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DESIGN AND EVALUATION OF BILAYER & TRILAYER TABLET COMBINATION OF ANTIRETROVIRAL DRUGS

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Keywords:

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ABSTRACT: A non-nucleoside reverse transcriptase inhibitor (NNRTI) is Nevirapine. Zidovudine and Lamivudine are antiretroviral medications that are members of the nucleoside analogue class. Combination of three drugs commonly used in the management of the Human Immunodeficiency Virus (HIV) infection. Nevirapine exhibits a decent initial release, while Zidovudine and Lamivudine demonstrate sustained release in the produced trilayer and bilayer tablets. The outcome demonstrates that the release profile is not affected by layer separation and is highly dependent on the drug to polymer ratio. The results show that the release can be effectively controlled for up to 12 hours using a 1:1 ratio of zidovudine and HPMC and a 1:1 ratio of lamivudine and ethyl cellulose. It is clear that formulation F1, out of all formulations, has the best sustained release, drug content, and highest regression values. Nevirapine fits best in first order release of Zidovudine in all of the F1–F6 formulations.

INTRODUCTION: The outbreak of acquired immune deficiency syndrome is one of the biggest problems the medical profession is now confronting combinations of three medications that are frequently prescribed to treat HIV infections [1, 2]. Nevirapine is the first non-nucleoside reverse transcriptase inhibitor and a strong inhibitor of HIV-1 replication. Nevirapine has a long first-pass metabolism and a about 45-hour relative elimination half-life. With its wide range of applications in treating AIDS, Zidovudine (AZT), the first anti-HIV compound approved for clinical use, is soluble in water, soluble at all pH values, and absorbs throughout the gastrointestinal tract.

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For these reasons, sustained release tablets [3] are a better option than conventional dosage forms. A strong antiviral medication called lamivudine is used to treat AIDS [4]. A strong nucleoside analogue reverse transcriptase inhibitor is lamivudine. After oral consumption, lamivudine is quickly absorbed and has a bioavailability of more than 80%. Because lamivudine [5] has a moderate half-life of five to seven hours, it is delivered numerous times a day. Hydroxypropyl Methylcellulose is frequently utilised in controlled drug delivery systems that are hydrophilic. In controlled-release dosage formulations, ethyl cellulose has been widely employed as a release retardant because to its hydrophobic properties [6].

METHODS:

Preparation of Standard Curve: Nevirapine obeys Beer-Lambert's law, its spectrophotometric estimate of 312 nm can be obtained using 0.1 N HCL as a medium and falls between 5 and 25

µg/ml. Since zidovudine obeys Beer's-Lambert's law, its spectrophotometric estimate of 267 nm can be obtained using 0.1 N HCL as a medium [7] and a range of 5–25 µg/ml. Since lamivudine obeys Beer's-Lambert's law, its spectrophotometric estimation at 270 nm falls between 5 and 25 µg/ml when 0.1 N HCL is used as the medium.

Preparation of the Trilayer Tablets: The composition of Tri layer tablets of the different formulations was given in the **Table 1.**

Preparation of Nevirapine Immediate Release Layer: Nevirapine, super disintegrant, and excipients make up the instant release layer. One super disintegrant that was used was sodium starch glycolate. Excipients, super disintegrant, and the necessary quantity of medication were taken and mixed. Zidovudine sustained release layer preparation [2]. The polymer HPMC K100M was utilised to prepare the zidovudine sustained release layer. Zidovudine and HPMC E 15 LV are present in the formulations in the following ratios: 1:0.5,1:0.75, and 1:1. Using a 12 mm curved punch and the wet granulation process, the tablets were made.

Preparation of Lamivudine Sustained Release Layer: The polymer ethylene cellulose was used to create the lamivudine sustained release layer. Lamivudine and ethyl cellulose are present in the formulations in the following ratios: 1:0.5,1:0.75, and 1:1. The tablets were made utilising a 12 mm curved punch and the wet granulation process [5].

TABLE 1: COMPOSITION OF TRILAYER TABLETS

Composition	F1	F2	F3
	Immediate release layer Qty (mg)/tab		
Nevirapine	200	200	200
Sodium starch glycolate	20	20	20
Micro crystalline cellulose	20	245	132.5
	Sustained release layer Qty (mg)/tab		
Zidovudine	300	300	300
HPMC E 15 LV	300	150	225
	Sustained release layer Qty (mg)/tab		
Lamivudine	150	150	150
Ethyl cellulose	150	75	112.5

Preparation of the Bilayered Tablets: The composition of Bilayer tablets [8, 9] of the different formulations was given in the **Table 2.**

Preparation of Nevirapine Immediate Release Layer: Nevirapine, super disintegrant, and excipients make up the instant release layer. One super disintegrant that was used was sodium starch glycolate. Excipients, super disintegrant, and the necessary quantity of medication were taken and mixed.

Preparation of Zidovudine and Lamivudine Sustained Release Layer: Ethyl cellulose and the polymer HPMC E 15 LV were used to create the sustained release layer for zidovudine [3, 10, 11] and lamivudine [12, 13]. The formulations include the following ratios: 1:0.5, 1:0.75, and 1:1 for zidovudine and HPMC E 15 LV, and 1:0.5, 1:0.75, and 1:1 for lamivudine and ethyl cellulose. Using a 12 mm curved punch and the wet granulation process, the tablets were made.

TABLE 2: COMPOSITION OF BILAYER TABLETS

Composition	F4	F5	F6
	Immediate release layer Qty(mg)/tab		
Nevirapine	200	200	200
Sodium starch glycolate	20	20	20
Micro crystalline cellulose	20	245	132.5
Zidovudine	Sustained release layer Qty(mg)/tab		
	300	300	300
Lamivudine	150	150	150
HPMC E 15LV	300	150	225
Ethyl cellulose	150	75	112.5

***In-vitro* Drug Release Studies:**
Dissolution Parameters:

Medium: 0.1 N HCl (pH 1.2), Phosphate buffer pH 6.8

Apparatus: USP, XXIII-type 2 (Paddle) RPM 50

Temperature: 37o ±0.5°C

Volume: 900 ml

Procedure: Utilizing a USP dissolving paddle assembly at 50 rpm and 37 o ±0.5 °C, the release of nevirapine, zidovudine, and lamivudine from the trilayer and bilayer tablets was investigated for up to two hours in 900 ml of 0.1 N HCl and 900 ml of phosphate buffer pH 6.8 for up to twelve hours as the dissolution medium. Using a UV Visible spectrophotometer set to 312 nm, 267 nm, and 270 nm, the drug content of nevirapine, zidovudine, and lamivudine was measured after an aliquot (1 ml) was extracted at predetermined intervals and diluted to 10 ml with the dissolving media.

To maintain the dissolution volume, an equivalent volume of new dissolving medium was added. For duration of 12 hours, three dissolution investigations were conducted, and the mean value was determined [14, 15].

Statistical Analysis: The Tucky post test and one-way analysis of variance (ANOVA) were used to statistically evaluate the various attributes of the formulations. Version 3.0.1 of the GraphPad Instat programme was used for this. The threshold for statistical significance was set at $p < 0.05$.

Kinetic Analysis of *In-vitro* Release Rates of Formulations: The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero-order kinetic model-cumulative percentage drug release versus time.
2. First- order kinetic model-log cumulative percentage drug release remaining versus time.
3. Higuchi's model-cumulative percentage drug released versus square root of time.
4. Korsmeyer's equation/peppa's model-log cumulative percentage drug released versus log time.

TABLE 3: MECHANISM OF DRUG RELEASE AS PER KORSEMEYER EQUATION/PEPPA'S MODEL

S. no.	n Value	Drug release
1.	n < 0.5	Fickian release
2.	0.5<n<1	Non- Fickian release
3.	n>1	Case II transport

RESULTS: Nevirapine dissolves in two hours in all formulations because sodium starch glycolate, a super disintegrant, is present. In contrast, Zidovudine and Lamivudine showed drug release for up to twelve hours in Formulations F1 and F4, ten hours in Formulations F2 and F5, and eight hours in Formulations F3 and F6. The findings imply that the ratio of medication to polymer has a more significant impact on zidovudine and lamivudine release patterns. Compared to formulations generated with ratios of 1:0.75 and 1:0.5, it was noted that the formulation developed with the drug and polymer ratio of 1:1 could control the release for up to 12 hours. The release data is not significantly affected by the layer separation; that is, the release patterns of formulations with trilayer and billayers do not differ significantly. Nevirapine fits best in first order release in all six formulations, while Lamivudine and Zidovudine fit best in zero order models. Every formulation follows a non-fickian release process, depending on the values of 'n'.

TABLE 4: COMPARATIVE *IN-VITRO* DRUG RELEASE OF ALL TABLET FORMULATIONS OF NEVIRAPINE

Time (min)	Cumulative % drug release*					
	Trilayer tablets			Bilayer tablets		
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	15.8±0.503	15.7±0.381	15.7±0.506	15.8±0.247	16.2±0.384	14.9±0.276
10	22.6±0.452	24.03±0.457	23.98±0.478	22.6±0.368	25.4±0.353	21.7±0.358
15	31.8±0.635	32.1±0.483	32.2±0.354	31.8±0.542	33.6±0.471	30.2±0.471
20	36.5±0.709	38.2±0.741	38.02±0.627	36.5±0.471	37.7±0.236	37.8±0.337
25	50.9±0.298	51.3±0.693	51.75±0.581	50.9±0.352	50.9±0.308	50.6±0.219
30	63.2±0.364	63.9±0.634	64.4±0.568	63.2±0.624	64.4±0.516	63.9±0.541
60	89.8±0.578	91.8±0.563	91.5±0.298	89.8±0.293	88.9±0.483	90.2±0.493
120	96.2±0.681	98.5±0.492	98.1±0.386	96.2±0.558	96.6±0.425	97.7±0.338

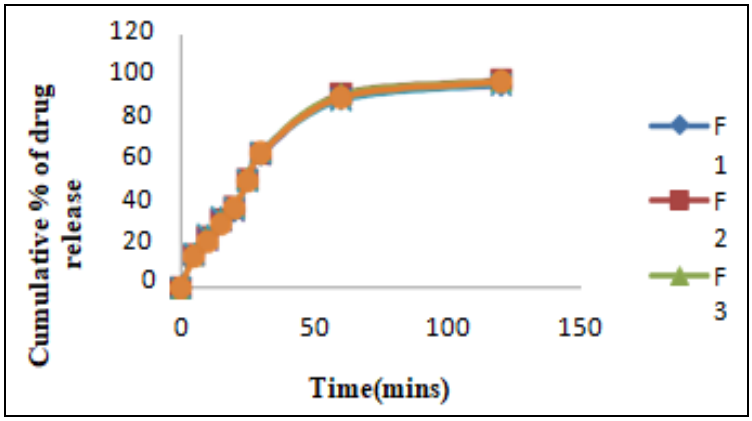

FIG. 1: COMPARATIVE *IN-VITRO* DRUG RELEASE OF NEVIRAPINE IN ALL FORMULATION

TABLE 5: COMPARATIVE *IN-VITRO* DRUG RELEASE OF ALL TABLET FORMULATIONS ZIDOVUDINE

Time (min)	Cumulative % drug release*					
	Trilayer tablets			Bilayer tablets		
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	9.75±0.324	24.7±0.458	19.2±0.483	8.3±0.568	19.3±0.365	18.9±0.412
60	14.7±0.275	29.2±0.412	26.3±0.524	12.6±0.625	28.4±0.427	25.6±0.353
120	22.8±0.549	38.4±0.397	34.4±0.611	19.4±0.422	36.6±0.526	33.2±0.473
180	25.23±0.693	46.9±0.648	43.9±0.435	22.1±0.584	44.7±0.378	42.4±0.246
240	35.1±0.334	57.3±0.593	49.8±0.371	30.4±0.345	55.9±0.609	48.5±0.546
300	41.4±0.451	68.2±0.486	57.2±0.374	38.9±0.298	67.4±0.458	56.6±0.492
360	49.95±0.634	79.1±0.651	65.5±0.528	43.16±0.414	75.6±0.381	64.9±0.587
420	59.4±0.368	91.5±0.495	74.9±0.487	54.4±0.526	87.2±0.435	73.8±0.237
480	63.0±0.695	98.6±0.527	86.8±0.249	61.3±0.418	95.9±0.548	84.3±0.534
540	72.6±0.582	-	94.9±0.584	69.1±.352	-	92.6±0.341
600	88.9±0.483	-	99.2±0.499	82.2±0.715	-	97.1±0.468
720	97.8±0.327	-	-	93.4±0.341	-	-

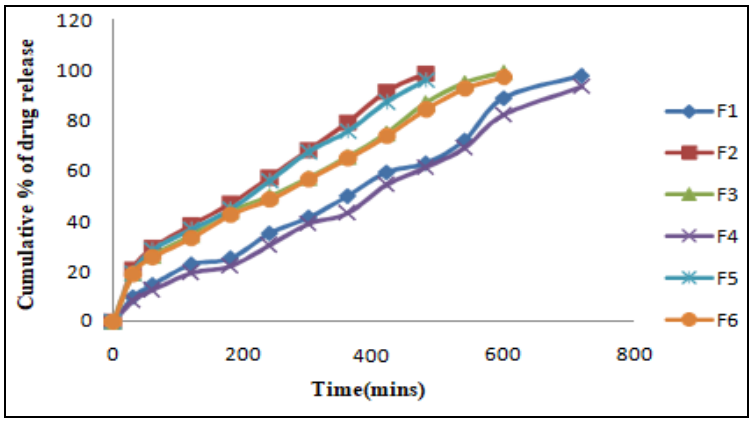

FIG. 2: COMPARATIVE *IN-VITRO* DRUG RELEASE OF ZIDOVUDINE IN ALL FORMULATIONS

TABLE 6: COMPARATIVE *IN-VITRO* DRUG RELEASE OF ALL TABLET FORMULATIONS OF LAMIVUDINE

Time (min)	Cumulative % drug release*					
	Trilayer tablets			Bilayer tablets		
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	9.42±0.523	19.1±0.608	16.5±0.654	8.63±0.482	17.7±0.512	14.7±0.356
60	16.02±0.435	26.4±0.522	24.4±0.598	14.5±0.367	24.9±0.385	22.5±0.415
120	21.48±0.655	37.5±0.443	35.2±0.556	19.3±0.571	35.6±0.426	31.2±0.289
180	30.54±0.543	48.2±0.652	44.1±0.485	26.6±0.384	46.8±0.605	42.4±0.368
240	33.12±0.364	59.3±0.418	56.4±0.394	30.15±0.626	57.3±0.391	54.4±0.347
300	44.4±0.705	66.4±0.396	63.8±0.582	38.2±0.384	64.6±0.545	62.6±0.536

360	48.6±0.234	78.9±0.354	69.2±0.478	46.4±0.275	77.1±0.264	68.3±0.604
420	64.2±0.421	90.3±0.451	77.4±0.346	59.1±0.537	88.4±0.453	76.5±0.528
480	72.0±0.554	98.1±0.624	86.8±0.482	68.3±0.498	96.9±0.492	85.9±0.409
540	81.0±0.604	-	93.2±0.634	78.9±0.476	-	92.7±0.391
600	92.4±0.452	-	98.9±0.621	89.2±0.348	-	96.9±0.452
720	99.0±0.414	-	-	96.2±0.417	-	

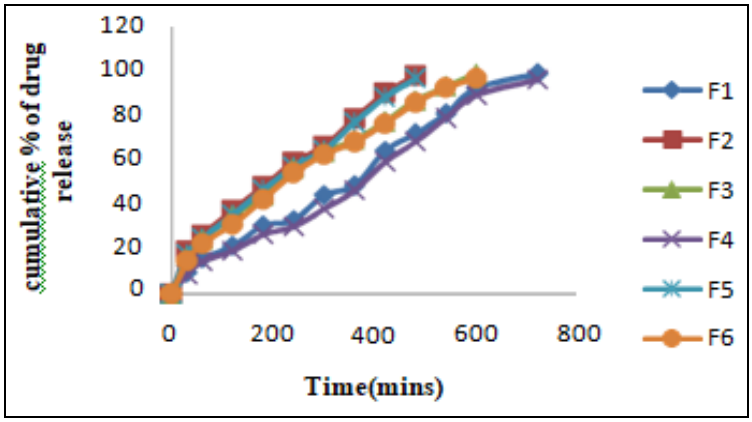

FIG. 3: COMPARATIVE IN-VITRO DRUG RELEASE OF LAMIVUDINE IN ALL FORMULATIONS

TABLE 7: KINETIC VALUES OF NEVIRAPINE IN ALL FORMULATIONS

Formulation Code	Zero order plot	First order plot
	R^2	R^2
F1	0.797	0.993
F2	0.792	0.985
F3	0.792	0.991
F4	0.786	0.962
F5	0.785	0.976
F6	0.791	0.982

TABLE 8: KINETIC VALUES OF ZIDOVUDINE IN ALL FORMULATIONS

Formulation Code	Zero order plot	First order plot	Higuchi's plot	Koresmeyer- Peppa's plot		Mechanism of drug release
	R^2	R^2	R^2	n	R^2	
F1	0.992	0.770	0.924	0.684	0.991	Non-Fickian release
F2	0.976	0.801	0.970	0.709	0.973	Non-Fickian release
F3	0.977	0.857	0.971	0.687	0.983	Non-Fickian release
F4	0.990	0.849	0.913	0.687	0.979	Non-Fickian release
F5	0.972	0.874	0.974	0.713	0.985	Non-Fickian release
F6	0.979	0.882	0.972	0.684	0.983	Non-Fickian release

TABLE 9: KINETIC VALUES OF LAMIVUDINE IN ALL FORMULATIONS

Formulation code	Zero order plot	First order plot	Higuchi's plot	Koresmeyer-Peppa's plot		Mechanism of drug release
	R^2	R^2	R^2	n	R^2	
F1	0.988	0.773	0.927	0.696	0.990	Non-Fickian release
F2	0.979	0.827	0.978	0.721	0.989	Non-Fickian release
F3	0.971	0.821	0.992	0.701	0.992	Non-Fickian release
F4	0.987	0.847	0.910	0.691	0.984	Non-Fickian release
F5	0.983	0.855	0.974	0.720	0.992	Non-Fickian release
F6	0.976	0.905	0.983	0.705	0.996	Non-Fickian release

CONCLUSION: Nevirapine exhibits a decent initial release, while Zidovudine and Lamivudine demonstrate sustained release in the produced trilayer and bilayer tablets. The drug to polymer ratio has a significant impact on the release profile, which is not affected by layer separation. This suggests that the release can be effectively controlled for up to 12 hours using a 1:1 ratio of

zidovudine and HPMC and a 1:1 ratio of lamivudine and ethyl cellulose. It is clear that Formulation F1 is the best formulation out of all of them due to its higher regression values, higher drug content, and better sustained release. It is clear that the bilayer and trilayer tablets containing zidovudine, lamivudine, and nevirapine are a viable alternative to the traditional dose form. Nevirapine fits best in first order release in all of the F1–F6 formulations, while Lamivudine and Zidovudine fit best in the zero order model. Every formulation follows a non-fickian release process based on the values of 'n'.

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