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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ZIDOVUDINE

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ABSTRACT

Zidovudine is widely used in ART as Nucleoside Reverse Transcriptase Inhibitors. In the present investigation an attempt has been made to design and develop Zidovudine S.R. tablets using various synthetic and natural hydrophilic polymers. Sustained release matrix tablets are prepared using Xanthan gum, HPMC K100M, Guar gum alone and in a combination by using direct compression method. A total of 7 formulations (3 formulations with Xanthan gum, HPMC, Guar gum respectively, 4 formulations containing HPMC and guar gum in combination with Xanthan gum in the ratio of 5:5 and 2.5:7.5 respectively) were prepared. All these prepared tablets are evaluated for weight variation, friability, thickness, hardness, drug content and drug release pattern. No significant variation from I.P. and U.S.P. limits was observed. The drug-excipient interaction studies were carried out by FTIR spectroscopy, DSC and visible inspection (by keeping drug excipient mixture for 1 month at room temperature). No significant interaction between rug and excipients was observed. The comparative evaluations of the dissolution profiles were done. From the data it was concluded that all formulations show Fickian diffusion or anomalous type drug release pattern. Of all the formulations F6 is the best formulation .From the above, it was concluded that few of the formulations (F1, F5, F6, and F7) follow the sustained release pattern of drug release.

Keywords: Zudovudine, Synthetic & natural polymers, *In-vitro* Evaluation, S.R Matrix Tablets.

INTRODUCTION

The basic rationale for sustained and controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecules inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs. Acquired Immuno Deficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation [1-10]. It is very crucial for the success of AIDS therapy to maintain the therapeutic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment. Zidovudine/Azidothymidine (AZT), the first anti-HIV compound approved for the clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents and Zidovudine is water soluble and soluble at all pH ranges and absorbs throughout the gastrointestinal tract and so sustained release tablet is better approach then the conventional dosage form. Since Zidovudine acts as a metabolic antagonist of thymidine and its antiviral effect is time dependant so a sustained release delivery of AZT is desired to maintain anti-AIDS effect and avoiding severe side effects [10-22]. By considering above facts, the present study was aim to formulate and evaluate the sustained release matrix tablets of Zidovudine to prolong the release of drug for extended period of time in order to; Improve patient compliance, Reduce dosing frequency Reduce side effects, Minimum plasma fluctuation, Increase

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bioavailability of the drug [22-30].

FORMULATION DEVELOPMENT

Preparation of Reagents

Preparation of 6.8 pH Phosphate Buffer [75]

0.2M Potassium dihydrogen phosphate

27.218 g of Potassium dihydrogen phosphate was weighed and transferred into a 1000ml volume flask. Sufficient quantity of distilled water was added and shook well until the content get dissolved and finally made up to 1000ml with distilled water.

0.2 M Sodium hydroxide

8.0 g sodium hydroxide pellets were weighed and transferred into 1000ml of volumetric flask. Sufficient quantity of distilled water was added and shook well until the content get dissolved and finally made up to 1000ml with distilled water.

Procedure

250 ml of 0.2 M Potassium dihydrogen phosphate and 112.0ml of 0.2 M sodium hydroxide was pipette to a suitable volumetric flask (1000 ml) and volume was made up to 1000 ml with distilled water.

Construction of Calibration Curve of Zidovudine

Preparation of Standard Curve

A standard curve was prepared by dissolving 25 mg of Zidovudine in 25 ml of water. Accurately weighed amount of 25 mg of Zidovudine was transferred to a 25 ml volumetric flask. It was dissolved in sufficient amount of water and volume was made up to 25ml with distilled water. This gives a solution having concentration of 1 mg/ml of Zidovudine stock solution. From the primary stock, exactly 1ml was withdrawn and diluted to 10 ml with distilled water. From the secondary stock 0.5, 1, 1.5, 2, 2.5 ml was taken separately and made up to 10 ml with distilled water to produce 5, 10, 15, 20, 25 µg/ml respectively. The absorbance values are determined at 264.99 nm using UV spectrophotometer. A graph of absorbance Vs concentration was then plotted.

FT-IR Studies [74]

Drug-Polymer interactions were studied by FT-IR spectroscopy using the instrument Bruker, Japan, FT-IR8400S. The spectra were recorded for pure drug Zidovudine. Samples were placed in KBr discs (2mg in 200mg KBr) with a hydrostatic press at a force of 5.2 N/m^2 for 3min. The scanning range was 400-4000cm^{-1}.

Evaluation of Flow Properties of the Powder Blend

Angle of Repose

Angle of Repose is defined as the maximum angle possible between surface of the pile of the powder and horizontal plane. The angle of repose was determined by the funnel method to assess the flow property of powder or granules. The accurately weighed powder blend was taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend above a paper that was placed on a horizontal surface. Accurately weighed powder was taken in a beaker. The blends were allowed to flow freely onto the surface of a paper to form a cone shaped pile. The diameter of the powder cone and the height of the pile were measured. The angle of repose was calculated using the following equation,

$$\tan\theta = h/r$$

Where, h and r are height and radius of the powder cone.

Bulk Density and Tapped Density [21]

Bulk Density is the ratio between the given mass of a powder or granules and its bulk volume. Tapped Density is the ratio between the given mass of a powder or granules and the constant or fixed volume of the powder or granules after tapping. An accurately weighed quantity of granules (W) (which was previously passed through sieve no. 40) was carefully transferred into 250 ml measuring cylinder and initial volume (V_o) was measured. The cylinder is then allowed to tap on to a wooden surface from a height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume (until constant volume) (V_d) was obtained. The bulk density and tapped density are calculated using the following formula.

Bulk Density =$W/(V_o)$, Tapped Density = $W/(V_d)$

Compressibility Index and Hausner Ratio [21]

In recent years, the Compressibility Index and the closely related Hausner Ratio have become the fast, simple and popular methods of predicting the powder flow characteristics. The Compressibility Index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of material. The Compressibility Index and Hausner Ratio are determined by measuring both the bulk volume (BD) and the tapped volume (TD) of the powder. The basic procedure of determining the compressibility index and Hausner ratio is to measure the unsettled apparent volume (V_0) of the powder after tapping of the material until there is no further volume change. The Compressibility Index and Hausner Ratio is calculated as follows,

$$\text{Compressibility Index} = [(V_0 - V_f)] \times 100]/V_0$$

$$\text{Hausner Ratio} = V_0/V_f$$

Evaluation Tests for Tablets [76, 77]

To design tablets and to monitor tablets production, qualitative, quantitative evaluation, assessment of tablets, physical, chemical and bioavailability properties must be done. There are various standards that must have set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters. The diameter and the shape of the

tablets depend on the die and the punches selected for compression of the tablets. The remaining specifications assure that the tablets do not vary from the one production lot to other. The following standards are the quality control tests should be carried out on compressed tablets. The formulated tablets of Zidovudine sustained release formulations were evaluated by the following tests.

General Appearance [76, 77]

The general appearance of the tablets, its visual identity and overall elegance of essential for consumer acceptance, control of lot-to-lot uniformity and general tablet-to-tablet uniformity and monitoring the production process. The control of general appearance involves measurement of attributes such as tablet size, shape, color, presence or absence of odor, taste, surface texture, physical flaws and consistency. The formulated tablets were evaluated for organoleptic character such as shape, color, odor etc.

Hardness test or Crushing strength [76, 77]

Hardness, which is now more appropriately called crushing strength determinations are made during tablet productions and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating, packing and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of usually 4kg is considered to be minimum for satisfactory tablets. Oral tablets generally have a hardness of 4-10 kg. However hypodermic and chewable tablets are much softer (3kg) and some sustained release tablets are much harder (10-20kg).

Hardness (diametric crushing stress) is the force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with different type of tablets. The force is measured in kilograms. The hardness was tested using Monsanto tester. The tablet was placed horizontally in contact with the lower plunger of the Monsanto hardness tester and zero reader was adjusted. The tablet was the n compressed by forcing the upper plunge until the tablet breaks. This force was noted.

Friability test [76, 77]

Friability is the loss of weight of tablet in the container, due to the removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation and shipment. It is usually measured by using Roche Friabilator. Ten tablets are weighed (W_1) and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4minutes or 100 revolutions, the tablets are weighed (W_2) and this weight is compared with the initial weight. The loss due to the abrasion is a measure of tablet friability. The value is expressed as percentage. A maximum weight loss or not more than 1% of the weight of the tablets being tested during the friability test is considered and generally accepted. Any broken or smashed tablets are not picked up. Normally when capping occurs, friability values are not calculated. The present friability was determined using the following formula,

$$\text{Friability} = [(W_1 - W_2)/W_1]100$$

Uniformity of Weight or Weight Variation test [76, 78]

This is an important in-process quality control test to check frequently (every half an hour). Corrections were made during compression of tablets. Any variation in the weight of the tablet (for any reason) may lead to over dose of under medication. Therefore every tablet in each batch should have a uniform weight, 20 tablets of each formulation were selected at random and weighed individually. The weight of individual tablet was noted, Average weight was calculated from the total weight of tablets. The individual weight was compared with the average weight. Not more than two of the tablets must differ from the average weight by not more than the percentages stated in the table below. The percentage deviation was calculated from the following formula,

$$\% \text{ Deviation} = [(\text{Individual weight} - \text{Average weight}] 100$$

Estimation of Drug Content

Drug Content was determined by accurately weighting 5 tablets and crushing them into mortar with the help of pestle. Then an Accurately weighed quantity of powder equivalent to 100 mg of drug was transferred to a 100 ml volumetric flask. 50 ml of distilled water was added and shaken. Volume was made up to 100 ml with distilled water. The solution was then filtered through Whatmann filter paper. First few ml of filtrate was discarded. Then 10 ml of filtrate was diluted to 100 ml with distilled water. From the above solution 1 ml was taken and diluted to 10 ml with distilled water. The absorbance of resulting 10 g/ml solution was recorded at 264.99 nm. Content uniformly was calculated using following formulas,

$$\%\text{Purity} = 10\ C\ (Au / As)$$

Where, C= Concentration, Au and As= Absorbance obtained from standard preparation and assay preparation respectively.

***In vitro* Drug Release Studies [40]**

Drug Release studies were carried out using USP dissolution rate apparatus (Apparatus 1, 50 rpm, 37^{o}C). A pH 6.8 Phosphate buffer was used as dissolution medium

and tested for drug release for 12h. Ten ml aliquots of the dissolution medium were withdrawn at hourly intervals for 12 h. The withdrawn amount was replaced with an equal amount of fresh dissolution medium kept at 37^{o}C. The withdrawn samples were analyzed at 269.99nm using UV Spectrophotometer. The release data was analyzed by fitting in the different kinetic equations to elucidate the release mechanism.

Release Kinetics [79]

The quantitative analysis of the values obtained in dissolution test was used in mathematical formulae to express the dissolution results as function of dosage form characteristics.

Zero-order Kinetics

Dissolution of drug from a dosage form that do not disaggregate and release the drug slowly that is where drug release rate is independent of its concentration can be represented

$$Q_t = Q_o + K_o t$$

Q_o initial amount of drug in the solution
Q_t amount of drug dissolved at time t
K_o proportionality constant

The dosage forms following this kinetic profile, release the same amount of drug by unit time and graphical representation of cumulative percent of drug dissolved verses time will be linear. This relation is used to determine the dissolution profile of various modified release dosage forms e.g. Transdermal systems, matrix tablets with low soluble drugs [80], osmotic systems coated forms, etc. and is considered to be the ideal method of drug release.

First-order Kinetics

first order kinetics was proposed for dissolution studies by Gilbadi and Feldman [81]. Here the drug release rate concentration id dependent. Graphical representation of logarithm of drug dissolved verses time will be linear.

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303$$

Q_o initial amount of drug in the solution
Q_t amount of drug dissolved at time t
K_1 first order rate constant

The dosage forms containing water soluble drug in a porous matri [82] generally follow this profile.

Hixon-Crowell Method

Drug release with change in the surface area and particle (tablet) diameter was given by Hixon-Crowell. They recognized that the particle regular area to be proportional to the cubic root of its volume. Thus derived an equation

$$Q_o^{1/3} - Q_t^{1/3} = K_{HC} t$$

Q_o initial amount of drug in the solution
Q_t amount of drug dissolved at time t
K_{HC} constant incorporating the surface volume relation

Plot of cube of initial concentration minus the cube root of percent remaining verses time gives Hixon-Crowell plot. This model is used by assuming that drug release rate is limited by the drug particle dissolution rate and not by diffusion.

Higuchi Model

Higuchi [82] developed model to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices.

$$Q = K_H t^{1/2}$$

Where K_H is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based in Fick's Law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release dosage forms, as in the case of some Transdermal systems [80] and matrix tablets with water soluble drugs.

Korsemeyer- Peppeas model

Korsemeyer Peppas developed a simple, semi-empiric model [85] when diffusion is the main drug release mechanism. In this model drug release is exponentially related to the elapsed time (t).

$$Q_t / Q_\infty = at^n$$

Peppas used this n value in order to characterize different release mechanisms. To the determination of the exponent n the portion of the release curve Q_t / Q_∞ should only be used. This model is generally used to analyze the release of pharmaceutical and polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

Preparation of Sustained Release Matrix tablets of Zidovudine

Matrix tablets were prepared by using direct compression method. First the drug (Zidovudine) and polymer along with diluents (Microcrystalline cellulose) were passed through sieve no. 80 and were mixed together uniformly in RMG for 10mins. This mixture was blended with Magnesium stearate. After blending the powder for sufficient time, the mixture was compressed using a 12 station rotary tableting machine equipped with round. Flat faced punches 12mm diameter. Polymer ratio was varied to get matrix tablets of varying polymer concentrations of Xanthan gum, HPMC K100M and Guar gum.

RESULTS AND DISCUSSION

FT-IR studies

The results of FTIR spectral studies showed that there was no significant interaction between the drug, polymer and other excipients. It was observed that there are no major degenerative interactions and hence the polymers and excipients could be used safely to formulate the matrix tablet. Pure drug showed sharp characteristic

peaks of carbonyl group in 1,678 cm^{-1} and of azide group in 2.085 cm^{-1}. One band in 1378 cm^{-1} is assigned to CH_2 and one band in 1285 cm^{-1} is assigned to C-O-C and the C-OH grouping. All the above characteristic peaks appeared in the spectrum of microcapsules too indicating there was no modification or interaction between drug and other excipients. This is also supported by the fact there was no appearance and disappearance of new or existing peaks.

Differential scanning Calorimetry

The compatibility of AZT in matrix tablets was evaluated through DSC analysis. The DSC thermo grams of pure AZT and AZT-embedded matrix tablets are presented in Figure 12 & 13. It was evident from the DSC profile that AZT exhibited a sharp endothermic peak associated with crystal melting at a temperature of 126.79^0C, which corresponds to the reported melting temperature of the drug. A similar DSC profile Figure 13 of the drug appeared at the temperature corresponding to its melting point in the AZT-embedded matrix tablets but with a slight change in its sharp appearance. It appears that there is a minor reduction of drug crystallinity in the matrix tablets. The DSC study apparently revealed that the drug was compatible with the polymer and neither drug decomposition nor drug-polymer interactions occurred in the freshly prepared microcapsules.

According to the plan of work, sustain release matrix tablets of Zidovudine were prepared by direct compression method using controlled release polymers like Xanthan gum, HPMC K100M and Guar gum. The drug (300mg) was mixed with polymer and excipients and compressed into tablets(500mg) and a total of seven batches of formulations are fabricated i.e., F1, F2, F3,F4, F5, F6, F7 with varying concentrations of polymer in each formulation. The incompatibility studies were performed for drug, polymers and physical mixtures of drug and polymer by Fourier Transform Infra-red Spectroscopy (FTIR). There is no incompatibility found between drug and polymers. The spectra obtained from FTIR studies at wavelength from 4000 cm^{-1} to 400 cm^{-1}.Preformulation parameters were performed where Angle of Repose was less than 29^o and Carr's Index value was less than 18 for all formulations, indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all batches indicating good flow properties. The evaluation parameters were performed and results were satisfactory and within the acceptable limits; for the uniformity of weight (495-505mg), hardness (6-8 kg/cm^2), thickness (4.0-4.5), friability (NMT 1%) and drug content (98-102%).The formulations F1 to F3 were prepared by using 10% of Xanthan gum, HPMC, Guar gum respectively as rate controlling polymers, F4 and F5 were prepared by using combination of Xanthan gum with HPMC and Guar gum in the ratio of 5:5 respectively as rate controlling polymers, F6 and F7 were prepared by using combination of Xanthan gum with HPMC and Guar gum in the ratio of 7.5:2.5 respectively as rate controlling polymers. The release of formulation F6 was found to be higher when compared to other formulations. This may be due to increase in the concentration of Xanthan gum which retards the release of drug from the dosage form. The drug release kinetic studied shown that F6 as the best formulation as it releases the drug continuously up to 12 h. The *in vitro* drug release profiles of AZT were applied on various kinetic models in order to evaluate the mechanism of drug release. The different kinetic models evaluated were zero order, first order, Higuchi, Hixon-Crowell etc. After linearization of the results obtained in the dissolution test, the best fit with higher correlation coefficients (R2) was shown in Higuchi, Hixon-Crowell, first order and followed by zero order equations as given in the table 16. High correlation was observed from the Higuchi plot rather than Hixon-Crowell, first order and zero order equations, indicating that the drug release from matrix tablets was diffusion controlled. The data obtained were also put in Korsemeyer-Peppas model in order to find out *n* value, which describes the drug release mechanism. The *n* values of matrix tablets of optimized batch (F6) was 0.35 (< 0.5), indicating that the mechanism of the drug release was diffusion controlled based on Fick's law.

Table 1. List of Raw Materials Used

S. No.	Name of Ingredients	Name of suppliers
1	Zidovudine	Hetero Pharmaceuticals, Hyderabad, India.
2	HPMC K100M	Yarrow Chem Products, Mumbai, India.
3	Xanthan gum	Yarrow Chem Products, Mumbai, India.
4	Guar gum	Yarrow Chem Products, Mumbai, India.
5	Magnesium stearate	MyloChem, Mumbai, India.
6	Microcrystalline Cellulose	Oppokemi WGK, Germany.
7	Sodium hydroxide	Finar chemicals limited, Ahmadabad, India.
8	Potassium dihydrogen phosphate	Finar chemicals limited, Ahmedabad, India.

Table 2. List of Equipments Used

S. No.	Equipments	Manufacturers
1	Electronic weighing balance	Infra instruments Pvt. Ltd., Chennai, India.
2	Tablet compression machine	Rimek mini press-1, Ahmedabad, India.
3	Tablet dissolution apparatus	Electro lab TDT- 08L, Mumbai, India.
4	UV or Visible Spectrophotometer	Agilent technologies Cary- 60 UV- Visible, Penang, Malaysia.
5	Hot air oven	Micro Teknik, Ambala.
6	Friability test apparatus	DBK instruments, Mumbai, India.
7	Vernier Caliper	Linkar, Mumbai, India.
8	pH meter	Cyber Lab, Hyderabad, India.
9	FT-IR spectrophotometer	Bruker, Japan
10	Hardness tester	Shiv scientific stores, Delhi, India.
11	Glasswares	Borosil

Table 3. Flow Properties and Corresponding Angle of Repose [76]

S.NO	Flow Properties	Angle of Repose (θ)
1	Excellent	25-30
2	Good	31-35
3	Fair (aid not needed)	36-40
4	Passable	41-45
5	Poor (must agitate, vibrate)	46-55
6	Very Poor	56-65
7	Very, Very Poor	>66

Table 4. Scale of Flowability [76-77]

S. No.	Compressibility index	Flow properties	Hausner Ratio
1	1-10	Excellent	1-1.11
2	11-15	Good	1.12-1.18
3	16-20	Fair	1.19-1.25
4	21-25	Passable	1.26-1.34
5	26-31	Poor	1.35-1.45
6	32-37	Very Poor	1.46-1.59
7	>38	Very, Very Poor	>1.60

Table 5. Composition of Zidovudine Sustained Release matrix tablets

S.No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
1	Drug (Zidovudine)	300	300	300	300	300	300	300
2	Xanthan gum	50	-	-	25	25	37.5	37.5
3	HPMC K100M	-	50	-	25	-	12.5	-
4	Guar gum	-	-	50	-	25	-	12.5
5	MCC	140	140	140	140	140	140	140
6	Magnesium stearate	10	10	10	10	10	10	10
7	Total Tablet Weight (mg)	500	500	500	500	500	500	500

Table 6. Weight Variation Parameters [78]

SL.NO	Average weight	Percent difference
1.	130 or less	10
2.	From 130 through 324	7.5
3.	More than 324	5

Table7. Interpretation of diffusional release mechanisms from polymeric film

Release Exponent(n)	Drug Transport Mechanism
0.5	Fickian diffusion

0.5<n<1.0	Anomalous transport (Non-Fickian)
1.0	Case-II
>1.0	Super Case-II

CALIBRATION CURVE OF ZIDOVUDINE:

Standard Calibration Curve of Zidovudinein 6.8 pH Phosphate Buffer

Table 8. Standard Calibration Curve data

S. No.	Concentration (mcg/ml)	Absorbance (nm)
1	5	0.22
2	10	0.411
3	15	0.616
4	20	0.822
5	25	1.048

Table 9. Pre-formulation Parameters

Characterization of Powder Blend

S. NO.	Formulation codes	Angle of repose(^{0})±SD	Bulk density (g/cm^3)±SD	Tapped density (g/cm^3)±SD	Carr's index (%)	Hausner's ratio(HR)
1	F1	29.9±0.2	0.53±0.2	0.62±0.4	14.51	1.16
2	F2	28.3±0.1	0.51±0.5	0.61±0.1	16.39	1.19
3	F3	26.9±0.3	0.52±0.3	0.63±0.2	17.046	1.21
4	F4	26.4±0.3	0.47±0.4	0.54±0.1	12.96	1.14
5	F5	27.6±0.2	0.49±0.3	0.55±0.3	10.90	1.12
6	F6	23.7±0.5	0.48±0.1	0.57± 0.6	15.78	1.18
7	F7	22.4±0.8	0.46±0.2	0.53± 0.5	15.21	1.15

All the values expressed are as mean ±SD, n=3

Table 10. Evaluation Parameters

Evaluation of Sustained Matrix Tablets

S. NO.	Formulation codes	Weight variation ±SD	Friability (%)	Thickness (mm)±SD	Hardness (kg/cm^2)±SD	Drug content (%)±SD
1	F1	498±2.9	0.43	4.1±0.07	7.2±0.2	99.5±1.4
2	F2	502±1.5	0.56	4.0±0.01	7.1±0.4	101.1±1.1
3	F3	503±0.7	0.42	4.2±0.06	7.3±0.4	99.08±0.3
4	F4	501±2.4	0.64	4.1±0.02	7.5±0.1	102.1±0.6
5	F5	499±3.2	0.38	4.2±0.05	7.2±0.3	99.1±1.5
6	F6	502±1.3	0.75	4.0±0.04	7.1±0.4	98.2±0.4
7	F7	501±3.9	0.32	4.1±0.04	7.1±0.2	99.4±1.5

All the values expressed are as mean ±SD, n=3

Table 11. *In-vitro* Release of Zidovudine from Formulations F1 to F7

***In-vitro* Dissolution Studies**

S. No.	Time (hrs)	% CDR						
		F1	F2	F3	F4	F5	F6	F7
1	0	0	0	0	0	0	0	0
2	0.5	13.51	63.12	71.97	48.96	67.75	28.36	16.83
3	1	24.32	81.24	87.32	56.19	70.19	39.87	24.76
4	2	36.24	87.12	88.04	68.01	83.27	51.63	34.91
5	3	45.63	96.32	87.96	71.27	83.54	53.75	42.67
6	4	51.08		91.02	81.06	83.96	63.97	49.34
7	5	57.96		93.94	89.12	84.09	65.18	52.18
8	6	63.14		96.03	90.2	85.61	72.47	58.68

9	7	66.76				87.54	74.62	59.78
10	8	72.06				88.02	77.94	65.69
11	9	69.98				90.02	79.95	67.99
12	10	77.32				92.98	84.42	77.62
13	11	78.71					87.71	81.84
14	12	80.11					94.76	86.97

Table 12. Release Kinetics of formulated batches F1 to F7

Formulations	Zero order		First order		Higuchi		Hixon-Crowell		Korsemeyer
	K	R^2	K	R^2	K	R^2	K	R^2	n
F1	5.977	0.884	0.1289	0.978	24.12	0.988	-0.143	0.965	0.536
F2	25.83	0.649	0.9902	0.945	54.62	0.895	-0.641	0.951	0.221
F3	9.47	0.419	0.3961	0.764	31.6	0.678	-0.205	0.834	0.095
F4	11.49	0.731	0.35	0.948	33.9	0.922	-0.295	0.98	0.252
F5	4.722	0.411	0.17	0.729	20.47	0.646	0.105	0.855	0.098
F6	5.994	0.841	0.184	0.930	24.27	0.971	-0.173	0.964	0.35
F7	6.113	0.936	0.1427	0.958	24.03	0.992	-0.156	0.994	0.494

Fig 1. U.V. Spectrometric graph of Zidovudine

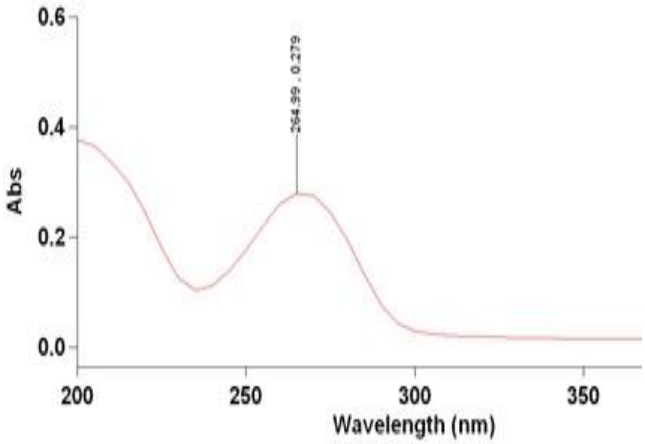


Fig 2. Calibration Curve of Zidovudine in pH 6.8 Phosphate buffer

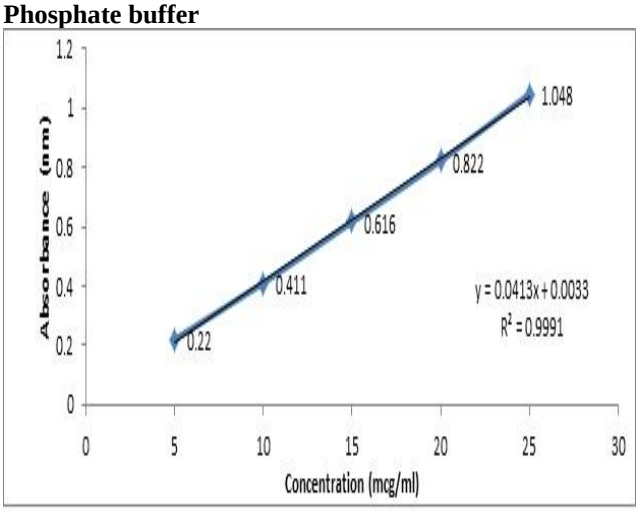


Fig 3. Illustration of the IR spectrum of Zidovudine

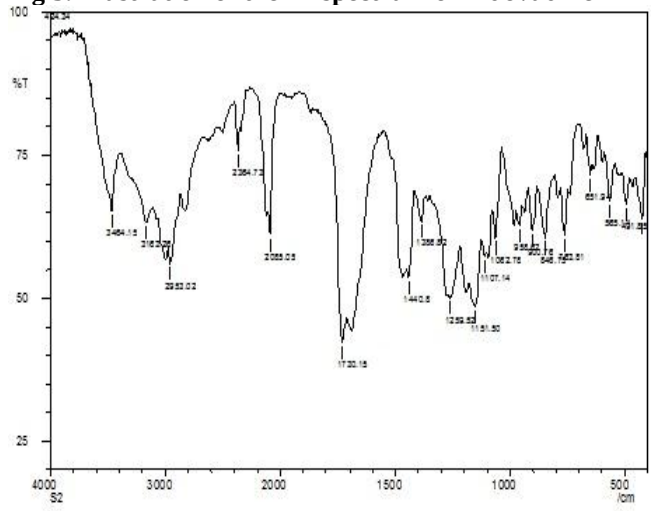


Fig 4. Thermal Analysis of Zidovudine

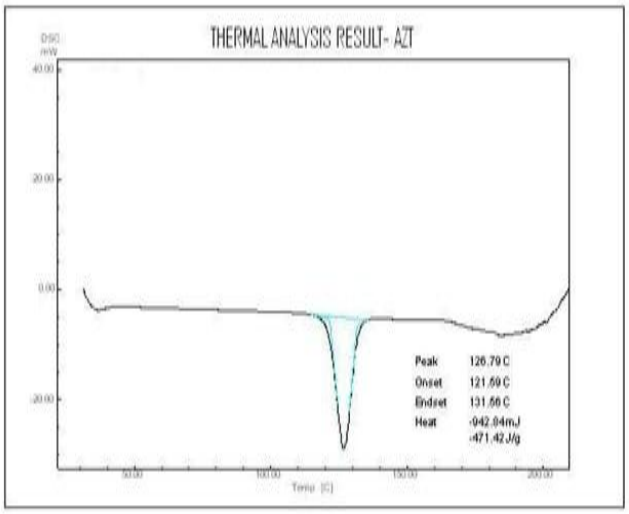


Fig 5. Thermal Analysis of Formulation Mixture

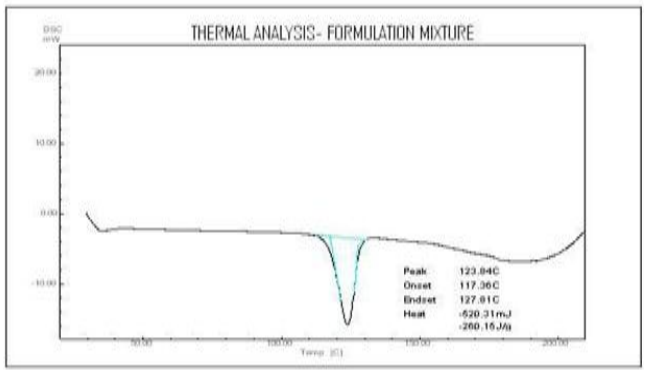


Fig 6. Comparative % CDR from different batches containing Zidovudine

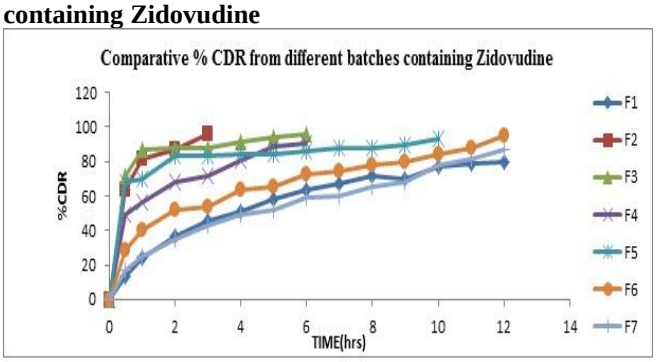


Fig 7. Zero order Release plot for Optimized formulation

Fig 8. First order Release plot for Optimized formulation

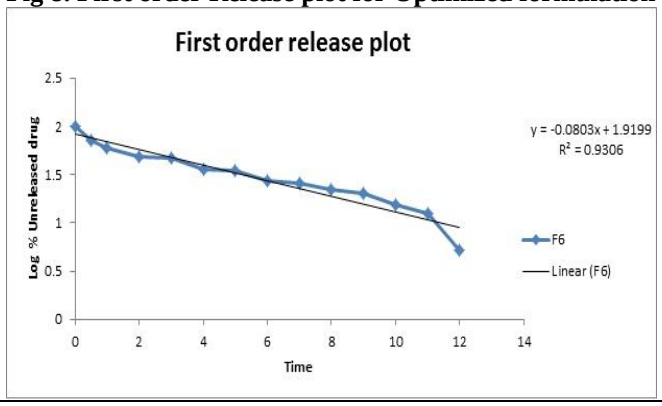


Fig 9. Hixon- Crowell plot for Optimized formulation

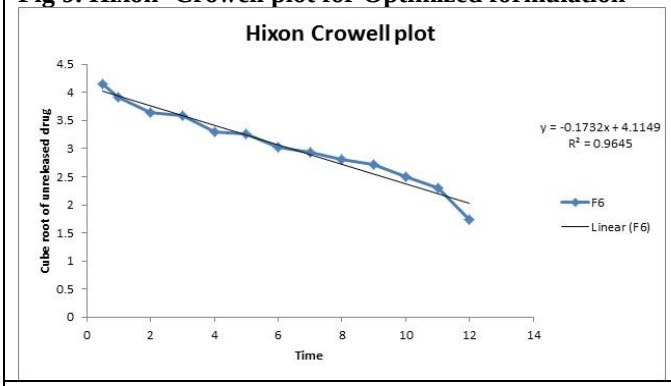


Fig 10. Higuchi plot for Optimized formulation

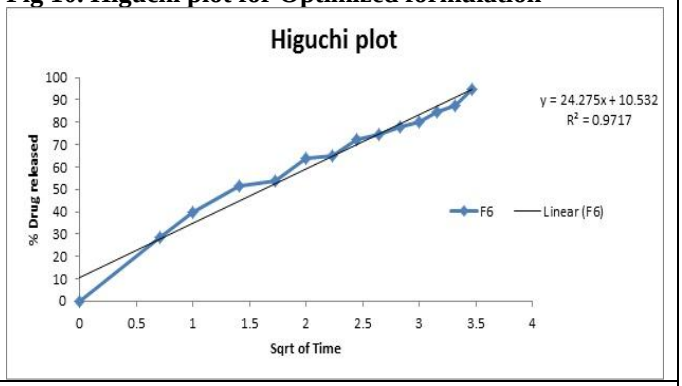
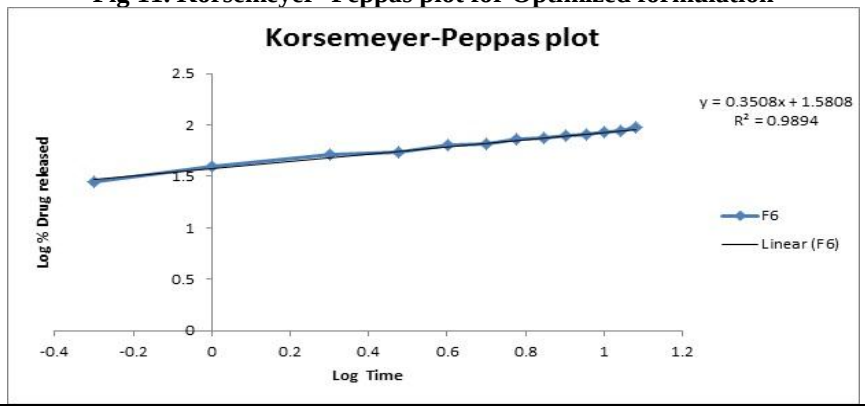


Fig 11. Korsemeyer- Peppas plot for Optimized formulation



SUMMARY AND CONCLUSION

Despite significant advances that have been made in understanding the mechanism of HIV infection and in identifying affective treatment approaches, the search for optimum treatment strategies for AIDS still remains a major challenge. Results obtained indicate that novel drug delivery systems clearly present an opportunity for formulation Scientists to overcome many challenges associated with ART. The use of such system began in the early 1990's but it is only within the past 5 years that there appears to be sudden surge of interest and publications in the use of NDDS for Anti-Retroviral drugs.

Zidovudine is widely used in ART as Nucleoside Reverse Transcriptase Inhibitors. In the present investigation an attempt has been made to design and develop Zidovudine S.R. tablets using various synthetic and natural hydrophilic polymers. Sustained release matrix tablets are prepared using Xanthan gum, HPMC K100M, Guar gum alone and in a combination by using direct compression method. A total of 7 formulations (3 formulations with Xanthan gum, HPMC, Guar gum respectively, 4 formulations containing HPMC and guar gum in combination with Xanthan gum in the ratio of 5:5 and 2.5:7.5 respectively) were prepared. All these prepared tablets are evaluated for weight variation, friability, thickness, hardness, drug content and drug release pattern. No significant variation from I.P. and U.S.P. limits was observed. The drug-excipient interaction studies were carried out by FTIR spectroscopy, DSC and visible inspection (by keeping drug excipient mixture for 1 month at room temperature). No significant interaction between rug and excipients was observed. The comparative evaluations of the dissolution profiles were done. From the data it was concluded that all formulations show Fickian diffusion or anomalous type drug release pattern. Of all the formulations F6 is the best formulation .From the above, it was concluded that few of the formulations (F1, F5, F6, and F7) follow the sustained release pattern of drug release.

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