Formulation and Evaluation of Sustained Release Matrix Tablet of Lamivudine

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ABSTRACT-

The main objective of present work was to formulate and evaluate sustained release matrix tablet of lamivudine using different polymers viz. Xanthan Gum, Ethyl Cellulose. Lamivudine an Antiretroviral agent which comes under BCS class III which has high solubility and low permeability, was chosen for the study. Formulation of matrix tablets was prepared by using powder blend of different ratios of polymer to get desirable drug release profile. Direct compression method was used to formulate tablets. The evaluation of physical properties of tablet were done, the in-vitro drug release study was performed in 0.1 N HCL for 2 hours and in phosphate buffer PH 6.8 up to 10 hours. Evaluation parameters of formulated matrix tablets were hardness, friability, thickness, drug content, weight variation, and the in-vitro drug release rate pattern results indicated that the formulation F3 was the most promising formulation as the drug release from this formulation was high as compared to other formulations. In formulation F3, percentage drug release of lamivudine sustained release was 98.81±0.63.

KEYWORDS: Matrix Tablets, Sustained Release, Lamivudine, Xanthan Gum, Direct Compression.

1. INTRODUCTION

A sustained-release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug". Development of sustained release tablets of highly water-soluble drugs has always been a challenge and therefore, most of these drugs if not formulated properly, may be released at a faster rate resulting in exceeding the maximum therapeutic levels, hence will lead to toxic side effects. Sustained delivery of such drugs ensures improved drug delivery and patient compliance, greater safety and efficacy, desired release kinetics and helps in maintaining the plasma drug concentration within the therapeutic window for extended period of time[1]. In long-term therapeutic concern for the treatment of chronic

disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation or first pass hepatic metabolism which leads to low systemic bioavailability and formation of inactive or toxic metabolites. 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].

Oral controlled drug delivery system represents one of the frontier areas of drug delivery system in order to fulfill the need for a long-term treatment with anti-HIV agents. Among the different controlled drug delivery (CDD) systems, matrix based controlled release tablet formulations are the most popularly preferred for its convenience to formulate a cost effective manufacturing technology in commercial scale. Development of oral controlled release matrix tablets containing water-soluble drug has always been a challenging because of dose dumping due to improper formulation resulting in plasma and fluctuation of accumulation toxic concentration of drug. The use of polymers in controlling the release of drugs has become an formulation important tool in the of pharmaceutical dosage forms. Over many years, numerous studies have been reported in the literature on the application of hydrophilic polymers in the development of controlled release matrix systems for various drug[3].

The acquired immunodeficiency syndrome (AIDS), a disorder in which the immune system begins to fail and life-threatening opportunistic infections develop, can be brought on by the human immune deficiency virus (HIV), a retrovirus. Both HIV-1 and HIV-2 are contagious and AIDS-causing agents. There are two types of HIV. Lack of host immune system control over HIV replication leads to disease development. A person develops aids once HIV infection weakens the immune system to the point where the body can no longer defend itself against other infections and malignancies (fewer than 200 CD4+ cells per microliter of blood). Despite the lack of a medicine to treat this illness, there are ways to limit its progression[4]. A synthetic nucleoside analogue called lamivudine is being used more frequently as the main component of an antiretroviral regimen to treat HIV infection. By competitively inhibiting viral reverse transcriptase and stopping proviral DNA chain extension, nucleoside analogues are phosphorylated intracellularly by endogenous kinases to putatively active 5'-triphosphate (3TC-TP) derivatives that stop HIV replication in vivo. Lamivudine belongs to BCS class III with high solubility and low permeability. Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability of 86% 16%, a peak serum concentration of lamivudine (Cmax) of 1.5 0.5 mcg/mL, and a mean elimination half-life (t) of 5-7 hours, lamivudine is rapidly absorbed after oral administration, necessitating frequent administration to maintain constant therapeutic drug levels[5].Therefore, the objective of present work is to provide a prolong action of pharmaceutical composition containing lamivudine in a sustained release matrix formulation, to maintain constant drug level into blood for prolong period of time.

2. MATERIALS AND METHODS

2.1 MATERIALS:

Lamivudine was obtained from Yarrow chem. Pharmaceuticals, Mumbai, India. Ethyl cellulose, Xanthan gum, Microcrystalline-cellulose, Magnesium stearate and talc were obtained from Research fine lab, Mumbai, India.

2.2 METHOD OF PREPARATION OF MATRIX TABLET OF LAMIVUDINE:

Tablets were prepared by direct compression method. For the preparation of powder blend all ingredients were weighted accurately. Lamivudine, Polymers, MCC were weighed properly and triturate thoroughly. The above blend was lubricated with talc and magnesium stearate and passed through sieve #40 to break any lumps. The powder blends were compressed into tablets by direct compression technique on rotary tabletting machine. Before compression the surface of die and punch were lubricated with talc and powder blend compressed into tablets. These Tablets of each formulation were further evaluated for various properties.

Table1. Formulation of Lamivudine Sustained Release Matrix Tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Lamivudine	150	150	150	150	150	150
Xanthan Gum	40	80	120	-	-	-
Ethyl Cellulose	-	-	-	40	80	120
MCC	97	57	17	97	57	17
Magnesium Stearate	8	8	8	8	8	8
Talc	5	5	5	5	5	5
Total	300	300	300	300	300	300

3. EVALUATION OF PREPARED SUSTAINED MATRIX TABLETS

A) Pre-compression studies: [6,7]

1) Angle of Repose-

Angle of repose was determined by funnel method. The accurately weighted quantity of granules was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules.

The granule 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

$\theta = \tan^{-1} h/r$

Where, h and r are the height and radius of the powder cone.

Table 2. Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-55
Poor	46-55
Very poor	56-65
Very very poor	<65

2) Bulk Density-

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of granules lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume observed, the cylinder was allowed to fall under its own height onto hard surface from the height of 2.5 cm at 2 seconds interval. The tapping was continued until no further change in the volume was noted. (LBD) and (TBD) were calculated by using the following formulas

LBD = Weight of the powder / volume of the packing

TBD = Weight of the powder /tapped volume of the packing

3) The compressibility index

The compressibility index of the granules was determined by Carr's compressibility index Carr's index (%) = [(TBD – LBD) x 100]/TBD

4) Hausner's Ratio

The Hausner's ratio was related to inter particle friction and it could be used to predict powder flow properties.

Hauser's factor = Tapped bulk density/Loose bulk density

B) Post compression studies-[8,9]

1) Appearance-

All tablets were inspected visually and found white coloured round shaped and biconvex.

2) Thickness-

Thickness and diameter of tablets was determined using Vernier calliper. Five tablets from each batch were used, and average values were calculated.

3) Weight variation Test-

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

4) Hardness-

For each type of formulation, the hardness values for 3 tablets were determined using Monsanto hardness tester.

5) Friability-

For each type of formulation, the friability was determined as follows

Twenty tablets were weighed accurately and placed in Roche friabilator. The speed rotation of Roche friabilator was kept 25 rpm for 4 min. The tablets were removed and weighed. The percentage friability was determined using following formula

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

6) In-Vitro Dissolution study-

The study was carried out using dissolution apparatus USP Type-II (paddle)

Speed of Paddle: 50 rpm.

Temperature of Dissolution Medium: 37°C ± 0.5°C.

In vitro Dissolution Study 900 ml of 0.1N HC1 was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37°C+0.5°C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 2 hours at 50 rpm. After completion of 2 hours remove the 0.1N HCL and add 6.8 phosphate buffer then continue the apparatus up to 10 hours. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analysed spectrophotometrically at λ_{max}=270 nm using a UV-spectrophotometer.

Table 3. Dissolution Parameters

Parameters	**Detail's**
Dissolution apparatus	USP-Type II (Paddle)
Medium	0.1 N HCL and 6.8 Phosphate buffer
Volume	900 ml
Speed	50 rpm
Temperature	37°C ± 0.5°C.
Sample Volume Withdrawn	1 ml
Time Points	1,2,4,6,8,10 and 12 hours
Analytical Method	Ultraviolet Visible Spectroscopy
λ_{max}	270 nm

7) In-Vitro Release Kinetics Studies:

Different kinetics models (Zero-order, First-order, Korsmeyer's and Hixon Crowell) were applied to interpret the release profile from matrix system. The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from ER was described by using zero order kinetics or first order kinetics. The mechanism of drug release from ER was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics:

It defines a linear relationship between the fractions of drug released versus time.

$Q= k_o t$.

Where, Q is the fraction of drug released at time t and k, is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

Log C= Log C_o -kt/2.303

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of log % drug remaining Vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

3. Higuchi equation:

It defines linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$Q=K_2t^1/2$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

4. Peppa's-Korsemeyer equation (Power Law):

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law).

$Mt/ M_\infty=K.t^n$

Where, Mt is the amount of drug released at time t

M_α, is the amount released at time α

M_t/M_α, is the fraction of drug released at time t,

K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using PCPDisso1.

4. RESULTS AND DISCUSSIONS

4.1. Pre-compression Studies:

The values for bulk density and tapped density were found to range from **0.49±0.06** to **0.62±0.02** and **0.38±0.03** to **0.44±0.03** respectively. These results were satisfactory and may further influences the properties of the tablets. The values of angle of repose (<30) indicates good flow properties of the powder. The Hausner’s ratio and Carr’s index results were in the limits.

Table.4 Pre-compression studies of Lamivudine SR tablet

Formulation Code	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hauser's ratio	Carr's Index (%)
F1	32.26±0.4	0.61±0.06	0.44±0.03	1.38±0.01	16.88±0.05
F2	31.13±0.7	0.58±0.01	0.41±0.05	1.41±0.04	15.87±0.07
F3	29.20±0.3	0.49±0.06	0.38±0.03	1.28±0.02	14.23±0.04
F4	33.12±0.5	0.62±0.02	0.43±0.06	1.44±0.06	17.32±0.01
F5	32.23±0.4	0.61±0.04	0.42±0.02	1.45±0.03	16.46±0.02
F6	30.46±0.6	0.50±0.05	0.39±0.04	1.28±0.04	15.39±0.03

4.2. Post-compression Studies

The average percentage deviation for all tablet formulation was found to be with in specified limit and all the formulation complied the weight variation test. All tablets showed hardness and thickness values were found the range between 5.8±0.46 to 6.3±0.27 and 4.10±0.13 to 4.21±0.09 respectively. The friability of all tablet formulations were found to be <1%, indicating that the friability is within the prescribed limits.

Table.5 Post- compression studies of Lamivudine SR tablet

Formulation code	Weight variation	Hardness	Friability	Thickness
F1	296.89±0.23	5.9±0.43	0.59±0.58	4.14±0.15
F2	294.88±0.45	5.8±0.46	0.67±0.33	4.10±0.13
F3	297.80±0.33	6.1±0.27	0.59±0.28	4.21±0.09
F4	299.88±0.61	5.9±0.49	0.61±0.36	4.16±0.03
F5	298.96±0.61	6.1±0.39	0.58±0.24	4.18±0.02
F6	298.74±0.56	6.2±0.34	0.59±0.36	4.13±0.07

4.3. In-vitro dissolution Parameters of Lamivudine SR tablets:

The in-vitro drug release study for all the batches of Lamivudine was carried out using paddle method (USP apparatus). Among all the formulations (F1 to F6), the rate and extend of drug release was decreased with increasing polymer concentration. Data for in-vitro drug release study is presented in the following table 6 and graphical representation of graphical drug release vs. time graph is shown in the figure 1.

Table.6 Percentage Drug Release of Each Batch of Lamivudine

Time (Hours)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	23.31±0.47	17.88±0.23	22.51±0.42	35.86±0.55	19.36±0.41	21.26±0.36
2	41.25±0.24	32.55±0.29	31.09±0.54	59.36±0.61	29.65±0.36	30.56±0.37
4	61.63±0.31	46.22±0.44	42.86±0.56	84.25±0.45	42.25±0.21	42.59±0.51
6	83.22±0.40	65.84±0.35	55.36±0.35	99.96±0.32	56.24±0.25	52.68±0.46
8	99.86±0.28	88.23±0.65	68.25±0.84		74.96±0.34	66.89±0.71
10		98.47±0.54	83.76±0.25		97.78±0.43	84.58±0.44

12			98.81±0.63			92.78±0.53

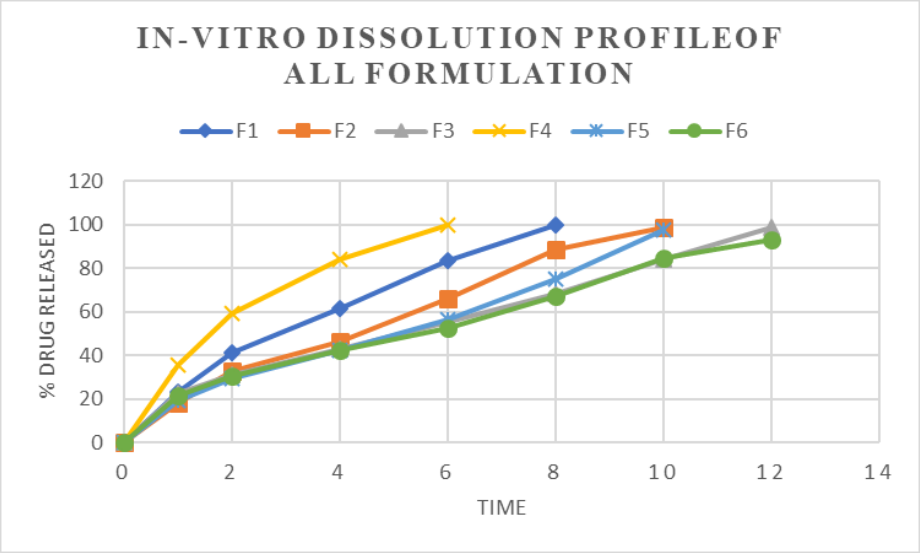

Figure.1 In-vitro dissolution profile of all formulations

4.4. In-Vitro Release Kinetics Studies:

The In -vitro dissolution data of lamivudine SR formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression including regression coefficients are summarized in Table 7 and plots shown in Fig.2. It was observed from the above, that dissolution of all the tablets followed zero order kinetics with co-efficient of determination (R^2) values above 0.984. Kinetic data also treated for Peppas equation, the absorbed slope (n) value is 0.9935 that shows Non-Fickian diffusion mechanism. The kinetic result reveals that, the best fit model for F3 formulation is Korsmeyer-Peppas models with highest correlation coefficient (r2) value i.e. 0.9935.

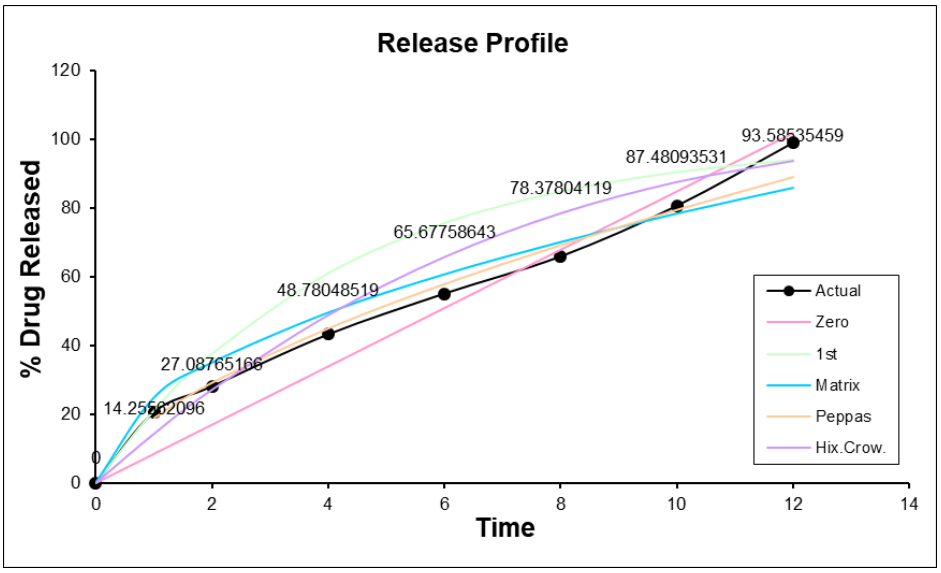

Figure.2 In-vitro Kinetics profile of F3 formulation

Table 7. Kinetics Study Table

	R	K
Zero Order	0.9927	8-4847
First Order	0.8868	-0.2358
Matrix	0.9777	24-7541
Peppas	0.9935	19-0911
Hix-Crow.	0.9374	-0-0500

4.5. Stability Study:

Stability study for the developed formulation F3 were carried out as per ICH guideline by storing at 40°C/75% RH up to three months. The formulation F3 was selected on the basis of their high cumulative percentage drug release.

Table 8. Stability study

Parameters	Initial	Final
Hardness	5-6	5-6
% of Drug Release (Batch F3)	98.81	97.65

The stability study showed that the formulation F3 was physically stable when stored at 40±20°C and 75±5% RH for three months and there was no significant difference in dissolution parameters of optimized formulation.

CONCLUSION

The present work was to formulate and evaluate sustain release matrix tablets of Lamivudine by using natural and semi-synthetic polymer to sustain the drug release from matrix tablet. The sustained release drug delivery was a promising approach to achieve a prolonged therapeutic action of drug. The matrix forming polymers, Xanthan gum, Ethyl Cellulose were studied. The amount of drug release for optimized formulation F3 was found to be 98.81±0.63. The cumulative percentage drug was decreased by increase in polymer concentration.

Physiochemical characteristics were used to assess the prepared tablet. The physiochemical analysis of the tablet reveals a white colour, a round form, and a smooth look. The formulation F3 as an optimized formulation because of this batch showed satisfactory result of the tablets parameter. Result of in vitro % drug release profile an indicated that formulation (F3) was the most promising formulations as the drug release from this formulation was high as compared to other formulations. So, F3 was found to be optimized formulation and was selected for further stability study. Also, Stability study of optimized batch is showed satisfactory result.

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