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Research Article

Formulation Development and Evaluation of Lamivudine Sustained Release Tablets

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Abstract

Lamivudine is used widely in treatment of Hepatitis B and AIDS either alone or in combination with other antiviral drugs because of its water solubility and shorter half-life (5-7 hrs) drug requires frequent dosing by oral route, off various recent techniques for controlling drug release. The study was undertaken with an aim to formulation development and evaluation of Lamivudine sustained release tablets using polymers hydroxypropylmethylcellulose and ethylcellulose. Lactose monohydrate was used as channeling agent and or as filler. Preformulation study was done initially and results directed for the further course of formulation. Based on preformulation studies different formulations of Lamivudine were prepared using selected excipients. FT-IR study performed for the identification and compatibility study of drug with polymers and found the characteristics peaks of various groups and matched with pharmacopoeial standard. Powder and blends were evaluated for tests - bulk density, tapped density, compressibility index, Hausner's ratio before being punched as tablets. From the above results and discussion it is concluded that formulation of sustained release tablet of Lamivudine containing 80 mg of hydroxypropyl-methylcellulose E15 (high viscosity grade) and 80 mg of ethylcellulose i.e. formulation F7 can be taken as an ideal or optimized formulation of sustained release tablets for 16 hours release as it fulfills all the requirements for sustained release tablet and our study encourages for the further clinical trials and long term stability study on this formulation.

Keywords: Lamivudine, sustained release tablets, hydroxypropyl-methylcellulose E15, ethylcellulose.

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CONTENTS

1. Introduction

Lamivudine (β-L-2',3'-dideoxy-3'-thiacytidine), one of the dideoxycytidine (ddC) analogue NRTIs, is the first nucleoside analogue approved to treat chronic HBV infection and has been shown to benefit various categories of patients. These include HBe-positive and -negative patients, nonresponses to interferon-α therapy, and patients with decompensated cirrhosis. Hepatitis B is a serious disease caused by a virus that attacks the liver. The virus, which iscalled Hepatitis B virus (HBV), can cause lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death. Matrix tablets composed of drug and release retarding material (e.g., polymer) offer the simplest approach in designing a sustained release system. Matrix tablets of Lamivudine are prepared by direct compression method using polymers HPMC and Ethyl cellulose. Matrix dosage form can remain the intestinal region for several hours and hence significantly prolong the intestinal residence time of the drugs. Prolonged transit time improve bioavailability, reduce drug wastage, and improve solubility for drugs that are less soluble in a high pH environment. The matrix tablets prepared in the present study by direct compression method have advantages over the tablets prepared by wet granulation in time and energy consumption, thus making it possible to formulate tablets at a lower cost. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression.

2. Methodology

Materials

Lamivudine USP (Hetero Drugs Ltd., Medak (Andhra Pradesh), lactose mono hydrate BP (Cepam Specialties Ltd., Punjab), HydroxypropylMethylcellulose E-15 USPNF (Huzhou Zhanwang Pharmaceuticals Co. Ltd., China), Ethyl cellulose BP (Zhongbao Chemicals, China), Colloidal Silicon dioxide(Aerosil®-200) USPNF (Nippon Aerosol Co. Ltd., Tokyo, Japan), Magnesium Stearate BP (Arian Enterprises, Delhi).

Preparation of lamivudine sustained release tablets:

All ingredients were collected and weighed accurately. Sifted Lamivudine USP with lactose and polymers through sieve no. 60# and then rinsed with remaining excipients. Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#. Preblending of all ingredients (except lubricant- magnesium stearate) in blended for 15 minutes. Blend then again blended for 5-6 min. then added magnesium stearate blended 5 min. Lubricated powder was compressed by using 9 station single rotary machine having 9.5 mm diameter and circular standard concave shaped punch, with pressure of 7-8 tons. Compressed tablets were examined as per official standards and unofficial tests (discussed below). Tablets were packaged in well closed light resistance and moisture proof containers.

Evaluation of lamivudine sustained release tablets:

The powder blend was subjected for the following studies

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

Angle of repose:

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a 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 powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The results were tabulated in Table 3.

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

Where,

h = height of the powder cone

r= radius of the powder cone

Bulk density and tapped density:

A quantity of 10gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table 3.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index:

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The formula for carr's Index is given below and the results were tabulated in Table 3.

$$\text{Carr's index}\,(\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula. The results were tabulated in Table 3.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Post compression studies:

A. Tablet Description

General appearance of tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identify markings.

B. Uniformity of weight

The USP weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP test if no tablet differs by more than two times of percentage deviation.

C. Thickness and Diameter

Thickness and diameter of 5 tablets is measured by using Vernier caliper.

D. Mechanical Strength

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, transportation and handling before usage depends in its hardness. Hardness of tablets of each formulation was determined using Pfizer hardness tester. Hardness of 10 tablets of each formulation were evaluated by Pfizer hardness tester.

Abrasion

Friability test is a measure of mechanical strength of tablets. The test was performed by using Electro lab friabilator test apparatus.The preweighed tablets were placed in the friabilator. Friabilator consists of a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches in each revolution. The tablets were rotated in friabilator for 4 minutes. At the end of test, tablets were reweighed. The % weight loss in weight of tablet is the measure of friability and is expressed in B as,

$$B = 100 [1 – W / W_0]$$

Where W is initial weight and W0 is final weight after abrasion.

***In-Vitro* Dissolution Study**

Placed the 900 ml of pH 6.8 phosphate buffer in the vessel of apparatus and assembled, equilibrate the dissolution medium to 37 ±0.5 °C. Placed 1 tablet in basket and immediately operated the apparatus at 100 rpm. Withdrawn the 5 ml samples at 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 16 hours, from midway between the surface of dissolution medium and the top of the rotating basket, not less than 1 cm from the vessel wall and replaced with fresh buffer solution. After appropriate dilution the samples were analyzed. Cumulative percentage of the drug released was calculated, and the mean of 6 tablets from formulations was used in data analysis.

TABLE: 1 Quantity of Raw Materials per Tablet (Mg)

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1.	Lamivudine USP	100	100	100	100	100	100	100	100
2.	Lactose monohydrate	132	132	132	132	132	132	132	132
3.	Hydroxypropyl Methylcellulose E-15	30	35	40	50	60	70	80	90
4.	Ethylcellulose	130	125	120	110	100	90	80	70
5.	Colloidal Silicon Dioxide (Aerosil®)	4	4	4	4	4	4	4	4
6.	Magnesium Stearate	4	4	4	4	4	4	4	4

*Total weight of per unit tablet is 400 mg.

3. Results and Discussion

Standard Curve of Lamivudine in pH 6.8 phosphate buffer:

In the present study, analytical method obeyed the Beer-lamberts law in the concentration range of 1-10 µg/ml and was suitable for the estimation of lamivudine in phosphate buffer of pH 6.8. The value of r (correlation coefficient) for the linear regression equation was found to be more than 0.99 which indicates a positive correlation between the concentration of drug and the corresponding absorbance values.

TABLE: 2 Standard Curve of Lamivudine

Concentration in mcg/ml	Absorbance at 270 nm
1	0.027
2	0.051
3	0.089
4	0.105
5	0.136
6	0.159

7	0.179
8	0.202
9	0.231
10	0.254

A. FT-IR of Lamivudine USP (Pure)

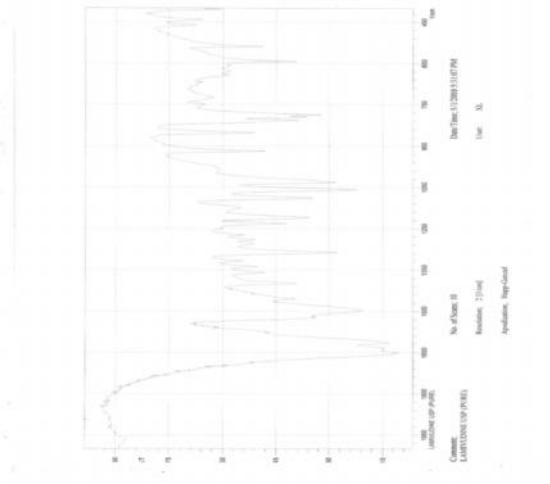

Fig.1 FT-IR of Lamivudine USP (pure)

B. FT-IR of HPMC E-15 (Pure)

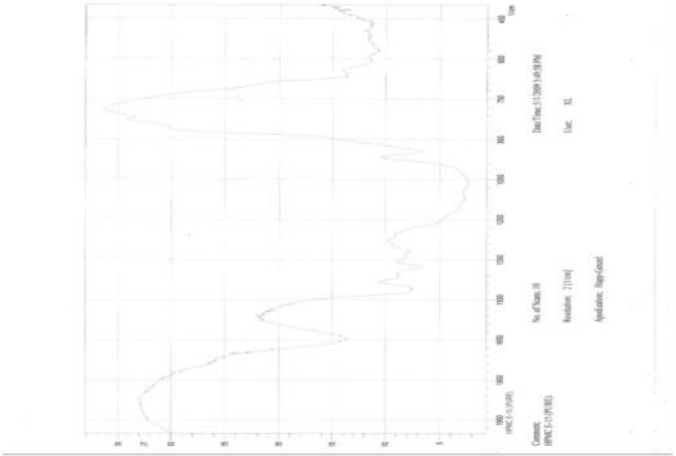

Fig. 2 FT-IR of HPMC E-15 (Pure)

C. **FT-IR of Ethyl cellulose (Pure)**

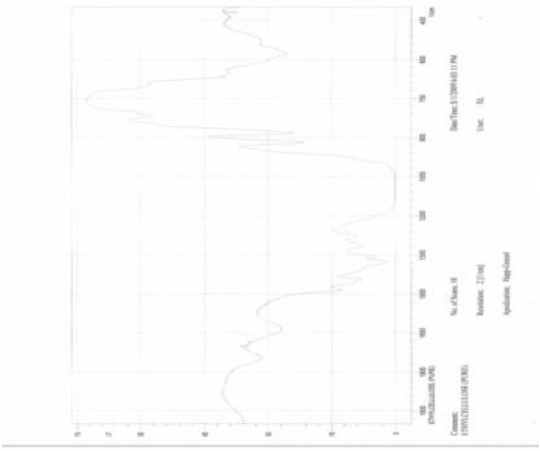

Fig. 3 FT-IR of Ethyl cellulose (Pure)

D. FT-IR of Lamivudine + HPMC E-15+Ethylcellulose

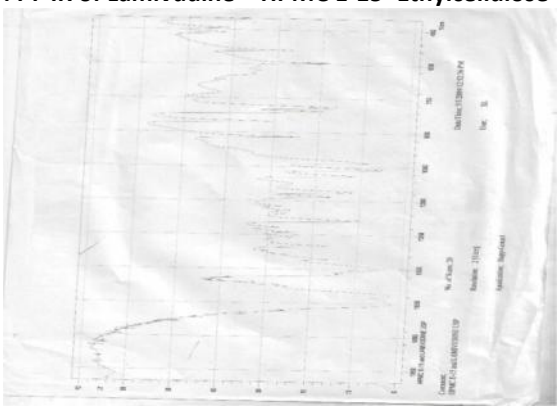

Fig. 4 FT-IR of HPMC, Ethyl cellulose and Lamivudine

FT-IR spectra of lamivudine and lamivudine with Polymers were shown Figure 1, 2, 3 and 4. Pure lamivudine showed principal absorption peaks at 699.36 cm^{-1} (C-H Bending), 1184.55 cm^{-1} (C-N stretching), 1650.48 cm-1 (N-H bending) 1742.11 cm^{-1} (C=O stretching) and 3214.87 (O-H stretching). The identical peaks of C-H Bending, C-N stretching, N-H bending, C=O stretching and O-H stretching vibrations were also noticed in the spectra of drug with polymers. FT-IR spectra revealed that there was no interaction between the drug and the polymer used for tablet formulations.

Evaluation of lamivudine sustained release tablets

Precompression parameters

Table: 3 Evaluations of Lubricated Blends

Parameters	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Mean Angle of repose* ± S.D.	33˚43′ ±0.309	31˚77′ ±0.284	34˚42′ ±0.280	36˚09′ ±0.257	33˚66′ ±0.241	31˚00′ ±0.216	32˚37′ ±0.226	31˚95′ ±0.402
Mean Apparent bulk density * (g/cm^3) ± S.D	0.593 ±0.002	0.622 ±0.003	0.597 ±0.004	0.629 ±0.003	0.616 ±0.002	0.676 ±0.003	0.603 ±0.003	0.578 ±0.002
Mean Tapped bulk density* (g/cm^3) ± S.D.	0.704 ±0.003	0.688 ±0.002	0.739 ±0.003	0.720 ±0.002	0.666 ±0.003	0.696 ±0.002	0.656 ±0.003	0/701 ±0.003
Compresibility Index* (%)	17.040	17.983	16.576	15.282	18.607	17.667	19.339	19.403
Hausner's Ratio*	1.190 ±0.096	1.183 ±0.14	1.165 ±0.070	1.147 ±0.18	1.129 ±0.025	1.206 ±0.035	1.176 ±0.16	1.166 ±0.066

**Value shown in tables are mean of three determinations*

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.578 to 0.676 gm/ml, whereas the tapped density was observed between 0.656 to 0.739 gm/ml. From the values of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 15.282 to 19.339. The values for hausner's ratio were found in between 1.129 to 1.206. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30.00 which indicate good flow of powder. Overall, these values indicate good flow properties of powder blend, uniform die fill and better compression ability.

Postcompression parameters

Table: 4 Observations of All Tablets Evaluation Parameters

PARAMETERS	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Uniformity of weight (mg)*	400 ± 6	400 ± 8	400 ± 7	400 ± 5	400 ± 7	400 ± 6	400 ± 6	400 ± 5
Thickness (mm)*	4.9 ± 0.26	4.9 ± 0.17	4.9 ± 0.33	4.9 ± 0.20	4.9 ± 0.43	4.9 ± 0.39	4.9 ± 0.26	4.9 ± 0.30
Diameter (mm)*	9.5 ± 0.02	9.5 ± 0.03	9.5 ± 0.02	9.5 ± 0.01	9.5 ± 0.03	9.5 ± 0.01	9.5 ± 0.01	9.5 ± 0.02
Friability (%)*	0.06	0.11	0.19	0.14	0.16	0.11	0.09	0.07

Tablet Hardness (Kp)*	11 ± 0.08	11 ± 0.05	11 ± 0.06	11 ± 0.09	11 ± 0.10	11 ± 0.14	11 ± 0.74	12 ± 0.09

*** n=3**

Hardness test for all formulations was carried out and observations obtained were in the range of 0.05 to 0.74 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be uniform as it was obtained in the range of 0.17 to 0.43 mm. Friability test was conducted for all formulations, % friability was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The % weight variation of all formulations was found to be in the range of less than 7.5%. None of the tablet was found to deviate from the average weight of tablets (variation with deviation less than ± 7.5, which complies with USP specification) signifies that there is uniformity in flow of powder blend which leads to uniform die fill.

***In vitro* dissolution study:**

Table 5: Comparative dissolution data of Lamivudine sustained release tablets

Time in Hours	F1	F2	F3	F4	F5	F6	F7	F8
1	12.961	13.411	17.162	21.682	25.613	26.193	28.453	27.173
2	23.623	29.113	33.634	38.144	41.175	44.945	46.675	42.275
4	41.005	51.656	56.126	61.197	65.517	67.277	68.778	65.237
8	57.696	68.248	71.238	76.549	78.269	79.189	81.239	79.199
12	64.237	78.279	81.159	84.239	88.170	89.530	90.580	89.990
16	71.068	82.689	88.630	89.280	90.130	94.891	98.901	97.681

The amount released in fixed duration was of more importance and were performed with precision and accuracy, the change in amount of polymer was largely dependent on the hydrophobic and hydrophilic nature of polymers used in the dissolution study and it suggested many parameter to control for next batches.The release of Lamivudine from sustained release tablet of various formulations varied according to the amount and hydrophilic and hydrophobic nature of polymer. As the amount of ethyl cellulose was decreased and amount of HPMC was increased there is increase in release rate in the order F1 to F7, probably the reason for this was hydrophilic nature of HPMC and hydrophobic nature of ethyl cellulose. The formulation F7 was found to give best release rate with 98.901 (Cumulative % drug release).

Comparison of Formulation-7 and Marketed Tablets

The formulations obtained in evaluation studies were compared with marketed product (Epivir HBV Tablets). The evaluation parameters tested and compared were physical and analytical parameters. The Physical parameter values obtained are recorded in results and discussion part. The Analytical parameters formulation F-7 and marketed product (Epivir HBV Tablets) gave Table-6 and Table-7 of formulation is constructed graphically. The graphical comparison is shown in Figure 5. The above study has shown that the contents of drug*, In-Vitro* drug release profile and physical parameters of F-7 formulations were found to be better as compared with that of marketed product of Lamivudine (Epivir HBV Tablets).

Table: 6 Content Uniformity of Active Ingredients

Parameters	F-7*	Lamivir HBV Tablets*
Contents uniformity of Drug (%)	100.05% ± 0.66	101.09% ± 0.78

***** Average of three determinations

Table: 7 physical characteristics.

Parameters	Formulation F-7	Epivir HBV Tablets
Appearance	Circular standard concave round shaped uncoated tablets.	Capsule shaped uncoated tablets
Colour	White	Light Brown
weight ± SD%	400 mg ± 1.63%	465 mg ± 0.85
Thickness	4.90 ± 0.02 mm	4.2 ± 0.06 mm
Hardness	11 Kp ± 0.61	10 Kp ± 0.69

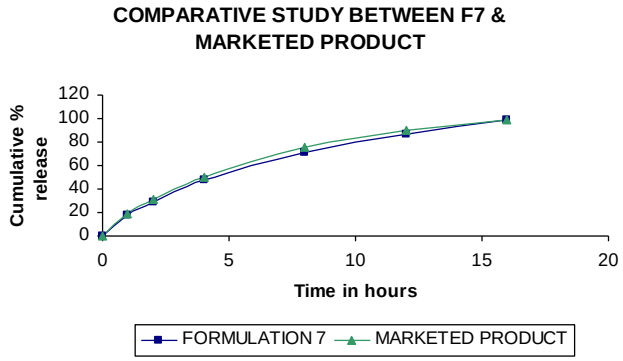

Figure: 5 Comparative study optimized formulation (F7) and Marketed product

4. Conclusion

The study was undertaken with an aim to formulation development and evaluation of Lamivudine sustained release tablets using polymers hydroxypropylmethyl cellulose and ethylcellulose. Lactose monohydrate was used as channeling agent and or as filler. Preformulation study was done initially and results directed for the further course of formulation. Based on preformulation studies different formulations of Lamivudine were prepared using selected excipients. FT-IR study performed for the identification and compatibility study of drug with polymers and found the characteristics peaks of various groups and matched with pharmacopoeial standard. Powder and blends were evaluated for tests - bulk density,tapped density, compressibility index, Hausner's ratio before being punched as tablets. Tablets were prepared by direct compression method by using 9 station single rotary tablet compression machine with application of 6-7 tons pressure. After in process evaluations (discussed below) tablets are packed in well closed moisture proof, light resistance container, labeled, and kept at dry place.Tablets were tested for official and unofficial tests like- weight variation test, thickness, hardness, friability and *In vitro* drug release as per official procedure was performed to observe diffusion and release mechanism of drug through polymeric membrane.From the above results and discussion it is concluded that formulation of sustained release tablet of Lamivudine containing 80 mg of hydroxypropyl-methylcellulose E15 (high viscosity grade) and 80 mg of ethylcellulose i.e. formulation F7 can be taken as an ideal or optimized formulation of sustained release tablets for 16 hours release as it fulfills all the requirements for sustained release tablet and our study encourages for the further clinical trials and long term stability study on this formulation.

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