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Formulation and Evaluation of Controlled Release Floating Matrix Tablets of Lamivudine

I. Nagendran[1,*], S. Vidyadhara[2] A. Ramu[2], K. Swapna[2] and D. Swathi[2]

[1]Department of Biotechnology, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India.

[2]Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chowdavaram, Guntur-500 019, Andhra Pradesh, India.

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ABSTRACT

The present study outlines a systematic approach for the development of Lamivudine floating matrix tablets to enhance bioavailability and therapeutic efficacy of the drug. Floating matrix tablets of Lamivudine are designed to prolong the gastric residence time after oral administration. These tablets have shown controlled release and there by proper duration of action at a particular site is achieved. The matrix tablets were prepared by using direct compression technique, by using polymers such as HPMCK_{15}M, carbopol, gum karaya and other standard excipients. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effect of different concentrations of polymers on drug release profile and floating properties were investigated. LF16 prepared by HPMCK_{15}M and gum karaya with effervescent agent was found to be more effective amongst all formulations. FTIR, DSC and SEM analysis were carried out to study drug excipients interactions and surface characteristics which indicated no drug excipient interaction. All the formulations were found to extend the drug release, while some of the formulation exhibited floating characteristics also.

Introduction

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patience compliance, least sterility constraints and flexible design of dosage forms. One of the methods of fabricating controlled release drug delivery system is by using hydrophilic matrices, also referred as hydrogels [1]. Development of a successful oral controlled release drug delivery dosage form requires an understanding of 3 aspects: (1) gastrointestinal (GI) physiology, (2) physiochemical properties of the drug and (3) dosage form characteristics [2, 3]. The gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms that reside in the stomach for a prolonged period of time than conventional dosage form [4]. One of most feasible approaches for achieving prolonged and predictable drug delivery in gastrointestinal tract is to control gastric residence time (GRT). Prolonged gastric retention improves bioavailability, reduces drug wastage and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine .The best drug delivery system for increasing the gastric retention of most of the drugs is Floating drug delivery system [5]. The design of floating drug delivery Systems (FDDS) should be primarily aimed to achieve more predictable and increased bioavailability. These systems due to the less bulk density than that of gastric fluids and remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time by incorporating number of low density fillers into the systems such as hydroxy cellulose, lactates or microcrystalline cellulose[6]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. The buoyancy action provided by the FDDS seems to offer a greater safety for clinical uses. Infact, no adverse effects due to floating devices have been reported till date, but the sudden gastric emptying often affects their therapeutic efficacy. Lamivudine is a potent nucleoside analogue reverse transcriptase inhibitor (nRTI) and has *invitro* activity against HIV. Lamivudine is a analogue of cytidine that can inhibit type 1 and type 2 of HIV reverse transcriptase and also reverse transcriptase of Hepatitis B. Lamivudine is absorbed rapidly following oral administration producing peak plasma concentration within 1 hr and with a reported bioavailability of about 86%. The virustatic drug has a half life of 5 to 7 hrs [7]. Based on the above physicochemical properties, Lamivudine was selected as a drug candidate for developing floating drug delivery systems to reduce the severity of toxicity and also to improve patient compliance. Lamivudine was selected for the design of FDDS because the drug absorbs in the upper GIT. The physicochemical and short half life of lamivudine makes it as a suitable candidate for floating drug delivery. Hence, it is aimed to design controlled release floating matrix tablets of lamivudine which reduces the repeated administration, increases the retention time and also prolongs duration of action. The aim of present investigate to design and evaluate FDDS of lamivudine, with swellable polymers, gel forming hydrocolloids, and natural gums such as hydroxyl methyl cellulose (HPMC K_{15}M), carbopol, gum karaya by employing gas generating agent/ effervescent agent such as sodium bicarbonate and citric acid.

Materials And Methods:

Lamivudine was a gift sample from M/s Apotex Pharma Ltd., Bangalore, Hydroxylpropyl methyl cellulose (Methocel) (HPMCK_{15}M) was gift sample from Colorcon Asia Pvt. Ltd.,

Tele:
E-mail addresses: svidyadhara@gmail.com

Mumbai, Carbopol 940P, Damar gum, gum copal, and gum karaya were commercially procured from Yarrow chem. Products, Mumbai. Avicel pH 102 was a gift sample from M/s Aurobindo Pharma Ltd., Hyderabad, Sodium Bicarbonate, Citric acid, Magnesium Stearate and Talc were commercially procured from SD Fine Chemicals Ltd., Mumbai. All other materials used were of Pharmacopoeial grade.

Determination of Stability of Lamivudine in 0.1N HCl:

Lamivudine stability in 0.1N HCl was analysed by dissolving drug in the 0.1N HCl. The drug solution was set aside for 24hrs and at specific time intervals, a small volume of sample was withdrawn and with subsequently diluted with 0.1N HCl to get 10µg/ml, standard dilution. The dilution was analyzed by UV Spectrophotometric method at 280nm. The absorbance values obtained for the samples at various time intervals were given in table 1. The amount of drug present in each sample at various time intervals was measured based on the absorbance values.

Preparation of Lamivudine Controlled Release Floating Matrix Tablets:

Lamivudine controlled release floating matrix tablets were prepared by direct compression process. The drug concentration was maintained constantly while polymer proportions were varied. The weight of all the tablet formulations was maintained uniformly by using MCC as diluent.

The materials were individually weighed, passed through sieve no: 60 and blended for 15 minutes by using double cone blender. Then sodium bicarbonate and citric acid were mixed one by one. The powder blends were evaluated for flow properties such as angle of repose and compressibility index. The powder blends were lubricated with 1% talc and magnesium stearate and were directly compressed as matrix tablets with 6mm flat, round punches by using clit-10 station mini press. To minimize the processing variables all batches of tablets were compressed under identical conditions. The compositions of various tablet formulations were given in table 2.

Evaluation of Physical Parameters:

The physical parameters such as weight uniformity, hardness, friability and drug content were evaluated for the prepared floating matrix tablets as per the Indian Pharmacopoeial standards [8].

Dissolution Rate Studies on Lamivudine Floating Matrix Tablets:

Dissolution studies on each floating matrix tablet formulation was performed in a calibrated 8 station dissolution test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium. The paddles were operated at 50rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 12hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 280nm. The dissolution studies on each formulation were conducted in triplicate. The dissolution profiles of various controlled release floating matrix tablets of Lamivudine were shown in fig 1, 2, 3, 4.

Evaluation of Dissolution Parameters:

To analyse the mechanism of drug release from the obtained dissolution data, various kinetic calculations based on the equations of first order constant, higuchi constant and koresmeyer peppas constant respectively were used. The following are the equations:

$\ln Q = k.t$ --------1

$Q = k.t^{1/2}$ --------2

$M_t/M_\infty = kt^n$ ----3

Where Q in the equation (1) is cumulative percent drug remained, while Q in equation (2) is cumulative amount of drug released, M_t/M_∞ in equation 3 is the fraction of drug released at time and k is the constant incorporating the structural and geometrical characteristics of the release device. If the value of n=0.45 indicates case I (Fickian) diffusion or square root of time kinetics, 0.45< n < 0.89 indicates anomalous (non Fickian, drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, n = 0.89 indicates supercase II transport [9, 10]. The *in vitro* dissolution parameters of various Lamivudine controlled floating tablets were given table 3.

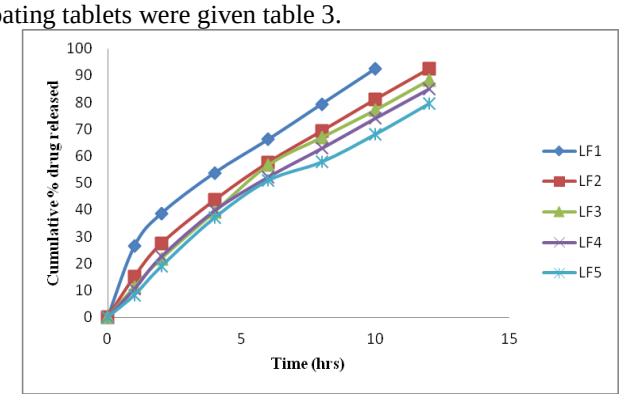


Figure 1: Dissolution profiles of lamivudine floating matrix tablets containing HPMC K15M as polymer with sodium bicarbonate as gas generating agent.

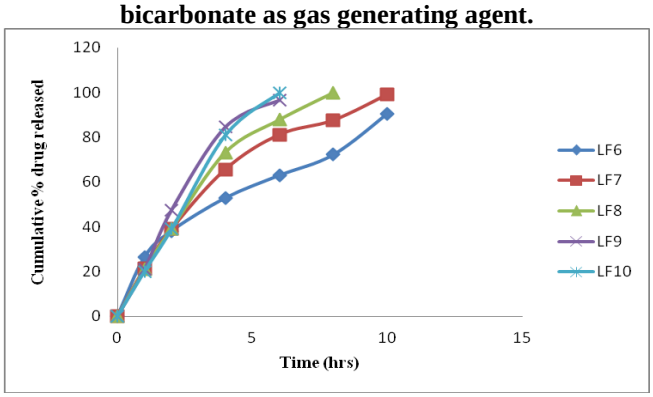


Figure 2: Dissolution profiles of lamivudine floating matrix tablets containing carbopol 940P as polymer with sodium bicarbonate as gas generating agent.

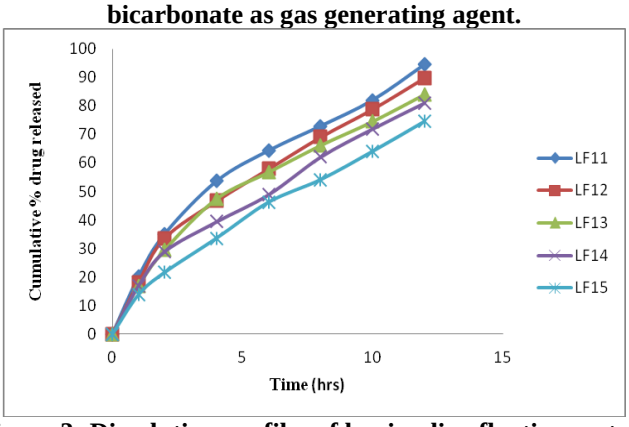


Figure 3: Dissolution profiles of lamivudine floating matrix tablets containing HPMCK15M and gum karaya as polymer s with sodium bicarbonate as gas generating agent

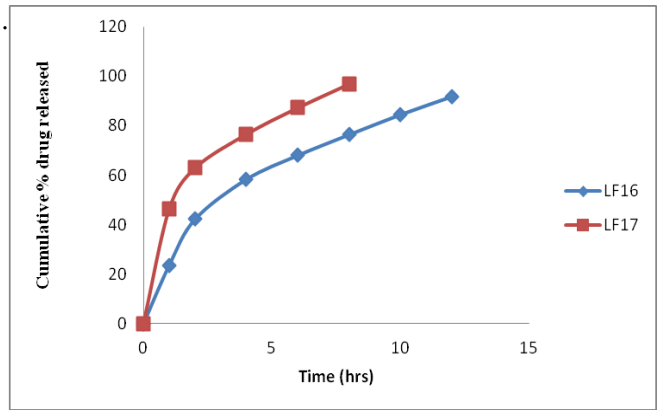
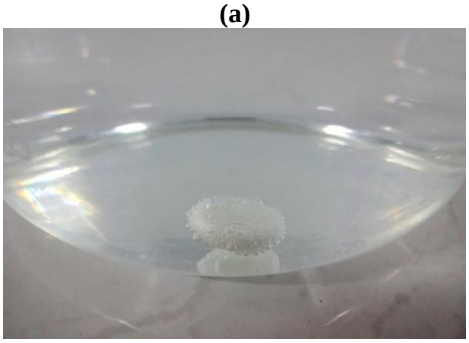


Figure 4: Dissolution profiles of lamivudine floating matrix tablets containing HPMCK15M and gum karaya as polymers sodium bi carbonate and citric acid as effervescent agents.

***Invitro* Buoyancy Studies:**

All the prepared floating matrix tablet formulations were subjected to *invitro* floating buoyancy studies. The *invitro* buoyancy study was characterized by floating lag time and total floating time [11, 12]. The test was performed using a USP type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5^0 C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as floating lag time and total floating time respectively. The floating behaviour of LF16 was shown in fig 5 and results were given in table 4.

(a)



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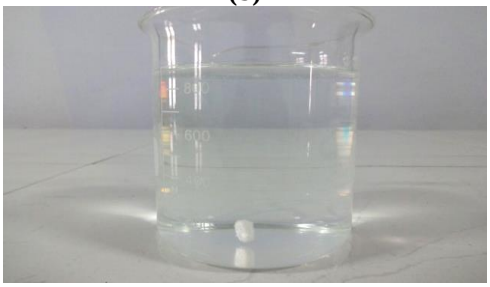

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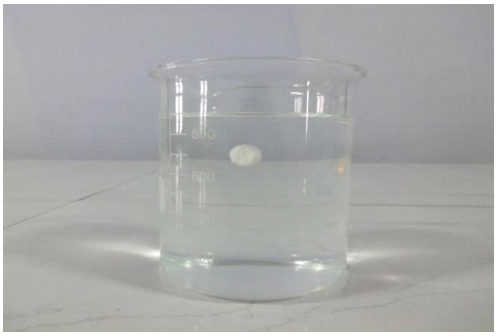

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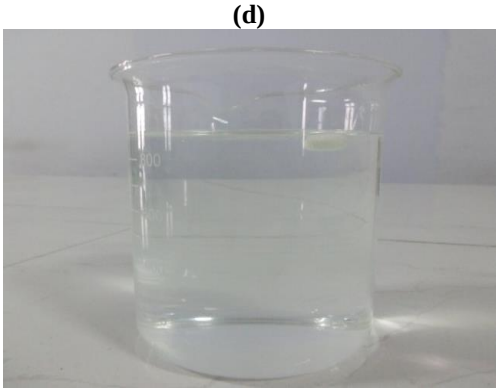

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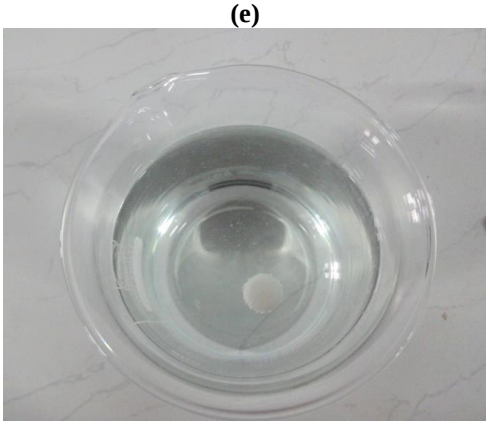


(f)

Figure 5: Floating behaviour of formulation LF16

Swelling Index:

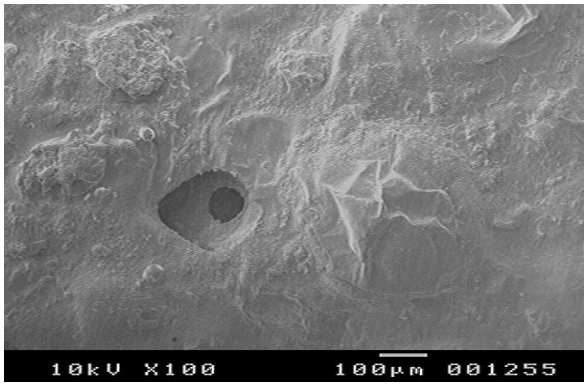
The swelling behaviour of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1N HCl at 37±0.5^0C. After 1, 2,4, 6 and 8 hrs, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120) [13, 14] . The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula

$$\text{Swelling index} = \frac{(\text{Wet weight of tablet} - \text{Dry weight of tablet})}{\text{Dry weight of tablet}}$$

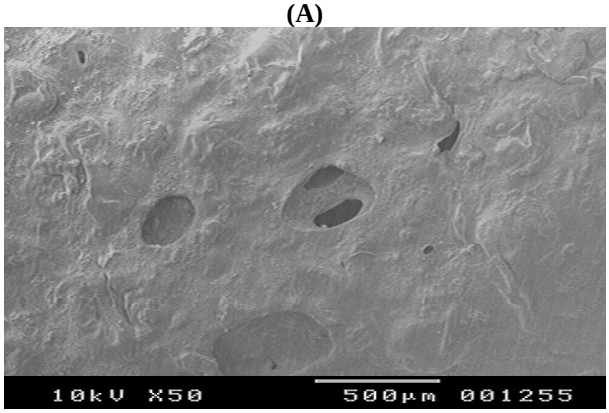
The % swelling index values and swelling index profiles for the selected formulations were given in table 5.

Characterization:

Based on the dissolution studies performed on all the formulations, some of the optimized formulations were selected for further investigations such as DSC, and SEM Analysis [15]. The SEM photomicrographs and DSC thermograms of selected controlled release floating matrix tablets were shown in fig 6, 7.



(A)



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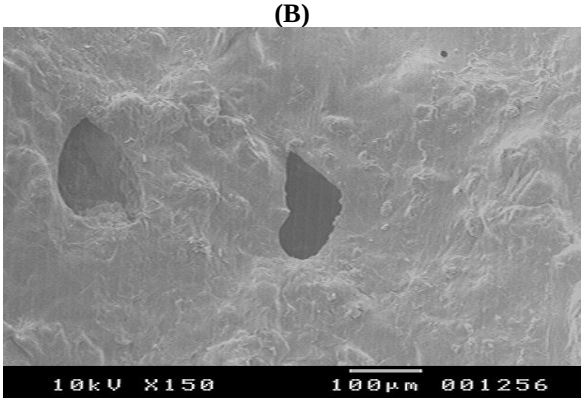
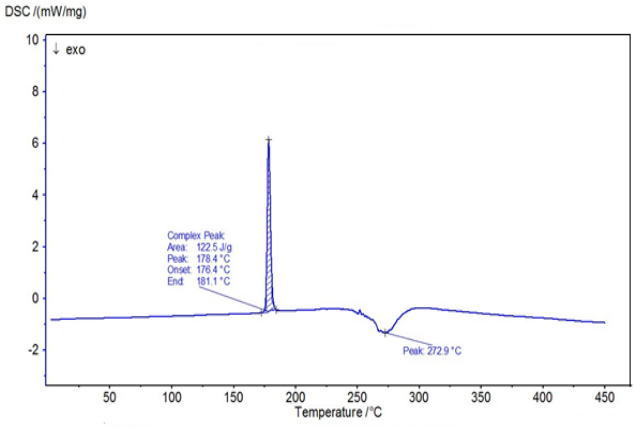
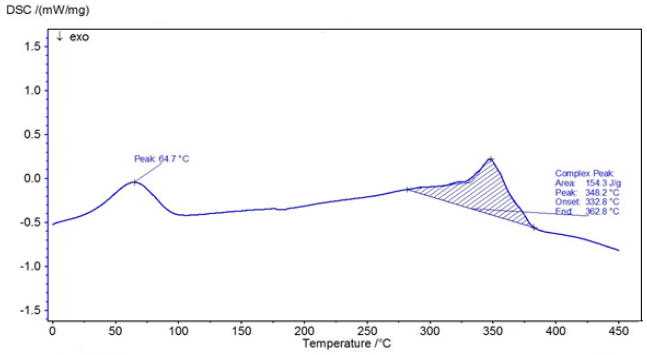


(C)

Figure 6: Scanning electron microscope photographs of lamivudine floating tablets containing (A) LF5 (B) LF14 (C) LF16



(a)



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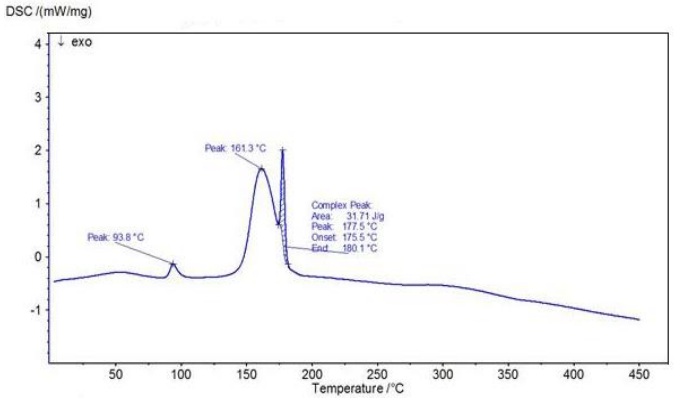

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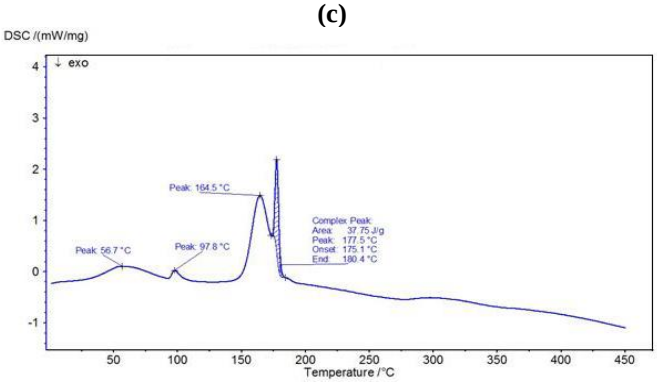

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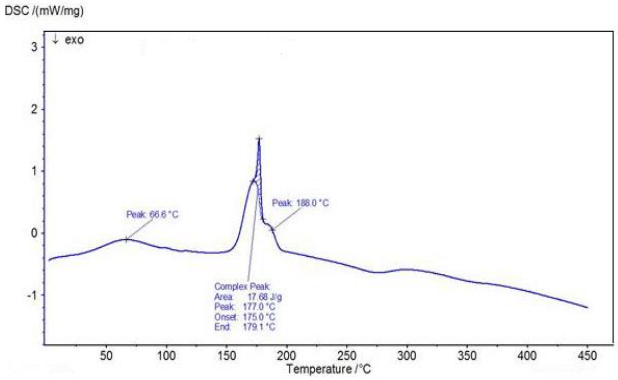

(e)

Figure 7: Differential scanning Calorimetry curves for lamivudine (a) Pure Drug (b) HPMC K15M (c) LF5 (d) LF14 (e) LF16

Accelerated Stability Studies:

The formulations which showed good invitro performance were subjected to accelerated stability studies. The floating matrix tablets LF16 was subjected to accelerated stability studies. These studies were conducted, using stability testing chamber at temperature and relative humidity of 25 $\pm$ 2^0C, 60 $\pm$ 5% RH for 6 months and 40 $\pm$ 2^0C, 75 $\pm$ 5% RH for 3 months.

Table 1: Stability of Lamivudine in 0.1N HCl

S. No.	Time (hr)	Absorbance	Amount of drug (µg)
1	1	0.6095	9.9
2	2	0.6130	9.9
3	3	0.6064	9.9
4	4	0.6075	9.9
5	8	0.5984	9.8
6	12	0.5995	9.8
9	24	0.6074	9.9

Table 2: Composition of various lamivudine controlled release floating matrix tablets

Ingredients (mg/tab)	Formulations																
	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9	LF10	LF11	LF12	LF13	LF14	LF15	LF16	LF17
Lamivudine	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
$HPMCK_{15}$ M	250	250	250	250	250	-	-	-	-	-	187.5	187.5	187.5	187.5	187.5	187.5	187.5
Carbopol 940P	-	-	-	-	-	250	250	250	250	250	-	-	-	-	-	-	-
Gum Karaya	-	-	-	-	-	-	-	-	-	-	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Sodium bicarbonate	35	70	105	140	175	35	70	105	140	175	35	70	105	140	175	93.3	116.6
Citric Acid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	46.6	58.3
MCC	151	116	81	46	11	151	116	81	46	11	151	116	81	46	11	46	11
Magnesium Stearate	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Total Tablet Weight(mg)	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700

Table 3: *Invitro* dissolution parameters of lamivudine controlled release floating matrix tablets

Formulation	Zero Order		First Order		Higuchi		Peppas	
	K_0 (mg/hr)	R^2	K_1 (h^{-i})	R^2	K_H ($mg.h^{1/2}$)	R^2	n	R^2
LF1	8.30	0.8557	0.229	0.9454	71.01	0.9931	0.53	0.997
LF2	7.37	0.7470	0.193	0.9447	68.57	0.9977	0.71	0.998
LF3	7.28	0.8656	0.167	0.9730	67.50	0.9980	0.80	0.995
LF4	6.92	0.7638	0.148	0.9774	73.15	0.9985	0.80	0.990
LF5	6.52	0.7640	0.125	0.9854	66.14	0.9967	0.78	0.984
LF6	8.08	0.6512	0.210	0.9541	70.24	0.9903	0.52	0.994
LF7	9.50	0.8584	0.268	0.9973	84.59	0.9834	0.69	0.981
LF8	12.52	0.7207	0.359	0.9832	114.05	0.9864	0.82	0.989
LF9	16.56	0.8362	0.569	0.9576	133.92	0.9762	0.86	0.967
LF10	17.14	0.7768	0.424	0.9294	143.66	0.9894	1.00	0.999
LF11	7.14	0.8529	0.185	0.9744	68.66	0.9949	0.58	0.987
LF12	6.88	0.8864	0.174	0.9712	69.15	0.9961	0.61	0.989
LF13	6.51	0.8753	0.141	0.9884	65.00	0.9969	0.62	0.990
LF14	6.26	0.7116	0.132	0.9758	63.15	0.9879	0.61	0.992
LF15	5.83	0.7472	0.105	0.9879	59.59	0.9923	0.67	0.999
LF16	6.85	0.8825	0.191	0.9825	64.76	0.9859	0.51	0.975
LF17	10.15	0.6604	0.389	0.9604	65.51	0.9893	0.64	0.992

Table 4: Floating lag times and floating times of matrix tablets of lamivudine

Formulation	Floating lag Time	Total Floating Time
LF1	2.30hrs	>12hrs
LF2	9min	>12hrs
LF3	1min	>12hrs
LF4	30sec	>12hrs
LF5	20sec	>12hrs
LF6	-	-
LF7	3min	5hrs
LF8	1:30min	3:30hrs
LF9	15sec	4hrs
LF10	10sec	5hrs
LF11	4hrs	>12hrs
LF12	3:30hrs	>12hrs
LF13	28min	>12hrs
LF14	20min	>12hrs
LF15	15min	>12hrs
LF16	15sec	>12hrs
LF17	10sec	>12hrs

Table 5: Swelling index of controlled release floating matrix tablets of lamivudine

Formulation	Swelling index (%)			
	1 hr	2 hr	4 hr	8 hr
LF5	49.41	66.54	83.47	100.5
LF15	45.42	56.88	78.34	96.38
LF17	40.12	59.45	72.67	100.3

The tablets were evaluated after storage for physical parameters and drug release studies.

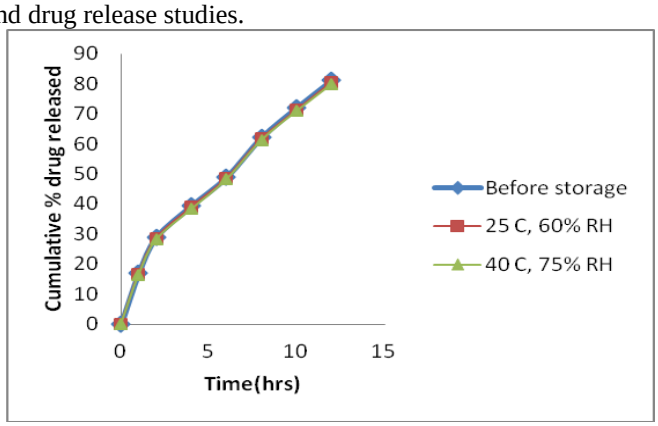

Figure 8: Release of Lamivudine Floating Matrix Tablet Formulation Before and After Storage at Different Condition LF16

Results and discussion:

The present work was mainly aimed to achieve floating drug delivery system of Lamivudine. Lamivudine stability in 0.1N HCl was performed for a period of 24hrs. The values obtained at various time intervals were found to be linear. This showed that the drug remains stable in 0.1N HCl over a period of 24 hrs. The absorbance values and their corresponding concentrations were given in table 1.All the matrix tablet formulations were prepared by direct compression method as per the composition shown in table 2. Before compression process the powder blends were evaluated for flow properties such as Angle of Repose and Carr's index. The angle of repose values for various powder blends were in the range of 25.42±0.05-27.32±0.05 Carr's index values for all the powder blends were in the range of 11.20±0.02-14.87±0.01. The direct compression process was found to be suitable for compressing powder blends as matrix tablets. All the batches of tablets were compressed under identical conditions to minimise processing variable.

Then the compressed matrix tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability and drug content. The hardness of all the tablet formulations were in the range of 5.5-5.8 kg/cm^2.Weight uniformity of all the tablet formulations were in the range of 698 ± 4.0 and 700 ± 3.0 mg respectively. Friability loss of the tablet formulations was negligible and was in the range of 0.12-0.20%. Drug content estimated for all the tablet formulations was highly uniform within the range of 248.2 ± 0.5 – 251.9 ± 0.2. These studies revealed that all the tablet formulations were found to be stable and meeting I.P specified limits for weight uniformity, friability and drug content.

Dissolution studies were performed on all the tablet formulations by using USP paddle method (apparatus II). The drug release from the matrix tablet formulations were extended up to 12 hrs in the formulations LF1 - LF5 containing HPMC K_{15}M as rate controlling polymer. Formulations LF11 – LF15 containing HPMC K_{15}M in combination with Gum Karaya, showed initial rapid drug release due to presence of gas generating, while extending the drug release up to 12 hrs. The formulations LF6 – LF10 containing Carbopol 940P along with sodium bicarbonate, have failed to extend the drug release upto 12hrs, due to the presence of high concentrations of gas generating agent. The formulation LF17 containing combination of HPMC K_{15}M with Gum Karaya along with effervescent agents, have failed to extend the drug release upto 12hrs, due to the presence of high concentrations of effervescent agents. It was also observed that the concentration of gas generating agent increased the drug release from the floating matrix tablets was decreased in the formulations LF1- LF5 containing HPMC K_{15}M as a rate controlling polymer. Among the formulations LF5, LF14, LF16 were found to extend the drug release over a prolonged period of time due to the presence of HPMC K_{15}M and Gum Karaya.

All the floating matrix tablets were found to be linear with first order release rate with R^2 values in the range of 0.9294 – 0.9973. Thus the rate of drug release from all the matrix tablet formulations were concentration dependent and were linear with first order release rate K. The higuchi constants for all the floating matrix tablet formulations were in the range of 59.143 mg. $h^{1/2}$ indicating the controlled drug release from the dosage form. The amount of drug released Vs square root of time plots were found to be linear with R^2 values in the range of 0.983 – 0.998. The release exponent (n values) for all the matrix tablet formulations were in the range of 0.5 – 0.8 indicated that the drug release was by non Fickian diffusion. The log cumulative percentage drug release Vs log time plots were found to be linear with R^2 values in the range of 0.967 – 0.999. Thus the drug release from the matrix tablet formulations was by diffusion of the drug from the polymeric matrix followed by erosion of the polymer. The dissolution profiles of various controlled release floating matrix tablets of Lamivudine were shown in fig 1, 2, 3, 4. The invitro dissolution parameters were given in table3.

Invitro buoyancy studies were performed on all the floating tablet formulations containing gas generating agent. The formulations containing carbopol 940 P alone failed to float throughout the duration upto 12 hours. The formulations LF1 containing HPMC K_{15} M shows the floating with a lag time of 2 hour 30 minutes due to low concentration of gas generating agent. The formula LF2 – LF5 floated with a minimum lag time of 20 sec – 9 minutes due to gas generating agent and remained floating throughout the duration upto 12 hours. Formulation LF11 – LF17 containing combinations of HPMC K_{15}M and gum karaya floated with a floating lag time of 10secs -2 minutes and continued to float throughout the duration of 12 hours. The floating lag time and total floating time for various Lamivudine floating matrix tablets were given in table 4 and the floating behaviour for LF16 was shown in fig 5.

Swelling index characteristics were performed on selected floating matrix tablet formulations. The formulations with HPMC K_{15}M alone as a polymer tends to swell at a rapid rate compared to that of formulations with combination of HPMC K_{15}M with Gum Karaya. The formulation LF5 was found to have high swelling rate compared to other formulations. The %

swelling index values and swelling index profiles for some of the formulations were shown in table 5.

The SEM photographs were taken for formulations LF5, LF14 and LF16. The SEM photographs of LF5 and LF14 showed pores on the surface due to the presence of gas generating agents, which indicated the drug release by both diffusion and polymer erosion. The SEM Photomicrograph of LF16 showed deeper pores on the surface and erosion on the surface due to gas generating and effervescent agents. This indicates that drug was rapidly released by both drug diffusion and polymer erosion. The SEM photomicrographs of selected floating matrix tablets were shown in Fig 6.

DSC studies of Lamivudine and optimized formulations were carried out to study the interaction between the drug and excipients used. The DSC Thermogram of Lamivudine showed sharp endothermic peak at 181.1^0C, while that of HPMC K_{15}M showed broad endothermic peak at 64.7^0C. The DSC Thermograms of optimized formulations LF5, LF14, and LF16 showed sharp endothermic peaks for Lamivudine at the temperatures 180.1^0C, 180.4^0C, and 179.10C respectively. This indicated that there were no drug excipients interactions in the formulations. The DSC thermograms for selected tablets formulations were shown in Fig 7.

The accelerated stability studies for selected floating matrix tablets LF5, LF14, LF16 were carried by investigating the effect of temperature on the physical properties of the tablets and on drug release of the floating tablets. The results indicated that there was no visible and physical changes observed in the matrix tablets after storage. It was also observed that there was no significant change in drug release from the floating matrix tablets. The drug release profiles of LF16 before and after storage was shown in fig 8. Thus the drug release characteristics of controlled release floating tablets designed were found to be stable.

Conclusion:

From the evaluation studies of all formulations the formulation LF5, LF14, LF15 containing HPMC K_{15} and gum karaya combination showed best results regarding floating time as well as total buoyancy time and also showed extended release for prolonged period than compared to other formulations. Hence, it can be concluded that floating matrix tablets showed the best results when the polymer ratio of HPMC K_{15}M and gum karaya was maintained at 1:0.25. Hence, the floating matrix tablet of lamivudine was a novel approach so as to avoid the disadvantage of anti retroviral conventional dosage forms.

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