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INFLUENCE OF HYDROPHILIC AND HYDROPHOBIC POLYMERS ON LAMIVUDINE RELEASE FROM MATRIX TABLETS

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ABSTRACT

The present work reports the study of different Lamivudine (LAM): excipient formulations, in order to determine the effect of the polymer substitution and type of diluents on the drug-release mechanism. Seven formulations were prepared using either HPMC K15M alone or in combination with Ethyl Cellulose (EC). Release kinetics was evaluated by using United States Pharmacopeia (USP)-22 type I dissolution apparatus. The tablets were tested for their drug content, weight variation, hardness, thickness, tensile strength, friability, swelling and release ratio. Polymers HPMC K15M was found not to be appropriate for the preparation of modified release LAM hydrophilic matrix tablets, while combination of HPMC K15M and EC showed to be advantageous. The analysis of the release profiles in the light of distinct kinetic models (zero-order, first-order, Higuchi and Korsmeyer–Peppas) led to the conclusion that the concentration of polymer did not influence the release mechanism of the drug. The mean dissolution time (MDT) and t_{50}% was determined, the highest MDT and t_{50}% value being obtained for HPMC and EC formulations. Moreover, the drug-release process was not found to be influenced by the type of diluents, either MCC or DCP.

Key words: Lamivudine, HPMC, Ethyl Cellulose

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INTRODUCTION

AIDS is considered to be an epidemic, and according to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) AIDS Epidemic Update 2005, 38 million adults and 2.3 million children were living with the human immunodeficiency virus (HIV) at the end of 2005. The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient-compliant antiretroviral medications are available at affordable prices.[1] The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost.[2, 3] Lamivudine (LAM) is a potent antiviral agent used in the treatment of AIDS. Conventional oral formulations of LAM are administered multiple times a day (150 mg twice daily) because of its moderate half-life (t1/2 = 5-7 hours).[4,5] Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. [6] Hence Lamivudine is an appropriate model drug for formulation of controlled release dosage forms to overcome some of these problems.

However, developing oral controlled release tablets for water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of the drug on oral administration. In recent years, the use of hydrophilic polymers, in particular cellulose derivatives, has attracted considerable attention for the development of controlled release technology in the formulation of pharmaceutical products, due to their ability to form gels in aqueous medium. Previous studies developed by Williams led to the conclusion that the type and level of excipient influenced the rate and extension of drug release[7]. Recently[8] investigated the effect of polymer blends on release profiles of sodium diclofenac from matrices and the results showed that the drug release depends on the kind of polymer, its proportion in the formulation and its viscosity grade. Hydroxypropylmethylcellulose is used to control drug release from several pharmaceutical systems because of its non-toxic nature, easy compression, swelling properties and accommodation to high levels of drug. This cellulose derivative excipient has been widely investigated in our laboratory [9, 10, 11]. Despite the high number of papers on this subject, few of them discuss the drug-release processes from methylcellulose[12, 13] and hydroxypropylcellulose [14].

The main objective of the present study is to evaluate the effect of polymers on the kinetics of the drug release, using distinct formulations, in order to understand how they rule this process. This will hopefully allow the design of more suitable cellulose matrices. The influence of the diluents is also examined. The cellulose ether polymers Hydroxypropylmethylcellulose (HPMC) alone or mixed with ethyl cellulose (EC), the Microcrystalline Cellulose (MCC) and Dicalcium phosphate (DCP), and the lubricants talc and magnesium stearate were studied.

MATERIALS AND METHODS

Lamivudine (LAM) was obtained as a gift sample from Cipla laboratories Ltd (Mumbai, India). Hydroxypropyl methylcellulose (HPMC K 15 M) were obtained from Sun Pharma, Ahemadabad, Dicalcium Phosphate (DCP), Micro crystalline cellulose (Avicel PH 101), talk, Mg stearate and ethyl cellulose were obtained from Glenmark, Goa. All other chemicals and reagents used in the study were of analytical grade.

Preparation of the matrix tablets

The distinct formulations of the matrix tablets analyzed along this study are provided in Table 1. The tablets were prepared containing 50 % of drug (LAM) and different concentration of polymers and diluents (MCC or DCP), 1% of talc and 2.5% of magnesium stearate as lubricants. The drug, polymer and diluents were passed through a 35 mesh sieve and thoroughly mixed in a plastic bag for 15 min. Talc and magnesium stearate were sieved (35 mesh), added to the previous mixture and blended for 5 min more. The lubricated blend was directly compressed on 16-station tablet compression machine using different punches. (Cadmach Machinery Co, Ahmadabad, India), using flat 10 mm diameter punches.

Assay of LAM in matrix tablets

The drug content of the manufactured tablets of each batch was determined in duplicate. For each batch, 20 tablets were taken, weighed, and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in pH 6.8 phosphate buffer and analyzed after making appropriate dilutions.

Weight, hardness and friability of tablets

The weight variation was determined by taking 20 tablets using an electronic balance (Sartorious, BT-2245). Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (Roche Friabilator) for 4 minutes at 25 rpm.

Swelling

Swelling studies were carried out for all formulations. Three metallic baskets containing a matrix tablet of each formulation were weighed, and placed in 1000 ml of phosphate buffer (pH 6.8) at 37.0 ± 0.5^{0}C. At hourly intervals, the previously weighted baskets with the tablet were removed, gently wiped with a tissue to remove surface water, re-weighted and then placed back into the vessel as quickly as possible. The mean weights were determined for each formulation and the degree of swelling (S) was calculated according to the relationship[16].

$$S = \frac{W_S - W_d}{W_d} \times 100 \qquad (1)$$

Where W_d and W_s are the dry and swollen matrix weights, respectively, at immersion time t in the buffer. The swelling degree was the mean value of three measurements.

Drug release analysis

Release rate for all the designed formulations was studied up to 12 hours using a tablet dissolution tester (Dissolution Tester [US Pharmacopeia] TDT-08L, Electrolab, Mumbai, India), type 1 (basket method), in 900 mL of pH 6.8 phosphate buffer at 37.5-C ± 0.5^{0}C. The stirring speed was set at 100 rpm. At predetermined time intervals, a 10-mL sample was withdrawn and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed. Cumulative percentage of the drug released was calculated, and the mean of 6 tablets from3 different batches was used in data analysis.

Kinetic mechanism

Different mathematical models may be applied for describing the kinetics of the drug-release process from matrix tablets, the most suited being the one which best fits the experimental results.

The kinetics of LAM release from hydrophilic cellulose formulations was determined by finding the best fit of the dissolution data (drug-released fraction versus time) to distinct models: zero-order (2), first-order (3) and Higuchi (4) [17-18]:

$$Q_t = Q_0 + \mathrm{k}_0\, t \qquad (2)$$

Where Q_t is the amount of drug released at time t; Q_0 the amount of drug in the solution at t = 0; (usually, $Q_0 = 0$) and k_0 the zero-order release constant

$$Q_t = Q_\infty(1 - e^{k_1 t}) \qquad (3)$$

Q_∞ being the total amount of drug in the matrix and k_1 the first-order kinetic constant.

$$Q_t = \mathrm{k}_H\ t^2 \qquad (4)$$

k_H representing the Higuchi rate constant.

Furthermore, in order to better characterize the drug release behavior for the polymeric systems studied, namely to understand the corresponding mechanism, the Korsmeyer– Peppas (5) semi-empirical model was applied [19].

$$\frac{Q_t}{Q_\infty} = kt^n \qquad (5)$$

Where Qt/Q_∞ is the fraction of drug released at time t; k a constant comprising the structural and geometric characteristics of the tablet, and n; the release exponent, is a Parameter which depends on the release mechanism is thus used to characterize it [20]. For the case of cylindrical tablets [20], in particular, a value of $n<0.45$ indicates Fickian or Case I release; $0.45<n<0.89$ for non-Fickian or anomalous release; $n=0.89$ for Case II release; and $n>0.89$ indicates Super Case II release.

Mean dissolution time

To further characterize the drug-release process, the mean dissolution time (MDT) was calculated according to the following equation:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}\Delta\, Q_j}{\sum_{j=1}^{n} \Delta\, Q_j} \qquad (6)$$

Where j is the sample number, n is the number of dissolution sample times, $t\hat{}_j$ is the time at midpoint between t_j and t_{j-1} and ΔQ_j is the additional amount of drug released between t_j and t_{j-1}.

Statistics

All results were expressed as mean values ± standard deviation (SD). In order to assess the statistical significance between the data, a single-factor analysis of variance (ANOVA) was carried out, at a 5% significance level.

RESULTS AND DISSCUSION

Characterization of Various Formulations

The main objective of this research work to enhance therapeutic performance of LAM by developing matrix tablets. HPMC K15M alone or in combination with EC was selected as matrix former.

The various formulation compositions of the prepared tablets are shown in the Table 1. The physical attributes of the prepared tablets were found to be satisfactory. Typical tablet defects such as capping, chipping, & picking were not observed.

As summarized in Table 2, the evaluation of the prepared hydrophilic matrix tablets containing LAM showed that the drug content of all formulations ranged from 99.5 to 101.05%, indicating a uniform amount of drug in the formulations.

Table 1: Composition of different formulations

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7
Lamivudine	200	200	200	200	200	200	200
HPMC K 15 M	40	60	80	100	80	80	80
EC	-	-	-	-	20	30	30
MCC	146	126	106	86	86	76	-
DCP	-	-	-	-	-	-	76
Magnesium Stearate	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4

Table 2: Physical characterization of LAM hydrophilic matrix tablets

Formulations	**Weight (mg)[a]n = 20**	**Weight RSD (%)**	**Hardness (N) n = 10**	**Thickness (mm) n = 10**	**Friability (%) n = 20**	**Drug content (mg) n = 3**
F1	400.17(±2.3)	0.57	5.65(±0.55)	4.2(±2.3)	0.31	200.34(±0.6)
F2	401.15(±2.2)	0.54	5.72(±0.48)	4.3(±2.3)	0.12	199.01(±1.01)
F3	401.01(±2.4)	0.59	5.9(±0.65)	4.2(±2.3)	0.39	201.28(±0.9)
F4	399.92(±3.1)	0.77	6.1(±0.69)	4.1(±2.3)	0.34	200.58(±0.7)
F5	400.92(±2.7)	0.67	6.67(±0.84)	4.2(±2.3)	0.4	201.24(±0.6)
F6	400.87(±2.5)	0.62	6.36(±0.83)	4.1(±2.3)	0.5	201.85(±0.4)
F7	401.19(±2.1)	0.52	6.78(±0.73)	4.1(±2.3)	0.52	202.01(±0.6)

Where [a] n is the number of measurements.

The physical characteristics of these tablets provided good weight uniformity, as indicated by the very low relative standard deviation obtained (RSD, 1% in all formulations). Other parameters like hardness and friability were within the acceptance limit.

Swelling studies

Swelling studies were carried out, in order to investigate whether the extent of swelling varied for the different formulations. When a matrix comes into contact with an aqueous solution, wetting occurs, first at the surface and then progressing into the matrix through microscopic

pores. The nature of the polymer plays an important role in this swelling process of the matrix tablets. The presence of water in the polymer causes a certain amount of stress, resulting in hydration of the polymer, which starts to swell yielding a gelatinous viscous layer[22].

The results obtained from these represented in Figure 1. From analysis of this data, it was possible to conclude that the variation in contents of HPMC influence showed significantly ($p < 0.01$), which can be evidenced by evaluating the formulations F1 to F4. The water uptake in these systems occurs in favor of a gradient of concentration that cause the liquid penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix, thus impairing extension of release. However in formulations F5 to F7 the deviation in uptake characteristic was observed due to presence of hydrophobic polymer (EC), which hinders swelling and polymer relaxation.

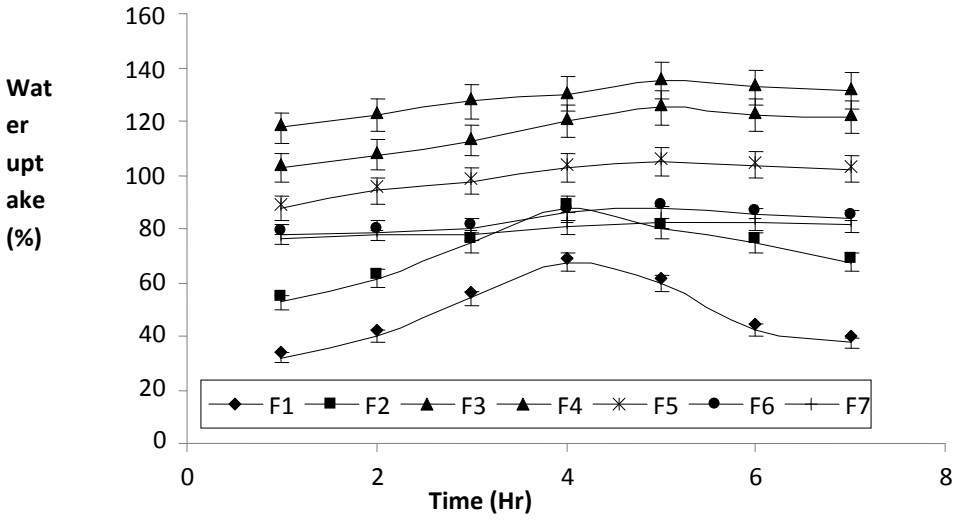

Figure 1. Graphical representation of the water uptake versus time of all formulations

Drug release analysis

When release rate of matrix embedded CR tablet formulations of LAM using HPMC K15M was observed, the release rate decreased and the drug release extended as the polymer proportion was increased. Lower polymer proportions not significantly retard the release pattern to get the desire release limit. In formulations F1 and F2 containing 10and 15 percent polymer of total tablet weight released 95.875% and 92.085% in seven hours, Figure 2. However drug released decreased significantly ($p<0.5$) from formulations F3 containing 20 percent of polymer. Further

increased the concentration of polymer formulation F4 did not significantly ($p>0.5$) increased the release rate, on that basis in order to optimize the release pattern of hydrophilic drug judiciously one of the hydrophobic polymer EC of different concentration formulation F5 and F6 was prepared and evaluated.

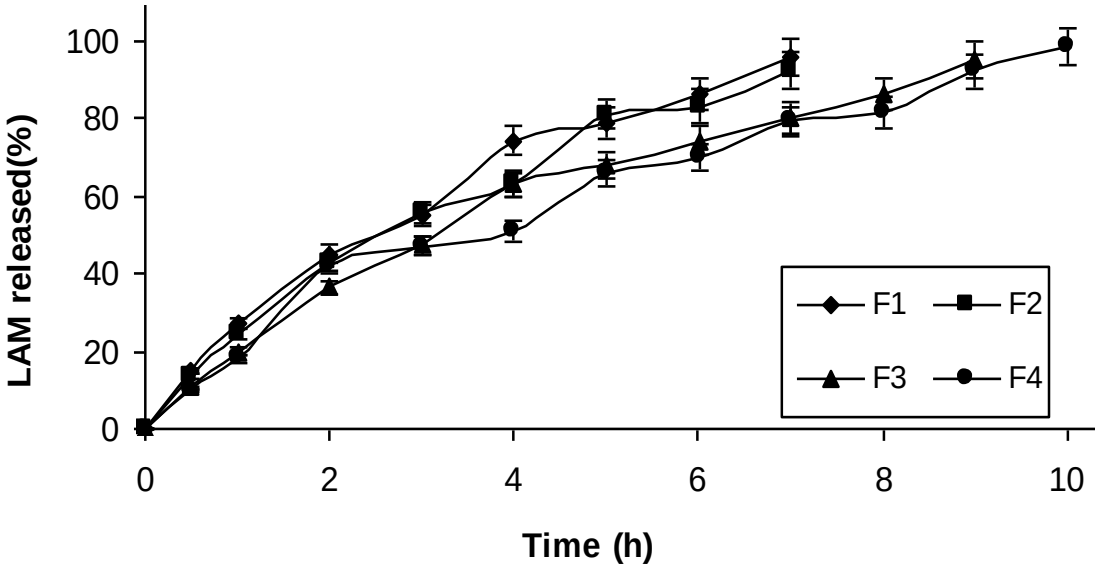

Figure 2. Drug-release profiles for LAM from only HPMC -K15M containing formulations

Formulation F5 containing 20 percent HPMC and 5 percent EC, released 95.1313% drug in 12 hours, however in F6 formulations the 99.6503% drug released in 12 hours, Figure 3. From the above two formulations it was conclude that EC has the significant effect in release pattern this is due to its prevention of entry of the dissolution fluid into the intact matrices. Ethyl cellulose has higher fragmentation rate and extensive plastic deformation which result lower porosity and more sustained of the tablet even if lower compression force [23].

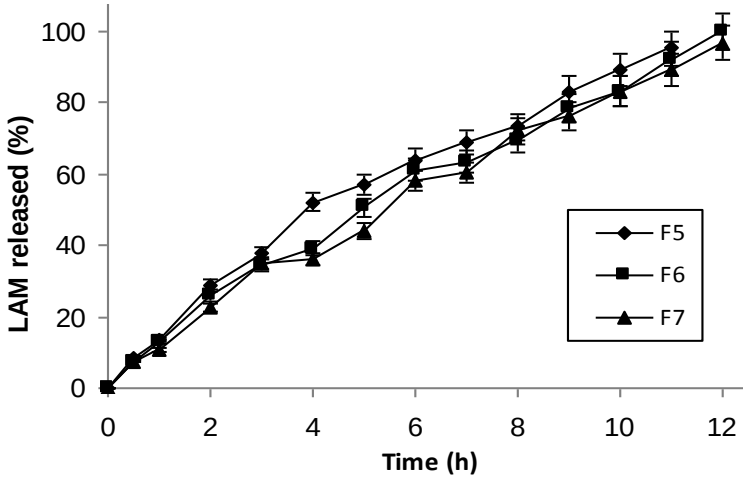

Figure 3. Drug release profiles for LAM from formulations containing both HPMC & EC

The MDT and t_{50}% calculated values for all the matrices was investigated (Figure 4).The above parameter reflects the release process, larger the value indicating higher drug retarding ability of the formulations. In fact, it was verified that polymer concentration gradients influence the MDT and t_{50}%. Thus, larger values were calculated as the concentration was increased and also the above two parameters increased significantly when aqueous insoluble polymer was used

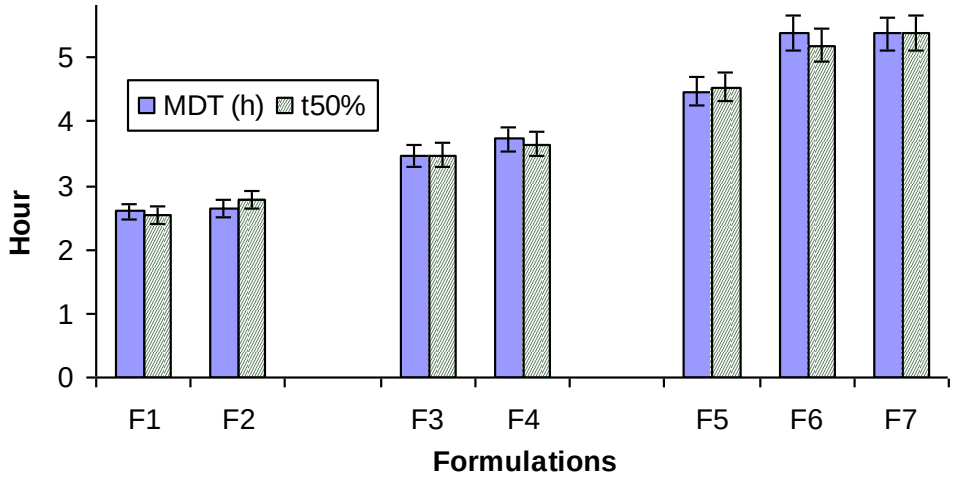

Figure 4. Comparative representation of MDT and t_{50}% of different formulations

Kinetic mechanism

The drug release mechanism from swellable matrices is complex and not yet completely understood. Although some processes may be classified as either purely diffusional or purely erosion controlled, many others can only be interpreted as being governed by both.

The analysis of experimental data in the light of the Korsmeyer–Peppas Equation (5), as well as the interpretation of the corresponding release exponent values (n); leads to a better understanding of the balance between these mechanisms.

For F1 and F2 formulations, n was determined to be equal to 0.69 and 0.72, respectively (Table 4), indicating that the release mechanism of LAM from these matrices is an anomalous (non-Fickian) transport, which suggests that both diffusion of the drug in the hydrated matrix and its own erosion modulate drug release. However increased the concentration of polymer lead to increase the n value in formulations F3 and F4. This may be attributed by more rigidity of the polymer. In formulations F5 to F7 the n value also increased as compared to other formulations this is due to prevention of glassy-rubbery transition of polymer. In most of the formulations Higuchi release mechanism showed the R^2 values which implies that diffusion is the predominant mechanism of drug release, however in formulation F6 and F7, the release pattern was case II transport because of highest R^2 values of zero order.

Table 4. Fitting results of the experimental LAM release data to different kinetic equations, for several formulations

Formulation	Zero order		First order		Higuchi		Korsmeyer Peppas		
	K_0 (%h^{-1})	R^2	K_1 (h^{-1})	R^2	K_0 (%$h^{-1/2}$)	R^2	K_{kp} (h^{-n})	n	R^2
F1	13.125	0.953	0.391	0.931	38.02	0.983	26.23	0.69	0.99
F2	12.824	0.961	0.336	0.965	36.9	0.98	23.88	0.72	0.993
F3	10.095	0.953	0.282	0.932	33.511	0.983	19.724	0.745	0.988
F4	9.28	0.943	0.297	0.896	32.718	0.979	19.13	0.741	0.972
F5	8.382	0.971	0.232	0.925	30.684	0.98	15.104	0.792	0.991
F6	7.934	0.991	0.193	0.9233	29.933	0.966	13.49	0.8	0.997
F7	7.870	0.988	0.223	0.868	29.624	0.96	12.43	0.826	0.992

CONCLUSION

From the above experiments it was concluded that, formulations containing HPMC K15M released the drug more than the expected due to more hydration of gel layer, which could be prevented by using EC along with HPMC. It was again observed that influence of insoluble diluents has little effect on the release profile of the formulation.

The swelling experiments, in turn, showed that the water uptake increases with the polymer viscosity, which is a rather important factor to consider when preparing hydrophilic matrix tablets.

The release mechanism of LAM from each formulation tested was evaluated in the light of zero order, first-order, Higuchi's and Korsmeyer–Peppas kinetic models. Non-Fickian (anomalous) transport was observed for all cellulose ethers. Neither the effect of cellulose substitution nor the type of diluents was determined to have a significant impact on the release mechanism of LAM from the hydrophilic matrix tablets investigated.

The present results provide useful information on the type of polymers and additives that should be employed on the formulation of hydrophilic matrix tablets, namely of those containing LAM or similar drugs.

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