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## Design and Characterization of Matrix Tablets of Lamivudine by Using Natural Polymers for Controlled Release

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### ABSTRACT

The purpose of this research was to prepare and evaluate controlled drug delivery system of Lamivudine. Controlled release matrix tablets of Lamivudine were developed to prolong drug release time and to enhance its bioavailability. Lamivudine controlled release matrix tablets were prepared by wet granulation technique with cashew nut tree gum and *Moringa oleifera* in different ratios. Lamivudine controlled release granules were prepared and evaluated for the angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. All the formulation showed good flow properties. The compressed tablets were evaluated for the hardness, uniformity of weight, friability, drug content and in-vitro dissolution studies. All the formulations were in compliance with pharmacopeial standards. Through FTIR & DSC studies it was confirmed that there was no interaction between drug, polymer and other excipients. Among all the formulations F3 (i.e., drug and cashew nut tree gum ratio 1:1) showed prolong release when compare to the other formulations. The drug release kinetics followed zero order. The diffusion exponent (n) values are found to be more than 0.5 ( $n > 0.5$ ) which indicated that the drug release was predominantly controlled by non fickian diffusion.

**Keywords:** Controlled Release, Anti HIV agent, Matrix Tablets, Lamivudine, *Moringa oleifera* gum, *Anacardium occidentale* gum, *Delonix regia* seed gum.

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## INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians. In long-term therapy 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 tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects and increase the safety margin for high-potency drugs [2].

Lamivudine (Figure.1) is a potential anti- HIV agent, used for the long term treatment of HIV-1 infection as well as for the treatment of chronic Hepatitis B. It has an elimination half-life of around 5-7 hours[3]. Lamivudine requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable candidate for matrix formulation. Matrix based CR formulations are the most popular and easiest to formulate on commercial scale.

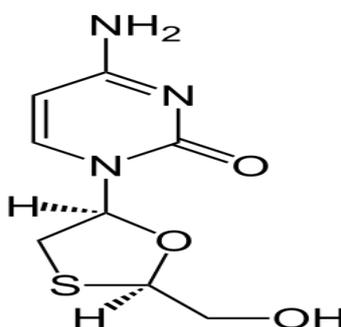


Figure 1: Chemical Structure of Lamivudine

## MATERIALS AND METHODS

**Materials:** Lamivudine was a gift sample from Mylan Laboratories, Hyderabad. PVP K-30, lactose, talc and magnesium stearate were purchased from S. D. Fine Chemicals Ltd (Mumbai, India). All other ingredients were of analytical grade.

### Methods:

#### A) Isolation and Purification of Natural Gums

Occasionally plant polysaccharides are available naturally in a relatively pure form. This is true of the various gums and mucilages exuded from the bark of trees and also from the seeds and fruits. Such gums can often be purified simply by dissolving in water, dialysing to remove low molecular weight compounds, precipitating by pouring into ethanol and collecting and drying.

##### i) *Cashew nut tree gum*[4]

The collected crude cashew nut tree gum (100g) was crushed by using mortar and pestle. The crushed gum was dissolved in water (300ml). The solution was filtered through several folds of muslin cloth and the filtrate was collected. To the filtrate, alcohol (90% v/v) was added in 1:1 ratio and precipitate was obtained. The precipitate was filtered and dried in a hot air oven at 45<sup>o</sup>C. 100 g of powder obtained was dissolved in 100 ml water, filtered through several folds of muslin cloth. Then the filtrate was centrifuged at 3000 rpm for 10 minutes and the supernatant layer was collected, evaporated and dried to obtain solid mass. This mass was passed through 80 # sieve and stored in an air tight container for further studies.

##### ii) *Moringa oleifera tree gum* [5]

The gum was collected from incisions of trees. The gum was dried and crushed by using mortar and pestle. It is passed through sieve no.100. Dried gum was stirred in distilled water (300ml) for 4 – 5 hours at

room temperature. The supernatant layer was obtained by centrifugation. The residue was washed with water; this procedure was repeated for three times. Finally the supernatant layer was made up to 500ml and treated with twice the volume of acetone by continuous stirring. The precipitate material was washed with water and dried at 50 – 60 °C under vacuum.

### iii) *Delonix regia* seeds endosperm gum [6]

The pods of *Delonix regia* were collected and these pods were imbibed in the water for an overnight to separate the seeds from the pods. The seeds mainly contain the three parts seed kernel, endosperm, and dicotyledon. The seeds (500g) were boiled in the distilled water for 3 hrs until the seed kernels were swelled which was then removed by the hands. The gum part was separated from the yellow dicotyledons. The gum portion was dried in an oven at 45°C for 12 hrs and then was grounded in the multi mill. The resulting powder was passed through 60 # sieve.

## B) Physicochemical & Phytochemical Characterization of Gums [6]

- **pH determination:** pH was determined by shaking a 1% w/v solution of the sample in water for 5 min and the reading were noted by digital pH meter.
- **Viscosity Determination:** The viscosity of 1% (w/v) gum solution was measured according to the USP specification, using Brookfield DV-E Viscometer.
- **Swelling index (SI):** About 1 gm of gum powder was accurately weighed and transferred to a 100 ml measuring cylinder. The initial volume of the powder in the measuring cylinder was noted.

The volume occupied by the gum sediment was shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24 h. swelling capacity of gum was expressed in terms of swelling Index. Swelling Index was expressed as a percentage and calculated according to the following equation:

$$\text{SI} = \frac{X_t - X_0}{X_t} \times 100$$

Where;  $X_0$  is the initial height of the powder in graduated cylinder and  $X_t$  denotes the height occupied by swollen gum after 24 h.

- **Water retention capacity:** The contents from the measuring cylinder from the above test (SI) were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100 ml graduated cylinder. The volume of water collected was noted and the difference between the original volume of the mucilage and the volume drained was taken as water retained by the sample referred as water retention capacity or water absorption capacity of the polysaccharide.
- **Moisture sorption capacity:** Moisture sorption study was performed using programmable environmental test chamber (Remi Labs, Mumbai, India). One gram of powdered gum was taken in a Petri dish and spread uniformly. Then it was kept in programmable environmental test chamber  $37 \pm 1$  °C and 100% relative humidity for two days. The moisture sorption was calculated by recording weight difference of the sample before and after exposure to programmable environmental test chamber.
- **Hydration capacity:** Powdered gum was taken in the 15 mL tarred centrifuge tube. Then 10 mL of distilled water was added to it and allowed to centrifuge for 10 min. After the centrifugation process the tarred centrifuge tube was taken out and inverted to remove the supernatant. The decanted tube then weighed on digital balance.
- **Preliminary phytochemical screening:** A preliminary phytochemical screening of gum powder extract was carried out for the detection of various phyto constituents. The presence of Carbohydrate (Molisch's test), Reducing sugar (Fehling's solution), Alkaloid (wagner test), for Gum (ruthenium red test), Flavonoids (Shinoda test), Steroids (Lieberman Burchard test), and Tannins (ferric chloride test) were analyzed.

**Table: 1 – Physicochemical Properties of Gums**

S. No	Property	Moringa oleifera tree gum	Anacardium occidentale tree gum	Delonix regia seed gum
1	pH of 1% w/v solution	8.1	7.3	6.9
2	Viscosity of 1% w/v solution	1500cps	1150cps	1000cps
3	Swelling index%	750	640	490
4	Water retention capacity	3.6ml	3.1ml	2.2ml
5	Hydration capacity	1.5±0.03	1.2 ± 0.06	1.3±0.02
6	Moisture sorption capacity	1.57±0.52	1.44±0.21	1.41±0.32

**Table: 2 – Phytochemical Analysis of Natural Gums**

S. No	Name of the test	Delonix regia seed gum	Anacardium occidentale tree gum	Moringa oleifera tree gum
1	Test for carbohydrates (Molish test)	+	+	+
2	Test for Gums (Ruthenium red)	+	+	+
3	Test for Reducing sugars (Fehling's test)	+	+	+
4	Test for Alkaloids (Wagner test)	-	-	-
5	Test for Steroids (Salkowski test)	-	-	-
6	Test for Flavonoids (Shinoda test)	-	-	-
7	Test for Tannins (ferric chloride test)	-	-	-

+ Present, - absent

### C) Preformulation Studies

- **IR Spectral Analysis:** IR Spectral analysis is used to study the interactions between the drug, polymer and the excipients. The drug and excipients must be compatible with one another to produce a product stable, efficacious and safe. The drug and polymers were mixed in 1:1 ration keep a side for 24hrs. The IR study was carried out by using Bruker-Alpha FTIR.

### D) Preparation of Lamivudine Matrix Tablets [7, 8]

Matrix tablets of Lamivudine were prepared by using different drug:polymer ratios (1:0.5, 1:0.75 & 1:1). The tablets were formulated by employing wet granulation method using PVP K 30 as binder and isopropyl alcohol as granulating fluid. All the formulations contain 200 mg of Lamivudine, lactose as diluent, magnesium stearate as lubricant and talc as glidant. The details of composition of each formulation are given in table-3.

**Table: 3 – Composition of Lamivudine matrix tablets formulated with different concentrations of natural gums.**

Ingredients	LF <sub>1</sub>	LF <sub>2</sub>	LF <sub>3</sub>	LF <sub>4</sub>	LF <sub>5</sub>	LF <sub>6</sub>	LF <sub>7</sub>	LF <sub>8</sub>	LF <sub>9</sub>
Lamivudine	200	200	200	200	200	200	200	200	200
Cashew nut tree Gum	100	150	200	-	-	-	-	-	-
Moringa oleifera Gum	-	-	-	100	150	200	-	-	-
Endo sperm gum of Delonix regia seeds	-	-	-	-	-	-	100	150	200
PVP K 30	30	30	30	30	30	30	30	30	30
Lactose	150	100	50	150	100	50	150	100	50
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Isopropyl alcohol	QS								
Total weight	500	500	500	500	500	500	500	500	500

**E) Evaluation of Matrix Tablets[9-11]**

➤ **Evaluation of Flow properties**

The prepared granules were evaluated for flow properties. Different tests that were carried out are angle of repose, bulk density, tapped density, compressibility index, and Hausner ratio was calculated. The results were shown in table-4.

**Table: 4 – Micromeritic properties of Lamivudine granules formulated with different concentrations of natural polymers**

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Compressibility index (%)	Hausner's ratio
LF <sub>1</sub>	0.52 ± 0.015	0.62 ± 0.01	21.14° ± 1.23	13.88 ± 1.6	1.16 ± 0.02
LF <sub>2</sub>	0.53 ± 0.05	0.68 ± 0.03	22.14° ± 1.51	13.91 ± 1.1	1.16 ± 0.05
LF <sub>3</sub>	0.57 ± 0.02	0.66 ± 0.08	24.14° ± 1.35	12.70 ± 1.1	1.14 ± 0.06
LF <sub>4</sub>	0.53 ± 0.04	0.63 ± 0.01	20.26° ± 1.43	15.07 ± 1.5	1.17 ± 0.03
LF <sub>5</sub>	0.54 ± 0.05	0.62 ± 0.02	21.37° ± 1.89	12.82 ± 1.9	1.14 ± 0.09
LF <sub>6</sub>	0.51 ± 0.05	0.61 ± 0.02	23.23° ± 1.85	15.08 ± 1.1	1.17 ± 0.06
LF <sub>7</sub>	0.59 ± 0.06	0.62 ± 0.03	22.25° ± 1.90	15.36 ± 1.5	1.15 ± 0.08
LF <sub>8</sub>	0.58 ± 0.08	0.65 ± 0.02	21.35° ± 1.53	14.95 ± 1.9	1.14 ± 0.05
LF <sub>9</sub>	0.54 ± 0.05	0.64 ± 0.01	21.36° ± 1.62	13.56 ± 1.5	1.18 ± 0.05

➤ **Hardness**

Hardness was determined using ten tablets for each test and mean was taken. The hardness of the tablet was measured by Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The hardness was measured in terms of kg/cm<sup>2</sup>; the values are given in table-5.

**Table: 5 – Evaluation test for Lamivudine matrix tablets formulated with different concentrations of natural polymers**

Formulation	Hardness (kg/cm <sup>2</sup> )	Weight variation	Friability (%)	Drug Content (%)
LF <sub>1</sub>	4.77 ± 0.09	498.9 ± 1.12	0.37	100.15
LF <sub>2</sub>	4.80 ± 0.07	501.2 ± 1.13	0.73	100.78
LF <sub>3</sub>	4.43 ± 0.03	499.4 ± 1.06	0.52	99.62
LF <sub>4</sub>	4.61 ± 0.09	498.8 ± 1.09	0.74	101.52
LF <sub>5</sub>	4.32 ± 0.1	500.7 ± 1.21	0.69	99.87
LF <sub>6</sub>	4.4 ± 0.2	499.5 ± 1.19	0.67	100.67
LF <sub>7</sub>	4.42 ± 0.1	499.5 ± 1.28	0.53	100.38
LF <sub>8</sub>	4.59 ± 0.2	500.26 ± 1.15	0.59	99.92
LF <sub>9</sub>	4.38 ± 0.5	500.9 ± 1.14	0.45	100.05

➤ **Friability**

Ten tablets were carefully weighed and loaded into the drum of a friabilator and operated for 4 min at 25 rpm. Then tablets were collected, dedusted between tissue towels and reweighed. Percentage friability was calculated and given in table-5.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

➤ **Weight Variation**

Twenty tablets from each batch at random were taken and weighed. The average weight was calculated, then each tablet was weighed individually and weights of each tablet were noted. The weights of individual tablets were then compared with the average weight that was already calculated.

The deviation if any in the weight of individual tablets from the average weight was checked. If any weight variation is there, that should be within the I.P limits. The test was considered correct if not more than two tablets fall outside the I.P limits out of twenty tablets taken for the test. Results were given in the table-5.

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

➤ **Uniformity of Drug Content**

Matrix tablet of Lamivudine from a batch was taken at random and was crushed to a fine powder and was transferred into a 250ml volumetric flask and add 200ml phosphate buffer 6.8 pH to it. It was shaken occasionally for about 30 minutes and the volume was made up to 250ml by adding phosphate buffer 6.8 pH. The resulting solution was set aside for few minutes and the supernatant solution was collected, filtered by using wattman filter paper. Then the filtrate was subsequently diluted and the absorbance was measured at 270nm. The Results were shown in the table-5.

➤ **Swelling Index[11]**

Formulated tablets were weighed individually ( $W_0$ ) and placed separately in Petri dish containing 50 ml of phosphate buffer 6.8 pH. The Petri dishes were placed in an incubator maintained at  $37 \pm 0.5^\circ\text{C}$ . The tablets were removed from the petri dish, at predefined intervals of time and reweighed ( $W_t$ ), and the % swelling index was calculated using the following formula and the results were shown in table-6.

$$\% \text{ Wu} = \frac{W_t - W_0}{W_0} \times 100$$

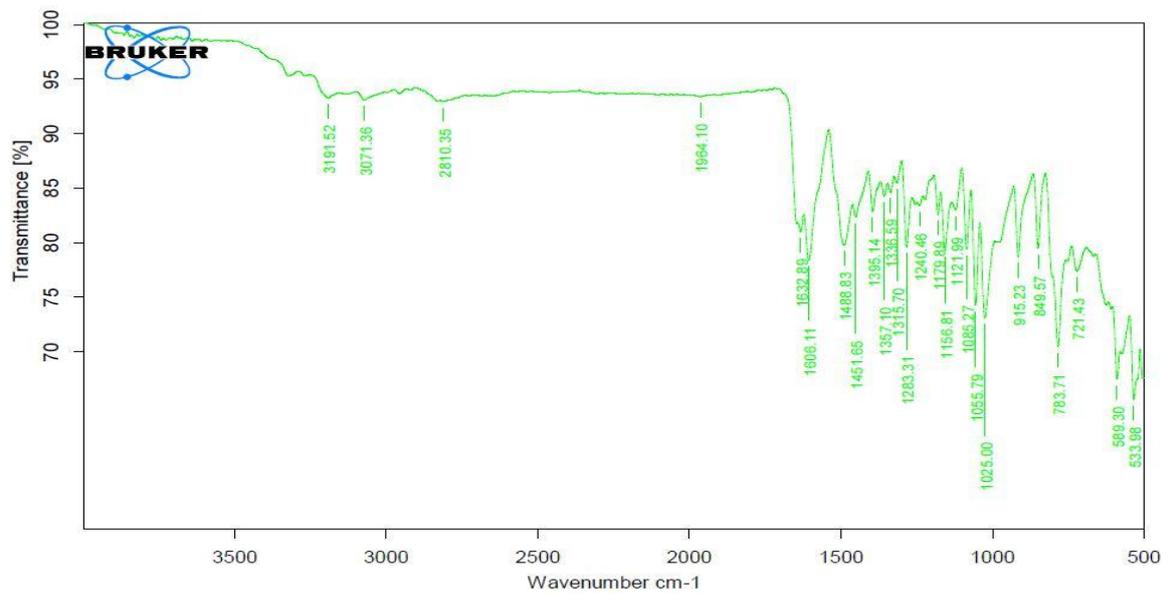
Where:  $W_0$  – Water uptake  
 $W_t$  – Weight of tablet at time t  
 $W_0$  – Weight of tablet before immersion

**Table: 6 – Swelling index values of Lamivudine matrix tablets formulated with different concentrations of natural polymers**

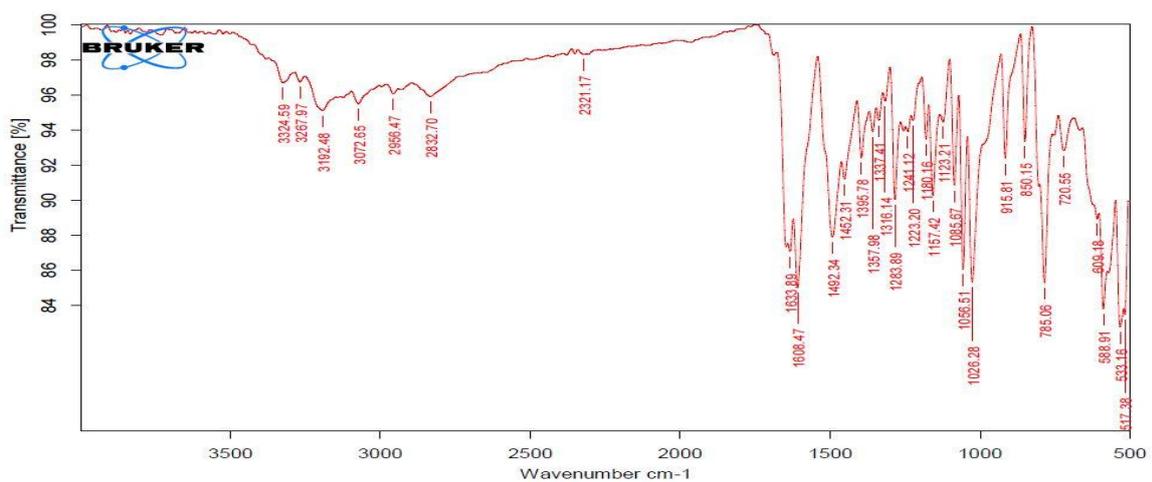
Formulation code	Swelling index ( Time in hours)		
	after 1 hour	after 2 hours	after 8hours
LF <sub>1</sub>	54.34	78.93	149.24
LF <sub>2</sub>	57.45	91.46	157.23
LF <sub>3</sub>	60.12	98.56	171.39
LF <sub>4</sub>	52.69	76.64	145.00
LF <sub>5</sub>	55.24	89.89	154.00
LF <sub>6</sub>	58.53	96.10	168.50
LF <sub>7</sub>	51.25	90.25	156.23
LF <sub>8</sub>	54.91	94.36	159.66
LF <sub>9</sub>	58.25	97.23	163.95

Table: 7 – *In-vitro* drug release kinetic data of Lamivudine matrix tablets formulated with different concentrations of natural polymers

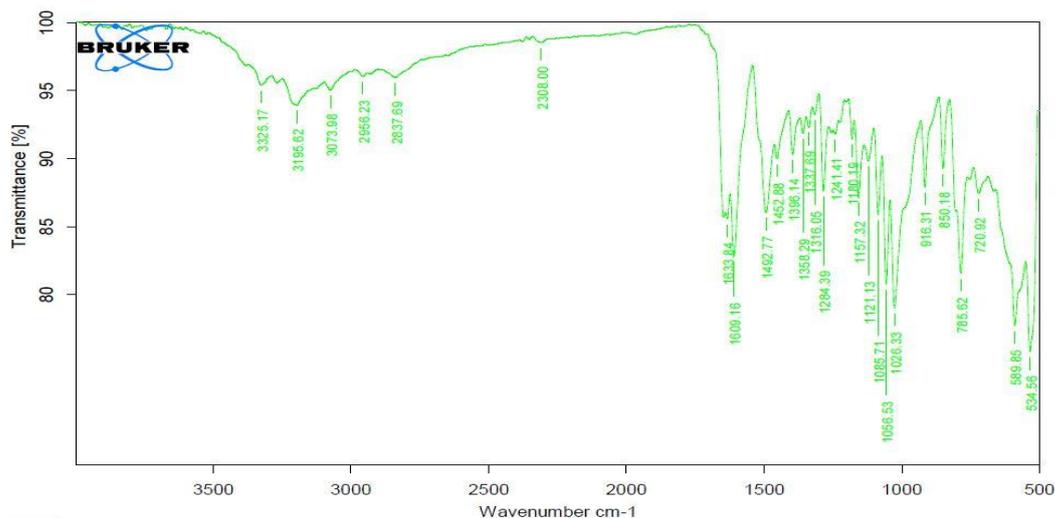
Formulation	Correlation Coefficient Value			Peppas (n) value
	Zero Order	First Order	Higuchi	
LF <sub>1</sub>	0.979	0.768	0.911	0.741
LF <sub>2</sub>	0.987	0.745	0.897	0.790
LF <sub>3</sub>	0.999	0.727	0.862	0.973
LF <sub>4</sub>	0.978	0.821	0.909	0.748
LF <sub>5</sub>	0.986	0.841	0.898	0.792
LF <sub>6</sub>	0.999	0.752	0.851	0.974
LF <sub>7</sub>	0.975	0.843	0.843	0.731
LF <sub>8</sub>	0.982	0.824	0.824	0.768
LF <sub>9</sub>	0.998	0.798	0.798	0.922



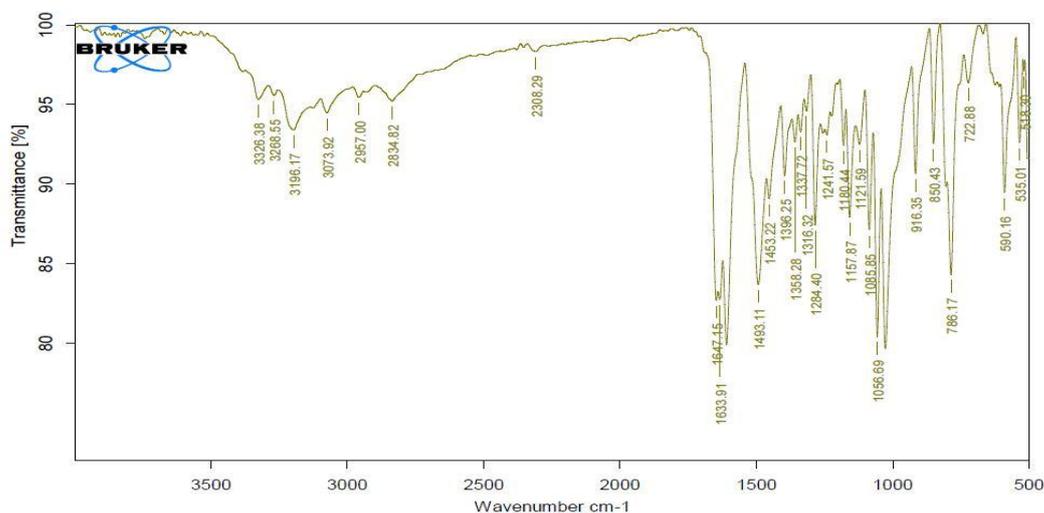
2(a) - Lamivudine



2(b) – Lamivudine and Cashew nut tree gum



2(c) – Lamivudine and Moringa oleifera gum



2(d) – F<sub>3</sub> Formulation containing drug and cashew nut tree gum in 1:1 ratio

Figure 2: Comparative FTIR Spectral analysis of Lamivudine matrix tablets formulated with different polymers with pure drug

➤ **In-Vitro Dissolution Studies[12]**

Dissolution studies on each formulation were performed by using USP type II apparatus, employing 900ml of phosphate buffer 6.8 pH as a dissolution medium. The paddles were operated at a 50rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 12hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by 'thermo scientific' double beam UV – VIS spectrophotometer at 270nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies.

➤ **Evaluation of Kinetics[13]**

Various dissolution parameters such as zero order rate constant, first order rate constant, Higuchi constant and Peppas constant were calculated from the dissolution data obtained from various formulations. The following mathematical expressions were used to calculate various drug release mechanisms from the dissolution data,

- **Zero order equation,**

$$C_t = C_0 - K_0 t$$

Where,  $K_0$  = zero order rate constant;  $t$  = time

- **First order equation,**

$$\log C_t = \log C_0 - K_1 t / 2.303$$

Where,  $K_1$  = first order rate constant

- **Higuchi equation,**

$$\text{Cumulative amount of drug released} = K_H t^{1/2}$$

Where,  $K_H$  = Higuchi constant

- **Korsmeyer - Peppas Constant,**

$$\log Q = \log K_p + n \log t$$

Where,  $n$  = release exponent

### RESULTS AND DISCUSSION

The hardness was found to be in between 4.32 – 4.80 kg/cm<sup>2</sup>. The tablets satisfied friability requirement, as the % friability values were less than 1%. The drug content estimations showed values in the range of 99.62 to 101.52%, which reflects good uniformity in drug content among all formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ± 5% of the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. These values were shown in table-5. The swelling index of tablets formulated with Cashew nut tree gum was found to be higher than that of moringa oleifera and delonix regia gums which can be attributed to high viscosity and high water retention property. These results were shown in table 6.

The results of the in vitro drug release studies for formulations containing natural gums were shown in figure-3. Among all the formulations F3 formulation containing drug and cashew nut tree gum in the ratio of 1:1 showed the prolonged drug release. The controlled drug release may be due to increased proportion of polymer. Based on the release rate constant and % of drug release at the end of 12 hours the release retarding capacities of the polymers were arranged in the following order, Cashew nut tree gum > Moringa oleifera > Endo sperm gum of Delonix Regia seeds.

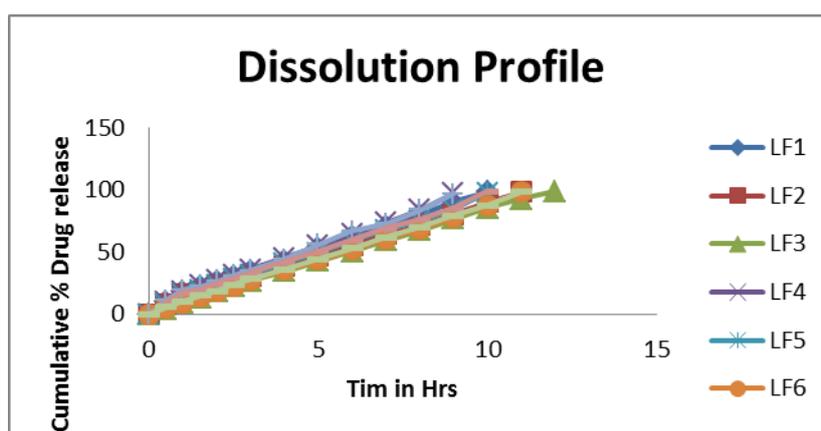


Figure: 3 – Dissolution profile of all formulations

To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order kinetics, Higuchi and Peppas models. The correlation coefficient value ( $r$ ) revealed that the dissolution profiles follow Zero order kinetics and the mechanism of drug release was governed by Peppas model. The kinetics plots were shown in figures 4-7. The diffusion exponent ( $n$ ) values are found to be more than 0.5

( $n > 0.5$ ) indicated that the drug release was predominantly controlled by non fickian diffusion. Among all the formulations, formulation F<sub>3</sub> showed a controlled drug release for a period of 12 hours.

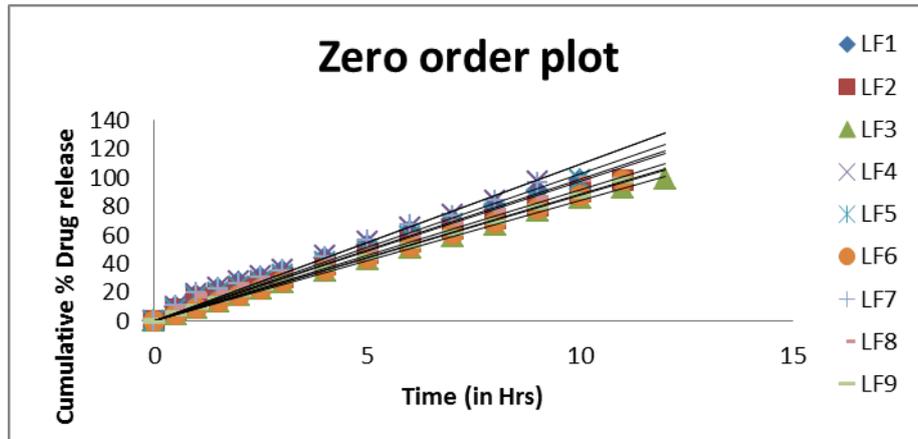


Figure: 4 – Zero order profile of all formulations

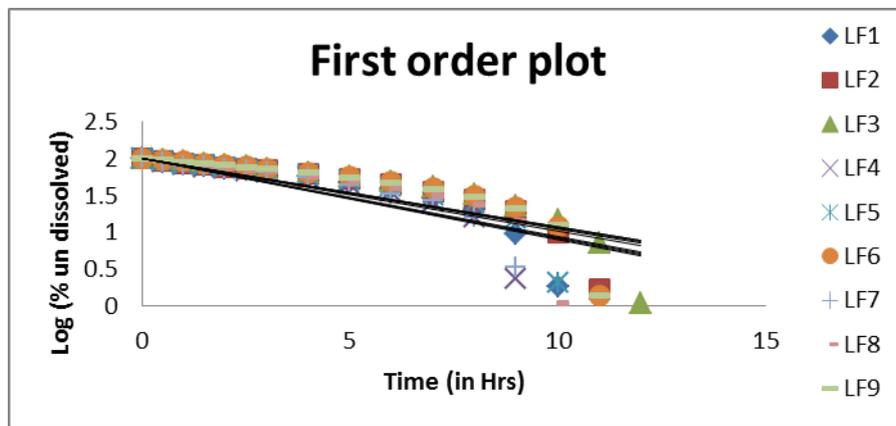


Figure: 5 – First order profile of all formulations

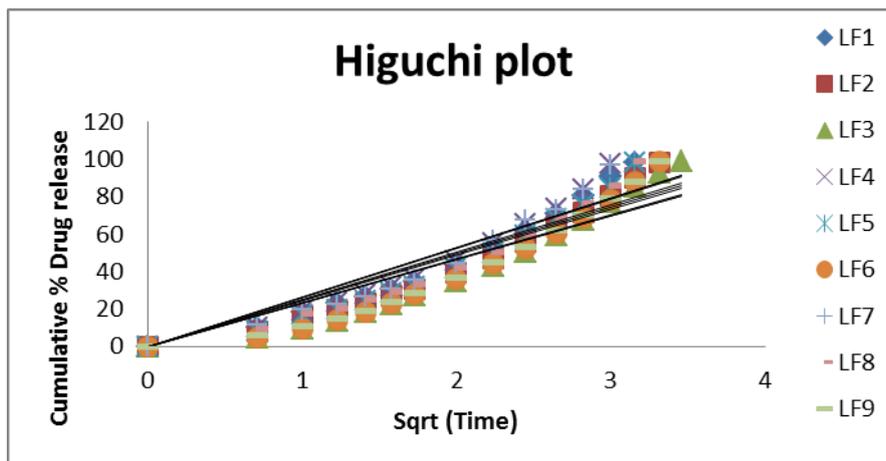


Figure: 6 – Higuchi profile of all formulations

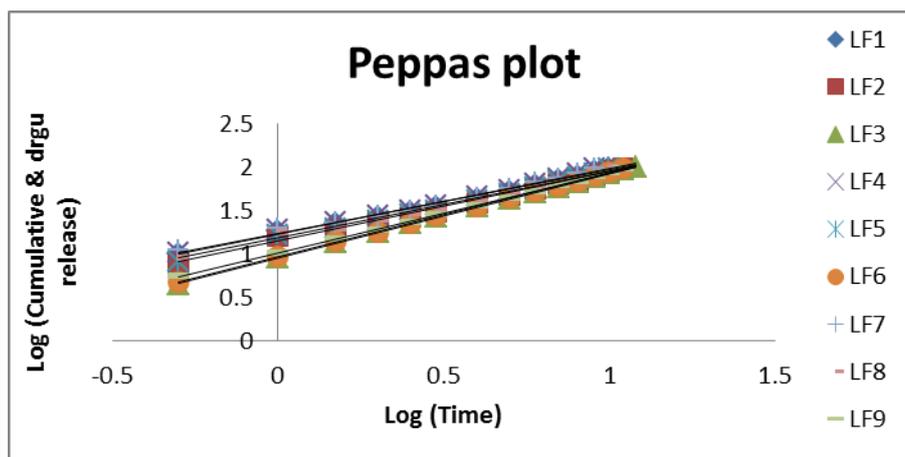


Figure: 7 – Peppas profile of all formulations

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