ORIGINAL ARTICLE

Formulation Design and Characterization of Lamivudine Controlled Release Matrix Tablets

Itishree Jogamaya Das[1], Himansu Bhusan Samal[2], Sthithapragnya Panda[2], Saiveena Parvathapuram[2], Sai Kiran Rallapalli[2]

[1]Department of Pharmaceutics, Royal College of Pharmacy and Health Sciences, Berhampur, Odisha, India, [2]Department of Pharmaceutics, Guru Nanak Institutions Technical Campus - School of Pharmacy, Ibrahimpatnam, Hyderabad, Telangana, India

Abstract

Aim: To design and characterize oral controlled release matrix tablets of lamivudine to improve efficacy and patient compliance. **Materials and Methods:** Lamivudine matrix tablets were prepared by wet granulation method using various proportions of hydrophilic polymers such as sodium carboxymethylcellulose (Na CMC), hydroxypropyl methylcellulose (HPMC), Eudragit-L155, and xanthan gum alone or in combination with hydrophobic polymer ethyl cellulose (EC). *In-vitro* release studies were performed using USP Type II dissolution apparatus 900 ml of pH - 6.8 phosphate buffer at 100 rpm. Drug release kinetics was analyzed using zero-order, first-order, Higuchi and Hixon equation. No chemical interaction between drug and the polymer was seen as confirmed by Fourier transform infrared studies. **Results and Discussion:** All the formulations showed good results which were compliance with pharmacopeial standards. Formulations X_2, X_3, X_4, X_5, X_7, X_9, X_{12}, and X_{14} containing a combination of two polymers, i.e., xanthan gum, combine with EC, Na CMC, HPMC, and Eudragit-L155 in the different ratios shows zero-order kinetic of release with 80-97% of drug released. But in the presence of Na CMC in the formulation X_4, X_9, and X_{14}, the drug released in 12 h was in the range of 75-85% and shows zero-order kinetics. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and therefore followed non-Fickian or anomalous release. The formulation X_4 containing xanthan gum with Na CMC gave more sustaining action, i.e., 79.16% in 12 h. **Conclusion:** Based on the *in-vitro* drug release study, it can be concluded that among the prepared formulations, X4 is the optimized formulation and can overcome the demerits of conventional lamivudine tablet.

Key words: Controlled release, lamivudine, matrix tablets, release kinetics

INTRODUCTION

Oral route is the most suitable route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians. For the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[1] Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects and increase safety margin for high potency drugs.[2]

The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance and high cost of the therapy.[3,4] Lamivudine is a potent hydrophilic antiviral agent indicated for the treatment of AIDS and belongs to BCS Class III drug with high solubility and low permeability. However, the main limitation to the therapeutic effectiveness of lamivudine is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability.[5] The biological

Address for correspondence:
Itishree Jogamaya Das, Department of Pharmaceutics, Royal College of Pharmacy and Health Sciences, Berhampur, Odisha, India. Phone: +91-9493393994.
E-mail: itishree.14@gmail.com

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half-life ($t_{½}$) of lamivudine is 5-7 h, thus necessitating frequent administration (150 mg twice daily) to maintain constant therapeutic drug levels.[6,7] Treatment of AIDS using conventional formulations of lamivudine is found to have many drawbacks such as adverse side effects due to the accumulation of the drug in multi-dose therapy, poor patient compliance, and high cost.[8,9] Hence, CR formulations of lamivudine can overcome some of these problems.

Lamivudine is absorbed throughout the gastrointestinal tract. The drug is freely soluble at any pH; hence judicious selection of release retarding excipients is necessary for achieving constant *in-vivo* release. The most commonly used method of modulating the drug release is to include it in a matrix system. Matrix tablets can be prepared via wet granulation or by direct compression.[10] Many polymers have been used in the formulation of matrix based CR drug delivery systems. Reports are found on the use of hydrophilic polymers such as hydroxypropyl methylcellulose, methylcellulose, sodium carboxymethylcellulose (Na CMC),[11] carbopols,[12] and polyvinyl alcohol[13] for the preparation of CR formulations of different drugs. Hydrophilic polymer matrix systems[14-19] are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[20] Hydrophilic polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the CR dosage forms. However, the use of hydrophilic matrix alone for extending drug release for highly water-soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs, it becomes essential to include hydrophobic polymers in the matrix system.[21]

Hence, in this work, an attempt has been made to formulate the CR matrix tablets of lamivudine using hydrophilic matrix material (hydroxypropyl methylcellulose [HPMC], Na CMC, xanthan gum, and Eudragit-L155) alone or in combination with hydrophobic polymer material (ethyl cellulose [EC]), evaluate the physical characters of prepared sustained release tablets, elucidate the effect of polymer composition, on the release kinetics and determine the chemical compatibility of formulation containing various ratios of polymer and drug.

MATERIALS AND METHODS

Lamivudine was received as a gift sample from Cipla Ltd. Goa, EC, xanthan gum, HPMC-ELV-15, magnesium stearate and starch (potato) from Loba Chemie Pvt. Ltd., CMC from Merck Specialities Pvt. Ltd, and Eudragit-L155 gift sample from Cipla Ltd. Goa, potassium dihydrogen phosphate and sodium hydroxide from Merck Specialities Pvt. Ltd., Compression Machine Rimek Mini Press, Karnavati, Ahmedabad, India, Fourier transforms infrared (FTIR)-Spectrophotometer model NEXUS 870 (THERMO NICOLET), eight stage dissolution apparatus model TDT-08L ELECTROLAB, Roche Friabilator Indian Equipment Corporation, Bombay, Monsanto Hardness Tester Rupa Industries, India. Hot air oven, Unilab, India.

Preparation of lamivudine matrix tablet

Different tablet formulations (Batch size of 50 tablets) were prepared by wet granulation technique X_1 to X_{15} [Table 1]. Before preparing the tablets all the ingredients to be pass through sieve No. 60. Drug and polymers were mixed uniformly using mortar and pestle. Granulation was done using granulating agent 15% w/w of aqueous solution of starch, and the dump mass of drug and polymer was passed through Sieve No. 10 and dried at 60°C in hot air oven till the granules contain <5% of moisture. After drying the granules were passed through a sieve No. 22 screen. The prepared granules are lubricated with specified amount of magnesium stearate until it was well mixed. Finally, the lubricated granules are compressed by 12-station rotary tableting machine using flat-faces 10 mm die.

Evaluation of drug loaded granules

Angle of repose

The angle of repose[22] of granules was determined by funnel method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 g of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base, and the radius of the powder cone was measured.

Bulk density

Bulk densities[23] of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10 ml graduated cylinder. The volumes occupied by the sample were recorded. Bulk density was calculated:

$$\text{Bulk density (g / ml)} = \frac{\text{Weight of sample in gms}}{\text{Volume occupied by the smaple}}$$

Tapped density

Tapped densities[23] of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from a height of 2 inches until a constant volume was obtained. Volumes occupied by the sample after tapping were recorded, and tapped density was calculated.

$$\text{Tapped density (g / ml)} = \frac{\text{Weight of sample in g}}{\text{Volume occupied by the smaple}}$$

Table 1: The lamivudine matrix tablets (quantity in mg/tablets)

Ingredients	Formulation batch														
	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	X_{12}	X_{13}	X_{14}	X_{15}
Lamivudine	240	240	240	240	240	240	240	240	240	240	240	240	240	240	240
Xanthan gum	250	125	125	125	125	225	112.5	112.5	112.5	112.5	150	75	75	75	75
EC	-	125	-	-	-	-	112.5	-	-	-	-	75	-	-	-
HPMC - (E. LV-15)	-	-	125	-	-	-	-	112.5	-	-	-	-	75	-	-
Na CMC	-	-	-	125	-	-	-	-	112.5	-	-	-	-	75	-
Eudragit-L155	-	-	-	-	125	-	-	-	-	112.5	-	-	-	-	75
Magnesium stearate (% wt/wt)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Starch paste (15%)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

q. s indicates quantity sufficient. Na CMC: Sodium carboxymethylcellulose, HPMC: Hydroxypropyl methylcellulose, EC: Ethyl cellulose

Carr's compressibility index

% compressibility was determined by the Carr's compressibility index.[23]

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio

It is the ratio of tapped density and bulk density.

Evaluation of matrix tablets

The prepared matrix tablets were evaluated for dimension, weight variation**,** hardness, friability, and content uniformity as per the reported procedure.[24]

Dimension (thickness and diameter)

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets were determined using Vernier Caliper. 20 tablets from each type of formulation were used, and average values were calculated.

Weight variation

Weight variation was evaluated on 20 tablets using an analytical electronic balance (Adventurer [DHAUS], Essae-Teraoka Ltd.) and the test was performed according to official method.

% Friability

Friability is the measure of tablet strength. Friability was determined by taking 10 tablets in a Roche Friabilator for 4 min at 25 rpm. % friability was calculated using the formula:

% Friability = (Loss in weight/Initial weight) × 100

Tablet hardness

Tablet hardness was determined for 6 tablets using a Monsanto hardness tester.

Drug content

About 20 tablets were weighed accurately and powdered. Powder equivalent to 100 mg of lamivudine was accurately weighed and transferred to a 100 ml volumetric flask. Initial about some amount of pH 6.8 phosphate buffer was added to the volumetric flask, and the flask was shaken for 10 min, and then the mixture was sonicated. Finally, the volume was made up to 100 ml with phosphate buffer and then filtered using of 0.45 µm membrane filter paper. The filtrate was suitably diluted with pH 6.8 phosphate buffers and analyzed against blank (pH 6.8 phosphate buffers) solution for the drug content by spectrophotometrically at 268.0 nm.

FTIR spectroscopy

FTIR spectral studies were conducted for the pure drug and the formulations with a different polymer to check the compatibility using SHIMADZU FTIR-8400 S. The spectrum was recorded in the range of 4000-400 cm^{-1}. Interaction between the components, if any, was indicated by either producing additional peaks or absence of characteristic peak corresponding to drug and polymer.

In-vitro drug release studies

Drug release was evaluated by conventional *in-vitro* dissolution testing. The dissolution tests for matrix tablets were performed using dissolution tester (USP) – eight stages paddle model. The medium was 900 ml of pH-6.8 phosphate buffer at 37°C ± 0.5°C. The paddles were rotated a 100 rpm., 10 mL of sample was withdrawn at every 1 h interval and replaced with the fresh dissolution medium. After appropriate dilution, the samples were analyzed using a double beam ultraviolet spectrophotometer at 268.0 nm.

RESULTS AND DISCUSSION

This investigation was to fabricate and evaluate the sustain release formulation lamivudine matrix tablet. The CR granules of lamivudine were prepared using combined

polymers, i.e., xanthan gum with EC, HPMC (E. Lv-15), Na CMC, Eudragit-L155 and EC with HPMC (E. Lv-15), Na CMC, and Eudragit-L155. Other ingredients including starch paste as binder and magnesium stearate as a lubricant were in incorporated for matrices. The matrices were prepared by wet granulation method in different ratios and finally compressed. In each batch 50 tablets were prepared.

The granules of formulations prepared from xanthan gum with different polymers (i.e., X_1 to X_{15}) showed angle of repose between 19° and 25° indicating excellent flow behavior. Compressibility index of all the formulations was found to come within the range of 13-19% and in the case of packing factor value of all formulations shown about 1.24 indicating good flow properties [Table 2].

The tablets of different batches were subjected to various evaluation tests such as dimension, weight variations, friability, and hardness according to procedures specified in Indian Pharmacopoeia (IP). The thickness of matrix tablets was measured by Vernier Caliper and was ranged between 4.46 and 4.55 mm for all formulation. The weight variation test revealed that the weight was within the specified limits and found to be <4%. The friability test of different batches was carried out, and the result showed that it was below 1% ranging from 0.09 to 0.43, respectively, which are well under the acceptable criteria as per IP. The hardness of the tablets compressed form in various formulations was measured using Monsanto hardness tester. The hardness was found to be 6.4 ± 0.35 to 9.8 ± 0.01 kg/cm^2 [Table 3].

All the formulations were assayed for drug content. The drug content in formulation batches X_3, X_4, X_6, X_7, and X_{12} was found in the range between 92.75% and 98.85%, whereas in formulation batches X_1, X_2, X_5, X_9, X_{11}, and X_{14} were found in the range between 100.98% and 113.02% [Table 3].

FTIR spectra of the lamivudine and the optimized formulation (X_4) were recorded in the range of 4000-400 cm^{-1} and shown in Figures 1 and 2. Lamivudine shows some prominent and characteristic peaks. The peaks at 1685.33 cm^{-1} are due to stretching vibrations of the carbonyl group (present in the cytidine nucleus C=O). A band of peaks at 3462.64, 3159.78, and 3031.92 cm^{-1} owing to primary amino, amino, and hydroxyl groups; and peaks at 1280.80 and 1089.88 cm^{-1} owing to asymmetrical and symmetrical stretching of the C-O-C system (oxathiolane ring), respectively, in all the spectrum, indicate the stable nature of lamivudine. In the optimized formulation (X_4), the presence of all the characteristic peaks of the lamivudine indicates that no interaction was occurred between the drug and the excipients.

Dissolution study

In this study formulation X_1, X_2, X_4, and X_6, the drug release was found in the range between 58% and 79% within 12 h. Due to the nature of polymer's characteristics. The formulation X_1, X_6, and X_{11} containing only xanthan gum exhibited swelling without erosion throughout the study. Due to non erosion effect, the total drug could not release and show fast order release kinetics. But in the case of X_{11}, the release kinetics is zero-order with correlation factor 0.99272.

The formulation X_3, X_4, X_5, X_7, X_9, X_{12}, and X_{14} shows zero-order kinetic of release with 80-97% of drug released.

Table 2: Evaluation of granules of formulation batches X_1 to X_{15}

Formulation batch	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio	Angle of repose (°)
X_1	0.314	0.389	19.2	1.237	25.0
X_2	0.368	0.426	13.6	1.157	19.0
X_3	0.399	0.476	16.2	1.193	20.0
X_4	0.421	0.512	17.7	1.215	23.0
X_5	0.458	0.534	14.3	1.166	20.0
X_6	0.369	0.454	18.7	1.230	25.0
X_7	0.356	0.406	12.3	1.140	19.0
X_8	0.358	0.424	15.5	1.183	19.0
X_9	0.421	0.505	16.6	1.199	22.0
X_{10}	0.465	0.536	13.2	1.152	21.0
X_{11}	0.396	0.484	18.1	1.221	24.0
X_{12}	0.365	0.418	12.7	1.145	19.0
X_{13}	0.412	0.486	15.2	1.179	20.0
X_{14}	0.389	0.464	16.1	1.191	24.0
X_{15}	0.432	0.493	12.4	1.141	19.0

As these formulations containing a combination of two polymers, i.e., xanthan gum, combine with EC, Na CMC, HPMC in the different ratios, which helps to erosion of the polymer network. But in the presence of Na CMC in the formulation X_4, X_9, and X_{14} the drug released in 12 h was in the range of 75-85% and shows zero-order kinetics. The drug release was depends on the concentration of Na CMC, i.e., by increasing the concentration of Na CMC the formulation gives more sustaining action. Formulation X_4 containing Na CMC with xanthan gum in the ratio 1:1 gave more sustaining action, i.e., 79.16% in 12 h. From the above study, it was concluded that the presence of Na CMC gives zero-order release kinetics and the linearity ranges from 0.990 to 0.996. It has also good drug entrapment efficiency ranges from 96% to 106% of the drug. The release kinetics of formulations X_1 to X_{14} was shown in Figure 3 and Table 4.

From the above discussion, it was concluded that the formulation containing Na CMC with xanthan gum gives CR of the drug more than 12 h.

SUMMARY AND CONCLUSION

In this investigation, lamivudine matrix tablets were successfully fabricated using selected polymers as detailed in the formulation table and evaluated for its CR properties. From the results obtained, it can be concluded that stable formulation

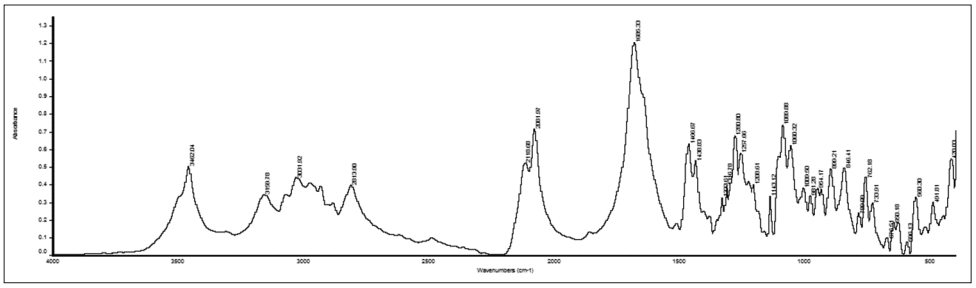

Figure 1: Fourier transforms infrared study of lamivudine

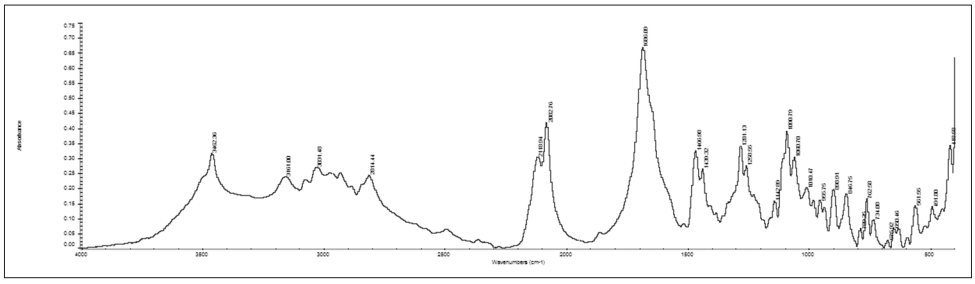

Figure 2: Fourier transforms infrared study of the optimized formulation

Table 3: Physical evaluation of matrix tablet

Formulation batch	Thickness (mm)	Weight variation (%)	Friability (%)	Hardness (kg/cm²)	Drug content (%)
X_1	4.55	±4.0	0.12	7.8±0.13	113.02
X_2	4.54	±2.0	0.39	6.7±0.18	105.93
X_3	4.46	±3.0	0.24	7.3±0.02	95.89
X_4	4.50	±2.0	0.11	9.8±0.01	98.53
X_5	4.53	±3.0	0.43	6.8±0.07	105.12
X_6	4.52	±2.0	0.13	7.2±0.21	95.81
X_7	4.51	±4.0	0.36	6.4±0.35	92.75
X_8	4.47	±4.0	0.24	7.1±0.13	85.53
X_9	4.49	±2.0	0.12	8.7±0.11	100.98
X_{10}	4.50	±2.0	0.39	6.7±0.03	85.94
X_{11}	4.48	±3.0	0.09	7.4±0.16	105.15
X_{12}	4.53	±3.0	0.29	6.5±0.41	98.85
X_{13}	4.52	±3.0	0.18	7±0.32	86.98
X_{14}	4.51	±3.0	0.13	8.5±0.06	102.57
X_{15}	4.55	±4.0	0.31	6.9±0.12	88.65

Table 4: Kinetic values obtained from different plots of formulation X_1-X_{14}

Formulation batch	Correlation coefficient			
	Zero-order	First-order	Higuchi'Plot	Hixon-Crowell plot
X_1	0.987	0.996	0.966	0.997
X_2	0.961	0.994	0.985	0.988
X_3	0.950	0.930	0.954	0.988
X_4	0.990	0.936	0.884	0.962
X_5	0.988	0.803	0.920	0.938
X_6	0.979	0.993	0.978	0.994
X_7	0.991	0.891	0.926	0.944
X_9	0.994	0.931	0.893	0.961
X_{11}	0.992	0.963	0.963	0.982
X_{12}	0.966	0.866	0.952	0.966
X_{14}	0.990	0.931	0.914	0.969

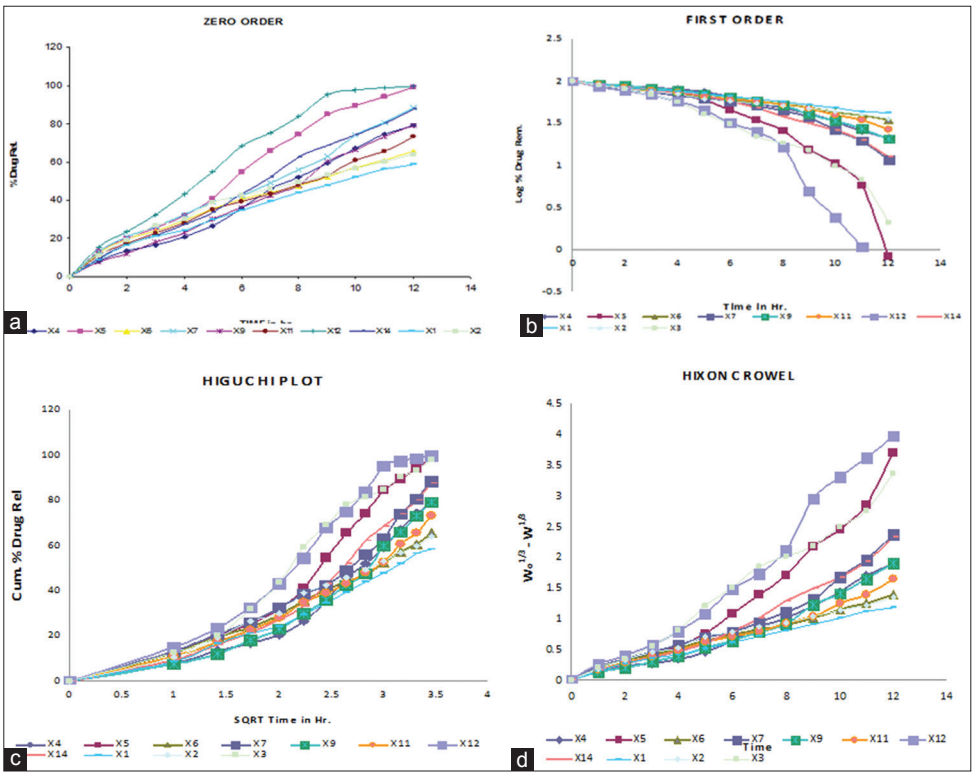

Figure 3: (a-d) Comparative release profile of lamivudine matrix tables

could be developed by incorporating Na CMC with xanthan gum in a definite proportion so that CR profile is maintained for an extended periods of time. Drug release was found to follow a non-Fickian or anomalous release mechanism. Based on the *in-vitro* drug release study, it can be concluded that among the prepared formulations, X_4 is the optimized formulation.

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