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FORMULATION AND EVALUATION OF CONTROLLED RELEASE FLOATING TABLETS OF LAMIVUDINE EMPLOYING HPMC K4M AND SODIUM ALGINATE

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ABSTRACT

Lamivudine, a BCS Class I synthetic nucleoside analogue, has a a short biological half-life of 5–7 and is mainly absorbed in the upper gastrointestinal tract. The purpose of the study is to develop a controlled release floating tablets of lamivudine employing HPMC K4M and sodium alginate. The floating tablets of lamivudine were prepared employing HPMC K4M and sodium alginate as matrix formers and sodium bicarbonate as an effervescent agent. The tablets formulated were evaluated for tablet weight variation, drug content uniformity, hardness, friability, floating behaviour and in-vitro drug release. All the formulations fulfilled the official requirements for tablet weight variation, drug content uniformity, hardness and friability. Tablets formulated by using a combination of HPMC K4M/sodium alginate and HPMC K4M alone gave a lesser floating lag time when compared with tablet formulated with sodium alginate alone. All the tablets were found to remain buoyant in 0.1N HCl for a period >24h. The drug release from the prepared tablets was found to be diffusion controlled and followed first order kinetics. Non-Fickian diffusion was the drug release mechanism from all tablets formulated. Lamivudine release form the formulations containing 44.5% (F6) and 40% (F7) of HPMC K4M respectively were found to be slow and spread over 24h. Hence HPMC K4M was found to be more suitable as a matrix former than sodium alginate alone in formulation of controlled release floating tablets of lamivudine.

INTRODUCTION: The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [1].

Floating drug delivery systems are gaining importance in the recent days as they can overcome the limitations of the conventional controlled release dosage forms by sustaining the dosage form in the gastric region for the desired period of time and also releasing the drug in a controlled fashion.

Lamivudine, a BCS Class I synthetic nucleoside analogue, is commonly employed as a part of highly active antiretroviral therapy (HAART). Prescribed in a dose of 100–150 mg twice a day, the drug is well absorbed in the upper gastrointestinal tract with a short biological half-life of 5–7 h [2].

Decreasing the frequency of medication to a once-a-day regimen tends to decrease systemic side effects and improve patient convenience and compliance to HAART in HIV infected patients [3].

The objective of the present study was to formulate controlled release floating tablets of Lamivudine for once a day administration using the release retardant polymers – HPMC K4M and sodium alginate and evaluate the in-vitro performance of the prepared tablets.

MATERIALS AND METHODS

Materials: Lamivudine is a gift sample from M/s Hetero Drugs Limited, Hyderabad. HPMC K4M, Sodium Alginate, Sodium Bicarbonate, Dibasic Calcium Phosphate (DCP) and Aerosil were procured from commercial sources. All other materials were of pharmacopoeial grade.

Methods:

Preparation of Lamivudine Floating Tablets: Tablets containing 200 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 half the quantity of sodium bicarbonate were added and mixed thoroughly. A dough mass was prepared by adding required quantity of Isopropyl Alcohol. Wet granules were prepared by passing the dough mass through sieve # 12 and were dried in hot air oven at 60^{o}C for nearly an hour.

The dried granules obtained were passed through sieve # 16. Aerosil (sieve # 100) and the remaining half the quantity of sodium bicarbonate were added to the above dried granules and blended in a well closed polyethylene bag. The tablet granules were then compressed into tablets of 550mg using 16 station tablet punching machine (M/s Cadmach Engineering Pvt. Ltd., Ahmadabad) to a hardness of 5-6 kg/cm^2 using 12 mm flat punches.

TABLE: 1 FORMULATIONS OF CONTROLLED RELEASE FLOATING TABLETS OF LAMIVUDINE BY WET GRANULATION TECHNIQUE

Ingredients (mg/tablet)	Purpose	Tablet Formulations						
		F1	F2	F3	F4	F5	F6	F7
Intra Granular								
Lamivudine	API	200	200	200	200	200	200	200
Sodium Alginate	Controlled Release polymer	200	150	100	50	-	-	-
HPMC K4M	Controlled Release polymer	-	50	100	150	200	244.5	220
$NaHCO_3$	Effervescent Agent	50	50	50	50	50	50	50
DCP	Diluent	44.5	44.5	44.5	44.5	44.5	-	24.5
Extra Granular								
$NaHCO_3$	Effervescent Agent	50	50	50	50	50	50	50
Aerosil	Lubricant	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Total weight of Tablet		**550**	**550**	**550**	**550**	**550**	**550**	**550**

***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:** 5 tablets were individually weighed and powdered. A quantity of powder equivalent to 1 tablet was extracted in 25ml of methanol and suitable dilutions were made with 0.1 N HCl. The drug content was determined by UV Spectrophotometer at 280 nm.

3. **Tablet Hardness:** Hardness of 5 randomly selected tablets was determined using Monsanto hardness tester.

4. **Tablet Friability:** 5 tablets were randomly selected and friability was checked using Roche friabilator.

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 [4]. A tablet was placed in a glass beaker, containing 200ml of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 $^{\circ}$ C. The floating lag time and total floating duration were recorded.

6. **Drug Release Studies:** The drug release from the controlled release floating tablets of lamivudine formulations were tested in 900ml of 0.1 N HCl at 37±0.5^{o}C using USP 8 station Dissolution Rate Test

Apparatus (M/s Labindia Disso 8000) at paddle rotation speed of 50rpm. Samples (5ml) of dissolution medium were withdrawn at different time intervals and replaced with a fresh medium of 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 fitted to zero-order, first-order, Higuchi [5] and Korsmeyer–Peppas kinetic models [6]. The model with the highest correlation coefficient was considered to be the best fitting one.

RESULTS AND DISSCUSSION:

Physical characteristics of Tablets: Controlled release floating tablets of lamivudine were formulated using release retardant polymers like HPMC K4M and/or sodium alginate and effervescent agent like sodium bicarbonate.

DCP was incorporated in the tablets to improve the compression properties and to further retard the release rate by its hydrophobic properties.

The physicochemical properties of the tablets were summarised 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 549.5-552 mg. The percentage of drug content was found to be in the range of 98.20 – 101.21. 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 and sodium alginate. The in vitro testing revealed that all the formulations remained buoyant for more than 24 hrs. The gel layer formed by the polymers enabled efficient entrapment of generated gas bubbles and made the tablet float on the test medium (0.1 N HCl) for extended period of time [7].

As shown in **Table 2**, the HPMC K4M/Sodium Alginate ratio has marked effect on the floating lag time of prepared formulations from F1 – F4 with a constant sodium bicarbonate ratio, 20 % w/w. The lag time of formulation F1, containing sodium alginate alone, was 182sec, which was higher than that of formulations containing increasing concentrations of HPMC K4M, this might be due to the higher specific gravity of sodium alginate than that of HPMC K4M. In the case of formulations F4 to F7, the floating lag time decreased with increase in the HPMC K4M concentration. This might be attributed to the faster gel formation with the increase in HPMC K4M concentration.

TABLE 2: PHYSICAL 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	550 ± 2.54	5.9 ± 0.45	0.53 ± 0.10	99.55 ± 1.5	182 ± 5.27	> 24
F2	549.5 ±1.5	5.6 ± 0.98	0.42 ± 0.12	98.20 ±1.29	148 ± 4.23	> 24
F3	550 ± 2.33	5.8 ± 0.72	0.34 ± 0.13	101.19±1.42	127 ± 5.35	> 24
F4	552 ± 1.14	5.6 ± 0.99	0.29 ± 0.14	101.21±0.98	93 ± 4.58	> 24
F5	551 ± 1.89	5.3 ± 0.78	0.31 ± 0.07	98.99 ± 0.92	75 ± 3.38	> 24
F6	550 ± 2.78	5.1 ± 0.35	0.22 ± 0.06	99.23 ± 1.15	40 ± 5.98	> 24
F7	550 ± 1.54	5.5 ± 0.54	0.19 ± 0.04	100.5 ± 0.92	45 ± 4.56	> 24

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. 1**. Dissolution parameters are given in **Table 3**.

The drug release studies showed the formulations from F1 to F5 could not sustain the release of drug for 24h. This might be attributed to the inefficiency of the polymer concentration in controlling the drug release upto 24h. A slow and spread over release of drug for 24 hrs was found with formulations F6 and F7.

Formulations F6 and F7 were formulated by employing HPMC K4M at concentrations of 44.5 % w/w and 40 % w/w respectively. A 100% drug release was achieved in formulation F7 when compared with formulation F6 which has a release of only 89 % in 24h. The higher viscosity of HPMC K4M would promote the formation of highly viscous gel layer upon contact with the aqueous fluids and promotes the retardation of drug release from the formulated tablets.

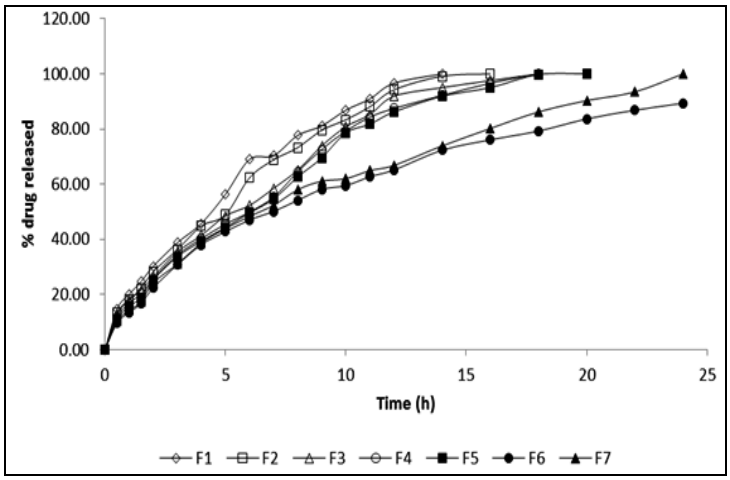

FIG. 1: DISSOLUTION PROFILES OF LAMIVUDINE CONTROLLED RELEASE FLOATING TABLETS PREPARED EMPLOYING HPMC K4M AND SODIUM ALGINATE

TABLE 3: RELEASE CHARACTERISTICS OF LAMIVUDINE CONTROLLED RELEASE FLOATING TABLETS PREPARED EMPLOYING HPMC K4M AND SODIUM ALGINATE

Formulation	$t_{50\%}$ (h)	$t_{90\%}$ (h)	K_1 (min^{-1})
F1	4.3	10.9	0.232
F2	5.2	11.3	0.202
F3	5.7	11.6	0.175
F4	6.1	12.5	0.159
F5	6.3	12.7	0.150
F6	7	>24	0.107
F7	6.7	18.9	0.118

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 K15M and/or sodium alginate, other processes take place, like relaxation of polymer chains, imbibition of water causing polymers swelling and considerable volume expansion [8,9] . When the release data were analysed as per zero and first order models the correlation coefficient (R^2) values were relatively higher in 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 was also obeyed Higuchi and Peppas models with R^2 values greater than 0.96. When percentage drug released was plotted against √time, linear regressions with 'R^2' > 0.966 were observed with all floating tablets prepared indicating that the drug release from all these formulations was diffusion controlled.

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 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.

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	0.874	0.92	0.9772	0.993	0.619	Non-Fickian
F2	0.914	0.9416	0.9724	0.9922	0.636	Non-Fickian
F3	0.864	0.9155	0.9704	0.9932	0.622	Non-Fickian
F4	0.893	0.9316	0.9667	0.9937	0.64	Non-Fickian
F5	0.912	0.9452	0.9682	0.9928	0.648	Non-Fickian
F6	0.923	0.9743	0.9918	0.9928	0.594	Non-Fickian
F7	0.918	0.9917	0.9914	0.9925	0.6	Non-Fickian

CONCLUSION: Controlled release floating tablets of lamivudine formulated by using HPMC K4 M at a concentration of 40% w/w and sodium bicarbonate at 20% exhibited a floating lag time of less than 50sec, with a floating duration greater than 24h. A slow and spread over release of lamivudine for 24h was also observed with these tablets. HPMC K4M is found to be more suitable as a matrix forming agent when compared with sodium alginate in formulation of a tablet for once a day administration of lamivudine.

REFERENCES:

1. S.T. Prajapati, L.D. Patel, D.M. Patel: Gastric floating matrix tablets: design and optimization using combination of polymers. Acta Pharm. 2008; 58:221–229.
2. Raffanti SP, Haas DW. Antimicrobial Agents: Antiretroviral Agents, in Goodman & Gilman's The Pharmacological Basis of Therapeutics. Mc Graw Hill Medical Publishing Division, 10th edn. Hardman JG, Limbird LE, eds. New York: 2001: 1349–1380.
3. Willig JH et al.: Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. AIDS 2008; 22: 1951–1960.
4. M. Rosa, H. Zia, T. Rhodes: Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm. 1994; 105: 65–70.
5. T. Higuchi: Mechanism of sustained action medication. J. Pharm. Sci. 1963; 52: 1145–1149.
6. R.W. Korsmeyer, R. Gurny, E. Docler, P. Buri, N.A. Peppas: Mechanism of solute release from porous hydrophilic polymers'.Int. J. Pharm. 1983; 15: 25–35.
7. 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: 332-339.
8. F. Madsen, K. Eberth, J.D. Smart: A rheological examination of the mucoadhesive/mucus interaction: The effect of mucoadhesive type and concentration. J. Control. Release 1998; 50 (1-3): 167–178.
9. M.D. Chavanpatil, P. Jain, S. Chaudhari, R. Shear and P.R. Vavia: Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int. J. Pharm. 2006; 316: 86–92.

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