



FORMULATION AND EVALUATION OF LAMIVUDINE FLOATING TABLETS

Nalini Kondireddy and K. Ravi Shankar*

KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada

*Corresponding author E-mail: kunderuravi@gmail.com

ARTICLE INFO

ABSTRACT

Key Words

Lamivudine
HPMC K100 M
PEG 4000



The objective of the present study is to formulate and evaluate floating tablets of lamivudine. Floating tablets each containing 100 mg of lamivudine were prepared using HPMC K100 M as rate controlling matrix polymer, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers and PEG 4000 as release enhancer. The tablets were prepared by wet granulation method and were evaluated for hardness, friability, drug content, size, floating time, floating lag time, drug release characteristics. All the lamivudine floating tablets prepared are of good quality with respect to hardness, friability and drug content. Lamivudine release from all the FTs prepared was slow and spread over longer periods of time. Drug release from all the FTs was diffusion controlled and followed first order kinetics. Non-Fickian diffusion was the release mechanism from all FTs except F2 and F4, from which drug release was rapid. Addition of bees wax and ethyl cellulose reduced floating lag time and drug release respectively. Formulation F7 which was prepared employing HPMC K100M as rate controlling matrix former, sodium bicarbonate as gas generating agent and PEG 4000 as release modifier is recommended as best floating tablet for lamivudine.

INTRODUCTION

Oral drug delivery is the most preferred route for administering therapeutic agents due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms¹. In spite of several advantages the oral route of administration suffers from several limitations like short residence time of the dosage form in the GI tract, unpredictable gastric emptying and degradation of the drug in GI contents. Gastric emptying is a complex process and makes the performance of the formulation uncertain. This variability can be overcome by formulating as floating drug delivery systems^{2, 3}. Bulk densities of floating drug delivery systems (FDDS) is

less than that of gastric fluids and hence remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The drug is released slowly at the desired rate from this system while the formulation is floating on the gastric contents. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric residence time and a better control of the fluctuation in plasma drug concentration^{4, 5}. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.

Several approaches are currently used to retain the dosage in the stomach. These include bio adhesive systems⁶, swelling and expanding systems^{7,8}, floating systems^{9,10} and other delayed gastric emptying devices^{11,12}. The principle of floating tablets offers a simple and practical approach to achieve enhanced residence time in the stomach and upper g.i. tract to increase the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets requires a strong matrix forming polymer, a gas generating agent and a floating enhancer such as beeswax. Several polymers such as various viscosity grades of HPMC, Carbopol 934P, Eudragit RL, calcium alginate, Chitosan, Xanthan gum, guar gum, ethyl cellulose etc., have been used in the design of floating tablets of various API. Sodium bicarbonate is the preferred gas generating agent in the formulation of floating tablets. Lamivudine, a BCS Class I synthetic nucleoside analogue, has a short biological half-life of 5–7 h and is absorbed primarily from the upper part of intestinal tract¹³. Because of its shorter biological half life and its absorption site at upper part of intestinal tract, lamivudine was selected for formulation of floating tablets. The objective of the present study is to formulate and prepare floating tablets of lamivudine and to evaluate the formulated tablets for their physical parameters, floating and drug release characters.

MATERIALS AND METHODS

Materials: Lamivudine is a gift sample from M/s Aurobindo Pvt Limited, Hyderabad. HPMC K100M, Sodium Bicarbonate, Beeswax, Ethyl Cellulose, PEG 4000, Dibasic Calcium Phosphate (DCP) and were procured from commercial sources. All other materials were of pharmacopoeia grade.

Estimation of Lamivudine:

An UV Spectrophotometric method was used for the estimation of Lamivudine at 270 nm in 0.1N HCl... The method was

checked for linearity, accuracy, precision and interference. The method obeyed Beer's law in 1-10 µg/ml concentration range. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95% and 1.02% respectively. No interference by the excipients used in the study was observed.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

The compatibility of lamivudine with various excipients used in the in the formulation of floating tablets was evaluated by FTIR studies. FTIR Spectra of lamivudine and floating tablet formulations were recorded on a FTIR spectrophotometer (Make: Bruker Optics, Model: Alpha) using KBr disk.

Preparation of Lamivudine Floating Tablets: Tablets containing 100 mg of lamivudine were prepared by employing wet granulation technique as per the formulae given in Table 1. Required quantities of the drug and polymer were taken in a mortar and to this; dibasic calcium phosphate and sodium bicarbonate were added and mixed thoroughly. In case formulations containing bees wax, bees wax was melted, to it required quantities of the drug, polymer, dibasic calcium phosphate and sodium bicarbonate were added and mixed thoroughly. A dough mass was prepared in both the cases by adding required quantity of (1:1) hydroalcoholic solution. Wet granules were prepared by passing the dough mass through sieve # 12 and were dried in hot air oven at 50°C for nearly an hour. The dried granules obtained were passed through sieve # 16. Talc and Magnesium stearate (sieve # 100) were added to the above dried granules and blended in a well closed polyethylene bag. The tablet granules were then compressed into tablets of 300mg using 8 station tablets punching machine (M/s Cadmach Engineering Pvt. Ltd., Ahmadabad) to a hardness of 5-6 kg/cm² using 9 mm flat punches.

Evaluation of the prepared tablets: The tablets were tested for drug content, hardness, friability, floating lag time, floating time and drug release characters.

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. Required amount of 0.1 N HCl was added, mixed and filtered, the filtrate was suitably diluted with 0.1N HCl and analyzed for lamivudine content against blank by UV spectrophotometer at 270 nm for Lamivudine.

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

Tablet friability: Ten tablets were randomly selected and friability was checked using Roche friabilator.

Tablet floating behaviour: The floating behaviour of the tablets was visually determined (n=3), according to the floating lag time method⁵. A tablet was placed in a glass beaker, containing 200ml of 0.1 N HCl, maintained in a water bath at $37 \pm 0.5^\circ\text{C}$. The floating lag time and total floating duration were recorded.

Drug Release Study: The drug release from the prepared controlled release floating tablets of lamivudine formulations were tested in 900ml of 0.1 N HCl at $37 \pm 0.5^\circ\text{C}$ using USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) using paddle at a rotation speed of 50rpm. 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 analyzed for lamivudine content spectrophotometrically at 270 nm. All the dissolution experiments conducted was in triplicate (n=3).

Kinetic modelling of drug release profiles: The dissolution profiles of all formulations in 0.1 N HCl were plotted by zero-order, first-order, Higuchi¹⁴ and Korsmeyer–Peppas¹⁵ kinetic models. The model with the highest correlation

coefficient was considered to be the best fitted one.

RESULTS AND DISCUSSION

The objective of the study is formulate and evaluate floating drug delivery system of lamivudine in the form of tablets and microspheres. Floating tablets each containing 100 mg of lamivudine were formulated employing HPMCK100M as rate controlling matrix forming polymer, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers and PEG 4000 as release enancer. The floating tablets were prepared by wet granulation method. An FTIR study was carried out to check the compatibility of lamivudine with various excipients used in the in the formulation of floating tablets. All the tablets prepared were tested for hardness, friability, drug content, floating lag time, floating time and drug release characters.

FTIR STUDY:

FTIR spectra of pure Lamivudine and Lamivudine floating tablets are shown in Fig 1. The characteristic peak of the drug carbonyl group (C=O stretching) present in the cytidine nucleus at 1650.07cm^{-1} , a band peak at 1494.78cm^{-1} owing C=C stretching (aromatic) confirms the presence of Lamivudine. Characteristic bands peak at 3217.9cm^{-1} owing to presence of hydroxy group (O-H stretching)/ primary amine (NH₂ stretching). Peaks present at 1287.70cm^{-1} and 1160.84cm^{-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. The IR spectra of lamivudine floating tablets also showed all the above mentioned characteristic peaks of lamivudine.

Table 1: Formulae of Lamivudine Floating Tablets

Ingredient (mg/tab)	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈
Lamivudine	100	100	100	100	100	100	100	100
Sodium bicarbonate	20	17.5	40	35	40	40	40	40
Bees wax	-	-	-	-	-	20	-	-
Ethyl cellulose	-	-	-	-	20	-	-	-
PEG 4000	-	-	-	-	-	-	10	4
HPMC K100 M	100	75	100	75	100	100	100	100
Dicalcium phosphate	72	99.5	52	82	32	32	42	48
Talc	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Magnesium stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total weight (mg)	300	300	300	300	300	300	300	300

Table 2: Physical Parameters of Lamivudine Floating Tablets

Formulation	Hardness (Kg/cm ²)	Friability (% wt. loss)	Drug Content (mg/tablet)	Floating lag time (min- sec)	Floating Time (h)
F ₁	4.5±0.012	0.48±0.02	99.98±1.88	18-15	>12
F ₂	4.0±0.014	0.79±0.01	100.56±1.96	15-47	>12
F ₃	4.5±0.012	0.68±0.02	99.98±1.88	1-15	>12
F ₄	4.0±0.014	0.59±0.01	100.56±1.96	1-47	>12
F ₅	4.5±0.017	0.78±0.02	101.25±1.75	1-20	>12
F ₆	4.0±0.014	0.85±0.01	99.87±1.65	0-60	>12
F ₇	4.0±0.013	0.60±0.01	98.97±1.58	1-19	>12
F ₈	4.0±0.015	0.75± 0.02	99.50±1.45	1-45	>12

Table 3: Coefficient of determination (R²) Values in the Analysis of Release Data of Lamivudine Floating Tablets Prepared as per Different Kinetic Models

Formulation	Release Rate		Release Exponent (n)
	K ₀ (mg/h)	K ₁ (h ⁻¹)	
F ₁	6.45	0.154	0.558
F ₂	9.29	0.342	0.440
F ₃	6.70	0.176	0.527
F ₄	9.56	0.380	0.348
F ₅	6.66	0.151	0.651
F ₆	5.33	0.094	0.590
F ₇	7.58	0.296	0.604
F ₈	7.10	0.227	0.505

Table 4: Release Parameters of Lamivudine Floating Tablets

Formulation	Zero order	First order	Higuchi	Korsemeyer –Peppas
F1	0.913	0.991	0.993	0.985
F2	0.873	0.932	0.988	0.986
F ₃	0.889	0.968	0.987	0.986
F ₄	0.830	0.935	0.972	0.982
F ₅	0.917	0.987	0.984	0.978
F ₆	0.926	0.982	0.990	0.972
F ₇	0.900	0.931	0.986	0.966
F ₈	0.931	0.971	0.992	0.970

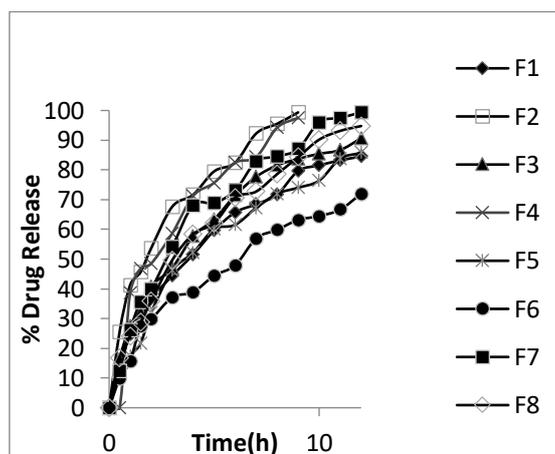


Fig: 2- Drug Release Profiles of Floating Tablets of Lamivudine Prepared

These IR spectral observations indicated no chemical interaction between the lamivudine and the excipients used in the formulation of floating tablets. The hardness (4.0 -6.0 kg/sqcm), friability (0.59--0.85 percent) and lamivudine content (100 ±2 percent of labelled content) of the tablets prepared were satisfactory and within acceptable limits. All the FTs exhibited floating over more than 12h. The floating lag time was in the range 60 seconds to 2 min with all the tablets formulated using sodium bicarbonate at 20 percent strength. Formulations F1 and F2 which are formulated using sodium bicarbonate at 10 percent strength exhibited a delay in floating lag time than other formulations which are formulated using sodium bicarbonate at 20 percent strength. As the concentration of sodium bicarbonate was increased the floating lag time was found

to be decreased. Addition of bees wax and ethyl cellulose greatly reduced the floating lag time. Lamivudine release from the FTs prepared was studied in 0.1N HCl of pH 1.2 Lamivudine release from all the FTs was slow and extended over varying periods of time depending on the composition of the tablets. Drug release data were analysed as per various kinetic models namely zero order, first order, Higuchi and Korsemeyer-Peppas equation models. Drug release data of all formulations more obeyed Higuchi and Korsemeyer-Peppas equation models. R² values were higher in these Models indicating diffusion as the release mechanism from all the FTs prepared. Drug release was relatively rapid from F2 and F4 formulations which contain HPMC at a strength of 4:3 ratio of drug : polymer. Other formulations containing 1:1 ratio of drug : polymer gave slow release

of drug for more than 12h. The release exponent (n) was 0.348 and 0.440 in the case of F2 and F4 indicating Fickian diffusion as the drug release mechanism from F2. With all other formulations the n value is in the range 0.527---0.651 indicating Non-Fickian diffusion as the drug release mechanism. Comparison of R² values in zero and first order models indicated that the R² values were higher in first or I model. This result suggests that drug release is not according to zero order kinetics and mixed or anomalous type may be operating in drug release. Formulations F5 and F6 also were formulated using 10 percent bees wax and ethyl cellulose as floating enhancers respectively. The release rate (K0) was 6.66 and 5.33. A decrease in release rate was observed with addition of beeswax and ethylcellulose (hydrophobic excipients) where as an increase in the release rate was observed with addition of PEG 4000 (hydrophilic excipient). Formulation F7 which gave slow and complete release of lamivudine in 12 h with a floating lag time of 79 seconds and floating time of more than 12h is considered as the best floating tablet formulation for Lamivudine.

CONCLUSIONS

The objective of the study is prepare and evaluate floating tablets of lamivudine. Floating tablets each containing 100 mg of lamivudine were prepared using HPMC K100 M as rate controlling matrix polymer, sodium bicarbonate as gas generating agent ,bees wax and ethyl cellulose as floating enhancers and PEG 4000 as release enhancer were prepared by wet granulation method and were evaluated. All floating tablets prepared were evaluated for hardness, friability, drug content, size, , floating time, floating lag time, drug release characteristics. From the results obtained the following. Conclusions are drawn:

1. All the lamivudine floating tablets prepared are of good quality with

regard to hardness, friability and drug content.

2. Lamivudine release from all the FTs prepared was slow and spread over longer periods of time.
3. Drug release from all the FTs was diffusion controlled and followed first order kinetics.
4. Non-Fickian diffusion was the release mechanism from all FTs except F2, from which drug release was rapid
5. Addition of bees wax and ethyl cellulose reduced drug release and drug release was slow and extended up to 12 h.
6. Formulation F7 which was prepared employing HPMC K100M as rate controlling matrix former, sodium bicarbonate as gas generating agent and PEG 4000 as release modifier is recommended as best floating tablet formulation for lamivudine.

Acknowledgements

The authors are very much thankful to Management of SAGTE and Dr G Devala Rao, Principal, KVSR Siddhartha College of Pharmaceutical Sciences for their constant support and encouragement.

REFERENCES:

1. Ansel HC, Allen LV, Popovich NG. Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia, Lippincott Williams and Wilkins Chapter -3, 2003:23-31.
2. Agyilirah, and Ducret, Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet, Int.J.Pharm., 75,241,1991.
3. Hoffman, A.F, Pressman, J.H. and Code, C.F., Controlled entry of orally- administered drugs;

- physiological considerations. Drug Dev. Ind. Pharm., 9, 1077, 1983.
4. Mayavanshi AV, Gajar SS. Floating drug delivery system to increase gastric retention of drug: A Review. J. Pharm. Res., Oct-dec .2008: 1940:345-348.
 5. Vachhanisavan R, Patel Dipen, Prajapati ST, Patel CN. Formulation and in-vitro evaluation of floating capsules of Loratadine; J Chem. Pharma Res., 2010; 2 (2):57-64.
 6. Santus, G., Lazzarini, G. and Bottoni.G.,Eur. J. Pharm. Bioparm., 44, 39, 1997.
 7. Deshpande, A.A, Rhodes, C.T., Shah, N.H. and Malick, A.W.,Controlled-Release Drug Delivery Systems for Prolonged Gastric Residence: An Overview, Drug Dev. Ind. Pharma., 22, 531, 1996.
 8. Deshpande, A.A., Shah, N.H. Rhodes, C.T. and Malick, W., Development of a novel controlled-release system for gastric retention. Pharma. Res., 14, 815, 1997.
 9. Menon, A., Ritshel, W.A. and Sakr,A., Development and evaluation of a monolithic floating dosage form for furosemide. , J. Pharm. Sci. 83, 239, 1994.
 10. Whitehead, L., Fell, J.T., Collett, J.H., Sharma, H.L., and Smith, A. M., Floating dosage forms: an in vivo study demonstrating prolonged gastric retention, J. Control Release, 55, 3, 1998.
 11. Singh, B. and Kim, K., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Control Release, 63, 235, 2000.
 12. Chawla, G. and Bansal, A., Pharm.Tech. 27, 50, 2003.
 13. Suresh and Veerreddy K., Formulation and *In-Vitro* Evaluation Of Controlled Release Floating Tablets of Lamivudine, IJPSR, 2014; 5(3): 900-906.
 14. Higuichi T. Mechanism of Sustained- Action Medication Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices, J .Pharm. Sci., 52: 1145. 1963
 15. Korsmeyer RW, Gurny R, Doelkar E, Buri P, Peppas NA. Mechanisms of Solute Release from Porous Hydrophilic Polymers, Int. J .Pharm. 15: 25. 1983