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DESIGN, FORMULATION AND *IN VITRO* EVALUATION OF LAMIVUDINE HYDROCHLORIDE SUSTAINED RELEASE TABLETS

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ABSTRACT

The study was design, formulation and evaluation of oral sustained release tablets of Lamivudine Hydrochloride using different natural polymers such as Chitosan, Guar gum and Xanthan gum. The Lamivudine Hydrochloride oral sustained release tablets were prepared by using wet granulation method. The formulated different ratio of oral sustained release tablets of Lamivudine were evaluated by different parameters. The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The tablets were evaluated to thickness, weight variation test, hardness, friability, drug content, *in vitro* release and kinetic release studies. The results conclude that FL-7 () can be considered as a optimized formula for sustained release of drug for 24 hours. Kinetic treatment to the *in vitro* release data revealed that the drug release followed first order, non - fickian diffusion, It means the release of drug from tablet diffusion mechanisms are used.

KEYWORDS

Lamivudine Hydrochloride, Wet granulation method, Natural polymers such as Chitosan, Guar gum, Xanthan gum and *In vitro* kinetic release studies.

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INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral 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]. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady

drug plasma concentration[2-3]. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms.

Lamivudine Hydrochloride 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[4]. Lamivudine Hydrochloride is an analogue of cytidine. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

Lamivudine Hydrochloride is an active antiretroviral drug belongs to nucleosides reverse transcriptase cross inhibitor. Lamivudine Hydrochloride treatment has gained immense popularity in the AIDS treatment in the present era conventional oral formulations of Lamivudine Hydrochloride are administered multiple times a day because of its moderate half-life ($t_{1/2}$ = 5-7 hours)[5]. Treatment of AIDS using conventional formulations of Lamivudine is found to have many draw backs, such as adverse side effects resulting from accumulation of drug, in multi dose therapy[6], poor patient compliance and high cost.

MATERIAL AND METHOD

Material

Lamivudine Hydrochloride was obtained as a gift sample from Strides Arcolab, Bangalore. Chitosan, Guar gum, Xanthum gum, Magnesium stearate, Talc were obtained from Apex Pharmaceutical Pvt. Ltd. Polyvinyl pyrrolidone K-30 was a Gift sample from Loba chemistry, Mumbai. All other chemicals and ingredients were used for study are of Analytical grade.

Method

Preparation of Lamivudine Hydrochloride sustained release tablets

Tablets were prepared by wet granulation method. Lamivudine Hydrochloride (300 mg) was mixed with required amount of polymers and other excipients (Table No.1). All the excipients were passed through sieve no.40, mixed and granulated with 10% solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve no.16 and dried at 45^{o}C for 2 hrs. Dried granules were passed through sieve no.20 and mixed with magnesium stearate and talc[7].

EVALUATION PARAMETERS[7-10]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR spectroscopy.

Pre-compression studies of tablet granules

Bulk density

3gm of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated bulk density according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the granules bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of Granules/ Tapped volume of Granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied

stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

$$\theta = \mathbf{Tan^{-1}\ (h/r)}$$

Where,

θ = Angle of repose,
h = Height of the granules cone,
r = Radius of the granules cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where,
TD = Tapped density
BD = Bulk density.

Hausner's Ratio

It indicates the flow properties of the granules and ratio of Tapped density to the Bulk density of the granules.

Formula

Hausner's Ratio = Tapped density/Bulk density

Post compression studies of Lamivudine Hydrochloride tablets

Hardness or Crushing strength Test[9]

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets have a hardness of 3 kg and some sustained release tablets have a hardness of 10 -20 kg.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Venire caliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight
F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X - X^*/ X] \times 100$$

X - Actual weight of the tablet
X*- Average weight of the tablet.

Estimation of Drug Content

An accurately weighed amount of powdered Lamivudine Hydrochloride (100 mg) was extracted with water and the solution was filtered through 0.45 μ membrane filter paper. The absorbance was measured at 270 nm after suitable dilution.

Calculation

The amount of Lamivudine Hydrochloride present in tablet can be calculated using the formula

$$A_t/As \times S_w/100 \times 100$$

Where,
A_t = Absorbance of sample preparation
A_s = Absorbance of Standard preparation
S_w = weight at Lamivudine Hydrochloride working standard (mg).

***In vitro* drug release studies**

The dissolution was carried out using rotating basket method (USP dissolution testing apparatus I); freshly prepared 0.1N Hcl (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C and 100 rpm for first 2 h. Then replaced with 6.8 pH phosphate buffer and continued for 24 h. Aliquot volume of 10 ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. After filtration, the sample is measured the absorbance at 270 nm by using UV Spectrometer. The dissolution data obtained were plotted as percentage drug release versus time.

RESULTS AND DISCUSSION

Preformulation Studies

Drug-excipients Compatibility Studies

To study the compatibility of the drug with various natural polymers, IR spectra of drug and formulation components were carried out. The IR spectra of the drug and natural polymers were shown in Figure No.1 to 2. It indicates that drug is compatible with the natural polymers.

Precompression studies of granules

Bulk density

From the results it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the granules. Values are showed Table No.2.

Tapped density

From the results it can be seen that the tapped density values are within the limits. This indicates good flow characteristics of the granules. Values are showed Table No.2.

Angle of Repose

It can be observed that the angle of repose for various batches of the granules is found to be less than 40^0, it indicates good flow properties of the granules. Values are showed Table No.2.

Compressibility Index or Carr's Index

It can be observed that the Carr's Index for various batches of the granules is found to be less than >10; it indicates good flow properties of the granules. Values are showed Table No.2.

Hausner's Ratio

It can be observed that the Hausner's Ratio for various batches of the granules is found to be less than 1.35; it indicates good flow properties of the granules. Values are showed Table No.2.

Postcompression studies

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the sustained release tablets. Values are showed Table No.3.

Thickness Test

The thicknesses of tablets were almost uniform in the all formulations and were found to be in the range of 0.5mm. Values are showed Table No.3.

Friability Test

The sustained release tablets friability values are found to be less than 1% in all cases and considered to be satisfactory. Values are showed Table No.3.

Weight variation test

All this sustained release tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values are showed Table No.3.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of drug and excipients. Values are showed Table No.3.

***In vitro* Dissolution Studies**

All the seven formulations were subjected for the *in vitro* dissolution studies using USP-type II dissolution apparatus (paddle type). The samples were withdrawn at different time intervals and analyzed at 270 nm. Cumulative drug release and cumulative % drug retained were calculated on the basis of mean amount of Lamivudine Hydrochloride present in the respective tablet. The results obtained in the *in vitro* drug release for the formulations FLH-1 to FLH-7 are tabulated in Table No.4. The plots are shown from Figure No.3 for % cumulative drug release vs time.

Table No.1: Formulations of Lamivudine Hydrochloride (FLH) sustained release tablets

S.No	Ingredients	FLH-1	FLH-2	FLH-3	FLH-4	FLH-5	FLH-6	FLH-7
1	Lamivudine Hydrochloride	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
2	Chitosan	180 mg	-	-	90 mg	-	90 mg	60 mg
3	Guar gum	-	180 mg	-	90 mg	90 mg	-	60 mg
4	Xanthan gum	-	-	180 mg	-	90 mg	90 mg	60 mg
5	PVP K_{30}	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
6	Talc	10mg	10mg	10mg	10mg	10mg	10mg	10mg
7	Magnesium stearate	10mg	10mg	10mg	10mg	10mg	10mg	10mg

Total weight of the tablet – 500mg/Tab

Table No.2: Precompression studies of granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FLH-1	0.759	0.783	32.25	3.06	1.031
2	FLH-2	0.765	0.789	33.02	3.04	1.031
3	FLH-3	0.769	0.797	33.46	3.51	1.036
4	FLH-4	0.779	0.806	34.21	3.34	1.034
5	FLH-5	0.785	0.819	30.38	4.15	1.043
6	FLH-6	0.791	0.831	28.94	4.81	1.050
7	FLH-7	0.802	0.845	26.32	5.08	1.053

Table No.3: Post compression studies of Lamivudine Hcl sustained release tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	FLH-1	12.52	0.5	0.5	99.2	99.0
2	FLH-2	12.58	0.5	0.6	99.2	99.2
3	FLH-3	12.64	0.5	0.5	99.4	99.2
4	FLH-4	12.75	0.5	0.6	99.5	99.3
5	FLH-5	12.83	0.5	0.6	99.5	99.4
6	FLH-6	13.02	0.5	0.6	99.6	99.4
7	FLH-7	13.25	0.5	0.5	99.6	99.8

Table No.4: Comparative dissolution study of different formulations with various ratios of natural polymers

S.No	Time (hrs)	% of drug release (FLH-1)	% of drug release (FLH-2)	% of drug release (FLH-3)	% of drug release (FLH-4)	% of drug release (FLH-5)	% of drug release (FLH-6)	% of drug release (FLH-7)
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	1	02.45	02.25	02.08	02.40	02.16	02.04	01.75
3	2	07.43	06.87	05.92	07.25	06.62	05.25	04.58
4	3	22.85	18.15	15.74	20.25	16.52	13.32	11.25
5	6	39.57	35.48	31.52	29.53	27.28	25.54	23.14
6	9	58.72	53.86	49.86	47.15	45.57	43.65	40.21
7	12	77.92	72.64	69.13	66.95	65.78	62.25	48.24
8	15	92.84	88.32	86.23	83.76	81.02	79.68	63.78
9	18	106.5	103.2	100.8	94.12	92.13	91.02	74.32
10	21	-	-	-	103.5	102.2	100.7	88.21
11	24	-	-	-	-	-	-	97.16

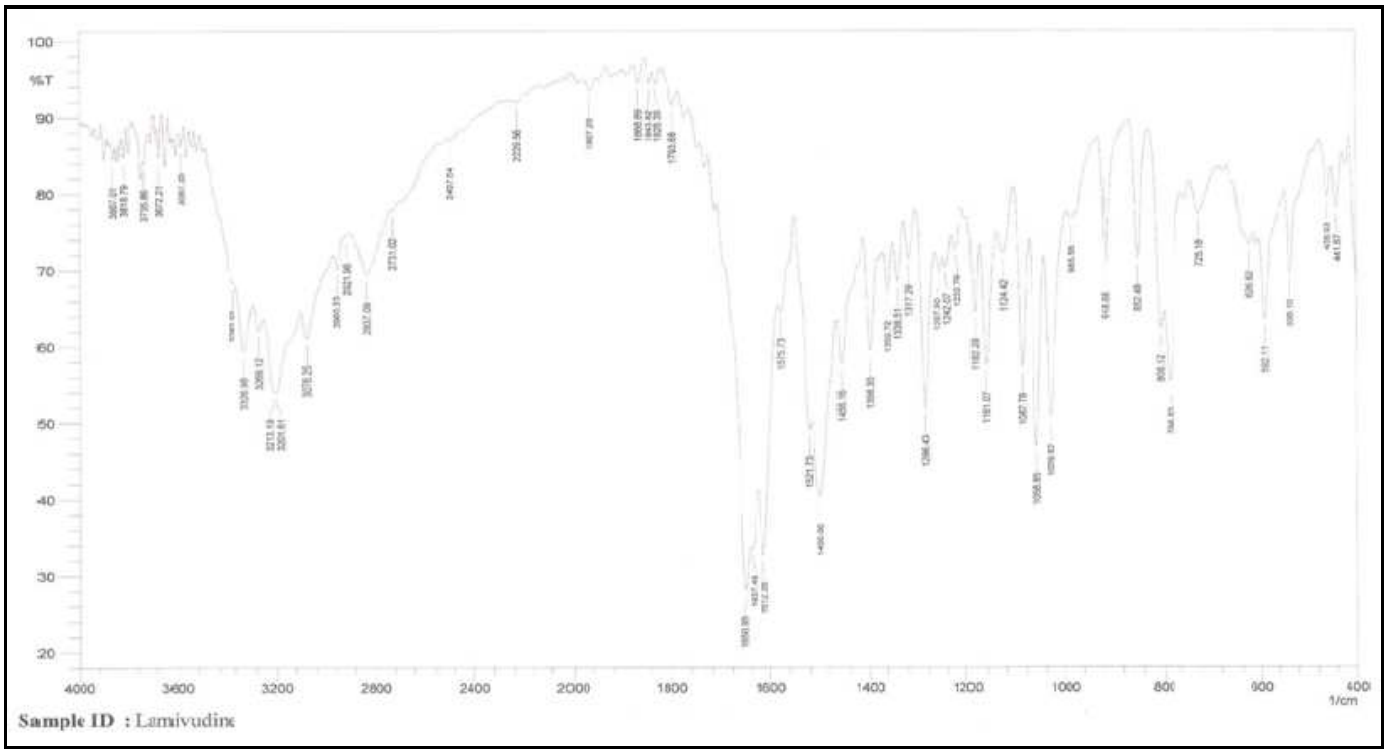

Figure No.1: Pure Drug of Lamivudine Hydrochloride

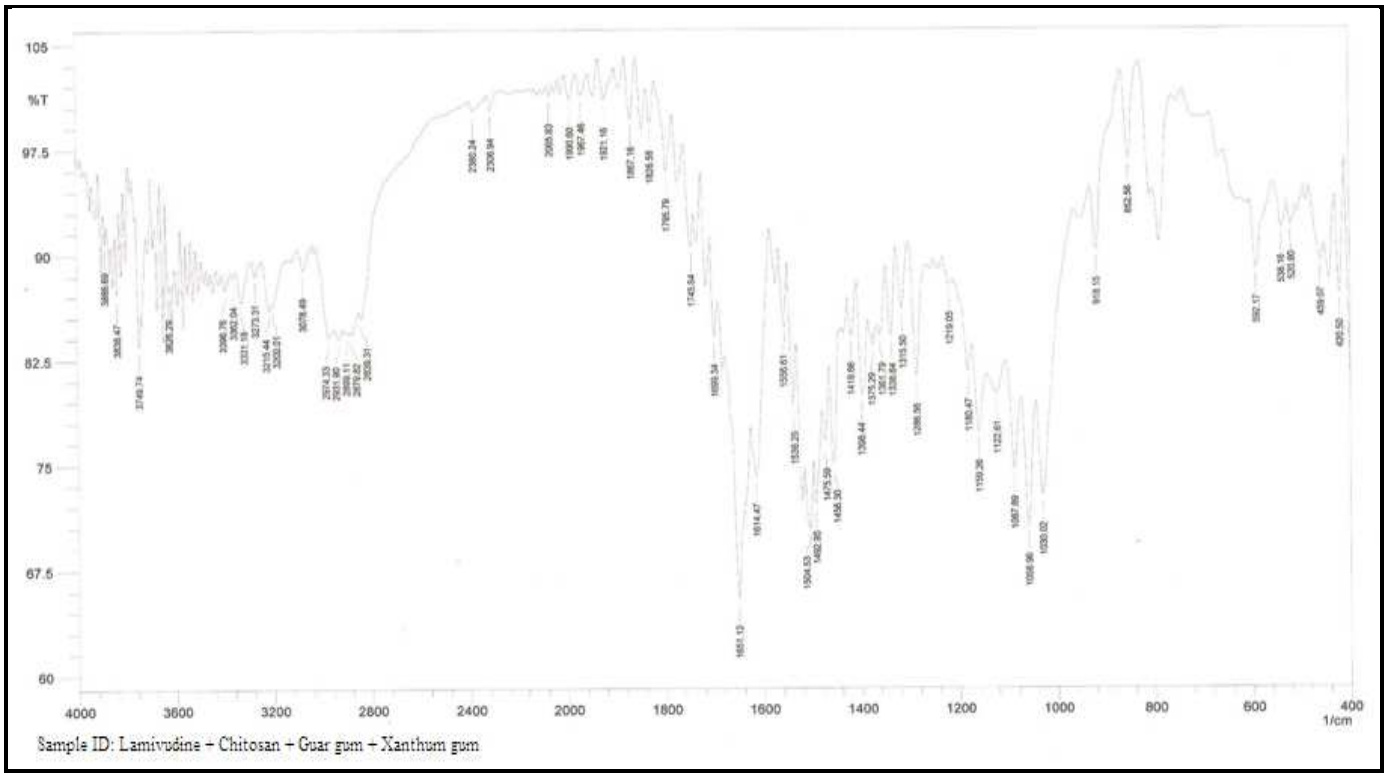

Figure No.2: Lamivudine Hydrochloride + Chitosan + Guar gum + Xanthum gum

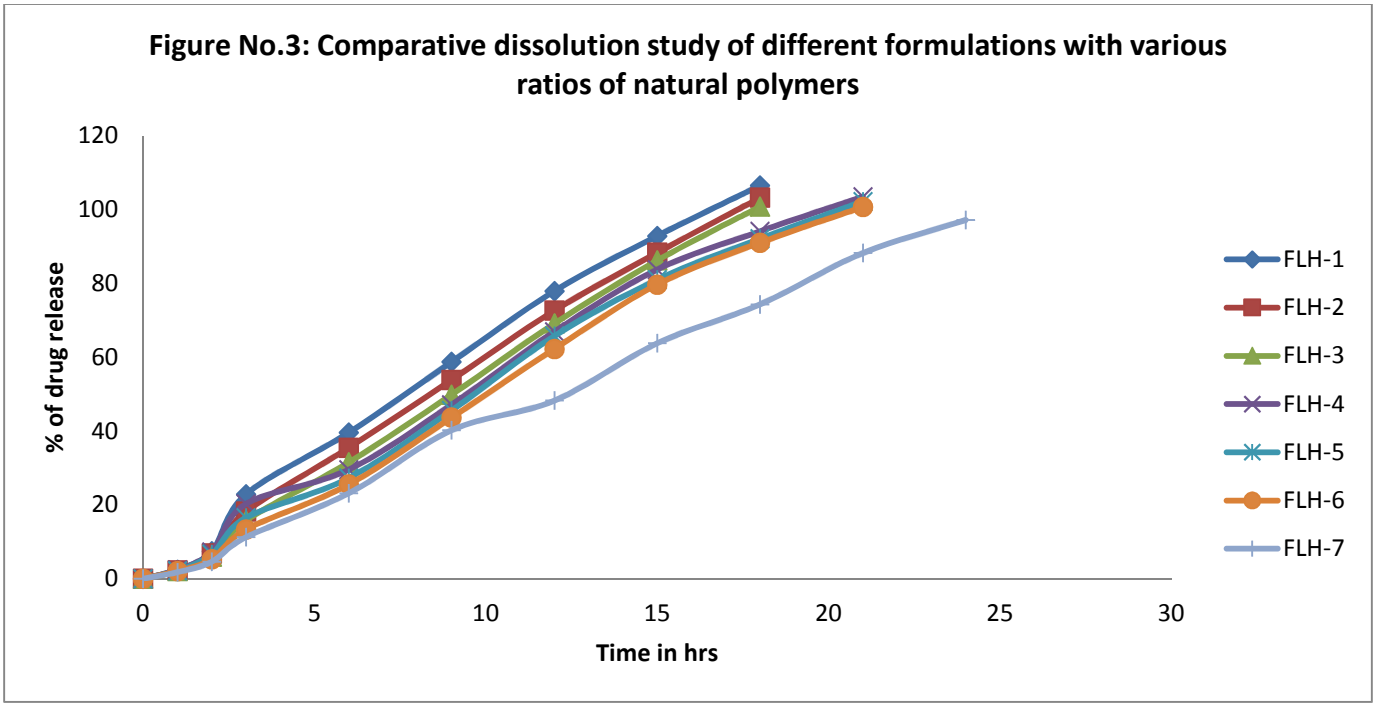

Figure No.3: Comparative dissolution study of different formulations with various ratios of natural polymers

CONCLUSION

The conclusion of study was carried out to develop the Lamivudine Hydrochloride sustained release tablet for the treatment of viral disease. All the batches showed good to satisfactory of free flowing properties, hardness, thickness, weight variation, friability, and the values are within the pharmacopeia limit. The *in vitro* studies showed that this formulation FLH-7 is given best drug release when compared to other formulations. From the results was concluded that a optimum formulation is combination of Lamivudine Hydrochloride with three natural polymers.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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