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Research

Formulation And In Vitro Evaluation of Controlled Release Matrix Tablets of Zidovudine

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Abstract

Objective: This study aimed to develop and evaluate controlled-release matrix tablets of Zidovudine, with the goal of extending the drug's release profile to enhance therapeutic efficacy and patient compliance.

Methods: Zidovudine matrix tablets were formulated using various polymers to achieve a controlled-release mechanism. The tablets were prepared through direct compression, and their physical properties—including hardness, friability, drug content, and weight uniformity—were assessed. In vitro dissolution studies were conducted under simulated gastrointestinal conditions to evaluate the release kinetics and determine the suitability of the matrix tablets for controlled drug delivery.

Results: The formulated matrix tablets exhibited satisfactory physical characteristics, including appropriate hardness and minimal friability. The in vitro dissolution studies revealed a prolonged and consistent release of Zidovudine, with the tablets demonstrating a controlled-release profile that effectively sustained drug release over an extended period. The release data indicated that the matrix tablets followed a controlled-release mechanism, with a steady drug release rate that met the desired therapeutic requirements.

Conclusion: The development of controlled-release matrix tablets for Zidovudine proved to be effective in providing a sustained release of the drug, potentially improving therapeutic efficacy and patient adherence by reducing dosing frequency. The results suggest that the matrix tablets are stable and capable of achieving the intended controlled-release profile.

Keywords: Zidovudine Controlled Release Tablets

INTRODUCTION

Tablets are one of the well-known and conventional oral solid dosage forms. First tablet was formulated by hand operated device in 1843. Tablets can be divided into various categories like core (uncoated), coated (sugar and film coating), dispersible, effervescent, chewable, sublingual, buccal, and modifies release tablets (delayed, prolonged sustained and controlled release tablets).[1]

0ver past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

Tablets are of two types, immediate & extended drug release tablets. Immediate release tablets release drugs directly after administration within 30 min and extended release tablets are further categorized as controlled and sustained release tablets. Drug release in a fixed rate for a specific time interval in controlled release tablets where as in sustained release tablets, there is no influence on drug release rate.[2] Controlled release tablets can be further classified delayed-release, prolonged release, site and receptor targeted release.[3]

The first oral controlled drug release delivery system was developed by Israel lipowski in 1938, who worked on coated pellets. The oral sustained release delivery system developed in 1940, and the development of controlled release system in 19505 . Drug delivery is generally influenced by disintegration and dissolution of matrix in which the active pharmaceutical ingredient is blended.[4]

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in 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. Sustained release constitutes any dosage form that provides medication over and extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that can not be considered controlled release system. In general, the goal of a sustained release dosage from is to maintain therapeutic blood or tissue levels of drug for an extended period this is usually accomplished by attempting to obtain zero-order release from the dosage form; zero-order release constitutes drug release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug is a slow first order fashion. In recent year sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. New and more sophisticated controlled release, sustained release delivery systems are constantly being developed and tested.

Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

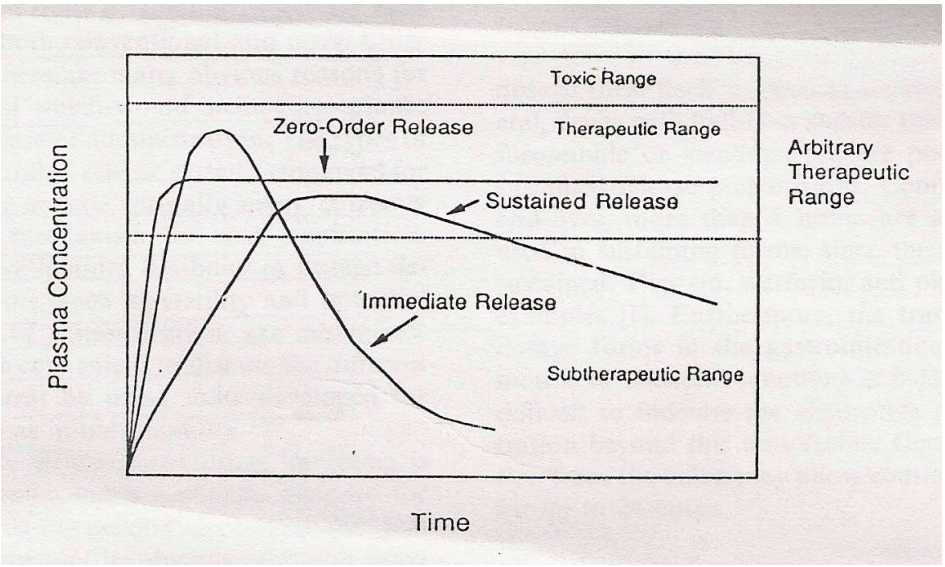

Fig 1: Drug level verses time profile showing differences between zero order, controlled release, slow first order sustained release and release from conventional tablet.

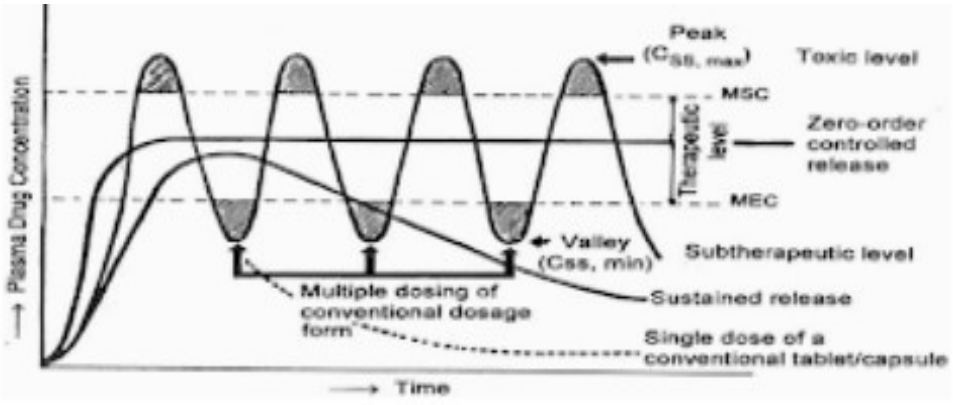

Fig 2: Hypothetical plasma concentration time profile from multiple conventional, sustained and controlled delivery formulation.

Controlled release systems release drugs at predetermined and predicted rate in a programmed mode and hence controls therapeutic level and maintains steady state concentration to specific site or receptor. [5]Controlled release tablet formulations offer various advantages such as better patient compliance, drug uniformity in blood, decrease overall dosing frequency, side effects, and enhance safety margin for highly potent medicaments. Among the different CRDDS systems, matrix based formulations are the preferred mostly because of convenient and cost-effective formulation process.[6]

Classifications of The Controlled Release Matrix Tablets It can be categorized into three types based on following parameters.

1. Void fraction
2. Polymer used
3. Miscellaneous ways

Void fraction

Macro-porous matrices

Drug diffusion takes place through pores of relatively larger size of 0.1–1.0 micrometer range. Matrix porous of the system is larger than diffusant dimension.

Macroporous matrices

are appropriate for drugs with < 200 angstrom molecular mass.

Non-porous matrices

Drug diffusion take place through the network meshes instead of pores as there are no pores available. Polymer used

i. Hydrophilic matrices
ii. Hydrophobic matrices
iii. Fat wax matrices
iv. Biodegradable matrices
v. Mineral matrices.[25]

MATERIALS

Zidovudine	Provided by SURA LABS, Dilsukhnagar, Hyderabad.
HPMC-K100	Merck Specialities Pvt Ltd, Mumbai, India
Sodium alginate	Merck Specialities Pvt Ltd, Mumbai, India
Xanthan gum	Merck Specialities Pvt Ltd, Mumbai, India
MCC	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India
Magnesium Stearate	Merck Specialities Pvt Ltd, Mumbai, India

Methodology

Determination of Zidovudine Melting point

The melting point of Zidovudine was determined by capillary tube method according to the USP. A sufficient quantity of Zidovudine powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Zidovudine in the tube passed into liquid phase**.**

Determination of Zidovudine Solubility

Determination of solubility of drug by visual observation, an excess quantity of Zidovudine was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

Tan θ = h / r

Tan θ = Angle of repose

h = Height of the cone,

r = Radius of the cone base

Table 1: Formulation composition for tablets

Formulation code	Zidovudine	Polymers	mg	Glidant	Lubricant	Diluent	Total weight
				Talc	Magnesium Stearate	Lactose	
F1	25	HPMC-K100	20	4	5	Q.S	140
F2	25		40	4	5	Q.S	140
F3	25		60	4	5	Q.S	140
F4	25	Sodium alginate	20	4	5	Q.S	140
F5	25		40	4	5	Q.S	140
F6	25		60	4	5	Q.S	140
F7	25	Xanthan gum	20	4	5	Q.S	140
F8	25		40	4	5	Q.S	140
F9	25		60	4	5	Q.S	140
All the quantities were in mg							

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400cm^{-1}.

Analytical Method

Graphs of Zidovudine were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 266 nm and 268 nm respectively.

Table 2: Observations for graph of Zidovudine in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.117
10	0.235
15	0.353
20	0.465
25	0.581

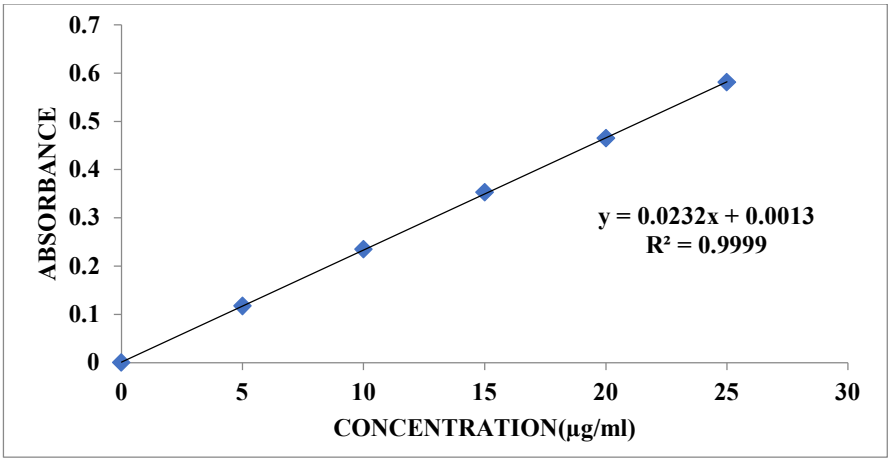

Fig 3: Standard curve of Zidovudine

Table 3: Standard graph values of Zidovudine at 268 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.112
10	0.234
15	0.347
20	0.461
25	0.583

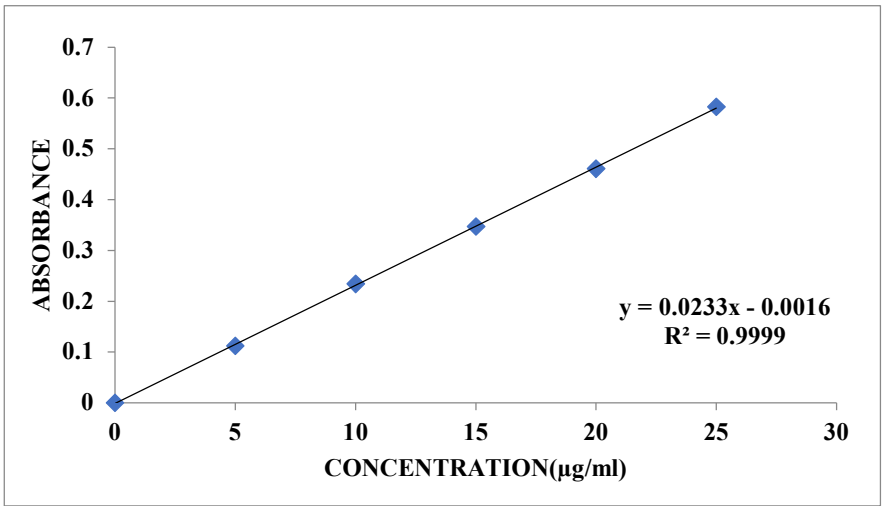

Fig 4: Standard curve of Zidovudine

Pre formulation parameters of powder blend

Table 4: Pre-formulation parameters of Core blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	24.29±0.32	0.526±0.006	0.572±0.005	8.04±0.021	1.08±0.07
F2	25.26±0.20	0.516±0.005	0.567±0.004	8.99±0.022	1.09±0.08
F3	23.76±0.10	0.490±0.003	0.565±0.004	13.27±0.031	1.15±0.10
F4	22.46±0.21	0.526±0.004	0.555±0.002	5.22±0.018	1.05±0.05
F5	21.58±0.15	0.500±0.002	0.553±0.002	9.58±0.024	1.10±0.10
F6	25.64±0.21	0.521±0.006	0.564±0.004	7.62±0.020	1.08±0.07
F7	22.84±0.62	0.513±0.006	0.575±0.007	10.78±0.026	1.12±0.10
F8	23.89±0.26	0.510±0.003	0.555±0.002	8.10±0.022	1.08±0.07
F9	23.62±0.12	0.517±0.004	0.564±0.004	8.33±0.021	1.09±0.08

All the values represent n=3

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 136.89 to 140.25 mg, so the permissible limit is ±7.5% (>140 mg). The results of the test showed that, the tablet weights were within limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 3.8 to 4.7 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 1.06 to 1.82 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 96.22 – 99.60 %.
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 5: Dissolution Data of Zidovudine Tablets

TIME (H)	CUMULATIVE % OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
In dissolution media 0.1 N HCL									
0	0	0	0	0	0	0	0	0	0
0.5	09.15	7.51	6.92	21.39	15.53	10.31	18.82	12.90	9.98
1	16.21	12.98	10.28	28.12	20.10	16.02	25.16	18.51	15.63
2	21.82	19.36	16.39	33.04	25.54	20.39	31.65	26.78	20.17
In dissolution media 6.8 Phosphate Buffer									
3	26.28	25.52	21.35	40.63	30.82	26.11	36.22	31.33	26.84
4	32.77	28.10	25.42	48.14	36.14	30.58	42.15	38.45	31.18
5	36.96	39.78	32.37	59.77	43.01	35.20	48.89	45.18	38.99
6	45.20	44.12	39.14	65.91	52.33	38.97	51.50	49.25	44.01
7	49.41	56.35	47.96	70.52	56.12	42.16	59.19	55.87	51.55

8	53.57	59.05	56.69	77.17	64.75	46.29	62.56	59.93	57.31
9	56.51	64.14	59.75	84.28	71.41	51.87	68.24	63.21	62.78
10	65.48	71.09	64.27	89.35	78.22	69.31	72.11	68.58	65.47
11	70.87	75.14	70.33	93.11	82.08	73.21	81.80	72.12	70.16
12	89.33	80.97	75.98	99.13	93.17	82.50	90.02	85.75	79.50

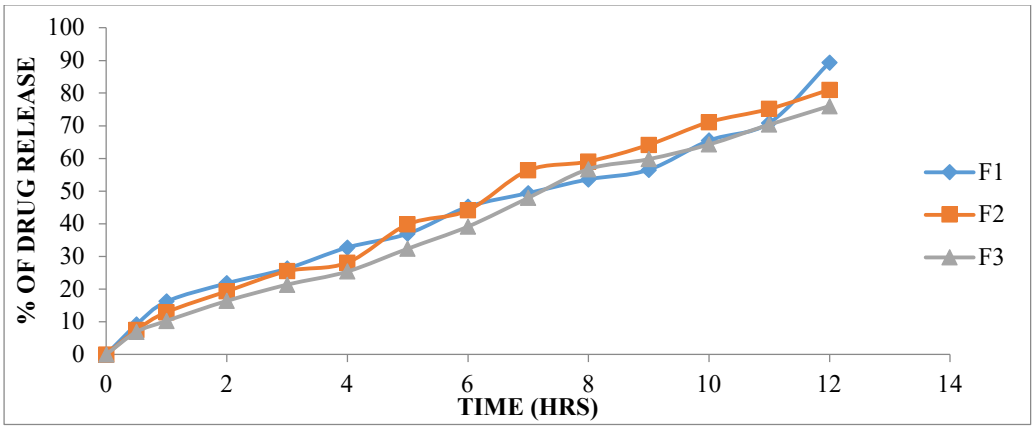

Fig 5: Dissolution profile of Zidovudine (F1, F2, F3 formulations)

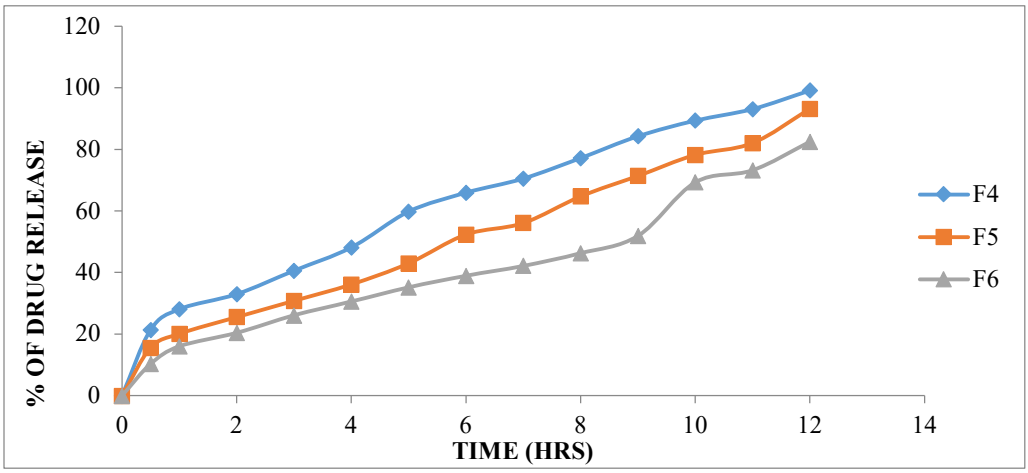

Fig 6: Dissolution profile of Zidovudine (F4, F5, F6 formulations)

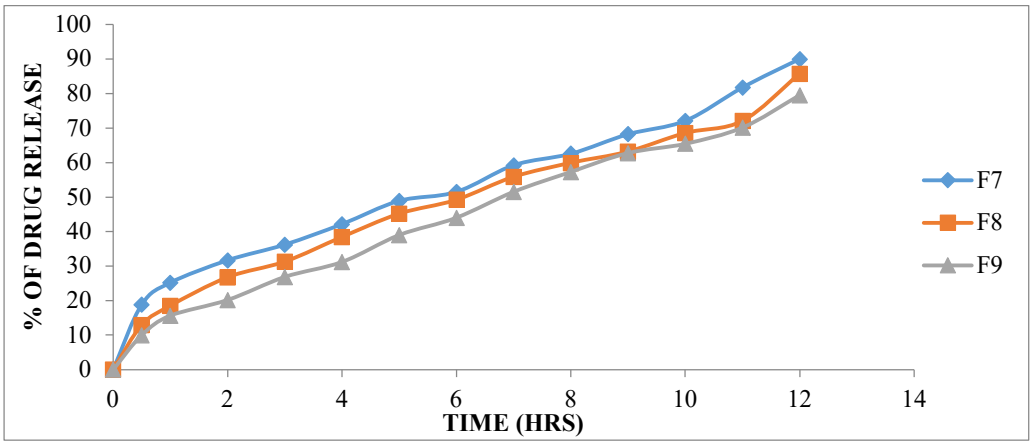

Fig 7: Dissolution profile of Zidovudine (F7, F8, F9 formulations)

Table 6: Release Kinetics

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE %	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
21.39	0.5	0.707	1.330	-0.301	1.895	42.780	0.0468	-0.670	78.61	4.642	4.284	0.358
28.12	1	1.000	1.449	0.000	1.857	28.120	0.0356	-0.551	71.88	4.642	4.158	0.484
33.04	2	1.414	1.519	0.301	1.826	16.520	0.0303	-0.481	66.96	4.642	4.061	0.581
40.63	3	1.732	1.609	0.477	1.774	13.543	0.0246	-0.391	59.37	4.642	3.901	0.740
48.14	4	2.000	1.683	0.602	1.715	12.035	0.0208	-0.317	51.86	4.642	3.729	0.912
59.77	5	2.236	1.776	0.699	1.605	11.954	0.0167	-0.268	40.23	4.642	3.426	1.215
65.91	6	2.449	1.819	0.778	1.533	10.985	0.0152	-0.181	34.09	4.642	3.242	1.399
70.52	7	2.646	1.848	0.845	1.470	10.074	0.0142	-0.152	29.48	4.642	3.089	1.552
77.17	8	2.828	1.887	0.903	1.359	9.646	0.0130	-0.113	22.83	4.642	2.837	1.805
84.28	9	3.000	1.926	0.954	1.196	9.364	0.0119	-0.074	15.72	4.642	2.505	2.137
89.35	10	3.162	1.951	1.000	1.027	8.935	0.0112	-0.049	10.65	4.642	2.200	2.441
93.11	11	3.317	1.969	1.041	0.838	8.465	0.0107	-0.031	6.89	4.642	1.903	2.739
99.13	12	3.464	1.996	1.079	-0.060	8.261	0.0101	-0.004	0.87	4.642	0.955	3.687

Optimised formulation F4 was kept for release kinetic studies. From the above graphs it was evident that the formulation F4 was followed Higuchi release kinetics mechanism.

Drug – Excipient Compatability studies

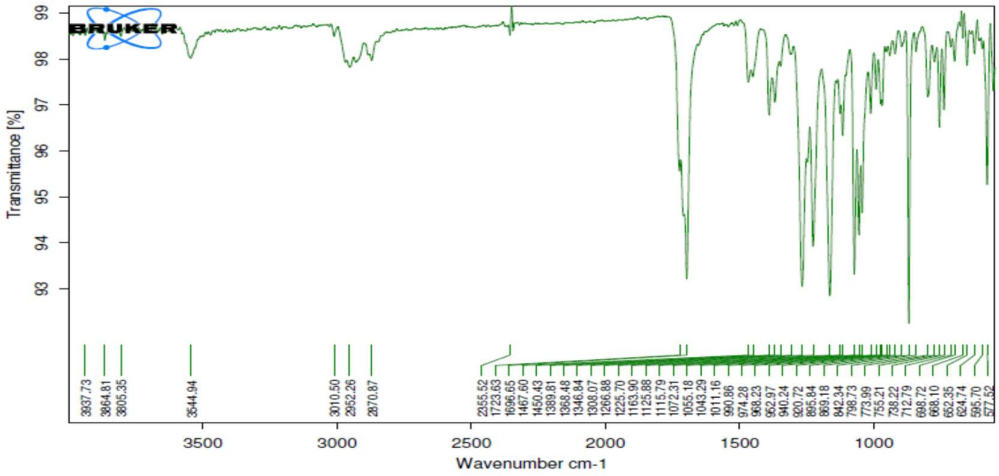

Fig 8: FT-TR Spectrum of Zidovudine pure drug

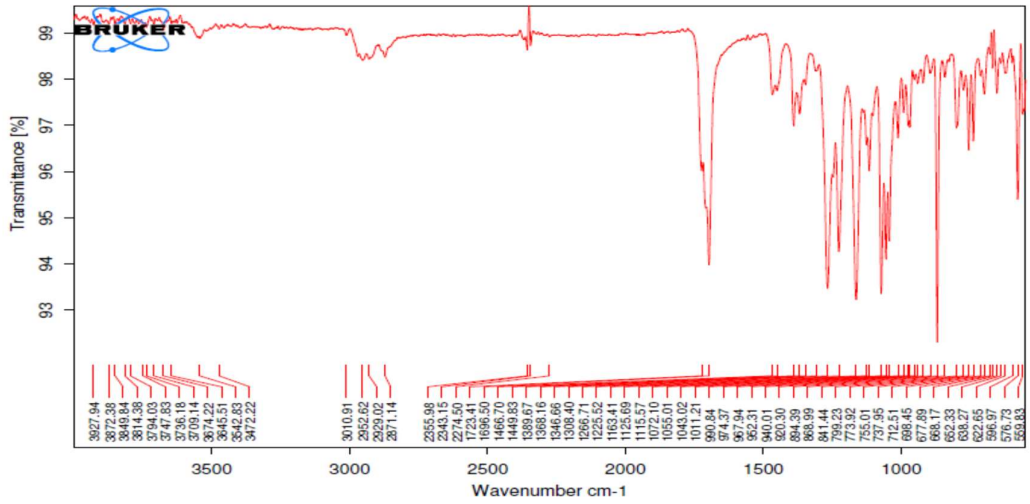

Fig 9: FT-IR Spectrum of Optimised Formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Zidovudine is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

The formulation and in vitro evaluation of controlled-release matrix tablets of Zidovudine have successfully demonstrated the potential to improve therapeutic outcomes by providing a sustained release of the drug over an extended period. The developed matrix tablets exhibited desirable physical properties, including adequate hardness, minimal friability, and uniform drug content. The in vitro release studies confirmed that the controlled-release matrix tablets effectively maintained a prolonged and consistent release of Zidovudine, aligning with the intended release profile. The release kinetics indicated that the tablets achieved the desired controlled-release behavior, which is crucial for optimizing therapeutic efficacy and enhancing patient compliance. Overall, the successful development and evaluation of these controlled-release matrix tablets highlight their potential to improve Zidovudine therapy by offering prolonged drug action and potentially reducing dosing frequency.

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