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Formulation And Evaluation Of Lamivudine Extended Release Floating Tablets By Using Hpmc Polymers And Xanthan Gum.

Sandeep A.Wathore
SVP College of Pharmacy, Hatta-431705

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ABSTRACT
Lamivudine has a low half-life of 0.8-1.5 hr and therefore needs recurrent administration to sustain stable beneficial drug plasma levels. In order to enhance and preserve the stable drug level of Lamivudine for round the clock, gastroretentive systems (floating low-density formulations that cause buoyancy on the gastric fluid in the stomach) may prove to be advantageous for releasing the drug content from the matrix tablet reservoirs for several hours. Materials and Methods: The current research endeavors towards formulating the Lamivudine floating tablet formulations (F1-F9) employing rate modifying polymers such as HPMC K15M, xanthan gum and HPMC K100M using multiple punch tablet compression machine containing 9 mm diameter, round flat-faced punches to form 80 mg tablet with a batch size of 100. The drug-polymer compatibility was investigated through Fourier-Transformed Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). Results: The Lamivudine floating tablet formulations were successfully fabricated. The pre-compression characteristics (tapped density, bulk density, Hausner's ratio, Carr's index and angle of repose) as well as postcompression characteristics (appearance, hardness, dimension, drug content, friability, swelling index, weight variation, in vitro drug release, in vitro buoyancy, accelerated stability and drug release kinetics for 90 days) of the formulations were comprehensively studied. Conclusion: This research study on Lamivudine will definitely open several new milestones for anti-retroviral pharmacotherapeutics in the upcoming future perspectives by enhancing the half-life of the drug employing the floating extended-release attributes.

Keywords: Lamivudine, Floating, Tablet, Gastroretentive, Xanthan, HPMC.

I. INTRODUCTION

The United States Food and Administration (USFDA) approved anti-retroviral drug Lamivudine, is a nucleoside thymidine analog that is employed exclusively for treating HIV-AIDS and its related conditions.1 It is recommended often as a single product or with additional antiviral drugs for various ailments.2 Under the influence of the cellular kinases, the drug molecule is metabolized into Lamivudine triphosphate (the active metabolite).3 This metabolite, in turn, inhibits the HIV-1 reverse transcriptase by contending with the thymidine triphosphate and ultimately leading to the termination of deoxyribonucleic acid (DNA) chain, followed by its integration into the viral DNA.4 Lamivudine is characteristically administered through the oral route as a capsule formulation and an oral solution.5 It has been perceived that the AIDS patients receiving Lamivudine in therapeutic dose develop neuropathy and lactic acidosis.6 The side effects of Lamivudine are usually dose-dependent and thus reducing the total administered drug level will eventually reduce the associated toxicity.7 Lamivudine has a low half-life of 0.8-1.5 hr and consequently necessitates recurrent administration to sustain stable beneficial drug plasma levels.8 In order to enhance and maintain the steady drug level of Lamivudine for round the clock, gastroretentive systems (floating low-density formulations that cause buoyancy on the gastric fluid in the stomach) may prove to be beneficial for releasing Lamivudine from the matrix tablet reservoirs for several hours.9 This will lead to an expansion in the drug solubility in acidic enhancement, extend the gastric residence time, the drastic enhancement in the patient compliance, results in the drug bioavailability enhancement, diminution in the wastage of drug, extensive advantages for patients, minimizes the dose-related side effects and new curative possibilities.10 Drawing inspiration from the studies done so far and employing the above logics for providing long-term anti-retroviral pharmacotherapeutics, the formulation of extended-release floating Lamivudine tablets remain a bright option.11 The current research endeavors towards the development of Lamivudine floating tablet

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formulations (F1-F9) employing rate modifying polymers such as HPMC K15M, xanthan gum and HPMC K100M using multiple punch tablet compression machine containing 9 mm diameter, round flat-faced punches to form 80 mg tablet with a batch size of 100. The rationality of using these three specific polymer excipients such as HPMC K15M, xanthan gum and HPMC K100M is that these semi-synthetic to natural components played key role in fabricating a traditional floating tablet product, a number of previously reported floating formulation has HPMC as the primary excipient; secondly, the existing combination is novel for producing the floating formulation of this particular drug material; and thirdly, these polymers have good characteristics for both wet granulation process as well as dry granulation process. The drug-polymer compatibility was investigated through Fourier Transformed Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). The pre-compression characteristics (tapped density, bulk density, Hausner's ratio, Carr's index and angle of repose) and post-compression characteristics (appearance, hardness, dimension, drug content, friability, swelling index, weight variation, in vitro drug release, in vitro buoyancy, accelerated stability and drug release kinetics for 90 days) of the fabricated formulations were comprehensively studied.

II. MATERIALS AND METHODS

Materials

Lamivudine was obtained from Cipla Ltd., Mumbai, India as a gift sample. The polymers (HPMC K15M and HPMC K100M) and microcrystalline cellulose PH 102 were purchased from Griffon Laboratories Pvt. Ltd., Mumbai, India. Analytical grade hydrochloric acid (HCl) and ethanol (95%) were purchased from SD Fine-Chem Ltd., Mumbai, India. Qualigens Fine Chemicals Ltd., Mumbai, India supplied the xanthan gum, sodium bicarbonate, polyvinylpyrrolidone, magnesium stearate, methanol, propylene glycol, isopropyl alcohol, acetone, sodium chloride and talc.

Instruments

Electronic balance (Shimadzu® BL-220H), Bulk density apparatus (Indolab® VTAP/MATIC-II), Hot air oven (Chemi® Equipments), Friability apparatus (Veego® Scientific VFT-DV), Hardness tester (Monsanto®), UVVis spectrophotometer (Shimadzu® 1700 Pharmaspec), FTIR spectrophotometer (Shimadzu® S4008), Differential scanning calorimeter (Shimadzu® DSC 60), USP tablet dissolution apparatus Type-II (Veego® Scientific VDA-8DR), Vernier caliper (Indolab®), Stability chamber (Labtech®), Standard sieve (Jayant® Scientific Ltd., India) and Sixteen punch tablet compression machine (Cadmach®) were utilized exclusively for developing, optimizing and characterizing the stavudine floating tablet formulations.

Drug-polymer compatibility

Fourier Transformed Infrared Spectroscopy

For formulating the floating formulation, the compatibility of the antiviral drug Lamivudine with the applied polymers (HPMC K15M, xanthan gum and HPMC K100M) was studied through the physical mixture by utilizing the FT-IR spectrometer (KBr disk method) in the scanning range of 4000 to 500 cm-1. 12

Differential Scanning Calorimetry

The compatibility of the pure drug Lamivudine with the used hydrophilic polymers was investigated from the physical mixtures by employing the differential scanning calorimeter where the sample for analysis were heated under the inert nitrogen atmosphere (20 mL/min) in the 30-300°C temperature range at 10°C/min heating rate.13

Formulation of powder blend

The ingredients employed in the formulation of the blend (Table 1) were carefully weighed and separately

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamivudine	100	100	100	100	100	100	100	100	100
HPMC K15M	40	80	120	--	--	--	--	--	--
HPMC K100M	--	--	--	40	80	120	--	--	--
Xanthan gum	--	--	--	--	--	--	40	80	120
Sodium bicarbonate	90	90	90	90	90	90	90	90	90
Polyvinylpyrolidone	50	50	50	50	50	50	50	50	50
Microcrystallne Cellulose pH 102	206	166	126	206	166	126	206	166	126

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Talc	9	9	9	9	9	9	9	9	9
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total	500	500	500	500	500	500	500	500	500

Table 1: Composition of Lamivudine floating tablet formulations.

passed through #40 mesh. The drug content was taken in a mortar and blended suitably with the limited quantity of polymers using a pestle. Further, the residual mass of the polymer added and the content was blended for the duration of 20 min. The blend was passed through the #20 mesh and further evaluated for the flow attributes.

Characterization of powder blend

Bulk density

It applies to particle packing. To calculate the amount of medication filling the volume in g/mL, bulk density was used. Using a graduated cylinder, the bulk density of the ingredients was measured. It is the ratio of the gross powder mass to the amount of powder in bulk. By pouring the weighted sum of powder into a graduated measurement cylinder, it was weighed and the volume was noted. It is expressed in g/mL and measured using the formula below:14 = Mass of the powder (W) Bulk density Untapped volume (V0)g/ml

Tapped density

It is the ratio of the total mass of powder to the amount of powder being tapped. The tapped amount was determined according to USP by tapping the 10, 500 and 1250 powder taps in the tap density apparatus. The mix was subjected to 500 taps; the percent variation in volume was measured and subjected to a further 1250 taps and the percent variation from the formula was calculated:14 ρ = Mass of the powder (w) Tapped density (t) Tapped volume of the powder (Vf)

Hausner's ratio

It determines the flow properties of the granules and is determined from the tapped density: the ratio of bulk density. From the formula, it is decided:14 = Tapped density Hausner's ratio Bulk density

Carr's index

A significant metric that can be derived from the bulk and tapped densities is the compressibility index. Theoretically, the thinner the compressible object, the more flowable it is. The free-flowing material is described as a material with values below 20 percent. The relationship between percent compressibility indexes and flowability is given by:14 − = × Tapped density Bulk density Compressibility index 100 Tapped density

Angle of repose

The resting angle is an example of the friction forces that occur between the components of the granule. That is the maximum possible angle between the face of the pile and the horizontal smooth surface of the granules. By passing the set volume of powder from the funnel at constant height until the top of the pile created by the powder reaches the funnel, the angle of repose was determined. By measuring the angle of repose by the process of fixed height, the flowability of the granules was determined:14 − θ = 1 tan (h/r) where, θ = angle of repose; h = height of pile; r = average radius of powder cone.

Compression of blend into tablets

Using several punch tablet compression machines with 9 mm diameter, round flat-faced punches, the floating tablet formulations were prepared by direct compression process after the assessment of the powder blend. Each tablet had 80 mg of Lamivudine, with a batch size of 100 tablets made.

Evaluation of floating tablets

Appearance

For development defects such as capping, chipping and lamination, the produced Lamivudine floating tablets were visually observed. All such detected defects have been identified.

Dimension

In terms of uniformity of the tablet scale, the thickness and diameter of the established Lamivudine floating tablets is a crucial feature and were estimated using a Vernier calliper. Three tablets were used from each of the types of tablet formulations produced and the mean values were recorded.15

Hardness

The hardness of 6 tablets was calculated using the Monsanto hardness tester from each of the Lamivudine floating tablet formulations

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produced. Every tablet was held in between the two jaws of the Monsanto hardness tester along its oblong axis where the reading should be 0 kg/cm2. The constant force was also applied by rotating the tester's knob until the tablet formulations were split and the value was expressed in kg/cm2 . 16

Friability

The measure of tablet power is friability. This test subjects tablets to the combined shock scrape stress by making use of a circular plastic compartment that spins at 25 rpm speed and with each revolution further lowers the items to 6 inches distance. In the Roche Friabilator, 6 pre-weighed tablets were placed and the machine was worked for 100 revolutions. The tablets were de-dusted and measured again. Under the criteria for pharmacopoeia, a reduction of < 1 percent in total weight is usually considered acceptable. From the following formulation, the percent friability (percent F) was determined:17 % F 100 Initial weight

Weight Variation

20 tablets from each floating mixture were independently weighted using the balance to assess the weight difference. In order to measure the deviation, the average weight of the tablets was measured and each actual weight of the tablet was compared. The findings were analyzed from the pharmacopoeia spectrum.18

Drug content

In each batch of floating formulations, the Lamivudine content was determined by simply crushing the 5 tablets and taking a powder equal to 25 mg. The contents of the 100 mL beaker containing 0.1 N HCl were added and mixed for 10 min. The solution was filtered through a 0.45 µm membrane filter, diluted correctly and spectrophotometrically measured the absorbance at λmax 266 nm, using blank 1 N HCl.19

In vitro buoyancy

The in vitro buoyancy was determined from floating lag time and overall floating time where the floating tablets were put in a 0.1 N HCl-containing 100 mL beaker (37°C ± 1°C). The period taken to lift the tablet to the medium's surface is referred to as floating lag time or lag time for buoyancy. The period during which the tablets have stayed continuously on the surface of the medium, on the other hand, is referred to as overall floating time or total buoyancy time.20

Swelling Index

By assessing the weight gain, the swelling activity of the floating tablets was determined. The tablets were put at a temperature of 37°C ± 0.5°C in a dissolution test apparatus basket containing 750 mL of 0.1 N HCl. The tablets were extracted from the dissolution medium every 1 hr. The weight was calculated on the analytical balance after draining the free water present on the surface of tablets with a tissue paper by basic blotting and the water content gained was estimated. The index of swelling (SI) was determined using a formula:21 − = weight of tablet at time t weight of tablet before immersion SI weight of tablet before immersion

In vitro dissolution studies

The in vitro dissolution properties of the floating tablet were tested in 900 mL simulated gastric fluid media without any enzymes, held at a temperature of 37°C ± 0.5°C at a stirring speed of 50 rpm, using the paddle-type dissolution test apparatus. The tablet was placed in the dissolution medium at the bottom of the paddle attached to a variable velocity generator. 5 mL of sample was extracted from each vessel at a given interval of time, pumped through a 0.45 µm membrane, analytically diluted and spectrophotometrically analyzed at λmax 266 nm. The equivolume pre-warmed fresh dissolution medium was replenished with the device for each sampling to maintain the steady volume during the experiment. The total releases were carried out in a triplicate fashion from the formulations and the analysis was expressed as a percentage.22

Release kinetics

A selection of kinetic models were used to map the combined drug release data collected from in vitro drug release studies,23 where: Zero-order is represented as the rate of the cumulative amount of drug released (Equation 1) C Kt = 0 (1) Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in minutes. A graph of concentration vs. time would yield a straight line with a slope equal to K0 and intercept the origin of the axes. First-order is presented as the rate of Log cumulative % of remaining drug (Equation 2) LogC LogC K /2.303 = −0 t (2) Where C0 is the initial concentration of the drug, K is the first order constant and t is the time. Higuchi's model is depicted as the squared rate of cumulative % of drug released (Equation 3) = 1/2 Q K t t (3) Where Qt is the amount of drug release in time t, K is the kinetic constant and t is

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the time in minutes. Korsmeyer-Peppas exponential model is Log rate of Log cumulative percentage of drug released (Equation 4). = 1 n Mt M1 Kt 4 (4) The release exponent n and K value were calculated through the slope of the straight line. If the exponent n = 0.43 then the drug release mechanisms Fickian diffusion,if 0.43<n<0.85 then it is Non Fickian diffusionor anomalous diffusion,If n<0.85 mechanism is non Fickian case-II diffusion.

Accelerated stability study

Although keeping with the Q1A Recommendation of the International Council for Harmonization of Technical Specifications for Pharmaceuticals for Human Use (ICH), an accelerated stability analysis was carried out over a span of 3 months for the optimized Lamivudine floating tablet formulation under changed short-term conditions (40°C temperature / 75 percent relative humidity). As per the protocol, the tablet formulation was wrapped in an aluminum foil and held in the stabilization chamber. The tablets were retested for post-compression parameters after 90 days (hardness, drug content, floating lag time, total floating time and in vitro drug release).24

III. RESULTS AND DISCUSSION

Drug-polymer compatibility study

FTIR spectra demonstrated that there was no major difference in the peaks of the drug in the physical mixtures containing polymers such as HPMC K15M (3421 cm-1, 3043 cm-1, 1693 cm-1, 1681 cm-1 and 1643 cm-1), HPMC K100M (852 cm-1, 690 cm-1 and 578 cm-1) and xanthan gum (2819.73 cm-1,1268 cm-1 and 1091 cm-1), when compared with the spectra of pure drug (3421.48 cm-1, 3043.46 cm-1, 2819.73 cm-1, 1693.38 cm-1, 1681.81 cm-1, 1643.24 cm-1, 1268.07 cm-1, 1091.63 cm-1, 852.48 cm-1, 690.47 cm-1 and 578.60 cm-1). No important interface between the drugs with the employed polymers were perceived and therefore it could be specified that there was no inaptness between the drug and different polymers (Figure 1)

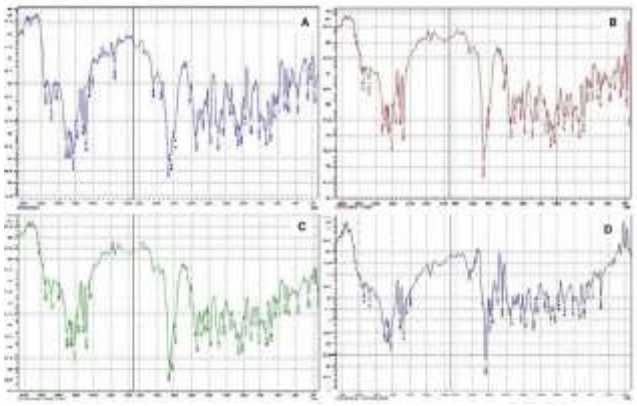

Figure 1: Drug-polymer compatibility analysis through FT-IR spectra: (A) Lamivudine (B) Lamivudine + HPMC K15M; (C) Lamivudine + HPMC K100M; and (D) Lamivudine + Xanthan gum.

DSC thermogram showed that there was no major difference in the onset temperature, end set temperature and peak temperature of the drug in the physical mixtures containing polymers such as HPMC K15M (170.76°C), HPMC K100M (159.59°C) and xanthan gum (169.75°C),when compared with the spectra of thermogram pure drug (172.24°C). No prominent interactions between drug and polymers were observed and therefore it could be specified that there was no such incongruity between the drug and different polymers (Figure 2).

Characterization of pre-compression aspects

The powder blends of formulations have the bulk density ranged between 0.732±0.01 to 0.745±0.01 gm/mL. The powder blends of formulations have the tapped bulk density ranged between 0.822±0.01 to 0.838±0.00 gm/mL (Table 2). These values indicate good packing characteristics and the powder was not bulky. Carr's index for all the fabricated batches was recognized to be below 12% (range: 10.86% to 11.14%) indicating that the powders have excellent compressibility. The Hausner's ratio for all the formulated batches was observed to be<1.25indicating good flow properties. The flow properties of granules were analyzed by

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determining the angle of repose which was found to be between 20.29±0.21 to 22.11±0.21, indicating excellent flow property.

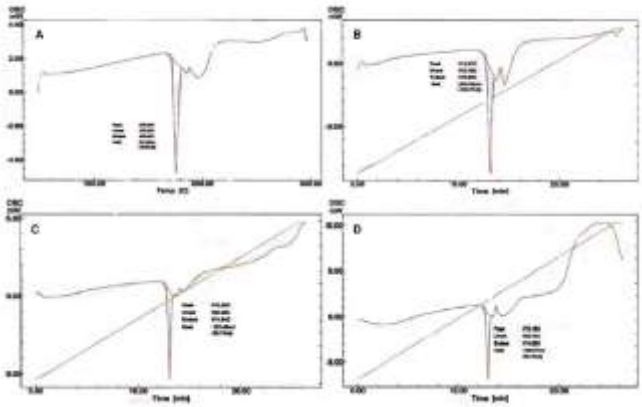

Figure 2: Drug-polymer compatibility analysis through DSC thermograms: (A) Lamivudine (B) Lamivudine + HPMC K15M; (C) Lamivudine + HPMC K100M; and (D) Lamivudine + Xanthan gum.

Characterization of post-compression aspects

The formulations were visually examined and none of the tablets presented common imperfection such as chipping, lamination and capping. The physical attributes of Lamivudine floating tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results of the developed formulations were perceived to be within the limits specified in official monographs and pharmacopeia guidelines. The diameter and thickness specifications may be set on an individual product basis. There were no noticeable disparity in the diameter and thickness of formulations within each batch indicated a consistent performance of the granules all over the compression process. The size (diameter) of the tablets of all formulations was found to be 9.0±0.0 mm and thickness ranged between 3.15±0.12 to 3.31±0.11 mm. A disparity in the formulation hardness revealed the distinction in porosity and tablet density which in turn are thought to produce various drug release patterns by influencing the penetration rate of the dissolution fluid over the product surface and gel barrier formation. The tablet hardness was observed to lie within the range of 5.5±0.44 kg/cm2 to 5.8±0.25 kg/cm2 . This indicates good tablet strength (Table 3). The percentage friability of all the formulations was found between 0.28%±0.06 to 0.41%±0.05 which indi-

Formulation Code	Loose bulk density (gm/cm³)	Tapped bulk density (gm/cm³)	Hausner ratio	Carr's index	Angle of repose (θ°)
F1	0.745±0.01	0.838±0.00	1.124±0.001	11.12±0.06	21.17±0.21
F2	0.732±0.01	0.822±0.01	1.122±0.00	10.93±0.05	21.19±0.58
F3	0.743±0.00	0.836±0.01	1.125±0.00	11.11±0.05	20.54±0.49
F4	0.743±0.02	0.836±0.02	1.124±0.001	11.11±0.06	22.11±0.21
F5	0.732±0.00	0.822±0.01	1.121±0.005	10.86±0.06	20.82±0.11
F6	0.733±0.01	0.823±0.02	1.122±0.001	10.96±0.07	20.29±0.21
F7	0.745±0.01	0.838±0.00	1.124±0.005	11.12±0.06	21.39±0.47
F8	0.732±0.01	0.822±0.01	1.121±0.001	10.89±0.06	20.59±0.50
F9	0.744±0.02	0.837±0.01	1.125±0.005	11.14±0.05	20.76±0.78

Table 2: Pre-compression characteristics of Lamivudine floating tablet formulations.

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Formulation Code	Diameter (mm)	Thickness (mm)	Hardness (kg/ cm²)	Friability (%)	Weight variation (%)	Drug content (% w/w)
F1	9.0±0.0	3.18±0.14	5.8±0.25	0.41±0.05	±2.11	99.81±1.4
F2	9.0±0.0	3.16±0.12	5.7±0.27	0.31±0.08	±2.16	99.67±1.7
F3	9.0±0.0	3.15±0.12	5.5±0.44	0.36±0.03	±2.02	98.75±0.5
F4	9.0±0.0	3.28±0.11	5.6±0.41	0.37±0.01	±1.75	99.47±1.3
F5	9.0±0.0	3.13±0.10	5.7±0.27	0.36±0.08	±2.46	100.07±0.5
F6	9.0±0.0	3.23±0.16	5.58±0.62	0.28±0.06	±1.85	100.38±0.8
F7	9.0±0.0	3.18±0.14	5.58±0.37	0.41±0.03	±1.89	100.01±1.7
F8	9.0±0.0	3.21±0.14	5.5±0.44	0.36±0.12	±1.86	98.24±0.6
F9	9.0±0.0	3.31±0.11	5.66±0.32	0.34±0.10	±1.90	99.39±1.5

Table 3: Post-compression characteristics of Lamivudine floating tablet formulations.

Formulation code	Floating lag time (S)	Total floating time (hr)
F1	193±1.73	>12
F2	161±2.08	>24
F3	132±2.64	>24
F4	113±1.52	>24
F5	93±1.52	>24
F6	66±1.15	>24
F7	227±0.57	>24
F8	215±2.08	>24
F9	181±1.00	>24

Table 4: In vitro buoyancy of Lamivudine floating tablet formulations.

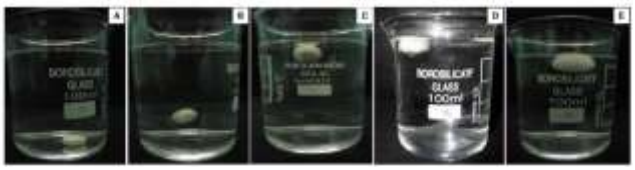

Figure 3: Floating characteristics of the Lamivudine tablet formulation: (A) At initial time; (B) Tablet started to rise up; (C) After 93 sec; (D) After 6 hrs; and (E) After 12 hrs

cated good handling property of the prepared floating tablet that will handle transport oriented wear and tear. A tablet is formed to enclose a definite quantity of the drug. When the average mass of the tablet is 500 mg the pharmacopoeia limit for percentage deviation is ±5%. The % average tablet weight deviations for all batches were observed to lie within the particular pharmacopoeia specifications and therefore all the batches complied with the specified weight variation guidelines. The content of active ingredients in the formulation was found to be between 98.24±0.6 to 100.38±0.8 % w/w, which was with accordance to the particular Indian pharmacopeia limit. All the formulations exhibited short floating lag times owing to the sodium bicarbonate contents. The formulation containing the low-viscosity grade HPMC K100 displayed short floating lag time and floated for a longer period as compared to the formulations having high viscosity grade xanthan gum and HPMC K15M. This designated that the viscosity of the polymer HPMC or molecular weight distribution that eventually influence the in-vitro buoyancy. All the prepared tablets show thetotal floating time >24 hrs except the F1 batch shows only more than 12 hr (Table 4). From the observations, it can be indicated that as the overall polymeric concentration augments, a decline in the floating lag time and an augmentation in the total floating time happens. The floating lag times of the formulations were observed to be the function of

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polymer concentration. This may be because due to low gelation attributes of polymers at a lower concentration. Hence, HPMC K100M polymer demonstrated good floating characteristics. The floating characteristics of the fabricated Lamivudine tablet formulation are depicted in Figure 3. The swelling ratio expressed the quantity of water present within the formulation at equilibrium and was a component of hydrophilicity, network structure and the functional groups ionization. For 12 hr, the swelling study was carried out for formulations. The data acquired for the swelling index and the plot of swelling index against the time of different formulations with different concentrations of polymers are depicted. From the obtained data, it was seen that with the passage of time, the swelling augments as the polymer absorbs high amount of water gradually owing to hydrophilicity characteristics. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. Xanthan gum and HPMC are hydrophilic polymers and depending on the substitution and molecular weight, they dissolve more or less rapidly. When this matrix comes in contact withwater or aqueous gastrointestinal fluid, the polymer absorbs the water and undergoes swelling and hydrates. Tablet hydration capacity was important to be considered because the water penetration was responsible for drug release. From the study, it was observed that xanthan gum and HPMC K100M showed good swelling as compared to HPMC K15M, which indicates that the rate of swelling was directly proportional to the viscosity of polymer, since xanthan gum and HPMC K100M have more viscosity than HPMC K15M. The formulations (F3, F6 and F9) containing the highest concentration (40%) of each polymer showed the highest swelling index (Table 5). The maximum swelling indices were attained in 7-9 hrs, 8-9 hr and 9-10 hrs for HPMC K15M, xanthan gum and HPMC K100M, respectively, after which the polymer started eroding slowly in the medium.

Time (hours)	Swelling Index								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.76±0.015	0.97±0.02	1.21±0.015	1.25±0.025	1.59±0.05	1.74±0.020	1.01±0.017	1.22±0.020	1.52±0.015
2	0.92±0.015	1.21±0.015	1.49±0.020	1.53±0.045	1.91±0.025	1.91±0.020	1.46±0.020	1.57±0.015	1.88±0.015
3	1.02±0.030	1.34±0.015	1.76±0.020	1.69±0.030	2.19±0.015	2.04±0.015	1.66±0.005	1.82±0.015	2.19±0.015
4	1.26±0.015	1.63±0.026	1.89±0.015	1.91±0.025	2.4±0.020	2.21±0.010	1.8±0.015	2.02±0.015	2.58±0.020
5	1.42±0.015	1.7±0.030	2.02±0.015	2.13±0.025	2.53±0.015	2.59±0.015	1.97±0.010	2.2±0.015	2.58±0.015
6	1.66±0.015	1.95±0.015	2.17±0.015	2.37±0.020	2.78±0.015	2.91±0.015	2.19±0.015	2.47±0.020	2.99±0.015
7	2.04±0.02	2.18±0.015	2.45±0.015	2.63±0.020	2.92±0.015	3.02±0.015	2.33±0.015	2.8±0.020	3.15±0.032
8	2.1±0.015	2.4±0.025	2.56±0.015	2.91±0.020	2.99±0.01	3.1±0.015	2.61±0.020	2.97±0.015	3.31±0.015
9	1.95±0.015	2.74±0.020	2.93±0.020	2.64±0.025	3.21±0.015	3.35±0.025	2.8±0.015	3.16±0.020	3.42±0.015
10	1.83±0.02	2.58±0.005	2.82±0.020	2.45±0.025	3.03±0.015	3.23±0.015	2.68±0.015	3.32±0.015	3.57±0.020
11	1.62±0.015	2.27±0.015	2.69±0.015	2.27±0.025	2.87±0.025	2.97±0.015	2.48±0.015	3.2±00.015	3.35±0.032
12	1.54±0.02	2.03±0.015	2.46±0.015	2.08±0.030	2.71±0.02	2.81±0.015	2.33±0.020	3.04±0.020	3.19±0.015

Table 5: Swelling index of Lamivudine floating tablet formulations.

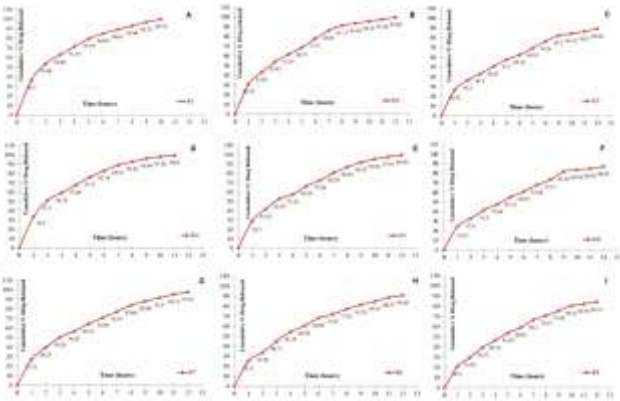

Figure 4: In vitro drug release profile of Lamivudine floating tablet formulations (F1 to F9).

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Lamivudine was a water-soluble drug; its release from the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The polymeric concentration in the product was a key factor in supporting the release of drug. The drug release from formulations F1-F3 containing HPMC K15M at three concentration levels of 13.5%, 27% and 40% was found to be 99.79±0.25%, 99.68±0.26% and 89.24±0.85%, respectively. The drug release from formulation F4-F6 containing HPMC K100M at three concentration levels of 13.5%, 27% and 40% was found to be 99.60±0.26%, 99.59±0.39% and 86.89±0.37%, respectively. While the drug release from formulation F7-F9 containing xanthan gum at three concentration levels of 13.5%, 27% and 40% was found to be 97.53±0.41%, 90.86±0.43% and 84.21±0.57%, respectively (Figure 4). When cumulative % drug release plotted versus time, it was noticed that, for three of the polymers used, an increase in the polymeric concentration from 13.5% to 40%, induce a lessening in the drug release rate. The drug release rate from the xanthan gum matrix was observed to be less as compared to HPMC K15M and HPMC K100M. This might be owing to the sluggish hydration of the formulation matrix and its attributes to create a thick layer of gel, which retard the drug release from the tablet. Whereas formulation containing HPMC K15M (F1-F3) gave higher drug release as compared to the formulation containing HPMC K100M (F4-F6) and xanthan gum (F7-F9), which may be due to quick hydration of polymer matrix, after which matrix might get started to erode. In addition to the concentration of polymer, the type and viscosity of polymer also influence drug release. When the drug

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K (mg h^{-1})	R^2	n	
F1	0.7653	0.2060	0.8648	0.0072	0.9903	4.3504	0.9947	0.4335	Peppas
F2	0.8305	0.1722	0.9086	0.0059	0.9945	3.9429	0.9949	0.5040	Peppas
F3	0.8805	0.1486	0.9947	0.0030	0.9977	3.3831	0.9970	0.5119	Higuchi
F4	0.7761	0.1899	0.9406	0.0064	0.9916	4.1901	0.9938	0.4542	Peppas
F5	0.8618	0.1684	0.8979	0.0055	0.9983	3.8121	0.9981	0.5113	Higuchi
F6	0.9031	0.1449	0.9936	0.0029	0.9952	3.2893	0.9963	0.5459	Peppas
F7	0.8706	0.1631	0.9693	0.0043	0.9988	3.7182	0.9988	0.5225	Higuchi
F8	0.8766	0.1517	0.9970	0.0032	0.9979	3.4572	0.9968	0.5389	Higuchi
F9	0.9149	0.1393	0.9978	0.0026	0.9949	3.1577	0.9983	0.5900	Peppas

Table 6: Applications of different kinetic models for Lamivudine floating tablet formulations.

Formulation code	Time of % drug release (hrs)		
	25% (t_{25})	50% (t_{50})	90% (t_{90})
F1	0.42	1.93	7.24
F2	0.65	2.62	8.73
F3	0.92	3.65	>12
F4	0.51	2.10	7.72
F5	0.83	2.77	9.16
F6	1.25	4.21	>12
F7	0.83	2.98	9.51
F8	0.91	3.54	>12
F9	1.42	4.65	>12

Table 7: Time of drug release values of t25, t50 and t90 for Lamivudine floating tablet formulations.

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release data acquired from the dissolution analysis of diverse polymers at 13.5% concentration is plotted against the time, it was detected that low concentration of polymer induces more drug release. This is owing to the creation of a thin barrier around the formulation through which drug can diffuse from polymer matrices. Among three polymers, HPMC K15M at three concentration levels (13.5%, 27% and 40%) gave more drug release as compared to xanthan gum and HPMC K100M, as it has low viscosity as compared to xanthan gum and HPMC K100M. A huge quantity of highly viscous polymeric contents tempted the development of gelatinous layer that deliberately diminished the water diffusion rate into the tablet matrix and therefore resulted in the reducing the release of drug. The comparative effect of three diverse polymeric contents over the release profile of Lamivudine from the floating formulations in terms of percentage dissolution efficiency (% DE) showed that formulations containing xanthan gum delayed the drug release than those containing HPMC K15M and HPMC K100M. It was observed that formulations having low values of mean dissolution time (MDT) indicated the faster release of the drug than the other formulations. The release profiles of all the formulation batches were made to fit in different models. But the superiority of other models was however statistically insignificant with the Higuchi matrix model as depicted by the goodness of fit test (t-test). Thus, it may be concluded that the drug release from the regiospecific floating tablet of Lamivudine is best explained by Higuchi's matrix model (Table 6). The intercept and values of slope for the Higuchi's matrix model were used to find out time required to release 25% drug (t-25), time taken to release 50% drug(t-50) and time taken to release 90% drug (t-90) drug for each batch (F2, F5 and F7) of the best formulation of HPMC K15M, xanthan gum and HPMC K100M polymers (Table 7). The drug release profile of selected formulations shows that the formulation F5 showed the sustained drug release profile for 12 hrs as compared to formulations F2 and F7. It is observed from in vitro buoyancy study and swelling index that formulation F5 shown less floating lag time (93 sec) with good total floating time (>24 hrs) and higher swelling index as compared to selected formulations F2 and F7. From the above study, it was indicated that the product F5 showed the sustained drug release profile with good matrix integrity, less floating lag time with higher swelling index and good total floating time as compared with the selected batches for this reason the formulation F5 was deemed as the most optimized product among other formulations of this series. Hence, the formulation F5 was selected for the further stability study.

Table 8: Stability studies of optimized formulation (F5).

Characteristics	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm^2)	5.7±0.27	5.83±0.288	5.66±0.288	5.83±0.288
Drug content (mg/tablet)	100.07±0.5	100.04±1.5	99.39±1.5	99.47±1.32
Floating lag time (sec)	93±1.52	98±2.64	95±2.00	97±2.64
Total floating time (hr)	>24	>24	>24	>24
In vitro drug release at 12th hr	99.59±0.39	99.21±0.15	98.16±0.36	98.07±0.11

No major difference was found between evaluated parameters before and after stability studies and all was found to be within acceptable limits (Table 8). The tablets showed agreeable physical stability at 40°C temperature and 75% RH.

IV. CONCLUSION

The current research endeavors towards the development of Lamivudine floating tablet formulations (F1-F9) employing rate modifying polymers such as HPMC K15M, xanthan gum and HPMC K100M using multiple punch tablet compression machine containing 9 mm diameter, round flat-faced punches to form 80 mg tablet with a batch size of 100. The pre-compression characteristics demonstrated that the powders have excellent compressibility, excellent flow property, good packing characteristics and the powder was not bulky. The formulations showed no defects such as chipping, capping and lamination. The post-compression attributes of the tablets such as drug content, friability, hardness and weight variation were found to be within the limits

specified in Indian Pharmacopoeia. A desired level of the in vitro dissolution levels, swelling index and in vitro buoyancy levels were observed for all the formulations. No major differences was found between evaluated parameters before and after stability studies and all were found to be within acceptable limits. No important interface between the drugs with the employed polymers was perceived in any formulations. This research study on Lamivudine will definitely open several new milestones for anti-retroviral pharmacotherapeutics in the upcoming future perspectives by enhancing the half-life of the drug employing the floating extended-release attributes.

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