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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF ZIDOVUDINE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

Sustained release formulation of zidovudine based on monolithic - matrix technology was developed and evaluated. Zidovudine is water-soluble drug so it is suitable to develop sustained release matrix tablet. Zidovudine is a short acting drug, so developed formulation provides the advantages of sustained release formulations. Zidovudine is a first potent antiviral agent used in the treatment of AIDS. Zidovudine is rapidly absorbed from the gastrointestinal tract, with peak serum levels achieved with in about one hour. Oral sustained release matrix tablets of zidovudine were prepared by dry granulation technique using hydroxyl propyl methyl cellulose polymer (HPMC) different grades. Hydroxyl propyl methyl cellulose polymer (HPMC) is water soluble and rate controlling polymer. The effect of the concentration of the polymer was studied. The studies indicated that the drug release can be modulated by varying the concentration of the polymer. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations) and in-vitro drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. Release kinetics was evaluated by using United States Pharmacopeia (USP)-22 type II dissolution apparatus. The in vitro release study of matrix tablets were carried out in purified water for 12 hours. Among all the formulations, F-3 shows 96.52% release at the end of 12 hours. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero-order to evaluate the kinetics and mechanism of the

drug release. Kinetic modeling of in-vitro dissolution profiles revealed the release mechanism ranges from diffusion controlled or quasi-Fickian transport to anomalous type or non-Fickian transport, which was only dependent on the type and amount of polymer used. The drug release follows first order kinetics and the mechanism was found to be diffusion coupled with erosion. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Keywords: Zidovudine, Hydoxy propyl methyl cellulose, Matrix tablets, dry granulation, sustained release.

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions. Conventional formulations are required to be administered multiple doses and therefore have several disadvantages.[1]

The primary benefit of a sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug.[2]

Hydrophilic polymer matrix systems are widely used for designing oral sustained drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[3] The hydrophilic polymers selected for the present study were HPMC K100,HPMC100 LV. These polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms.[4]

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 biological half-life, and poor bioavailability. Conventional formulations of AZT are administered multiple times

a day depending on the dose (300mg twice daily or 200mg thrice daily) due to its short half-life (t112=0.5 to 3h). [5,6]

After oral administration, AZT is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 ug|ml at 0.8 hours. 4 In the systemic circulation, it is first converted to AZT-troposphere, which is pharmacologically active and prevents the replication of 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 a nd avoiding the strong side effects. These side effects are usually associated with excessive plasma level of AZT immediately after intravenous or oral administration.

MATERIALS AND METHODS

Materials: Zidovudine ,HPMC K100 M,HPMC 100LV,Lactose11SD,Micro crystalline cellulose, Aerosil 200,and Magnesium Stearate were purchased from Aurobindo Pharma Ltd.Hyderabad.

Preparation of matrix tablets

The matrix tablet was prepared from granules by conventional dry granulation method. Zidovudine matrix tablets the detail process was as follows

1. Sifting: Zidovudine, magnesium sterate and aerosil are sifted through sieve no; 60.
HPMC, lactose ,MCC 101are sifted through sieve no ;30.

2. Preparation of Granules

(a) In intragranular: zidovudine , HPMC, lactose are taken in full quantites ,where as MCC and magnesium sterate are taken in half of its quantites. By these materials flakes are prepared by using roller compactor at pressure of 4 tons. flakes are milled trough co -mill (sieve no: 30).fines and retains are separated by using sieve no: 60.

(b)In extragranular: aerosil and remaining quantities of MCC and magnesium sterate are added.

3. Mixing: Intra and extragranular materials without magnesium sterate are blended in octacone blender for 10 minutes.

4. Lubrication: finally magnesium sterate is added and again blended for 5 minutes.

5. Compression: With this blend tablets were compressed using Rotary tablet machine with 12.1 mm flat-shaped punches. Tablet weight was (600mg) kept constant as shown in table 1.

Evaluation of granules: The angle of repose was measured by using funnel method which indicates the flow ability of the granules.[7] Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder /volume of the packing.[8] TBD= weight of the powder /tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.[9] The physical properties of granules were shown in Table 2.

Evaluation of tablets: All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods[10] shown in Table 3.

Uniformity of drug content: Accurately weighed quantity of the powder tablet equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 100 ml of purified water was added.Mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45µm. 5 ml of the filtrate was diluted to 100 ml with purified water and examined under UV Spectrophotometer at 266 nm.

Table 1: Tablet composition of different formulations of Zidovudine sustained release matrix tablets.

INGREDIENTS	FORMULATION CODE							
	F1	F2	F3	F4	F5	F6	F7	F8
Zidovudine	300	300	300	300	300	300	300	300
HPMC K 100 M	150	75	50	25	40	_	_	60
HPMC K 100 LV	_	_	_	_	_	150	100	_
Lactose 11 SD	108	108	108	108	108	108	108	108
Micro crystalline cellulose	33	108	133	158	143	33	83	123
Aerosil 200	6	6	6	6	6	6	6	6
Magnesium Stearate	3	3	3	3	3	3	3	3

Table 2: Granular properties of formulations F1 to F8 of Zidovudine sustained release matrix tablets.

Formulation No.	Angle of repose	Loose bulk density (LBD) (g/ml)	Tapped bulk density(TBD) (g/ml)	Compressibility index (%)
F1	24.22 ± 1.25	0.238 ± 0.008	0.263 ± 0.010	9.54 ± 0.71
F2	27.22 ± 1.59	0.028 ±0.009	0.259 ± 0.014	11.71 ± 1.56
F3	25.15 ± 1.31	0.242 ±0.009	0.277 ±0.018	12.63± 1.78
F4	28.39 ± 1.52	0.236 ± 0.007	0.267 ± 0.012	11.20 ± 1.23
F5	29.74 ± 1.67	0.237 ± 0.006	0.265 ± 0.011	10.56 ± 0.78
F6	25.20 ± 0.261	0.2127 ± 0.001	0.2564 ± 0.016	17.04 ± 0.78
F7	24.44 ± 0.380	0.2150 ± 0.003	0.2500 ± 0.012	14.00 ± 0.70
F8	24.69 ± 1.54	0.3702 ± 0.05	0.4081 ± 0.005	13.63 ± 0.20

Table 3: Tablet properties of formulations F1 to F8 of Zidovudine sustained release matrix tablets with natural, synthetic polymers and fillers.

Formulation No.	Thickness(mm)	Hardness(kg/cm^2)	Friability (%)	Drug content (%)
F1	3.78 ± 0.16	6.2 ± 0.10	0.334	98.76 ± 0.256
F2	3.77 ± 0.37	6.3 ± 0.12	0.289	99.19 ± 0.121
F3	3.74 ±0.23	5.63 ± 0.52	0.178	99.52 ± 0.17
F4	3.85 ± 0.09	6.5 ± 0.00	0.403	99.45 ± 0.126
F5	3.87 ± 0.12	6.83 ± 0.35	0.354	99.89 ± 0.121
F6	4.33 ± 0.016	6.6 ± 0.02	0.129	100 ± 0.41
F7	4.28 ± 0.043	5.9 ± 0.10	0.095	99.65 ± 0.25
F8	4.18 ± 0.02	7.0 ± 0.20	0.28	99.19 ± 0.19

Table 4: Correlation coefficients of different mathematical models for formulations F- 1 to F-8.

Formulation No.	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope N
F1	0.987	0.868	0.998	0.996	0.703
F2	0.994	0.661	0.963	0.973	0.637
F3	0.948	0.938	0.998	0.996	0.601
F5	0.970	0.712	0.920	0.925	0.648
F6	0.997	0.692	0.975	0.975	0.640
F8	0.992	0.868	0.999	0.999	0.640

Characterization of Drug Release Kinetics: To study the release kinetics, data obtained form *in vitro* drug release studies were plotted in various kinetic models: zero order (equation 1), as the cumulative percentage of drug release Vs time, first order (equation 2), as the log of

the amount of drug remaining to be released Vs. time and Higuchi model (equation 3), as the cumulative percentage of drug release Vs. square root of time.

$C = K\,t\,o$ ... … … … … … … … … … ..(equation 1)

$Log\ C = Log\ C_0 - K_1\,t/\,2.303$ … … … … (equation 2)

$Q = K_h t^{1/2}$ … … … … … … … … … … … (equation 3)

The Korsmeyer and Peppas equation is: $Mt/M = kt^n$. Where M_t/M is the fraction of drug released at time *t*, k is a constant incorporating the properties of the macromolecular polymeric system and the drug and *n* is an exponent used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $0.45 < n < 0.89$ for anomalous behavior or non-Fickian transport, $n = 0.89$ for Case II transport, and $n > 0.89$ for Super Case II transport. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion.[11,12]

Stability Study: The optimized formulation was subjected to stability at $25^{o}C \pm 2^{0}C$ / 60% ± 5% RH, $30^{0}C \pm 2^{0}C$ / 65% ±5% RH and $40^{0}C \pm 2^{0}C$ / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.[13]

FTIR spectroscopy: The FT-IR Spectrum of pure Zidovudine and its physical mixture with polymers and different excipients are shown in Figure: 1 – 6.

Infrared spectra of drug and polymers were used to study the compatibility between them. No change in peak shows that there was no interaction between drug and polymers.

Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Tables 2. Angle of repose was in the range 24.22 $\pm$ 1.25 to 29.74 $\pm$ 1.67 , which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.028 $\pm$0.009 to 0.3702 $\pm$ 0.05gm/cc, the tapped density was in the range of 0.2500 $\pm$ 0.012 to 0.4081 $\pm$ 0.005gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 9.54 $\pm$ 0.71 to 17.04

± 0.78 indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical evaluation of matrix tablets

Tablets with a weight of 600 mg were subjected to quality control tests such as thickness hardness, friability and drug content (Table 3). The contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the10 units tested was within the range of 98.76 ± 0.256 to 100 ± 0.41 and the relative standard deviations were less than 2.0% indicating uniform mixing of polymers and drug. The mean values for hardness were over 6.0 kg/cm2 and all formulations exhibited a friability of not more than 0.6% during the friability determination. The punches used to compress the tablets were 12.1 mm spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 6 ± 0.02 to 6.5 ± 0.12 Kg/cm^2. It was within the range of monograph specification. Thickness of the tablets was found to be in the range of 3.57 ± 0.14 to 4.42 ± 0.014. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

***In-Vitro* Release Study**

In vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing basket at 50rpm using 900ml of purified water as dissolution medium. The results were evaluated for 12 hours. As per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7 and F-8 showed 55.50%, 72.71%, 96.52%, 99.22%, 98.48%, 99.68%, 99.37%, and78.15% release over a period of 12 hours. Formulation F-4, F-5, F-6, F-7 failed to sustain release beyond 10 hours. Among all the formulation, F-1, F-2, F-3 and F-4 showed 55.50%, 72.71%, 96.52% and 78.15% release at the end of 12 hours. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration.

Hence formulation F-3 were found to be most promising formulation as it showed sustained release (96.52%) as well as maintained excellent matrix integrity during the period of study (figure 7). Also all other parameters like hardness, thickness, friability, drug content and weight variation for these formulations were within the range. So, formulation F-3 were selected as the optimized formulations.

Figure:1. FTIR Spectroscopy of pure drug (Zidovudine)

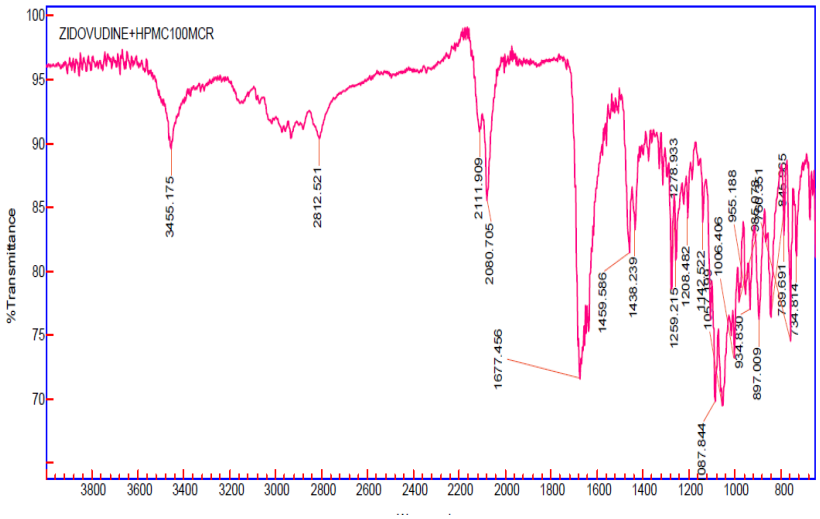

Figure:2. FTIR Spectroscopy of drug +HPMC 100MCR

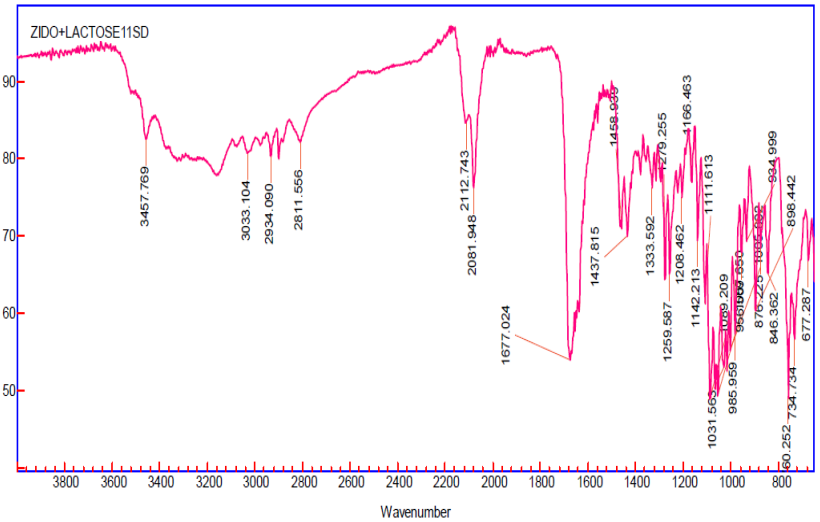

Figure:3. FTIR spectroscopy of drug+Lactose 11SD

Figure:4. FTIR spectroscopy of drug +Mcc101

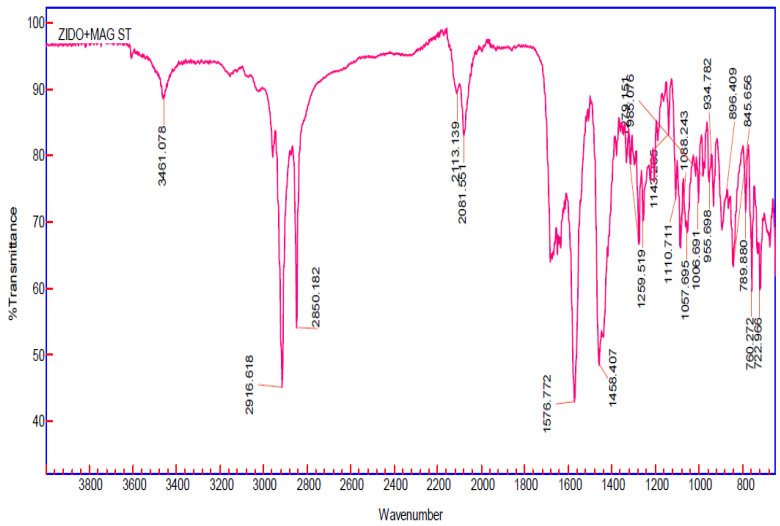

Figure:5. FTIR spectroscopy of drug + Magnesium sterate

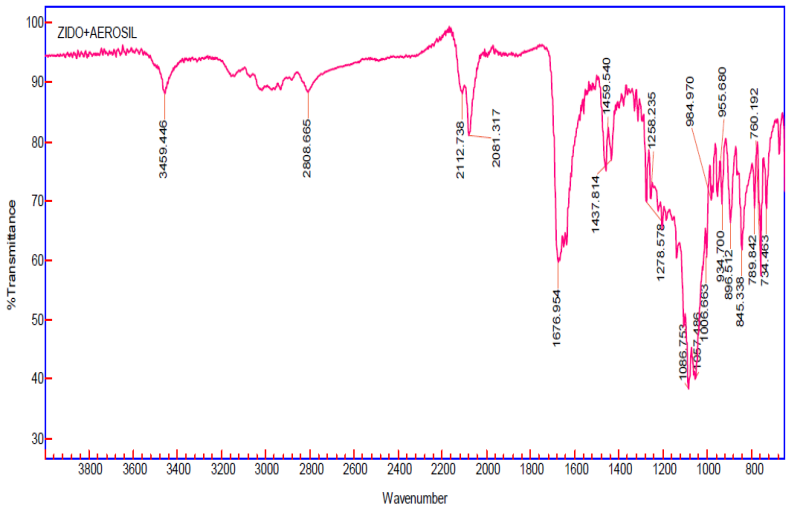

Figure:6.FTIR Spectroscopy of drug +Aerosil

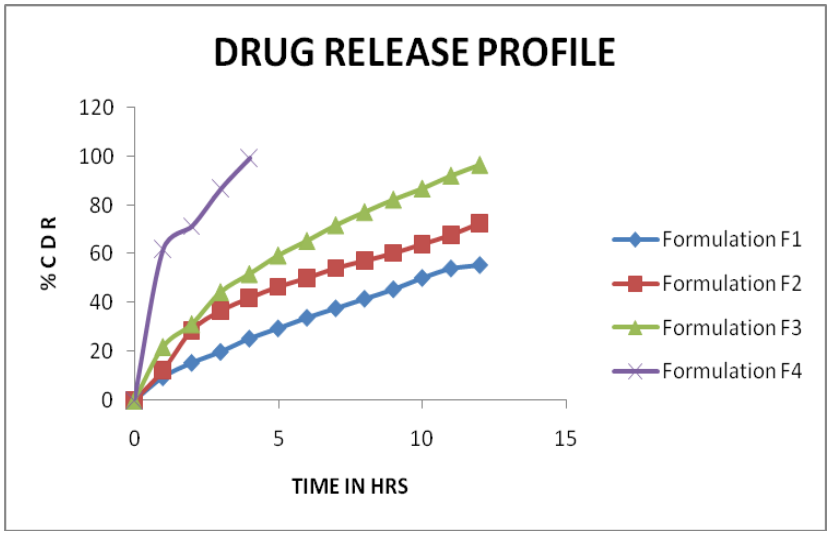

Figure:7. *In Vitro* Dissolution Profile of F-1 to F-4Formulations

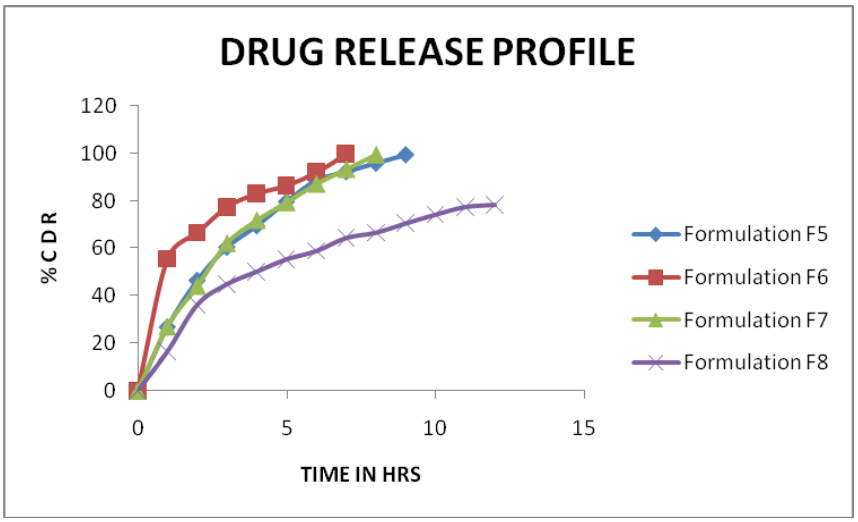

Figure:8. *In Vitro* Dissolution Profile of F-7 to F-8 Formulations

Determination of the release kinetics

Different models like Zero order, First order, Higuchi's, and Peppas plots were drawn. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, and Peppas plots (figure 19 and table 21) formulation F-3 were found to be 0.948, 0.938, 0.998, 0.996. The optimized formulations F-3 follows Higuchi's plot since the regression coefficient is 0.998 plot is also found to be linear, this confirms that the drug release through the matrix was diffusion.

CONCLUSION

In this study matrix tablet of zidovudine was prepared by dry granulation technique, using HPMC K-100M, and HPMC 100LV polymers as retardant. Use of hydrophobic polymer like

HPMC 100MCR was successful in the formulation of matrix retarding the drug release. The formulations F-3 showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release etc. were evaluated for these formulation. Based on these results formulation F-3 were found to be the most promising formulation. The optimized formulations F-3 follows Higuchi's plot since the regression coefficient is 0.996 plot is found to be linear, this confirms that the drug release through the matrix was diffusion. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 90 days which revealed the stability of the formulations. The results suggest that the developed controlled-release tablets of zidovudine could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of zidovudine in the management of HIV.

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