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FORMULATION AND *IN-VITRO* EVALUATION OF LAMIVUDINE EXTENDED RELEASE TABLETS

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Abstract:

The objective of this study was to design oral controlled release matrix tablets of lamivudine using hydroxypropyl methylcellulose (HPMC) as the retardant polymer and to study the effect of various formulation factors such as polymer proportion, polymer viscosity, and compression force on the in-vitro release of drug. In-vitro release studies were performed using US. Paddle method (USP apparatus-II) in 900 mL of pH 0.1N HCL at 50 rpm. Increase in compression force was found to decrease the rate of drug release. Matrix tablets containing 60% HPMC K100M were found to show good initial release (25% in first hour) and extended the release up to 12 hours. No incompatibility was observed between the drug and excipients used in the formulation of matrix tablets. The developed controlled release matrix tablets of lamivudine, with good initial release (20%–25% in first hour) and extension of release up to 16 to 20 hours, can overcome the disadvantages of conventional tablets of lamivudine.

Keywords: *Controlled release, Matrix tablets, Hydroxypropyl methylcellulose, Lamivudine*

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INTRODUCTION:

Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an antiretroviral regimen for the treatment of HIV infection.[1,2] *In vivo*, nucleoside analogs are phosphorylated intracellularly by endogenous kinases to putatively active 5′- triphosphate (3TC-TP) derivatives that prevent HIV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension.

Lamivudine belongs to class III of the BCS Classification with High solubility and low permeability. Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability of 86% ± 16%, peak serum concentration of lamivudine (Cmax) of 1.5 ± 0.5 mcg/mL and mean elimination half-life (t½) of 5 to 7 hours. It is bound to plasma proteins less than 36%. thus necessitating frequent administration to maintain constant therapeutic drug levels [3]

Lamivudine (ß-L-2', 3'-dideoxy-3'-thiacytidine) (LAM), one of the dideoxycytidine analogue NRTIs, is the first nucleoside analogue approved to treat chronic HBV infection and AIDS. Conventional oral formulations of LAM are administered multiple times a day (150 mg twice daily) because of its moderate half-life (t1/2 = 5-7 hours). Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. Controlled release once daily formulations of LAM can overcome some of these problems [4].

Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the in vivo environment.

Hence an attempt is made in this research work to formulate controlled release (CR) tablets of LAM using HPMC K 100M, Sodium CMC & Eudragit RLPO. Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The CR tablets formulation by direct compression method is most acceptable in large scale production [7].

MATERIALS AND METHODS:

Materials used in this study were obtained from the different sources. Lamivudine was a gift sample from Pharma Train Lab, Hyderabad, India. HPMC K 100M, Sodium CMC & Eudragit RLPO were procured from (LAB INDIA).

Formulation development of Lamivudine controlled release tablets:

Controlled release oral matrix tablets for Lamivudine were prepared by direct compression method using Elite 10 station mini press. The direct compression process used for the preparation of matrix tablets was found to be ideal and is easy to reproduce. As many of the polymers and the excipients used are hydrophilic, the involvement of water or moisture makes the wet granulation process highly problematic. Therefore, a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics is desirable. Hence the dry process such as direct compression technique was employed in the present investigation for the preparation of controlled release oral matrix tablets.

Table 1: Composition of Various Lamivudine Controlled Release Oral Matrix Formulations

Ingredients (mg)	L1	L2	L3	L4	L5
Lamivudine	250	250	250	250	250
HPMC K15M	75	100	125	150	175
Sodium CMC	50	50	50	50	50
MCC	164	139	114	89	64
Magnesium stearate	5.5	5.5	5.5	5.5	5.5
Talc	5.5	5.5	5.5	5.5	5.5
Total tablet weight(mg)	550	550	550	550	550

Table 2: Composition of Various Lamivudine Controlled Release Oral Matrix Formulations

Ingredients (mg)	L6	L7	L8	L9	L10	L11	L12	L13	L14
Lamivudine	250	250	250	250	250	250	250	250	250
EUDRAGIT RLPO	50	75	100	125	150	175	--	--	--
PEO	--	--	--	--	--	--	100	150	200
Sodium CMC	50	50	50	50	50	50	50	50	50
MCC	154	149	109	79	54	29	109	54	26
PVP K 30	10	10	10	10	10	10	10	10	10
Magnesium stearate	7	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7	7
Total tablet weight(mg)	550	550	550	550	550	550	550	550	550

Table 3: Composition of Various Lamivudine Controlled Release Oral Matrix Formulations

Ingredients (mg)	L15	L16	L17	L18	L19	L20	L21	L22	L23	L24	L25
Lamivudine	250	250	250	250	250	250	250	250	250	250	250
HPMC K100 M	75	100	125	150	175	200	---	---	---	---	--
Eudragit RSPO	---	---	---	---	---	--	75	100	125	150	175
Sodium CMC	50	50	50	50	50	50	50	50	50	50	50
PVP K 30	10	10	10	10	10	10	10	10	10	10	10
MCC	149	109	79	54	76	26	149	109	79	54	76
Magnesium stearate	7	7	7	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7	7	7	7
Total tablet weight(mg)	550	550	550	550	550	550	550	550	550	550	550

Preparation of Lamivudine controlled release tablets:

Dissolution studies on lamivudine 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 280nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies.

RESULT AND DISCUSSION:

Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of HPMC was taken as L**1** and

concentration of sodium CMC was taken as L**5**. Experimental design was given in the Table 4. Formulae for all the experimental batches were given in Table 4 [5,6].

Table 4: Flow Properties of Powder Blends of Lamivudine Controlled Release MatrixTablets

Formulation	Angle of repose (θ)	Compressibility Index (%)	Hausner's Ratio
L1	26.94±0.02	12.10±0.024	1.120±0.03
L2	25.69±0.03	14.20±0.022	1.118±0.02
L3	25.42±0.05	11.89±0.009	1.121±0.05
L4	26.85±0.02	14.87±0.017	1.123±0.04
L5	27.01±0.03	13.68±0.014	1.128±0.02
L6	25.76±0.05	12.37±0.024	1.129±0.01
L7	26.40±0.07	14.24±0.019	1.120±0.04
L8	27.32±0.09	11.20±0.027	1.127±0.05
L9	26.54±0.13	12.75±0.017	1.129±0.05
L10	25.87±0.07	11.78±0.014	1.16±0.02

Table 5: Flow Properties of Powder Blends of Lamivudine Controlled Release MatrixTablets

Formulation	Angle of repose (θ)	Compressibility Index (%)	Hausner's ratio
L11	25.76±0.05	12.37±0.024	1.129±0.03
L12	26.40±0.07	14.24±0.019	1.120±0.03
L13	27.32±0.09	11.20±0.027	1.127±0.02
L14	26.54±0.13	12.75±0.017	1.129±0.04
L15	25.69±0.03	11.78±0.014	1.128±0.03
L16	25.42±0.05	14.87±0.017	1.129±0.05
L17	26.85±0.02	13.68±0.014	1.120±0.02
L18	27.01±0.03	12.37±0.024	1.127±0.01
L19	25.76±0.05	14.24±0.019	1.129±0.03
L20	26.94±0.02	14.20±0.022	1.120±0.04
L21	25.69±0.03	11.89±0.009	1.118±0.04
L22	25.42±0.05	14.87±0.017	1.121±0.05
L23	26.94±0.02	13.68±0.014	1.123±0.03
L24	25.69±0.03	12.37±0.024	1.118±0.02
L25	25.42±0.05	11.20±0.027	1.121±0.01

DISCUSSION:

Before compression process the powder blends were evaluated for flow properties such as angle of Repose, compressibility index and Hausner's ratio. The flow property values obtained for various powder blends were in the range of good flow characteristics, as depicted in the tables 25 and 26. The angle of repose values obtained for various powder blends were in the range of 25.42 to 27.32. Carr's index values obtained were in the range of 11.20 to 14.87. Hausner's ratio values obtained were in the range of 1.118- 1.129. Thus all the powder blends were found to be stable and suitable for compression as matrix tablets.

Evaluation of Physical Properties of Lamivudine 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 6: Physical Properties of Lamivudine Controlled Release MatrixTablets

Formulation	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (%)	Drug content* (mg/tablet)
L1	550±2.0	5.5±0.4	0.19	248.5±0.5
L2	549±3.0	5.7±0.3	0.12	251.3±0.5
L3	550±3.0	5.5±0.3	0.18	250.4±0.5
L4	549±2.0	5.8±0.2	0.17	251.9±0.2
L5	549±4.0	5.5±0.3	0.15	249.2±0.3
L6	700±2.0	5.6±0.2	0.18	249.8±0.5
L7	700±3.0	5.7±0.3	0.16	250.6±0.5
L8	700±3.0	5.5±0.4	0.18	249.8±0.3
L9	700±2.0	5.8±0.1	0.14	248.2±0.5
L10	700±3.0	5.6±0.2	0.20	250±0.2
L11	698±2.0	5.8±0.2	0.17	250.6±0.5
L12	699±4.0	5.5±0.3	0.15	249.8±0.3
L13	701±2.0	5.6±0.2	0.18	248.2±0.5
L14	699±3.0	5.7±0.3	0.16	250.0±0.2

Table 7: Physical Properties of Lamivudine Controlled Release MatrixTablets

Formulation	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (%)	Drug content* (mg/tablet)
L15	702±3.0	5.5±0.4	0.12	250.4±0.5
L16	701±2.0	5.8±0.1	0.18	251.9±0.2
L17	698±4.0	5.6±0.2	0.17	248.5±0.5
L18	702±3.0	5.5±0.4	0.15	251.3±0.5
L19	700±3.0	5.7±0.3	0.19	250.4±0.5
L20	698±2.0	5.5±0.3	0.18	248.5±0.5
L21	699±4.0	5.8±0.2	0.14	251.3±0.5
L22	701±2.0	5.7±0.3	0.20	250.4±0.5
L23	702±3.0	5.5±0.3	0.16	251.9±0.2
L24	700±3.0	5.8±0.2	0.18	249.2±0.3
L25	699±3.0	5.5±0.4	0.14	251.9±0.2

Discussion:

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 5.5-6.0 kg/cm^2.Weight uniformity of all the tablet formulations was in the range of 550± 3.0 and 700 ± 3.0 for lamivudine. 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 spectro photometric method. The drug content in all the Matrixtablet formulations were within the claimed limits.

Evaluation of Lamivudine controlled release tablets:

Hardness [7]

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm2 is considered adequate for mechanical stability.

Friability [5]

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Content uniformity [7]

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

Assay

Lamivudine 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 for 12hrs ,drug released was estimated by ELICO double beam spectrophotometer at 280nm.

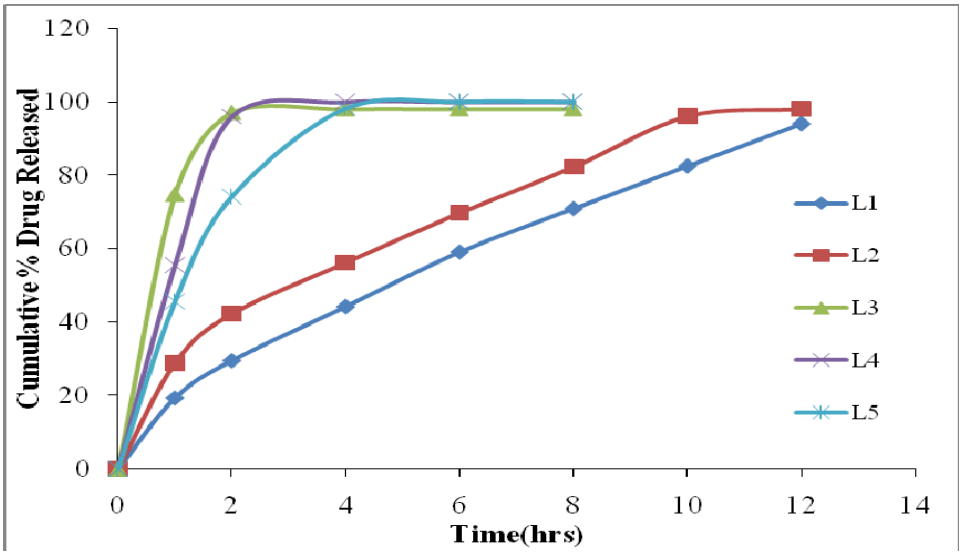
***In-vitro* dissolution study:**

Dissolution studies on lamivudine 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 [8-10]. 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 280nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies.

Table 9 : Drug Release Profile of Lamivudine Controlled Release MatrixTablets

Time(hrs)	Cumulative % Drug Release from Various Formulations				
	L1	L2	L3	L4	L5
0	0	0	0	0	0
1	19.35	28.85	74.73	55.53	45.63
2	29.52	42.24	97.24	96.22	74.20
4	44.24	56.17	98.25	100.00	98.20
6	59.1	69.68	--	--	--
8	70.91	82.22	--	--	--
10	82.50	96.35	--	--	--
12	94.00	98.44	--	--	--

Graph 1: Release Profiles from Various Controlled Release MatrixTablet Formulations of Lamivudine

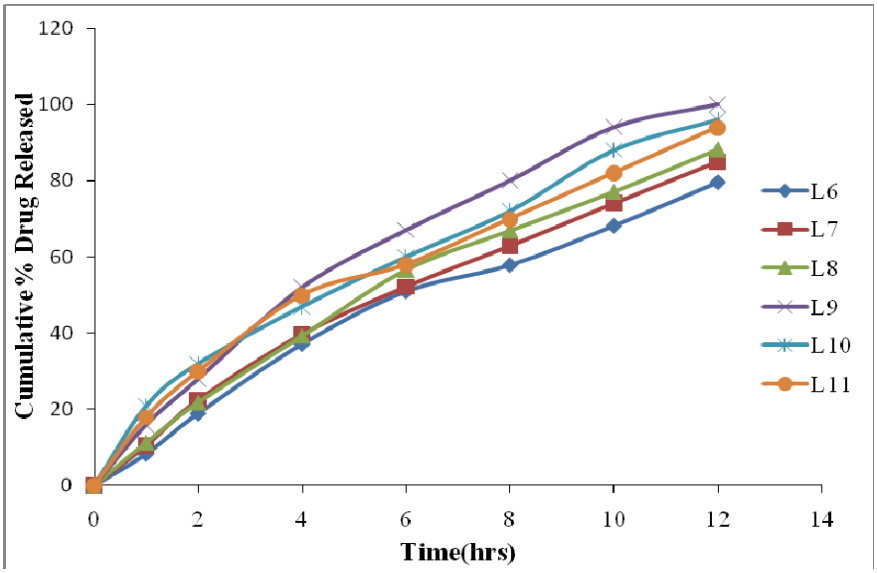


Discussion:

Dissolution studies were performed on all the Matrixtablets of Lamivudine formulations by using 0.1 N HCl as dissolution medium by USP paddle method (apparatus II). Matrix tablet formulations L1 and L5 containing HPMC and sodium CMC as polymers extended the drug release upto 12 hours.

Table 10 : Drug Release Profile of Lamivudine Controlled Release MatrixTablets

Time(hrs)	Cumulative % Drug Release from Various Formulations					
	L6	L7	L8	L9	L10	L11
0	0	0	0	0	0	0
1	8.30	10.56	11.34	16.85	20.90	18.24
2	18.90	22.58	21.80	28.45	32.24	30.25
4	37.10	39.75	39.34	52.35	47.05	50.33
6	50.91	52.2	56.62	67.32	60.64	58.01
8	57.84	62.97	66.93	80.33	72.44	70.05
10	68.10	74.14	77.10	94.01	88.66	82.22
12	79.54	85.00	88.20	100.0	96.45	94.00



Graph:2 Release Profiles from Various Controlled Release MatrixTablet Formulations of Lamivudine

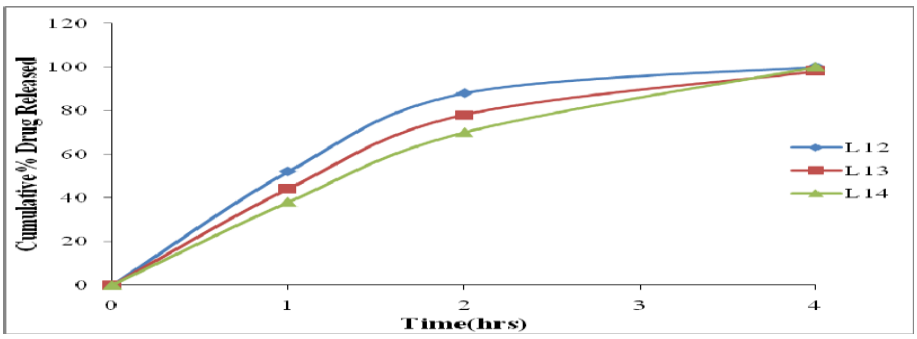
Discussion:

Formulations L6 to L11 containing Eudragit RLPO and sodium CMC as polymer with varying concentrations of Eudragit RLPO 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 RLPO is increased in all the formulations.

Table 11: Drug Release Profile of Lamivudine Controlled Release MatrixTablets

Time(hrs)	Cumulative % Drug Release from Various Formulations		
	L12	L13	L14
0	0	0	0
1	52.54	44.24	38.12
2	88.62	78.32	70.24
4	100.22	98.24	100.22

Graph3: Release Profiles from Various Controlled Release MatrixTablet Formulations of Lamivudine

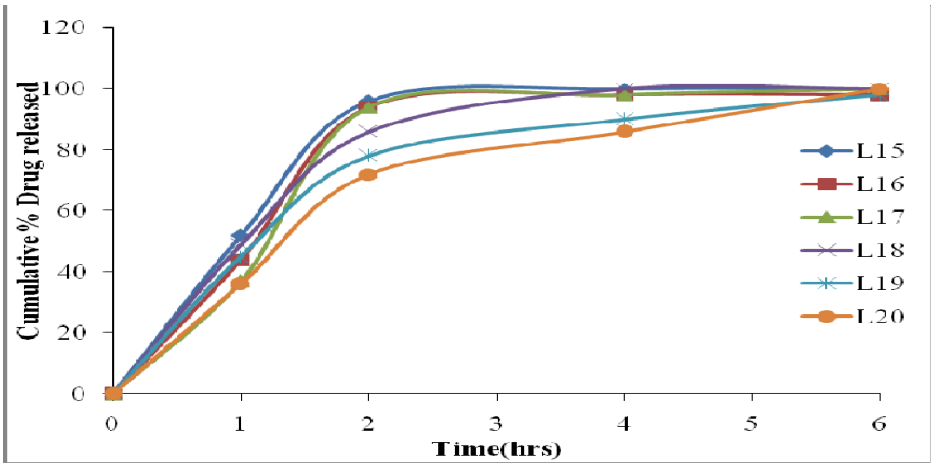


Discussion:
Formulations L12 to L14 containing Eudragit RLPO with PEO with eudragit RLPO in varying concentration of failed to extend the drug release upto 12 hours.

Table 12: Drug Release Profile of Lamivudine Controlled Release MatrixTablets

Time(hrs)	Cumulative % Drug Release from Various Formulations					
	L15	L16	L17	L18	L19	L20
0	0	0	0	0	0	0
1	52.02	44.36	37.52	49.69	45.96	36.32
2	96.24	94.25	94.63	86.36	78.63	72.36
4	100.33	98.25	98.22	100.25	90.04	86.22
6	100.01	98.00	100.0	100.24	98.44	100.02

Graph4: Release Profiles from Various Controlled Release MatrixTablet Formulations of



Lamivudine

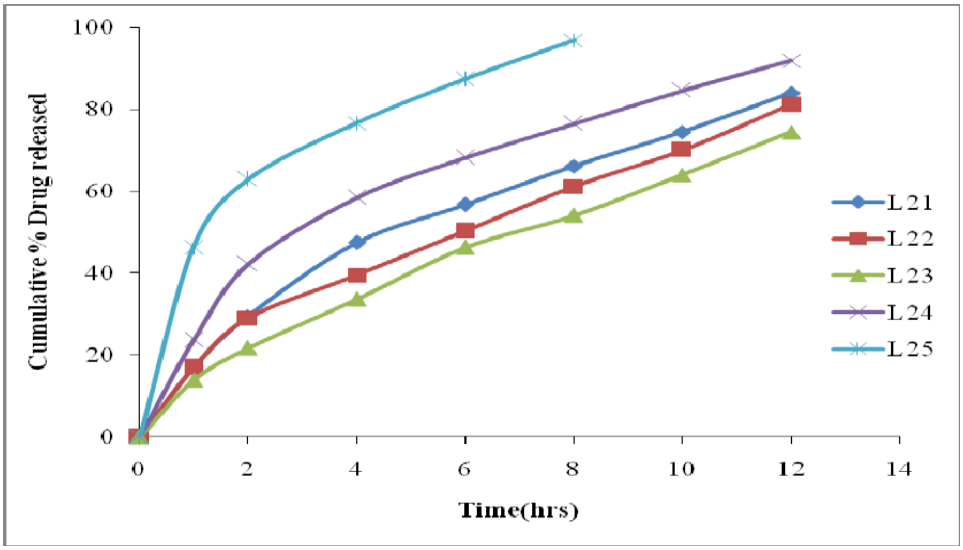
Discussion:

Formulations L15 to L20 containing HPMC K 100 M and sodium CMC with varying concentration of HPMC K 100 M failed to extend the drug release upto 12 hours.

Table 13 : Drug Release Profile of Lamivudine Controlled Release MatrixTablets

Time(hrs)	Cumulative % Drug Release from Various Formulations				
	L21	L22	L23	L24	L25
0	0	0	0	0	0
1	16.80	16.92	13.84	23.62	46.33
2	29.42	28.95	21.64	42.23	62.97
4	47.48	39.44	33.66	58.44	76.65
6	56.77	50.22	46.27	68.16	87.35
8	66.16	61.12	54.15	76.55	96.92
10	74.55	70.00	64.22	84.64	--
12	84.02	81.15	74.52	91.98	--

Graph 5: Release Profiles from Various Controlled Release MatrixTablet Formulations of Lamivudine



Discussion:
Formulation L21 to L24 containing combination of polymers Eudragit RSPO and Sodium CMC exhibited the drug release upto 12 hours.

CONCLUSION:

The formulations which showed good *in vitro* performance were subjected to the extended tablets were prepared Lamivudine. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and on drug release from the matrix tablets L11 and L25 for lamivudine. The results of these studies were given in tables 9- 13 and shown in graph 1 to 5. The results thus indicated that there were no visible and physical changes observed in the matrix tablets after storage. It was also observed that there was no significant change in drug release from the Matrixtablets. The slow and controlled drug release characteristics of the Matrixtablets remained unaltered.

REFERENCES:

1. Katlama C, Valantin MA, Matheron S, Coutellier A, Calvez VD, Descamps D, et al. Efficacy and tolerability of stavudine plus lamivudine in treatment-naive and treatment experienced patients with HIV-1 infection. Ann Intern Med. 1998;129:525-31.
2. Merrill DP, Moonis M, Chou TC, Hirsch MS. Lamivudine or stavudine in two- and three-drug combinations against human immunodeficiency virus type 1 replication in vitro. J Infect Dis. 1996;173:355-64.
3. Himadri Sen, Surva Kumar J, inventors. Long acting composition containing zidovudine and Lamivudine. US patent publication US 20050175694A1. August 11, 2005.
4. Shanmugam S, Kamaraj K, Vetrichelvan T. Formulation and evaluation of lamivudine sustained release matrix tablets using synthetic polymers. J Pharm Res 2012;5(2):1063-6.
5. Nagarwal RC. In Situ Forming Formulation: Development, Evaluation, and Optimization Using 33 Factorial Design. AAPS PharmSciTech. 2009;10 (3):977-84.
6. Gunda RK, Suresh Kumar JN, Babu CA, Anjaneyulu MV. Formulation Development and Evaluation Of Lamotrigine Sustained Release Tablets Using 3 2 Factorial Design, IJPSR. 2015;6(4):1746-52.
7. Sirisha VNL, Kumarrao YK, Eswaraiah MC. Formulation and Evaluation of Lamivudine and Zidovudine Extended Release Tablets. International Journal of Research in Pharmaceutical and Biomedical Sciences.
8. Turner S, Federici C, Hite M, Fassihi R. Formulation development and human in vitro - in vivo correlation for a novel, monolithic controlled-release matrix system of high load and highly water soluble drug Niacin, Drug Dev Ind Pharm. 2004;30(8):797-807.
9. Fernandes CM, Ramos P, Amilcar CF, Veiga FB. Hydrophilic and hydrophobic cyclodextrins in a new sustained release oral formulation of Nicardipine: In vitro evaluation and bioavailability studies in rabbits, J. Control.Release. 2003;88(1):127-34.

10. Atul K, Ashok KT, Narendra KJ, Subheet J. Formulation and in vitro, in vivo evaluation of extended-release matrix tablet of zidovudine: influence of combination of hydrophilic and hydrophobic matrix formers. AAPS Pharm Sci Tech. 2006;7 Suppl 1:E1-E9.
11. Al-saidan SM, Krishnaiah YSR, Patro S, Satyaranayana V. In vitro and in vivo evaluation of guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. AAPS Pharm Sci Tech. 2005;6 Suppl 1:E14-E21.
12.Althaf AS. Design and Study of Lamivudine Oral Sustained Release Tablets, Der Pharmacia Sinica. 2010;1(2):61-76.
13.Lachmann L, Lieberman HA, Kanig JL. The Theory & Practice of Industrial Pharmacy. Varghese Publishing House, Bombay, 3rd Edition; 1991. p. 430.