long period of time. Further to under---stand the mechanism and order of drug release from the dosage form the release profile was fitted to var---ous mathematical equations. The results are presented in Table 2. The diffusion coefficient values for formula---tions Z2- Z4, Z6, Z7, Z9, Z10 and Z12 were found to be less than 0.45 indicating the fickian diffusion mecha---nism, whereas in case of other formulations, the 'n'

Table 2: Results of curve fitting analysis

Formulation code	Korsmeyer-Peppas K_{KP} (h^{-n})	R^2	Higuchi K_H ($h^{-1/2}$)	R^2	Zero-order K_0 (h^{-1})	R^2	First-order K_1 (h^{-1})	R^2
Z1	24.17±1.40	0.9993	24.83±0.37	0.9985	10.25 ± 1.40	0.8011	0.17±0.01	0.9916
Z2	26.22±0.86	0.9994	23.00±0.40	0.9979	9.39 ± 0.84	0.6576	0.15±0.01	0.9807
Z3	31.78±0.67	0.9997	24.74±0.73	0.9940	10.04 ± 1.12	0.5181	0.17±0.02	0.9723
Z4	27.45±0.79	0.9996	23.86±0.42	0.9979	9.75 ± 0.91	0.6601	0.16±0.01	0.9806
Z5	22.33±1.52	0.998	23.57±0.42	0.9978	9.76 ± 1.09	0.8233	0.15±0.02	0.9896
Z6	24.21±1.27	0.9986	21.41±0.42	0.9973	8.77 ± 0.55	0.6815	0.13±0.01	0.9769
Z7	20.08±0.87	0.9991	19.76±0.22	0.9991	8.14 ± 0.98	0.7781	0.12±0.01	0.9836
Z8	20.12±0.64	0.9995	19.17±0.19	0.9993	7.88 ± 0.31	0.7515	0.11±0.02	0.9812
Z9	22.06±1.39	0.988	19.17±0.85	0.9871	8.40 ± 0.57	0.7324	0.12±0.01	0.9775
Z10	21.91±0.80	0.9993	19.46±0.32	0.9981	7.96 ± 0.91	0.685	0.11±0.02	0.9753
Z11	24.07±1.39	0.9993	24.95±0.37	0.9992	10.30 ± 1.32	0.8064	0.17±0.02	0.9924
Z12	24.93±0.86	0.9997	21.42±0.42	0.9987	8.75 ± 0.59	0.6486	0.13±0.01	0.9753

value was found to be greater than 0.45 indicating non-fickian anomalous release mechanism. The regression value for first order was close to 1 indicating that the order of release from the dosage form was found to follow first order.

Statistical analysis

The initial statistical analysis was performed for the selection of model and it was found to be a linear mixture model, thus the study was further navigated by using a linear mixture model (LM). The model term for Y1, Y2, Y3 and Y4 was found to be significant with a p value less than 0.05, followed by a high regression value close to 1 indicates the adequate fitting to LM model. Table 3 shows the ANOVA results, the LM X1, X2 and X3 was found to be significant for all the study response variables. These results support that the polymers selected for this research work are capable of controlling the release of AZT individually.

Further to check the effect of binary mixture and ternary mixture the regression coefficient values are studied which is presented in Table 4. The ternary mixture was found to highly significant for the responses Y1 to Y3. A negative effect was observed in case of Y1 and Y2, means increasing the concentration of ternary blend, the drug release was found to be decreased. A positive effect was observed in case of Y3 indicating that increasing the concentration ternary blend increases the time required for 50% of drug release. Such behavior may be attributed due to the formation of high viscous gel around the tablet capable of controlling the release of highly water soluble AZT for a long period of time. The result, almost confirms the contribution of all the studied polymers for controlled release of highly water soluble drug AZT for a long period of time.

Optimization studies

Further to identify the appropriate composition of ternary blend, a numerical optimization technique by desirability function was adapted. The optimal composition was arrived 20% < Y_1 > 22%; 65% < Y_2 > 71%; 5 < Y_3 > 7hr; 0.45 < Y_4 > 0.53. The optimal levels of factor X1, X_2 and X_3 were 94mg, 56mg and 50mg with a maximum desirability value of 1. Even though, to challenge the reliability of the response surface model, the new optimized formulation was prepared according to the predicted model and evaluated for the responses. The results are shown in the Table 5.

Stability studies

The drug content (297.33 ± 1.94mg) and hardness (8.5 ± 0.0.5 kg/cm^2) of the optimized formulation before and after 6 months of stability studies were subjected to statistical analysis using the paired *t*-test and based on the p-value (drug content; 0.0727 and hardness; 0.2711) it was concluded that no significant difference were observed before and after stability studies. The release profiles (Figure 5) appear to be almost super impossible and the calculated f_2 value was 81.71.

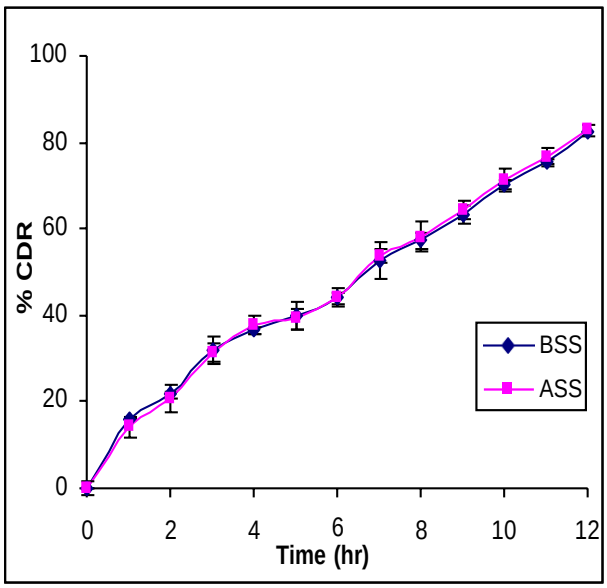

Figure 5: Comparison of release profile of optimized dosage form of AZT before (BSS) and after (ASS) stability studies

Table 3: Summary of ANOVA Table from SLD

Source	Sum square	d.f.	Mean square	F value	Probability*
% drug release at 1h (%) R^2 = 0.9607					
Model	136.80	6	22.80	20.40	0.0023
LM	25.71	2	12.85	11.50	0.0135
X_1X_2	24.89	1	24.89	22.27	0.0052
X_1X_3	69.91	1	69.91	62.54	0.0005
X_2X_3	5.00	1	5.00	4.47	0.0881^{ns}
$X_1X_2X_3$	11.30	1	11.30	10.11	0.0245
% drug release at 8 hr (%) R^2 = 0.9728					
Model	317.82	6	52.97	29.85	0.0009
LM	148.65	2	74.33	41.89	0.0008
X_1X_2	70.56	1	70.56	39.77	0.0015
X_1X_3	0.07	1	0.07	0.04	0.8498^{ns}
X_2X_3	24.14	1	24.14	13.60	0.0142
$X_1X_2X_3$	74.39	1	74.39	41.93	0.0013
$T_{50\%}$ (hr) R^2 = 0.9605					
Model	7.55	6	1.26	20.28	0.0023
LM	3.21	2	1.61	25.91	0.0023
X_1X_2	0.2547	1	0.2547	4.11	0.0986^{ns}
X_1X_3	0.1733	1	0.1733	2.79	0.1554^{ns}
X_2X_3	0.0492	1	0.0492	0.7926	0.4141^{ns}
$X_1X_2X_3$	3.85	1	3.85	62.16	0.0005
Releae exponent (n) R^2 = 0.9807					
Model	0.0309	5	0.0062	61.18	< 0.0001
LM	0.0021	2	0.0011	10.48	0.0110
X_1X_2	0.0014	1	0.0014	13.86	0.0098
X_1X_3	0.0155	1	0.0155	153.28	< 0.0001
X_2X_3	0.0119	1	0.0119	117.80	< 0.0001

* P<0.05 Significant, ^{ns} P>0.005

Table 4: Regression coefficients for the response variables

Coefficient	Y1	Y2	Y3	Y4
X_1	22.65345	70.57296	4.647969	0.519808
X_2	28.18734	66.33254	4.964304	0.41688
X_3	25.3412	61.33881	5.614159	0.428389
X_1X_2	-23.0981	ns	ns	-0.15759
X_1X_3	36.69641	-1.16551	ns	-0.49541
X_2X_3	ns	22.74515	ns	0.459495
$X_1X_2X_3$	-107.619	-276.084	62.84726	nd

ns= Non-significant, nd = not defined

Table 5: Comparison between the Experimented (E) and Predicted (P) values for the most probable optimal formulation

Dependent variables	Optimized formulation	
	E	P
Y_1 (%)	17.92 ± 0.66	21.85
Y_2 (%)	55.74 ± 1.22	65.06
Y_3 (hr)	6.55 ± 0.15	5.12
Y_4 (n)	0.64 ± 0.04	0.48

***In vivo* studies**

For *in vivo* studies in rabbit, the optimal formula obtained was reduced to half the quantity and compressed by using 8.5mm punch. The mean plasma concentration of AZT (150mg) following oral administration of optimized CR tablets is shown in Figure 6. The average time required for maximum plasma concentration (3.36 ± 0.84µg/ml) is 4hr. The average half-life of optimized CR tablets was found to be 6.26 ± 0.650hr

with average mean residence time (MRT) of 11.30 ± 0.75hr (Table 6).

Level A *in vitro-in vivo* correlation was performed by using percent AZT dissolved versus the percent AZT absorbed data at the same four data points (Figure 7). A regression value of 0.9762 indicated a linear relation---ship between fraction dissolved and fraction absorbed.

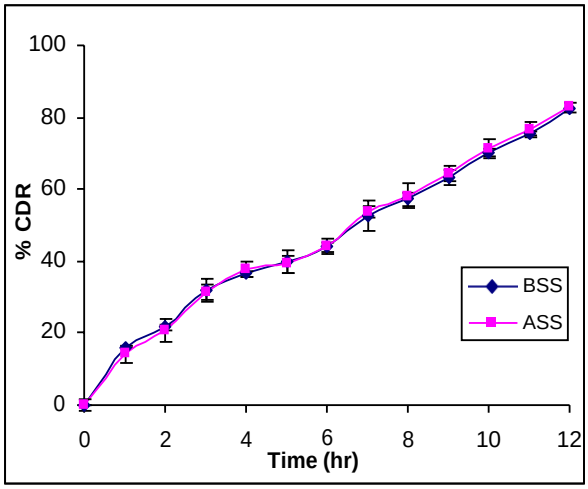

Figure 6: Comparison of release profile of optimized dosage form of AZT before (BSS) and after (ASS) sta---bility studies

Table 6: Pharmacokinetics Parameters of optimized formulation

Parameters	Optimized CR tablet
C_{max} (µcg/ml)	3.36 ± 0.84
T_{max} (hr)	4 ± 0.0
AUC_{0-24} (µ.hr/ml)	40.46 ± 12.63
AUC_{tot} (µ.hr /ml)	44.60 ± 13.41
$AUMC_{0-24}$ (µ.hr^2/ml)	367.46 ± 76.57
$AUMC_{tot}$ (µ.hr^2/ml)	504.38 ± 127.46
$t_{1/2}$ (hr)	6.26 ± 0.65
MRT (hr)	11.30 ± 0.75
K_e (hr^{-1})	0.1107 ± 0.06

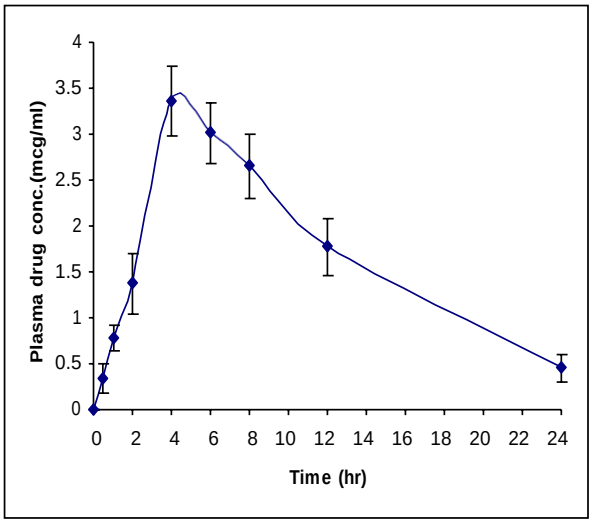

Figure 7: Mean plasma concentration time profile of optimized CR Zidovudine tablets

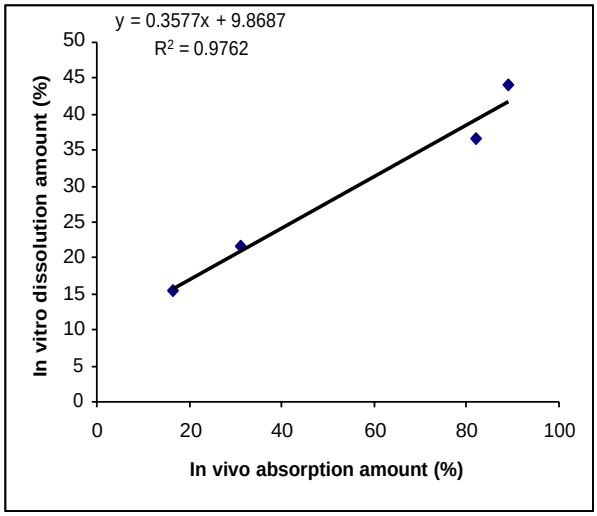

Figure 8: Relationships between the percent Zidovu---dine released and absorbed for optimized CR tablet

CONCLUSIONS

This research was centered towards formula develop---ment for controlled release of AZT utilizing simplex design. The results of the study clearly indicate that an appropriate amount of HPC, HPMC k100 and guar gum is very much essential as a rate controlling polymers. A numerical optimization tech was performed and identi--fied the exact composition of ternary blend. The re---producibility of obtaining optimal composition was validated. Further, its behavior was evaluated by using the rabbit as an animal model and from the results it is concluded that the controlled release AZT can achieved from the optimal CR tablet.

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