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Formulation and evaluation of lamivudine sustained release matrix tablets using synthetic polymers

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ABSTRACT

The present investigation is aimed at formulating and evaluating sustained release matrix tablets of Lamivudine using different synthetic polymers such as Hydroxypropylmethylcellulose (HPMC K4M), Ethyl cellulose and Methyl cellulose taken at 10%, 20% and 30% of the total weight of the tablet. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). The sustained release tablets were prepared by direct compression method. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and hausner's ratio etc.The powder blend showed satisfactory flow properties.The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in-vitro release studies. All the formulations showed good results which were compliance with Pharmacopoeial standards. In-vitro drug release studies were carried out using USP dissolution apparatus type I at 100 rpm with 900 ml phosphate buffer solutions (PBS) of pH 6.8, maintained at 37±0.5°C. The release kinetics was analyzed using the zero-order, first-order model equation, higuchi's square-root equation, and the Korsmeyer-peppas model. In vitro release studies revealed that the release rate decreased with increases in polymer proportion. The sustained release matrix tablets containing 30% Hydroxypropylmethylcellulose (HPMC K4M) (Formulation LF3) were found to show good initial release (20.41% in two hours) and extended the release upto 12 hours and can overcome the disadvantages of conventional tablets of Lamivudine. The n value obtained from korsmeyer – Peppas model confirmed that the drug release was non- fickian diffusion mechanism.

Keywords: Lamivudine, Matrix tablets, Hydroxypropylmethylcellulose, Ethyl cellulose, Methyl cellulose.

INTRODUCTION

The oral route is the most common route used for administration of drugs. Tablets are the most popular oral solid 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].

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). As of 2009, AVERT (also known as the AIDS Education and Research Trust) estimated that there are 33.3 million people worldwide living with HIV/ AIDS, with 2.6 million new HIV infections per year and 1.8 million annual deaths due to AIDS.

When HIV infects a cell, a viral enzyme, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus. Reverse Transcriptase Inhibitors blocks the reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying [3].

Developing oral-sustained release formulations for highly water-soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets. Most of the researchers have worked on matrix tablets and multilayered matrix tablets. In the present study, a sustained release dosage form of Lamivudine has been developed that enables less frequent administering of drug [4].

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The objectives of this work are: (1) to evaluate the physical characters of prepared sustained release tablets, (2) to elucidate the effect of polymer composition, on the release kinetics and (3) to determine the chemical compatibility of formulation containing various ratios of polymer and drug. 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 [5]. Conventional oral formulations of LAM are administered multiple times a day (150 mg twice daily) because of its moderate half-life ($t_{1/2}$ = 5-7 hours)[6].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,[3] poor patient compliance, and high cost. Sustained release once-daily formulations of LAM can overcome some of these problems.

MATERIALS AND METHODS

Materials

Lamivudine and Methyl cellulose was obtained from Shasun pharmaceuticals, Puducherry. HPMC K4M and ethyl cellulose obtained from Tri star formulation Pvt. Ltd; Puducherry. Poly vinyl pyrrolidone and microcrystalline cellulose was obtained from Nickon laboratories Pvt. Ltd; Puducherry. Magnesium stearate and talc was purchased from Loba chemie Pvt. Ltd; Mumbai. All other chemicals and reagents used were of analytical grade.

Method

Direct compression method

The composition of different formulations of lamivudine matrix tablets were

shown in Table 1. Pre weighed ingredients were passed through Sieve no. 60 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed in a polythene bag for 15 minutes to get a uniform mixture. Talc and magnesium stearate were added to the powder mixture and compressed on a 16- station rotary tablet compression machine using 11mm round flat face punch.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 400 mg with different drug polymer ratios like 1:0.2, 1:0.4, and 1:0.6. The various polymers used were hydroxypropylmethyl cellulose (HPMC K4M), ethyl cellulose and methyl cellulose.

In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose (HPMC K4M), ethyl cellulose and methyl cellulose. Microcrystalline cellulose (MCC) is used as diluent. Magnesium stearate 1% and talc 2 % were used as lubricant and glidant [7].

Evaluation Parameters

Angle of Repose

The angle of repose of powders was determined by the funnel method. The accurately weighed physical mixture was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$

where h and r are the height and radius of the powder cone, ? is the angle of repose.

Loose Bulk Density (LBD)

An accurately weighed powders from each formulation was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powders was measured which gave bulk volume. The loose bulk density (LBD) of powders was determined using the following formula.

Loose bulk density = Total weight of powders / Total volume of powders

Tapped bulk density (TBD)

An accurately weighed powders from each formulation was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powders was determined by the following formula.

Tapped bulk density= Total weight of powders / Tapped volume

Carr's Compressibility Index

It is a simple index that can be determined on small quantities of powders. In theory, the less compressible a material the more flowable it is. The compressibility index of the powders was determined using following formula [8].

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Where, TBD = Tapped Bulk Density
LBD = Loose Bulk Density

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties[9]. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. And greater than 1.5 indicates that poor flow, in between these values passable.

Evaluation of tablets

Appearance

The tablets were visually observed for capping, chipping, and lamination.

Dimension (Thickness and Diameter)

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a Vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

Tablet Hardness

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

Percent Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

Friability = 100 X (1-W2/W1)

Where, W1: Initial weight before friabilator
W2: Final weight after friabilator.

Weight Variation

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method [8].

Drug Content

Twenty tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets equivalent to100 mg of lamivudine was extracted with pH 6.8 phosphate buffer and the solution was filtered through whatmann filter paper. The absorbance was measured at 271.5 nm after suitable dilution [10].

In -Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus (Basket method) at 100 rpm in 900 mL of phosphate buffer pH 6.8 throughout the dissolution up to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered

through whatmann filter paper and drug content in each sample was analyzed by UV-Visible spectrophotometer at 271.5 nm [11].

Drug Release Kinetics

Data obtained from dissolution studies were fitted to various kinetic equations. The kinetic models used were zero order(cumulative percentage of drug released vs time), first order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time) and Korsmeyer (log cumulative percentage of drug released vs log time) equation [12]. The data were fitted into the PCP disso V3 software to find out R^2 value.

RESULT AND DISCUSSION

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content and in-vitro drug dissolution studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Characterization of powder blend

The powders prepared for compression of sustained release tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range of 21.48±0.17° to 23.93±0.77° which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.455±0.00 to 0.500±0.00 g/ml; the tapped density was in the range of 0.526±0.00 to 0.556±0.00 g/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 10.000±0.00 to 14.286±0.00, the hausner ratio was found to be in the range of 1.11±0.00 to 1.17±0.00, indicating compressibility of the tablet blend is good. These values indicate that the prepared powders exhibited good flow properties.

Evaluation of matrix tablets

The lamivudine matrix tablets were white, smooth, and round, biconcave shaped in appearance. The results of physicochemical characterizations are shown in Table 3. The thickness of matrix tablets was measured by vernier caliper and was ranged between 4.46±0.05 and 4.55±0.07 mm for all formulation. The weight variation for different formulations (LF1 to LF9) was found to be 0.299±0.22% to 0.657 ± 0.43%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the matrix tablets was measured by Monsanto tester and was controlled between 7.35±0.67 and 8.10±0.39 kg/cm^2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for LF1 to LF9 was found to be in between 98.48±0.52 to 100.90±0.45 % of Lamivudine, it complies with official specifications.

In- vitro release study

In-vitro dissolution studies of all the formulations of matrix tablets of Lamivudine were carried out in pH 6.8 phosphate buffer solution. The study was performed for 12 hours, and percentage drug release was calculated at 1 hour time intervals. The results of in-vitro dissolution studies of all formulations were shown in Figure1. The lower initial drug dissolution was observed in tablets containing HPMC K4M (LF3), methyl cellulose (LF6) and ethyl cellulose(LF9). This showed that in high concentration polymers in the presence of pH 6.8 phosphate buffer solution. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. It is expected that the developed formulation should have the following theoretical drug release profile. The drug released from formulation LF1 toLF3 containing HPMC K4M at three concentration levels of 10%, 20%, 30% were found to be 92.56±1.85, 89.57 ± 0.63, and 81.28 ± 1.23% for Lamivudine respectively. The drug released from formulation LF4 to LF6 containing methyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 96.63 ± 1.05, 93.52 ± 0.63 and 89.95 ± 0.82% for Lamivudine respectively. The drug released from formulation LF7 to LF9 containing ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 94.71 ± 0.81, 91.26 ± 0.98 and 86.92 ± 0.70% for Lamivudine respectively at the end of 12 hours.

Table 1:Composition of Lamivudine matrix tablet

Ingredients(mg/tablet)	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9
Lamivudine	200	200	200	200	200	200	200	200	200
HPMC K4M	40	80	120	-	-	-	-	-	-
Methyl cellulose	-	-	-	40	80	120	-	-	-
Ethyl cellulose	-	-	-	-	-	-	40	80	120
Microcrystalline- cellulose pH 102	128	88	48	128	88	48	128	88	48
Polyvinyl pyrrolidone-k30	20	20	20	20	20	20	20	20	20
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8
Total weight	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Table 2:Flow properties of powders

Formulation code	Angle of repose (º)*	Loose bulk density(g/ml)*	Tapped bulk density(g/ml)*	Hausner ratio*	Carr's index (%)*
LF1	22.19±0.98	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
LF2	21.48±0.17	0.500±0.00	0.556±0.00	1.11±0.00	10.000±0.00
LF3	22.36±0.98	0.500±0.00	0.556±0.00	1.11±0.00	10.000±0.00
LF4	23.44±0.73	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
LF5	23.05±0.19	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
LF6	22.30±0.17	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
LF7	23.93±0.77	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
LF8	23.20±0.61	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
LF9	22.49±0.36	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00

**All the values are expressed as mean± SE, n=3.*

Table 3: Physico-chemical characterization of Lamivudine matrix tablets

Formulation code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (%)	Drug content (%w/w)**
LF1	4.55±0.07	8.05±0.44	0.150	400.4±1.50	99.87±0.28
LF2	4.46±0.07	7.95±0.37	0.099	402.15±2.94	98.48±0.52
LF3	4.50±0.07	8.10±0.39	0.050	400.9±2.73	99.11±0.53
LF4	4.46±0.05	7.75±0.42	0.075	401.25±3.57	99.45±0.92
LF5	4.49±0.06	8.05±0.44	0.124	402.2±3.61	100.08±0.45
LF6	4.52±0.04	8.00±0.58	0.100	401.75±2.22	99.40±0.31
LF7	4.54±0.10	7.55±0.55	0.087	400.8±3.24	100.15±0.43
LF8	4.49±0.07	7.35±0.67	0.050	403.05±3.12	100.90±0.45
LF9	4.51±0.06	8.05±0.44	0.100	402.95±2.28	98.93±0.86

**All the values are expressed as mean± SE, n=10;*
***All the values are expressed as mean± SE, n=3.*

Table 4: Different Kinetic models for Lamivudine matrix tablets (LF1 to LF9)

F. Code	Zero order R^2	First order R^2	Higuchi R^2	Korsemeyer- R^2	Peppas n	Best fit model
LF1	0.978	0.918	0.970	0.987	0.720	Peppas
LF2	0.988	0.895	0.950	0.989	0.749	Peppas
LF3	0.988	0.927	0.945	0.992	0.759	Peppas
LF4	0.981	0.849	0.967	0.986	0.698	Peppas
LF5	0.986	0.890	0.962	0.989	0.731	Peppas
LF6	0.989	0.899	0.955	0.990	0.743	Peppas
LF7	0.983	0.888	0.967	0.987	0.726	Peppas
LF8	0.988	0.892	0.957	0.989	0.736	Peppas
LF9	0.989	0.922	0.955	0.990	0.759	Peppas

Table 5: $t_{50\%}$ drug release of formulation LF1 to LF9

Parameter	Formulation code LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9
$t_{50\%}$ (hrs)	5.2	6.3	8.0	5.3	5.8	6.2	5.3	6.0	6.4

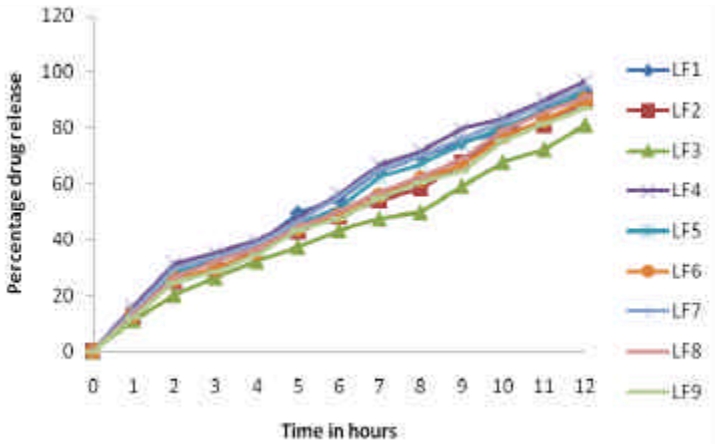

Figure 1: In-vitro drug release of formulation LF1 to LF9

The release rate from the HPMC K4M polymer was found to be less as compared to Ethyl cellulose and methyl cellulose. This might be due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The regression coefficient obtained for formulation LF1 to LF9 korsmeyer peppas kinetics were found to be higher (R^2: 0.986 to 0.992) when compared with other kinetic models (first order, zero order, higuchi). The results were shown in Table 4. Drug release data was also fitted to peppas model, which showed the slope (n) value (0.698 to 0.759), indicating a anomalous diffusion release mechanism. Lamivudine exhibited anomalous diffusion as dominated mechanism for optimized formulation (LF3).

Based on the *In- vitro* drug release data, the $t_{50\%}$ was calculated and the results given in the Table 5. From this data, the formulation LF3 showed the maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation LF3 was best formulation among all the nine formulations.

CONCLUSION

This study deals with the investigation carried out with the objective of developing oral sustained release formulation of Lamivudine using Hydroxypropylmethylcellulose, Ethyl cellulose and Methyl cellulose. Preparation of matrix tablet by direct compression technique was found to be more effective in sustaining the release of drug. Drug content for all formulations were found to be complies with pharmacopoeial standards. Formulation LF3 containing HPMC K4M with hardness 8.1 kg/cm^2.The controlled and efficient drug delivery system developed in the present study will maintain the plasma Lamivudine levels better, which will overcome the drawbacks associated with the conventional therapy. The kinetics of drug release was optimized formulation explained by peppas equation. The drug release from the tablets was sufficiently sustained and anomalous diffusion mechanism of the drug from tablets was confirmed. Based on the in-vitro drug release data, the formulation LF3 it was concluded as best formulation. In conclusion the present study demonstrated the successful preparation of sustained release matrix tablet of Lamivudine.

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