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RESEARCH ARTICLE

Development and Evaluation of Floating Sustained Release Bilayer Tablets Containing Lamivudine

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ABSTRACT

Bilayer floating tablets of Lamivudine were developed by direct compression method. Immediate release layer contains 30mg of drug and super disintegrant sodium starch glycolate, serves the purpose of loading dose. Sustained release layer contained HPMC K4M, natural polymers like xanthan gum, guar gum, locust bean gum, karaya gum release the drug for 12 hrs time. Sodium bicarbonate and citric acid are used to produce effervescence. Floating lag time of optimised tablet is 92 sec, whereas floating duration is more than 12 hrs. FTIR results revealed that there was no interaction between drug and HPMC K4M / xanthan gum. The post compression parameters of developed tablet are satisfactory. In this study it was confirmed that the formulations containing HPMC K4M, have shown better floating properties and finally the formulation containing a combination of HPMC K4M and Xanthan Gum in 3:1 ratio, has shown slower *in vitro* drug release properties. The release kinetics of optimised formulation prepared with the combination of HPMC K4M and xanthan gum followed zero order kinetics.

KEYWORDS

Floating Bilayer Tablet, Lamivudine, HPMC K 4M, Xanthan Gum, FTIR

INTRODUCTION

Floating drug delivery systems (FDDS) are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from upper GIT. Floating drug delivery systems offer a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract[1]. The ideal drug candidate for FDDS are drugs that are acting locally in upper gastro intestinal tract (GIT) or drugs that are degrading in lower GIT or drugs that show poor intestinal absorption or drugs that are absorbed only in stomach.

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Acid labile drugs and other drugs that are causing gastric lesions are unsuitable for such formulations. The gastric retention of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states. Out of all available gastro retentive systems floating tablets, floating beads, floating granules, and floating microspheres have gained major importance in the formulation development more recently[2].

Lamivudine drug comes under the class - Nucleoside Reverse Transcriptase Inhibitors (NRTIs). It is a nucleoside analogue, chemically (-)-4-amino-1-[(2*R*, 5S)-2-(hydroxy methyl)-1, 3-oxathiolan-5-yl] pyrimidin-2(1*H*)-one; CAS Reg. NO. 134678-17-4 (Figure 1), which was

originally licensed for the treatment of HIV. It is now additionally licensed for the treatment of chronic hepatitis B with evidence of viral replication[3]. For the treatment of AIDS, the dosage of conventional oral formulations of Lamivudine is 300 mg per day (i.e. 150 mg twice daily)[4].

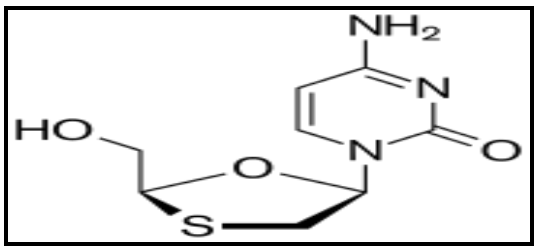

Figure 1: Chemical Structure of Lamivudine

Recent literature on floating drug delivery systems is collected to develop Lamivudine floating bilayer tablets[5-10]. In the present study, Lamivudine floating bilayer tablets were developed to get sustained release of the drug thereby to improve treatment therapy. The prepared tablets were evaluated for their floating properties and *in vitro* drug release.

MATERIALS AND METHOD

The chemicals used in this study were pure drug like Lamivudine (Sigma Aldrich India) and polymers like HPMC K4M, Xanthan gum, Guar gum, Karaya gum, Locust bean gum (Hi media Lab Pvt Ltd, Mumbai) and other excipients like micro crystalline cellulose, magnesium stearate, talc, sodium bicarbonate, citric acid (Yarrow Chem, Mumbai).

Preformulation Study

Preformulation studies were conducted to confirm the compatibility of drug with polymers used. These studies were conducted by using FTIR spectrophotometer. In this method, the IR spectra of pure drug, physical mixtures containing drug and polymers (1:1) and tablet triturate were analysed.

Evaluation of Flow Properties

Prepared powder blend of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index.

Preparation of Floating Bilayer Tablets

The drug and excipients for immediate release layer mentioned in Table 1 were passed through a 60 # size mesh prior to the preparation of the dosage form. All the ingredients sufficient to produce 20 tablets are weighed separately and mixed thoroughly for 10 min the mixture of first layer was subjected to slight compression to using ten station rotary tablet machine (Shakti Pharmatech Pvt. Ltd Ahmedabad).

Drug and excipients for sustained release layer mentioned in Table 1 were passed through a 60 # size mesh prior to the preparation of the dosage form. All the ingredients where weighed separately and mixed thoroughly for 10 min. These mixtures is placed over the first layer and subjected for final compression to produce tablet with 6±0.5 Kg/cm^2 hardness. Bilayer tablet containing immediate release layer (IR) and sustained release layer (SR) is termed as formulations F1, F2 and so on.

FTIR

FTIR spectra of pure Lamivudine and tablet triturate (F6) were analysed using Agilent Technologies FTIR and the result are shown in Figures 2A to 2F.

Characterization of Tablets for Physicochemical Parameters

The prepared Lamivudine floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

In Vitro Floating Lag Time

The *in vitro* buoyancy was determined by placing the tablets in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37ºC. The time required for the tablet to rise to the surface and float was determined as floating lag time.

In Vitro Floating Duration Time

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of 0.1 N HCl.

Table 1: Formulation of immediate (IR) and sustained (SR) drug release layers of Lamivudine bilayer tablets

Ingredients	Immediate release layer														
	Lamivudine		Sodium starch glycolate			Micro crystalline cellulose			Polyvinyl pyrolidone			Magnesium stearate			
	30 mg		40 mg			123 mg			5 mg			2 mg			
	Sustained Release Layer (Weight in mg)														
	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9	SR10	SR11	SR12	SR13	SR14	SR15
Lamivudine	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
HPMC K4M	100	-	-	-	-	75	75	75	75	75	75	75	75	75	75
Xanthan gum	-	100	-	-	-	25	-	-	-	12.5	12.5	12.5	-	-	-
Guar gum	-	-	100	-	-	-	25	-	-	12.5	-	-	12.5	12.5	-
Locust bean gum	-	-	-	100	-	-	-	25	-	-	12.5	-	12.5	-	12.5
Karaya gum	-	-	-	-	100	-	-	-	25	-	-	12.5	-	12.5	12.5
Citric acid	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Sodium bicarbonate	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21
MCC	44	44	44	44	44	44	44	44	44	44	44	44	44	44	44
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

The time interval that the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration time.

In Vitro Drug Release

The release of Lamivudine from floating tablets was determined by using dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5ºC temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbance of the diluted samples was measured at 270nm for Lamivudine by using UV spectrophotometer. Cumulative percentage drug release was calculated using an equation Y=0.05±0.043 obtained from calibration graph.

Characterization of Drug in Floating Tablets

FTIR studies were conducted for characterisation of selected optimised formulation (F6). Floating tablets were powdered and IR spectra were recorded using Fourier transform infrared spectrophotometer. The IR spectra of pure lamivudine and powder of tablet were taken, interpreted and compared with each other.

RESULTS AND DISCUSSION

Standard graph of Lamivudine has shown good linearity with R^2 value 0.9909 in pH 0.1 N HCl, which suggests that it obeys the "Beer-Lambert's law".

Evaluation of Drug –Polymer Interactions

FTIR spectra of pure Lamivudine and Lamivudine bilayer tablet is shown in Figure 2A to 2F.

The characteristic peak of the drug carbonyl group (C=O stretching) present in the cytidine nucleus at 1650.07cm^{-1}, a band peak at 1494.78 cm^{-1} owing C=C stretching (aromatic) confirms the presence of Lamivudine. Characteristic bands peak at 3217.9 cm^{-1}owing to presence of hydroxy group (O-H stretching)/ primary amine (NH2 stretching). Peaks present at1287.70 cm^{-1} and 1160.84 cm^{-1} owing to oxathiolane ring (asymmetrical and symmetrical C-O-C stretching) of Lamivudine.

Peaks present at 1054.70cm^{-1}, 787.30cm^{-1} owing to primary alcohol (C-O stretching) and primary amine group (N-H bending) respectively, confirms the presence of Lamivudine in case of physical mixture and tablet triturate.

Evaluation of Flow Properties

Prepared powder blend of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, and compressibility index, results are shown in Table 2.

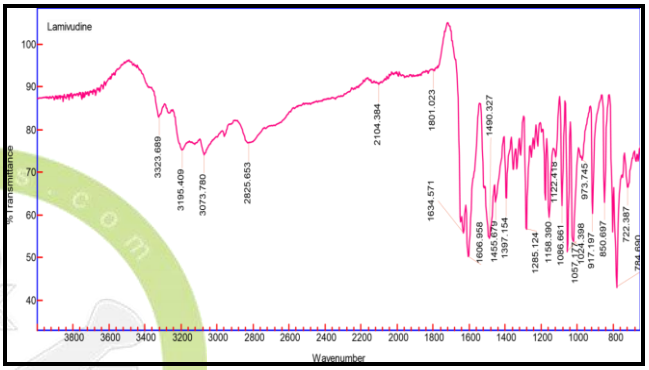

Figure 2A: FT-IR of Lamivudine

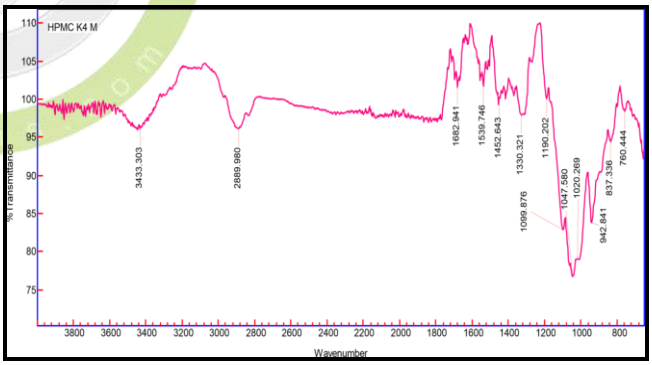

Figure 2B: FT-IR of HPMC K4M

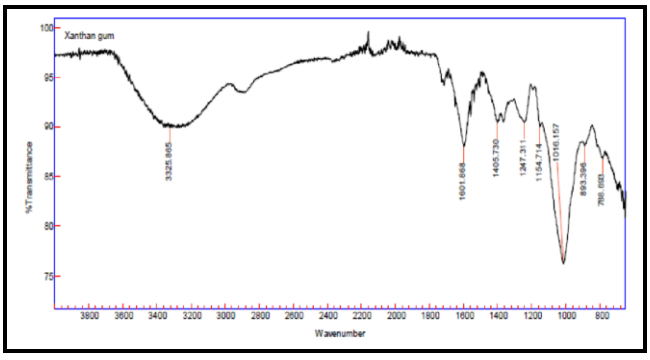

Figure 2C: FT-IR of Xanthan gum

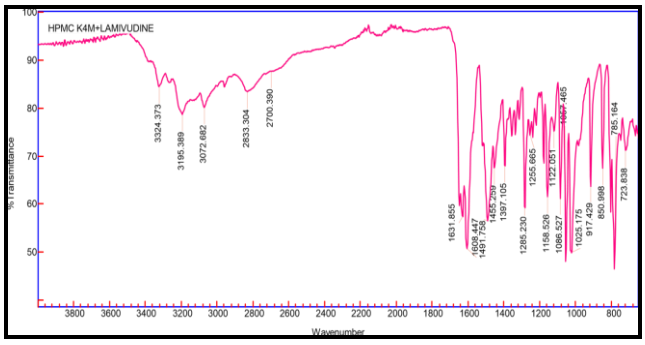

Figure 2D: FT-IR of Lamivudine+HPMC K4M

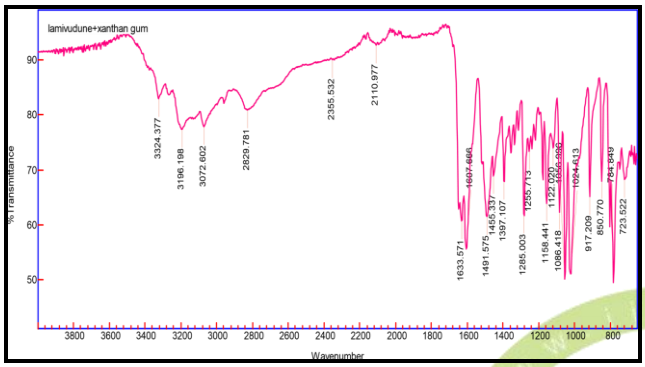

Figure 2E: FT-IR of Lamivudine + Xanthan GUM

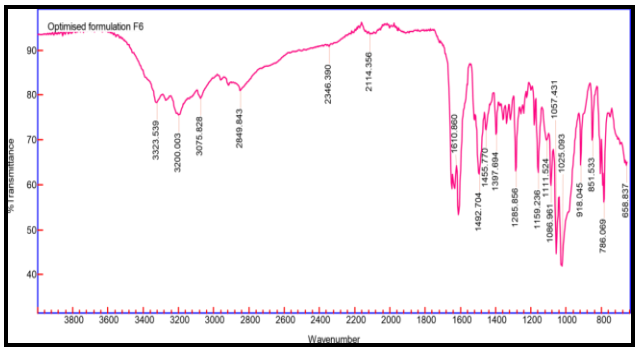

Figure 2F: FT-IR of Optimised Formulation F6

Evaluation of Bilayer Tablet

The Lamivudine tablet was evaluated for hardness, thickness, friability, weight variation and drug content uniformity. The hardness was in the range of 6.2 to 7.6 kg/cm^2, which was in accordance with the bi-layer tablet. The thickness was from 3.41 to 3.62 mm suggested uniformity in thickness for bi-layer tablet. The friability was less than 1% indicated good handling of the layer. The weight variation results suggested uniformity in weight of layers.

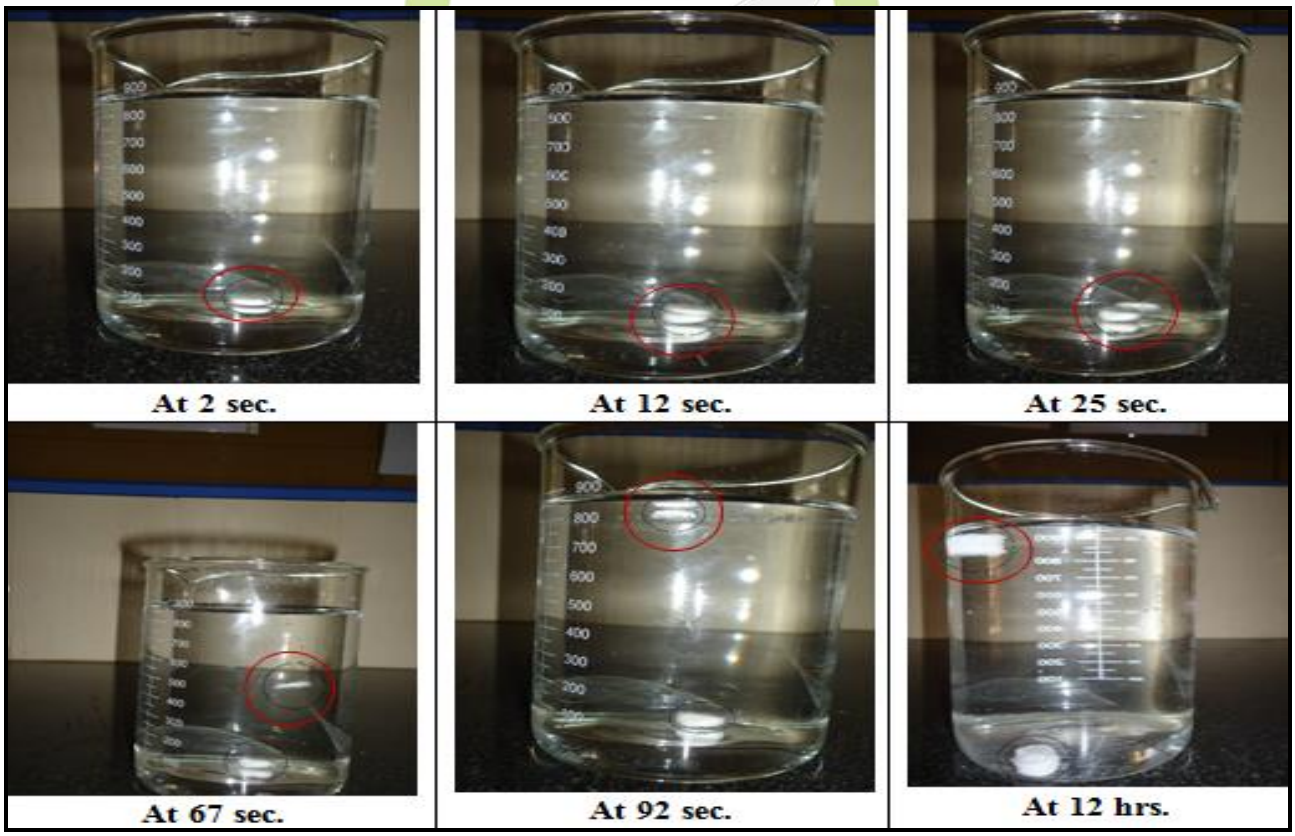

Figure 3: Determination of buoyancy lag time of optimised formulation F6

Table 2: Precompression parameters for Lamivudine immediate release and sustained release layers

Batch code	Untapped bulk density (gm/cm^3)	Tapped bulk density (gm/cm^3)	Carr's index (%)	Hausner ratio	Angle of repose(θ)
Immediate release layer					
IR	0.265± 0.05	0.318±0.002	14.76±0.010	1.15±0.02	24.35±0.05
Sustained release layer					
SR1	0.476±0.05	0.545± 0.02	12.45±0.06	1.12±0.05	25.20±0.01
SR2	0.568±0.04	0.651±0.02	14.33±0.04	1.18±0.06	22.56±0.02
SR3	0.502±0.04	0.571±0.02	11.82±0.03	1.13±0.04	23.42±0.02
SR4	0.515±0.07	0.595±0.03	13.95±0.04	1.15±0.04	24.40±0.02
SR5	0.519±0.04	0.591±0.02	12.86±0.03	1.13±0.05	24.40±0.02
SR6	0.499±0.02	0.582±0.04	12.08±0.02	1.15±0.08	23.10±0.03
SR7	0.531±0.04	0.610±0.03	13.76±0.02	1.15±0.07	23.51±0.04
SR8	0.532±0.03	0.591±0.03	14.25±0.03	1.13±0.05	24.42±0.02
SR9	0.488±0.03	0.553±0.03	11.43±0.03	1.12±0.07	22.90±0.01
SR10	0.568±0.04	0.651±0.02	14.33±0.04	1.18±0.06	22.56±0.02
SR11	0.591±0.04	0.591±0.02	12.86±0.03	1.13±0.05	24.40±0.02
SR12	0.531±0.04	0.610±0.03	13.76±0.02	1.15±0.07	23.51±0.04
SR13	0.476±0.05	0.545±0.02	12.45±0.06	1.12±0.05	25.20±0.01
SR14	0.515±0.07	0.595±0.03	13.95±0.04	1.15±0.04	24.40±0.02
SR15	0.488±0.03	0.553±0.03	11.43±0.03	1.12±0.07	22.56±0.02

Each value represents as mean ± SD of three determinants.

Table 3: Post compressional parameters of Lamivudine bilayer tablets

Batch code	Hardness (kg/cm^2)	Thickness (mm)	Friability %	Weight Variation (mg)	Drug content %
F1	7.1±0.02	3.41±0.06	0.10±0.05	499.3±9.15	98.73±0.31
F2	6.2±0.04	3.40±0.06	0.19±0.02	498.9±9.98	98.53±0.58
F3	6.3±0.02	3.41±0.08	0.18±0.07	497.9±9.78	98.57±0.33
F4	6.2±0.02	3.41±0.07	0.23±0.04	499.5±9.91	98.58±0.51
F5	6.2±0.03	3.40±0.07	0.26±0.02	499.5±9.91	98.57±0.68
F6	7.4±0.05	3.50±0.03	0.10±0.08	499.2±9.85	99.65±0.01
F7	7.6±0.04	3.61±0.08	0.11±0.08	499.1±9.19	98.57±0.78
F8	7.5±0.02	3.58±0.09	0.15±0.03	497.9±9.99	98.58±0.91
F9	7.6±0.05	3.60±0.06	0.13±0.02	498.5±9.83	98.57±0.32
F10	7.6±0.06	3.59±0.08	0.15±0.07	499.8±8.97	98.57±0.30
F11	7.4±0.05	3.62±0.05	0.16±0.02	498.6±9.59	97.02±0.08
F12	7.6±0.03	3.54±0.01	0.11±0.01	499.1±9.87	98.57±0.52
F13	7.3±0.07	3.62±0.01	0.13±0.02	498.5±9.89	97.06±0.03
F14	7.1±0.08	3.49±0.09	0.12±0.03	498.9±9.87	98.57±0.01
F15	7.4±0.03	3.52±0.07	0.14±0.02	499.3±9.87	99.41±0.01

Each value represents as mean ± SD of three determinants.

Table 4: Buoyancy studies of formulations F1-F15

Formulation Code	Floating lag time (sec)	Floating duration (hrs)
F1	74	>12
F2	5	4.5
F3	3	4.1
F4	4	4.0
F5	6	4.0
F6	92	>12
F7	85	>12
F8	72	>12
F9	77	>12
F10	89	>12
F11	92	>12
F12	73	>12
F13	91	>12
F14	85	>12
F15	87	>12

The content uniformity was in range of 97.02 to 99.65% indicated uniform dispersion of Lamivudine in the layers. The results are shown in Table 3.

Buoyancy Studies

The *in vitro* floating behaviour of the tablets was studied by placing them in 1000ml glass beaker filled with 900 ml of 0.1 N HCl (pH 1.2). The gas generating agents immediately evolves carbon dioxide in presence of HCl solution generating sufficient porosity which helped the dosage unit to float. Formulations F2, F3, F4and F5 showed floating lag time of 5, 3, 4 and 6 sec respectively and floating duration of 4.5, 4.1, 4, and 4 hrs. Because they do not contain HPMC K4M, so that diffusion of surrounding media into the dosage form is rapid. Formulation F1, F6, F7, F8, F9, F10, F11, F12, F13, F14, and F15 showed floating lag time of 74, 92, 85, 72, 77, 89, 92, 73, 91, 85 and 87 sec, respectively and floating duration of more than 12 hours. Because they contain HPMC K4M, so that diffusion of surrounding media into the dosage form is delayed. These results are shown in Table 4 and Figure 3. Bilayer tablet is intact for 12 sec, later tablet intact to separate into two layers and separated after 25 sec. lag time 92 sec was required to bring up the sustained release layer to the top of medium.

***In vitro* Drug Release Studies**

The floating sustained release layer of Lamivudine tablet were designed using individual HPMC K4M, xanthan gum, guar gum, locust bean gum and karaya gum alone and also in combination of two polymers (3:1 HPMC K4M : Natural polymer) and three polymers (3:0.5:0.5 HPMC K4M : Natural polymer : Natural polymer). The total weight of the polymers in the formulation used was 33.33% of total weight of SR layer. All the batches of formulated layers were produced under similar condition to avoid processing variables. The *in vitro* release study of Lamivudine study was conducted in 0.1N HCl for 12 hours. The *in vitro* release data of Lamivudine is shown in Table 5 and illustrated in Figure 4A & 4B. The *in vitro* release is depending upon nature of drug, nature of polymer, drug to polymer conc. and the medium used. In the present work HPMC K4M, xanthan gum, guar gum, locust bean gum and karaya gum were used as hydrophilic polymers in the preparation of sustained release layer. The highest release for 12 hrs was observed with HPMC K4M which is commonly used hydrophilic matrix, gets swelled and forming viscous gel thereby rapidly releasing the drug. Among all the formulation, formulation F6 contained 15% HPMC K4M and 5% of xanthan gum releases 99.65% of drug upto 12 hrs.

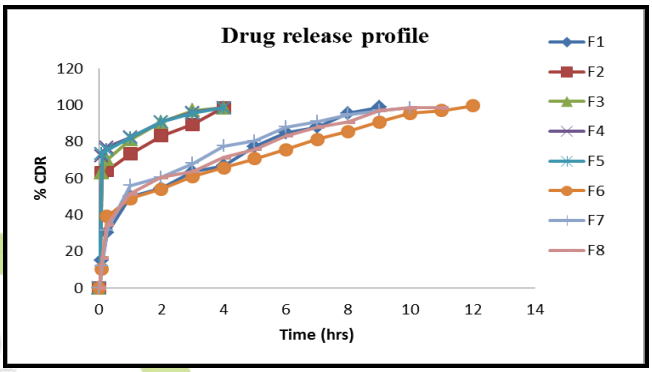

Figure 4A: *In vitro* release profile of F-1 to F-8 Formulations

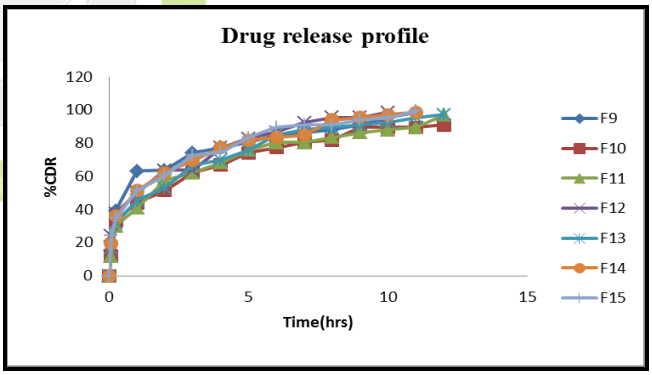

Figure 4B: *In vitro* release profile of F-9 to F-15 Formulations

Release Kinetics

The *in vitro* release data from Lamivudine was processed to plot different kinetics approaches. The obtained kinetics data is plotted as follows zero order (percent of drug release vs time), first order (logarithm of the percent drug remained vs time), Higuchi (percentage CDR vs square root of time), Korsmeyer-Peppas (log percent drug release vs log time) in order to establish drug release mechanism and kinetics of drug released.

Table 5: Percentage drug release of formulations F1-F15

Time	Percentage of drug released							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
5 min	51.00	63.00	63.00	72.00	73.50	10.50	12.00	16.50
15 min	30.17	64.32	70.22	76.92	75.45	39.22	31.67	34.69
1 hr	49.95	73.22	80.98	82.33	82.08	48.96	55.98	51.47
2 hr	54.58	83.10	90.77	90.67	90.76	53.98	60.64	60.62
3 hr	63.65	89.37	97.05	95.55	95.55	60.99	68.21	63.68
4 hr	66.72	98.53	98.57	98.58	98.57	65.76	77.30	71.24
5 hr	77.29	--	--	--	--	70.77	80.36	75.81
6 hr	84.89	--	--	--	--	75.55	87.92	86.39
7 hr	87.95	--	--	--	--	81.23	90.98	87.96
8 hr	95.51	--	--	--	--	85.67	94.86	93.33
9 hr	98.73	--	--	--	--	90.79	97.06	97.05
10 hr	--	--	--	--	--	95.53	98.57	98.57
11 hr	--	--	--	--	--	97.06	--	98.58
12 hr	--	--	--	---	--	99.65	--	--

Time	Percentage of drug released						
	F9	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
5 min	15.00	12.00	12.00	24.00	16.50	19.50	24.00
15 min	39.22	33.18	30.17	37.71	31.67	36.20	34.69
1 hr	63.06	43.92	46.92	49.98	45.42	51.48	51.47
2 hr	63.69	51.53	57.57	63.62	53.04	62.12	60.62
3 hr	74.26	62.12	62.16	63.67	66.66	69.72	72.73
4 hr	77.33	66.71	68.22	77.31	69.72	77.31	74.31
5 hr	80.37	74.27	75.85	82.72	75.80	81.87	83.37
6 hr	84.91	77.33	80.36	86.72	84.88	83.41	89.45
7 hr	86.44	80.37	80.38	92.48	87.95	84.92	90.99
8 hr	87.95	81.89	83.40	95.53	89.47	93.98	91.00
9 hr	90.98	89.44	86.43	95.55	90.99	95.54	94.02
10 hr	95.52	89.48	87.96	98.57	92.51	97.06	95.54
11 hr	98.57	89.48	89.47	--	95.53	98.57	99.41
12 hr	--	90.91	97.02	--	97.06	--	--

The goodness of best fit was evaluated by regression analysis of the said models (Figure 5). The kinetics of *in vitro drug* release from the entire formulated bilayer layer tablet obeyed zero order with the high regression r^2 value of 0.999 as compared to first order which showed less r^2 values.

As the polymers used were matrix material hence Higuchi model was applied which showed good linearity with high regression 0.995 to 0.843 suggested that the release mechanism was diffusion controlled. The *in vitro* release data was subjected to Korsmeyer-Peppas model, which shows good linearity with high r^2 value of 0.997 to 0.961. In a parallel line, Siepmann and Peppas suggested that the drug release from HPMC matrices is sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. (ii) Due to the imbibition of water, HPMC swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) With increasing water content, the diffusion coefficient of the drug increases substantially. Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fick's diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet, when n takes the value of 0.45 it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (anomalous transport). The n value of optimized formulation F6 is 0.309 and it is clear that all formulae have n values below 0.45.This indicates that the drug release majorly depends on diffusion-controlled phenomenon.

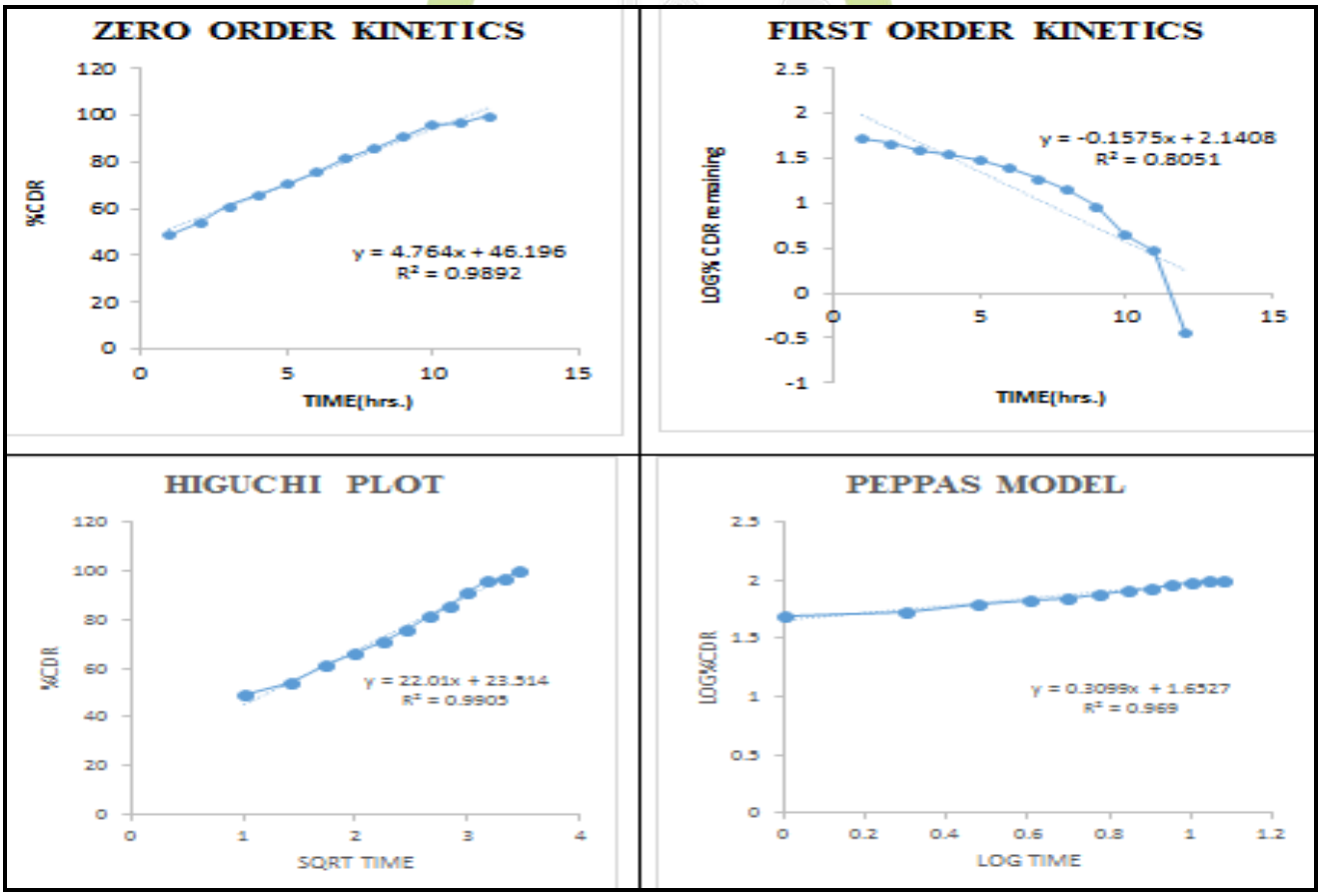

Figure 5: Kinetics of *in vitro* release data of formulation F6 bilayer tablet

Stability Studies

Stability studies were carried out on selected formulation (F6) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant change in drug content, physical stability, hardness, friability and drug release Table 6.

Thus, it can be concluded that HPMC K4M with suitable natural polymer can be utilised as matrix material to float the tablet in stomach and also to get sustained release.

Thus bilayer tablet of Lamivudine could improve the patient compliance by reducing the dosage frequency.

Table 6: Percentage drug release, floating lag time of optimized formulation (F6) after stability studies

No. of days	% Drug release			Floating lag time (sec)		
	25 °C / 60 %RH	30 °C / 65 %RH	40°C / 75 %RH	25 °C / 60 %RH	30 °C / 65 %RH	40°C / 75 %RH
0	98.72	97.95	99.15	92	89	90
15	98.44	98.89	97.12	84	90	89
30	99.12	97.63	98.45	91	87	89
45	97.12	96.33	97.12	89	89	91
60	98.56	98.51	98.87	90	85	90
75	97.43	99.67	97.63	89	93	91
90	98.65	98.49	96.78	91	90	93

CONCLUSION

Lamivudine floating tablets were developed using one synthetic polymer and four natural polymers in order to achieve sustained release of drug. To develop sustained release layer the polymers were used individually and also in combination. Among all formulation F6 containing HPMC K4M and xanthan gum (3:1) released almost all amount of incorporated drug during the period of 12 hrs. This optimised formulation was observed to float in the dissolution media more than 12 hrs.

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