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PREPARATION AND *IN-VITRO* EVALUATION OF LAMIVUDINE MATRIX TABLETS FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM USING METHOCEL K15M CR POLYMER

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ABSTRACT: Purpose: The present work reports the learning of different proportion of Lamivudine: Methocel K15M, which will, describe the effect of polymer proportion and diluent on the drug release mechanism. We used Lamivudine, an anti-HIV agent as the model drug to evaluate its release characteristics from different matrices. **Method:** Direct compression method used for preparation of Matrix tablets of Lamivudine using Methocel K15M CR polymer. In vitro release studies were performed using US Pharmacopeia type 1 apparatus (basket method) in 900 ml of pH 6.8 phosphate buffer at 100 rpm for 8 hours (Initial 2 hours in simulated gastric fluid (pH 1.2)). Surface properties of matrices are determined by using Scanning Electron Microscopy (SEM). Drug release analyzed according to their kinetic models. **Results:** Statistically substantial difference found among the drug release outline form different formulations. When polymer used as lower content (10% of total tablet weight), the rate of drug release evaluated while polymer content in higher range (25% to 30%) in the matrix release extended > 8 hours due to increased tortuosity and decreased porosity. The release mechanism explored and explained with zero order, first order, Higuchi and Korsmeyer and Hixon-Crowell equations. **Conclusion:** The results produced in this study exhibited that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug. By suitable modulation could be developed controlled delivery of such type of drug.

INTRODUCTION: AIDS is considered to be an epidemic, and according to estimates from the Joint United Nations Programmed 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 expect to increase for many years to come, unless more effective and patient-compliant antiretroviral medications are available at affordable prices (Joint United Nations Programme, 2006).

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 cost⁸.

Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an antiretroviral regimen for the treatment of HIV infection^{13, 18}. *In-vivo*, nucleoside analogs are phosphorylated intracellularly by endogenous kinases to putatively active 5'-triphosphate (3TC-TP) derivatives that prevent HIV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension^{2, 7, 14}. Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability of 86% ± 16%, peak serum concentration of lamivudine (C_{max}) of 1.5 ± 0.5 mcg/mL and mean elimination half-life (t_{1/2}) of 5 to 7 hours, thus

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necessitating frequent administration to maintain constant therapeutic drug levels⁹.

Therefore, the objective of the present work is to provide a long acting pharmaceutical composition containing lamivudine in a sustained release matrix formulation, to maintain the blood levels of the active ingredient for a prolonged period of time¹⁹. Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms¹.

Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and at constant rate for desired time period⁶.

The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate²⁰. A wide array of polymers has employed as drug retarding agents each of which presents a different approach to the matrix concept.

TABLE 1 FORMULATION OF LAMIVUDINE SUSTAINED RELEASE MATRIX TABLETS

Formulation Code	Weight (mg) / Tablet					
	Methocel K15M CR	Lamivudine mg	Avicel PH 102	Talc	Mg - stearate	Total mg
L1	40	200	144	12	4	400
L2	60	200	124	12	4	400
L3	80	200	104	12	4	400
L4	100	200	84	12	4	400
L5	120	200	64	12	4	400

During granulation procedure matrix-forming agents, talc, Methocel, magnesium stearate, avicel pH 102 and the active ingredient deliberated properly. Firstly active ingredient, talc and Methocel were mixing for 10 minutes properly and dried the granules, which produced during mixing than dried granules sieved through 20-mesh SS

Polymers that primarily forming insoluble or skeleton matrices considered as the first category of retarding materials and classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which was potentially erodable and the third group exhibits hydrophilic properties.

There are three primary mechanisms for releasing of active ingredient that are diffusion, degradation and swelling and diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Methocel K15M CR, used in this study is hydrophilic polymer that hydrated, swollen and facilitates to diffuse the drug²³.

Matrix based CR tablet formulations are the most popular and easiest to formulate on a commercial scale. The matrix can be prepared via wet granulation or by direct compression¹⁶.

MATERIALS AND METHODS:

Materials

Lamivudine obtained as gift sample from Beximco Pharmaceuticals Ltd. Tongi, Bangladesh. HPMC (Methocel K15M CR) was a gift sample received from Colorcon Asia Pvt. Limited. Avicel pH 102 purchased from Ming Tai Chemical Co.Ltd., (Taiwan). Magnesium stearate and talc taken from Hanua Chemicals Limited, (Japan).

Preparation of matrix tablets

Tablets prepared by direct compression process. In all cases, the amount of the active ingredient was 200 mg and the total weight of the tablet was 400 mg (Table 1).

screen to get compressible particle. Lubricants added during blending part in case of blending total mass has taken in a container and blended in a laboratory designed small drum blender machine for about 30 minutes. Finally, the prepared granules compressed using Pressima D type 4-station compression machine with a 10.00 mm punch.

Before compression, the surfaces of the die and punch has lubricated with purified talc. All the preparations stored in airtight containers at room temperature for further study.

Control tests for matrix tablets

Different formulation (L1 to L5) evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of 10 matrix tablets from each formulation measured using Hardness tester (Erweka GMBH, 300H model, Germany). Friability of the tablets was determined by testing 10 tablets in a Roche friabilator (Campbell Electronics, Mumbai) for 4 minutes at 25 rpm. A slide calipers had used to measure the thickness for 5 tablets.

Weight variation test has performed by taking 10 tablets using an electric balance (OHAUS LS 200, Switzerland) according to the official method. Drug content for Lamivudine has determined by measuring the absorbance of the sample at 271 nm using Shimadzu 1240 UV visible spectrophotometer, Japan and comparing the content from a calibration curve prepared with standard Lamivudine in the same medium by taking 20 tablets has taken, weighed and finely powdered.

An accurately weighed quantity of this powder has taken, suitably dissolved in pH 6.8 phosphate buffer, making dilution and analyzed and carried out in triplicate and mean was taken.

In vitro dissolution study of tablets

Dissolution studies were shown using a tablet dissolution apparatus-I, VEEGO VDA 8 DR, Germany), type 1 (basket method), in 900 mL of pH 6.8 phosphate buffer at $37.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and stirring speed was 100 rpm. During dissolution, 10 ml of sample has taken and same amount replaced to maintain sink condition than that sample was filtered with filter paper than, the sample solution was analyzed at 271 nm for Lamivudine by UV spectrophotometer (Shimadzu 1240, UV visible spectrophotometer, Japan).

The amounts of drug present in the samples calculated with the help of straight-line equation obtained from the calibration curves for respective

drug. The mean of six tablets from each formulation placed in data analysis. The dissolution study was continued for 8 hours (Initial 2 hours in simulated gastric fluid (pH 1.2) and next 6 hours in phosphate buffer of pH 6.8) to get a simulated picture of the drug release in the *in-vivo* condition and drug dissolved at identified time periods was plotted as percent release versus time (hours) curve. This drug release profile fitted into several mathematical models to get an idea of the release mechanism¹⁵.

Kinetic modeling of the drug release

Different kinetic models (zero-order, first-order, Higuchi's, korsmeyer's and Hixon Crowell) applied to interpret the release profile from matrix system. To study the mechanism of drug release from the matrix tablets, the release data fitted to zero-order, first-order, and Higuchi equation.

However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems (Korsmeyer *et al.*, 1983).

$$\text{Log (Mt / Mf)} = \text{Log k} + n \text{ Log t} \dots\dots\dots (1)$$

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved plotted against log time for each batch according to the equation 1. A value of $n = 0.45$ indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release³. The Hixon - Crowell cube root equation is:

$$\text{M}^{1/3} = \text{M}_0^{1/3} - \text{Kct} \dots\dots\dots (2)$$

Where, K_c is the cube root dissolution rate constant. Cube roots of percent releases (Cube root of initial drug load minus cube root of % drug remaining) are plotted against time (hour) to demonstrate the Hixson Crowell plot.

Mean dissolution time (MDT) calculated from dissolution data using the following equation (Mockel et al., 1997).

$$\text{MDT} = (n / n+1) \cdot K^{-1/n} \dots\dots\dots (3)$$

Scanning Electron Microscopy

Then tablets were position into sample holder to the microscope and visualized under scanning electron microscope (SEM), (HITACHI, Model: S-3400N). Tablets have taken using different magnifications. The magnifications used for taking tablets were 100-10000 (SE-Secondary Electron).

RESULTS

Physical Evaluation of Lamivudine matrix tablets

The tablets of the projected formulations (L1 to L5) evaluated for hardness, weight variation, thickness, friability and drug content. The thickness (mean $\pm$ SD, $n=5$) of the tablets were (4.71 ± 0.01 , 4.72 ± 0.02 , 4.72 ± 0.03 , 4.71 ± 0.02 , 4.750 ± 0.04 respectively) ranged from 4.71 to 4.75 mm. The hardness (mean $\pm$ SD, $n=10$) and percentage friability ($< 1\%$) of the tablets of all batches (6.05 ± 0.27 , 6.10 ± 0.27 , 6.15 ± 0.27 , 6.20 ± 0.27 and 6.25 ± 0.28 respectively) ranged from 6.05 to 6.25 kg/cm² and 0.75 to 0.85 %, respectively. The average percentage weighted deviation of 10 tablets of each formula was less than $\pm 5\%$. Drug content (mean value $\pm$ SD within 0.9) among different batches of tablets ranged from 200.6501mg to 200.6505mg.

Effect of methocel K15M CR on release pattern of Lamivudine

Matrix tablets of Lamivudine formulated using direct compression technique. Different Methocel K15M CR matrix tablet containing Lamivudine as active ingredient having methocel K15M CR polymer 10%, 15%, 20%, 25% and 30% respectively of total tablet weight (i.e. 20%, 30%, 40%, 50% & 60% respectively of total drug) in the matrix tablet with the formulation code L1, L2, L3, L4, L5 were prepared to evaluate the effect of this polymer. After preparation according to formulation shown in the **Table 1**, their dissolution

studies were carried out in basket method at 100 rpm in 900ml, phosphate buffer pH 6.8 medium at 37 $^{\circ}\text{C}$ ($\pm 0.50^{\circ}\text{C}$). Six tablets from each formulation used in dissolution study. The release profile of Lamivudine monitored up to 8 hours (Initial 2 hours in simulated gastric fluid (pH 1.2) and next 6 hours in phosphate buffer of pH 6.8). The average release pattern shown in **Figure 1**.

FIGURE 1: ZERO ORDER PLOT OF RELEASE (MEAN $\pm$ SD) OF LAMIVUDINE MATRIX TABLETS FROM L1 (■), L2 (□), L3 (Δ), L4 (○) AND L5 (×) FORMULATIONS

A release profile of Lamivudine containing methocel K15M CR matrix tablet of five formulations obtained from the graphs. The total % of Lamivudine release (mean value $\pm$ SD within 0.9, $n = 6$) from the formulation L1, L2, L3, L4, L5 was 90.52%, 79.59%, 75.64%, 66.96%, and 57.48% respectively.

It has been observed that the release rate has been extended with the increase of polymer % and with the decrease of avicel percent. The highest percent of drug release within 8 hours, obtained from LAMF1 where polymer content is 10% of total tablet weight and that of avicel was 36 %. But in LAMF5, the polymer content is 30% of total tablet weight and avicel is 16%, the release of drug is controlled with 57.48 % within 8 hours.

The rate of drug release found to be inversely proportional to the amount of methocel K15 M CR present in the matrix structure, i.e. the drug release increased with decrease in the polymer content of the matrix tablet. The release rate was significantly dependent on the proportion of polymer. A statistically significant decrease ($P < .05$, F_{crit} (4,

25) = 2.76 and $F_{cal} = 405.95$), at the end of first hour, ($P < .05$, $F_{crit} (4, 25) = 2.76$ and $F_{cal} = 2423.87$) at the end four hours, ($P < .05$, $F_{crit} (4, 25) = 2.76$ and $F_{cal} = 884.61$), at the end of eight hours, was observed % drug release in the

formulation L1 to L5 as the polymer proportion increase from 10% to 30% of the total drug weight. The release kinetics data has been mention in the **Table 2**.

TABLE 2: RELEASE KINETICS OF FORMULATED LAMIVUDINE FROM METHOCEL K15M BASED MATRICES

Code	Zero order		First order		Higuchi		Korsmeyer		Hixon Crowell	
	R^2	K_0 % h^{-1}	R^2	K_1 % h^{-1}	R^2	K_h % $h^{-0.5}$	R^2	n	R^2	K_c % h^{-1}
L1	0.834	9.957	0.989	-0.124	0.979	32.899	0.970	0.455	0.543	0.384
L2	0.859	8.660	0.976	-0.081	0.991	28.345	0.989	0.453	0.551	0.366
L3	0.941	8.449	0.989	-0.072	0.996	26.497	0.998	0.561	0.619	0.373
L4	0.948	7.577	0.991	-0.056	0.995	23.665	0.999	0.583	0.629	0.362
L5	0.939	6.608	0.985	-0.044	0.996	20.738	0.999	0.586	0.625	0.346

R^2 , Correlation coefficients, K_0 , K_1 , K_h , K_c Release rate constant for zero order, first order, Higuchi, and Hixon Crowell release equation, respectively, n, diffusional exponent, indicative of release mechanism in Korsmeyer equation. L1-L2 = Fickian Release (Case I), L3-L5 = Non-Fickian (Anomalous) Release

$T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and MDT values of the designed tablets are also shown in **Figure 2**.

FIGURE 2: SUCCESSIVE DISSOLUTION TIME [$T_{25\%}$ (□), $T_{50\%}$ (■), $T_{80\%}$ (▨), MDT VALUE (▤)] OF LAMIVUDINE CONTAINING METHOCEL K15M MATRICES

In case HPMC 15000 cps (Methocel K15) containing formulations, formulation L1 showed lowest MDT (mean dissolution time) values of all as it increased the release rate. But, as the concentration of HPMC 15000 cps increased in the latter formulations (L2, L3, L4, L5), MDT values were increased i.e. increase polymer load increase MDT value.

Formulation L5 showed highest MDT (7.4 hr) value. The MDT values increased significantly $P < .05$, $F_{crit} (4, 25) = 2.76$ and $F_{cal} = 701.21$) as polymer load was increased 10% to 30% of the total drug weight.

Scanning electron microscope analysis
Matrix tablets were prepared at different

concentration of methocel K15M CR polymer and different polymers like avicel PH102, talc, magnesium stearate. Morphology and surface properties of the tablets examined with a Scanning Electron Microscope "SEM" (**Fig 3**) (HITACHI, Model: S-3400N). Tablets have taken using different magnifications.

The magnifications used for taking tablets were 100-10000 (SE-Secondary Electron). Morphology and surface properties of the tablets found to be affected by the polymer concentration.

FIGURE 3: SEM OF METHOCEL K15M CR ON LAMIVUDINE SUSTAINED RELEASE TABLETS

A. 100 SE (Magnification x 100) D. 2.00k SE (Magnification x 2000)
B. 500 SE (Magnification x 500) E. 5.00k SE (Magnification x 5000)
C. 1.00k SE (Magnification x 1000) F. 10.0k SE (Magnification x 10000)

DISCUSSIONS:

Physical Evaluation of Lamivudine matrix tablets

The present study carried out to formulate oral sustained release drug delivery system for Lamivudine as Matrix Tablets. The drug content of all formulations was between 100.30 and 100.31 %, indicating the presence of an acceptable amount of drug in the formulations. Furthermore, all the formulations showed acceptable hardness and friability.

In vitro dissolution study of tablets

The formulations, L1 L2 showed initial burst release within the 2-hour dissolution test period in pH 1.2 buffer. This is due to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core (Ebube et al., 1997).

However the later formulations L3 to L5 containing higher proportion of methocel K15 polymer no burst release was observed within two hours probably to the low solubility of the drug at pH 1.2 and retained their shape throughout the 8 hour dissolution period. They showed slow drug release from 0 to 2 hours followed by faster but controlled release from 3rd to 8th hour.

The release rate decreased and the drug release prolonged as the polymer proportion was increase. Such increase in polymer content results in decreased in the drug release rate due to a decreased in the total porosity i.e. release is extended to long period. Avicel caused a decreased tortuosity of the path of the drug due to its preferential solubility than methocel K15 M CR, by its swelling effect, additionally weakened the integrity of the matrix.

For the formulation, L5 containing highest proportion of polymer drug release is more controlled both pH 1.2 (less than 20% in acidic media) and phosphate buffer pH 6.8 (extended more than 8 hours).

This may be owing to a more rigid complex formed by presence of higher proportion of HPMC, which helped in retaining the drug in matrix and did not allow rapid diffusion of drug from the matrix.

Among these formulations (L1 to L5), the rate and extent of drug release decreased with increasing the amount of Methocel K15M CR. This polymer has known for retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate related to its viscosity. Processing factors including particle size, hardness, porosity and compressibility index etc. also can affect the release rate of drug from tablets. The hydration rate of HPMC depends on the nature of the substituent like Hydroxypropyl group content. Hence, Methocel K15M CR used because it forms a strong viscous gel in contact with aqueous media, which may be useful in controlled delivery of drug (Hogan, 1989).

Kinetic modeling of the drug release

The drug release data obtained extrapolated by Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations. In this experiment, the *in vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (R^2 : 0.98 to 0.99). To confirm the diffusion mechanism, the data fitted into Korsmeyer-Peppas equation (Korsmeyer et al., 1983).

The formulations showed good linearity (R^2 : 0.97 to 0.99) with slope (n) values ranging from 0.4527 to 0.5856 indicating that diffusion was the predominant mechanism of drug release from these formulations indicating that the release mechanism was non-fickian or anomalous release ($0.45 < n < 0.89$).

It can be inferred that the release was dependent on both drug diffusion and polymer relaxation, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion (Peppas, 1985), when plotted according to Korsmeyer-Peppas equation, the formulations L4 to L5 showed highest linearity (R^2 : 0.999). The poor correlation coefficients (R^2 values ranged from 0.83 to 0.94) observed for the kinetic parameters based on the zero-order model equation were mainly due to the drug release mechanism. First order plot for all formulation showed good

linearity. The release profile of Lamivudine from all these formulations displayed very poor fitting with Hixson-Crowell cube root model of drug release, which related, with the method of manufacture followed.

Scanning electron microscope analysis (SEM)

Study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the surface of matrix tablet. Morphology and surface properties of the tablets has affected by the polymer concentration.

CONCLUSIONS: From above study, it is possible to conclude that the selected excipients are likely to be suitable for the preparation of tablet formulations direct compression method. According to the release studies, formulations having low level of polymer are not appropriate for the preparation of modified hydrophilic matrix tablets while higher level may be advantageous as release rate of the drug from matrix tablets was dependent on the proportion and type of the polymer used. The results of release studies indicated the possibility of achieving a suitable modulation of Lamivudine release rate by opportunely varying the methocel K15M CR in the matrix tablet.

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