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Research Article

Formulation and Evaluation of Sustained Release Lamivudine Matrix Tablets

M. Puli Singh*, Md. Arshiya, J. Anand, Allam Vamshikrishna, Sai Krushna Padhy
Department of Pharmaceutics, Sana College of Pharmacy, Kodad, Nalgonda Dist., Andhra Pradesh-508206, India

***Corresponding author**
M. Puli Singh
Email: **pulising10@gmail.com**

Abstract: The present work is aimed at preparing and evaluating sustained release matrix tablets of Lamivudine using different polymers and polymer combinations. Matrix tablets were prepared by direct compression method taking Carbopol, Ethyl Cellulose, Chitosan, Guar Gum, and Xanthan Gum as polymer as different composition and M1 to M10 total ten formulation were prepared. The powder are evaluated for flow properties and tablet were evaluated for hardness, friability, dissolution rate, kinetics studies etc. In result it was found that the formulation containing Carbopol, Chitosan, Ethyl Cellulose, and HPMC combinations controlled the drug release better than the compositions with Guar Gum and Xanthan Gum combinations.
Keywords: Matrix tablet, Carbopol, Chitosan, Ethyl Cellulose, Direct compression method

INTRODUCTION

Lamivudine drug comes under the class - Nucleoside Reverse Transcriptase Inhibitors (NRTIs). It is a nucleoside analogue, chemically (-)-4-amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one; CAS Reg. NO. 134678-17-4 (Fig-1), which was originally licensed for the treatment of HIV [1]. It is now additionally licensed for the treatment of chronic hepatitis B with evidence of viral replication [2,3]. For the treatment of AIDS, the dosage of conventional oral formulations of Lamivudine is 300mg per day (i.e. 150 mg twice daily, multiple times a day)[4].

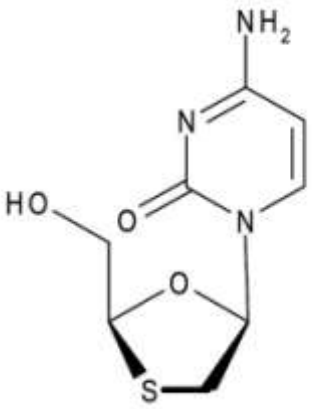

Fig-1: Chemical Structure of Lamivudine

In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release. Modified-release tablets and capsules are commonly taken as once daily doses compared with counterpart conventional forms that may need to be taken three to four times daily to achieve the same therapeutic effect. Typically, controlled release products provide an immediate release of drug, which promptly produces the desired therapeutic effect, which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time [5,6,7]. The term "modified-release drug product" is used to describe products that alter the timing and/or the rate of release of the drug substance. Among various modified release approaches, extended release products were found to be suitable for the Lamivudine.

A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form is called as Extended-release drug product. The types of extended-release dosage forms include controlled-release, and sustained-release dosage forms [8]. The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery [9].

Matrix tablets are an interesting option to develop an oral modified release Lamivudine formulation, because of its simplicity, ease of manufacturing, low cost, high level of reproducibility, stability, ease of scale up, and process validation [10].

So, the present work is aimed at preparing and evaluating sustained release matrix tablets of Lamivudine using different polymers and polymer combinations.

MATERIAL AND METHODS

Drugs and Excipients

Lamivudine, Ethyl Cellulose, Hydroxy Propyl Methylcellulose –Hpmc, Carbopol, Chitosan, Xanthan

Gum, Guar Gum(E412), Microcrystalline Cellulose, Talc(E553b), Magnesium Stearate,

Preparation of Lamivudine Standard graph

Lamivudine (1 to 12 mcg/mL) concentrations were prepared in 6.8 pH phosphate bufeer solutions. The absorbances of above solutions were recorded at λ_{max} (271 nm) using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Compatibility of Lamivudine with drug-polymer

The pure drug and drug-polymer combinations of various physical mixtures were subjected to IR spectroscopy using Fourier Transform Infrared spectrophotometer (Bruker, Germany). Their spectra were obtained over the wave number range of 4000 – 400 cm^{-1}.

Preparation of Matrix Tablet

Matrix tablets were prepared by direct compression method. To prepare the tablets, the ingredients were weighed accurately and were screened through mesh (No.60). Lamivudine and other polymers were mixed in a polybag for 15mins, and the mixture was passed through mesh (No.60), following the addition of diluent MCC and further mixing (5-10mins). The composition of various formulations is given in Table (5-11). Finally, add Talc and Magnesium Stearate to the previous blend and blend it again (15-10mins) for uniform distribution before the compression. Different formulae, having different combinations and ratios of polymers were developed to study the effect of polymer(s) on drug release. Tablets were compressed using 6 station Rotary tablet punching machine with 14 mm oval shape punches.

Table-1: Compositions of Matrix Tablets prepared with Carbopol, Ethyl Cellulose, Chitosan, Guar Gum, and Xanthan Gum

Composition (mg)	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**
Lamivudine	200	200	200	200	200	200	200	200	200	200
Carbopol	80	160	-	-	-	40	80	-	-	-
Ethyl Cellulose	80	-	160	80	-	80	-	80	80	80
Chitosan	-	-	-	80	160	40	80	-	-	-
Guar Gum	-	-	-	-	-	-	-	40	80	-
Xanthan Gum	-	-	-	-	-	-	-	40	-	80
MCC	132	132	132	132	132	132	132	132	132	132
Talc	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
TOTAL	500	500	500	500	500	500	500	500	500	500

MCC-Micro Crystalline Cellulose

Evaluation of Powder [11,12]

Angle of Repose

Angle of Repose was determined by funnel method. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Accurately weight powder blend were taken in the funnel. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation

$\tan\theta = h/r$

h- height, r- radius of the powder cone, θ - angle of repose.

Bulk density (BD)

Accurately weighed amount of blend was transferred to 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following formula-

Bulk density = Weigh of powder/ Bulk volume

Tapped density (TD)

Accurately weighed amount of blend transferred to 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanical tapped density tester which provides a fixed drop. Calculate the tapped bulk density in gm/ml by the following formula-

Tapped density = Weigh of powder / Tapped volume

Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below -

Carr's index (%) = [(TD-BD)*100] / TD

Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flowability of a powder. It is the ratio of tapped density and bulk density. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Husner's Ratio = TD / BD

Evaluation of Matrix Tablet

Weight Variation Test

To study weight variation, individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% Weight variation = $(W_A – W_I) \times 100 / W_A$

Drug Content Uniformity Determination

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 5 tested tablets lies within the range of 97% to 103% of the standard amount. Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100mg) was extracted with pH 6.8 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured by using UV Spectrophotometer (Elico, India) at 271 nm after suitable dilutions.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Thickness

Twenty tablets from the representative batch were randomly taken and individual tablet thickness was measured by using vernier caliper. Average thickness and standard deviation values were calculated.

Friability Test

From each batch, twenty tablets were accurately weighed and placed in the friability test apparatus (Electrolab- friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss. % friability was calculated as follows

% Friability = $(W_1 – W_2) \times 100 / W_1$

W_1 = Initial weight of the 20 tablets, W_2 = Final weight of the 20 tablets after testing.

In-vitro dissolution studies

In-vitro drug release studies were carried out for 3 tablets in each batch by using USP XXII dissolution apparatus type II (Electrolab, TDT-DBL, India) at 100 rpm. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer, maintained at 37 ± 0.5^0c. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Elico, India) at 271 nm. pH 6.8 phosphate buffer was prepared by using 11.45gms of Potassium Dihydrogen Phosphate and 28.8gms of Disodium Hydrogen Phosphate (for 1000ml buffer).

Kinetic Analysis of Dissolution Data [13,14]

To analyze the dissolution data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \qquad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\log C = \log C_0 - K_1 t / 2.303 \qquad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \qquad (3)$$

where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} – Q_t^{1/3} = K_{HC} t \qquad (4)$$

where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

RESULT AND DISCUSSION

The Standard Graph of Lamivudine

The standard graph of Lamivudine has shown good linearity with R^2 value 0.993 in pH 6.8 buffer (Fig-2), which suggests that it obeys the "Beer-Lambert's law".

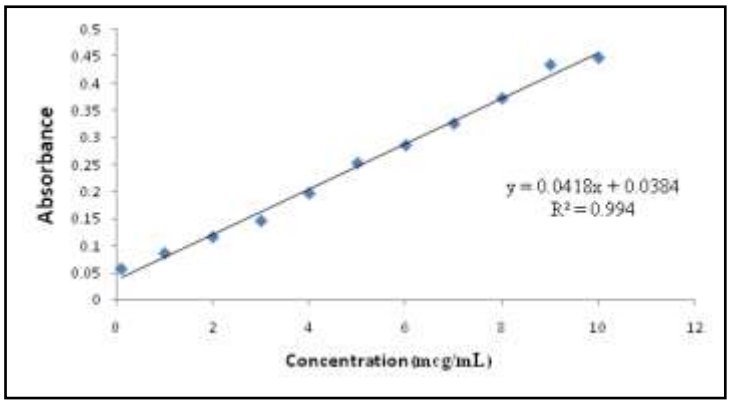

Fig-2: Standard graph of Lamivudine in phosphate buffer (6.8 pH)

Compatability Studies Evaluation of Drug – Polymer interaction

FTIR spectra of pure Lamividine and solid admixtures of Lamividine with dissimilar polymers and their various combinations are given in Fig-3 and Fig-4. The characteristic peak of the carbonyl group (C=O stretching) present in the cystedine nucleus at 1650.07 cm-1, a band peak at 1494.78 cm^{-1} owing C=C stretching (aromatic) confirms the presence of Lamivudine. Characteristic bands peak at 3217.91 cm-1 owing to presence of hydroxy group (O-H streching)/ primary amine (NH_2 stretching). Peaks present at 1287.70 cm-1 and 1160.84 cm-1 owing to oxathiolane ring (asymmetrical and symmetrical C-O-C stretching) of Lamivudine. Peaks present at 1054.70cm^{-1}, 787.30 cm^{-1} owing to primary alcohol (C-O stretching) and primary amine group (N-H bending) respectively, confirms the presence of Lamivudine.

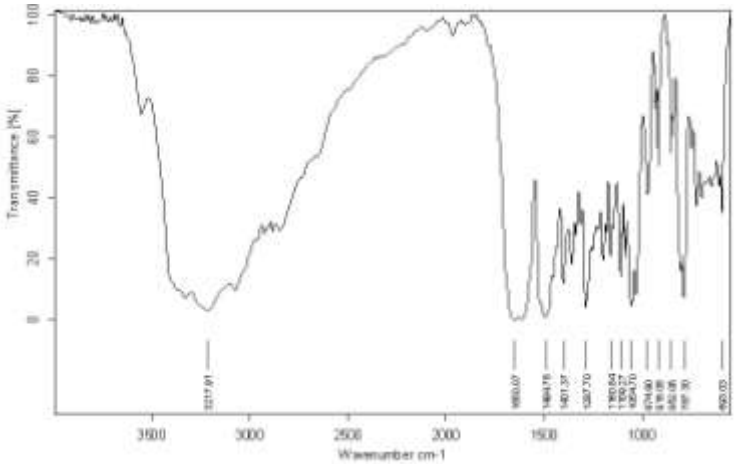

Fig-3: Fourier transform infrared spectra of pure Lamivudine

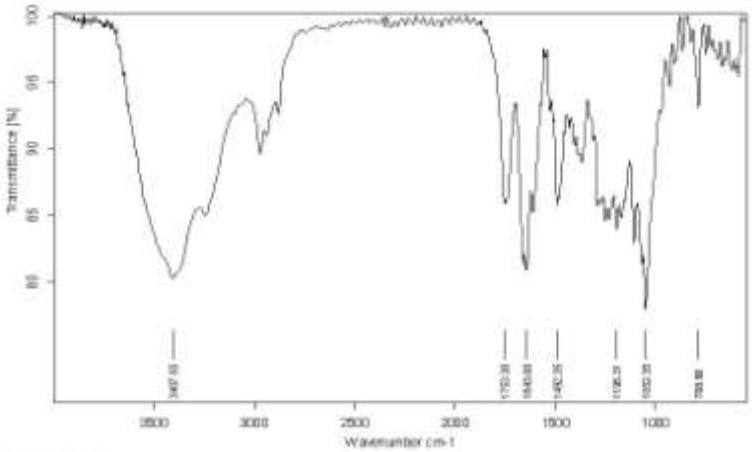

Fig-4: Fourier transform infrared spectra of Lamivudine with Ethyl Cellulose, Carbopol and HPMC

Evaluation of Flow properties

Prepared powder blend of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, and compressibility index given in Table-2.

Table-2: Flow Properties of various batches containing Carbopol, Ethyl Cellulose, Chitosan, Guar Gum, and Xanthan Gum

Powder Blend	Angle of Repose	Bulk Density	Tapped Density	Carr's index %	Hausner's Ratio
M1	28.3	0.491	0.587	16.35	1.197
M2	28.9	0.498	0. 592	15.8	1.188
M3	30	0.492	0.59	16.6	1.199
M4	29	0.489	0.581	15.8	1.188
M5	28.8	0.49	0.583	15.9	1.189
M6	29	0.487	0.593	17.8	1.23
M7	29.1	0.49	0.592	17.2	1.233
M8	31	0.491	0.598	17.8	1.127
M9	30.6	0.497	0.591	15.9	1.189
M10	31.2	0.495	0.596	16.9	1.2

Evaluation of Matrix Tablet

All prepared matrix tablets were evaluated for its uniformity of hardness, weight, friability, content uniformity, and thickness according to official methods[70]. The weight variation was determined by taking 20 tablets using an electronic balance (Schimadzu, Japan). 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 (Electrolab, ET2, India) for 4 minutes at 25 rpm. Results are shown in Table-4.

Hardness, thickness and friability were found to be in range of 4.7 to 5.9, 3.2 to 3.4 (for the formulations with final weight 410mg); 3.8 to 4.2 (for the formulations with final weight 495-500mg) and 0.08 to 0.21 respectively, which showed acceptable ranges in tablet formulation. In a weight variation test, pharmacopoeias limit for the percentage deviation for tablets of more than 155 mg is ±5%. Average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of all the formulation ranged from (4.7 to 5.9) kg/cm^2. Tablets hardness is, however, not an absolute indicator of strength. The percentage friability of the tablets of all the formulations ranged from (0.08% to 0.21%). In the present study, the percentage friability for all for formulations was below 1% w/w, indicating that the friability is within the prescribed limits.

Table-4: Evaluation of Matrix Tablets containing Carbopol, Ethyl Cellulose, Chitosan, Guar Gum, and Xanthan Gum

Formulation Code	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Avg.wt(mg)	Assay (%)
M1	4.9±0.1	3.8±0.1	0.11	502±1.2	99.89
M2	5.5±0.2	4.2±0.2	0.09	503±1.1	100
M3	5.1±0.1	4.2±0.1	0.08	503±1.0	100
M4	5.4±0.1	4.1±0.09	0.09	502±0.9	99.99
M5	5.2±0.2	4.1±0.2	0.09	501±0.8	99.87
M6	5.6±0.2	4.1±0.1	0.10	502±1.0	100
M7	5.8±0.2	3.9±0.1	0.12	500±0.8	99.67
M8	5.2±0.3	4.0±0.2	0.09	501±1.0	99.81
M9	5.5±0.1	3.9±0.1	0.12	500±0.8	99.84
M10	5.2±0.2	4.1±0.09	0.12	501±1.1	99.92

Dissolution Studies

The cumulative percentage drug release for all the formulations were measured at various time intervals, and a graph was plotted against time vs cumulative percent drug release. The formulations M3, M4, M5, M6, M8, and M10 released almost 80% of the drug in the first 1hour. M1 and M9 released the drug 36.3% and 51.5% respectively in the first hour. Formulations with Carbopol and EC, Chitosan and EC, EC and Xanthan Gum, EC and Guar Gum do not controlled the drug release in a proper way, the formulations M2 and M7 (Chitosan and Carbopol) showed good release profile than the others. The combination of Carbopol and Chitosan provided a better drug release profile than the formulations with individual polymer. Almost 97-99% drug was released up to 24hours.

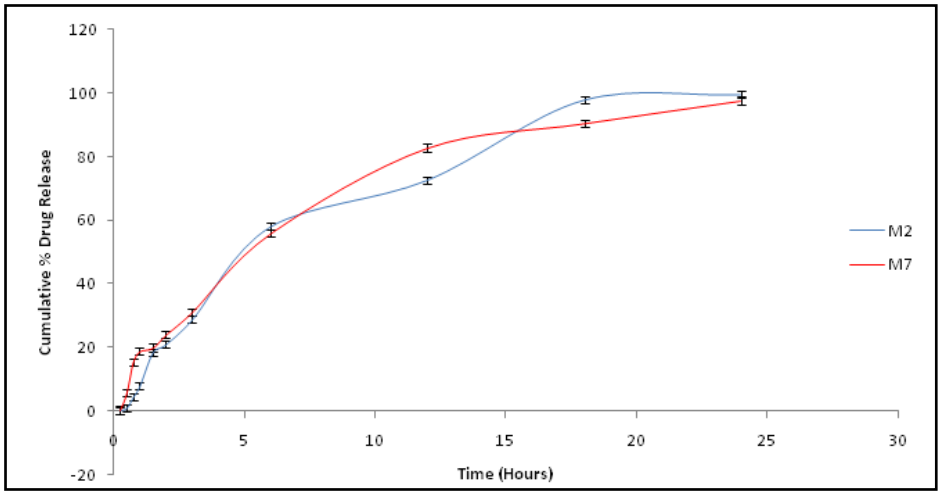

Fig-5: Drug Release Profiles of batches M2 and M7

Kinetic analysis of dissolution data

To evaluate drug release mechanism from the matrix tablets, plots of cumulative percentage release vs square root of time (Higuchi's equation), log cumulative percent release vs log time (Korsmeyer-Peppas) and W_0-Wt (W0-Cube root % drug remaining) vs time (Hixon Crowell) were constructed individually.

Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The applicability of the formulation to the Hixson –Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time. Korsmeyer- Peppas equation indicates the coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

Table-5: Kinetic Values* Obtained From Different Plots of Formulations containing Carbopol, Ethyl Cellulose, Chitosan, Guar Gum, and Xanthan Gum

Formulation Code	Zero Order		First Order		Higuchi	Hixon Crowell	Korsmeyer- Peppas	
	R^2	K_0	R^2	K_1	R^2	R^2	R^2	n
M1	0.610	3.27	0.930	0.082	0.774	0.841	0.774	0.550
M2	0.931	5.57	0.953	0.094	0.971	0.988	0.880	1.173
M3	0.564	1.15	0.891	0.082	0.710	0.862	0.852	0.098
M4	0.770	1.07	0.894	0.079	0.906	0.914	0.976	0.070
M5	0.701	0.74	0.642	0.039	0.789	0.790	0.883	0.053
M6	0.903	0.77	0.824	0.060	0.976	0.974	0.969	0.048
M7	0.899	4.11	0.984	0.064	0.978	0.984	0.770	0.942
M8	0.497	0.78	0.639	0.043	0.655	0.700	0.840	0.066
M9	0.712	2.25	0.935	0.058	0.862	0.897	0.939	0.225
M10	0.702	0.64	0.685	0.044	0.820	0.864	0.928	0.045

(n=Slope)

From the Table-5, we can conclude that formulations M1, M2, M3, M4, M7, M8 and M9 follow the first order release (The regression coefficients obtained for first order kinetics were found to be higher when compared with those of zero order kinetics) indicating that the rate of drug release is concentration dependent, and formulations M5, M6 and M10 follow zero order release, indicating that rate of drug release is independent of concentration.

Among all the formulations M1 (Carbopol and Ethyl Cellulose in 1 1 ratio), M2 (only Carbopol), M3 (only Ethyl Cellulose) and M7 (Carbopol and Chitosan in 1 1 ratio) showed high R^2 values in Hixon Crowell equation; hence the release mechanism involves dissolution control, i.e. erosion process as per Hixon Crowell model. Formulations M4 (Ethyl Cellulose and Chitosan in 1 1 ratio), M5 (only Chitosan), M8 (Ethyl Cellulose, Guar gum and Xanthan gum in 1 0.5 0.5 ratio), M9 (Ethyl Cellulose and Guar gum in 1 1 ratio) and M10 (Ethyl Cellulose and Xanthan gum in 1 1 ratio) showed high R^2 values in Korsmeyer- Peppas equation; hence the release mechanism is a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process. Among all the formulations only M6 (Carbopol, Ethyl Cellulose and Chitosan in 0.5 1 0.5 ratio) followed Higuchi model, so the release mechanism is a diffusion process, i.e. diffusion controlled drug release.

All the formulations except M2 and M7 followed Fickian diffusion ($n < 0.45$). M2 and M7 showed higher n values ($n > 0.89$), so they followed Super case-II transport refers to the erosion of the polymeric chain.

CONCLUSSION

Identification of the active pharmaceutical ingredient Lamivudine was done by using FTIR spectroscopy. Then it is subjected to preformulation study, which encompasses the "Drug-polymer compatibility study" and the results obtained with selected all polymers showed good compatibility with Lamivudine. Results of angle of repose indicated good flow properties. This was further supported by lower Carr's index values and Hausner's ratio values; which indicate good flow and compressible properties. The direct compression method yielded uniform and reproducible matrix tablets with all the polymers used. The hardness, friability, weight variation and drug content assay were uniform and reproducible. All were found within the limits. Finally, in dissolution study it was found compositions which contain Carbopol, Chitosan, Ethyl Cellulose, and HPMC combinations controlled the drug release better than the compositions with Guar Gum and Xanthan Gum combinations.

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