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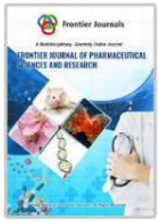

Original Research Paper

EXTENDED RELEASE TABLETS OF LAMIVUDINE: FORMULATION AND IN VITRO EVALUATION

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ABSTRACT

The main objective of the present work is to formulate and evaluate extended release tablets of Lamivudine using different polymers viz. Hydroxyl Propylmethyl Cellulose, Eudragit RPLO, Polyethoxyoxides, Poly Vinyl pyrrolidine K30 (PVP K30), Sodium Carboxymethyl Cellulose, Microcrystalline Cellulose (MCC). Then the release rates were get retarded by increasing the polymer concentrations from lower to higher and it shows release of drug from polymer for extended periods of time. In this study, the extended relase tablets are prepared by direct compression technique by using the various polymers in increasing concentration. The pre-compression and post-compression studies are performed like Bulk density, Tapped density, Angle of repose, Cars index, Hauser's ratio. The post-compression evaluation studies like thickness, weight variation, hardness, friability, uniformity of drug content, dissolution. After evaluation of physical properties of tablet, the in-vitro drug release study of extended release tablet of Lamivudine was performed in 0.1N HCl for 2 hours and in phosphate buffer pH 7.4 up to 24 hours. The formulation F4 and F9 shows maximum drug release with in 24 h due increasing the concentration of HPMC K15 M and the Eudragit RPLO. Eudragit RPLO and HPMC K 15M shows maximum cumulative drug release of 99.78% and 99.99%. Then both formulations taken as optimum formulations and conducted stability studies to these two formulations for 3 months. Then again evaluated the pre-compression and post-compression stability. Results obtained from the stability studies cannot observe any changes after conducting the stability studies.

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1. INTRODUCTION

The present study was aimed to develop the generic formulation of extended release tablets of Lamivudine using controlled release polymer. The selection of excipients a plays a vital in role in drug release. The selected excipients are necessary to achieve a constant drug release to the body. The matrix tablets compose and drug and the drug release retarding polymers/ an excipients offer undemanding approach in designing an extended release system[1]. Hydrophilic matrices containing swellable polymers are referred to as swellable controlled release systems or hydrophilic matrix tablets. A number of

polymers have been investigated to develop in situ gel forming systems, due to the ability of these matrices to release an entrapped drug in aqueous medium and to regulate release of such drug by control of swelling and cross linking. Hydroxypropyl Methylcellulose (HPMC), Eudragit, Sodium alginate and Guar gum are the polymers most widely used as gel forming agents in the formulation of solid, liquid, semisolid and even controlled release dosage forms[2,3]. Extended release dosage forms that allow at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release form. Ex: Controlled release, Sustained release. Lamivudine is a Nucleoside Reverse Transcriptase Inhibitor (NRTI), used for the treatment of HIV and chronic Hepatitis B. Long-term AIDS therapy with the conventional tablets of Lamivudine found to have some drawbacks, accumulation of drug in multi-dose long-term therapy, poor patient compliance and high cost. For the treatment of AIDS, the dosage of conventional oral formulations of Lamivudine is 300 mg per day (i.e. 150 mg twice daily, multiple times a day) with an absolute bioavailability of 86 % ± 16 %, peak serum concentration of Lamivudine (C_{max}) of 1.5 ± 0.5 mcg/ml and mean elimination half-life (t½) of 4 to 6 hours, thus necessitating frequent[4,5].

2. MATERIAL AND METHODS

Lamivudine was obtained from Mylan Labs, Hyd. HPMC K15M, Eudragit RPLO, Polyethylene oxide, Sodium CMC, Poly vinyl pyrrolidone K 30, Microcrystalline cellulose, Magnesium stearate, Talc was obtained from Merck chemicals and S.D fine chemicals Mumbai.

Preparation of Lamivudine Extended Release Tablets

Extended release of oral matrix tablets for Lamivudine was prepared by direct compression method by 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. All ingredients were collected and weighed accurately. Polymers such as Hydroxy Propyl Methyl Cellulose (HPMC K15 M), Eudragit and HPMC K 100M were used in the preparation of matrix tablets with incorporation of Sodium CMC as the trade of release would be as per. These polymers were found to be ideal for the preparation of extended release matrix tablets. Twenty five oral matrix tablet formulations were prepared with Lamivudine by employing various polymers at different concentrations[6-7].

3. EVALUATION OF LAMIVUDINE TABLETS

Pre-Compression Parameters

Bulk density (D_b)

Bulk density is elucidated that the ratio of mass of powder (w) to the bulk volume (V_b).

Generally, the bulk volume is measured by weighing 25 g of blended mixture and transferred it into a 50 ml of measuring cylinder. The volumes of blended mixture that are occupied in the measuring cylinder are taken as bulk volume and then calculate the bulk density by using formula.

Bulk density (ρ) = weight of granules (w)/ bulk volume (V_b)

Tapped density (D_t):

Tapped density is elucidated that the ratio of mass of powder (w) to the tapped volume (V_t). Approximately 50 g of granules are introduced into a 100 ml measuring cylinder. The volume occupied by the granules is noted initially. Tapped volume is measured by tapping the cylinder (containing granules) on to hard wooden surface 3 times from a height of 1 inch at 2 second intervals. Tapped volume is the volume occupied by the same mass of powder after a standard tapping of measure.It is expressed in g/cc and is given by

Tapped density = weight of granules / tapped volume

Angle of repose

Angle of repose is elucidated that the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose (θ) is intended by using the below given formula.

$$\text{Tan } \theta = (h/r)$$

Method:

A glass funnel is fixed to the stand by using a clamp. Approximately 50 g of granules is passed through a 20 number mesh sieve and the obtained granules are transferred into the glass funnel, the orifice of the funnel blocked by the thumb. The thumb is removed from the orifice and the powder is emptied from the funnel. The distance between the bottom of the funnel stem and the top of the powder pile must be 6.4mm. The height and radius of pile is measured with the ruler. The angle of repose is thus estimated by using above formula. A value for angle of repose ≥ 40° suggests a poorly flowing material.

Carr's Consolidation Index (Compressibility index)

Compressibility index can be measure of the potential strength that the granules could build up in its arch in a hopper and also ease with which such an arch could be broken.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

Hausner's ratio

Hausner's ratio is elucidated that ratio of tapped density to the bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio (HR)} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post Compression Parameters

Tablet thickness

The thickness of extended release tablets was measured by placing the randomly selected 5 tablet between the arms of the Vernier Callipers.

Weight variation

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weightand percentage weight variation.

Weight variation = (Individual weight –Avg weight/Individual weight) x 100

Hardness

Tablet hardness was determined for 10 tablets using a Monsanto hardness tester. Hardness are used to measure the degree of force (in kilograms, pounds, or in arbitrary units) required to break a tablet. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet.

Friability

Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed Sample tablets were placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

$$F = (W_1 - W_2 / W_1) \times 100$$

Where, W_1 – is weight of the tablet before and

W2 - is weight of the tablet after test

Drug Content uniformity test

Ten tablets of Lamivudine were selected randomly and then weighed, crushed in a motar and pestle. Lamivudine powder equivalent to 300 mg was transferred to a 250 ml volumetric flask and 10 ml methanol is added. The drug is dissolved in methanol by vigorously shaking the volumetric flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and kept aside for 12 h. Then filtered the solution of Lamivudine and made dilution by taking 0.1ml solution and diluted to 10ml with distilled water. The Lamivudine content was estimated by using UV spectrophometry at 270nm. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

In-vitro drug release study

The in-vitro dissolution studies of Lamivudine from formulated extended release matrix tablets were carried out firstly with the 900 ml dissolution medium of 0.1N HCl for 2 hrs then it was replaced with 900 ml of 7.2 pH phosphate buffer. The studies were performed in USP dissolution apparatus type II (paddle) at rotation speed of 100 rpm/min and temperature of 37 ± 0.5˚C. A single Lamivudine tablet (300mg) was dropped in 900 of dissolution medium. The samples were withdrawn at 0, 1, 2, 4, 6, 8, 10, and 12 h and samples were replaced with fresh dissolution medium. Then samples were analyzed for Lamivudine content at 270nm by using UV spectrophotometer[8-9].

Accelerated Stability studies

The formulated Lamivudine ER tablets, formulation F4 and F9, which gave in-vitro drug release in predetermined rate, were kept for a short term accelerated stability study in stability chamber at 40±2 ºC/75±5% RH for three months as per ―International Conference on Harmonization states (ICH) guidelines. Samples were withdrawn for every month of storage and evaluated for appearance, hardness, Uniformity of weight, Friability and drug content.

4. RESULTS & DISCUSSION

Table 1 Composition of Lamivudine Extended Release Oral Matrix Formulations by using various polymers

Name of Ingredients (mg)	Quantity of Ingredients per each Tablet (mg)													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Lamivudine	300	300	300	300	300	300	300	300	300	300	300	300	300	300
HPMC K 15M	75	100	125	150	175	50	75	100	125	150	175	130	185	213
Sodium CMC	50	50	50	50	50	50	50	50	50	50	50	50	50	50
MCC	164	139	114	89	64	154	149	109	79	54	29	109	54	26
Magnesium streate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Total tablet weight (mg)	600	600	600	600	600	600	600	600	600	600	600	600	600	600

Table 2 Pre-compression properties of Lamivudine powder blend

Formulatiton code	Loose bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of Repose (θ)	Carr's Compressibility index	Hausner' ratio
F1	0.60±0.03	0.76±0.01	26.94±0.02	12.10±0.024	1.120±0.03
F2	0.60±0.01	0.78±0.01	25.69±0.03	14.20±0.022	1.118±0.02
F3	0.62±0.02	0.77±0.02	25.42±0.05	11.89±0.009	1.121±0.05
F4	0.61±0.01	0.77±0.01	26.85±0.02	14.87±0.017	1.123±0.04
F5	0.60±0.03	0.77±0.3	27.01±0.03	13.68±0.014	1.128±0.02
F6	0.67±0.04	0.77±0.02	25.76±0.05	12.37±0.024	1.129±0.01
F7	0.64±0.01	0.79±0.01	26.40±0.07	14.24±0.019	1.120±0.04
F8	0.62±0.02	0.78±0.01	27.32±0.09	11.20±0.027	1.127±0.05
F9	0.69±0.01	0.77±0.02	26.54±0.13	12.75±0.017	1.129±0.05
F0	0.65±0.02	0.78±0.02	25.87±0.07	11.78±0.014	1.16±0.02
F11	0.63±0.01	0.80±0.01	25.76±0.05	12.37±0.024	1.129±0.03
F12	0.65±0.02	0.77±0.01	26.40±0.07	14.24±0.019	1.120±0.03
F13	0.62±0.03	0.79±0.03	27.32±0.09	11.20±0.027	1.127±0.02
F14	0.68±0.01	0.77±0.01	26.54±0.13	12.75±0.017	1.129±0.04

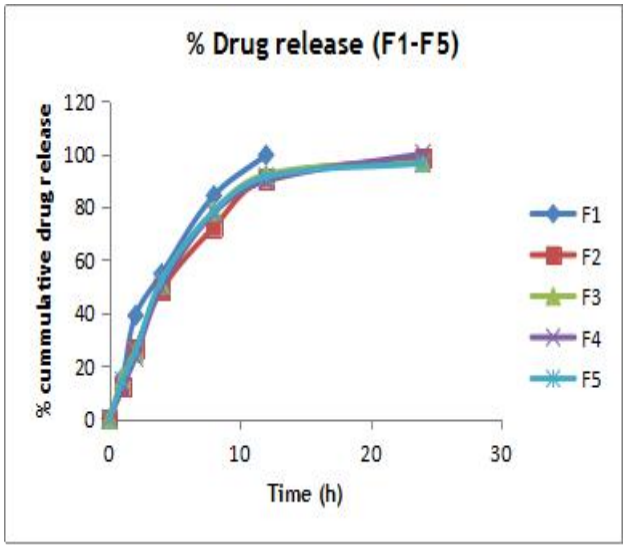
Table 3 Evaluation of extended release Lamivudine tablets

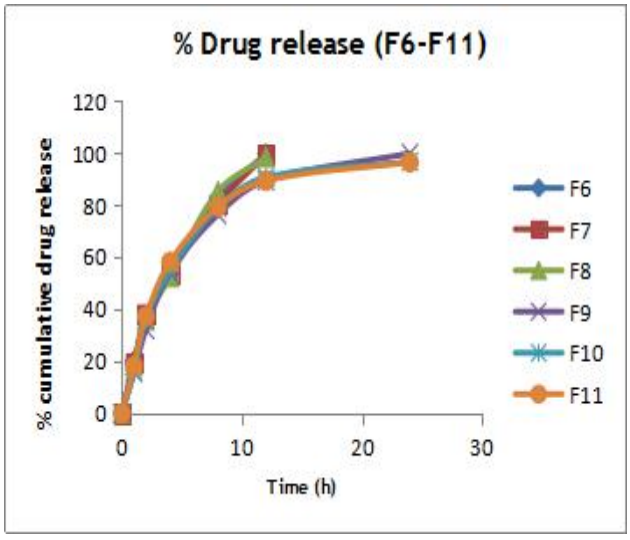
Formulation code	Parameters				
	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm^2)	Friability	% drug content
F1	3.9±0.02	600±2.0	5.5±0.4	0.19	298.5±0.5
F2	4.1±0.01	598±3.0	5.7±0.3	0.12	296.3±0.5
F3	4.2±0.03	600±3.0	5.5±0.3	0.18	298.6±0.5
F4	4.0±0.01	599±2.0	5.8±0.2	0.17	299.9±0.2
F5	4.1±0.01	599±4.0	5.5±0.3	0.15	298.2±0.3
F6	4.3±0.02	605±2.0	5.6±0.2	0.18	297.8±0.5
F7	3.8±0.02	600±3.0	5.7±0.3	0.16	298.6±0.5
F8	4.2±0.02	599±3.0	5.5±0.4	0.18	299.8±0.3
F9	4.4±0.01	600±2.0	5.8±0.2	0.14	300.2±0.5
F10	4.2±0.02	599±3.0	5.6±0.1	0.20	298.2±0.2
F11	4.3±0.03	605±2.0	5.8±0.2	0.17	300.6±0.6
F12	4.5±0.01	601±4.0	5.5±0.3	0.15	298.2±0.3
F13	4.4±0.04	599±2.0	5.6±0.2	0.18	298.2±0.5
F14	4.4±0.01	598±3.0	5.7±0.3	0.16	298.3±0.1

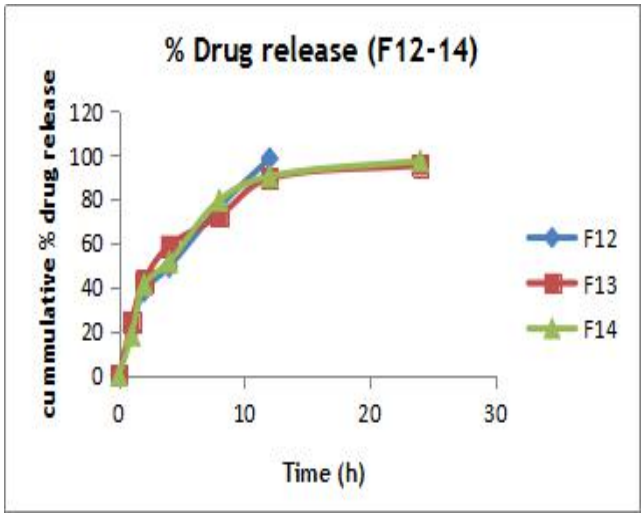
Table 4 In-vitro drug release of Lamivudine extended release tablets

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	15.34	12.21	15.65	11.56	14.23	20.24	19.36	18.24	15.64	16.23	18.12	20.23	24.36	18.23
2	38.95	26.37	25.12	23.24	25.68	35.26	38.21	35.84	32.12	36.14	37.24	38.25	42.89	41.02
4	54.72	48.74	50.68	49.35	52.31	50.54	53.47	52.31	53.94	54.67	58.12	49.23	58.62	51.47
8	84.19	72.36	78.34	77.64	78.39	82.94	80.24	85.19	76.31	78.98	79.28	76.23	72.36	79.32
12	99.52	90.65	92.12	89.64	91.25	99.58	99.26	98.27	89.24	90.57	89.26	98.26	89.23	90.23
24	-	98.32	96.78	99.99	96.35	-	-	-	99.78	96.54	96.34	-	95.23	97.21

FIG 1-3 Drug release of Lamivudine extended release tablets







In this study, Fourteen Formulations of Lamivudine extended release tablets were prepared successfully by using various concentration of polymer like HPMC K 15M, Eudragit RLPO, PEO (as per the formula given in table 1) in various ratios of concentration with respect to drug, which could release the drug in predetermined rate for 12 by direct compression method.

Tablets were evaluated for pre-compression properties, thickness weight variation, hardness, friability, drug content uniformity, In-vitro dissolution study and stability studies[10].

The results of loose of bulk density and tapped density of Lamivudine was obtained in range from (0.60±0.03

gm/cm^3 to 0.69±0.01gm/cm^3) and (0.77±0.02 gm/cm^3 to 0.80±0.01 gm/cm^3) respectively. The results of angle of repose, Carr's consolidation index (%) and Hausner's ratio of Lamivudine blended powder was obtained in range from (25.42±0.05 to 27.32±0.09), (11.20±0.02 to 14.89±0.01) and (1.118±0.02 to 1.129±0.04), respectively. The obtained results of angle of repose (< 30), carr's index (<16 %) and Hausner's ratio was indicated that have a good flow properties of Lamivudine powder blend.

The extended release tablets of Lamivudine mean thickness was almost uniform in all the formulations. The thickness varies between 3.8±0.02mm to 4.5±0.01 mm. The prepared extended release tablets of Lamivudine have own good mechanical strength with sufficient hardness in the range of 5.5±0.3 kg/cm^2 to 5.8±0.2 kg/cm^2. The friability values of the all the formulations of the Lamivudine were obtained in range 0.1-0.2% that indicated the tablets have good mechanical resistance. The weight variation of all fourteen formulations of Lamivudine extended release tablets was found to be 549±2.0 to 701±3.0 mg. All the tablets of Lamivudine from each formulation have passed weight variation test, as the % weight variation was within the pharmacopoeial limit of ±5% of the tablet. The percentage drug content of all the Lamivudine ER tablets was found to be between 248.2±0.5 to 251.9±0.2 of Lamivudine which was within the acceptable limits[11].

In-vitro drug release

The dissolution rate of the all the fourteen formulations were performed successfully. All the formulations shows drug release. So it was concluded that formulation F4 and F9 is an optimized batch because its drug release profile (fig.1-3) shows drug release for 24 hours in predetermined rate. At higher percentage of HPMC and Eudragit in tablets, when in contact with release medium, HPMC may swell and form a thick gel, thus may decrease the size of the pores present in the tablet and reducing the drug release.

Formulation F4 and F9 which showed promising results, were subjected to stability studies at ambient room conditions for 3 months. After 3 months, extended release tablets did not show any change in physical appearance or drug content.

5. CONCLUSION

Lamivudine extended release tablets were prepared by direct compression method. Here, HPMC 15KM and Eudragit RPLO and PEO polymers are used in lower to higher concentration with respect to the Lamivudine. It is finally concluded that the formulation of F4 and F9 containing HPMC 15KM and Eudragit RPLO with respect to Lamivudine gives drug release in 24 h at predetermined rate from all the other formulation F1 to F14. As well we increase the concentration of the polymer then the drug release gets decreased and retarded. In this study, we finally concluded that by increasing the polymer concentration that may shows the extended release of drug from the polymer.

6. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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