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DESIGN AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LAMIVUDINE

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ABSTRACT

The objective of the study was to develop sustained release matrix tablets of Lamivudine. Matrix tablets of Lamivudine, using various viscosity grades of hydroxyl propyl methyl cellulose and ethyl cellulose as retardant polymers were prepared by wet granulation method. The granules were evaluated for angle of repose, bulk density, compressibility index and hausners ratio. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and *in vitro* release studies. The granules showed satisfactory flow properties, compressibility. All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. The results of *in vitro* dissolution studies indicated that formulation SR8 is the most successful formulation of the study and exhibited highest drug release in the initial hours and the total release pattern was very close to the theoretical release profile of tablets. The rate of drug release decreased with increased polymer concentration. It was found that HPMC viscosity had a significant impact on the drug release from the prepared sustained release matrix tablets. The decrease in the release rate was observed with an increase in the polymeric system. Applying exponential equation, the formulations showed diffusion-dominated drug release and followed zero order kinetics. Optimized formulation of Lamivudine matrix tablets showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40°C / relative humidity 75% for 6 months. Thus, sustained release matrix tablets of Lamivudine using polymers were successfully formulated, evaluated.

INTRODUCTION

Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). It belongs to class III of the BCS Classification with High solubility and low permeability. Pharmaceutical research since 1950 turned to a new era towards optimizing the efficacy of the drug by designing the drug in different dosage forms posing challenges to the pharmaceutical technologists. The oral conventional types of drug delivery systems are known to provide a prompt release of drug. [1, 2] Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor (nRTI) and it is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine is rapidly absorbed with a bioavailability of over 80% following oral ingestion. The drug half-life in plasma is approximately 5-7 hours. It is bound to plasma proteins less than 36%. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. [3, 4, 5]

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) commonly referred to as HIV/AIDS, constitute one of the most serious infectious disease challenges to public health globally and has had a crippling effect in certain parts of the world. There are currently 33.2 million people living with HIV/AIDS globally. There are currently two known species of HIV, viz., HIV-1 and HIV-2 with their respective subspecies. HIV-1 is the globally common infection while HIV-2 is more prevalent in West Africa and takes a longer time to develop into immunodeficiency from infection than HIV-1. The virus infects the host cell by binding the viral gp120 protein to two transmembrane receptors, i.e., CD4+ and either of the two chemokine receptors, CCR5 and CXCR4. HIV infects macrophages and T-helper lymphocytes (CD4+) but the defining feature of AIDS is the depletion of CD4+ cells. The end stage of the disease may be characterized by a spectrum of diseases including opportunistic infections (such as Pnuemocystis carinii and Mycobacteruim tuberculosis), dementia and cancer. In addition to macrophages, lymph nodes, bone marrow, spleen and lungs, the CNS represents one of the most important anatomical sites of the virus after infection.

Although ARV drug therapy has contributed significantly to improved patient/disease management, its current use is associated with several disadvantages and inconveniences to the HIV/AIDS patient. Many ARV drugs undergo extensive first pass metabolism and gastrointestinal degradation leading to low and erratic bioavailability. The half-life for several ARV drugs is short, which then requires frequent administration of doses leading to decreased

patient compliance. The severe side effects associated with ARV therapy can therefore be attributed to the subsequent large doses essential for achieving a therapeutic effect, due to the inadequate drug concentrations at the site of action, and/or the poor bioavailability of several ARV drugs. [6]

The goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of drug by localization at the site of action, reducing the dose required or providing the uniform drug delivery. Sustained release constitutes any dosage form that provides medication over an extended time. [7]

MATERIALS AND METHODS

Materials

Lamivudine was gift sample from Cipla Ltd., Pune and Aurbindo Pharma., Hydrabad. HPMC K4M, HPMC K100M was gift sample from Colorcon Asia Ltd., Goa. All other ingredients used throughout the study were of analytical grade and were used as received.

Methods

Calculation of theoretical release profile of Lamivudine from sustained release formulations [8]

The total dose of Lamivudine for a once-daily sustained release formulation was calculated by using the fallowing equation.

Single and multiple oral dose ranging from 0.25 to 10 mg/kg (Therapeutic drug rang: 0.25 to 8 mg) Elimination rate constant = $0.693/t^{1/2}$, $t^{1/2}$ of Lamivudine = 0.693/7= 0.099 mg/h Hence availability rate = R = k.D = 0.099×70 = 6.93 mg/h Where D is usual dose of Lamivudine. The maintaince dose $D_m = R_h = R \times 24 = 6.93 \times 24 = 166.32$ mg Where h is number of hours for which sustained action is desired. Thus Total dose = $D + D_m = 70 + 166.32 = 236.32$ mg $D_{corrected} = D - R \times t_p = 70 - 6.93 \times 1.09 = 62.32$. Total dose = $D_{corrected} + D_m = 62.32 + 166.32 = 228.64 = 230$ mg Calculated total dose of Lamivudine was found to be 230 mg.

Method of preparation on sustained release matrix tablet of Lamivudine

Different tablet formulations were prepared by wet granulation method. Lamivudine was blended with HPMC K100M, HPMC K4M and Ethyl cellulose. The blend was dry mixed for 10 min. at 60 rpm in a mixer. The mixture was wetted with PVP (K30) solution and granulated for 5 min. using the same equipment and mixing speed. The wet mass was extruded at an extrusion speed

of 150 rpm by means of a gravity fed extruder. The extrudates were spheronized in a spheronizer using a friction plate with cross-hatched geometry. The pellets were dried in a fluidised bed dryer at 50°C for 10 min. This was followed by the addition of magnesium stearate and talc. The lubricated pellets were evaluated for precompression parameters and then compressed using 11 mm punch into tablets. [9]

Evaluation of sustained release matrix tablets

Tablets were evaluated for both its pre-compression parameters like bulk density, tapped density, Carr's index, Hausner ratio, angle of repose as well as their post compression parameters tablet thickness, hardness, friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for sustained release matrix tablet like swelling index and release rate of drug.

Precompression Parameters

I. Bulk density and Tapped density

Both bulk density (BD) and tapped density (TD) was determined. A quantity of 2 g of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced into 10 ml 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 second intervals. Tapping was continued until no further change in volume was noted. BD and TD were calculated using the following equations.

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Where, W - wt. of powder, V_0 - initial volume, W - wt. of powder, V_f - final volume.

II. Compressibility index and Hausner ratio

The compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated using measured values for bulk density (D_b) and tapped density (D_t) as follows:

$$\text{Compressibility index} = D_t - D_b / D_t \times 100$$

$$\text{Hausner ratio} = D_t / D_b$$

Where D_b- Bulk density, D_t - Tapped density

III. Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder 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.

$$\text{Tan } \Theta = h/r \quad \text{or} \quad \Theta = \tan^{-1}(h/r)$$

Where h = height of pile, r = radius of the base of the pile, Θ= angle of repose. [10]

Post- compression parameters

I. Tablet Hardness

The crushing strength ($kg/cm^{2)}$ of prepared tablets was determined for tablets of each batch by using Monsanto tablet hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.

II. Tablet Thickness

The thickness of the tablets was determined by using vernier caliper. Five tablets were used, and average values were calculated [11].

III. Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablets weighed over 250 mg, I.P. specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 5 % [12].

TABLE 1: PERCENTAGE DEVIATION ALLOWED UNDER WEIGHT VARIATION TEST AS PER I.P.

Average weight of tablet (X mg)	Percentage deviation
$X \leq 80$ mg	10
$80 < X < 250$ mg	7.5
$X \geq 250$ mg	5

IV. Friability Test:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. [1] The tablets were weighed again (W_f). The % friability was then calculated by

$$\% \text{ Friability} = (1-W_f/ W_0) \times 100$$

Where, W_0 -Weight of tablet before test, W_f -Weight of tablet after test.

V. Drug content uniformity:

Weigh and powder 20 tablets. Transfer a quantity of the powder containing about 230 mg of Lamivudine, accurately weighed, to a 500 ml volumetric flask. Add about 400 ml of water and dissolve using an ultrasonic bath if necessary. Make up to volume with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate. Dilute 5 ml of this solution to 50 ml with sulfuric acid (0.1 mol/l) VS. Measure the absorbance of this solution in a 1 cm layer at the maximum about 280 nm against a solvent cell containing the blank. [13]

VI. Water uptake

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The swelling capacity study of the tablet was done using USP XXII type I dissolution apparatus. The medium used was 0.1 N HCl (900 ml) and rotated at 100 rpm. The medium used was maintained at 37 ± 0.5 ^oC throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. [14] Swelling characteristics of the tablets were expressed in terms of swelling index (%).

$$\text{Swelling index (\%)} = W_f – W_i / W_i \times 100$$

Where, W_f - Weight of swollen tablet, W_i - Initial weight of table.

VII. *In vitro* Drug release studies

In vitro dissolution studies of Lamivudine tablets were studied in USP XXIII dissolution type II apparatus using paddles at 50 rpm. 900 ml of pH 1.2 buffer was used as a dissolution medium for first two hour and replaced with 6.8 phosphate buffer for specified time. The temperature of the dissolution medium was previously warmed to 37±0.50 C and was maintained throughout the experiment. One tablet was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of syringe fitted with a prefiter at known intervals of time (1 h). The

volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The sample was analyzed for drug release by measuring the absorbance at 271 nm using UV-visible spectrophotometer after suitable dilutions. All studies were conducted in triplicates. [15]

TABLE 2: COMPOSITION OF SUSTAINED RELEASE MATRIX TABLET

Sr. No.	Ingredients	S1	S2	S3	S4	S5	S6	S7	S8
1	Lamivudine	230	230	230	230	230	230	230	230
2	HPMC K100M	105	90	105	105	90	90	105	90
3	HPMC K4M	85	95	95	85	85	95	95	85
4	Ethyl Cellulose	15	15	15	10	15	10	10	10
5	Magnesium Stearate	5	5	5	5	5	5	5	5
6	Talc	5	5	5	5	5	5	5	5
7	Microcrystalline Cellulose	10	15	0	15	25	20	5	30

All quantities in mg

TABLE 3: PRECOMPRESSION PARAMETERS FOR FORMULATIONS S1-S8

Sr. No.	Batch	Angle of Repose	Bulk density (g/ml)	Tap density (g/ml)	Carr's index	Hausner Ratio
1	S1	24.56 ± 0.21	0.49± 0.020	0.57 ± 0.020	13.80 ± 0.030	1.10 ± 0.200
2	S2	23.62 ± 1.12	0.51 ± 0.030	0.66 ± 0.140	12.12 ± 0.020	1.13 ± 0.230
3	S3	23.89 ± 0.26	0.60 ± 0.022	0.73 ± 0.028	12.30 ± 0.140	1.14 ± 0.002
4	S4	22.84 ± 0.62	0.50 ± 0.028	0.68 ± 0.208	11.76 ± 0.210	1.13 ± 0.004
5	S5	25.64 ± 0.21	0.62 ± 0.130	0.68 ± 0.022	11.40 ± 0.231	1.12 ± 0.222
6	S6	21.58 ± 0.15	0.65 ± 0.281	0.74 ± 0.030	12.16 ± 0.003	1.13 ± 0.042
7	S7	22.46 ± 0.21	0.55 ± 0.232	0.63 ± 0.120	14.20 ± 0.004	1.16 ± 0.210
8	S8	23.76 ± 0.10	0.43 ± 0.030	0.55 ± 0.003	12.50 ± 0.002	1.14 ± 0.302

* All values are expressed as mean ± SD (n=5)

TABLE 4: POSTCOMPRESSION PARAMETERS FOR FORMULATIONS S1-S8

Batch Code	Hardness^ (Kg/cm^2)	Thickness^ (mm)	Weight variation* (mg)	Friability# (%)	Content uniformity^ (%)
S1	6.9±0.09	3.5±0.04	453±1.46	0.64±0.06	99.18 ± 0.55
S2	6.3±0.12	3.6±0.07	455±1.13	0.71±0.04	99.32 ± 0.28
S3	7.4±0.14	3.5±0.16	454±1.68	0.74±0.16	99.50 ± 1.13
S4	8.7±0.21	3.4±0.27	456±1.13	0.64±0.54	98.94±0.021
S5	7.5±0.16	3.6±0.22	455±1.86	0.73±0.96	96.76 ± 0.26
S6	7.0±0.13	3.6±0.09	451±1.63	0.78±0.55	97.89 ± 0.52
S7	6.5±0.11	3.5±0.08	454±1.54	0.76±0.23	99.76 ± 0.52
S8	7.3±0.17	3.5±0.11	455±1.98	0.68±0.09	99.89 ± 0.41

* All values are expressed as mean ± SD (n=20).

^ All values are expressed as mean ± SD (n=5).

All values are expressed as mean ± SD (n=10).

TABLE 5: % SWELLING INDEX AND % DRUG RELEASE PROPERTIES OF TABLETS

Batch code	% swelling index at the end of 12 h	% Drug release at the end of 24 h*
S1	140.07	91.45±0.32
S2	123.49	92.97±0.13
S3	147.77	86.78±0.42
S4	130.23	93.07±0.76
S5	110.44	94.76±0.14
S6	115.88	94.89±0.21
S7	149.97	89.33±0.16
S8	104.33	98.63±0.20

* All values are expressed as mean ± SD (n=6)

Treatment of drug release data with different kinetic equations

Different mathematical model may be applied for describing the kinetics of the drug release process from matrix tablets, the most suited being the one which best fits the experimental results. The kinetics of Lamivudine was determined by finding the best fit of the dissolution data to distinct models- Zero order, first order, Higuchi, Peppas.

I. Zero Order Kinetics: A zero-order release would be predicted by the following equation.

$$A_t = A_0 - K_0 t$$

Where

A_t - Drug release at time‘t’

A_0 - Initial drug concentration

K_0 - Zero-order rate constant

II. First Order Kinetics: A first-order release would be predicted by the following equation.

$$\text{Log } C = \text{Log } C_0 - 303.2\ K_f\ t$$

Where

C - Amount of drug remained at time‘t’

C_0 - Initial amount of drug

K_f - First-order rate constant

III. Higuchi’s Model: Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = K_h t^{½}$$

Where

Q - Percentage of drug released at time‘t’

K_h- Higuchi’s drug release rate constant

IV. Korsmeyer Model: The release rates from controlled release polymeric matrices can be described by the equation proposed by korsmeyer *et al*.

$$Q = K_m t^n$$

Where

Q - Percentage of drug released at time‘t’

K_m - Kinetic constant incorporating structural and geometric characteristics of the tablets

n - Diffusional exponent indicative of the release mechanism

The results of *in-vitro* drug release profile obtained for all the floating tablet formulations were plotted in modes of data treatment as follows:

i. Cumulative percent drug released versus time (zero-order kinetic model)

ii. Log cumulative percent drug remaining versus time (First-order kinetic model)

iii. Cumulative percent drug released versus square root of time (Higuchi's model)

iv. Log cumulative percent drug released versus log time (Korsmeyer equation) [16]

TABLE 6: KINETIC TREATMENT OF DRUG RELEASE DATA OF VARIOUS FORMULATIONS S1 to S8

Formulation code	Zero order	First order	Higuchi's matrix	Peppas model
	R^2			
S1	0.974	0.700	0.997	0.413
S2	0.976	0.672	0.998	0.468
S3	0.964	0.634	0.994	0.643
S4	0.980	0.670	0.998	0.578
S5	0.972	0.634	0.997	0.603
S6	0.987	0.682	0.993	0.559
S7	0.997	0.686	0.978	0.601
S8	0.984	0.640	0.998	0.603

Stability studies

Stability studies were carried out for optimized batch (S8 B) of sustained release matrix tablets of Lamivudine. The tablets were packed in aluminium foil placed in airtight container and kept at 4°C in refrigerator, 40°C /75% RH and 60°C for 60 days. At the interval of 15 days, the tablets were withdrawn and evaluated for physical properties and *in-vitro* drug release. [17] The results of stability studies are shown in following tables.

RESULT

The sustained release matrix tablets of Lamivudine were formulated by using different viscosity grades of HPMC (K4M, K100M) and ethyl cellulose by wet granulation technique. Microcrystalline cellulose was used as diluent. All the prepared tablets were found to be good without chipping, capping and sticking. The drug content was uniform (96.76 ± 0.26 to 99.89 ± 0.41) and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the tablets of same batch. The *in vitro* dissolution profiles of all the prepared sustained release matrix tablets of Lamivudine were found to control the drug release over a period of 24 h and the drug release decreased with increase in polymer concentration. Release of Lamivudine from most of the formulations was found to follow zero order kinetics (0.97 to 0.99) and derived correlation coefficient 'R^2' (0.99) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism controlling the drug release. When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.41 to 0.64) indicated that the drug release was by Non-Fickian mechanism. Among the various sustained release tablet formulations studied, formulation S8 containing polymer concentration HPMC K4M (85 mg) HPMC K100M (90 mg) ethyl cellulose (10 mg) showed promising results releasing 98.63% of the drug in 24 h with % swelling index 104.33 at the end of 12 h has been considered as an ideal formulation. Optimized batch of sustained release matrix tablet (S8 B) was further subjected for short term stability studies and found to be stable for 60 days.

DISCUSSION

The sustained release matrix tablets of Lamivudine were formulated using the wet granulation process using isopropyl alcohol as a granulating fluid. The evaluation data for properties such as hardness, friability, weight variation, drug content uniformity and water uptake indicated that the prepared sustained release matrix tablets were well within the specified standards. For sustained release matrix drug delivery system, the polymers used must be highly swellable in shortest time. Polymer with higher viscosity was shown to be beneficial than low viscosity polymer in retarding drug release. In order to retain the dosage form in the stomach for a long period of time and to avoid erosion and dissolution ethyl cellulose was used in combination with HPMC to retard the drug release, due to the low solubility of ethyl cellulose and hydrophobic nature of polymer. The viscosity of the polymer had major influence on swelling process, matrix integrity hence from the above results it can be concluded that linear relationship exists between swelling

process and viscosity of polymer. The mechanism and kinetics of drug release are dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer, with water soluble compounds released predominantly by diffusion.

CONCLUSION

Finally, it may be concluded that this matrix drug delivery system offers a valuable dosage form that can sustained the drug duration upto 24 h. The matrix tablets of Lamivudine provides a better option and reliability for treatment of HIV by allowing a better control of fluctuations observed with conventional dosage forms. Formulation S8 appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate clinical safety of these sustained release matrix tablets in suitable animal and human models.

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