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FORMULATION DESIGN AND CHARACTERIZATION OF MATRIX TABLETS OF LAMIVUDINE

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Abstract:

The aim of this study was to design oral controlled release lamivudine matrix tablets using hydroxypropyl methylcellulose (HPMC) as the retardant polymer, sodium alginate, acacia gum 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 (USP II) with paddle apparatus (basket method) in 900 mL of pH 6.8 phosphate buffer at 50 rpm. The release kinetics were analyzed using the zero-order model equation, Higuchi's square-root equation, and the Ritger-Peppas empirical equation. Compatibility of the drug with various excipients was studied. Increase in compression force was found to decrease the rate of drug release. Methematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release. 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 (32% in 4th hour) and extension of release up to 14 hours, can overcome the disadvantages of conventional tablets of lamivudine.

Keywords: *Controlled release, matrix tablets, hydroxypropyl methylcellulose, lamivudine*

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INTRODUCTION:

The oral route is most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs [2]. The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost.4,5 Lamivudine is a potent antiviral agent used in the treatment of AIDS. Conventional oral formulations of lamivudine are administered multiple times a day (150 mg twice daily) because of its moderate half-life (t1/2 = 5-7 hours) [3, 4]. Treatment of AIDS using conventional formulations of Lamivudine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multidose therapy [5], poor patient compliance, and high cost. CR once daily formulations of lamivudine can overcome some of these problems. The matrix tablets can be prepared via wet granulation or by direct compression [6]. Many polymers have been used in the formulation of matrix-based CR drug delivery systems. Reports were found on usage of hydrophilic polymers such as hydroxy propyl methylcellulose (HPMC), methylcellulose, sodium carboxy methyl cellulose [7], carbopols [8], and polyvinyl alcohol[9] for the purpose of CR formulations of different drugs. HPMC, a semi synthetic derivative of cellulose, is a swellable and hydrophilic polymer. Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs [10, 11].

The aim of this study was designing matrix tablets containing anti- HIV drug delivery system, with improved oral effectiveness of the principle anti-HIV agent, Lamivudine. With drug bioavailability concerns in mind, the investigation is sought to attain this goal from the perspective of creating an efficient novel drug delivery system of lamivudine matrix tablets.

MATERIALS AND METHODS:

Lamivudine was obtained as gift sample from Hetero Drugs Pvt. LtD.(Hyderabad, India). HPMC, Sodium alginate and Acacia gum was a gift sample from MYL CHEM Mumbai. All other chemicals and reagents used were of pharmaceutical or analytical grade.

Preparation of Lamivudine Matrix Tablets:

Matrix tablets containing Lamivudine were prepared by direct compression method. All ingredients except magnesium stearate mixed together by geometric mixing for period of 10minutes, magnesium stearate added prior to compression. Tablets were compressed using 16 station compression machine. The composition of various formulation were given in table 1.

Table 1: The composition of various formulations

Ingredients	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Lamivudine	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg
HPMC	175mg	150mg	100mg	75mg	100mg	75mg	100mg	50mg
Sodium Alginate	50mg	75mg	100mg	100mg	75mg	75mg	50mg	100mg
Acacia gum	25mg	25mg	50mg	75mg	75mg	100mg	100mg	100mg
MCCP	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg
Magnesium stearate	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Total Weight	710mg	710mg	710mg	710mg	710mg	710mg	710mg	710mg

Drug – Excipient Compatibility Study:

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation. 1-2 mg of solid fine powder of drug and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm^{-1} by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Micromeritics properties:

Angle of repose:

The angle of repose of powdered blend was determined by the funnel method. The accurately weight 15gm powdered blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The powdered blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$Tan\ \theta = \frac{h}{r}$$

Where, h –height of the powder cone r - radius of the powder cone

Bulk density and tapped density:

Both loose bulk density (LBD) and Tapped bulk density (TBD) were determined .A quantity of 15gm of blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 50ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at sec intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

$$\boldsymbol{LBD} = \frac{weight\ of\ the\ powdered\ blend}{bulk\ volume}$$

$$\boldsymbol{TBD} = \frac{weight\ of\ the\ powdered\ blend}{true\ volume}$$

Hausner's factor:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\boldsymbol{Hausner's factor} = \frac{Tapped\ density}{Bulk\ density}$$

Carr's compressibility index:

The compressibility index of the granules was determined by Carr"s compressibility index. (%) Carr"s Index can be calculated by using the following formula

$$\boldsymbol{Carr's\ Compressibility}\ \% = \frac{TD - BD}{TD} \times 100$$

POST COMPRESSIONAL PARAMETERS

Hardness

This is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauge in the barrel at which the tablet fractures.

Weight variation

Ten tablets were selected at random and average weight was determined. Then individual tablets were weighted and the individual weight was compared with an average weight. Not more than two of the individual weights deviate from the official standard (limit 7.5%).

Tablet size and Thickness

The size and thickness of the tablets were measured by using Vernier Calipers scale

Drug content analysis

Five tablets weighted and crushed in a mortar then weighed powder contained equivalent to 100 mg of drug transferred in 100ml of phosphate buffer to give a concentration of 100µg/ml. Absorbance measured at 275nm using UV- visible spectrophotometer.

***In vitro* dissolution studies for core tablets**

Dissolution rate of core tablets from all formulations were performed using LAB INDIA dissolution apparatus (USP II) with paddle. The dissolution fluid was 900 ml of 0.1N Hcl at a speed of 50 rpm and a temperature of 37º C were used in each test up to 1 hour after that tablets were placed into phosphate buffer pH 6.8.

***In vitro* dissolution studies for tablets**

Dissolution rate of matrix tablets from all formulations were performed using LAB INDIA dissolution apparatus (USP II) with paddle. The dissolution fluid was 900 ml 0.1N HCL for first 2hrs then replaced with phosphate buffer pH 6.8 at a speed of 50 rpm and a temperature of 37º C were used in each test. The dissolution experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 10, 12 and 14hrs) and were replaced with equal volume of phosphate buffer pH 6.8. The samples were analyzed at 275nm using a UV spectrophotometer.

Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent , Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube

root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t$$

where , K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303$$

where , C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2}$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data Cumulative % drug release vs. time (Zero order kinetic model); Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time (Higuchi model); And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

Mechanism of drug release

Korsmeyer *et al,* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

RESULTS AND DISCUSSIONS:

Matrix tablets containing 15% Acacia gum and relatively low polymer concentration (Formulation F2) were found to show good initial release (21.34% in initial hour) and allowed sustained release up to 14 hours. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on polymer concentration and it was found to be diffusion coupled with erosion. The rate of drug release decreased with increased polymer concentration. The developed controlled release matrix tablets of lamivudine, with sustained release characteristics might be able to minimize the demerits of conventional therapy having Lamivudine.

Fourier transformed infrared (FTIR) spectra of Lamivudine was taken by using the KBr disk method. The scanning range was 400 to 4000 Cm^{-1}.The major peaks in recorded spectra were compared with standard spectra there was a compatible between drug and polymers results were shown in figures 1 - 4. Pre compression parameters of granules were analysed, angle of repose values of all the formulations are in region of $18.25^0 \pm 0.025$ and $24.70^0 \pm 0.050$, bulk density was found to be in a range of 0.3803 ± to 0.4552 ± 0.011 gm/cc, and tapped density was found to be in a range of 0.4351 ±0.009 to 0.4899 ±0.008 gm/cc, Hausner Ratio from 0.8540 to 0.9407 and Carr's Index was found to be 5.923 to 14.595 % Thus all the formulations were found to suitable for compression as tablets given in table 2 .

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 5.0 to 5.9 kg/sq cm. Friability values below 1% were an indication of good mechanical resistance of the tablets. All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all the Eight formulations was found to pharmacopoeial limits of ±7.5% of the average weight. The percentage drug content of all the tablets was found to be between 97.6 to 100.3 % of Lamivudine which was within the acceptable limits, shown in table 3.

Among all formulations, F2 shows better drug release when compared with all other formulations. So formulation F2 selected as optimized formula.

By studying the release kinetics of lamivudine matrix tablets, as clearly indicated in table 5 and Figure 6, the formulations did not follow a first-order release pattern. When the data were plotted according to the first-order equation, the formulations showed regression values between 0.822 and 0.933, and the data were plotted according to the zero-order equation shown in table 5, the formulations showed a fair linearity, with regression values between 0.986 and 0.998. Release kinetics of lamivudine matrix tablets formulations followed a zero-order release pattern. Due to which shows more linearity in zero order rather than first order.

The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity with F2 values between 0.931 and 0.943 shown in table 5 and figure 7. It is indicating that diffusion mechanism involved in the release of the drug from the tablets. To confirm the diffusion mechanism, the data were fit into Korsmeyer Peppas equation. From the plots slope n values ranging from 0.940 to 0.997. it indicating that diffusion mechanism involved in formulations F1 to F8.

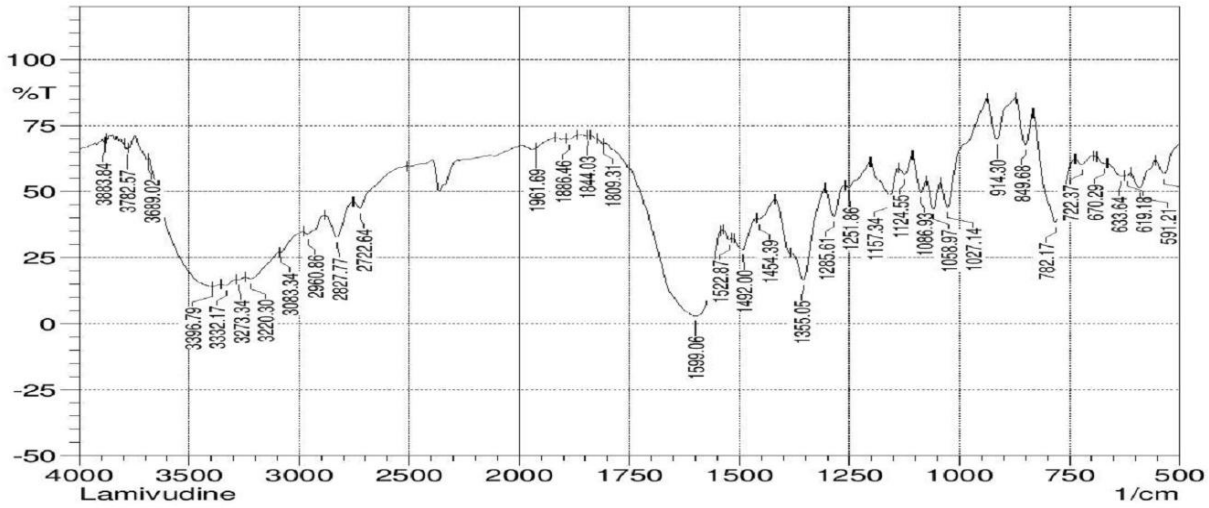

Fig 1: FTIR Spectra of Lamivudine pure drug

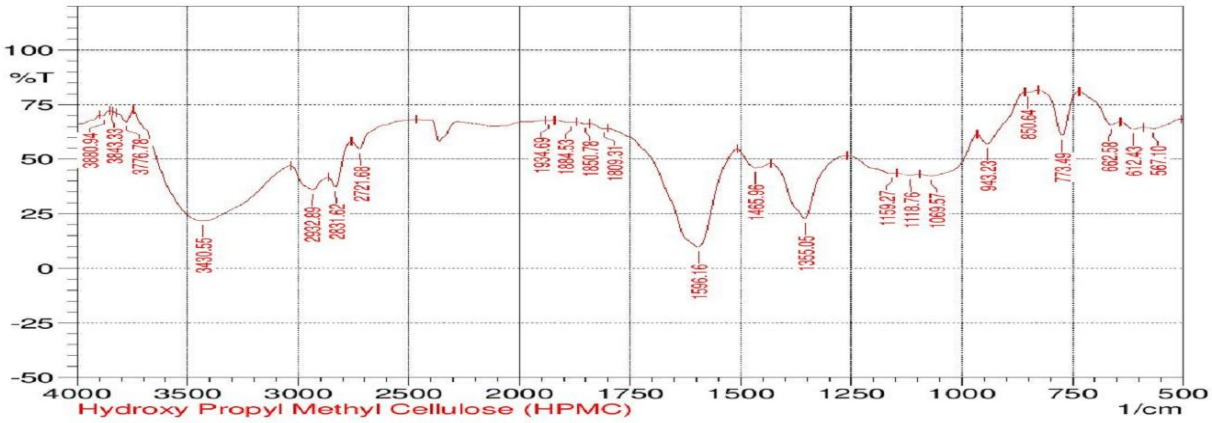

Fig 2: FTIR Spectra of Hydroxy propyl methyl cellulose (HPMC)

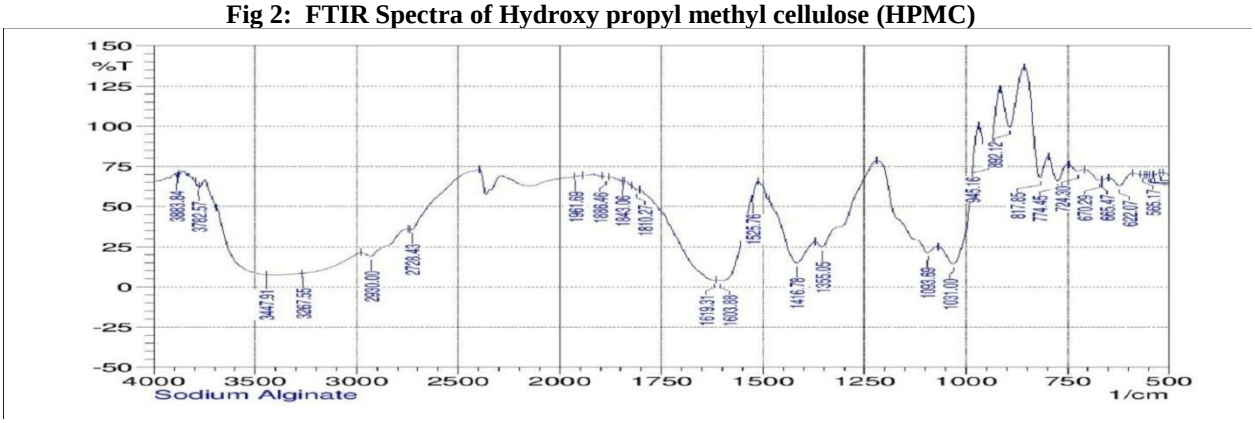

Fig 3: FTIR Spectra of Sodium alginate

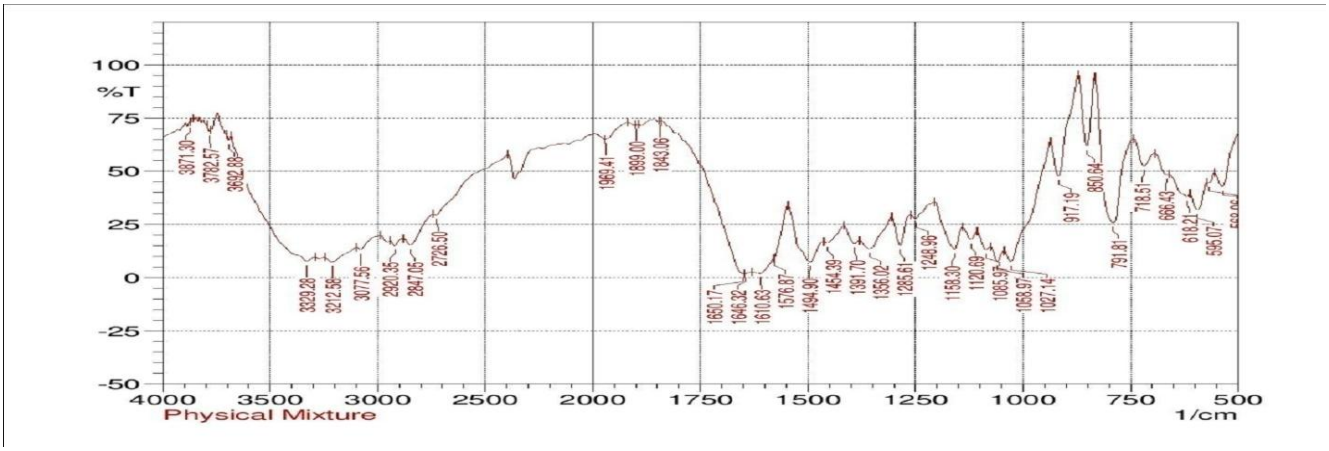

Fig 4: FTIR Spectra of Physical mixture

Table 2: Pre-formulation Parameters of Lamivudine Tablets Prepared By Direct Compression Method

Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Compressibility Index (%)	Angle of repose (^{0})	Hausner ratio
F1	0.4208±0.008	0.4503±0.001	6.551±0.052	22.05±0.015	**0.9344±0.022**
F2	0.4460±0.001	0.4752±0.004	6.144±0.065	19.20±0.020	**0.9385±0.034**
F3	0.4502±0.007	0.4803±0.007	6.685±0.043	21.45±0.019	**0.9373±0.014**
F4	0.4256±0.012	0.4524±0.003	5.923±0.012	18.25±0.025	**0.9407±0.009**
F5	0.3957±0.008	0.4351±0.009	9.055±0.034	21.60±0.030	**0.9094±0.026**
F6	0.3803±0.015	0.4402±0.007	13.607±0.075	24.70±0.050	**0.8639±0.010**
F7	0.4102±0.004	0.4803±0.003	14.595±0.109	21.35±0.040	**0.8540±0.045**
F8	**0.4552±0.011**	**0.4899±0.008**	**7.083±0.023**	**19.50±0.035**	**0.9291±0.008**

Table 3: Post formulation parameters of tablets

Formulation code	Hardness (Kg/cm^2)	Weight Variation (%)	Thickness (mm)	Friability (%)	Drug content (%)
F1	6.2±0.23	**2.4**±0.148	4.50±0.10	**0.091** ±0.068	**95.8±0.79**
F2	5.8±0.34	**2.8** ±0.182	4.25±0.32	**0.096** ±0.012	**98.9±0.98**
F3	7.9±0.56	**2.92** ±0.249	4.12±0.22	**0.095** ±0.028	**95.2±0.66**
F4	7.8±0.66	**1.03**±0.167	3.95±0.09	**0.084** ±0.088	**97.7±1.15**
F5	8.1±0.44	**2.1** ±0.102	3.82±0.43	**0.081** ±0.042	**98.9±0.98**
F6	7.2±0.39	**1.5** ±0.192	4.44±0.17	**0.095** ±0.028	**98.5±1.55**
F7	6.5±0.54	**1.79** ±0.196	3.92±0.52	**0.075** ±0.065	**97.7±1.15**
F8	**7.5±0.44**	**1.23±0.168**	**4.47±0.19**	**0.081 ±0.042**	**98.1±0.70**

Table 4: *In-vitro* Cumulative % Release of Drug From Matrix Tablets of Lamivudine

Time in Hours	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	14.85±0.45	19.82± 1.33	18.14± 1.76	13.23± 1.43	12.28± 1.32	12.21± 1.44	11.01± 0.80	10.85± 0.89
4	26.71±0.99	32.14± 1.65	29.25± 1.78	25.23± 1.66	22.12± 0.87	23.18± 1.44	21.77± 0.88	22.40± 0.94
6	38.82±1.23	46.52± 1.83	42.45± 1.61	36.48± 1.99	36.54± 0.78	34.63± 0.89	35.62± 1.33	31.85± 1.23
8	52.14±1.12	59.61± 1.61	58.62± 1.43	51.71± 1.39	49.82± 1.27	45.44± 1.23	42.85± 0.95	41.41± 0.76
10	65.61±1.18	72.23± 1.77	69.23± 1.57	66.85± 1.44	60.14± 0.37	57.23± 0.99	55.53± 1.37	52.21± 1.12
12	78.23±1.87	85.45± 1.22	81.45± 1.72	79.33± 1.37	74.83± 0.83	72.45± 1.19	78.45± 1.16	69.91± 0.31
14	94.23±1.45	97.33± 1.83	95.54± 1.85	92.41± 1.29	89.80± 1.41	85.22± 1.17	82.95± 1.39	78.11± 1.72

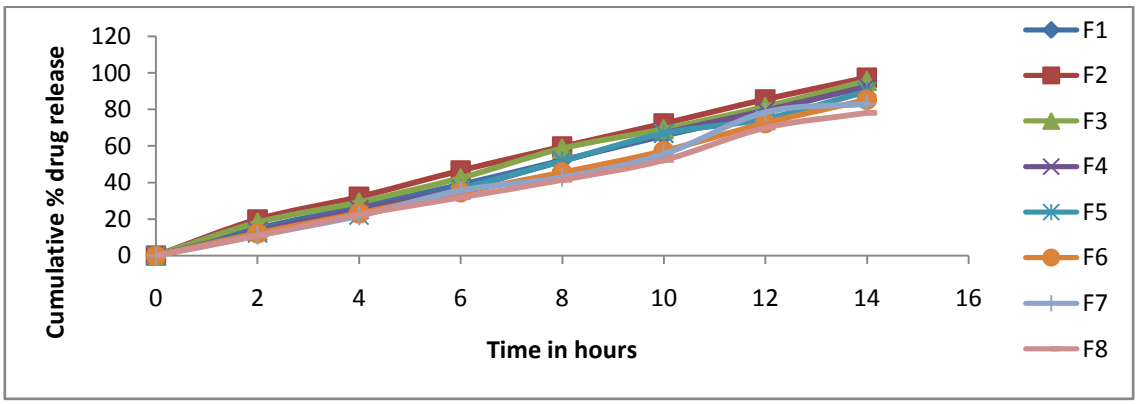

Fig 5: Cumulative % Drug Release of All Formulations.

Table 5: Coefficient of Determinations for Prepared Matrix Tablets of Lamivudine

FORMULATION CODE	Coefficient of Determination (R^2)			
	Zero order	First order	Higuchi square root	Peppas model
F1	0.998	0.834	0.909	0.954
F2	0.996	0.822	0.943	0.940
F3	0.997	0.843	0.931	0.945
F4	0.998	0.878	0.901	0.961
F5	0.996	0.902	0.900	0.965
F6	0.997	0.907	0.897	0.962
F7	0.986	0.907	0.880	0.967
F8	0.994	0.933	0.893	0.964

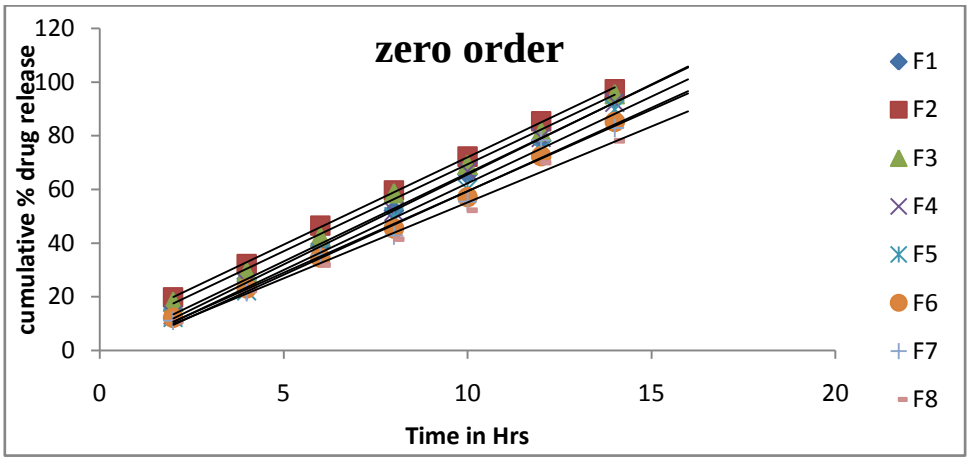

Fig 6: Zero order plot for optimized formulation

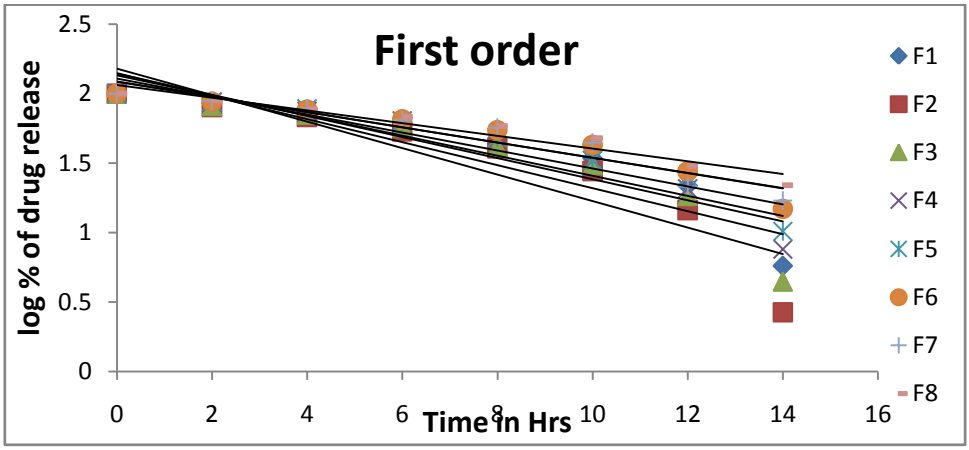

Fig 7: First order plot

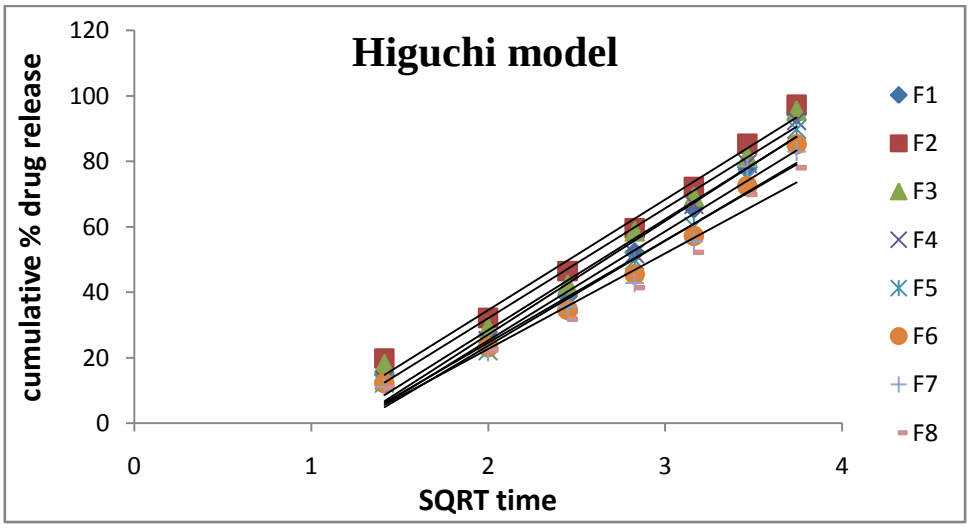

Fig 8: Higuchi plot for optimized formulation

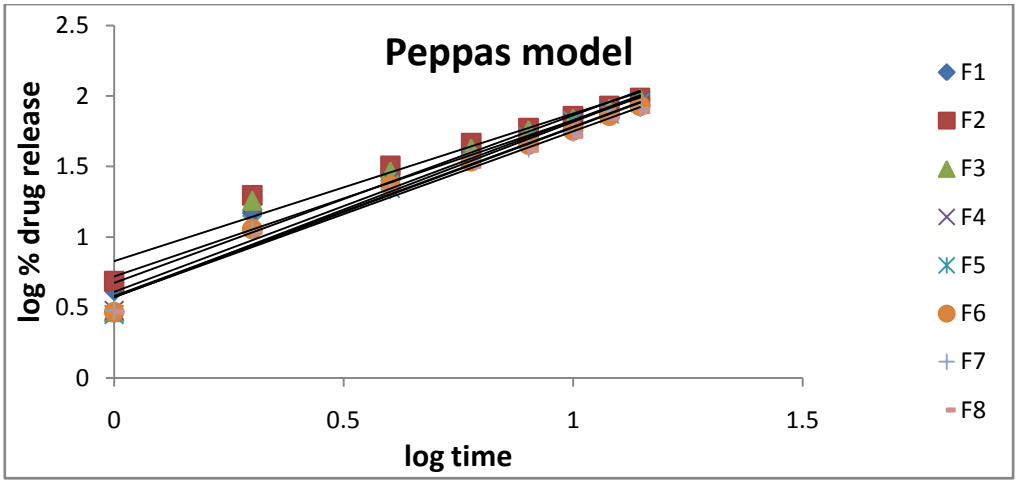

Fig 9: P**eppas model for all formulations.**

REFERENCES:

1. Chien YW. Novel drug delivery systems. In: Chien YW, ed. Oral Drug Delivery and Delivery Systems. New York, NY: Marcel Dekker; 1992:139-196.
2. Vyas SP, Khar RK. Controlled drug delivery: concepts and advances. In: Vyas SP, Khar RK, eds. Controlled Oral Administration. Delhi, India: Vallabh Prakashan; 2002:155-195.
3. Anthony SF, Clifford HL. Human immunodeficiency virus (HIV) disease: AIDS and related disorders. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine. New York, NY: McGraw-Hill; 2001:1852-1913.
4. Betty JD. Human immunodeficiency virus (HIV)—antiretroviral therapy. In: Herfindal ET, Gourley DR, eds. Textbook of Therapeutics: Drug and Disease Management. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:1555-1582.
5. Moyle G. Clinical manifestations and management of antiretroviral nucleoside analog-related mitochondrial toxicity. Clin Ther. 2000; 22:911-936.
6. Vargas CI, Ghaly ES. Kinetic release of theophylline from hydrophilic swellable matrices. Drug Dev Ind Pharm. 1999;25:1045-1050.
7. Ranga RKV, Padmalatha DK, Buri B. Cellulose matrices for zero-order release of soluble drugs. Drug Dev Ind Pharm. 1988;14:2299-2320.
8. Parojcic J, Duric Z, Jovanovic M, Ibric S. An investigation into the factors influencing drug release from hydrophilic matrix tablets based on novel carbomer polymers. Drug Deliv. 2004; 11:59-65.
9. Bravo SA, Lamas MC, Salomon CJ. Swellable matrices for the controlled-release of diclofenac sodium: formulation and in vitro studies. Pharm Dev Technol. 2004;9:75-83.
10. Velasco MV, Ford JL, Rowe P, Rajabi-Siahboomi AR. Influence of drug:hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC matrices. J Control Release. 1999;57:75-85.
11. Heng PWS, Chan LW, Easterbrook MG, Li X. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. J Control Release. 2001;76:39-49.