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Formulation and evaluation of gum based matrix tablets of Lamivudine

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ABSTRACT

The present investigation is aimed at formulating and evaluating gum based sustained release matrix tablets of Lamivudine using different natural polymers such as Guar gum, Xanthan gum, Rosin gum, Pectin, and Sodium alginate taken at 30%, 40% and 50% of the total weight of the tablet. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). It was found that the cumulative percent drug release decreased with increasing concentration of natural gums. All the formulations were able to retard the release of the drug beyond 18 hours except pectin and sodium alginate were unable to sustain the drug release from the matrix tablets. F5 (40% Xanthan Gum) formulation was selected as optimized formulation. The swelling study states that the swelling index was increased up to 6 hours and there after that the swelling index was decreased. No chemical interaction between Drug and the gum were seen as confirmed by FT-IR studies. Thus, sustained release matrix tablets of Lamivudine using natural Biodegradable and biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

Keywords: Lamivudine, Sustain release, Natural gums,

INTRODUCTION

Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). It belongs to class III of the BCS Classification with High solubility and low permeability. Pharmaceutical research since 1950 turned to a new era towards optimizing the efficacy of the drug by designing the drug in different dosage forms posing challenges to the pharmaceutical technologists. The oral conventional types of drug delivery

systems are known to provide a prompt release of drug [1-2]. Therefore, to achieve as well as to maintain the drug concentration with in the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery systems several times a day. This results in a significant fluctuation in drug levels often with sub-therapeutic and/or toxic levels and wastage of drug. 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 [3-8].

Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor (nRTI) and it is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine is rapidly absorbed with a bio-availability of over 80% following oral ingestion. The drug half-life in plasma is approximately 5-7 hours. It is bound to plasma proteins less than 36%. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B [8].

MATERIALS AND METHODS

Materials: Lamivudine , Xanthan gum, pectin gum, rosin gum, guar gum, Microcrystalline cellulose, Magnesium Stearate, Talc.

Calculation of Sustained-Release Dose of lamivudine

The total dose of lamivudine for once-daily SR formulation was calculated by Robinson Eriksen [3] equation using available pharmacokinetic data.

Hence an oral controlled release formulation of lamivudine should contain a total dose of 200 mg and should release 88 mg in first 1 hour like conventional tablets, and 11.55 mg/h up to 12 hours thereafter.

Preparation of Lamivudine Matrix Tablets

All the matrix tablets, each containing 200 mg of Lamivudine, were prepared by direct compression method.

Direct compression method. Pre weighed ingredients were passed through Sieve no. 60 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed in a polythene bag for 15 minutes to get a uniform mixture. Talc and magnesium stearate were added to the powder mixture and compressed on a 16- station tablet compression machine using 10mm round flat face punch.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 400 mg with different drug polymer ratios like 1:0.6, 1:0.8, and 1:1. The various polymers used were Guar gum, Xanthan gum, Rosin gum, Pectin, and Sodium alginate.

In the formulations prepared, the release retardants included were Guar gum, Xanthan gum, Rosin gum, Pectin, and Sodium alginate. Microcrystalline cellulose (MCC) is used as diluent. Magnesium stearate 1% and talc 2 % were used as lubricant and glidant [9].

Evaluation of Precompression Blend

Angle of Repose

The angle of repose of granules was determined by the fixed funnel-method. The accurately weighed physical mixture was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation .

$$\tan\theta = h/r$$

where h and r are the height and radius of the powder cone, θ is the angle of repose.

Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal [5].

The bulk density and the tapped density were calculated using the following formulae.

$$\text{Bulk density} = W/V_{0,} \qquad \text{Tapped density} = W/V_f$$

where, W= Weight of the powder

V_0 = Initial volume, V_f = final volume

Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable [5]

$$CI = (TD-BD) \times 100/TD$$

where, TD is the tapped density and BD is the bulk density.

Table 1. Composition of Matrix Tablets Containing Guar gum, Xanthan gum, and Rosin Gum

Formulation code	Drug (mg)	Guar Gum (mg)	Xanthum Gum (mg)	Rosin Gum (mg)	Avicel pH 101(mg)	Tablet weight(mg)
F1	200	120	-	-	68	400
F2	200	160	-	-	28	400
F3	200	200	-	-	-	≅400
F4	200	-	120	-	68	400
F5	200	-	160	-	28	400
F6	200	-	200	-	-	≅400
F7	200	-	-	120	68	400
F8	200	-	-	160	28	400
F9	200	-	-	200	-	≅400

Total tablet weight to polymer concentration is 30%, 40%, and 50% All formulations contain magnesium stearate 1% and talc 2% .

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties[5]. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. And greater than 1.5 indicates that poor flow, in between these values passable.

Table 2. Composition of Matrix Tablets Containing Pectin and Sodium alginate

Formulation code	Drug(mg)	Pectin(mg)	Sodium alginate(mg)	Avicel pH101(mg)	Tablet weight (mg)
F10	200	120	-	68	400
F11	200	160	-	28	400
F12	200	200	-	-	≅400
F13	200	-	120	68	400
F14	200	-	160	28	400
F15	200	-	200	-	≅400

**Total tablet weight to polymer concentration is 30%, 40%, and 50%.*
** All formulations contain magnesium stearate 1% and talc 2%.*

Evaluation of Matrix Tablets

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper [10].

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.

Friability Test

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

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

where W_1 = Initial weight of the 10 tablets.
W_2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable [10].

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.

$$\% \text{ weight variation} = (W_A - W_I) \times 100 / W_A$$

Drug Content Uniformity (Assay)

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 10 tested tablets lies within the range of 90% to 110% of the standard amount.

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 400 mg of lamivudine matrix tablet was transferred to a conical flask containing 100ml of pH 6.8 phosphate buffer solution. It was shaken by mechanical means for 24h.Then it was filtered through a Whatman filter paper (No. 1) and appropriate dilutions were made and the absorbance was measured at 268nm by using double beam UV-VIS spectrophotometer.

In -Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus (Basket method) at 100 rpm in 900 mL of phosphate buffer pH 6.8 throughout the dissolution up to 24 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 268 nm [11].

Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release 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 . 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 .

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

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

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \qquad (2)$$

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.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model); Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time (Higuchi model); And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law) [4].

Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms [4].

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table 10, for the cylindrical shaped matrices. 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 release .

Mean Dissolution Time

Due to the difference in drug release kinetics, the constant k, though one of the measure of release rate, should not used for comparison. Therefore, to characterize the drug release rates in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution according to Mockel and Kippold using the following equation:

$$MDT = (n/n+1)k^{-1/n}$$

Where n is the release exponent and k is the kinetic constant calculated from Korsmeyer equation.

Swelling Studies

The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in Petri dish containing 20-25 ml of pH 6.8 phosphate buffer. At the end of 2, 4, 6, 8, 10 and 12 hours tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula.

$$SI = 100(W_w – W_i) / W_i$$

where SI is the swelling index, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively[11-21].

FourierTransmission Infra Red (FTIR) Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

The physical mixture for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 3). Angle of repose was less than 25° and Carr's index values were greater than 25 for the powder of all the batches indicating excellent to poor flowability and compressibility. Hausner's ratio was found to be between 1.4 to1.7 for all the batches indicating that passable to poor flow properties. The drug content was more than 95 % for all the different formulations.

Table 3. Physical Properties of Pre compression Blend

Formulation code	Angle of repose(θ)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)
F1	20.85±0.34	0.499±0.56	0.75±0.45	1.50	33.466
F2	21.34±1.23	0.48±1.09	0.803±1.01	1.6	40.22
F3	22.54±0.98	0.53±0.98	0.785±0.89	1.47	32.48
F4	21.12±1.34	0.520±0.54	0.736±0.62	1.40	29.34
F5	20.23±1.1	0.524±0.67	0.76±0.92	1.46	31.05
F6	22.67±0.56	0.526±0.49	0.73±0.69	1.40	27.94
F7	20.89±1.56	0.405±0.13	0.685±0.57	1.68	40.87
F8	20.13±0.98	0.409±0.23	0.71±0.27	1.73	42.39
F9	20.67±1.98	0.414±0.56	0.695±0.19	1.68	40.43
F10	21.54±0.87	0.43±0.57	0.71±1.56	1.65	39.43
F11	21.98±0.78	0.49±0.91	0.69±0.09	1.40	28.98
F12	22.67±0.64	0.501±1.01	0.72±0.18	1.44	30.41
F13	21.45±0.76	0.44±0.98	0.71±1.51	1.61	38.02
F14	20.98±0.78	0.42±0.57	0.73±0.96	1.73	42.46
F15	20.56±1.67	0.41±0.29	0.72±0.94	1.75	43.05

Physical Evaluation of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 4. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 398.5mg and 405.5 mg. The hardness of the tablets ranged from 4.0 to 6 kg/cm^2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 3.30 to 4.31mm. All the formulations satisfied the content of the drug as they contained 95 to 99 % of lamivudine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control [18].

Table 4. Physical Evaluation of Matrix Tablets

Formulation code	Hardness ±SD †	Wt variation ±SD ‡	Friability	Thickness ±SD ‡	Assay ± SD*
F1	5.8±0.57	398.5±0.70	0.18	3.71±0.02	97.6±1.20
F2	4.0±0.50	400.0±1.41	0.27	4.23±0.01	96.0±0.63
F3	4.8±0.28	400.5±3.51	0.31	4.31±0.01	95.93±0.46
F4	4.3±0.28	398.5±0.70	0.67	3.32±0.02	99.61±1.28
F5	5.3±0.28	405.5±0.70	0.65	4.11±0.00	98.23±0.77
F6	5.0±0.2	400.5±2.10	0.71	4.36±0.01	97.96±1.28
F7	5.8±0.28	400.0±1.41	0.85	4.03±0.15	97.41±1.15
F8	4.8±0.28	398.5±3.51	0.62	4.17±0.02	99.93±1.31
F9	4.0±0.11	400.0±2.82	1.09	4.16±0.00	96.36±1.22
F10	4.3±0.15	401.2±1.56	0.69	4.06±0.13	98.98±0.79
F11	4.5±1.23	399.6±0.34	0.87	4.09±1.21	99.67±0.89
F12	4.3±2.01	400.9±1.43	0.65	4.17±1.23	98.96±1.21
F13	4.6±1.54	400.1±0.98	0.76	4.19±0.98	99.78±1.23
F14	4.57±0.78	399.78±0.67	0.86	4.09±1.14	98.67±1.89
F15	4.5±0.16	400.0±1.82	0.59	4.13±0.00	96.36±1.22

** All values represent mean ± Standard Deviation (SD), n=3*
† All values represent mean ± Standard Deviation (SD), n=6
‡ All values represent mean ± Standard Deviation (SD), n=20

Table 5. In-Vitro Release Data of Lamivudine from Guar gum Matrices*

Formulation code	F1	F2	F3
0	0	0	0
1	25.81±3.90	13.32±1.88	14.04±2.49
2	34.34±1.57	23.39±1.38	21.40±2.04
4	46.77±2.10	36.25±3.35	34.16±4.55
6	57.30±2.22	46.10±2.48	42.64±1.16
8	62.97±1.24	60.49±0.91	50.43±0.92
10	69.44±0.74	63.26±0.80	60.32±1.05
12	73.37±2.23	71.60±1.85	71.16±1.31
18	79.06±1.64	74.07±1.11	73.98±0.43
24	83.48±1.39	80.26±1.12	76.26±1.54

**All values represent mean cumulative percent drug released ± SD (n=3)*

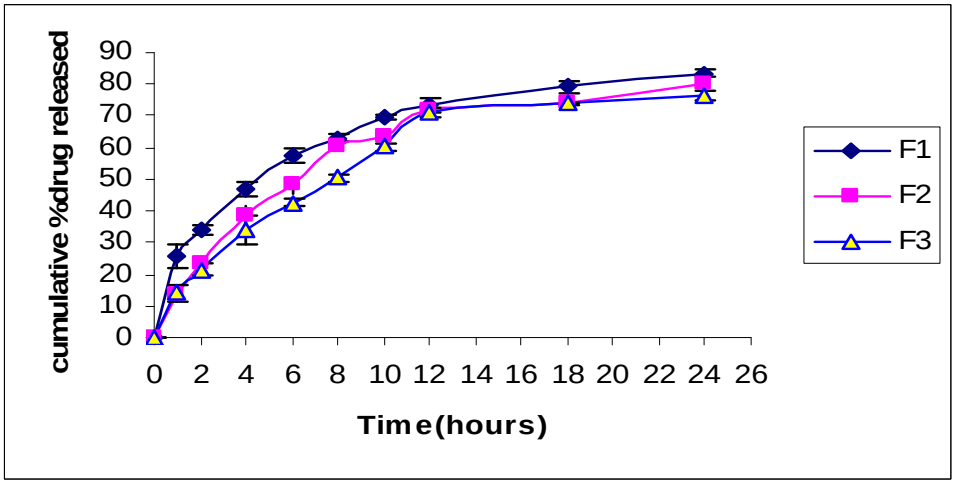

Figure 1. Release Profiles of Lamivudine from Guar gum Matrices

In-Vitro Drug Release Studies

Drug Release from Guar gum Matrices

The results of release studies of formulations F1 to F3 are shown in Table 15 and Figure 6. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F1 composed of drug polymer ratio of 1:0.6, beyond 18h. Formulations with drug polymer ratios 1:0.8 (F2), 1:1 (F3) have extended the drug release for 24h.

Drug Release from Xanthan gum Matrices

The results of release studies of formulations F4 to F6 are shown in Table 16 and Figure 7. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F4-F6 composed of drug polymer ratio of 1:0.6, 1:0.8, 1:1 have extended the drug release up to 24h. These formulations the swelling of the polymer is high than that of guar gum matrices. F4 formulation showed the 40% of the drug is released in first one hour.

Table 6. In-Vitro Release Data of Lamivudine from Xanthan gum Matrices*

Formulation code	F4	F5	F6
0	0	0	0
1	41.86±1.63	23.02±1.91	18.65±1.51
2	53.09±5.44	36.12±2.80	25.21±25.21
4	62.21±4.97	45.93±2.82	42.23±5.14
6	66.65±0.86	56.14±0.72	52.56±1.29
8	68.83±0.90	62.09±1.12	59.73±0.53
10	72.39±1.93	72.75±0.89	70.02±0.49
12	77.13±1.60	77.72±1.37	76.15±0.66
18	80.54±1.40	79.90±0.52	78.89±0.76
24	85.94±2.70	82.39±2.29	82.84±2.49

**All values represent mean cumulative percent drug released ±SD (n=3)*

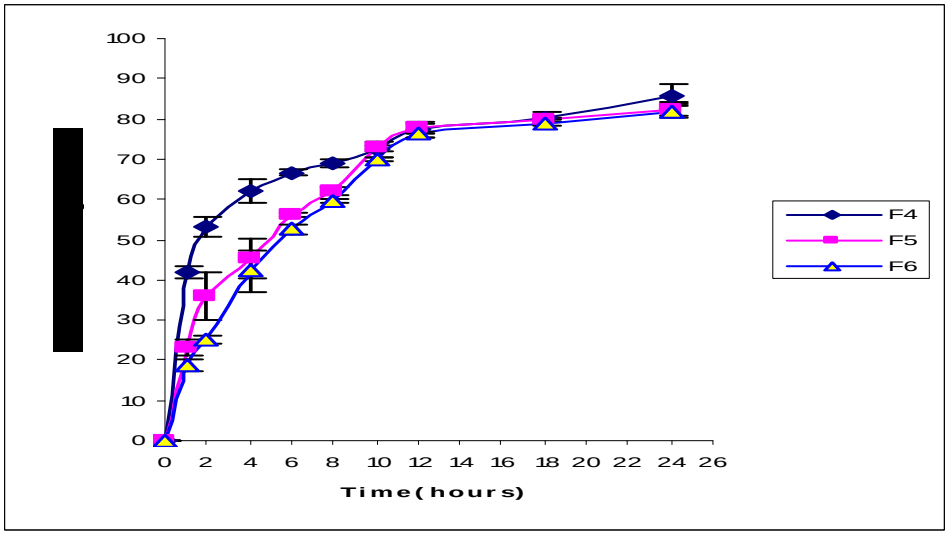

Figure 2. Release Profiles of Lamivudine from Xanthan gum Matrices

Drug Release from Rosin gum Matrices

The results of release studies of formulations F7 to F9 are shown in Table 17 and Figure 8. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F7-F9 composed of drug polymer ratio of 1:0.6, 1:0.8, 1:1 have extended the drug release up to 24h. Rosin gum is a hydrophobic natural polymer so it does not show any swelling behavior in dissolution study. It is moisture sensitive so when preparing the matrix tablets it shows the lamination and capping problems. So avoid the physical mixture exposed to moisture to avoid the lamination and capping problem [15].

Table 7. In-Vitro Release Data of Lamivudine from Rosin gum Matrices*

Formulation code	F7	F8	F9
0	0	0	0
1	29.17±5.62	26.47±2.29	24.45±1.13
2	48.86±1.04	47.64±0.73	29.96±1.83
4	62.10±0.94	53.87±1.11	37.83±2.01
6	65.07±1.17	58.99±0.56	40.73±1.48
8	69.96±1.80	62.52±0.48	47.96±1.76
10	75.03±0.24	68.15±1.53	53.48±1.21
12	77.59±0.19	71.19±1.60	60.22±0.78
18	79.67±0.09	74.93±1.31	64.35±2.19
24	82.29±0.16	77.37±0.89	72.53±1.19

**All values represent mean cumulative percent drug released ±SD (n=3)*

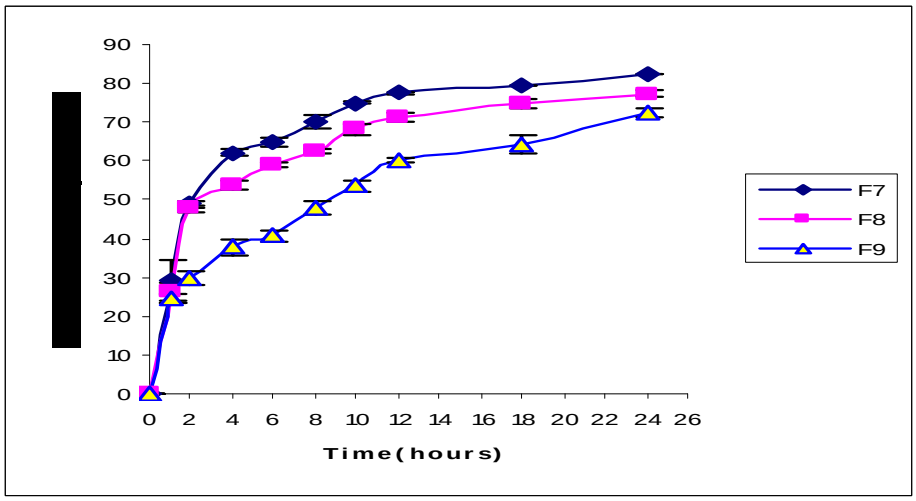

Figure 3. Release Profiles of Lamivudine from Rosin gum Matrices

Drug Release from Pectin Matrices

The results of release studies of formulations F10 to F12 are shown in Table 18 and Figure 9. Formulation F10-F12 composed of drug polymer ratio of 1:0.6, 1:0.8, 1:1 have extended the drug release only up to 8h. These formulations could not sustain the drug release.

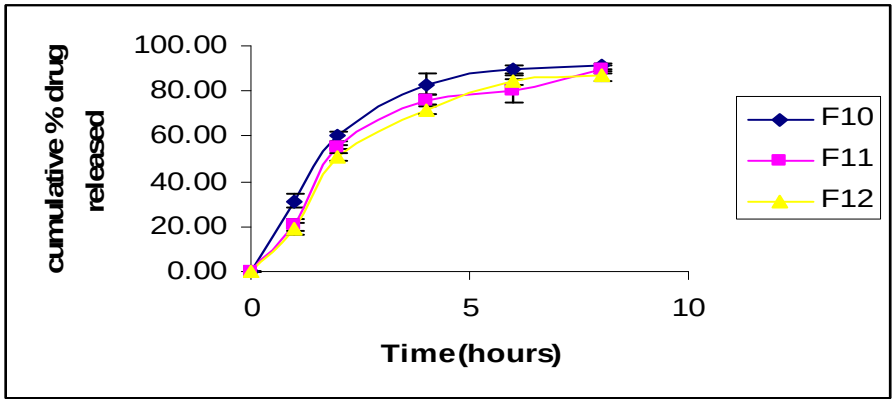

Figure 4. Release Profiles of Lamivudine from Pectin Matrices

Table 8. In-Vitro Release Data of Lamivudine from Pectin Matrices*

Formulation code	F10	F11	F12
0	0	0	0
1	31.15±3.12	20.62±2.69	19.02±4.03
2	60.06±2.04	55.16±2.73	50.86±1.13
4	83.09±5.04	75.87±1.51	71.95±1.31
6	89.59±1.57	79.91±0.86	84.56±0.65
8	91.06±1.09	89.71±3.08	86.65±0.76

**All values represent mean cumulative percent drug released ±SD (n=3)*

Table 9. In-Vitro Release Data of Lamivudine from Sodium alginate Matrices*

Formulation code	F10	F11	F12
0	0	0	0
1	25.52±2.35	32.50±2.56	30.79±1.56
2	65.58±1.65	66.43±4.65	62.51±4.06
4	81.26±2.75	76.23±2.78	73.78±1.75
6	84.93±4.01	79.42±2.86	76.36±2.09
8	88.85±2.30	83.09 ±4.08	77.70±3.31

**All values represent mean cumulative percent drug released ±SD (n=3)*

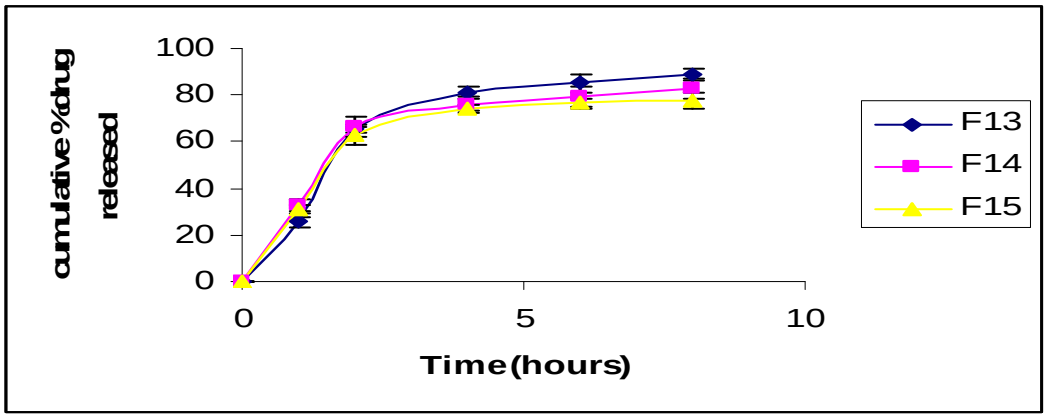

Figure 5. Release Profiles of Lamivudine from Sodium alginate Matrices

Drug Release from Sodium alginate Matrices

The results of release studies of formulations F13 to F15 are shown in Table 19 and Figure 10. Formulation F13-F15 composed of drug polymer ratio of 1:0.6, 1:0.8, 1:1 have extended the drug release only up to 8h. These formulations could not sustain the drug release [18-21].

Out of total 15 batches, the drug release was extended up to 24 hours for the formulations F3, F5, and F7. So, these three formulations selected for further studies like kinetic data analysis. Out of these three formulations F5 and F7 selected as optimized formulations. F5 is optimized formulation.

Kinetic analysis of dissolution data

The release rate kinetic data for the F5 is shown in Table 20. As shown in Figures 11-15, drug release data was best explained by Higuchi's equation (r^2 = 0.94). Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. Mean Dissolution Time of F5 formulation is found to be 3.88 [12-16] .

Mechanism of drug release

As shown in Figure 5, the corresponding plot (log cumulative percent drug release vs log time) for the Korsmeyer-Peppas equation indicated a good linearity (r^2 = 0.9642). The diffusion exponent n was 0.38, which appears to indicating a coupling of the diffusion and erosion mechanism (Quasi fickian diffusion) and may indicate that the drug release was controlled by more than one process.

Table 10. Drug Release Kinetics of Optimized (F5) Matrix Tablets*

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2	n	K_{KP} (h^{-n})
0.7312	3.0132	0.8778	0.072	0.94	17.791	0.8512	0.0722	0.9642	0.38	0.3658

* *r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.*

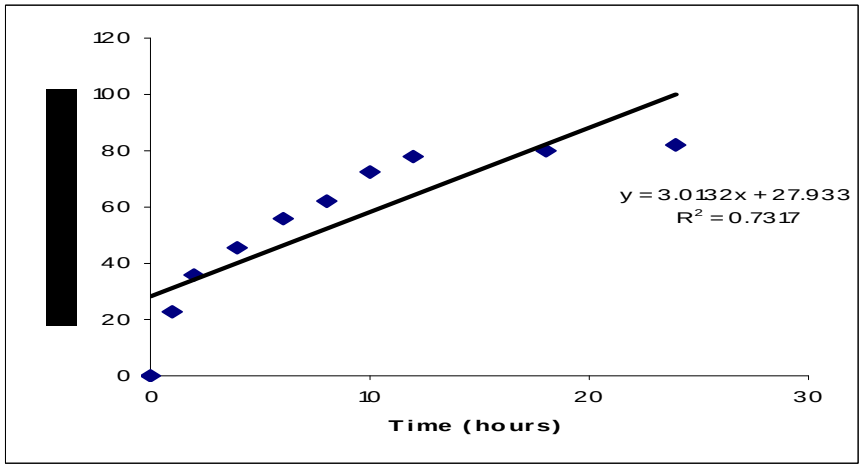

Figure 6. Zero Order Graph of Optimized Formulation (F5)

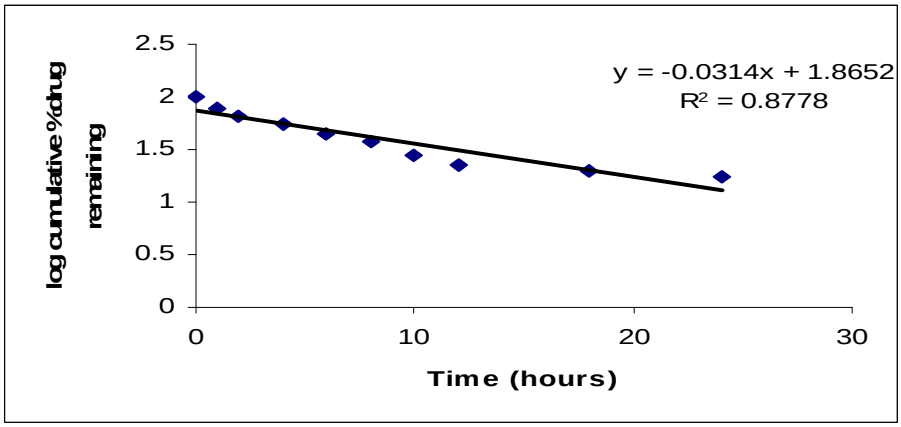

Figure 7. First Order Graph of Optimized Formulation (F5)

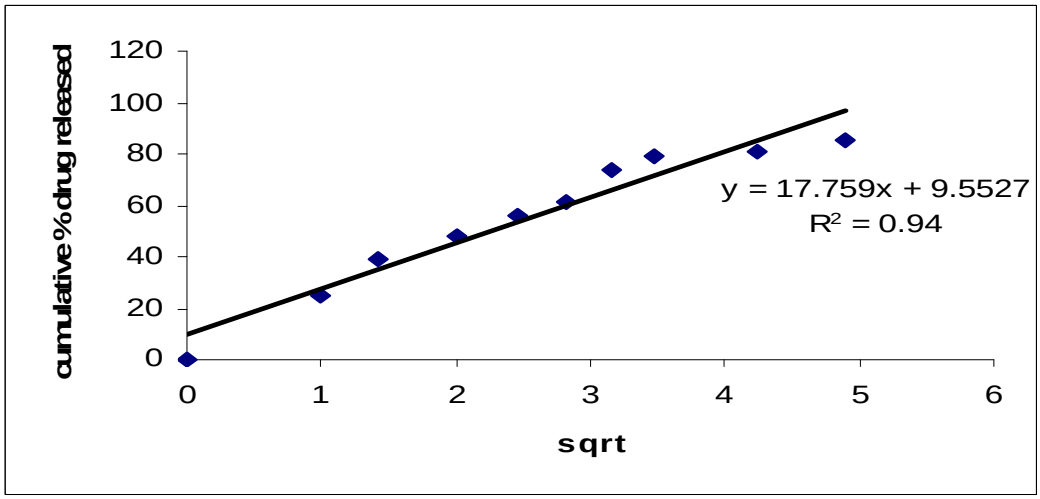

Figure 8. Higuchi Plot of Optimized Formulation (F5)

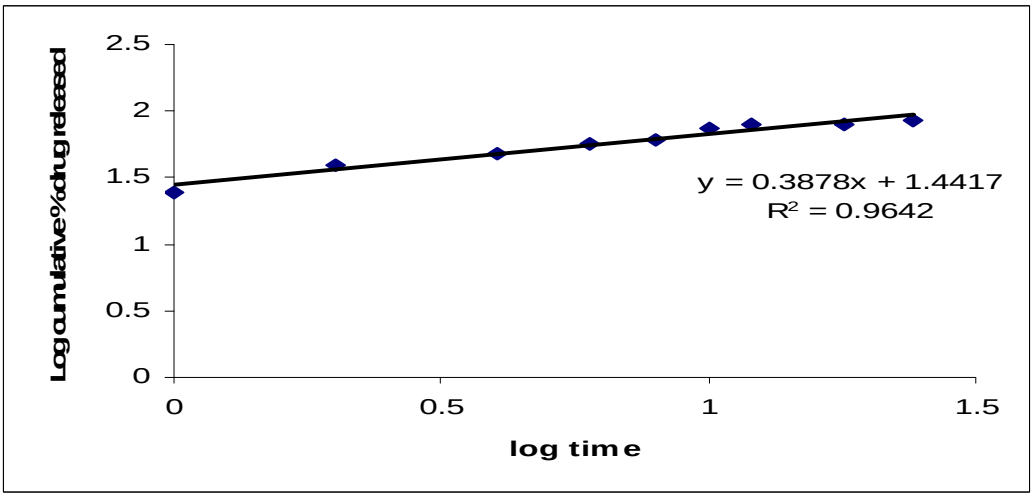

Figure 9. Korsmeyer-Peppas Graph of Optimized Formulation (F5)

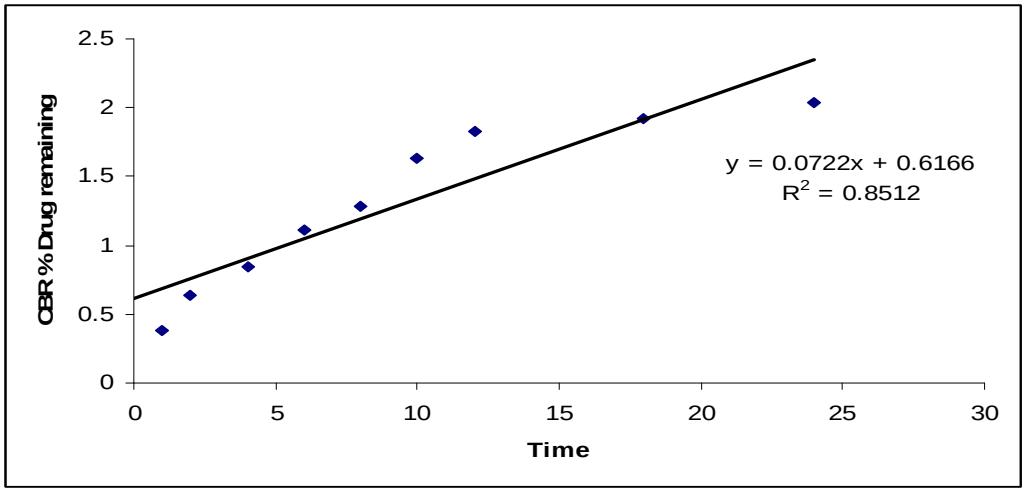

Figure 10. Hixson-Crowell Plot of Optimized Formulation (F5)

Determination of swelling behavior

Since the rate of swelling is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously with the swelling study, of polymer was determined. The percentage swelling of optimized tablet was shown in Figures16, and data was given in Table 21. Maximum swelling was observed in first 2 hours and gradually it was decreased

Table 11. Swelling Study of Optimized Formulation (F5)

Time (hours)	% Swelling
2	145.32
4	236.33
6	238.66
8	185.09
10	164.31
12	133.94

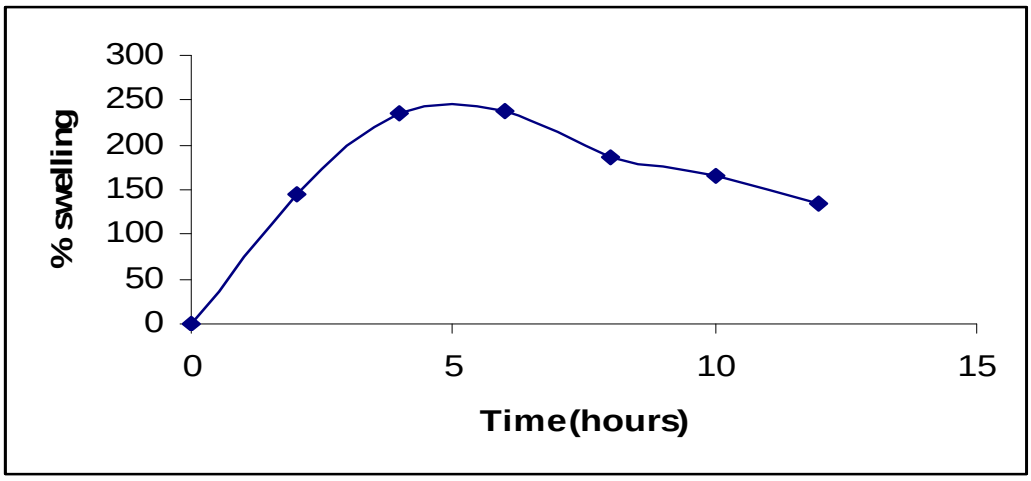

Figure11. Swelling Study of Optimized Formulation (F5)

Fourier transform infrared spectroscopy (FT-IR)

FTIR spectra of the drug and the optimized formulation were recorded in range of 4000-400 cm^{-1}. FTIR spectra of pure Lamivudine and solid optimized formulation (F5) with various excipients used in the preparation of CR tablet formulations, characterized are given in Figure16 and 17. The Lamivudine shows some prominent and characteristic peaks. The peaks at 1649 cm^{-1} is due to stretching vibrations of the carbonyl group (present in the cytidine nucleus C=O). A band of peaks at 3327, 3257, and 3199 cm-1 owing to primary amino, amino and hydroxyl groups; and peaks at 1286 and 1058 cm-1 owing to asymmetrical and symmetrical stretching of the C-O-C system (present in the oxathiolane ring), respectively, in all the spectrum, indicate the stable nature of Lamivudine. In the optimized formulation, the presence of all the characteristic peaks of the Lamivudine indicates that no interaction was occurred between the drug and the excipients [15-21].

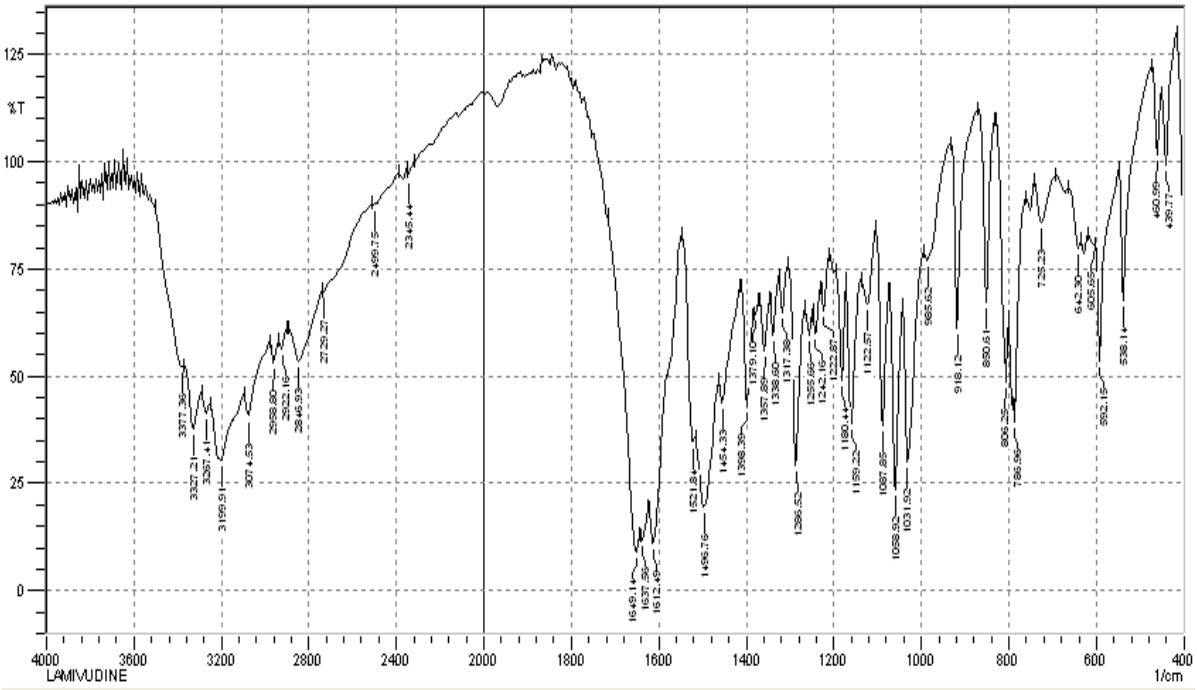

Figure 12.FTIR spectrum of Lamivudine

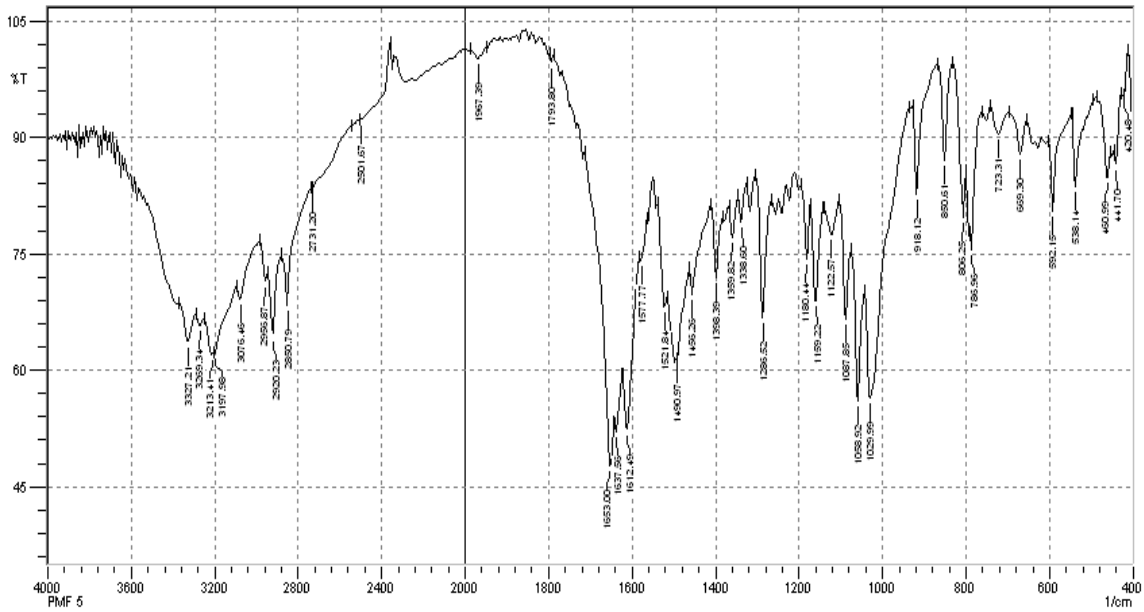

Figure 13. FTIR spectrum of Optimized formulation

CONCLUSION

Results of the present study demonstrated that both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of Lamivudine. Among the hydrophilic matrix formers, the rate of drug release was in the following order Guar gum>Xanthan Gum. The drug release rate was slower with hydrophobic Rosin gum when compare with hydrophilic gums. Majority of formulations have released the drug by non-Fickian diffusion. Optimized formulation F5 (drug to polymer ratio 1:0.8) which includes 40% Xanthan gum has successfully sustained the drug release for 18-24 hours and the drug release pattern was similar to theoretical release profile. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.38 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time, as indicated in Hixson-Crowell plot. FTIR studies proved the no chemical interaction in drug and polymer of the developed matrix tablets. Thus, sustained release matrix tablets of Lamivudine using natural Biodegradable and biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

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