Research Article

Formulation design and optimization of Sustained release matrix tablets of zidovudine by using experimental design

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ABSTRACT

Zidovudine (AZT), 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. However, the main limitation to therapeutic effectiveness of AZT is its, low therapeutic index, short biological half-life, and poor bioavailability. The biological half-life of AZT-triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. The aim of the present study is Formulation Design and Evaluation of oral matrix tablets of zidovudine by using Experimental Design. A rationale for developing zidovudine dosage form Sustained release allows delivery of a specific drug at a programmed rate that leads to drug delivery for a prolonged period of time. This improves bioavailability of the drug, reduces frequency of dosing, thus minimizing side effects and increase safety margin. In the present study, the oral matrix tablets of zidovudine were formulated by Experimental design by using combination of natural polymers (Xanthan gum/ Sodium alginate) as the retardant polymers each with three different levels. From FTIR results, confirm the absence of chemical interaction between the drug with the excipients used in tablet formulations. Also, there was no shift in the endotherm of in the drug- excipients mixtures indicating compatibility of drug with all the excipients. Matrix tablets were prepared by direct compression method and prepared tablets were evaluated for weight variation, percentage friability, hardness and drug content studies. All the formulations showed compliance with pharmacopeia standards. In vitro release studies revealed that, the formulation ZXA4 sustained release of drug for 12 hrs with 22% release of drug after 1hr and more than 96% at the end of 12 hrs.

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INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms [1]. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release. The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Modified-release drug products are designed for different routes of administration based on the physicochemical, pharmacologic, and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form [2]. The use of naturally occurring biocompatible polymeric material has been the focus of recent research activity in the design of dosage forms for oral controlled release administration. Natural gums and their derivatives are used widely in pharmaceutical dosage forms, their use as biodegradable polymeric material to deliver bioactive agents. These natural polysaccharide hydrophilic gels do hold advantages over the synthetic polymers, generally because they are non-toxic, less expensive, and freely available. Gums from natural sources hydrate and swell on contact with water and these have been used for the preparation of single unit dosage forms. The powdered drug is embedded uniformly in a matrix of the hydro gel and compressed to form a tablet, a production method that is relatively simple and cheap to perform [3].

Zidovudine (AZT), 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. However, the main limitation to therapeutic effectiveness of AZT is its dose-dependent 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 μ g/mL at 0.8 hours. In the systemic circulation, it is first converted to AZT triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of AZT-triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Since AZT acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of AZT is desired for maintaining anti-AIDS effect and avoiding the strong side effects. These side effects are usually associated with excessive plasma level of AZT immediately after intravenous or oral administration [4]. The aim of the present study is Formulation Design and optimization of oral matrix tablets of Zidovudine by using experimental Design. A rationale for developing zidovudine dosage form Sustained release allows delivery of a specific drug at a programmed rate that leads to drug delivery for a prolonged period of time. This improves bioavailability of the drug, reduces frequency of dosing, thus minimizing side effects and increase safety margin.

MATERIALS AND METHODS

MATERIALS

Zidovudine was obtained as a gift sample from Aurobindo Pharma Ltd, Hyderabad. Xanthan Gum and Sodium Alginate were obtained from Loba Chem (Mumbai, India). Micro Crystalline Cellulose and Mg. Stearate from Loba Chem (Mumbai, India). All other chemicals and ingredients were used for study are of commercial grade.

METHODS

Identification of drug

The drug was identified by Ultraviolet spectroscopy (UV), Infrared spectroscopy (IR) and Differential scanning calorimetry (DSC).

Ultraviolet Spectroscopy

The samples were subjected to UV Spectrophotometric analysis and were scanned for absorption maxima (λmax.) in the range of 200 to 400nm using UV-Visible Spectrophotometer in an appropriate medium and the same was compared with that of reference values in literature.

Infrared Spectroscopy

Infrared (IR) spectra of received gift sample of drugs was performed in the range of 4000cm^{-1} to 400 cm^{-1} by using FT-IR (DRS) technique (FT IR-Affinity-1 spectrophotometer (DRS-8000) SHIMADZU, Japan) and studied for the presence of characteristic peaks.

Drug-polymer compatibility study

It is well known that prior to the development of any dosage form with a new or old drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of the subsequent events and possible approaches in formulation development. Hydrophilic polymers, as well as other excipients, contain reactive functional groups that may give rise to chemical and physical transformations. Thus, when studying new pharmaceutical formulations, it is important to verify the possibility of occurrence of incompatibilities between the components of the formulation.

Fourier-Transform Infrared Spectroscopy (DRS)

Fourier-transform infrared (DRS) spectra were obtained by using an FT IR-Affinity-1 spectrophotometer (DRS-8000) SHIMADZU, Japan. The pure drug sample (Zidovudine) was previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:1 (Sample: KBr) ratio, respectively. The KBr powder was used as blank for background correction in FT-IR (DRS) studies. Forty-five scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Differential scanning calorimetry

The DSC measurements were performed on a DSC-4000 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 2 mg of sample or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10˚C min-1 from 50˚C to 350˚C. An empty aluminum pan was used as reference.

Experimental design [5]

Some possible experimental trials, generated by application of 3^2 factorial designs, were conducted to evaluate each independent factor at 3 levels. Formulation combinations (ZXA_1 – ZXA_9) using factorial design were done. The percentages Xanthan Gum (X_1) and Sodium Alginate (X_2) were chosen as control variables while, Y_1 (Cumulative % of drug released at 1 hr), Y_6 (Cumulative % of drug released at 6 hr), Y_{12} (Cumulative % of drug released at 12 hr)

were selected as response variables by using Design Expert Software.

Formulation development of matrix tablets of Zidovudine

Table 1. Batch Codes for drugs and polymers

Drugs and polymers	Batch Code
Zidovudine	**Z**
Xanthan Gum	**X**
Sodium Alginate	**A**
Xanthan Gum and Sodium Alginate combination	**XA**

Table 2. 3^2 full factorial design for the preparations of batches of Xanthan gum and Sodium alginate

Formulation No	Factors in Coded form	
	Xanthan gum	Sodium alginate
ZXA$_1$	0	0
ZXA$_2$	1	0
ZXA$_3$	0	-1
ZXA$_4$	-1	-1
ZXA$_5$	1	1
ZXA$_6$	0	1
ZXA$_7$	1	-1
ZXA$_8$	-1	0
ZXA$_9$	-1	1

Table 3. Factors used and coded level for 3^2 full factorial designs

Factors used	Coded Level		
	-1	0	+1
Xanthan gum (mg)	25	50	75
Sodium alginate (mg)	15	30	45

Brief manufacturing procedure for Preparation of Ciprofloxacin floating matrix tablet

Matrix embedded controlled release tablets of Zidovudine were prepared by direct compression technique using various concentrations of Xanthan Gum, Sodium Alginate. All the ingredients were sieved through the 40-mesh screen and mixed. All ingredients except magnesium stearate and aerosil were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, Magnesium stearate were added and mixed for additional 2-3 minutes. Microcrystalline cellulose was used as directly compressible vehicle. Magnesium stearate was used as lubricant and Aerosil was used as glidant. Finally, after proper mixing, the powder mixture was compressed on a 10-station tablet compression machine (rotary tableting machine, Rimek, Minipress–I, India) using 12-mm punches.

Table 4. Composition of various matrix tablets of zidovudine, xanthan gum and sodium alginate

Sl. No.	Ingredients (mg)	ZXA_1	ZXA_2	ZXA_3	ZXA_4	ZXA_5	ZXA_6	ZXA_7	ZXA_8	ZXA_9
1	**Zidovudine**	300	300	300	300	300	300	300	300	300
2	**Xanthan gum**	50	75	50	25	75	50	75	25	25
3	**Sodium alginate**	30	30	15	15	45	45	15	30	45
5	**Mcc**	110	85	125	150	70	95	100	135	120
6	**Aerosil**	5	5	5	5	5	5	5	5	5
7	**Magnesium stearate**	5	5	5	5	5	5	5	5	5
Total Tablet Weight (mg)		500	500	500	500	500	500	500	500	500

Evaluation of pre compression parameters [6,7,8]

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. The loose bulk density is accurately weighted amount of sample (5 gm) was transferred into a 25 ml measuring cylinder carefully to read the unsettled apparent volume to the nearest graduated unit. The tapped bulk density is accurately weighted amount of sample (5 gm) was transferred into a 25 ml measuring cylinder. The measuring cylinder was then tapped 100 times on a plane hard wooden surface and measure the tapped volume to the nearest graduated unit. Calculate the loose bulk density and tapped bulk density in

gm / ml by the following formula:

Loose bulk density (LBD) = Weight of granules / Apparent Volume

Tapped bulk density (TBD) = Weight of granules / Tapped volume

Compressibility Index

Percent compressibility of granules as determined by Carr's compressibility index is tapped bulk density minus loose bulk density divided by tapped bulk density.

Hausner's Ratio

Hausner ratio is tapped bulk density divided by loose bulk density.

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The value of angle of repose are calculated by using the following formula,

$\tan \theta = h/r$

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose,

h = Height of the heap and

r = Radius of the heap

Post Compression Parameters [9, 10]

Tablet Dimension

Thickness and diameter were measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly selected and hardness of the tablets was determined.

Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated 25rpm for 4minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Uniformity in Weight

Twenty tablets were selected randomly from each batch and weighed. Weight of each tablet was recorded with the help of digital balance. The readings were recorded and tabulated.

***In vitro* Drug Release Studies**

Three tablets of each formulation were used in the release experiment. In-vitro drug release of tablets was studied using USP type I apparatus at 37±0.5°C in 900ml 0.1N HCl solution (pH; 1.2) for first 2 hrs followed by pH 6.8 phosphate buffers for next 10hrs with a speed of 100 rpm. At appropriate time intervals 5ml of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed by using UV- visible Spectrophotometer. The dissolution data

obtained were plotted as percent cumulative drug release versus time.

RESULTS AND DISCUSSION

Identification of drugs

The received gift samples of Zidovudine were characterized by Ultraviolet (UV) spectroscopy, Infrared (IR) Spectroscopy and Differential Scanning Calorimetry (DSC).

Ultraviolet (UV) spectroscopy

In UV scanning from standard solutions of Zidovudine, the wavelength of maximum absorption (λ_{max}) was determined at different pH. It was found to be 265 nm in 0.1N HCl and 266 nm in 6.8 phosphate buffer which are similar to the values given in literature.

Infrared (IR) spectra

The IR spectra of the drugs were recorded by using FT-IR (DRS) technique. The spectrum showed peaks corresponding to the functional groups present in the drug structure.

Drug-polymer compatibility study

Interaction between the drug and added excipients plays a vital role in establishing stability of the formulation. Hence, the drug-excipient compatibility study is highly desirable before developing any formulation. Interaction between drug and excipient can occur by means of several mechanisms like adsorption, complexation, chemical interaction, pH effect, eutectic formation resulting in drug products with desired or undesired properties.

Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared (DRS) spectra were obtained by using an FT IR-Affinity-1 spectrophotometer (DRS-8000) SHIMADZU, Japan. The drug sample (Zidovudine) was previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:1 (Sample: KBr) ratio, respectively. The KBr powder was used as blank for background correction in FT-IR studies. Forty-five scans were obtained at a resolution of 4 cm^{-1} from 4000 to 400 cm^{-1}.

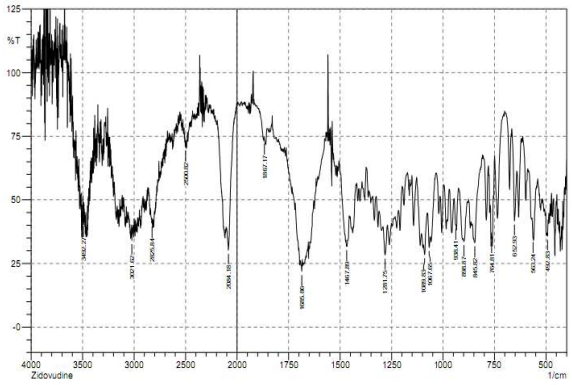


Figure 1: FTIR Spectra of Zidovudine

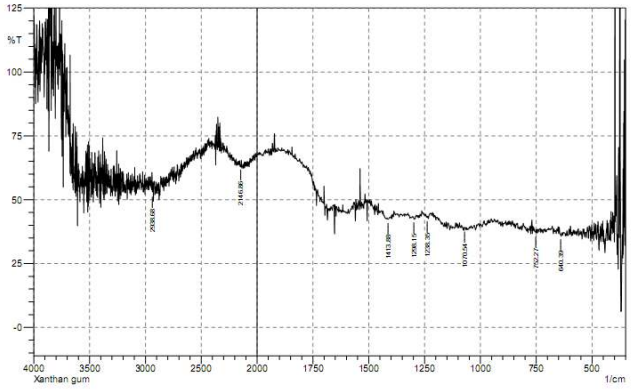


Figure 2: FTIR Spectra of Xanthan gum

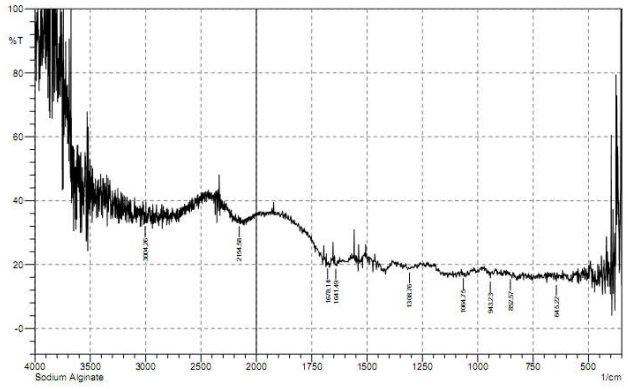


Figure 3: FTIR Spectra of Sodium alginate

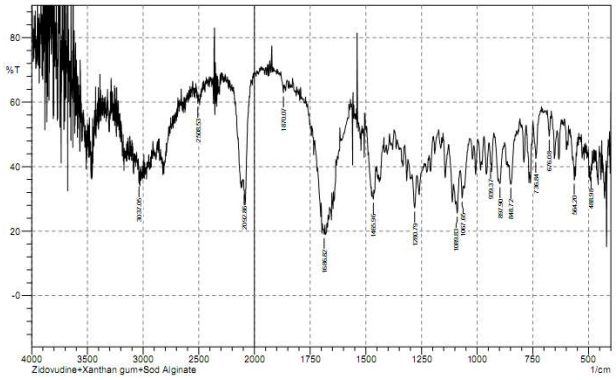


Figure 4: FTIR Spectra of Zidovudine with Xanthan gum and Sodium alginate

Differential Scanning Calorimetry

The interactions between drugs and a distinct mixture [1:1] were then investigated by DSC. Interactions in the sample are derived or deduced from DSC by changes in the thermal events, such as elimination of an endothermic or exothermic peak, or appearance of a new peak. However, some broadening of peaks leading to changes in the area, onset of peak, and changes in peak temperature occur simply due to mixing of the components without indicating any significant interaction.

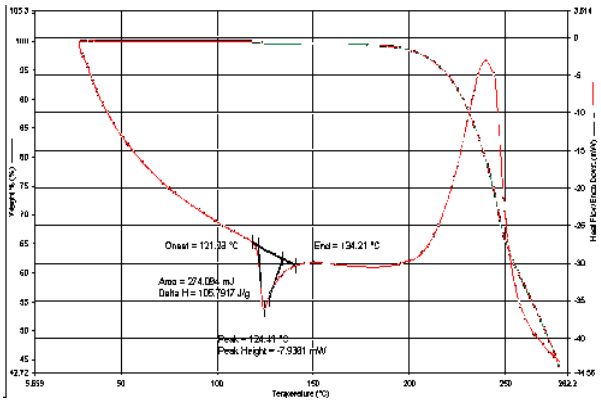


Figure 5: DSC thermogram of Zidovudine

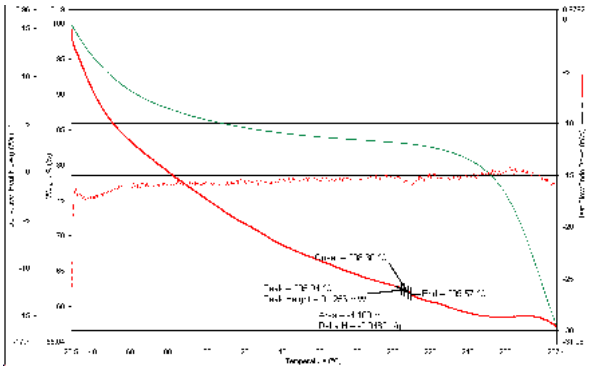


Figure 6: DSC thermogram of Xanthan Gum

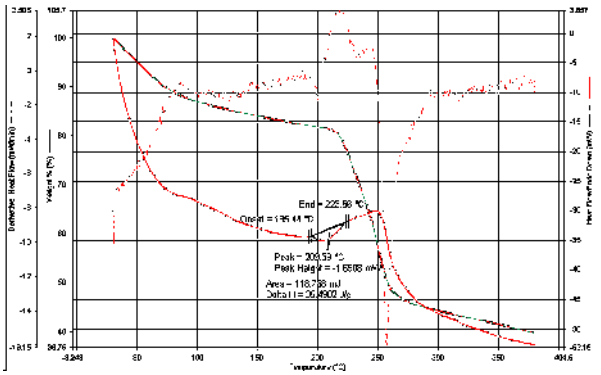


Figure 7: DSC thermogram of Sodium Alginate

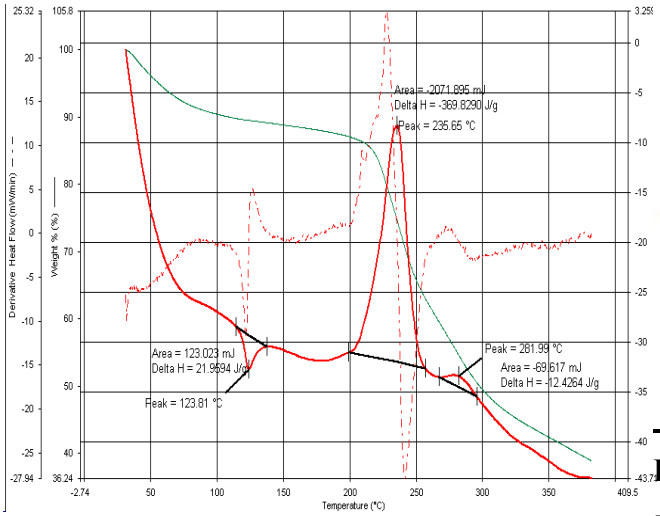


Figure 8: DSC thermogram of Zidovudine with Xanthan Gum and Sodium Alginate

Analytical method development

UV-Vis Spectrophotometric Method Development for Zidovudine

Serial dilution of Zidovudine was prepared in 0.1 N HCl and 6.8 Phosphate buffer on concentration ranging from 5µg/mL to 30µg/mL and scanned for absorption maxima ($\lambda_{max.}$) in the range of 200 to 400nm.

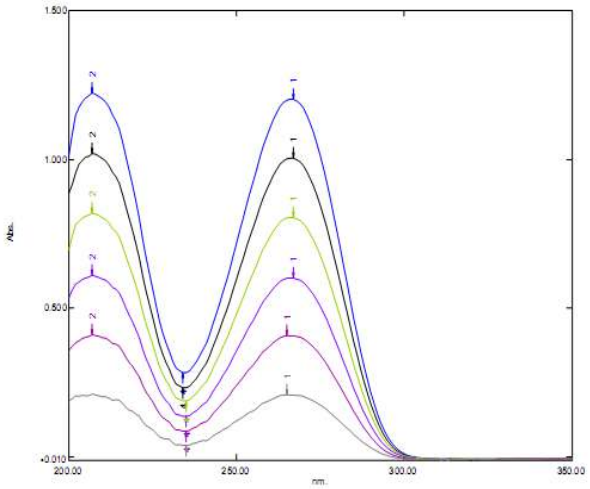


Figure 9: Overlay Spectra of Zidovudine in 0.1N HCl

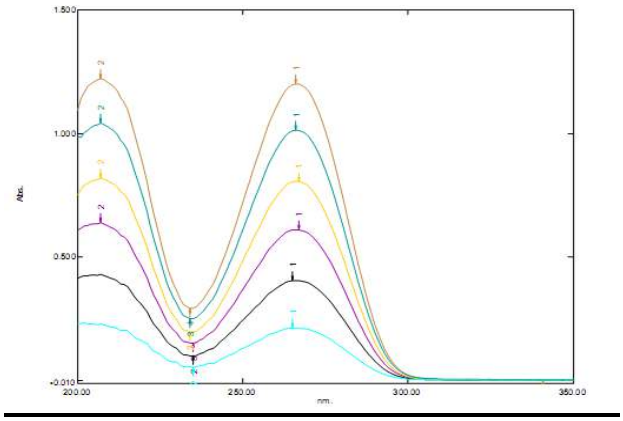


Figure 10: Overlay Spectra of Zidovudine in Phosphate buffer pH 6.8

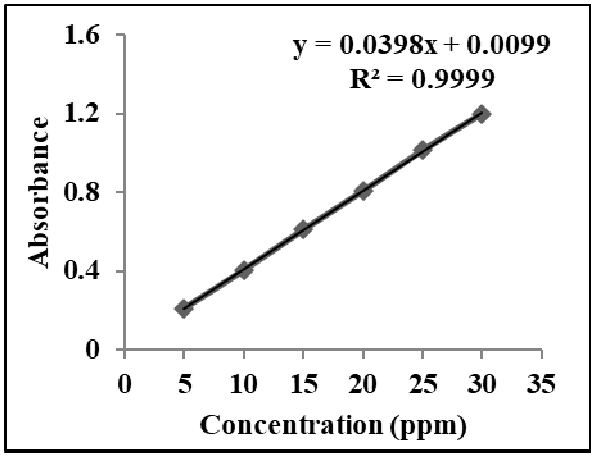


Figure 11: Calibration Curve of Zidovudine in 0.1N HCl

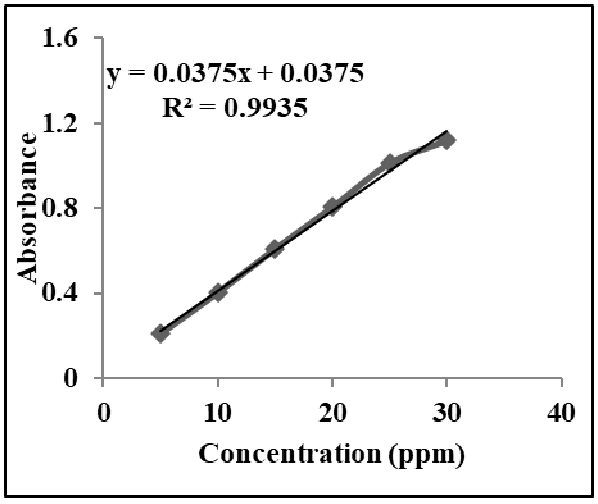


Figure 12: Calibration Curve of Zidovudine in Phosphate buffer pH 6.8

Experimental design

Some possible experimental trials, generated by application of 3^2 factorial designs, were conducted to evaluate each independent factor at 3 levels. Formulation combinations (ZXA_1 – ZXA_9) using factorial design. The percentages of Xanthan gum (X1) and Sodium alginate (X2) were chosen as control variables while Y1 (Cumulative % of drug released at 1 hr), Y_6 (Cumulative % of drug released at 6 hr), Y_{12} (Cumulative % of drug released at 12 hr) were selected as response variables by using Design Expert Software.

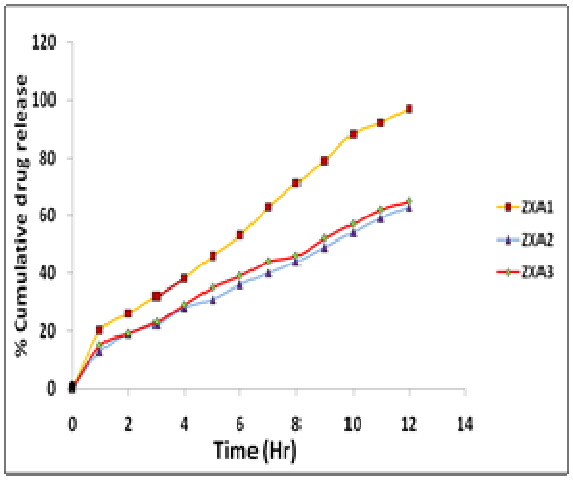


Figure 13: Dissolution curve of Zidovudine Matrix Tablet formulations containing Xanthan gum and Sodium alginate (ZXA_1 - ZXA_3)

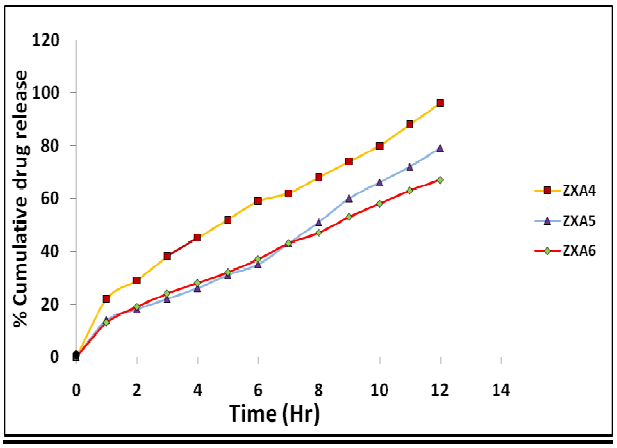


Figure 14: Dissolution curve of Zidovudine Matrix Tablet formulations containing Xanthan gum and Sodium alginate (ZXA_4 - ZXA_6)

Formulation development and evaluation of Zidovudine matrix tablets

Table 5: Physical Parameters of Zidovudine Tablet formulations ZXA1 to ZXA9

Blend Parameters	Batches								
	ZXA_1	**ZXA_2**	**ZXA_3**	**ZXA_4**	**ZXA_5**	**ZXA_6**	**ZXA_7**	**ZXA_8**	**ZXA_9**
Bulk Density (gm/ml)	0.616	0.534	0.513	0.452	0.481	0.482	0.572	0.513	0.581
Tapped Density (gm/ml)	1.153	0.616	0.581	0.604	0.621	0.594	1.14	0.581	1.133
Carr's Compressibility	0.534	13.31	11.8	25.65	22.54	18.9	0.502	11.8	0.513
Hausner's Ratio	0.581	1.153	1.133	1.336	1.291	1.23	0.616	1.133	0.604
Tablet Parameters									
Weight Variation (mg)	513 ± 5.3	503 ±5.27	500 ±5.22	509 ± 5.23	503 ± 5.27	498 ± 5.22	501 ± 5.23	506 ± 5.32	504 ± 5.26
Hardness (kg/cm^2)	5.7±0.32	6.1±0.71	5.7±0.52	5.5±0.54	6.3±0.54	5.8±0.53	5.7±0.23	5.7±0.52	5.7±0.26
Friability (%)	0.73	0.68	0.6	0.74	0.52	0.61	0.90	0.66	0.52
Drug Content	96.43	99.56	98.2	99.48	99.53	98.72	98.2	98.2	99.53

*± indicates S.D (n =3)

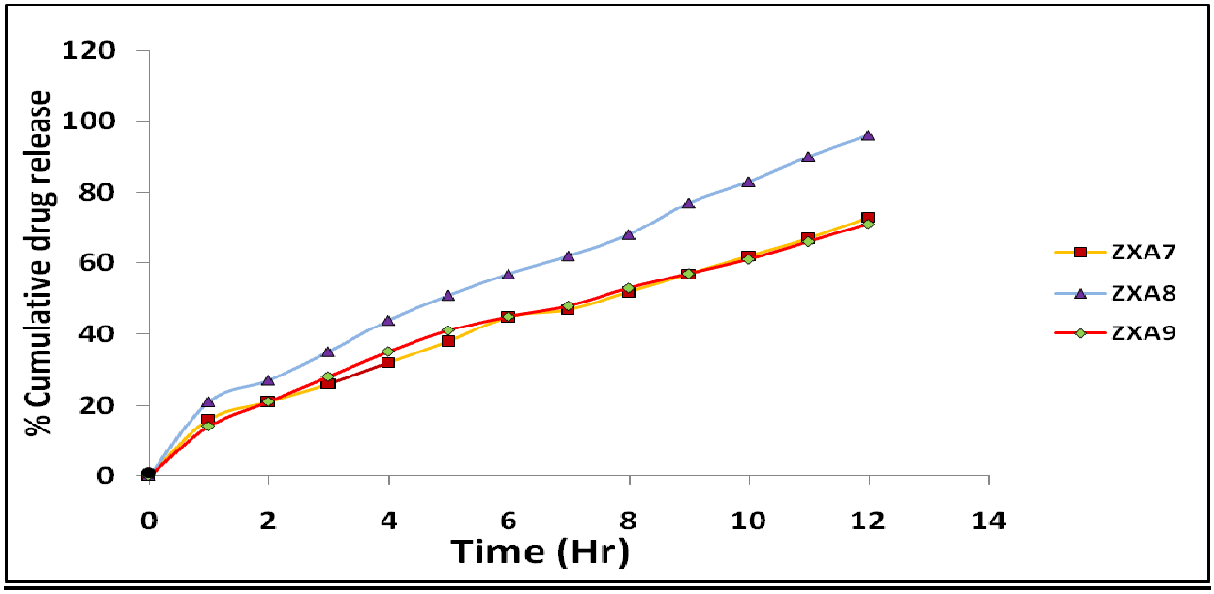


Figure 15: Dissolution curve of Zidovudine Matrix Tablet formulations containing Xanthan gum and Sodium alginate (ZXA_7 - ZXA_9)

Table 6: Factorial design of various polymer concentrations of Xanthan gum and Sodium alginate

Std	Run	Block	Factor 1 A:Xanthan gum mg	Factor 2 B:Sodium Algin mg	Response 1 Y1 % Release	Response 2 Y6 % Release	Response 3 Y12 % Release
9	1	Block 1	50.00	30.00	20	53	97
6	2	Block 1	75.00	30.00	13	36	63
7	3	Block 1	50.00	15.00	15	39	65
1	4	Block 1	25.00	15.00	22	59	96
4	5	Block 1	75.00	45.00	14	35	79
8	6	Block 1	50.00	45.00	13	37	67
2	7	Block 1	75.00	15.00	16	45	73
5	8	Block 1	25.00	30.00	21	57	96
3	9	Block 1	25.00	45.00	14	45	71

Table 7: Anova for Response surface quadratic model of Xanthan gum and Sodium alginate for Response Y_1

Response: Y1

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	77.44	5	15.49	1.88	0.3207
A	*32.67*	*1*	*32.67*	*3.96*	*0.1409*
B	*24.00*	*1*	*24.00*	*2.91*	*0.1868*
A^2	*0.89*	*1*	*0.89*	*0.11*	*0.7644*
B^2	*10.89*	*1*	*10.89*	*1.32*	*0.3341*
AB	*9.00*	*1*	*9.00*	*1.09*	*0.3733*
Residual	24.78	3	8.26		
Cor Total	102.22	8			

Std. Dev.	2.87	R-Squared	0.7576
Mean	16.44	Adj R-Squared	0.3536
C.V.	17.48	Pred R-Square	-1.3300
PRESS	238.18	Adeq Precisior	3.693

Factor	Coefficient Estimate	DF	Standard Error	95% CI Low	95% CI High	VIF
Intercept	17.56	1	2.14	10.74	24.37	
A-Xanthan gum	-2.33	1	1.17	-6.07	1.40	1.00
B-Sodium Alginate	-2.00	1	1.17	-5.73	1.73	1.00
A^2	0.67	1	2.03	-5.80	7.13	1.00
B^2	-2.33	1	2.03	-8.80	4.13	1.00
AB	1.50	1	1.44	-3.07	6.07	1.00

Final Equation in Terms of Coded Factors:

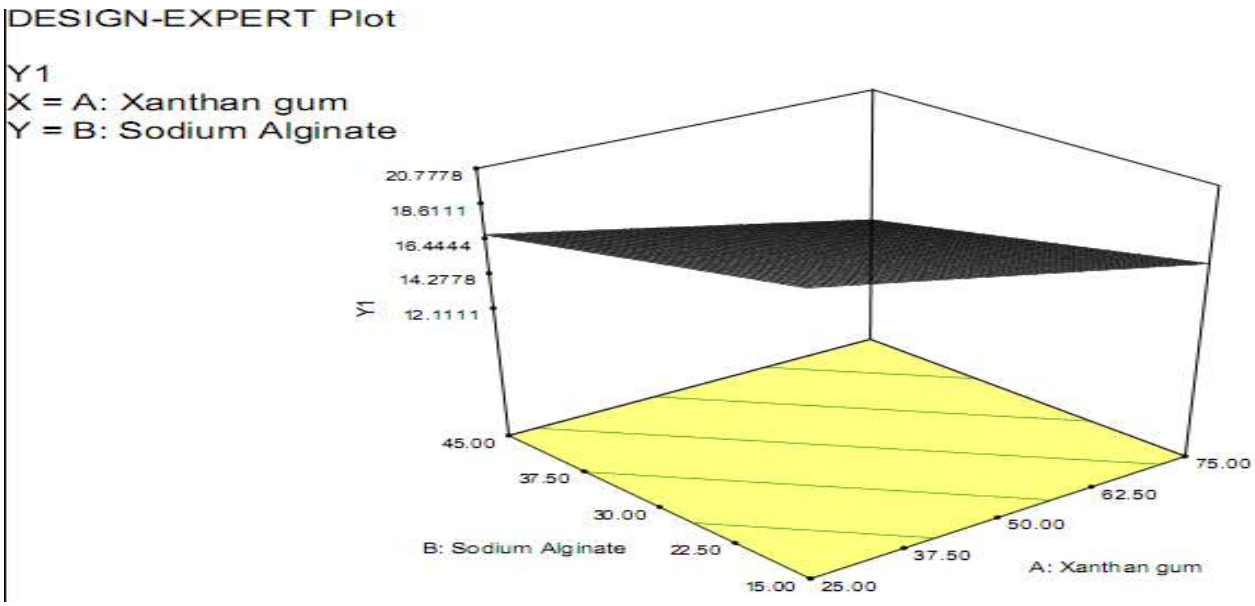
$$
\begin{aligned}
Y1 &= \\
&+17.56 \\
&-2.33 * A \\
&-2.00 * B \\
&+0.67 * A^2 \\
&-2.33 * B^2 \\
&+1.50 * A * B
\end{aligned}
$$

Final Equation in Terms of Actual Factors:

$$
\begin{aligned}
Y1 &= \\
&+25.55556 \\
&-0.32000 * \text{Xanthan gum} \\
&+0.28889 * \text{Sodium Alginate} \\
&+1.06667E\text{-}003 * \text{Xanthan gum}^2 \\
&-0.010370 * \text{Sodium Alginate}^2 \\
&+4.00000E\text{-}003 * \text{Xanthan gum} * \text{Sodium Alginate}
\end{aligned}
$$

Diagnostics Case Statistics

Standard Order	Actual Value	Predicted Value	Residual	Leverage	Student Residual	Cook's Distance	Outlier t	Run Order
1	22.00	21.72	0.28	0.806	0.219	0.033	0.180	4
2	16.00	14.06	1.94	0.806	1.534	1.626	2.700	7
3	14.00	14.72	-0.72	0.806	-0.570	0.224	-0.493	9
4	14.00	13.06	0.94	0.806	0.745	0.383	0.674	5
5	21.00	20.56	0.44	0.556	0.232	0.011	0.191	8
6	13.00	15.89	-2.89	0.556	-1.508	0.474	-2.502	2
7	15.00	17.22	-2.22	0.556	-1.160	0.280	-1.275	3
8	13.00	13.22	-0.22	0.556	-0.116	0.003	-0.095	6
9	20.00	17.56	2.44	0.556	1.276	0.339	1.540	1



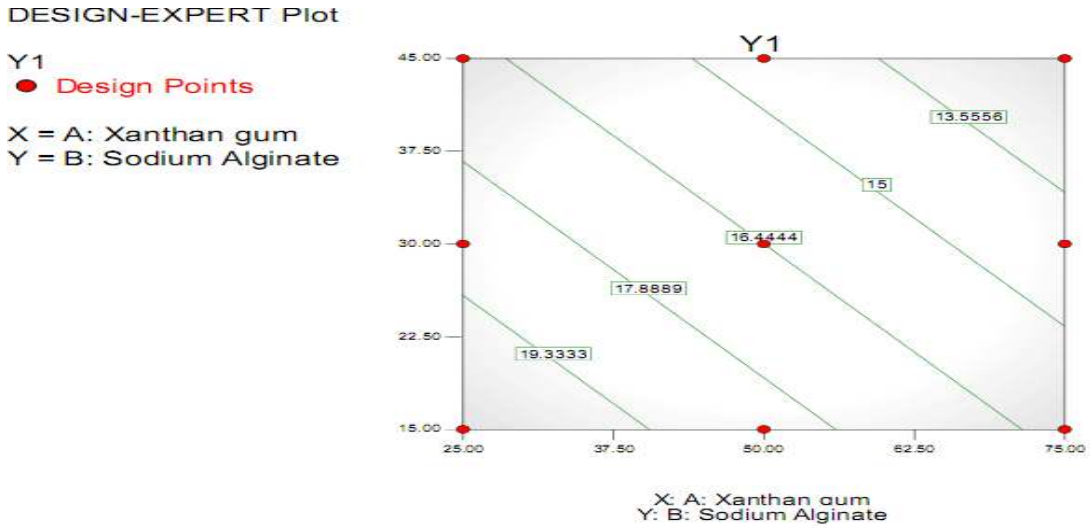


Figure 16: Surface design of response Y1 by varying quantities of Xanthan gum and Sodium alginate. (b) Related contour plot indicating various levels of the two polymers

Table 8: Anova for Response surface quadratic model of Xanthan gum and Sodium alginate for Response Y_6

Response: Y6

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	531.11	5	106.22	2.07	0.2913
A	*337.50*	*1*	*337.50*	*6.58*	*0.0828*
B	*112.67*	*1*	*112.67*	*2.20*	*0.2348*
A^2	*20.06*	*1*	*20.06*	*0.39*	*0.5760*
B^2	*56.89*	*1*	*56.89*	*1.11*	*0.3695*
AB	*4.00*	*1*	*4.00*	*0.078*	*0.7981*
Residual	153.78	3	51.26		
Cor Total	684.89	8			

Std. Dev.	7.16	R-Squared	0.7755
Mean	45.11	Adj R-Squared	0.4013
C.V.	15.87	Pred R-Square	-1.0889
PRESS	1430.66	Adeq Precisior	4.049

Factor	Coefficient Estimate	DF	Standard Error	95% CI Low	95% CI High	VIF
Intercept	46.56	1	5.34	29.57	63.54	
A-Xanthan gum	-7.50	1	2.92	-16.80	1.80	1.00
B-Sodium Alginate	-4.33	1	2.92	-13.64	4.97	1.00
A^2	3.17	1	5.06	-12.94	19.28	1.00
B^2	-5.33	1	5.06	-21.44	10.78	1.00
AB	1.00	1	3.58	-10.39	12.39	1.00

Final Equation in Terms of Coded Factors:

$$
\begin{aligned}
Y6 &= \\
&+46.56 \\
&-7.50 * A \\
&-4.33 * B \\
&+3.17 * A^2 \\
&-5.33 * B^2 \\
&+1.00 * A * B
\end{aligned}
$$

Final Equation in Terms of Actual Factors:

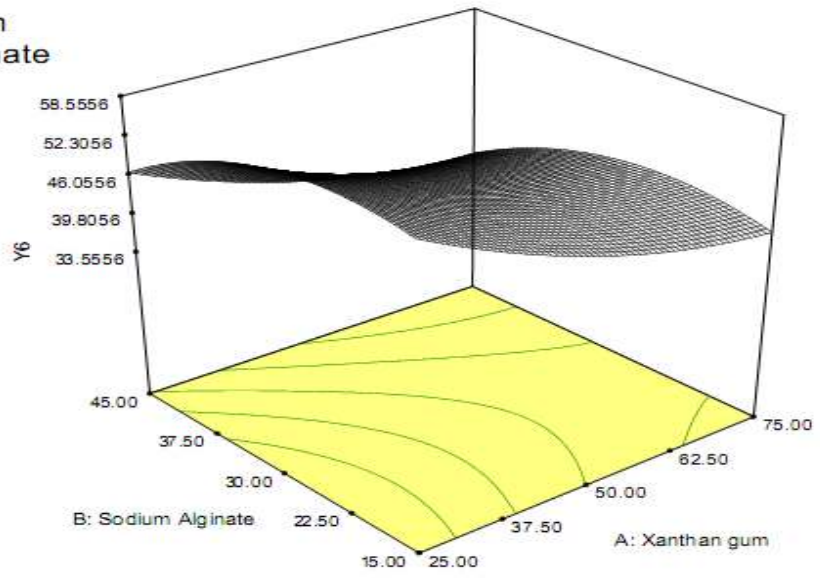
$$
\begin{aligned}
Y6 &= \\
&-65.55556 \\
&-0.88667 * \text{Xanthan gum} \\
&+1.00000 * \text{Sodium Alginate} \\
&+5.06667E\text{-}003 * \text{Xanthan gum}^2 \\
&-0.023704 * \text{Sodium Alginate}^2 \\
&+2.66667E\text{-}003 * \text{Xanthan gum} * \text{Sodium Alginate}
\end{aligned}
$$

Diagnostics Case Statistics

Standard Order	Actual Value	Predicted Value	Residual	Leverage	Student Residual	Cook's Distance	Outlier t	Run Order
1	59.00	57.22	1.78	0.806	0.563	0.219	0.486	4
2	45.00	40.22	4.78	0.806	1.513	1.581	2.540	7
3	45.00	46.56	-1.56	0.806	-0.493	0.168	-0.420	9
4	35.00	39.56	1.44	0.806	0.458	0.145	0.387	5
5	57.00	57.22	-0.22	0.556	-0.047	0.000	-0.038	8
6	36.00	42.22	-6.22	0.556	-1.304	0.354	-1.617	2
7	39.00	45.56	-6.56	0.556	-1.373	0.393	-1.841	3
8	37.00	36.89	0.11	0.556	0.023	0.000	0.019	6
9	53.00	46.56	6.44	0.556	1.350	0.380	1.760	1

DESIGN-EXPERT Plot

Y6
X = A: Xanthan gum
Y = B: Sodium Alginate



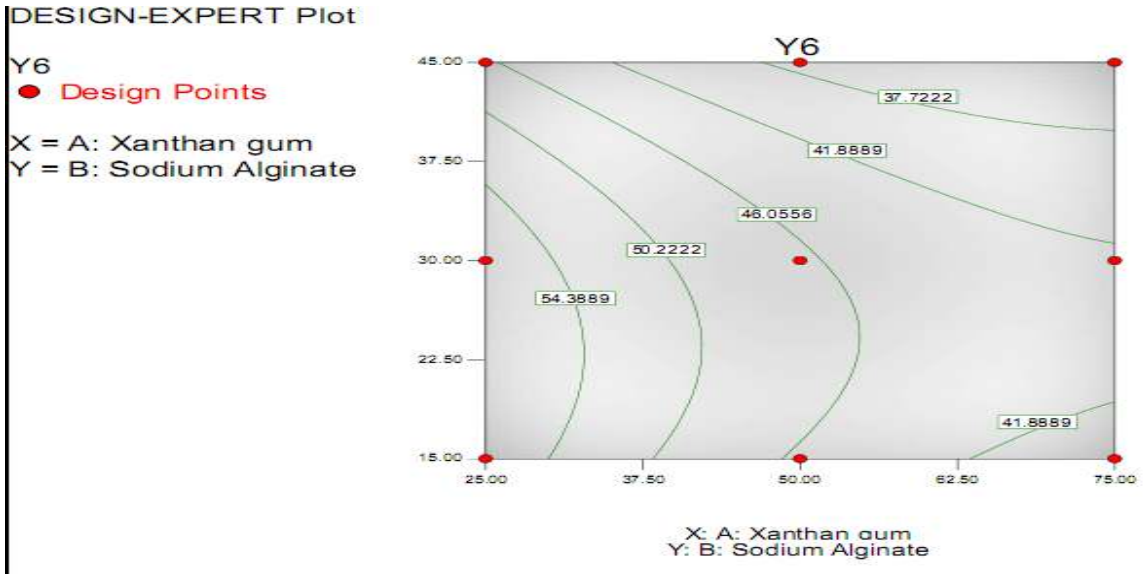


Figure 17: Surface design of response Y6 by varying quantities of Xanthan gum and Sodium alginate. (b) Related contour plot indicating various levels of the two polymers

Table 9: Anova for Response surface quadratic model of Xanthan gum and Sodium alginate for Response Y_{12}

Response: Y12

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	901.36	5	180.27	0.78	0.6248
A	*384.00*	*1*	*384.00*	*1.66*	*0.2882*
B	*48.17*	*1*	*48.17*	*0.21*	*0.6794*
A^2	*22.22*	*1*	*22.22*	*0.096*	*0.7770*
B^2	*206.72*	*1*	*206.72*	*0.89*	*0.4145*
AB	*240.25*	*1*	*240.25*	*1.04*	*0.3834*
Residual	694.86	3	231.62		
Cor Total	1596.22	8			

Std. Dev.	15.22	R-Squared	0.5647
Mean	78.56	Adj R-Squared	-0.1608
C.V.	19.37	Pred R-Square	-3.0148
PRESS	6408.54	Adeq Precisior	2.535

Factor	Coefficient Estimate	DF	Standard Error	95% CI Low	95% CI High	VIF
Intercept	83.11	1	11.34	47.01	119.21	
A-Xanthan gum	-8.00	1	6.21	-27.77	11.77	1.00
B-Sodium Alginate	-2.83	1	6.21	-22.61	16.94	1.00
A^2	3.33	1	10.76	-30.91	37.58	1.00
B^2	-10.17	1	10.76	-44.41	24.08	1.00
AB	7.75	1	7.61	-16.47	31.97	1.00

Final Equation in Terms of Coded Factors:

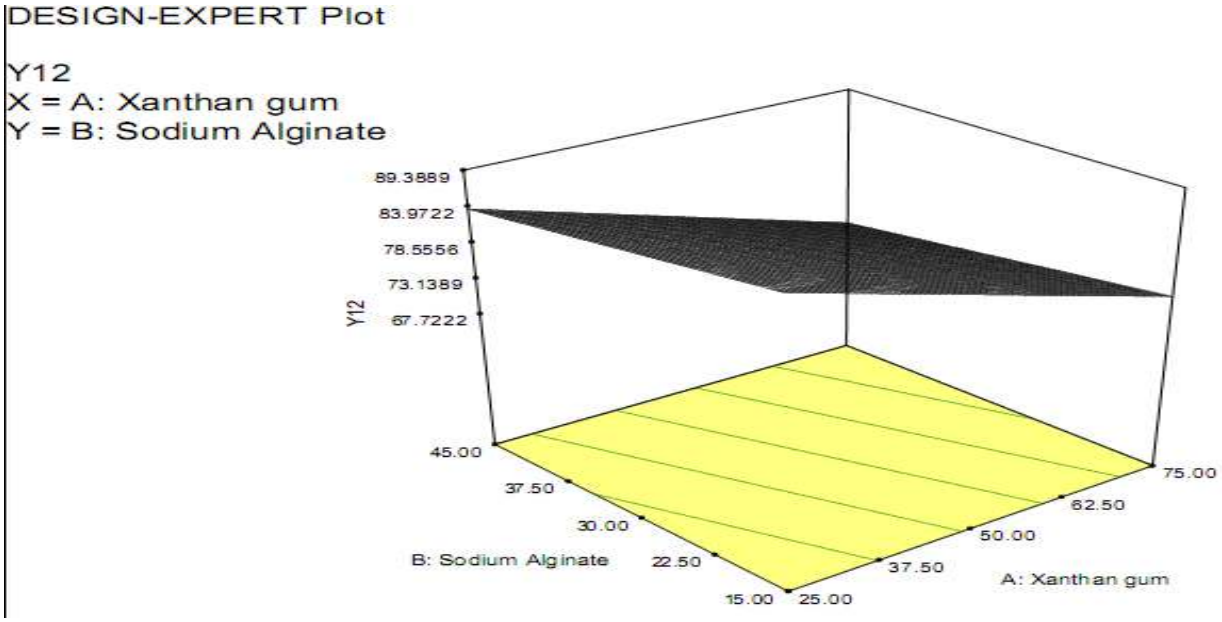
$$Y12 = +83.11 - 8.00 * A - 2.83 * B + 3.33 * A^2 - 10.17 * B^2 + 7.75 * A * B$$

Final Equation in Terms of Actual Factors:

$$Y12 = +108.44444 - 1.47333 * \text{Xanthan gum} + 1.48889 * \text{Sodium Alginate} + 5.33333E\text{-}003 * \text{Xanthan gum}^2 - 0.045185 * \text{Sodium Alginate}^2 + 0.020667 * \text{Xanthan gum} * \text{Sodium Alginate}$$

Diagnostics Case Statistics

Standard Order	Actual Value	Predicted Value	Residual	Leverage	Student Residual	Cook's Distance	Outlier t	Run Order
1	96.00	94.86	1.14	0.806	0.170	0.020	0.139	4
2	73.00	63.36	9.64	0.806	1.436	1.424	2.098	7
3	71.00	73.69	-2.69	0.806	-0.401	0.111	-0.337	9
4	79.00	73.19	5.81	0.806	0.865	0.517	0.815	5
5	96.00	94.44	1.56	0.556	0.153	0.005	0.126	8
6	63.00	78.44	-15.44	0.556	-1.522	0.483	-2.605	2
7	65.00	75.78	-10.78	0.556	-1.062	0.235	-1.098	3
8	67.00	70.11	-3.11	0.556	-0.307	0.020	-0.254	6
9	97.00	83.11	13.89	0.556	1.369	0.390	1.824	1



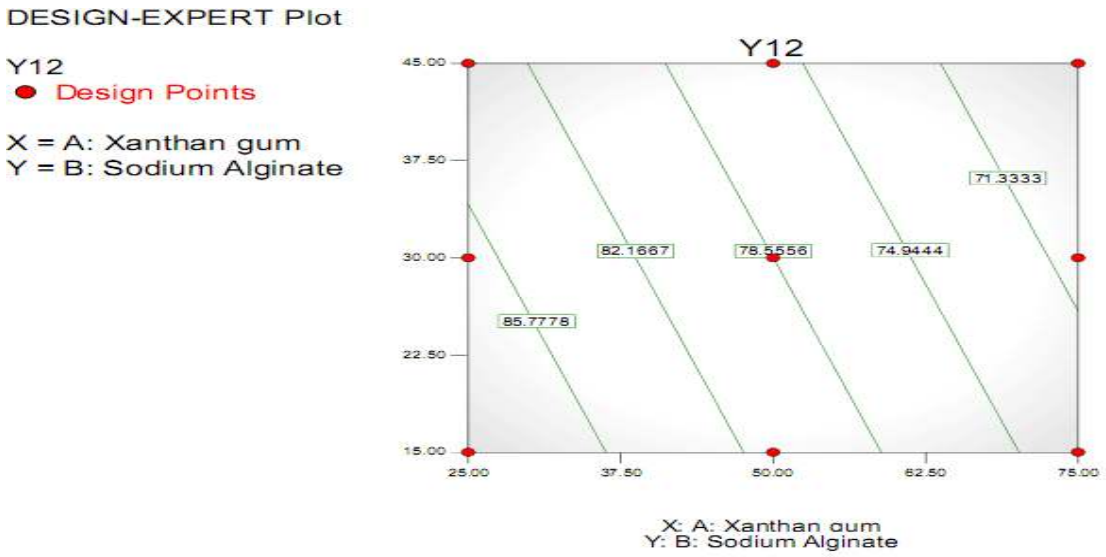


Figure 18: Surface design of response Y12 by varying quantities of Xanthan gum and Sodium alginate. (b) Related contour plot indicating various levels of the two polymers

SUMMARY

In the present study, the oral matrix tablets of Zidovudine were formulated by Experimental design by using combination of natural polymers (Xanthan gum/ Sodium alginate) as the retardant polymers each with three different levels with an approach to maintain uniform drug levels, reduce dose, side effects, increase the safety margin and improve drug bioavailability. From FTIR results, confirm the absence of chemical interaction between the drug with the excipients used in tablet formulations. Also, there was no shift in the endotherm of in the drug- excipients mixtures indicating compatibility of drug with all the excipients. Matrix tablets were prepared by direct compression method and prepared tablets were evaluated for weight variation, percentage friability, hardness and drug content studies. All the formulations showed compliance with pharmacopeia standards. In vitro release studies revealed that the release rate decreased with increase polymer proportion of retarding polymers. Formulation ZXA_4 sustained release of drug for 12 hrs by incorporating 5% of Xanthan gum along with 3% of Sodium alginate. The formulations ZXA_4 sustained release of drug for 12 hrs with 22% release of drug after 1hr and more than 96% at the end of 12 hrs. It can be concluded that Matrix tablets can be developed by incorporating in a definite proportion of xanthan gum with Sodium alginate, So that release profile is maintained for an extended periods of time. However, the more extensive in vivo studies should be carried out in different animal models and human volunteers to establish the above

developed matrix tablets for commercial existence as future work.

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