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Formulation and *in-vitro* evaluation of stavudine extended release tablets

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ABSTRACT

During the past two decades, there has been a steady increase in both the number of antiretroviral medications and the number of possible regimens available to manage human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). But still, regimen fails due to some reasons such as toxicity, adverse effects, and consequent difficulties with patient adherence. Stavudine is the Food and Drug Administration approved drug for clinical use for the treatment of HIV infection, AIDS, and AIDS related conditions, either alone or in combination with other antiviral agents. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity. To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. Hence, in the present work, an attempt has been made to develop once daily sustained release matrix tablets of Stavudine using putative hydrophilic matrix materials such as hydroxyl propyl methyl cellulose (HPMC) K15M, Sodium CMC and PEO. The prepared extended release tablets were then evaluated for various physical tests like diameter, thickness, weight variation, hardness, friability, and drug content uniformity. The results of all these tests were found to be satisfactory. Formulation and evaluation properties given best result by the extended release tablets of Stavudine.

Keywords: PEO, Extended release, HPMC K4M, Sodium CMC, Stavudine

INTRODUCTION

Solid dosage forms are popular because of ease of administration, self-medication, pain avoidance as compared with parenteral, and low cost. [1] One of the most common approaches used for prolonging and controlling the rate of drug release is to incorporate a drug in hydrophilic colloid matrix such as hydroxyl propyl methyl cellulose (HPMC K15M) and PEO available anti - human immunodeficiency virus (HIV) drugs can be classified into the following three categories: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. Most of these drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to

design drug delivery systems for antiHIV agents to: (a) reduce the dosing frequency, (b) increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract, (c) improve the central nervous system (CNS) penetration and inhibit the CNS efflux, and (d) deliver them to the target cells selectively with minimal side. [3] Stavudine (D4T, thymidine) is the Food and Drug Administration approved drug for clinical use for the treatment of HIV infection, acquired immune deficiency syndrome (AIDS) and AIDS related conditions, either alone or in combination with other antiviral agents. Stavudine is typically administered orally as a capsule and an oral solution. The virustatic drug has a very short half life (1.30 hours). However, patients receiving Stavudine develop neuropathy and lactic acidosis. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity. [4] To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. The drug is freely soluble in water, and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.[5] Hence, in the present work, an attempt has been made to develop once daily sustained release matrix tablets of Stavudine using putative hydrophilic matrix materials such as HPMC K15M, PEO and Sodium CMC.

MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Stavudine was a gift sample from Pharma Train Lab, Hyderabad, India. HPMC K 15M, Sodium CMC & PEO were procured from (LAB INDIA).

Preparation of Stavudine controlled release tablets

Dissolution studies on stavudine Matrixtablet formulations were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 50rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 12hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 266nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies.

RESULT AND DISCUSSION

Controlled release Matrixtablets for Stavudine were prepared by direct compression method. The direct compression process used for the preparation of matrix tablets was found to be ideal and is easy to reproduce. Polymers such as Hydroxy Propyl Methyl Cellulose (HPMC K15 M), PEO and sodium CMC were used in the preparation of matrix tablets with incorporation of Sodium bicarbonate as a gas generating agent and combination of sodium bicarbonate and citric acid as effervescent agents. All the powder blends exhibited good flow properties. These polymers were found to be ideal for the preparation of controlled release matrix tablets. Twenty five Matrixtablet formulations were prepared with Stavudine by employing various polymers at different concentrations.

Table 01: Flow Properties of Powder Blends of Stavudine Controlled Release matrixtablets

S.NO	Formulation	Angle of repose (θ)	Hausner's ratio	Compressibility Index (%)
1	S1	23.90	1.12±0.03	14.23

2	S2	22.34	1.12±0.03	12.17
3	S3	24.54	1.12±0.02	11.87
4	S4	23.18	1.12±0.04	11.41
5	S5	22.77	1.12±0.03	13.67
6	S6	21.32	1.12±0.05	13.30
7	S7	22.54	1.12±0.02	14.98
8	S8	23.30	1.12±0.01	15.77
9	S9	22.80	1.12±0.03	11.14
10	S10	23.04	1.12±0.04	14.93
11	S11	24.18	1.11±0.04	12.23
12	S12	23.43	1.12±0.05	12.08
13	S13	23.43	1.12±0.03	12.08
14	S14	23.43	1.11±0.02	12.08

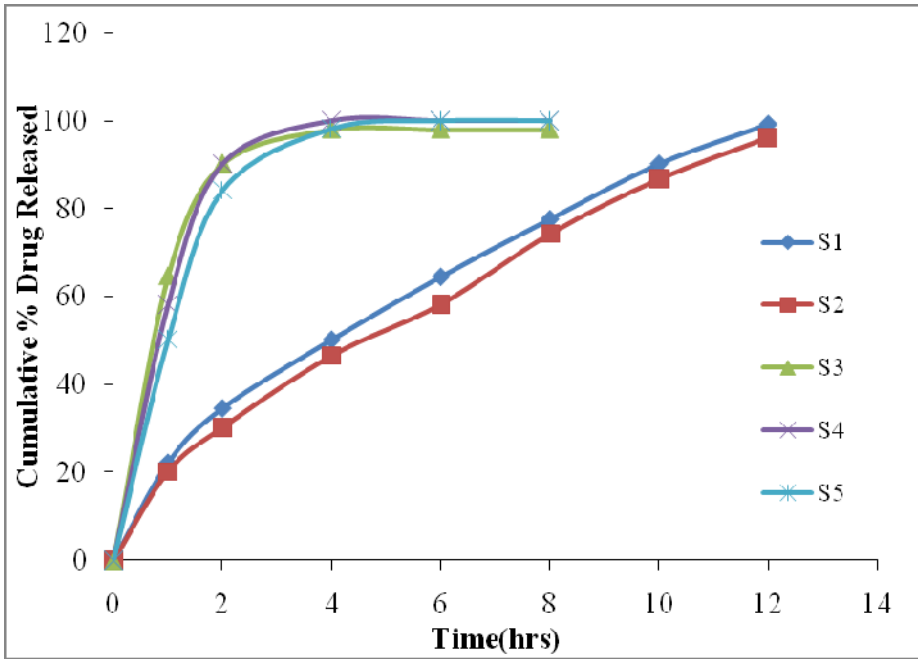
Table 02: Flow Properties of Powder Blends of Stavudine Controlled Release MatrixTablets

S.NO	Formulation	Angle of repose (θ)	Hausner's ratio	Compressibility Index (%)
1	S15	22.57	1.12±0.03	13.63
2	S16	21.36	1.12±0.03	11.57
3	S17	25.74	1.12±0.02	13.37
4	S18	22.14	1.12±0.04	12.61
5	S19	21.74	1.12±0.03	12.27
6	S20	24.62	1.12±0.05	12.37
7	S21	23.74	1.12±0.02	13.42
8	S22	21.37	1.12±0.01	12.87

9	S23	24.85	1.12±0.03	12.81
10	S24	24.54	1.12±0.04	13.83
11	S25	27.68	1.11±0.04	13.27

Table 03: Drug Release Profile of Stavudine Controlled Release MatrixTablets

Time(hrs)	Cumulative % Drug Release from Various Formulations				
	S1	**S2**	**S3**	**S4**	**S5**
0	0	0	0	0	0
1	22.24	20.24	64.66	58.24	50.24
2	34.66	30.26	90.24	90.22	84.22
4	50.24	46.56	98.12	100.00	98.25
6	64.56	58.22	98.14	100.11	100.0
8	77.66	74.22	98.32	100.12	100.0
10	90.24	86.66	---	---	---
12	99.26	96.12	---	---	---



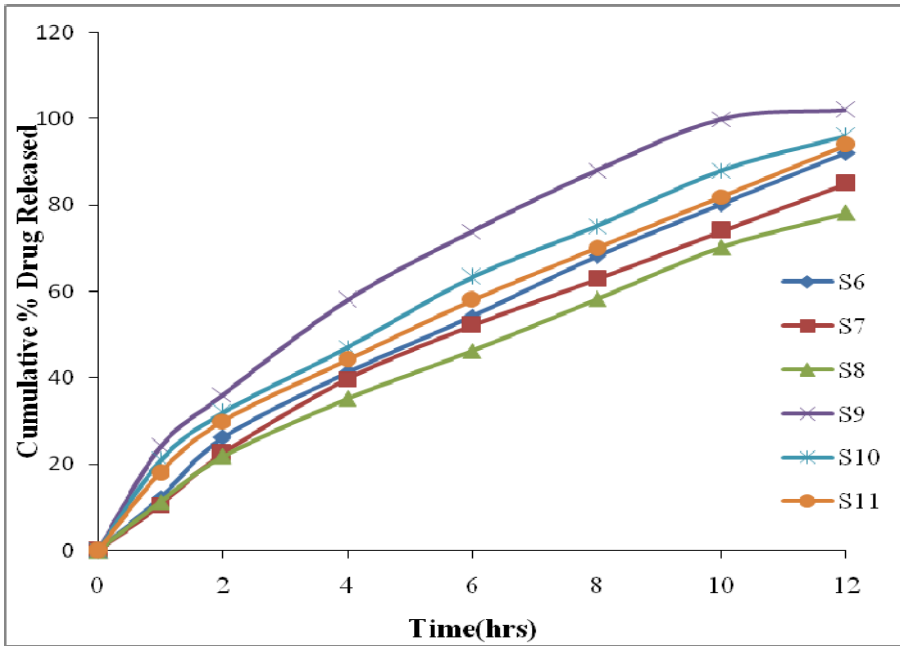
Graph 01: Release Profiles from Various Controlled Release MatrixTablet Formulations of Stavudine

Discussion

Dissolution studies were performed on all the Matrixtablets of **Stavudine** formulations by using 0.1 N HCl as dissolution medium by USP paddle method (apparatus II). Matrix tablet formulations S1 and S5 containing HPMC K 15 M and PEO with HPMC K 15 M in varying concentration as polymers respectively failed to extend the drug release upto 12 hours.

Table 04: Drug Release Profile of Stavudine Controlled Release MatrixTablets

Time (Hrs)	Cumulative % Drug Release from Various Formulations					
	S6	**S7**	**S8**	**S9**	**S10**	**S11**
0	0	0	0	0	0	0
1	12.24	10.50	11.30	24.24	20.90	18.25
2	26.22	22.50	21.80	36.22	32.21	30.22
4	41.24	39.70	35.24	58.26	47.02	44.21
6	54.26	52.20	46.24	74.24	63.36	58.36
8	68.22	62.90	58.22	88.22	75.21	70.24
10	80.24	74.10	70.24	100.0	88.28	82.24
12	92.20	85.00	78.20	100.0	96.00	94.63



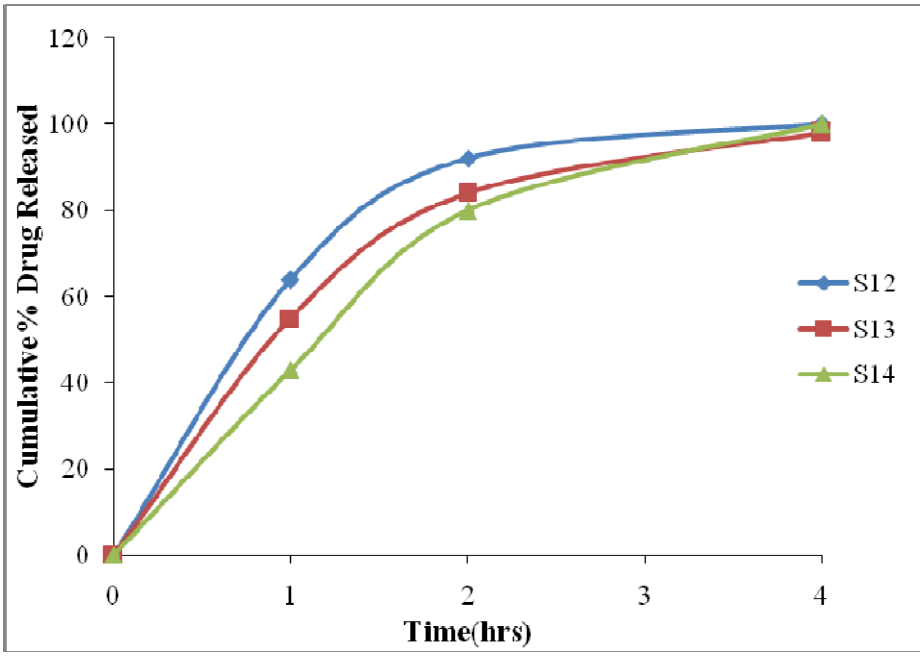
Graph 02: Release Profiles from Various Controlled Release MatrixTablet Formulations of Stavudine

Discussion

Formulations S6 to S11 containing Eudragit RSPO and HEC as polymers with constant concentration of PEO extended the drug release upto 12 hours It was observed that the drug release from the matrix tablets were decreased as the concentration of Eudragit RSPO is increased in all the formulations.

Table 05: Drug Release Profile of Stavudine Controlled Release Matrix Tablets

Time (Hrs)	Cumulative % Drug Release from Various Formulations		
	S12	**S13**	**S14**
0	0	0	0
1	64.12	55.24	43.21
2	92.22	84.26	80.24
4	100.00	98.32	100.00



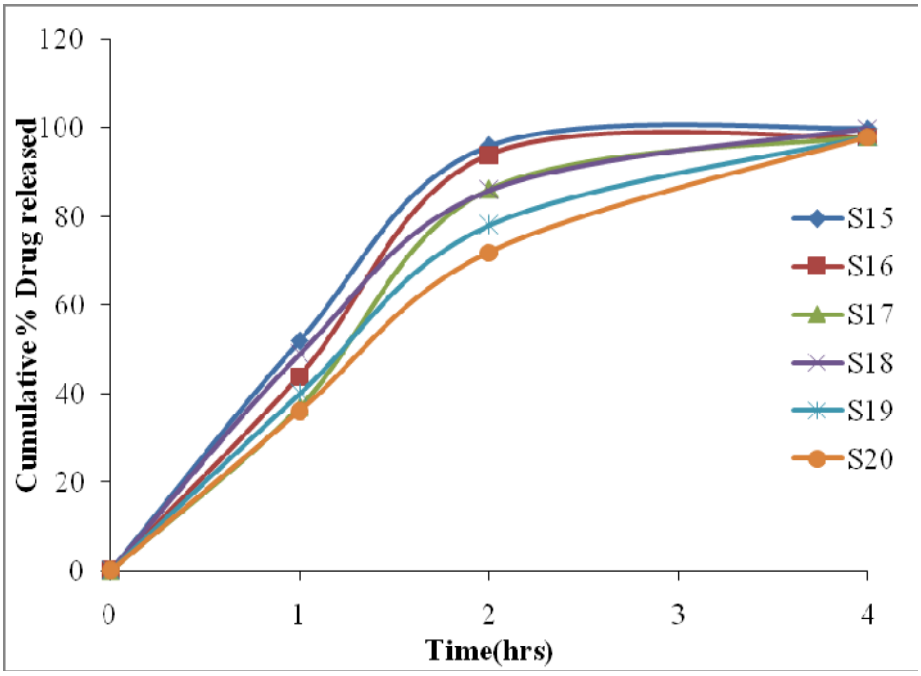
Graph 03: Release Profiles from Various Controlled Release MatrixTablet Formulations of Stavudine

Discussion

Formulations L12 to L14 containing PEO with failed to extend the drug release upto 12 hours.

Table 06: Drug Release Profile of Stavudine Controlled Release MatrixTablets

Time (Hrs)	Cumulative % Drug Release from Various Formulations					
	S15	S16	S17	S18	S19	S20
0	0	0	0	0	0	0
1	52.21	44.62	37.24	49.32	40.62	36.22
2	96.22	94.52	86.20	86.22	78.24	72.26
4	100.0	98.24	98.24	100	98.46	98.24



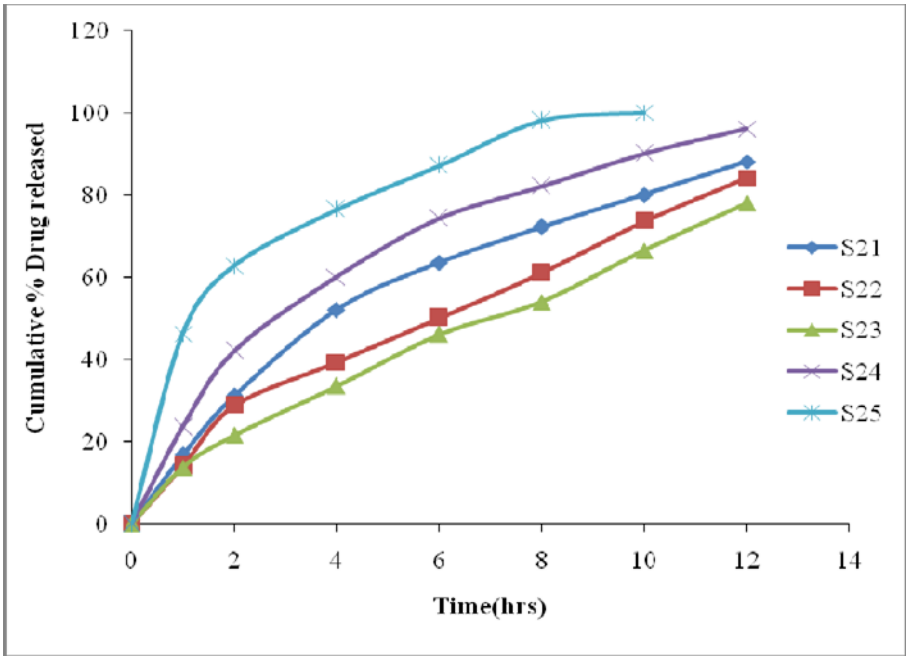
Graph 04: Release Profiles from Various Controlled Release MatrixTablet Formulations of Stavudine

Discussion

Formulations S15 to S20 containing HPMC K 100 M and PEO alone with varying concentration of HPMC K 100 M failed to extend the drug release upto 12 hours.

Table 07: Drug Release Profile of Stavudine Controlled Release MatrixTablets

Time (Hrs)	Cumulative % Drug Release from Various Formulations				
	S21	S22	S23	S24	S25
0	0	0	0	0	0
1	16.8	14.22	13.82	23.64	46.32
2	31.22	28.94	21.62	42.2	62.97
4	52.24	39.4	33.64	60.22	76.64
6	63.66	50.22	46.22	74.46	87.31
8	72.26	61.12	54.10	82.22	98.22
10	80.24	73.68	66.58	90.24	98.00
12	88.20	84.22	78.22	96.22	---



Graph 05: Release Profiles from Various Controlled Release MatrixTablet Formulations of Stavudine

Discussion

Formulation S21 to S24 containing combination of polymers Eudragit RSPO and PEO exhibited the drug release upto 12 hours

Evaluation of Various Dissolution Parameters

Various dissolution parameters such as zero order rate constant, first order rate constant, Higuchi constant and Peppa's constant were calculated from the dissolution data obtained from various formulations.

- A plot of cumulative percent drug released *vs* time (hrs) was plotted and the zero order release rate constant (K_0) was calculated from the slope.
- A plot of log% unreleased *vs* time (hrs) was plotted for all the formulations and the first order release rate constant (K_1) were obtained by multiplying slope with 2.303.
- A plot of cumulative amount of drug released *vs* square root of time was plotted for all the formulations and the Higuchi constant was calculated from the slope *[Higuchi, 1963]*.
- A plot of log Q *vs* log time was plotted for all the formulations and the 'n' values were noted from y-intercept of the straight line. *[Korsmeyer, 1983]*

The following mathematical expressions were used to calculate various dissolution parameters from the dissolution data *[Suvakanta D et al., 2010]*

Evaluation of Physical Properties of Stavudine Controlled Release MatrixTablets

Quality of a pharmaceutical product can be assured by evaluating different physical characteristics of the product such as weight variation test, hardness test, friability test etc. following standard methods given by different drug control authorities like USP, BP etc. Evaluation of the physical characteristics can ensure the quality of drug and thereby impart optimum therapeutic activity as well as bioavailability.

Table 08: Physical Properties of the Stavudine Controlled Release MatrixTablets

S.NO	Formulation	Weight uniformity(mg)	Hardness (kg/cm²)	Friability (%)	Drug content (mg/tablet)
1	S1	203±2.0	6.0±0.3	0.12	39.2±0.5
2	S2	204±2.0	6.0±0.3	0.12	40.2±0.5
3	S3	202±2.0	6.0±0.3	0.18	36.4±0.5
4	S4	200±2.0	6.0±0.3	0.17	39.9±0.2
5	S5	200±2.0	6.0±0.3	0.15	41.2±0.3
6	S6	202±2.0	6.0±0.3	0.18	38.8±0.5
7	S7	200±2.0	6.0±0.3	0.16	39.6±0.5
8	S8	201±2.0	6.0±0.3	0.18	40.8±0.3
9	S9	200±2.0	6.0±0.3	0.14	39.5±0.5
10	S10	203±2.0	6.0±0.3	0.16	40.4±0.5
11	S11	202±2.0	6.0±0.3	0.18	39.2±0.5
12	S12	200±2.0	6.0±0.3	0.16	41.2±0.5
13	S13	202±2.0	6.0±0.3	0.16	41.2±0.5
14	S14	200±2.0	6.0±0.3	0.16	41.2±0.5

Table 09: Physical Properties of the Stavudine Controlled Release MatrixTablets.

S.NO	Formulation	Weight uniformity(mg)	Hardness (kg/cm²)	Friability (%)	Drug content (mg/tablet)
1	S15	201±2.0	6.0±0.3	0.15	40.5±0.2
2	S16	202±3.0	6.0±0.3	0.13	39.4±0.3
3	S17	199±3.0	6.0±0.3	0.16	41.3±0.2
4	S18	201±2.0	6.0±0.3	0.18	40.7±0.5

5	S19	198±4.0	6.0±0.3	0.13	39.9±0.4
6	S20	199±43.0	6.0±0.3	0.15	41.5±0.3
7	S21	200±3.0	6.0±0.3	0.18	40.4±0.2
8	S22	201±3.0	6.0±0.3	0.19	39.7±0.5
9	S23	198±2.0	6.0±0.3	0.16	40.4±0.2
10	S24	199±3.0	6.0±0.3	0.14	40.2±0.3
11	S25	202±2.0	6.0±0.3	0.19	39.4±0.5

All the batches of matrix tablets were evaluated for the physical parameters such as weight uniformity, hardness, friability and drug content uniformity. All the matrix tablets were evaluated for weight uniformity. The weight ranges of all the matrix tablets were uniform and were within the IP limits. Hardness of the tablets was evaluated by using Monsanto hardness tester. The hardness of all the tablet formulations was in the range of 6.0±0.3 kg/cm^2. Weight uniformity of all the tablet formulations was in the range of 200.0 ± 3.0 respectively. Friability test for all the matrix tablets were performed to determine the ability of tablets to withstand abrasion during packing and transportation. The test was carried out in Roche friabilator. Friability loss of the tablet formulations was negligible and was in the range of 0.1-0.2%. Surface damages to the tablets were found to be negligible and the friability loss values were within the IP limits. Drug content estimated for all the tablet formulations was highly uniform with less than 3% variation. The drug content for the prepared matrix tablets of Lamivudine and Stavudine were evaluated by UV spectrophotometric method. The drug content in all the Matrixtablet formulations were within the claimed limits. The physical parameters evaluation values for all the formulations were given in the tables 08 and 09.

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