FORMULATION AND EVALUATION OF BILAYER TABLETS OF TENOFOVIR DISOPROXIL FUMARATE AND LAMIVUDINE

P. Rama Krishna Reddy[1]*, Dr. Pankaj Kumar Sharma[2], Dr. Jaya Sharma[2] and B. Chandana[3]

[1]Research Scholar- Pacific University, Pacific Hills, Pratapnagar Extn., Airport Road, Debari, Udaipur – 313003.
[2]School of Pharmaceutical Sciences, Jaipur National University, Jaipur.
[3]Assistant Professor, Tirumala College of Pharmacy, Tirumala Nagar, Bardipur (V), Dichpally (M), Dist. Nizamabad-503 230. Telangana.

*Corresponding Author: P. Rama Krishna Reddy

Research Scholar- Pacific University, Pacific Hills, Pratapnagar Extn., Airport Road, Debari, Udaipur - 313003.

ABSTRACT
The present study was carried out for developing the formulation of Bilayer tablets of Tenofovir, Lamivudine. SR16 contain HPMC K100M (Hydrophyllic Polymer) and Ethyl Cellulose (Hydrophobic Polymer). Formulations containing Eudragit S100 and Eudragit L100 not retard the drug release 24 hours hence those formulations did not take into consideration. SR16 formulation was shown best drug release (97.86%) within 24 hours. Finally Concluded that SR16 formulation was optimised formulation. SR16 which follows zero order release kinetics.

KEYWORDS: Lamivudine, Bilayer tablets.

INTRODUCTION

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Bi -layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi -layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity.

On the basis of these considerations, we have proposed a bilayer tablet, in which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is an controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer. Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredients (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property), to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery. Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the

development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers. However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. Therefore, the major problem, that has to be overcome, is to understand in detail the sources of these problems in micro-and macroscales and to develop remedies to solve them during solid dosage delivery design.

Homogenous type
Bilayer tablets are preferred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, wither as second dose or in an extended release manner.
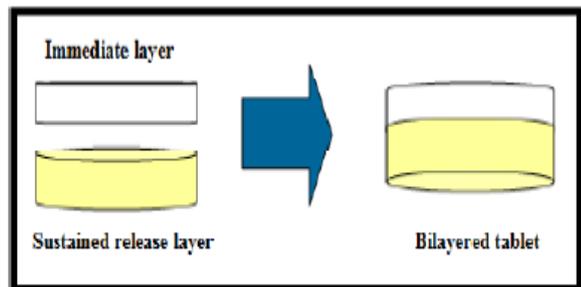

Fig.1 Bilayered tablets (same drug with different release pattern-homogenous).

Heterogenous type
Bilayer tablet is suitable for sequential release of two drugs in combination, separate two compatible substances.
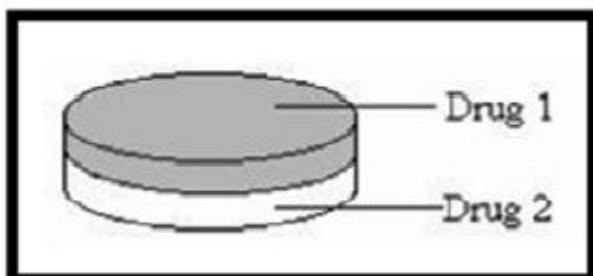

Fig.2: Bilayered tablets (with two different drugs-heterogenous).

Types of bilayer tablet press
1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.

Single sided press[7]
The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Fig: 3 Single sided tablet press.

Limitations of the single sided press[8,9,10]
1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.
3. Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
4. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

2. Double sided tablet press[7]
In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

3. Bilayer tablet press with displacement monitoring: The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

Fig 4: double sided tablet press.

Advantages
1. Weight monitoring / control for accurate and independent weight control of the individual layers.
2. Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
3. Independence from the machine stiffness.
4. Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
5. Maximum prevention of cross-contamination between the two layers.

6. Clear visual separation between the two layers and maximized yield.

PREPARATION OF BILAYER TABLETS[11, 12, 13, 14]
Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form.[8] The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included. To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression: it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation: it is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on layer 1 was found to be major factor influencing tablet delamination.
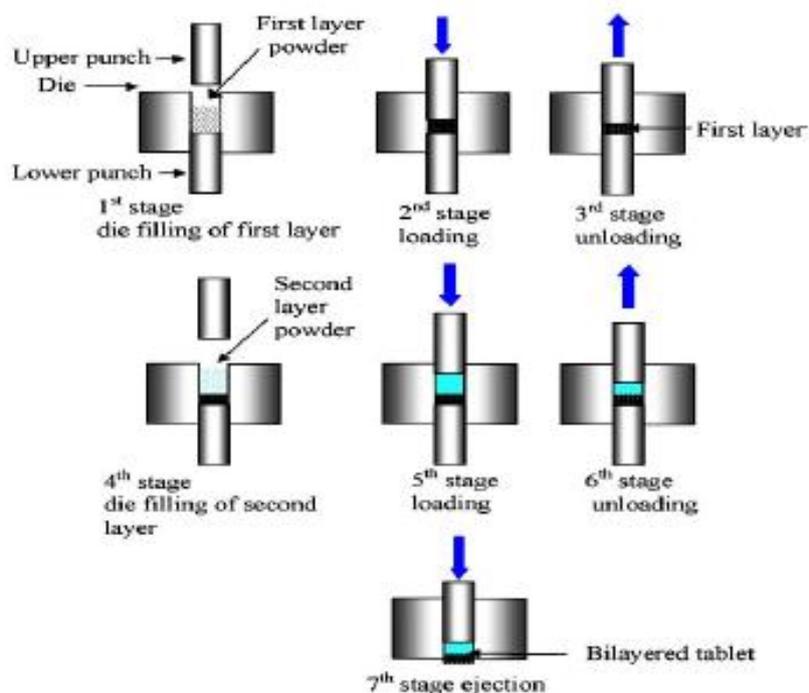

Fig 5: Preparation of bilayer tablet Compaction.

QUALITY AND GMP-REQUIREMENTS[11]

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the Selected press is capable of:[5]

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers.
5. High yield Accurate and individual weight control of the two layers.

These requirements seem obvious but are not so easily accomplished.

AIM AND OBJECTIVES

AIM

The aim of the study is to formulate and evaluate bilayer tablets of Anti Ritroviral Drugs.

OBJECTIVES

- To develop a pharmaceutically equivalent stable, cost effective and quality improved formulation of bilayered tablets and to compare with that of the Marketed dosage form.
- To delay disease progression.
- To increase the duration of survival by achieving maximal and prolonged suppression of HIV replication.
- To restorate and preserve immunological function.
- Combination therapy is more effective and has less chances of developing resistance than immunotherapy.

PLAN OF WORK

1. Literature Survey.
2. Selection and Procurement of suitable Drug candidate and Excipients.
3. Preparation of standard graph of Tenofovir Disoproxil Fumarate And Lamivudine in 0.1 n hcl.
4. Drug and Excipient compatibility studies using FTIR
5. Formulation of floating tablets of Tenofovir Disoproxil Fumarate And Lamivudine.
6. Optimisation of sodium bicarbonate Concentration.
7. Formulation development of Tenofovir Disoproxil Fumarate And Lamivudine floating tablets using polymers.
8. Precompression studies of Formulation blend of.
A. Angle of repose.
B. Bulk density.
C. Tapped density.
D. Carr's index.
E. Hausner's ratio.
7. Preparation of the Floating tablets of Tenofovir Disoproxil Fumarate And Lamivudine.
8. Post Compression Evaluation of prepared floating tablets of Tenofovir Disoproxil Fumarate and Lamivudine.

A. Weight variation.
B. Tablet Thickness.
C. Tablet Hardness.
D. Friability.
E. Assay.
F. *In-vitro* buoyancy studies.
i. Floating lag time.
ii. Total Floating time.
G. *In vitro* release studies.
9. Selection of optimised formulation.
10. Kinetic analysis of Optimised dissolution data.

RESULTS AND DISCUSSION

Analytical Method

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 278 nm.

b. calibration curve

Graphs of Cefpodoxime proxetil was taken in 0.1N HCL (pH 1.2).

Table: 1 Standard graph values of Lamivudine in 0.1N HCL.

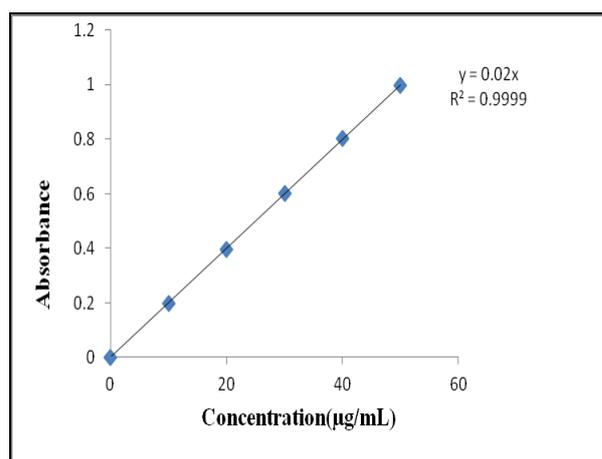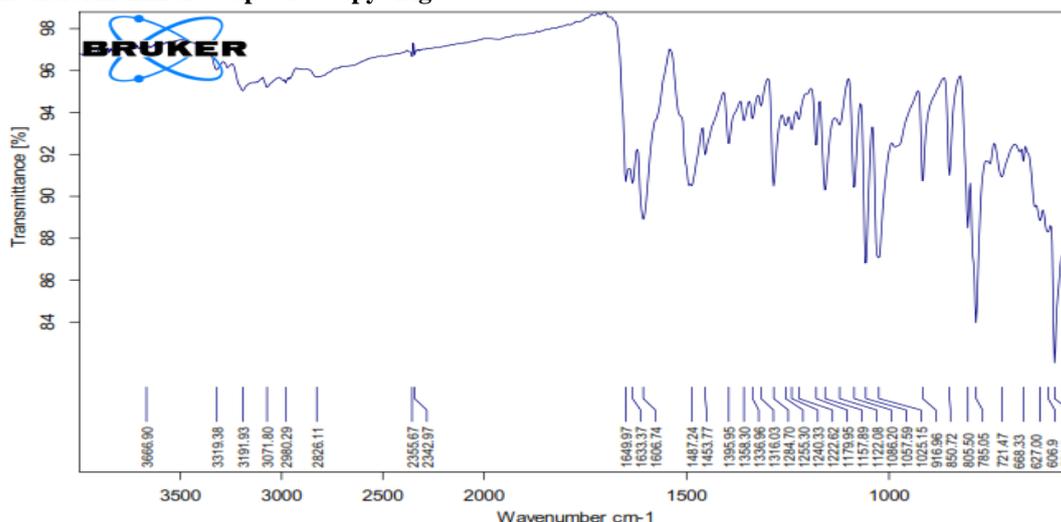| S.No	Concentration (µg/mL)	Absorbance
1	0	0
2	10	0.198
3	20	0.396
4	30	0.601
5	40	0.804
6	50	0.998

$y = 0.02x$
$R^2 = 0.9999$

Fig: 6 Standard graph of Lamivudine in 0.1N HCL.

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy: Fig 7

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.

Cefpodoxime proxetil 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.

Preformulation parameters of powder blend
Preformulation parameters of powder blend for Sustained Layer
Table: 2 Pre-formulation parameters of blend.

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
SR1	27.67	0.429	0.546	23.93	1.272
SR2	24.19	0.547	0.624	12.33	1.140
SR3	24.70	0.462	0.591	21.82	1.279
SR4	24.70	0.519	0.683	13.46	1.315
SR5	22.67	0.395	0.475	20.25	1.202
SR6	21.12	0.409	0.531	22.97	1.298
SR7	23.98	0.549	0.626	12.30	1.140
SR8	25.73	0.60	0.69	13.04	1.28
SR9	27.51	0.63	0.74	14.86	1.17
SR10	29.82	0.62	0.72	13.88	1.16
SR11	27.32	0.59	0.70	15.71	1.18
SR12	26.84	0.57	0.71	19.71	1.22
SR13	25.36	0.59	0.74	20.27	1.25
SR14	29.34	0.55	0.67	17.91	1.21
SR15	27.13	0.61	0.70	12.85	1.14
SR16	26.84	0.54	0.68	20.58	1.25
SR17	27.91	0.57	0.68	16.17	1.19
SR18	28.23	0.61	0.69	11.59	1.13
SR19	29.34	0.60	0.70	14.28	1.16
SR20	26.71	0.61	0.75	18.66	1.22
SR21	29.34	0.60	0.73	17.80	1.21
SR22	28.23	0.58	0.69	15.94	1.18
SR23	29.34	0.63	0.74	14.86	1.17
SR24	26.78	0.62	0.72	13.88	1.16
SR25	26.78	0.64	0.75	14.66	1.17
SR26	27.91	0.57	0.70	18.57	1.22
SR27	28.23	0.66	0.77	14.28	1.16

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48 to 0.59 (gm/cm³) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 to 0.66 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Table: 3 *In- vitro* quality control parameters for Bi layer tablets.

Formulation code	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
BT1	798.4	5.1	0.61	5.3	98.42
BT2	799.2	5.2	0.58	5.2	99.65
BT3	501.3	5.5	0.45	5.4	99.12
BT4	796.3	5.1	0.61	5.3	98.42
BT5	798.6	5.3	0.59	5.5	99.65
BT6	802.4	5.5	0.65	5.4	99.12
BT7	800.6	5.3	0.62	5.6	98.16
BT8	801.2	5.2	0.59	5.4	98.11
BT9	802.8	5.9	0.34	5.2	99.45
BT10	801.9	5.3	0.26	5.0	99.86
BT11	801.6	5.2	0.29	5.1	99.73
BT12	799.9	5.4	0.45	5.4	99.92
BT13	798.2	5.5	0.87	5.5	99.85
BT14	797.9	5.6	0.65	5.7	99.55
BT15	796.9	5.9	0.47	5.9	99.45
BT16	799.9	5.6	0.58	5.8	99.75
BT17	796.9	5.2	0.69	5.6	99.95
BT18	800.8	5.5	0.73	5.7	99.85
BT19	800.7	5.3	0.87	5.5	99.35
BT20	800.5	5.2	0.59	5.9	99.63
BT21	798.6	5.3	0.65	5.3	99.65
BT22	798.7	5.1	0.85	5.2	99.85
BT23	799.9	5.4	0.75	5.4	99.78
BT24	799.4	5.7	0.65	5.5	99.38
BT25	799.8	5.5	0.78	5.7	99.65
BT26	799.7	5.6	0.53	5.9	99.45
BT27	799.1	5.7	0.69	5.8	99.31

All the parameters for bi layer tablets such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

In Vitro **Drug Release Studies**
Table: 4 Dissolution data of Bilayer Tablets.

Time (Min)	SR 1	SR 2	SR 3	SR 4	SR 5	SR 6	SR 7	SR 8	SR 9
0	0	0	0	0	0	0	0	0	0
30 (0.5hr)	11.66	24.31	14.31	11.89	36.64	17.45	12.45	18.19	13.48
60 (1 hr)	24.64	48.31	27.56	21.31	41.12	35.48	35.43	39.91	38.49
120 (2 hr)	31.60	63.48	48.64	36.35	55.31	46.48	42.38	49.89	43.81
180 (3 hr)	47.37	88.61	59.49	48.26	73.83	68.86	51.43	58.74	52.24
240 (4 hr)	54.76	98.15	81.31	62.18	81.67	79.46	58.34	68.26	66.37
300 (5 hr)	78.48		99.41	78.48	99.24	89.84	66.91	76.84	72.41
360	99.82			94.34		98.86	71.28	88.84	82.64

(6 hr)								
420 (7 hr)			98.89			77.47	99.76	89.48
480 (8 hr)						83.64		98.46
540 (9 hr)						97.37		
600 (10 hr)								
660 (11 hr)								
720 (12 hr)								
960 (16 hr)								
1200 (20 hr)								
1440 (24 hr)								
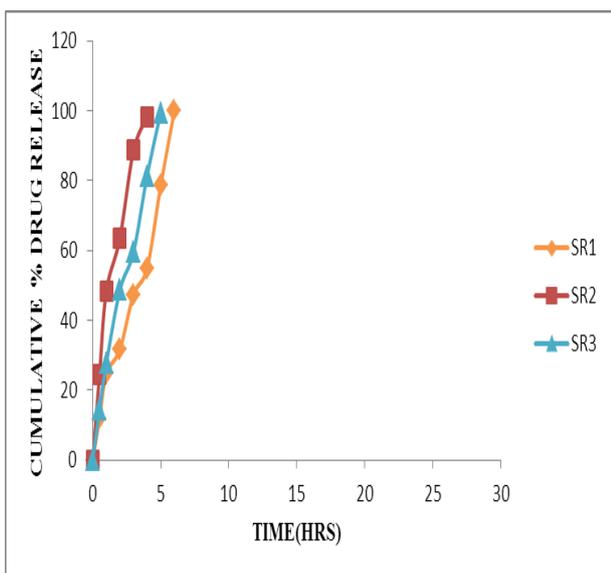
Fig: 8 Dissolution data of Lamivudine from 1 -3.
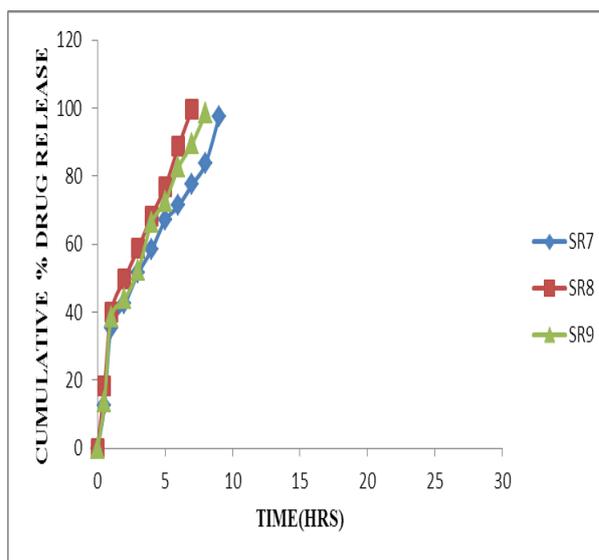
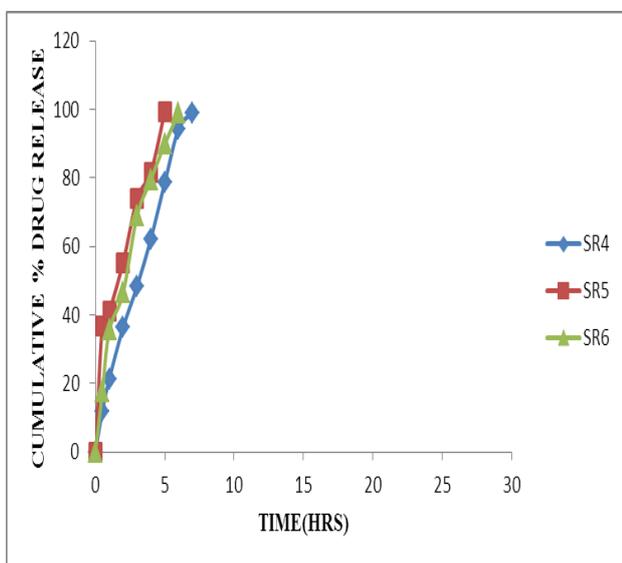**Fig: 10 Dissolution data of Lamivudine from 7-9.**

Fig: 9 Dissolution data of Lamivudine from 4-6.

Table: 5 Dissolution data of Bilayer Tablets using Hydrophillic and Hydrophobic polymers.

| Time (Min)	SR 10	SR 11	SR 12	SR 13	SR 14	SR 15	SR 16	SR 17	SR 18
0	0	0	0	0	0	0	0	0	0
30 (0.5hr)	19.29	9.65	13.26	16.31	29.06	17.51	7.79	39.10	15.18
60 (1 hr)	34.01	29.37	26.72	26.70	53.81	30.69	12.41	50.77	30.74
120 (2 hr)	49.67	34.63	51.95	39.26	64.26	39.66	17.65	62.87	45.83
180 (3 hr)	64.39	50.67	66.33	42.77	74.40	47.86	23.65	74.10	49.6
240 (4 hr)	71.96	71.34	83.94	49.67	82.14	57.64	29.90	80.15	59.62
300 (5 hr)	79.70	82.18	85.97	52.54	85.08	63.92	37.48	85.76	61.03
360 (6 hr)	84.60	98.51	96.43	55.72	88.31	76.13	42.81	90.30	65.63
420 (7 hr)	92.05		99.30	63.86	94.67	80.67	44.85	94.41	70.39
480 (8 hr)	95.71			77.70	98.04	91.92	52.44	95.05	77.91
540 (9 hr)	98.29			82.53		93.85	63.18	95.92	81.93
600 (10 hr)				88.16		96.32	74.50	96.35	84.68
660 (11 hr)				95.71		97.59	79.33		90.71
720 (12 hr)				97.38			83.67		94.11
960 (16 hr)							87.66		96.57
1200 (20 hr)							92.37		
1440 (24 hr)							97.86		
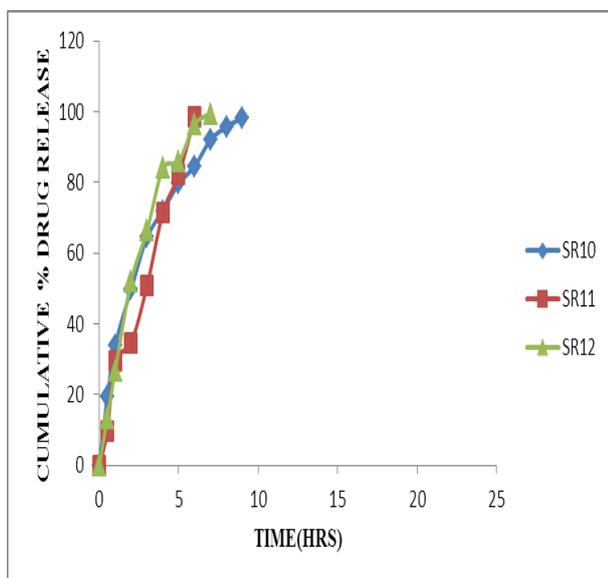
Fig: 11 Dissolution data of Lamivudine from 10-12.
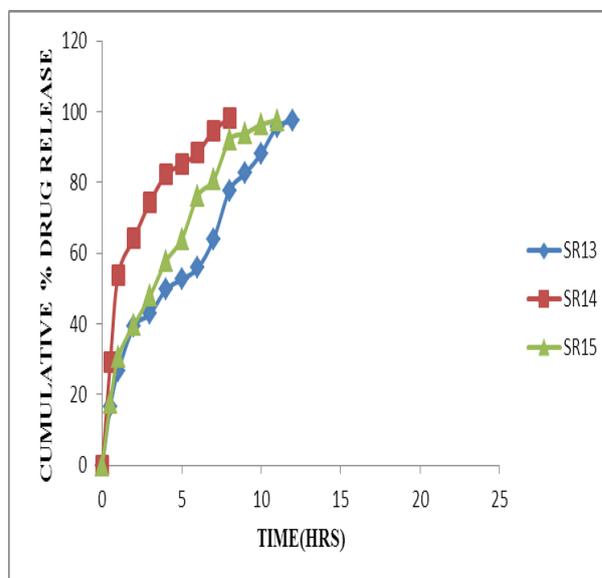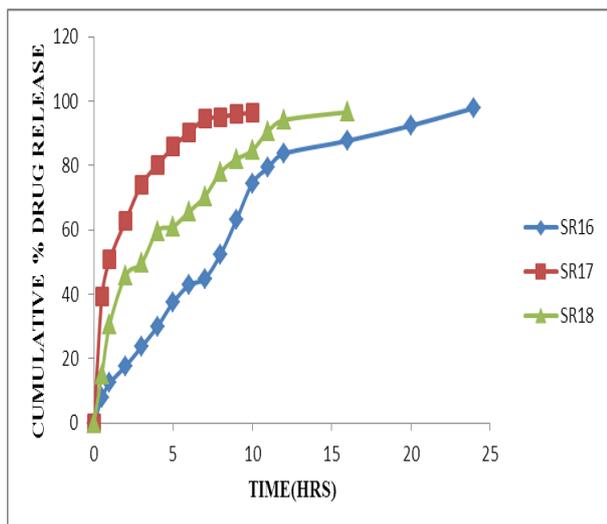

Fig: 12 Dissolution data of Lamivudine from 13-15.

Fig: 13 Dissolution data of Lamivudine from 16-18.

Table: 6 Dissolution data of Bilayer Tablets using Hydrophillic and Hydrophobic polymers.

| Time (Min)	SR19	SR 20	SR21	SR22	SR23	SR24	SR25	SR 26	SR 27
0	0	0	0	0	0	0	0	0	0
30 (0.5hr)	5.8	9.2	6.5	4.8	7.2	3.1	7.03	8.6	9.41
60 (1 hr)	12.3	18.6	12.4	8.7	11.8	6.5	9.19	11.1	13.75
120 (2 hr)	17.8	33.4	21.8	15.7	20.6	12.4	15.42	24.7	22.14
180 (3 hr)	22.8	41.8	30.9	19.8	29.1	21.8	25.71	30.5	26.43
240 (4 hr)	31.8	50.3	36.8	23.8	33.8	26.8	33.86	36.4	38.18
300 (5 hr)	39.3	63.4	39.2	31.7	40.8	30.9	43.90	45.2	42.27
360 (6 hr)	46.9	73.8	48.3	36.8	45.6	36.8	46.61	58.7	48.54
420 (7 hr)	51.8	75.4	55.8	43.2	54.3	39.2	49.55	64.4	53.78
480 (8 hr)	65.3	89.6	65.6	49.6	63.4	48.3	51.74	67.3	55.68
540 (9 hr)	76.6	97.52	85.6	58.6	71.8	55.8	53.17	71.8	67.35
600 (10 hr)	89.3		100.1	68.8	80.6	65.6	55.35	76.5	73.62
660 (11 hr)	95.21			81.6	100.4	85.6	62.14	83.4	76.43
720 (12 hr)				89.8		100.1	67.95	90.8	78.84
960 (16 hr)				100.6			70.34	94.36	83.28
1200 (20 hr)							72.85		89.36
1440 (24 hr)							76.43		89.36
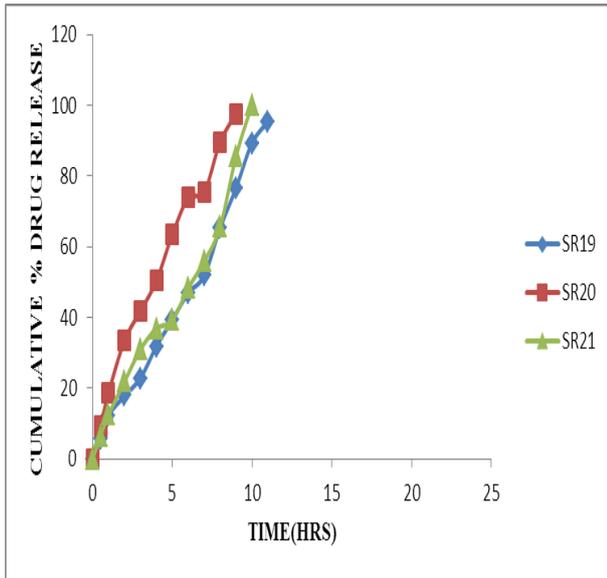
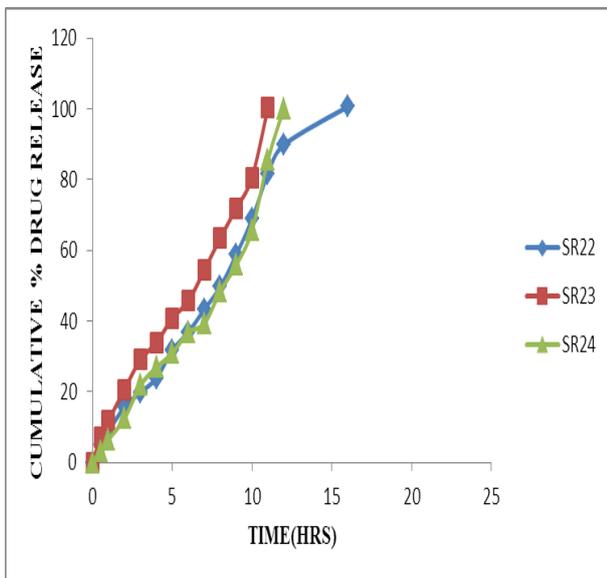**Fig: 14 Dissolution data of Lamivudine from 19-21.**

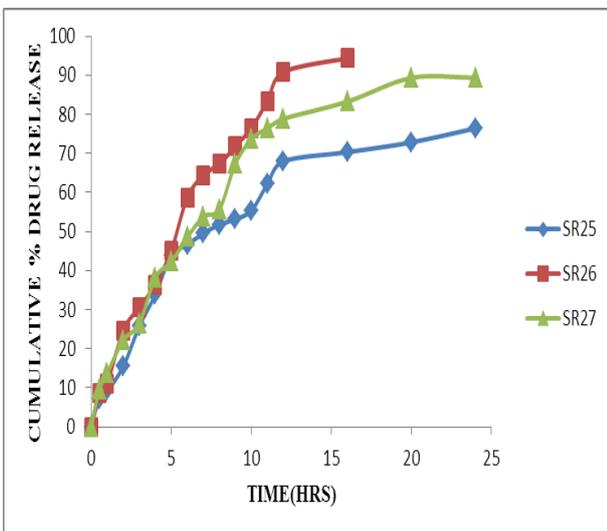**Fig: 15 Dissolution data of Lamivudine from 22-24.**

Fig 16: Dissolution data of Lamivudine from 25-27.

Table: 7 Application of Release Rate Kinetics to Dissolution Data for best formulations (SR16):

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	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
7.79	0.5	0.707	0.892	-0.301	1.965	15.580	0.1284	-1.108	92.21	4.642	4.518	0.124
12.41	1	1.000	1.094	0.000	1.942	12.410	0.0806	-0.906	87.59	4.642	4.441	0.201
17.65	2	1.414	1.247	0.301	1.916	8.825	0.0567	-0.753	82.35	4.642	4.351	0.291
23.65	3	1.732	1.374	0.477	1.883	7.883	0.0423	-0.626	76.35	4.642	4.242	0.399
29.9	4	2.000	1.476	0.602	1.846	7.475	0.0334	-0.524	70.1	4.642	4.123	0.518
37.48	5	2.236	1.574	0.699	1.796	7.496	0.0267	-0.426	62.52	4.642	3.969	0.673
42.81	6	2.449	1.632	0.778	1.757	7.135	0.0234	-0.368	57.19	4.642	3.853	0.789
44.85	7	2.646	1.652	0.845	1.742	6.407	0.0223	-0.348	55.15	4.642	3.806	0.835
52.44	8	2.828	1.720	0.903	1.677	6.555	0.0191	-0.280	47.56	4.642	3.623	1.018
63.18	9	3.000	1.801	0.954	1.566	7.020	0.0158	-0.199	36.82	4.642	3.327	1.315
74.5	10	3.162	1.872	1.000	1.407	7.450	0.0134	-0.128	25.5	4.642	2.943	1.698
79.33	11	3.317	1.899	1.041	1.315	7.212	0.0126	-0.101	20.67	4.642	2.744	1.897
83.67	12	3.464	1.923	1.079	1.213	6.973	0.0120	-0.077	16.33		2.537	
87.66	16	4.000	1.943	1.204	1.091	5.479	0.0114	-0.057	12.34		2.311	
92.37	20	4.472	1.966	1.301	0.883	4.619	0.0108	-0.034	7.63		1.969	
97.86	24	4.899	1.991	1.380	0.330	4.078	0.0102	-0.009	2.14		1.289	

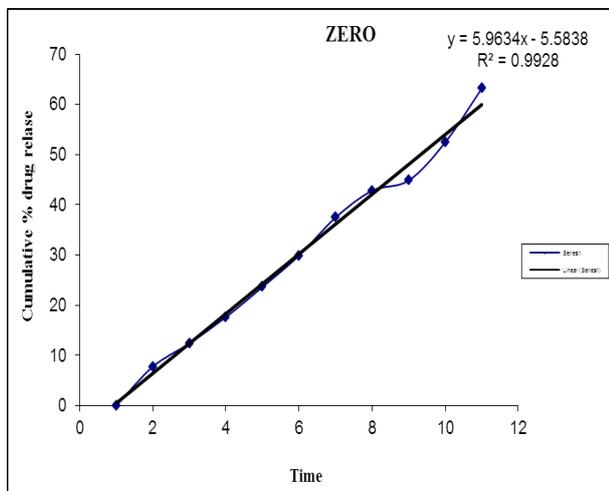| KINETICS	BT16
	SR16 LAYER
Zero order	$R^2 = 0.9928$
First order	$R^2 = 0.9182$
Higuchi	$R^2 = 0.923$
Kars mayer peppas	$R^2 = 0.9825$

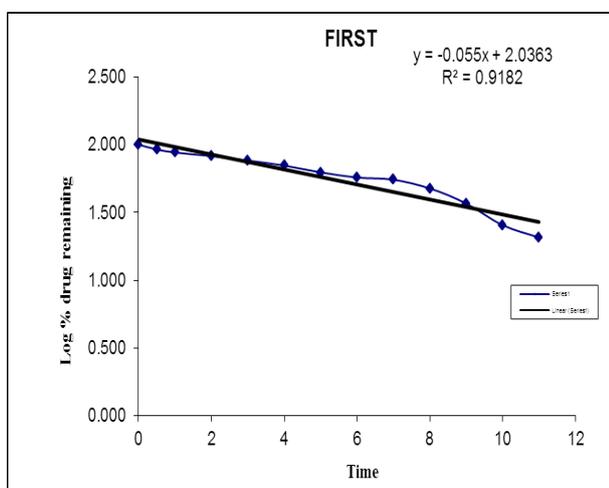**Figure: 17 SR16 Formulation Zero Order Release Kinetics.**

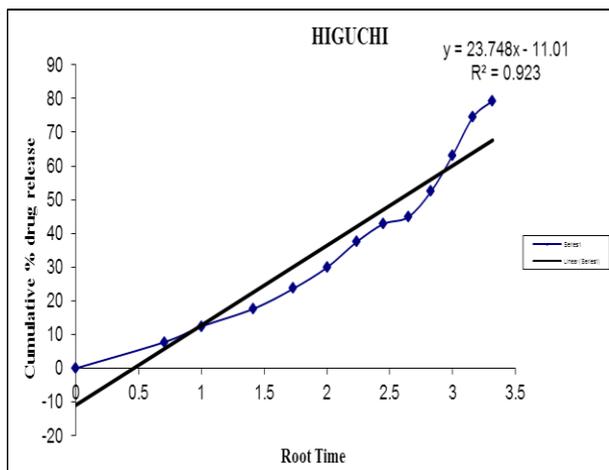**Figure:18 SR16 Formulation First order graph.**

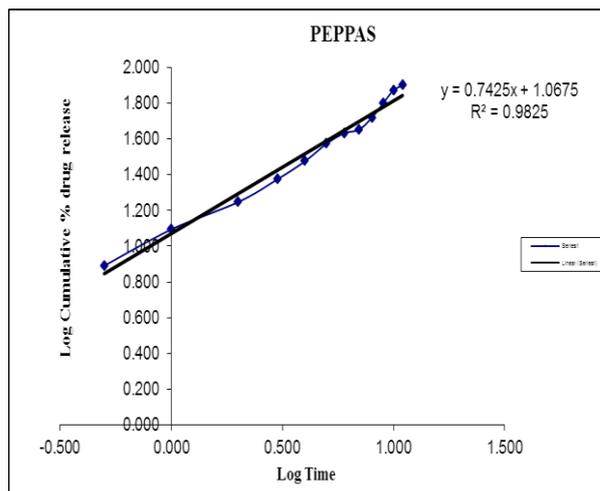**Figure:19 SR16 Formulation Higuchi graph.**

Figure: 20 SR16 Formulation Peppas graph.

B16 Bilayer Tablet Formulation is considered as optimised formulation which follows zero order release kinetics.

ACCELERATED STABILITY STUDIES
The stability study of the optimised tablets were carried out according to ICH guidelines at $40\pm2^{o}C/75\pm5\%$ RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. The results from stability studies are shown in table.

CONCLUSION
Sustained Release layers were prepared using various polymers. All the SR layer blends were performed for various pre and post compression studies. Those were found to be within limits. Bilayer tablets of Anti ritro viral formulations B1- B27 were developed by using optimised Immediate layer formulation (IR23) with combination of sustained release formulation blend powder. Immediate layer Formulations were developed by using Natural Superdisintegrants, Synthetic Superdisintegrants. Sustained Release formulations were developed by using Hydrophillic, Hydrophobic polymers. Sustained release formulations were contain the drug is Lamivudine. Dissolution carried out 24 hours. First 2 hours the dissolution media was 0.1 N HCL. After 2 hours the dissolution media was 6.8 Phosphate buffer. SR16 formulation was the best formulation. This formulation was retard the drug release 97.86% upto desired time period (24 hrs). B16 Bilayer Tablet Formulation is considered as optimised formulation which follows zero order release kinetics. SR16 Layer was following Zero order release kinetics.

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