Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 4, 2013

Research Article

FORMULATION AND EVALUATION OF EXTENDED RELEASE FLOATING TABLETS OF LAMIVUDINE EMPLOYING DIFFERENT GRADES OF HPMC

K.S.N. MADHURI*[1], S.N.V. SURESH[2], M. SRINIVASA RAO[3]

[1]Department of Pharmaceutics, KJR College of Pharmacy, Burugupudi, [2]Department of Pharmaceutics- VJ's College of Pharmacy, Rajahmundry, A.P, [3]Department of Quality Assurance, Beloorbayirbiotec Ltd., Tumkur, Karnataka, India. Email: madhuri.kalluri9@gmail.com

Received: 16 Oct 2013, Revised and Accepted: 07 Nov 2013

ABSTRACT

Objective: The investigation was concerned with the formulation and evaluation of extended release floating tablets of lamivudine employing different grades of HPMC in order to increase the gastric residence time of lamivudine for prolonged drug action and reduced dosage frequency.

Methods: The drug excepient compatibility studies were performed by DSC. The gastro retentive floating tablets were prepared by direct compression method. The prepared tablets were evaluated for physicochemical characteristics and *in-vitro* dissolution studies. The optimised formulation was subjected to stability studies.

Results and Discussion: The compatibility of the drug with excepients was confirmed by DSC study. The prepared tablets exhibited satisfactory physicochemical characteristics. The *in-vitro* drug release studies revealed that the drug release was sustained up to 24hrs for formulation F6 containing HPMC K15M as release retardant polymer at a concentration of 1:1 to the drug. Using Higuchi's model and the Korsmeyer equation, the drug release mechanism from the floating sustained release tablets was found to be Anomalous (non-Fickian) diffusion. The stability studies reported no significant change in physicochemical characteristics and drug release profile for optimised formulation.

Conclusion: The gastro retentive extended release floating tablets of lamivudine were successfully formulated and evaluated employing HPMC as release retardant polymer. A slow and spread over drug release upto 24 hrs was observed with the formulation F6 with HPMC K 15M at 1:1 concentration to the drug. Thus current investigation was successful in extending the drug release and reducing the dosing frequency.

Keywords: Lamivudine, Extended release, Floating tablets, HPMC, Non-fickian diffusion, Stability study.

INTRODUCTION

New drug delivery technologies are revolutionizing the drug discovery, development and creating R&D focused pharmaceutical industries to increase the momentum of global advancements. In this regard novel drug delivery systems (NDDS) have many benefits, which includes improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved site specific delivery to reduce unwanted adverse effects [1]. Lamivudine is a BCS Class I active anti-retroviral agent which belongs to non-nucleoside reverse transcriptase inhibitor. It is generally prescribed in the dose of 100-150 mg twice a day, and is well absorbed in the upper gastrointestinal tract with a short biological half life of 5-7 h [2]. By decreasing the dosing frequency to once a day systemic side effects can be decreased and the patient compliance can be improved.

The present work was aimed at the formulation of lamivudine floating tablets using 3 different polymers in 3 different concentrations, in order to decrease the dosing frequency, by sustaining the drug release for 24 hrs and to evaluate the prepared formulations.

MATERIALS AND METHODS

Materials

Lamivudine is a gift sample from MSN laboratories Ltd. HPMC K4M, HPMC K15M and, HPMC K100M were supplied by Colorcon Asia Pvt. Ltd., Goa, India. Sodium bicarbonate, Citric acid from SD Fine Chemicals, Mumbai, Avicel and Magnesium stearate were procured from commercial sources. All other materials were of Laboratory grade.

Methods

Drug Excipient Compatibility Studies by Differential Scanning Calorimetry

The DSC measurements were performed using differential scanning calorimeter (Netzsch DSC Q 1000, TA Instrument, Germany). The samples of about 5-10 mg were hermetically sealed in aluminium pans and heated at a constant rate of 10°C/ min over a temperature range of 50-300°C. An inert atmosphere was maintained by purging with nitrogen gas at a flow rate of 100 ml/ min. An empty aluminium pan was used as reference.

Preparation of Floating Tablets of Lamivudine

The formulations containing 300 mg of lamivudine were fabricated using Direct compression method using formulae mentioned in table 1. Required quantities of Drug, Polymer and other excipients except magnesium stearate were passed through 30# sieve together and blended to uniformity for 10 minutes. The powder blend was lubricated with magnesium stearate (pre-sifted through 60# sieve) and blended for 5 minutes. Then the powder blend was compressed into tablets of 900 mg by using 17.5 x 8.75 mm, caplet shaped punches.

Table 1: Formulae for preparation of Lamivudine Floating Tablets

Ingredients (mg/tablet)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamivudine	300	300	300	300	300	300	300	300	300
HPMC K4M	150	225	300	-	-	-	-	-	-
HPMC K15M	-	-	-	150	225	300	-	-	-
HPMC K100M	-	-	-	-	-	-	150	225	300
Sodium Bicarbonate	90	90	90	90	90	90	90	90	90
Avicel PH 102	333	258	183	333	258	183	333	258	183
Magnesium Stearate	9	9	9	9	9	9	9	9	9

In vitro evaluation of the prepared tablets

1. Tablet weight variation

The tablet weight variation test was performed as per procedure specified in Indian Pharmacopoeia (IP).

2. Drug content uniformity

Ten tablets from each formulation were powdered. The powdered sample equivalent to 50 mg of the drug was transferred to a 100ml volumetric flask. The required amount of 0.1 N HCl was added, mixed and filtered, the filtrate was suitably diluted with 0.1N HCl and analysed for Lamivudine content against blank by a UV spectrophotometer at 280nm (n=3).

3. Tablet hardness

Hardness of five randomly selected tablets was determined using Monsanto Hardness Tester.

4. Tablet friability

Ten tablets were randomly selected and friability was checked using Roche friabilator (n=2).

5. Tablet floating behaviour

The floating behaviour of the tablets was visually determined (n=3), according to the floating lag time method described by Rosa et al., [3]. A tablet was placed in a glass beaker, containing 200ml of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 ° C. The floating lag time and total floating duration were recorded.

6. Drug release studies

The drug release from the prepared controlled release floating tablets of lamivudine formulations were tested in 900ml of 0.1 N HCl at 37±0.5 ° C using USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) at the paddle rotation speed of 75rpm. Samples (5ml) of dissolution medium were withdrawn at different time intervals and replaced with a fresh medium of the same volume after each sampling. The samples were analysed for lamivudine content spectrophotometrically at 280nm. All the dissolution experiments conducted was in triplicate (n=3).

7. Kinetic modelling of drug release profiles

The dissolution profiles of all formulations in 0.1 N HCl were plotted by zero-order, first-order, Higuchi [4] and Korsmeyer–Peppas [5] kinetic models. The model with the highest correlation coefficient was considered to be the best fitting one.

8. Stability Study

The optimised formulation was subjected to stability studies at 40±2 ° C and 75±5% RH in a humidity chamber for a period of 1 month.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies-DSC

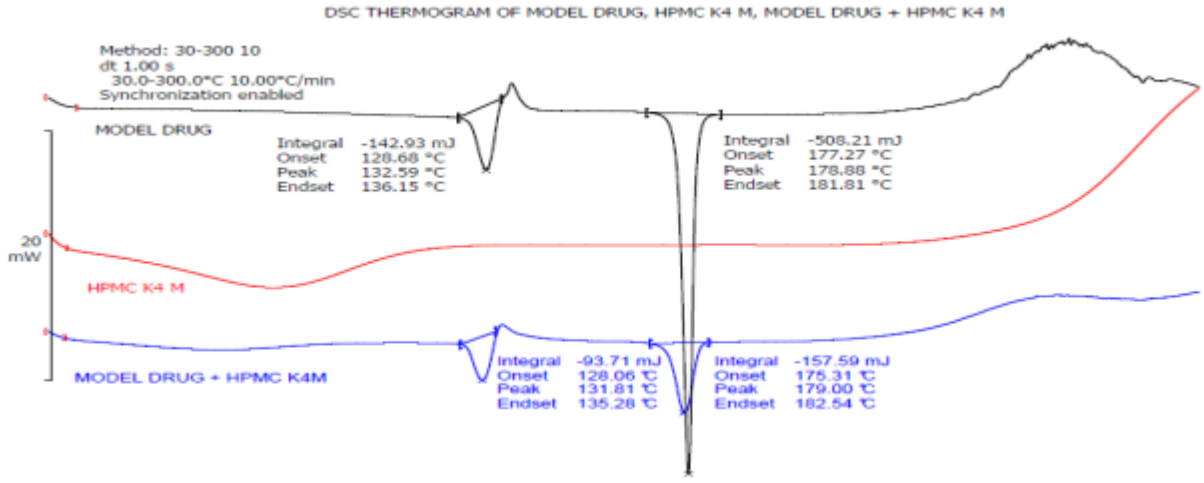

Fig. 1: Drug - HPMC K4 M

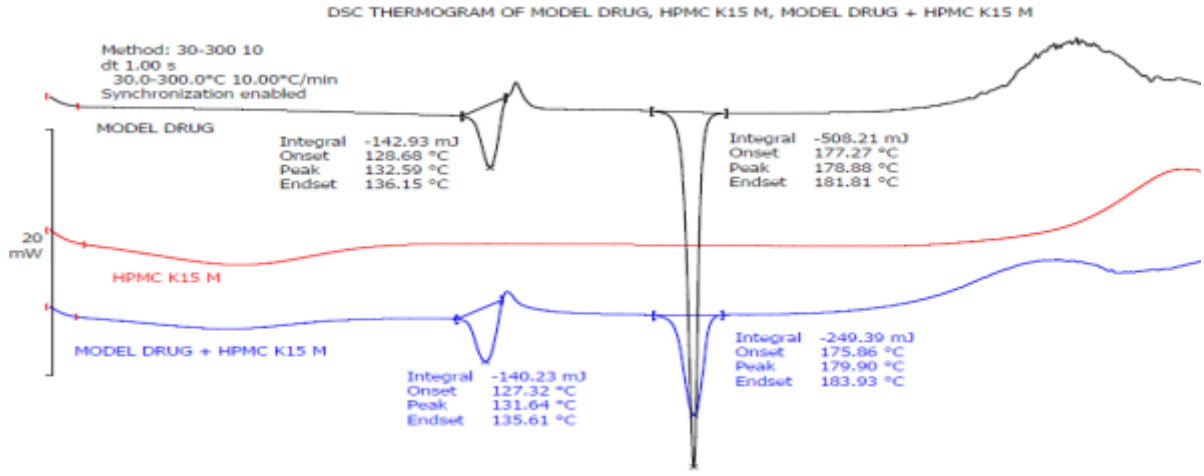

Fig. 2: Drug - HPMC K15M

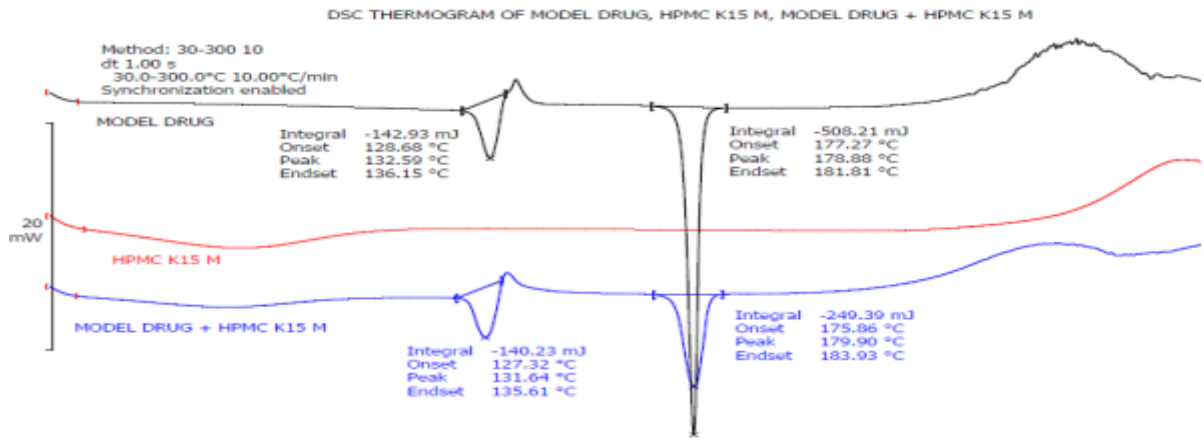

Fig. 3: Drug-HPMC K 100M

When the drug was studied in combination with HPMC K4M, HPMC K15M and HPMC K100M, individually, no change in melting point of the drug were observed, no additional peaks were observed indicating compatibility of the drug with the polymers. Sharp melting peaks were observed in drug indicating the crystalline nature of the drug.

Physicochemical characteristics of tablets

Controlled release floating tablets of lamivudine were formulated using release retardant polymers like HPMC K4M, HPMC K15M and HPMC K100M and effervescent agent like sodium bicarbonate.

The physicochemical characteristics of the tablets were summarized in the Table 2. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications (IP) for weight variation, drug content and friability. The weight of the tablet ranged from 890-917 mg. The percentage of drug content was found to be in the range of 98.4%-100.9%. The percentage friability for all the formulations was less than 1 %, indicating a good mechanical resistance.

Floating Lag Time and Duration

In the present study, the floating drug delivery systems were formulated by employing sodium bicarbonate as the effervescent agent, dispersed in the hydrogel matrix formed by the polymers HPMC K4M, HPMC K15M and HPMC K100M. The in vitro testing revealed that all the formulations, except F1, F2, and F4, remained buoyant for more than 24 hrs. The gel layer formed by the polymers enabled efficient entrapment of generating gas bubbles and made the tablet float on the test medium (0.1 N HCl) for an extended period of time [6].

As shown in the Table 2, the HPMC K4M/HPMC K15M/ HPMC K100M ratio has a marked effect on the floating lag time of prepared formulations with constant sodium bicarbonate proportion, 10 % w/w. The lag time of formulation F9, containing HPMC K100M (1:1) was 40 Sec, which was higher than that of formulations containing the other polymers, this might be due to the higher specific gravity of HPMC K100M in more concentration than that of other polymers. The floating lag time increased with increased concentrations of the polymers. This might be due to the increased density of the formulation as the polymer concentration increased.

Drug Release Studies

The drug release from different formulations was found to be dependent on the type and concentration of controlled release polymer(s) used. The drug release profiles of lamivudine from various formulations were shown in Fig. 4. Release parameters are given in Table 3

The drug release studies showed the formulations from F1 to F5 could not sustain the release of the drug for 24h. This might be attributed to the insufficiency of the polymer concentration in controlling the drug release upto 24h. A slow and spread over release of the drug for 24 hrs was found with the other formulations. F6, which was fabricated using HPMC K15M (300 mg), was found to be the best formulation among the other formulated tablets, with 100 % drug release. This might be due to the formation of high viscous gel with K15M, upon contact with the aqueous fluids, which can sustain the drug release for 24 hours.

The drug release from the polymeric systems is mostly by diffusion and is best described by Fickian diffusion. But in case of the formulations containing swelling polymers, as HPMC, other processes take place, like relaxation of polymer chains, imbibition of water causing polymers swelling and considerable volume expansion [7], [8]. When the release data were analysed as per zero and first order models the correlation coefficient (R^2) values were relatively higher in the first order model with all floating tablets formulated indicating that the drug release from all these tablets followed first order kinetics. Lamivudine drug release data also obeyed Higuchi and Peppas models with R^2 values greater than 0.97. When percentage drug released was plotted against √time, linear regressions with 'R^2' > 0.962 were observed with all floating tablets prepared indicating that the drug release from all these formulations was diffusion controlled.

Table 2: Physicochemical Characteristics of the Prepared Lamivudine Floating Tablets

Formulation	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)	Floating Lag Time (Sec)	Floating Duration (h)
F1	903±3.56	5±0.56	0.39±0.09	100.5±0.5	10±5	10
F2	903.5±4.32	5±0.34	0.415±0.12	98.4±1.26	15±7	20
F3	903.5±3.65	6±0.45	0.426±0.21	99.7±0.98	20±3	>24
F4	898±4.13	5±0.54	0.524±0.23	99.8±0.74	20±4	22
F5	904.5±2.75	5±0.65	0.541±0.13	100.9±1.23	23±7	>24
F6	903±3.47	6±0.43	0.39±0.34	99.9±1.45	25±2	>24
F7	903.5±4.23	6±0.59	0.344±0.32	99.9±0.89	30±3	>24
F8	904±3.34	5±0.63	0.314±0.16	100.1±0.76	35±4	>24
F9	898±4.56	5±0.55	0.325±0.18	100.5±0.76	40±6	>24

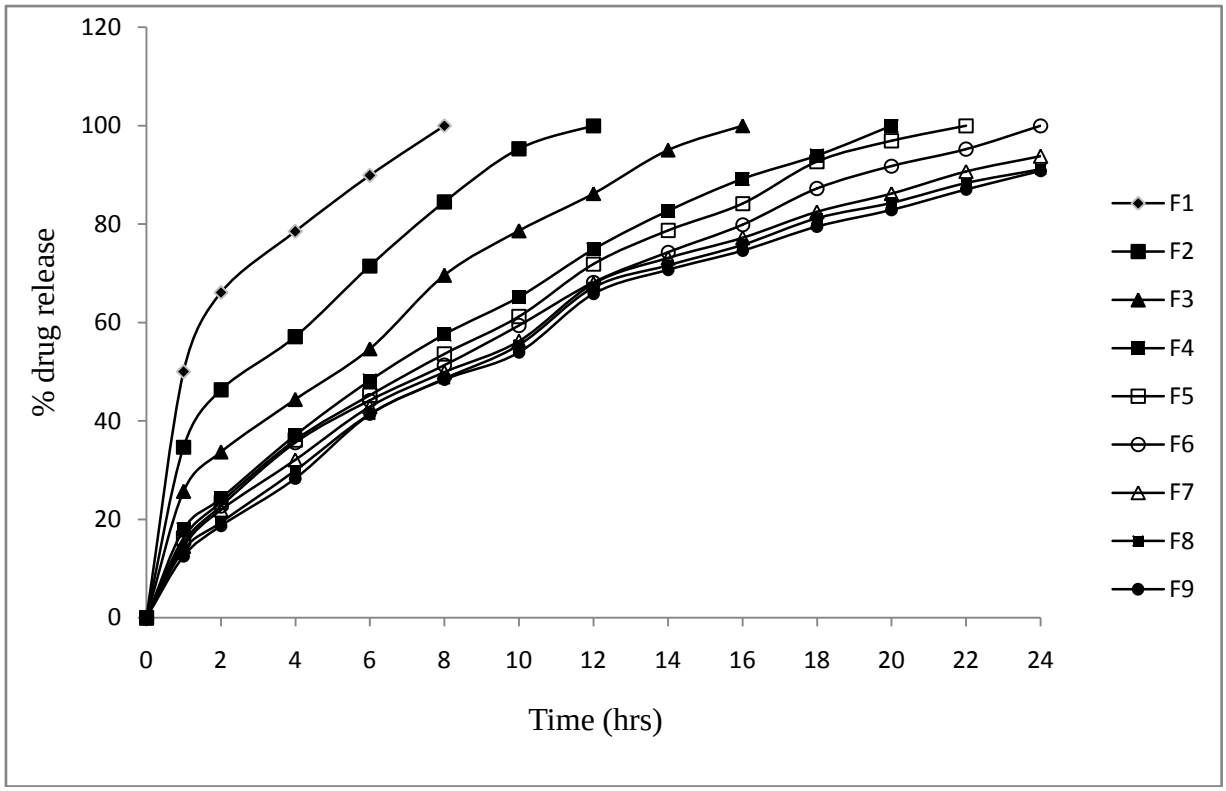

Fig. 4: Drug release Profiles of Lamivudine Controlled Release Floating Tablets Prepared Employing HPMC K4M, HPMC K15M, and HPMC K100M

Table 3: Release Characteristics of Lamivudine Controlled Release Floating Tablets Prepared Employing HPMC K4M, HPMC K15M and HPMC K100M

Formulation	$t_{50\%}$ (h)	$t_{90\%}$ (h)	K_1 (min^{-1})
F1	1	6	0.503
F2	2.2	8.5	0.267
F3	6	13	0.237
F4	6	16	0.180
F5	8	18	0.175
F6	8	24	0.150
F7	8	22	0.106
F8	8	24	0.096
F9	8	24	0.093

Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fickian 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 values of the diffusion exponent (n) with the corresponding correlation coefficients for all the formulations were shown in Table 3. The 'n' values of various formulations were found to be between 0.45 and 0.89, indicating anomalous transport. The relative complexity of the prepared formulations may indicate that the drug release is controlled by more than one process; a coupling of diffusion and erosion [9].

Table 4: Mathematical Modelling and Release Kinetics of Lamivudine Controlled Release Floating Tablets

Formulation	Zero order correlation coefficient R^2	First order correlation coefficient R^2	Higuchi's plot correlation coefficient R^2	Korsmeyer-Peppas plots Correlation coefficient R^2	Diffusional exponent n	Order of release
F1	0.880	0.915	0.962	0.993	0.463	Non-Fickian
F2	0.903	0.934	0.994	0.990	0.475	Non-Fickian
F3	0.855	0.948	0.994	0.988	0.508	Non-Fickian
F4	0.875	0.96	0.993	0.997	0.593	Non-Fickian
F5	0.875	0.965	0.991	0.998	0.604	Non-Fickian
F6	0.886	0.932	0.995	0.999	0.598	Non-Fickian
F7	0.977	0.950	0.993	0.997	0.599	Non-Fickian
F8	0.991	0.948	0.991	0.995	0.621	Non-Fickian
F9	0.984	0.950	0.990	0.995	0.643	Non-Fickian

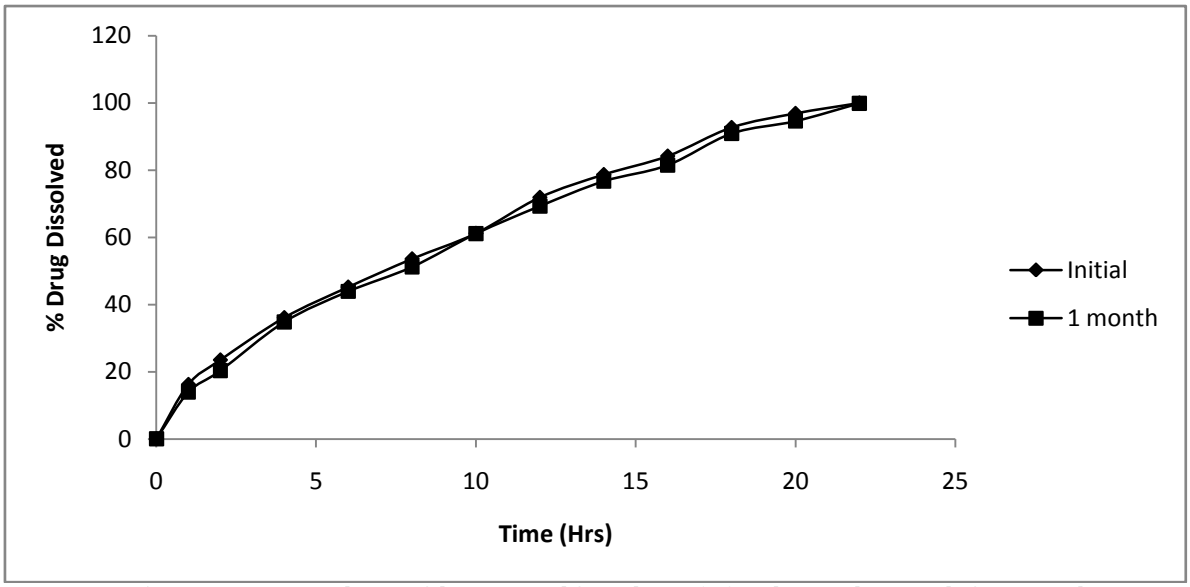

Fig. 5: Comparative Dissolution of the optimized formulation (F6) at the initial time and after 1 month

Stability Studies

The controlled stability sample showed no significant change in physicochemical properties and a comparable drug release profile with the initial release when exposed to 40° ± 2° C and 75% ± 5% RH in a humidity chamber for 1 month.

CONCLUSION

The controlled release floating tablets of Lamivudine were formulated using 3 different polymers, HPMC K4M, HPMC K15M and HPMC K100M, in three concentrations. A slow and spread over release of the formulations was shown except for formulations F1 to F5. Among the all formulations, the tablets formulated using 300 mg of HPMC K15M (F6) showed better results with 100% drug release at 24 hours. From the above results, F6 was thus found suitable for once a day administration of lamivudine, which can reduce dosing frequency.

REFERENCES

1. Amrita Bajaj, Mansi Desai Challenges and strategies in novel drug delivery technologies. Pharma Times 2006; 38:12-16.
2. Raffanti SP, Haas DW Goodman & Gilman's The Pharmacological Basis of Therapeutics. In: Hardman JG, Limbird LE, editors. Antimicrobial Agents: Antiretroviral Agents. 10th ed. New York: Mc Graw Hill Medical Publishing Division; 2001. p.1349–80.
3. Rosa M, Zia H, Rhodes T Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994; 105:65–70.
4. Higuchi T Mechanism of sustained action medication. J Pharm Sci 1963; 52: 1145–49.
5. Korsmeyer RW, Gurny R, Docler E, Buri P, Peppas NA Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15: 25–35.
6. Mina Ibrahim Tadros Controlled release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro-in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm 2010; 74: 332-39.
7. Madsen F, Eberth K, Smart JD A rheological examination of the mucoadhesive/mucus interaction: the effect of mucoadhesive type and concentration. J Control Release 1998; 50 (1-3): 167–78.
8. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavia PR Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int J Pharm 2006; 316: 86–92.
9. Srinivasa Rao M, Madhuri KSN, Vijaya Kumar G Formulation and evaluation of controlled release floating tablets of lamivudine employing HPMC K4M and sodium alginate. Int J Pharm Sci & Res 2013; 4(1): 396-400.