Formulation development and evaluation of Zidovudine sustained release tablets using 3^2 factorial design

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ABSTRACT

The main objective of present investigation is to formulate the sustained release tablet of Zidovudine using 3^2 factorial design. Zidovudine, antiretroviral drug belongs to BCS Class I. The SR tablets of Zidovudine were prepared employing different concentrations of Carboplol974P and Xanthan gum in different combinations as a rate retardants by Direct Compression technique using 3^2 factorial design. The quantity of rate retarders, Carboplol974P and Xanthan gum required to achieve the desired drug release was selected as independent variables, X_1 and X_2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) were selected as dependent variables. Totally nine formulations were designed and are evaluated for hardness, friability, thickness, % drug content, In-vitro drug release. From the Results it was concluded that all the formulation were found to be with in the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$. Validity of developed polynomial equations were verified by designing 2 check point formulations(C_1, C_2). According to SUPAC guidelines the formulation (F_5) containing combination of 5% Carboplol974P and 5% Xanthan gum, is the most similar formulation ($f_2=85.04$ & No significant difference, t= 0.20046) to marketed product (Retrovir). The selected formulation (F_5) follows Higuchi's kinetics, the mechanism of drug release was found to be Case-II transport or typical Zero order release (Non-Fickian, n= 0.915).

Keywords: Zidovudine, Factorial Design, Sustained Release Tablet, Carbopol974P, Xanthan Gum, Non Fickian Mechanism, Case-II Transport.
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INTRODUCTION

Oral administration is the most convenient, widely utilized for both conventional and novel drug delivery systems, and preferred route of drug delivery for systemic action. Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism as a result of which low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites [2].

Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs [1].

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Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, the goal in the designing sustained –or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery [3].

Sustained release dosage forms may be defined as any drug or dosage form modification that prolonged but not necessarily uniform release of drug. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from the dosage form. Zero-order release constitutes the drug release from the dosage form that is independent of the amount of drug in the delivery system (i. e., constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i. e., concentration dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery [4,5].

Sustained release tablet allowing a 2 fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form [6,7]. Sustained release products provide advantage over conventional dosage form by optimising biopharmaceutics, pharmacokinetics and pharmacokinetics properties of drug. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration [8,9].

Oral controlled drug delivery system represents one of the frontier areas of drug delivery system in order to fulfill the need for a long-term treatment with anti-HIV agents [10]. Among the different controlled drug delivery (CDD) systems, matrix based controlled release tablet formulations are the most popularly preferred for its convenience to formulate a cost effective manufacturing technology in commercial scale. Development of oral controlled release matrix tablets containing water-soluble drug has always been a challenging because of dose dumping due to improper formulation resulting in plasma fluctuation and accumulation of toxic concentration of drug [11]. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Over many years, numerous studies have been reported in the literature on the application of hydrophilic polymers in the development of controlled release matrix systems for various drugs [12,13,14].

Since the early 1950s, the application of polymeric materials for medical purposes is growing very fast. Polymers have been used in the medical field for a large extent [15]. Natural polymers remain attractive primarily because they are inexpensive, readily available, be capable of chemical modifications, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal stability and easy of compression [16]. This led to its application as excipient in hydrophilic drug delivery system. The various natural gums and mucilages have been examined as polymers for sustained drug release in the last few decades for example; guar gum, tragacanth gum, xanthan gum, pectin, alginates etc. In the development of a sustained release tablet dosage form. These dosage forms are available in extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. The future of sustained release products is promising in some area like chronopharmacokinetic system, targeted drug delivery system, mucoadhesive system, particulate system that provide high promise and acceptability.

Developing oral-sustained release formulations for highly water-soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets. Most of the researchers have worked on matrix tablets and multilayered matrix tablets. Among numerous approaches to oral SR formulation, matrix system of dosage form proves to be potential because of its simplicity, ease of manufacturing, low cost, high level of reproducibility, stability, ease of scale up, and process validation [17].

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms [18].

The selection of the drug candidates for sustained release system needs consideration of several biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug molecule [19].

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In the present study, a sustained release dosage form of Zidovudine has been developed that enables less frequent administering of drug.

Acquired immune deficiency syndrome (AIDS) is considered to be an epidemic, and according to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) AIDS Epidemic Update 2005, 38 million adults and 2.3 million children were living with the human immunodeficiency virus (HIV) at the end of 2005. The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient-compliant anti-retroviral medications are available at affordable prices (Joint United Nations Programme, 2006). As of 2009, AVERT (also known as the AIDS Education and Research Trust) estimated that there are 33.3 million people worldwide living with HIV/ AIDS, with 2.6 million new HIV infections per year and 1.8 million annual deaths due to AIDS.

The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost [20,21]

Zidovudine, the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. Zidovudine belongs to class III of the BCS Classification with High solubility and low permeability hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability.

After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 μg/mL at 0.8 hours. In the systemic circulation, it is first converted to zidovudine triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of zidovudine -triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Since zidovudine acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of zidovudine is desired for maintaining anti-AIDS effect and avoiding the strong side effects [22].

Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the in vivo environment.

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms.

Hence an attempt is made in this research work to formulate Sustained release (SR) Tablets of Zidovudine using Carbopol974P and Xanthan gum. Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The SR tablets formulation by direct compression method is most acceptable in large scale production.

A 3^2 full factorial design was employed to systematically study the drug release profile. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of Carbopol 974P and Xanthan Gum on the dependent variables, i.e. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (Time taken to release 10%,50%,75%,90% respectively)

MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Zidovudine was a gift sample from Aurobindo pharma Ltd, Hyderabad, India. Carbopol974P and Xanthan gum were procured from Loba Chemie Pvt. Ltd, Mumbai. Other excipients such as Aerosil and magnesium stearate were procured from S.D. Fine Chem. Ltd., Mumbai.

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Formulation Development of Zidovudine Sustained Release Tablets:
The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses [23] .

A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables Carbopol974P and Xanthan gum were used in formulation of Zidovudine sustained release (SR) Tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (Carbopol974P) at a concentration of 2.5%, 5%, 7.5%. three levels of factor X_2 (Xanthan Gum) at a concentration of 2.5%, 5%, 7.5%.(% with respect to total tablet weight) was taken as the rationale for the design of the Zidovudine SR tablet formulation. Totally nine Zidovudine sustained release tablet formulations were prepared employing selected combinations of the two factors i.e X_1, X_2 as per 3^2 Factorial and evaluated to find out the significance of combined effects of X_1, X_2 to select the best combination and the concentration required to achieve the desired prolonged/ sustained release of drug from the dosage form.

Preparation of Zidovudine Sustained Release Tablets:
All ingredients were collected and weighed accurately. Sift Zidovudine USP with Avicel PH 102 and polymers through sieve no. 60# and then rinse with remaining excipients. Sift colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#. Pre-blend all ingredients (except lubricant- magnesium stearate) in blender for 15 minutes. Add magnesium stearate and then again blend for 5-6 minutes. Lubricated powder was compressed by using rotary tablet punching machine (RIMEK), Ahmedabad). Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Experimental Design:
Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of Carbopol974P was taken as X_1 and concentration of Xanthan Gum was taken as X_2. Experimental design was given in the Table 1. Three levels were selected and coded as -1= 2.5%, 0=5%, +1=7.5%. Formulae for all the experimental batches were given in Table 2 [24,25].

TABLE 1: Experimental design layout

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1

TABLE 2: Formulae for the preparation of zidovudine sustained release tablets as per experimental design

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Zidovudine	300	300	300	300	300	300	300	300	300
Avicel PH 102	30	40	50	40	50	60	50	60	70
Carbopol974P	30	30	30	20	20	20	10	10	10
Xanthan Gum	30	20	10	30	20	10	30	20	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total Weight	400	400	400	400	400	400	400	400	400

EVALUATION OF ZIDOVUDINE SUSTAINED RELEASE TABLETS:
Hardness [25]
The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.

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Friability [25]

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

Friability(%)=[(Initial weight- Final weight) / (Initial weight)] x 100

Content Uniformity [25]

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

Assay

Weighed and finely powdered not less than 20 tablets were taken and transfer an accurately weighed portion of the powder equivalent to about 100 mg of Zidovudine was extracted with pH 6.8 buffer and the solution was filtered through 0.45 μ membranes. The absorbance was measured at 270 nm after suitable dilution using UV-visible spectrophotometer.

Thickness [25]

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

***In-vitro* Dissolution Study:**

The *In-vitro* dissolution study for the Zidovudine sustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for 2 hours followed by phosphate buffer pH 7.4 for next 10 hours at 75 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 267 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate.

Kinetic modeling of drug release:

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release [26,27,28].

RESULTS AND DISCUSSION

Sustained release tablets of Zidovudine were prepared and optimized by 3^2 factorial design in order to select the best combination of different rate retarding agents, CARBOPOL974P, XANTHAN GUM and also to achieve the desired prolong/sustained release of drug from the dosage form. The two factorial parameters involved in the development of formulations are, quantity of CARBOPOL974P & XANTHAN GUM polymers as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 300 mg of Zidovudine were prepared as a sustained release tablet dosage form by Direct Compression technique as per the formulae given in Table 2.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness as per official methods and results are given in Table 3. The hardness of tablets was in the range of 4.75-6.25 Kg/cm². Weight loss in the friability test was less than 0.52%. Drug content of prepared tablets was within acceptance range only. Results for all Post-compression parameters were tabulated or shown in Table 3. *In-vitro* Dissolution studies were performed for prepared tables using 0.1 N HCl as a dissolution media for first 2 hours followed by phosphate buffer pH 6.8 for next 10 hours at 75 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets are shown in Fig.1 and the dissolution parameters are given in Table 4. Cumulative % Drug release of Factorial Design Formulations F_1-F_9 at 12Hr were found to be in the range of 86.70-98.12 %. From the result it reveals that the release rate was higher for formulations containing Low level of Carbopol974P / Xanthan Gum compared with other Formulations containing Higher level, due to High concentration of polymer drug may have entrapped within a polymer matrix causing a decrease in rate of drug release. Therefore, required release of drug can be obtained by manipulating the composition of Carbopol974P and Xanthan Gum.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ due to formulation variables. Formulation F_5 containing 20 mg of CARBOPOL974P, 20 mg of XANTHAN GUM showed promising dissolution parameter ($t_{10\%=}$ 0.428 h,

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$t_{50\%} = 2.816$ h, $t_{75\%} = 5.633$ h, $t_{90\%} = 9.359$ h). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation[29].

TABLE 3: Post-compression parameters for the formulations

S.No.	Formulation Code	Hardness (kg/cm^2)	Diameter (mm)	Thickness (mm)	Friability (%)	Drug Content (%)
1	F$_1$	4.75	9.51	4.81	0.467	94.79±1.31
2	F$_2$	5.65	9.50	5.220	0.473	97.41±1.12
3	F$_3$	5.05	9.51	4.85	0.353	97.30±1.0
4	F$_4$	4.85	9.50	5.03	0.414	96.35±1.46
5	F$_5$	5.95	9.50	5.47	0.409	99.25±1.45
6	F$_6$	6.25	9.51	5.18	0.338	99.81±1.13
7	F$_7$	6.15	9.50	5.17	0.340	99.30±1.0
8	F$_8$	5.35	9.50	5.01	0.358	97.19±1.31
9	F$_9$	5.05	9.51	5.00	0.353	95.64±1.64
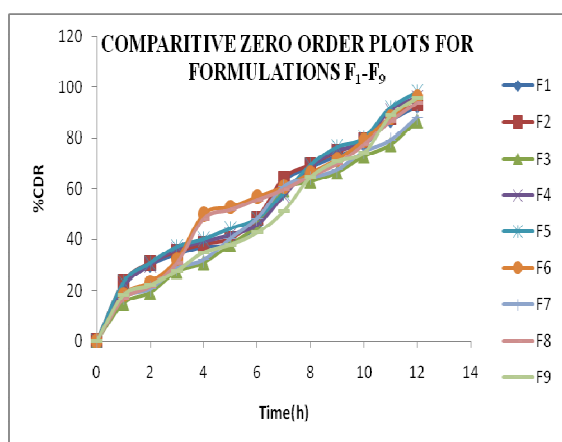
Fig.1 Comparative Zero Order Plots of F$_1$-F$_9$
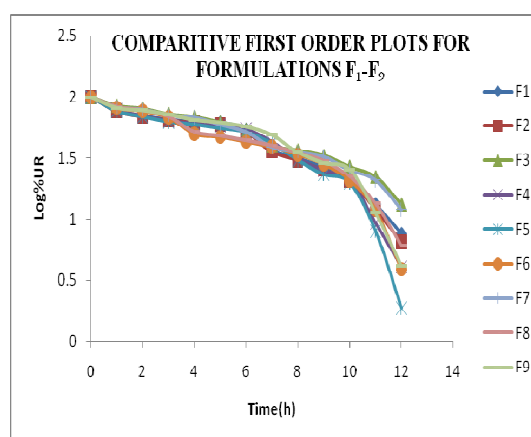
Fig.2 Comparative First Order Plots of F$_1$-F$_9$
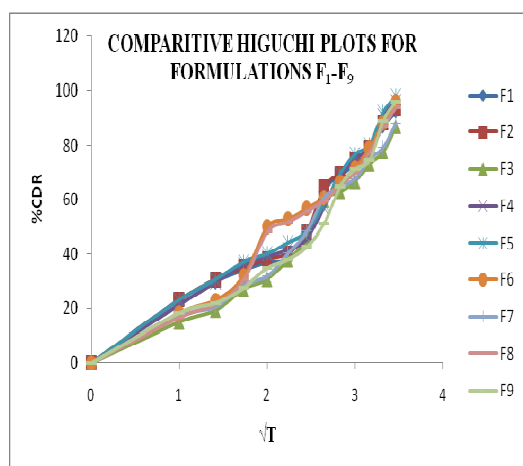

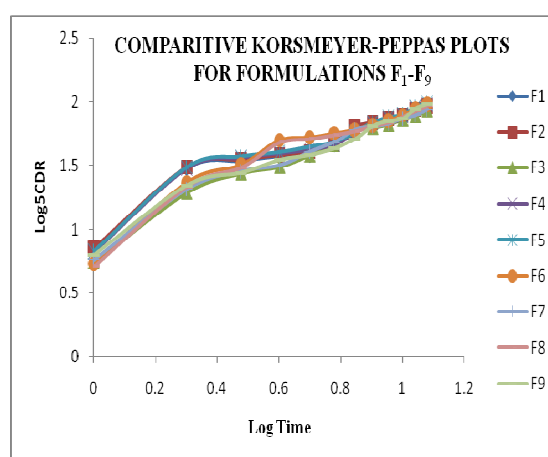**Fig.3 Comparative Higuchi Plots of F$_1$-F$_9$**

Fig.4 Comparative Korsmeyer-Peppas Plots

The *In -vitro* dissolution data of Zidovudine SR formulations was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients were summarized in Table 4 and plots shown in fig.1,2,3,4. It was observed from the above, that dissolution of all the tablets followed zero order kinetics with co-efficient of determination (R^2) values above 0.984. The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.953-0.983, which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.873- 1.019 that shows Non-Fickian

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diffusion mechanism (Case-II transport or typical Zero order release). Polynomial equations were derived for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis. The dissolution data (Kinetic Parameters) of factorial formulations F_1 to F_9 are shown in Table 5.

Polynomial equation for 3^2 full factorial designs is given in Equation

$$Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1{}^2+b_{22} X_2{}^2\ldots$$

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1. 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 term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms ($X_1{}^2$ and $X_2{}^2$) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration(C1, C2) using -0.75,+0.75.

The equations for K_1, $t_{10\%}$ and $t_{50\%}$ developed as follows,
$Y_1= 0.552-0.01967X_1+0.0515X_2-0.0265X_1X_2+0.119 X_1{}^2+0.0185X_2{}^2$ (for $t_{10\%}$)
$Y_2= 3.428-0.133X_1+0.351X_2-0.167X_1X_2+0.794 X_1{}^2+0.111X_2{}^2$ (for $t_{50\%}$)
$Y_3= 6.884-.210X_1+0.6607X_2-0.418X_1X_2+1.67 X_1{}^2+0.264X_2{}^2$ (for $t_{75\%}$)
$Y_4= 11.484-0.351X_1+1.0282X_2-0.69X_1X_2+2.627 X_1{}^2+0.508X_2{}^2$ (for $t_{90\%}$)
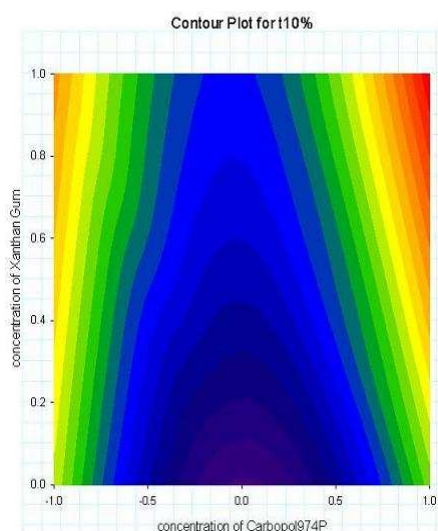

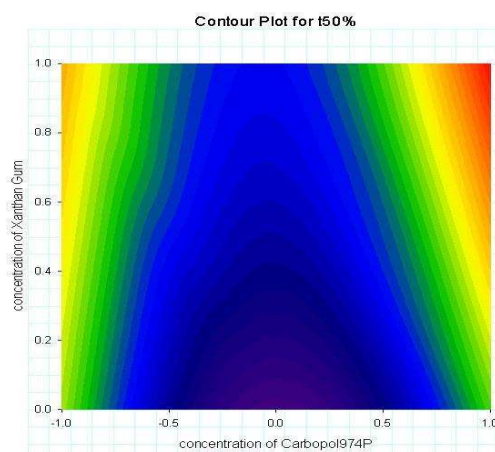**Fig.5 Contour Plot for $t_{10\%}$**
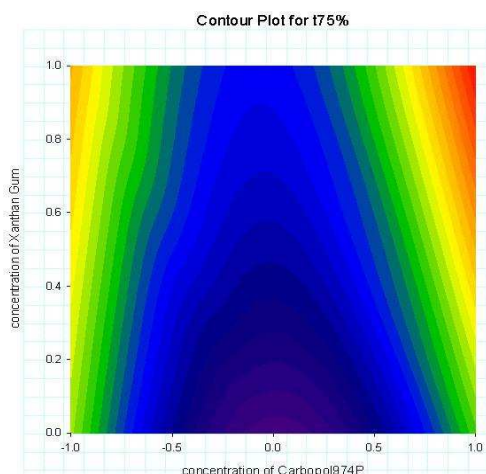

Fig.6 Contour Plot for $t_{50\%}$

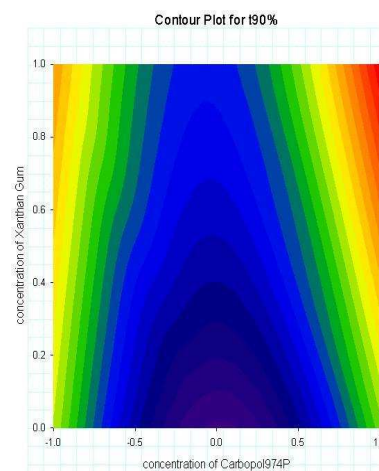**Fig.7 Contour Plot for $t_{75\%}$**

Fig.8 Contour Plot for $t_{90\%}$

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TABLE 4: Regression analysis data of 3^2 factorial design formulations of zidovudine

S.No	Formulation Code	Kinetic parameters											
		Zero order			First order			Higuchi			Korsmeyer-peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	9.22	7.02	0.99	2.08	0.08	0.95	8.64	26.65	0.97	1.01	0.90	0.96
2	F_2	10.34	7.06	0.99	2.08	0.08	0.95	7.85	26.90	0.97	1.02	0.90	0.96
3	F_3	5.07	6.88	0.99	2.06	0.07	0.97	12.08	25.98	0.97	0.87	1.02	0.98
4	F_4	9.12	7.19	0.99	2.12	0.09	0.91	8.99	27.23	0.97	1.01	0.92	0.96
5	F_5	10.14	7.27	0.99	2.16	0.11	0.88	8.34	27.59	0.97	1.02	0.92	0.96
6	F_6	10.28	7.20	0.98	2.10	0.09	0.91	9.00	27.76	0.98	0.94	1.01	0.96
7	F_7	6.29	6.91	0.99	2.06	0.07	0.97	11.16	26.19	0.97	0.90	1.00	0.98
8	F_8	9.36	7.13	0.99	2.08	0.08	0.94	9.63	27.44	0.98	0.92	1.02	0.96
9	F_9	4.21	7.36	0.99	2.14	0.09	0.89	13.16	27.34	0.95	0.91	0.98	0.98
10	MP	3.08	8.10	1.00	2.27	0.13	0.84	16.11	30.15	0.96	0.88	1.06	0.99

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.

TABLE 5: Dissolution parameters of zidovudine sustained release tablets 3^2 full factorial design batches

S. No	Formulation Code	Kinetic Parameters			
		$t_{10\% (h)}$	$t_{50\% (h)}$	$t_{75\% (h)}$	$t_{90\% (h)}$
1	F_1	0.572	3.764	7.529	12.509
2	F_2	0.545	3.584	7.167	11.908
3	F_3	0.510	3.330	6.998	11.609
4	F_4	0.490	3.227	6.454	10.723
5	F_5	0.428	2.816	5.633	9.359
6	F_6	0.411	2.653	5.225	9.115
7	F_7	0.678	4.457	8.915	14.812
8	F_8	0.557	3.662	7.324	12.169
9	F_9	0.510	3.356	6.711	11.151
10	MP	0.348	2.287	4.574	7.600

TABLE 6: Dissolution parameters for predicted and observed values for check point formulations

Formulation code	Predicted value				Actual observed value			
	$t_{10\% (h)}$	$t_{50\% (h)}$	$t_{75\% (h)}$	$t_{90\% (h)}$	$t_{10\% (h)}$	$t_{50\% (h)}$	$t_{75\% (h)}$	$t_{90\% (h)}$
C_1	0.534	3.510	7.018	11.66	0.54	3.49	7.01	11.53
C_2	0.559	3.674	7.348	12.21	0.54	3.75	7.25	12.11

The positive sign for co-efficient of X_2 in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of Xanthan gum increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ value increases. In other words the data demonstrate that both X_1 (amount of Carbopol974P) and X_2 (amount of Xanthan Gum) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$). From the results it can be concluded that, and increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The Dissolution parameters for predicted from the polynomial equatio0ns derived and those actual observed from experimental results are summarised in Table 6. The closeness of Predicted and Observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. The Contour Plots were presented to show the effects of X_1 and X_2 on $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$. The final best (Optimised) formulation (F_5) is compared with marketed product (Retrovir) shows similarity factor (f_2) 85.454, difference factor (f_1) 2.392 (There is no significant difference in drug release because t_{cal} is<0.05).

CONCLUSION

The present research work envisages the applicability of rate retarding agents such as Carbopol974P and Xanthan Gum in the design and development of sustained release tablet formulations of Zidovudine utilizing the 3^2 factorial design. From the results it was clearly understand that as the retardant concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be Non Fickian, Case-II transport or typical Zero order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation F_5 may be used once a day administration in the management of AIDS, other Viral Diseases.

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