FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LAMIVUDINE

A Dissertation Submitted to

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In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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CERFICATE OF APPROVAL

The foregoing thesis entitled **"FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LAMIVUDINE"** is hereby approved as creditable study of research topic and has been presented in satisfactory manner to warrant its acceptance as prerequisite to the degree for which it has been submitted.

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This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LAMIVUDINE"** was carried out by **MUTHUSAMY P (REG.NO: 261811457),** under the guidance of **Mr.K.MOHANKUMAR, M.Pharm.,** Associate Professor, Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637 207, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

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Mr. K.MOHAN KUMAR

Place: Namakkal

Date:

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By

MUTHUSAMY P

DECLARATION

We hereby declare that the matter embodied in the dissertation entitled **"FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LAMIVUDINE"** is a bonafide and genuine research work carried by us under the guidance of **Dr.K.MOHAN KUMAR, M.Pharm.,** Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637207.

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CONTENTS

S.NO	INDEX	PAGE NO
1	INTRODUCTION	1-8
2	LITERATURE REVIEW	9-13
3	AIM OF THE STUDY	14
4	PLAN OF WORK	15
5	DRUG PROFILE	16-18
6	POLYMER PROFILE	19-21
7	MATERIALS AND METHODS	25-34
8	RESULT AND DISCUSSION	35-65
9	CONCLUSION	66
10	REFERENCE	67-70

1.0 INTRODUCTION

AIDS is considered to be an epidemic and according to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) AIDS Epidemic Update 2005, 40 million adults and 2.5 million children are living with the human immunodeficiency virus (HIV). The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient compliant antiretroviral medications are available at affordable prices. The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost. India is the second largest burden of HIV infected persons. One of every six persons is affected with HIV infections in India[1].

HIV is human immunodeficiency virus. It is the virus that can lead to acquired immune deficiency syndrome (AIDS). The term mostly used resembles HIV I. Human immune virus and its subtypes are retrovirus. They were unknown until 1980's, and the scientists found out recently that they were spread from chimpanzees through different ways. HIV belongs to the family ribonucleic acid lentiviruses that are characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods. Molecular epidemiologic data suggest that HIV I subtype is the most common in humans, has been derived from the simian immune deficiency virus, called SIVcpz, of the subspecies Pan Troglodytes troglodytes- subspecies of chimpanzee.

HIV attaches outside to human cell, it exists as roughly spherical particle (called as virion). Surface of each particle is studded with lots of spikes. An HIV particle is around 0.1 micron and $1/7^{th}$ diameter of a human cell CD4+ white blood cell. They can be seen clearly under electron microscope. HIV is surrounded with a fatty material known as viral envelope. Projections from this are around 72 spikes, which are formed of protein gp120 and gp41. Below the viral envelope is a layer called matrix which is made of protein p17. Also enclose within a virion particle are Vif, Vpr, Nef, p7 and viral protease. HIV has several major genes coding for structural proteins that are found in all retroviruses and several non structural genes that are unique to HIV such as: GAG gene- these are physical infra structure of the virus POL gene- basic mechanism from which retroviruses develop.

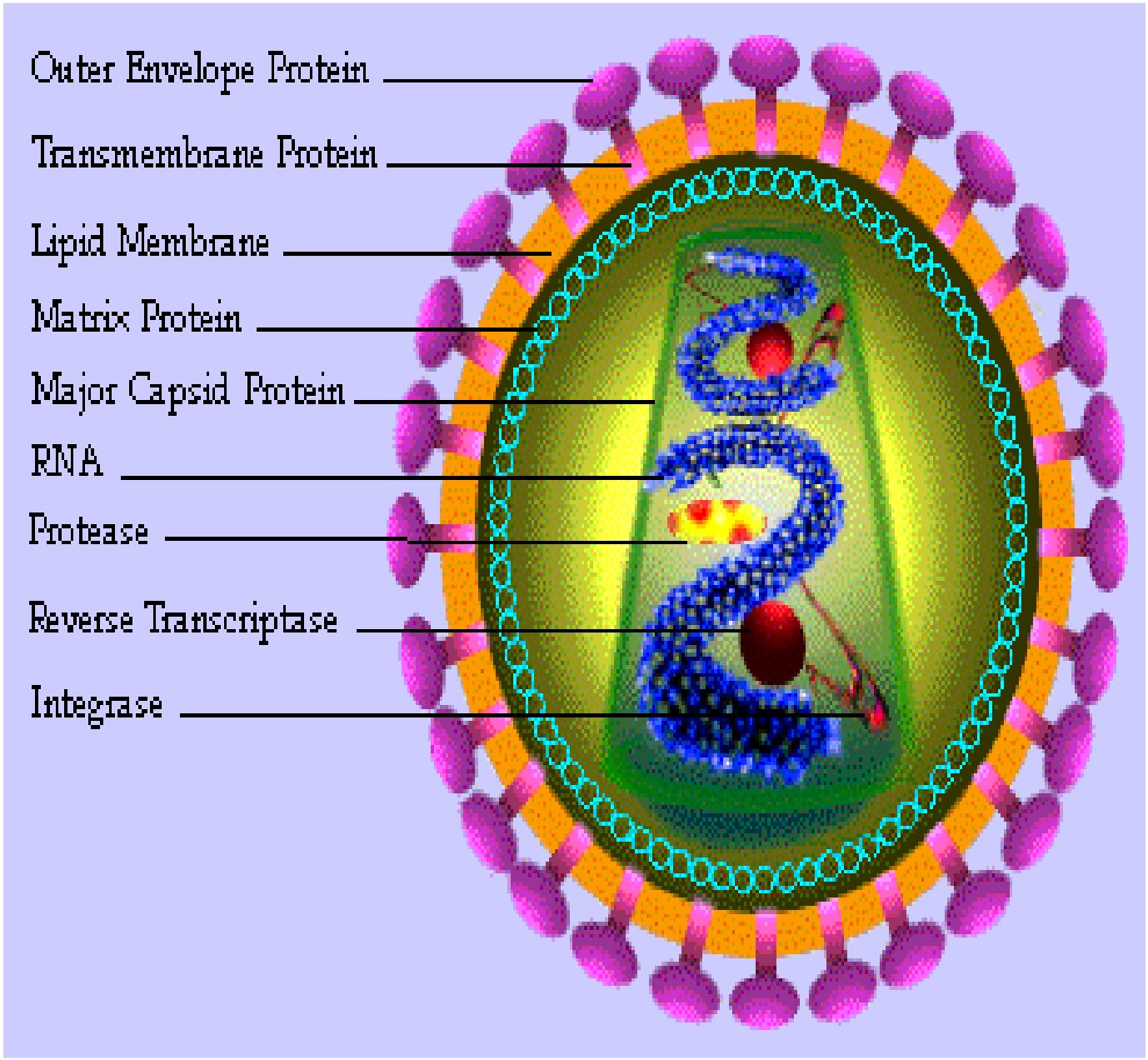


Figure: 1 STRUCTURE OF HIV

LIFE CYCLE OF HIV:

HIV can replicate only inside human cells. The process typically begins when a virus particle bumps into a cell that carries on its surface a special protein called CD4. The spike on the virus sticks on the surface of CD4 and allow the viral envelope to fuse with cell membrane. The contents of HIV particle are then released into the cell leaving the envelope behind. The following steps are seen in the life cycle of HIV.

* **REVERSE TRANSCRIPTASE AND INTEGRASE:**

Once inside the cell, the HIV enzyme reverse transcriptase converts the viral DNA which is compatible with human genetic material. This DNA is transported to the cell's nucleus where it is spliced into the human DNA by the HIV DNA is known as provirus.

* **TRANSCRIPTION AND TRANSLATION:**

The provirus remains dormant within a cell for long time. But when the cell becomes activated it treats HIV genes the same way as human genes. First it converts itself into mRNA and it is transported outside the nucleus and used as a blue print for producing new HIV proteins and enzymes.

* **ASSEMBLY, BUDDING AND MATURATION**:

Among the strands of mRNA produced by the cell are complete copies of HIV genetic material. These together with newly made HIV proteins and enzymes form new viral particles which were then released from the cell. The enzyme protease plays a role in chopping the long strands of protein in smaller pieces, which are used to construct mature viral core.

The newly mature HIV particles are ready to infect another cell and begin the replication. In this way the virus process all over again and quickly spreads through the human body. And over a person is infected, they can pass HIV onto others in their body fluids.

SYMPTOMS:

The following symptoms are found during HIV:

- Rapid weight loss
- Dry cough
- Recurring fever or profuse night sweats
- Profound and unexplained fatigue
- Swollen lymph glands in the arm pits, groin or neck
- Diarrhoea that lasts for more than a week
- White spots or unusual blemishes on the tongue in the mouth or throat
- Pneumonia
- Red, brown, pink or purplish blotches on or under the skin, inside the mouth, nose or eyelids
- Memory loss, depression and other neurological disorders.

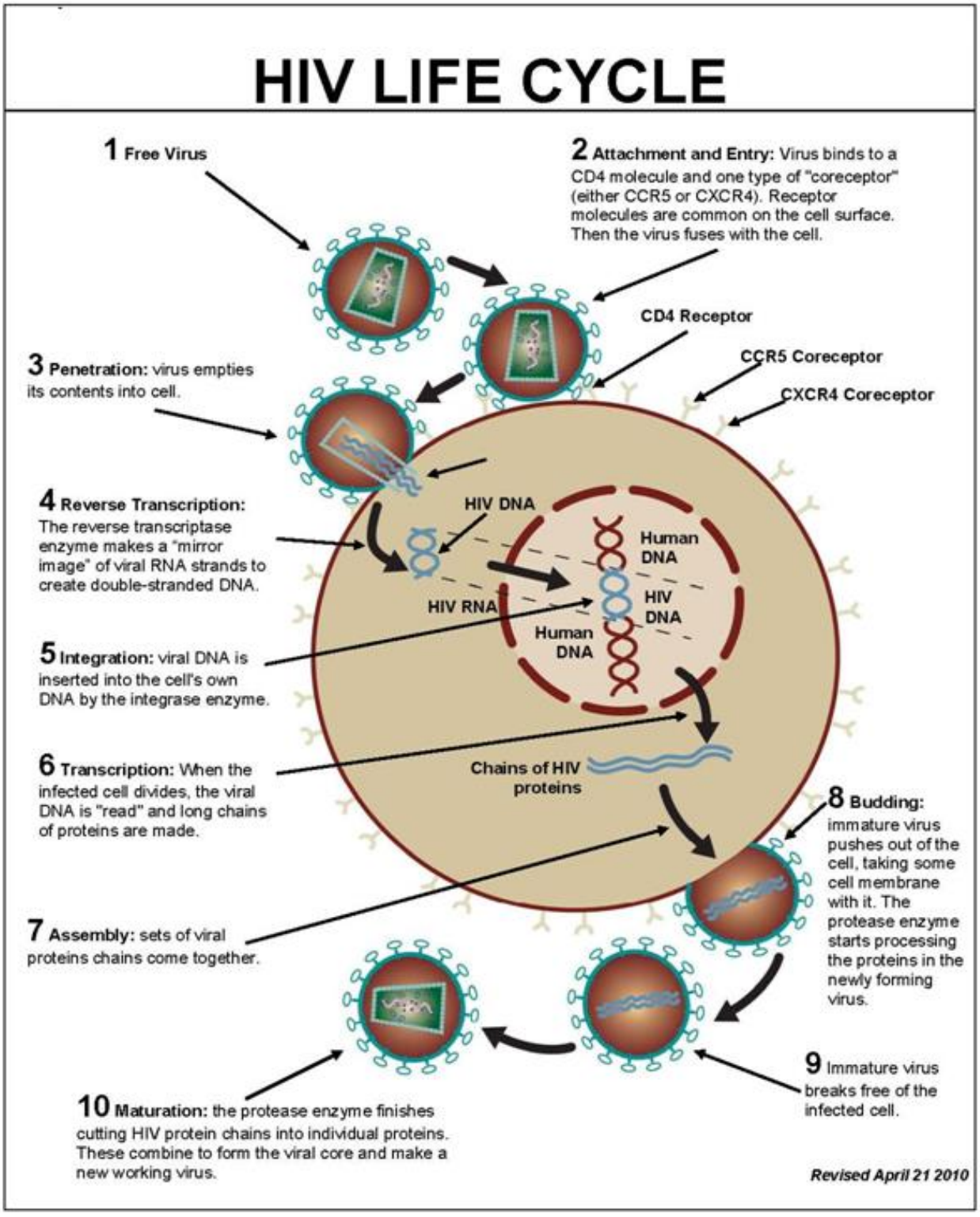


Figure: 2 HIV LIFE CYCLE

DRUG DELIVERY SYSTEM

The goal of drug delivery system is to provide the therapeutic amount of drug to proper site in the body to achieve promptly and maintain the desired drug concentration. Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations.[2]

Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy to formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs.

ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORMS:

- THERAPEUTIC ADVANTAGE: Reduction in drug plasma level fluctuation, maintenance of steady plasma level of the drug over a prolonged time period, ideally stimulating an i.v infusion of a drug.
- REDUCTION IN ADVERSE EFFECTS AND IMPROVEMENT INTOLERABILITY: Drug plasma levels are maintained with a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms.
- PATIENT COMFORT AND COMPLIANCE: Oral drug delivery system is the most common and convenient for patients, and a reduction in dosing frequency enhances compliances.
- REDUCTION IN HEALTHCARE COST: The total cost of therapy of the controlled release product could be much lower.
- AVOID NIGHT TIME DOSING: It is also good for patients to avoid dosing at night time.

DRUG RELEASE MECHANISM:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be faster than the diffusion rate of dissolved drug leaving the matrix.[3]

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release;
b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
c) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:

$$\mathbf{dM/dh=C_o.dh-C_s/2 \quad ---------1}$$

Where:

dM= Change in the amount of drug released per unit area

dh= Change in the thickness of the zone of matrix that has been depleted of drug

C_o= Total amount of drug in a unit volume of matrix

C_s= Saturated concentration of the drug within the matrix

Additionally, according to diffusion theory:

$$\mathbf{dM= (D_m.C_s/h).dt \quad ----------2}$$

Where:

D_m= Diffusion coefficient in the matrix

h= Thickness of the drug-depleted matrix

dt= Change in time

By combining equation 1 and equation 2 and integration:

$$M = [C_s.Dm.(2C_o - C_s).t]^{1/2} \quad \text{---------3}$$

Where the amount of drug is in excess of the saturation concentration, then:

$$M = [2C_s.Dm.C_o.t]^{1/2} \quad \text{----------4}$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line.

2.0 LITERATURE REVIEW

Atul Kuksal et al (2005) prepared and evaluated extended release of Zidovudine using hydrophilic eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. Formulated tablets were compared with conventional marketed tablet. The invitro studies showed that Eudragit preparation were able to sustain the drug release for only 6 hrs, where as the combination of Eudragit with ethyl cellulose sustains the drug for 12hrs.[4]

Hamdy abdelkader et al (2008) formulated controlled release Baclofen matrix tablets to investigate the influence of polymer level. The hydrogenated castor oil and eudragit RS-100, eudragit L-100 were taken as polymers. The Baclofen tablets were prepared by hot melt granulation process (wax tablets) and wet granulation process (eudragit tablets). The release kinetics was found to be governed by the type and content of the excipients. The increase in pH of the matrix microenvironment enhanced the dissolution and erosion of matrix tablets. The mechanism of drug release was fickian transport.[5]

Jeya ananthi et al (2008) formulated and evaluated controlled release matrix tablets of pentoxifylline. Two retardant polymers HPMC and gaur gum were employed in various concentrations and different ratio to obtain controlled release of the drug. All the formulations sustained the drug release upto 8 hours. The formulations with HPMC gave less drug release compared to guar gum.[6]

Sourabh Jain et al (2008) prepared and evaluated sustained release matrix tablets of furosemide using natural polymers pectin, guar gum, and xanthan gum. The tablets were evaluated for physical characteristics and in-vitro release with buffer 7.2 for fifteen hours. Guar gum exhibited greater swelling index and controlled drug release than those with pectin and xanthan gum.[7]

Patil et al (2009) studied the effect of formulation variables on the release profile of stavudine from hydroxyl propyl methyl cellulose. Stavudine tablets were prepared by wet granulation method, and various evaluations were made. Invitro drug release study revealed that increased amount of polymer around tablets provided gelation, which inhibits the release of stavudine. Also it indicates that higher viscosity HPMC retards the drug release immediately than lower viscosity HPMC, but its period depends upon the concentration used.[8]

Vasawant et al (2009) formulated and evaluated once daily sustained release matrix tablets of stavudine using HPMC alone, combination of two different viscosity grades of HPMC and combination of HPMC with EC. In this study, the hydrophilic polymer (HPMC) was used as matrix material and hydrophobic polymer (EC) was used to extend the drug release. The results of invitro dissolution study shown that the formulation having (HPMC K15: ethyl cellulose 1:1) exhibited satisfactory drug release pattern and total drug release pattern was very close to theoretical release profile. The mechanism of drug release from sustained release matrix tablet formulations was fickian diffusion.[9]

Raghavendra rao et al (2009) developed sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers like HPMC, karaya gum and carrageenan, with varying ratios of drug and polymer like 1:1 and1:2. Dissolution data was analyzed by korsmeyer-Peppas power law expression and modified power law expression which showed that release profile obeys non fickian diffusion. All the formulations show zero order kinetics.[10]

Suresh v kulkarni et al (2010) prepared and invitro evaluated controlled release matrix tablets of stavudine using natural and synthetic polymers. Among 6 formulations, f3 showed controlled release of drug for 12 hrs with 91.65% drug release. The release data was fitted to various models such as Higuchi, korsmeyer-peppas,1st order and zero order to evaluate the kinetics. Stability studies reveal that there was no significant change in drug content and dissolution profile of matrix tablets. Mechanism of drug release was found to be diffusion coupled with erosion.[11]

Dhirendra kumar et al (2010) formulated once daily sustained release matrix tablets of Stavudine by direct compression using different drug: polymer ratios. Hydrophilic polymers like HPMC, Sodium CMC and starch 1500 were used and the tablets were evaluated Formulations containing stavudine:HPMC K15: Na-CMC(1:2:0.5) showed the desired release profile. Invitro drug release characteristics were studied in both simulated gastric and intestinal fluids for a period of 24hrs. Mathematical analysis of release kinetics indicated a coupling of diffusion and erosion. Study proves that developed sustained release tablet is capable of releasing the drug in a sustained manner for 24 hrs.[12]

Ruali kale et al (2010) developed matrix diffusion controlled drug delivery system of Pentoxifylline using polymers like HPMC, eudragit, sodium alginate, guar gum. Pentoxifylline tablets were prepared by wet granulation method. Eudragit and guar gum formulations showed low dissolution rate indicating controlled release pattern of drug but their combination formulation showed high dissloution rate. The mechanism of drug release followed first order kinetics in higuchian diffusion method.[13]

Ganesh et al (2010) formulated and evaluated matrix tablets of Acarbose using HPMC and eudragit as polymers in various concentrations and combinations by using direct compression method. To analyse the mechanism of drug release, zero order, Higuchi model, korsmeyer-peppa's model were used. Drug release was studied till 12 hours. The polymers with HPMC showed linearization of drug release curve where formulation with eudragit showed quite long linearity drug release. The drug release rate was strongly influenced by the type and concentration of the polymer.[14]

Saravanakumar et al (2010) made an attempt to develop and evaluate once daily sustained release matrix tablets of Stavudine using (hydroxyl propyl methyl cellulose) K4M and carbopol 974P. It has been observed that using (HPMC) KM4 and carbopol 974P in combination retarded the drug release. Findings reveal that above a particular concentration, HPMC KM4 and carbopol 974P are capable of providing almost zero order drug release whose mechanism was diffusion coupled with erosion.[15]

Ranjit kumar et al (2010) designed and characterized oral controlled release matrix tablets of Stavudine which were prepared by wet granulation method using various proportions of polymer HPMC K 100M alone and in combination with polymer ethyl cellulose. The in vitro drug release studies reveal that Eudragit preparation was able to sustain the drug release for about 9 hours (98.54% release), but the combination of HPMC K 100M with the ethyl cellulose sustained the drug release for 12 hours (75.32% -98.12% release). The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-peppas, first order, and zero order to evaluate the kinetics and mechanism of drug release was found to be diffusion coupled with erosion.[16]

Nilesh V Ingle et al (2011) prepared and evaluated Ambroxol Hydrochloride matrix tablets with different polymers HPMC K4M and guar gum and studied the effect of polymer on drug release. In- vitro release revealed that the release rate decreased with increase polymer proportion and hydrophobic polymers retard the drug release more than hydrophilic polymers. The formulations showed sustained drug release for 12 hrs.[17]

Rakesh P. Patel et al (2011) formulated and evaluated and Tizinidine Hydrochloride tablets prepared by direct compression technique using guar gum, xanthan gum, glyceryl behenate, glyceryl monostearate and stearic acid in different proportions. Optimized batch was compared with marketed preparation. The formulation containing glyceryl behenate (30%) showed the release profile similar to marketed preparation with satisfactory physical properties of tablet.[18]

Suresh V Kulkarni et al (2011) prepared and evaluated Zolpidem tartarate sustained release tablet prepared by direct compression method using Carbopol 974 as release retardant. Granules are prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose showed satisfactory results. The in vitro drug release study of matrix was carried out in 0.01 N HCl for 4 hrs. All the formulation followed first order kinetics.[2]

Syed Namath Ulla et al (2011) formulated and evaluated Lornoxicam sustained release matrix tablet prepared using HPMC (K4M, K15M, K100M) by direct compression method. The formulations sustained the drug release for longer period of time and it followed zero order release.[19]

Potu apparao et al (2011) formulated and evaluated gum based matrix tablets of lamivudine using different polymers like guar gum, xanthan gum, rosin gum, pectin and sodium alginate which were taken at 30%, 40%, and 50% of total weight of tablet. The cumulative percent drug release decreased with increasing concentration of natural gums. The physical mixtures of matrix tablets were characterized. All the formulations showed drug release beyond 18 hrs except pectin and sodium alginate. The swelling studies were also conducted and resulted that the swelling index increases up to 6 hrs and there after it decreased.[20]

Ranjit kumar et al (2011) designed controlled release matrix tablet formulations for stavudine at different drug to polymer ratios which were prepared by direct compression method. The influences of the proportion of the polymer and several co-excipients on the release rate of the drug from the tablets were studied. Drug release studies were found to occur both by diffusion and swelling controlled mechanism exhibiting anomalous transport. The drug release was found to follow zero order kinetics. The three co-excipients lactose, microcrystalline cellulose and starch enhance the release rate of stavudine, while dibasic calcium phosphate exhibited a much slower release of drug from prepared matrices.[21]

Jadhav et al (2011) formulated and evaluated bilayered tablet of Piracetam and Vinpocetine. Wet granulation process was used for the formulation of both layers and the final film coated tablets were evaluated. The formulated tablet showed good release as compared to the innovator tablets. It was concluded that formulated bilayered tablets can be prepared successfully and would be alternative to the currently available conventional tablets.[22]

From the above literature review it is evident that not much work has been carried out with natural polymers or semi-synthetic polymers in retarding the release of Lamivudine from the matrix systems. So, it was planned to have an attempt in formulating the matrix tablets of Lamivudine using those categories of polymers which may cut down certain side effects associated with the usage of synthetic polymers.

3.0 AIM OF THE STUDY

The objective of the present work is to develop sustained release matrix tablets of Lamivudine using natural & semi-synthetic polymers.

The study was also proposed to evaluate the suitability of Guargum & SCMC as polymeric materials for matrix tablets able to adequately extend drug release. The effect of polymer concentration and its type on various physicochemical properties and the drug release behavior from the matrices is also to be examined.

4.0. PLAN OF WORK

The plan of the work can be arranged as follows:

- Construction of standard curve for Lamivudine
- Pre-Compression studies
    - Angle of repose
    - Bulk Density
    - True Density
    - Compressibility index
    - Hausner's ratio
    - Drug content
- Formulation of Lamivudine matrix tablets
- Physicochemical evaluation
    - Thickness of matrix tablets
    - Hardness
    - Friability
    - Drug content
- In- vitro dissolution studies
- Stability studies
- Evaluation of kinetic parameters

5.0 DRUG PROFILE[23, 24]

- **Drug:**

  Lamivudine

- **Class:**

  Nucleoside analog Reverse Transcriptase Inhibitor. (NARTI)

- **Category:**

  Antiviral drug

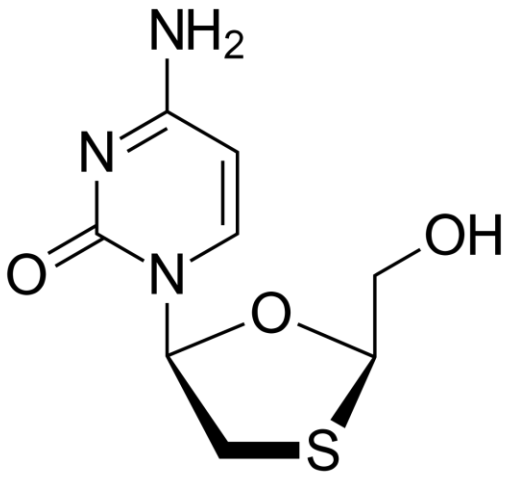
- **Empirical formula:**

  $C_8H_{11}N_3O_3S$

- **Molecular weight:**

  229.25 g/mol

- **Structure:**



- **Chemical name:**

According to IUPAC name:

2',3'-dideoxy-3'-thiacytidine

4-Amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one

Clinical pharmacology:

Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1) and hepatitis B (HBV) to disrupt viral DNA synthesis. When phosphorylated, lamivudine can form active metabolites that compete for incorporation into viral DNA. Via DNA incorporation, lamivudine metabolites competitively inhibit the activity of the HIV reverse transcriptase enzyme and act as a chain terminator of DNA synthesis. Due to the lack of a 3'-OH group, incorporated nucleoside analogues prevent the formation of a 5' to 3' phosphodiester linkage that is essential for DNA chain elongation.

Pharmacokinetics:

- Oral bioavailability: 86%

* The majority of lamivudine is eliminated unchanged in urine
* Apparent volume of distribution, IV administration = 1.3 ± 0.4 L/kg

- **Drug-drug interactions:**

Lamivudine should not be given along with

* Indinavir
* Zalcitabine
* Zidovudine

- **Indication:**

It is indicated for patients suffering from HIV infection

- **Contraindication:**

It should not be given to patients having

- Pancreatitis
- Peripheral neuropathy
- Renal dysfunction

- **Dose and administration:**
  - Adult: 40mg every 12hr oral >60kg body weight

    30 mg every 12 hr oral <60kg body weight
  - Children: 1mg/kg every 12hr <30kg body weight

    Adult dose >30kg body weight

- **Use:**

It shows activity against retroviruses including HIV

6.0 POLYMER PROFILE

6.1 SODIUM CARBOXY METHYL CELLULOSE[25]

Non proprietary names

BP: carmellose sodium

USP: carboxy methyl cellulose sodium

Synonym

Akucell, Aquasorb, cekol, cellulose gum, carboxy methyl sodium, E466, Finnfix, Nymcel, sodium cellulose glycolate, Tylose CB

Chemical name

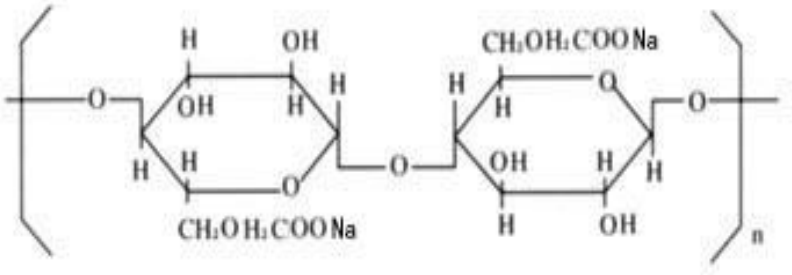
Cellulose, carboxy methyl ether, sodium salt

Empirical formula

USP describes carboxy methyl cellulose sodium as the sodium salt of polycarboxy methyl ether of cellulose.

Molecular weight 90000-700000D

Structural formula



Functional category

Coating agent, tablet and capsule disintegrant, water absorbing agent, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Application in pharmaceutical formulation technology

Carboxy methyl cellulose is widely used in oral and topical pharmaceutical formulation.

In topical products, carboxy methyl cellulose is also used as a viscosity increasing agent. Viscous aqueous solution are used to suspend powder

Description

It's a white to almost white colored fibrous, odourless, granular powder.

Typical properties

Bulk density	:	0.520 gm/cm
Tap density	:	0.783 gm/cm
Dissociation constant	:	4.3
Viscosity	:	8000-12000(mpas)(high viscosity)
Melting point	:	Browns at 227°c, chars at 252°c
Moisture content	:	Carboxy methyl cellulose sodium is hygroscopic and absorbs water at temperature up to 37°c at relative humidity of about 80%, it contains less than 10% of water.
Solubility	:	easily dispersed in water at all temperatures, forming clear, colloidal solutions. Particularly insoluble in acetone, acetone, ethanol, ether and toluene.

Stability and Storage

Carboxy methyl cellulose sodium is stable, though it is hygroscopic under high humidity condition. Solutions are stable between pH 2-10. Below pH 2 precipitation can occur while above pH 10 solution viscosity rapidly decreases. Generally solutions exhibit maximum viscosity and stability at Ph 7-9. Carboxy methyl cellulose sodium should be stored in a well closed container in a cool and dry place.

Incompatabilities

Carboxy methyl cellulose sodium is incompatible with strong acidic solutions and with the soluble salts of iron and some other metals. Such as aluminum, mercury and zinc. Precipitation can occur at pH -2 and when mixed with ethanol (95%).

Carboxy methyl cellulose sodium also forms complex coacervates with gelatin and pectin. It additionally forms a complex with collagen and is capable of precipitating certain positively charged proteins.

6.2 Guar gum[26]

Synonym:

Guaran, Gum cyamopsis, Guar flour

Chemical name:

Guar gum

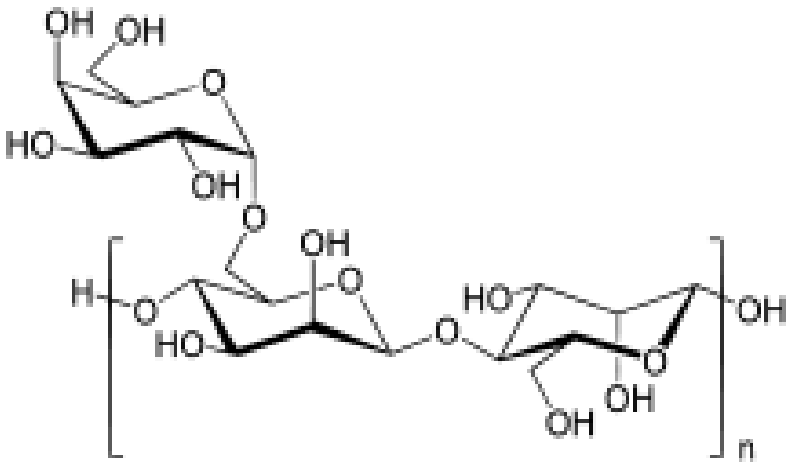
Empirical formula:

Guar gum has a molecular weight of about 220,000-250,000.

Molecular Weight:

220000.0 approximately

Structural formula:



Description:

White to yellowish-white, nearly odourless, free-flowing powder

Typical properties:

Bulk density	:	Loose - 45 – 49 lbs /cu. ft Packed - 47 – 51 lbs / cu. ft
Specific gravity	:	1.5 at 77°F
Viscosity	:	4000-4500 cps
Melting point	:	90° c
Solubility	:	easy solubility in both hot and cold water, water binding due to Hydrogen Bonding, fine film forming property, resistance to oils, greases & solvents
pH	:	5.0-6.5

Stability and storage conditions:

It is a better stabilizer as it has more galactose branch points. In water it is nonionic and hydro colloidal. It is not affected by ionic strength or pH, but will degrade at pH extremes at temperature (e.g. pH 3 at 50°C). It remains stable in solution over pH range 5-7. Combustible. A mixture of air and finely-divided powder is potentially explosive. Incompatible with strong oxidizing agents

USES:

Guar gum powder is used in pharmaceutical industries as

- Gelling/ Viscosifying/Thickening,
- Suspension, Stabilization,
- Emulsification,
- Preservation,
- Water Retention/Water Phase control,
- Binding,
- Clouding/Bodying,
- Process aid,
- Pour control for following applications.

In tablet manufacturing it is used as a binder and disintegrating agent and in micro-encapsulation of drugs.

- Suspensions
- Anti-acid formulations
- Tablet binding and disintegration agent
- Controlled drug delivery systems
- Slimming aids
- Nutritional foods

INCOMPATABILITIES:

Flammable or toxic gases are generated by combination with alkali metals, nitrides and strong reducing agents. It reacts with oxoacids and carboxylic acids to form esters and water. A mixture of air and finely divided powder is potentially explosive.

7.0 MATERIALS & METHODS

7.1 Materials used:

Table: 1

Material	Grade	Supplier
Poly Vinyl Pyrollidine	Analytical grade	Loba chemie
Magnesium stearate	Analytical grade	Loba chemie
Talc	Analytical grade	Loba chemie
Poly Vinyl Alcohol	Laboratory grade	Molychem
Micro crystalline cellulose	Laboratory grade	Merck

7.2 Equipments used

Table: 2

Instrument	Supplier / Manufacturer
USP XXVII Dissolution apparatus	Electrolab
U.V spectrophotometer	Perkin Elmer Lamda-25
Hardness tester	Monsanto
Friability tester	Veego
Digital weighing balance	Shimadzu ELB 300
pH meter	Hanna instruments, Japan.

7.3 METHODOLOGY

7.3.1. Standard curve for Lamivudine

Preperation of 0.1N HCl: [27]

8.5 ml of concentrated hydrochloric acid is taken and made to 1000ml with distilled water to get 0.1N HCl.

Stock solution:

100 mg of Lamivudine was dissolved in 100ml of 0.1N HCl, to get a solution of 1000µg/ml concentration.

Standard solution:

5ml of stock solution was made to 50 ml with 0.1N HCl thus giving a concentration of 100µg/ml. Aliquot of standard drug solution ranging from 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml and 3ml were transferred into 10ml volumetric flask and diluted up to the mark with 0.1N HCl. Thus the final concentration ranges from 5- 30µg/ml. absorbance of each solution was measured at 266nm against 0.1N HCl as a blank. A plot of concentrations of drug Vs absorbance was plotted.

Preperation of phosphate buffer P^H 7.4:[28]

Place 50ml of 0.2M potassium dihydrogen phosphate in a 200 ml volumetric flask, add the specified volume of 39.1 ml of 0.2 M sodium hydroxide and then add water to make up the volume.

Stock solution:

50 mg of Lamivudine was dissolved with pH 7.4 phosphate buffer, to get a solution of 1000µ/ml concentration.

Standard solution:

5ml of stock solution was made to 50 ml with pH 7.4 thus giving a concentration of 100µ/ml. Aliquot of standard drug solution ranging from 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml & 3ml were transferred in to 10ml volumetric flask. Thus the final concentration ranges from 5-30 µg/ml. absorbance of each solution was measured at 266nm against 0.1N HCl as a blank. A plot of concentrations of drug Vs absorbance was plotted.

7.3.2. PRE-COMPRESSION STUDY:

Evaluation of granules:

Angle of repose:

The angle of repose was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The blends were allowed to flow freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.[11]

$$\tan^{-1} \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Compressibility index:

To calculate the Carr's compressibility both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerate formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until

no further change in volume was noted. LBD and TBD was calculated and used to calculate the Carr's index and hausner's ratio.

LBD= weight of the powder / volume of the packing.

TBD = weight of the powder / tapped volume of the packing.

The compressibility index of the powder blend was determined by Carr's compressibility index.[8]

Carr's index (%) = [(TBD-LBD) x 100]/TBD

Hausner's ratio:

This value was calculated by making use of bulk and tap densities of powder samples.[21]

Hausner's ratio = TBD/LBD

Drug content:

An accurately weighed amount of powder blend (100 mg) was extracted with water and the solution was filtered through 0.45-μ membrane. The absorbance was measured at 266 nm after suitable dilution.[21]

7.3.3. PREPARATION OF MATRIX TABLETS: [11]

A non-aqueous granulation process was adopted to prepare Lamivudine tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in Table 1. All ingredients were sifted through sieve no: 40. Guar gum, mixed with Lamivudine manually and the obtained blend were mixed with Micro crystalline cellulose to form final blend. PVP K-30 was dissolved in PVA (5% w/v) and used for wet granulation of the final blend. The wet mass was passed through sieve no. 20 and wet granules dried at 50°C in an oven for 30 minutes. Dried

granules were sized by passing it through sieve no. 40 and mixed with magnesium stearate and talc for 1 minute and compressed into tablets. Tablet weight was (300mg) kept constant as shown in Table 3.

Table 3:

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6
Lamivudine	80	80	80	80	80	80
P.V.P	06	06	06	06	06	06
Guar gum	40	80	120	--	--	--
SCMC	--	--	--	40	80	120
Micro crystalline cellulose	88	48	08	88	48	08
Magnesium Stearate	03	03	03	03	03	03
Talc	03	03	03	03	03	03

Total weight of the tablet - 220mg

7.3.4. Evaluation of tablets:

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods. The weight variation was determined by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a friability tester for 4 minutes at 25 rpm.

Drug content:

Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with pH 7.4 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured at 266 nm after suitable dilution.[21]

In vitro release study:

The in vitro dissolution studies were carried out using USP XXII apparatus type II at 50 rpm. For the first 2 hr the dissolution medium was 0.1 N hydrochloric acid and phosphate buffer pH 7.4 from 3-24 hr (900 ml), maintained at 37˚C±0.50˚C. At each time point 5 ml of sample was withdrawn and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer. The release studies were conducted in triplicate, and the mean values were plotted versus time.[19]

7.3.5. Stability Studies:

The formulations were subjected to stability studies at 40 ± 2^0C and 75 ± 5 % RH for period of three months. After each month tablet samples were analyzed for physical characteristics and drug release profile.

7.3.6. Characterization of Release Kinetics:

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug release Vs Time, First order as log cumulative percentage of drug remaining Vs time, and Higuchi's model as cumulative percentage of drug released vs. square root of time.

$$C = K_o t \quad \text{..... (1)}$$

Where K_0 is the zero order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\text{Log } C = \log C_o - Kt/2.303 \quad \text{..... (2)}$$

Where C_0 is the initial concentration of drug, *k* is the first order constant, and t is the time.

$Q = kt^{1/2}$ …… (3)

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Mechanism of drug release:

The release of Lamivudine from the SR tablet was studied upto 2hrs in 900ml of 0.1 N HCl and 900ml of phosphate buffer pH 7.4 upto 24 hrs as dissolution medium using a USP dissolution paddle assembly at 50 rpm and $37^0C \pm 0.5^0C$. An aliquot was withdrawn at specific time intervals, filtered and diluted to 10ml with the dissolution medium, and drug content was determined by UV-Visible spectrometer at 266 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume.

Dissolution studies were performed 3 times for a period of 24 hrs and the mean value were taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Kinetic analysis: [29, 30]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero- order kinetic model- cumulative % drug released versus time.
2. First- order kinetic model-Log cumulative percent drug remaining versus time.
3. Higuchi's model- cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model- Log cumulative percent drug released versus log time.

Zero order kinetics:

Zero order release would be predicted by the following equation

$$A_t = A_o - K_o$$

Where,

A_t= Drug release at time‘t’

A_o=Initial drug concentration.

K_O=Zero-order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero-order release kinetics, with a slope equal to k^o.

First order kinetics:

First-order release would be predicted by the following equation

$$\text{Log } C = \log C_o - k_t/2.303$$

Where,

C = Amount of drug remained at time‘t’.

C_o= Initial amount of drug.

K = first- order rate constant (hr^{-1}) X

When the data is plotted as lo cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with the slope values.

Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = [D\varepsilon/\tau\,(2A - \varepsilon Cs)Cst]^{1/2}$$

Where,

Q = Amount of drug release ant time ‘t’

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs= the solubility of the drug in the matrix.

τ = Tortuosity.

ε = Porosity of the matrix.

When the data is plotted according to equation i.e. cumulative drug release versus square root time yields a straight line, indication that the dru was released by diffusion mechanism. The slope is equal to 'k'.

Korsmeyer equation/ Peppa's model.

To study the mechanism of drug release from the sustained-release matrix tablets of Lamivudine, the release data were also fitted to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems.

$$M_t/M_a=Kt^n$$

Where,

M_t/M_a= the fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristic of the drug / polymer system.

n = Diffusion exponent releated to the mechanism of the release.

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'k' can be obtained from y- intercept. For Fickian release 'n'=0.5 while for anomalous transport 'n' ranges between 0.5 and 1.0.

Table: 4

n Value	Drug Release
n<0.5	Fickian Release
0.5<n<1	Non-Fickian Release
n>1	Case II Transport

8.0 RESULTS & DISCUSSION

Standard Curve of Lamivudine was determined by plotting absorbance (nm) versus concentration (mcg/ml) at 266 nm and it was found to follow the Beer's law in the range 10 – 100 mcg/ml. The results obtained are as follows: -

8.1. STANDARD CURVE OF LAMIVUDINE IN 0.1N HCl

Table: 5

Sl. No	Concentration (mcg/ml)	Absorbance in 0.1N HCl
1	0	0
2	10	0.025
3	20	0.563
4	30	1.057
5	40	1.579
6	50	1.98
7	60	2.346
8	70	2.713
9	80	2.978
10	90	3.349
11	100	3.503
Slope		**0.0383**
Correlation Coefficient		**0.9862**

8.2. STANDARD CURVE OF LAMIVUDINE IN PO_4 BUFFER pH 7.4

Table: 6

Sl. No	Concentration (mcg/ml)	Absorbance in PO_4 buffer pH 7.4
1	0	0
2	10	0.137
3	20	0.281
4	30	0.445
5	40	0.558
6	50	0.717
7	60	0.860
8	70	0.979
9	80	1.121
10	90	1.246
11	100	1.374
Slope		**0.0138**
Correlation Coefficient		**0.9998**

The linear regression analysis was done on absorbance data points.

A straight-line equation *was* generated to facilitate the calculation of amount of drug. The equation is as follows.

(Y = mx+c)

Where ***Y***= Absorbance, ***m*** = slope, ***x*** = Concentration, ***c*** = Intercept.

8.3. PRE-COMPRESSION STUDIES:

Drug content determination: An accurately weighed amount of powder blend (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane. Aliquots of different concentration were prepared by suitable dilution after sonication and filtering the stock solution and absorbance was measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve. The drug content was obtained by linear regression analysis of calibration curve. The drug content of all formulations is given in table.

Table 7: PRE-COMPRESSION STUDIES

F. code	Angle of Repose (q)	Bulk Density	Tap Density	Compressibility index (%)	Hausner's ratio	% Drug Content
F1	24.29± 1.29	0.2762± 0.008	0.3250± 0.008	15.02±0.81	1.177±0.011	99.36± 0.304
F2	24.38± 1.52	0.2738± 0.011	0.3220± 0.017	14.92±1.12	1.175±0.015	99.19± 0.069
F3	29.20± 1.86	0.2622± 0.015	0.3145± 0.021	16.59±0.97	1.199±0.014	99.21± 0.185
F4	26.36± 1.73	0.2287± 0.009	0.2591± 0.014	11.71±1.56	1.133±0.020	99.27± 0.121
F5	27.35± 1.32	0.2154± 0.006	0.2467± 0.007	12.67±0.58	1.145±0.008	99.15± 0.209
F6	28.64± 1.58	0.2119± 0.006	0.2407± 0.005	11.98±1.58	1.136±0.021	99.36± 0.304

The results of angle of repose and compressibility index (%) ranged from (24.29 ± 1.29 to 29.20 ± 1.86) and (11.71 ± 1.56 to 16.59 ± 0.97) respectively. The results of loose bulk density and tapped bulk density ranged from (0.2119±0.006 to 0.2762±0.008) and (0.2407±0.005 to 0.3250±.008) respectively. The results of angle of repose (< 30) indicate good flow properties of granules. This was further supported by lower compressibility index values.

8.4. POST – COMPRESSION STUDIES:

Table 8: POST – COMPRESSION STUDIES

Formulation Code	**Hardness** $Kg\backslash cm^2$	**Friability (%)**	**Tablet weight(mg)**	**% Drug Content**
F1	**7.02 ± 0.13**	**0.120**	**220.94**	**99.11±0.185**
F2	**6.82 ± 0.12**	**0.039**	**220.21**	**99.15±0.121**
F3	**6.88 ± 0.20**	**0.080**	**220.45**	**99.07±0.304**
F4	**7.34 ± 0.32**	**0.079**	**220.81**	**99.19±0.185**
F5	**7.22 ± 0.18**	**0.099**	**220.04**	**98.95±0.184**
F6	**7.16 ± 0.14**	**0.139**	**220.05**	**99.19±0.304**

The physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table. Tablet hardness was found to be good (between 6.82 ± 0.12 to 7.34 ± 0.32 $kg/cm^{2)}$ depending on the compression force applied.

The percentage friability of the tablets of all the formulations ranged from (0.079 to 0.139 %), which is less than 0.5% (wt/wt) indicating that the friability is within the prescribed limits.

Weight variation results of matrix tablets ranged from to 220.04 to 220.94mg.For weight variation test, the pharmacopoeial deviation for tablets of more than 220 mg is ± 5%.The average percentage deviation of all tablet formulation was found to be within the above limit, incompliance with official standards.

Drug content was found to be uniform among different formulations of the tablets and ranged from 98.95±0.184 to 99.15±0.121 % indicating that the compression method utilized is an acceptable method for preparing good-quality matrix tablets of Lamivudine.

8.5. In-vitro Dissolution Studies:

The in vitro release profiles of Lamivudine from various matrix formulations are represented in Figure.

Table 9:

In vitro Dissolution profile of formulation F1

Sl No	Time (hrs)	Absorbance @ 266nm	*Cumulative percentage of drug released
1	0	0	0
2	0.5	0.0201	22.347 ± 0.90
3	1	0.0271	30.176 ± 0.42
4	2	0.0328	36.594 ± 0.55
5	4	0.0414	46.212 ± 1.10
6	6	0.0456	50.940 ± 0.66
7	8	0.0615	68.667 ± 1.00
8	10	0.0717	80.094 ± 0.49
9	12	0.0876	97.919 ± 0.65

*Average of three value

± Standard deviations

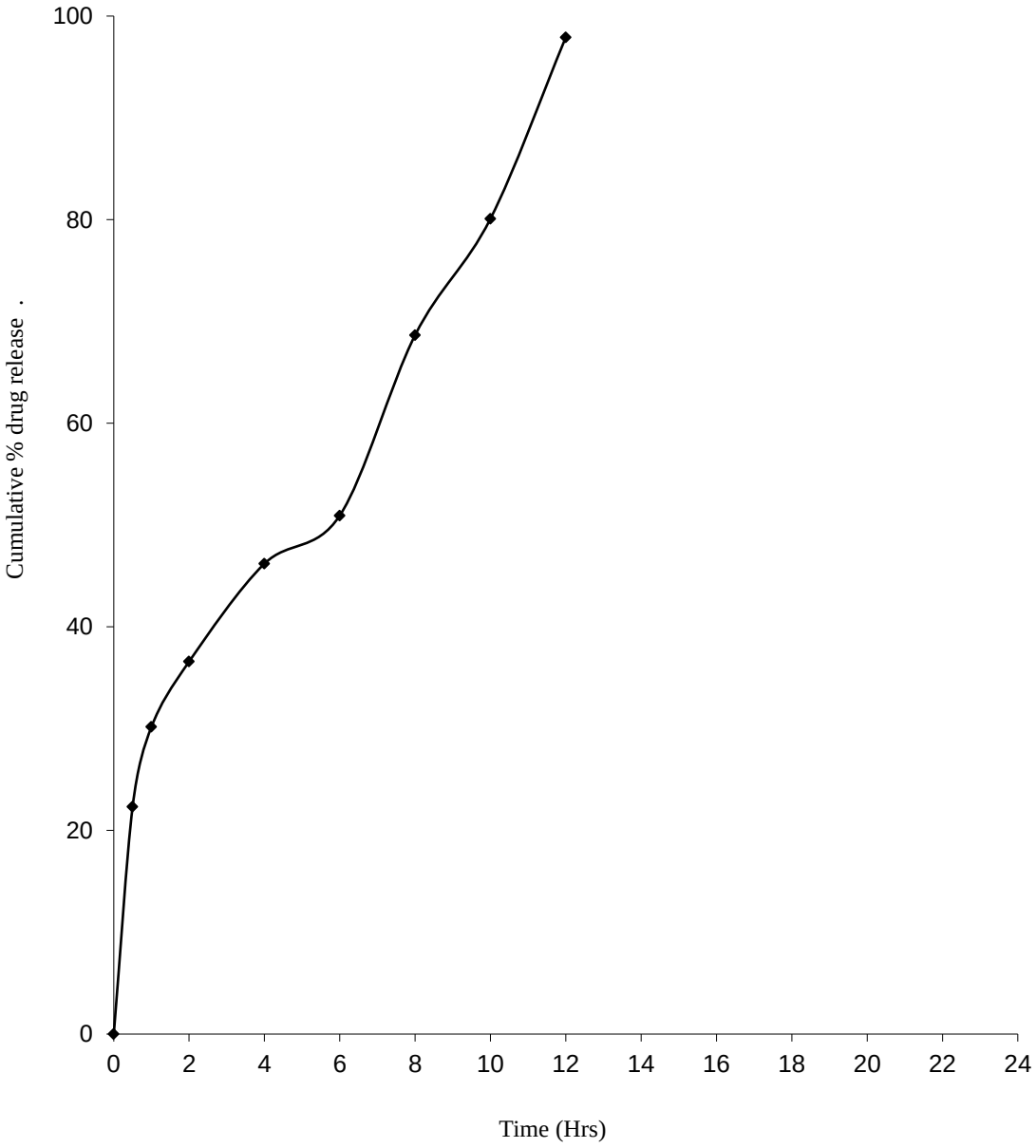


Fig: 3 In vitro dissolution release profile of formulation F1

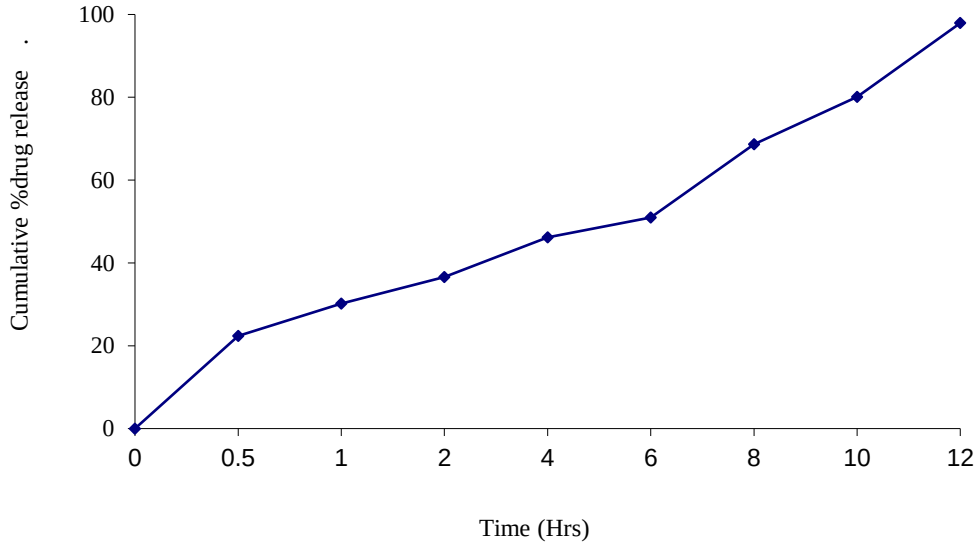


Fig: 4 Zero order release profile of formulation F1

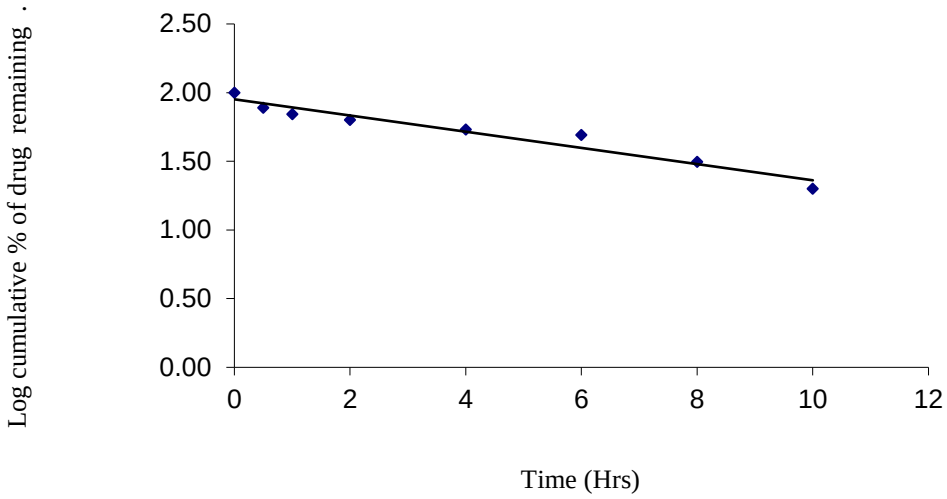


Fig: 5 First order release profile of formulation F1

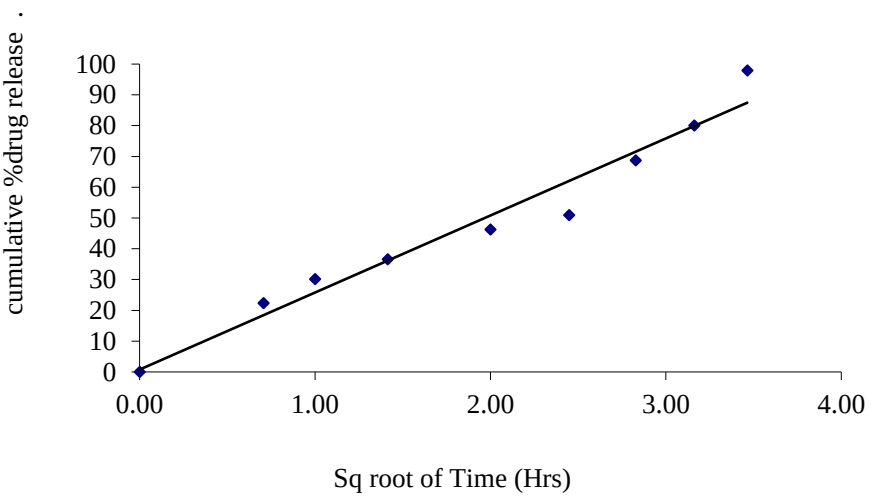


Fig: 6 Higuchi release profile of formulation F1

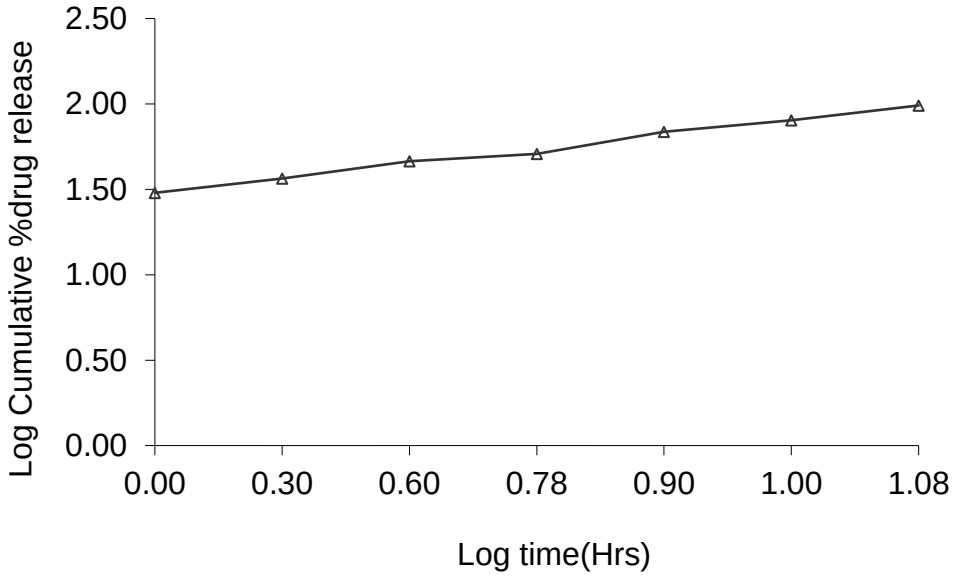


Fig: 7 Koresmeyer release profile of formulation F1

Table: 10

In vitro Dissolution profile of formulation F-2

Sl No	Time (hrs)	**Absorbance (nm)**	***Cumulative percentage of drug released**
1	0	0.000	0.00
2	0.5	0.016	17.50±0.80
3	1	0.020	22.40±0.75
4	2	0.028	31.23±0.65
5	4	0.044	49.09±0.90
6	6	0.050	56.25±0.54
7	8	0.068	75.44±0.49
8	10	0.077	86.51±1.40
9	12	0.081	91.09±0.90
10	16	0.088	98.61±0.80

*Average of three value

± Standard deviations

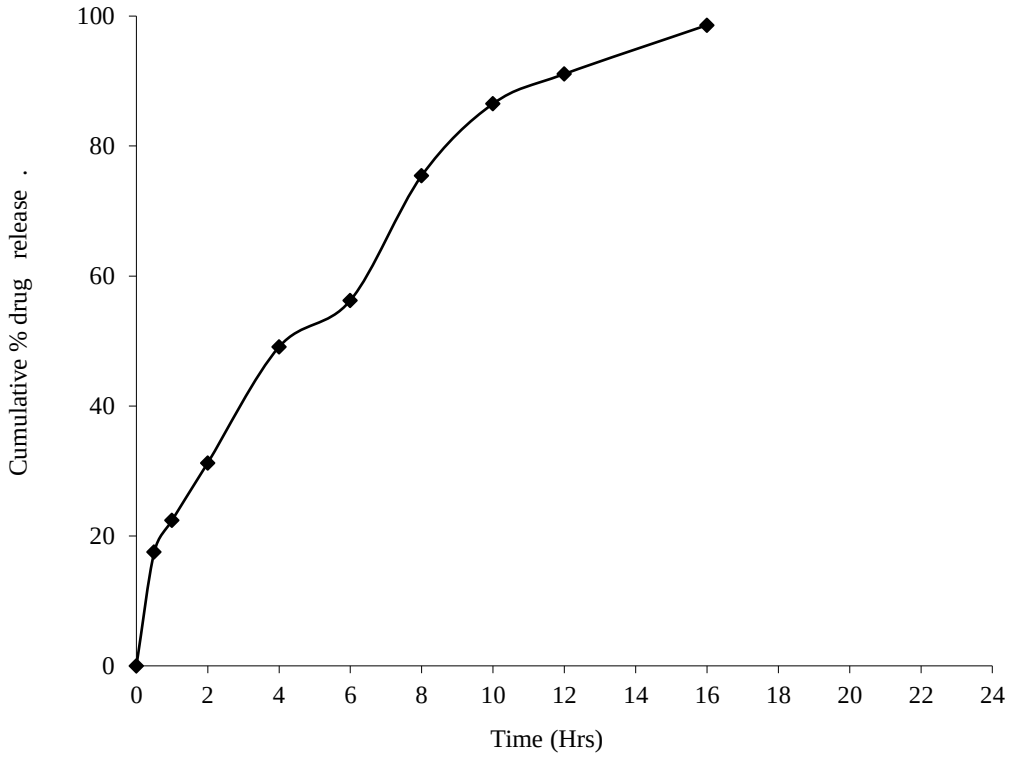


Fig: 8 In vitro dissolution release profile of formulation F2

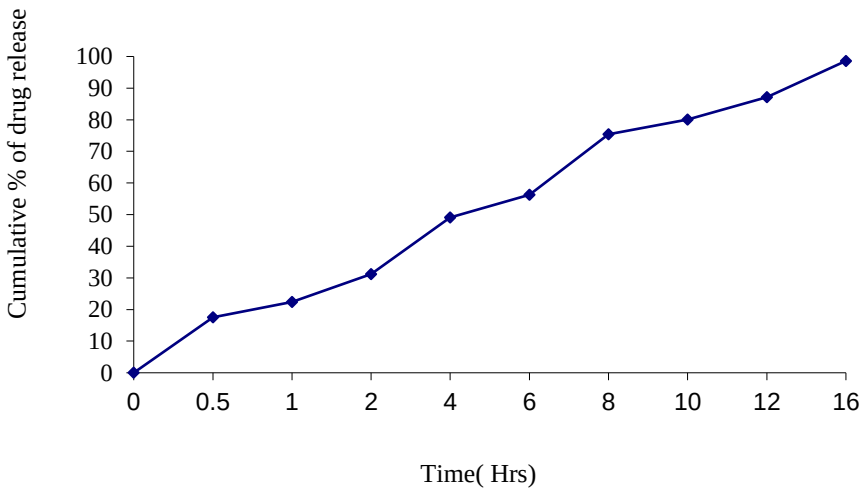


Fig: 9 Zero order release profile of formulation F-2

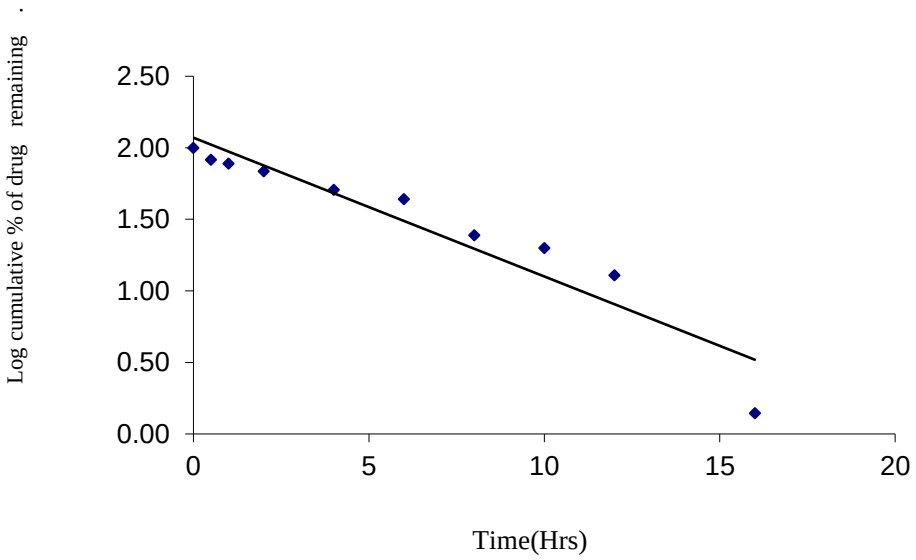


Fig: 10 First order release profile of formulation F-2

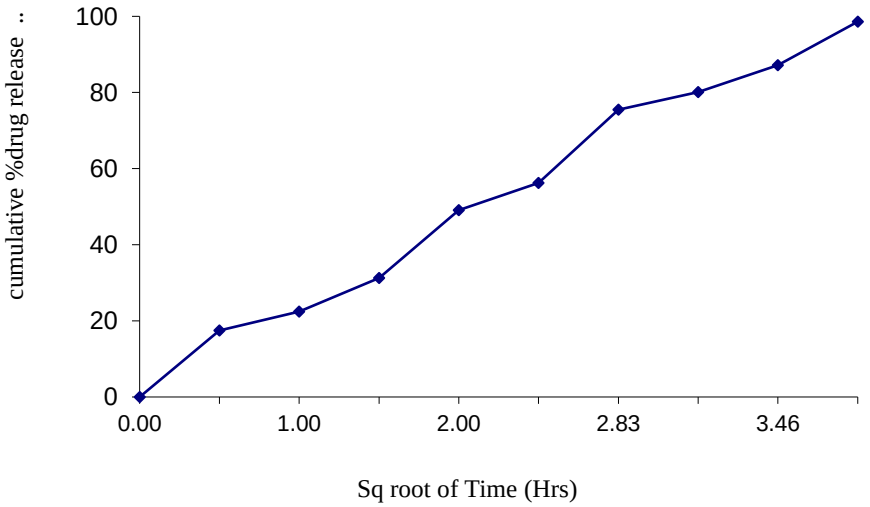


Fig: 11 Higuchi release profile of formulation F2

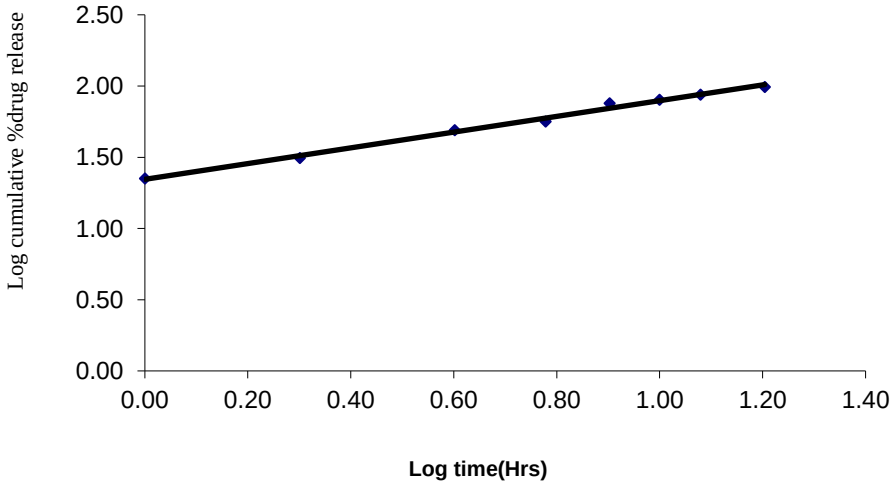


Fig: 12 Koresmeyer release profile of formulation F2

Table: 11

In vitro dissolution profile of formulation F3

Sl No	Time(hrs)	Absorbance (nm)	*Cumulative percentage of drug released
1	0	0	0.000
2	0.5	0.014	15.962±1.00
3	1	0.018	20.000±0.65
4	2	0.025	27.885±0.58
5	4	0.028	31.258±0.48
6	6	0.035	39.089±1.20
7	8	0.042	46.929±1.30
8	10	0.057	63.688±0.60
9	12	0.060	67.100±0.45
10	16	0.066	73.857±0.84
11	20	0.070	78.394±0.76
12	24	0.078	87.346±0.65

*Average of three value

± Standard deviations

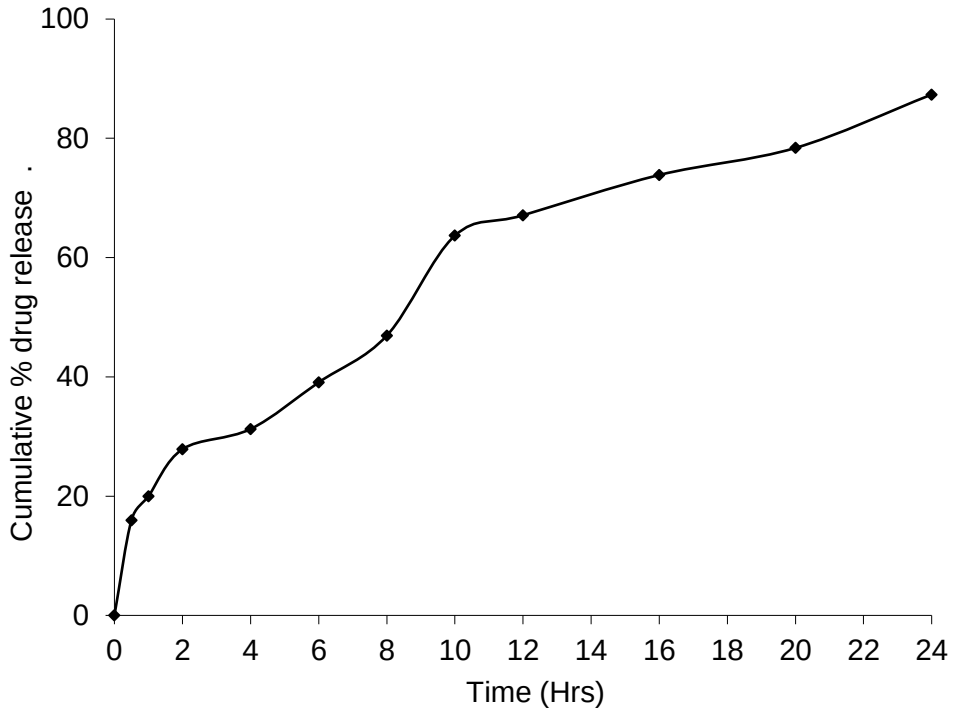


Fig: 13 In vitro dissolution release profile of formulation F3

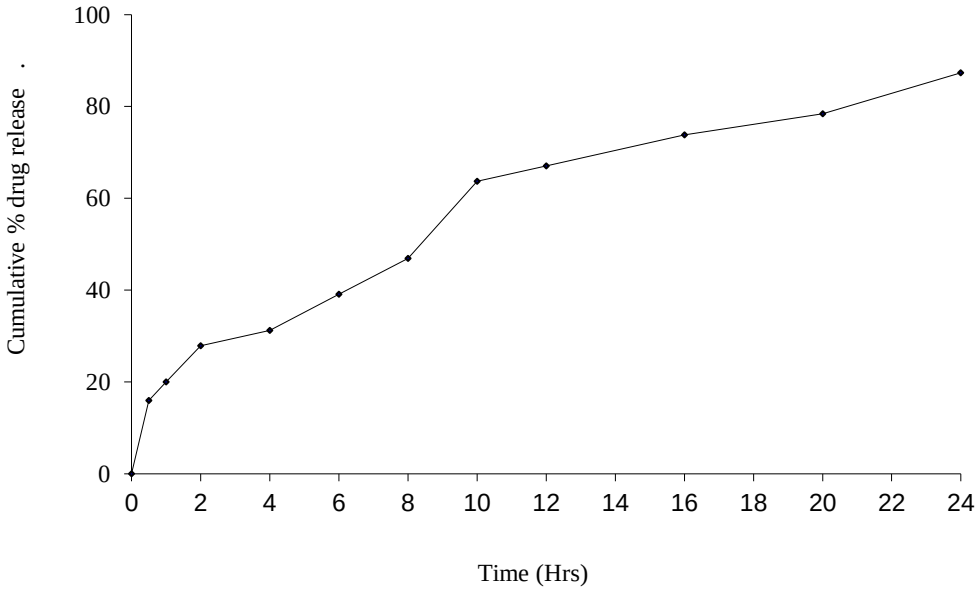


Fig: 14 Zero order release profile of formulation F3

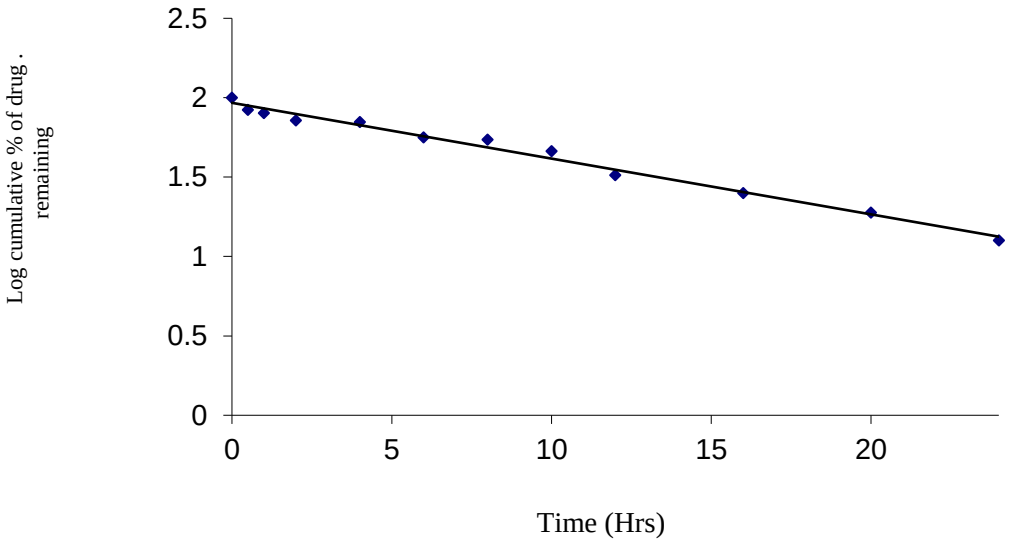


Fig: 15 First order release profile of formulation F-3

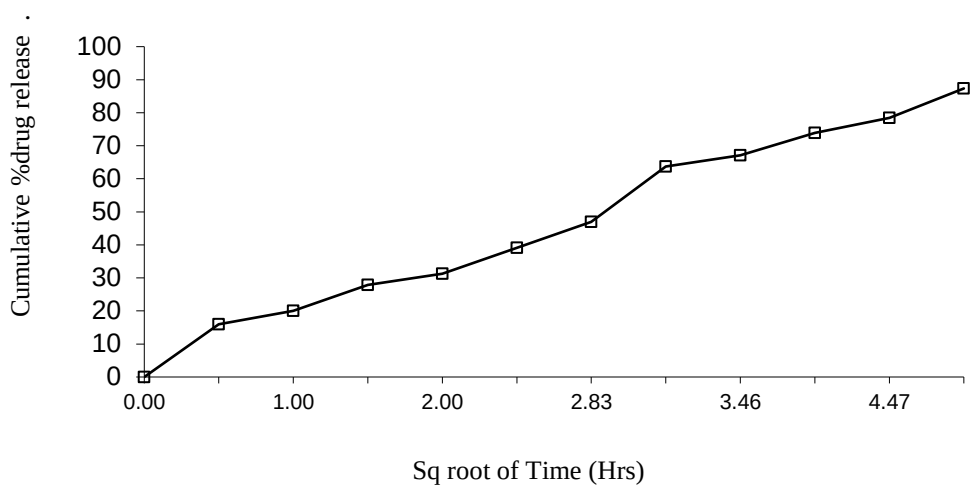


Fig: 16 Higuchi release profile of formulation F-3

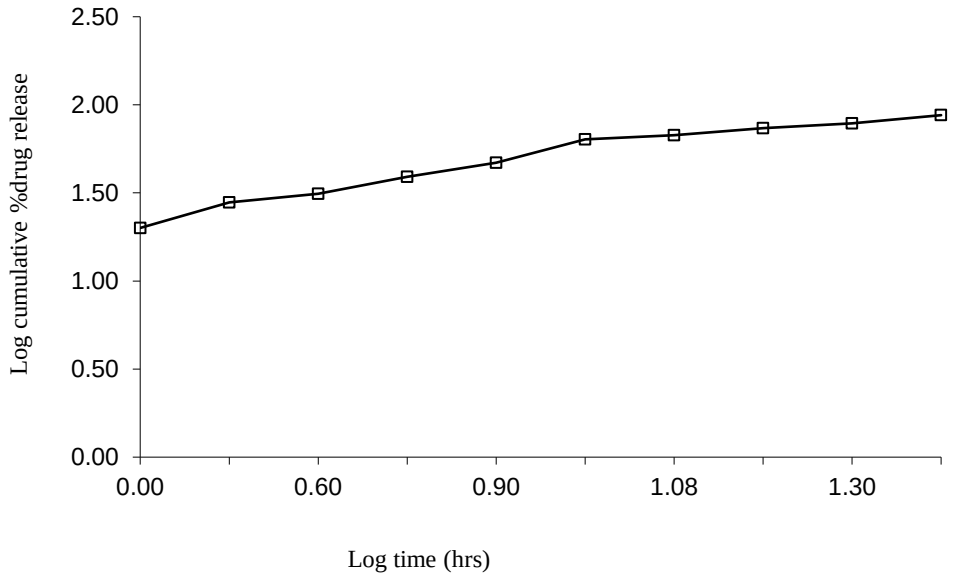


Fig: 17 Koresmeyer release profile of formulation F-3

Table: 12

In vitro dissolution profile of formulation F4

Sl No	Time(hrs)	**Absorbance (nm)**	***Cumulative percentage of drug released**
1	0	0.0000	0.000
2	0.5	0.0151	16.819±0.80
3	1	0.0195	21.738±0.55
4	2	0.0280	31.230±0.48
5	4	0.0350	39.061±0.55
6	6	0.0472	52.693±0.65
7	8	0.0525	58.654±0.48
8	10	0.0605	67.630±0.35
9	12	0.0681	76.170±0.90
10	16	0.0694	77.702±0.15
9	20	0.0744	83.357±0.20
10	24	0.0812	91.023±0.10

*Average of three value

± Standard deviations

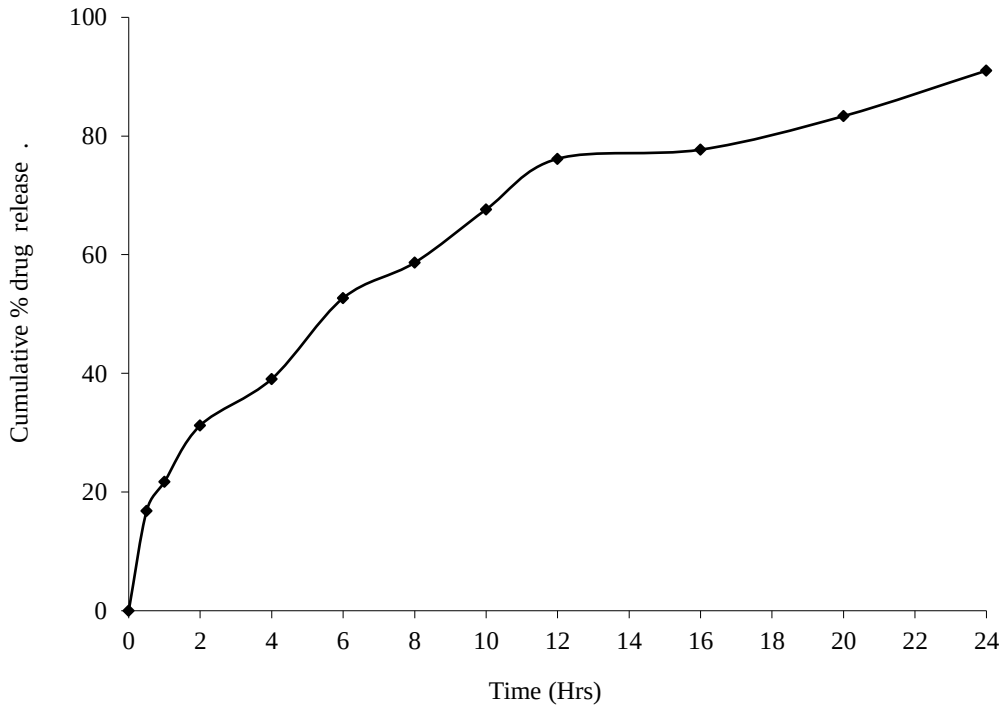


Fig: 18 In vitro dissolution release profile of formulation F4

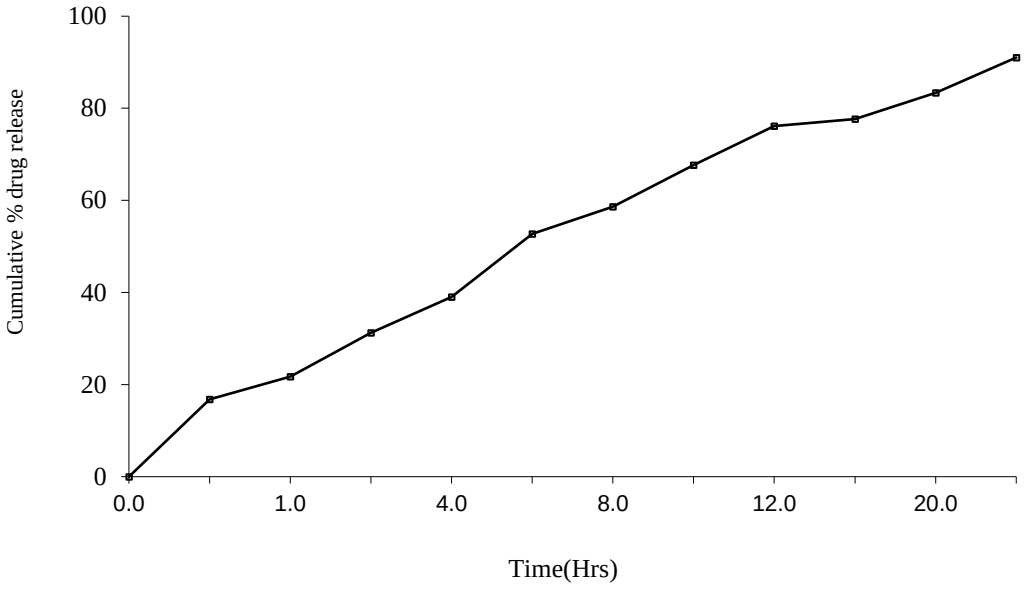


Fig: 19 Zero order release profile of formulation F4

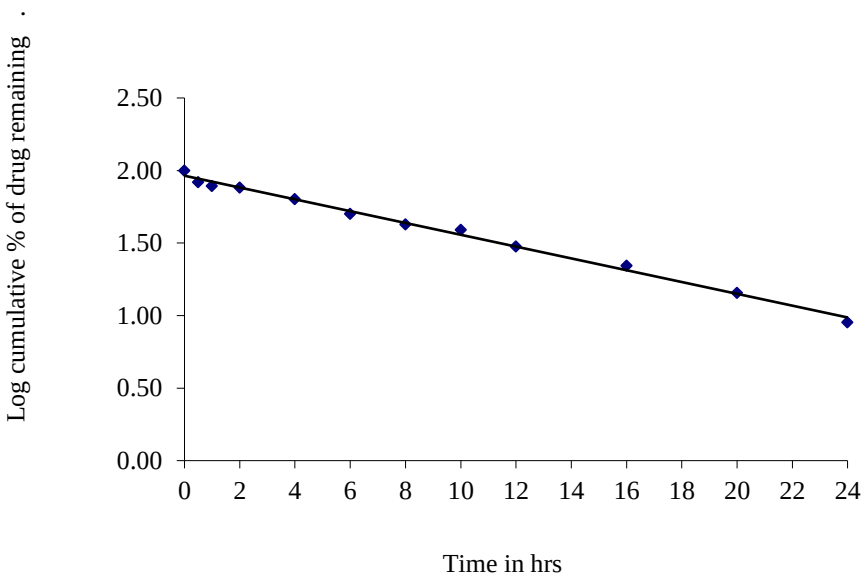


Fig: 20 First order release profile of formulation F4

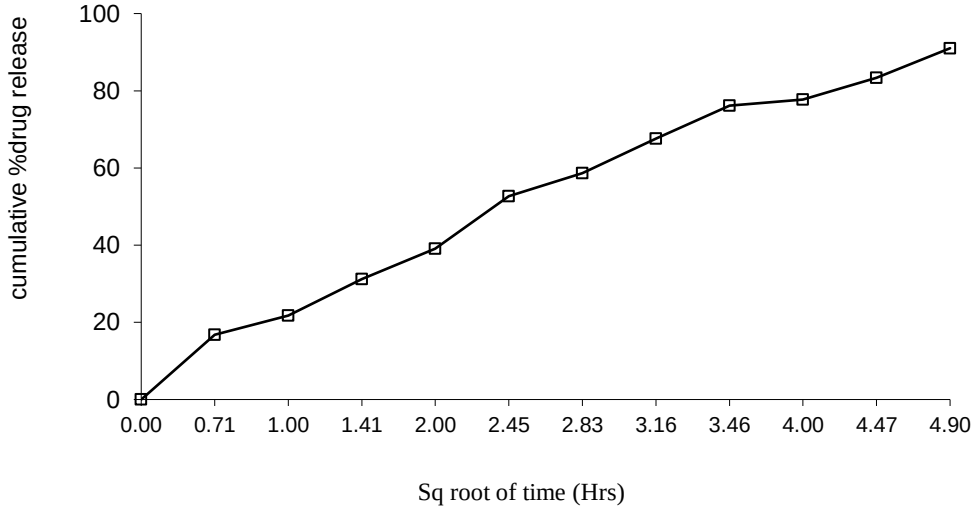


Fig: 21 Higuchi release profile of formulation F4

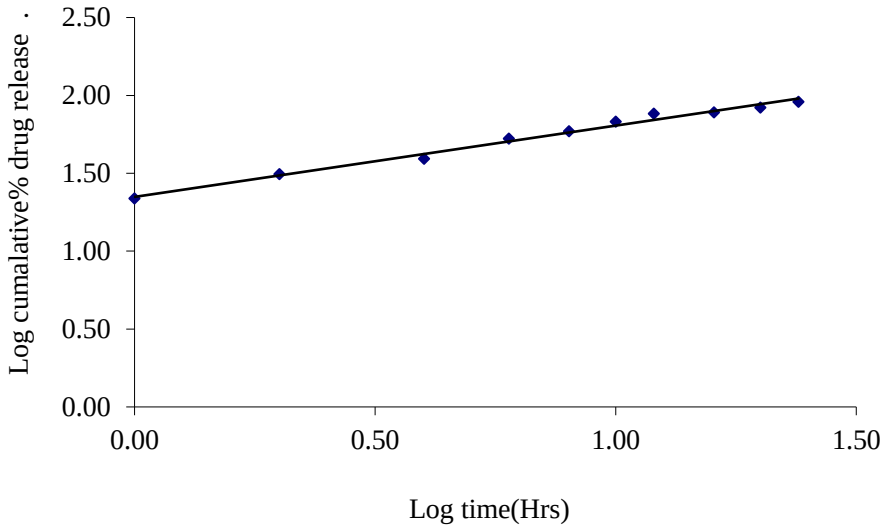


Fig: 22 Koresmeyer release profile of formulation F4

Table: 13

In vitro dissolution profile of formulation F5

Sl No	Time (hrs)	**Absorbance (nm)**	***Cumulative percentage of drug released**
1	0	0.0000	0.000
2	0.5	0.0170	18.900±0.60
3	1	0.0207	23.100±1.10
4	2	0.0250	27.892±0.34
5	4	0.0348	38.800±0.54
6	6	0.0496	55.317±0.45
7	8	0.0501	56.000±0.65
8	10	0.0585	65.394±0.45
9	12	0.0625	69.919±1.25
10	16	0.0715	80.055±0.46
9	20	0.0793	88.764±0.57
10	24	0.0829	92.915 ±0.53

*Average of three value

± Standard deviations

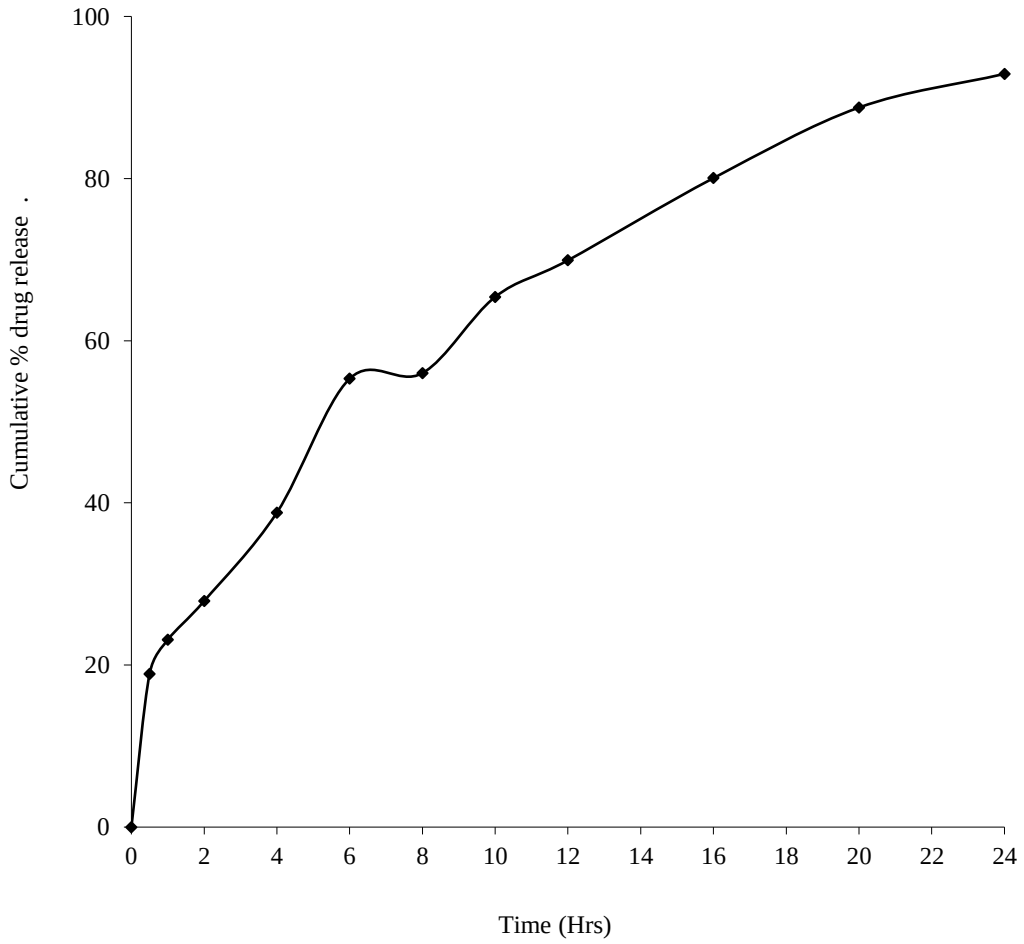


Fig: 23 In vitro dissolution release profile of formulation F5

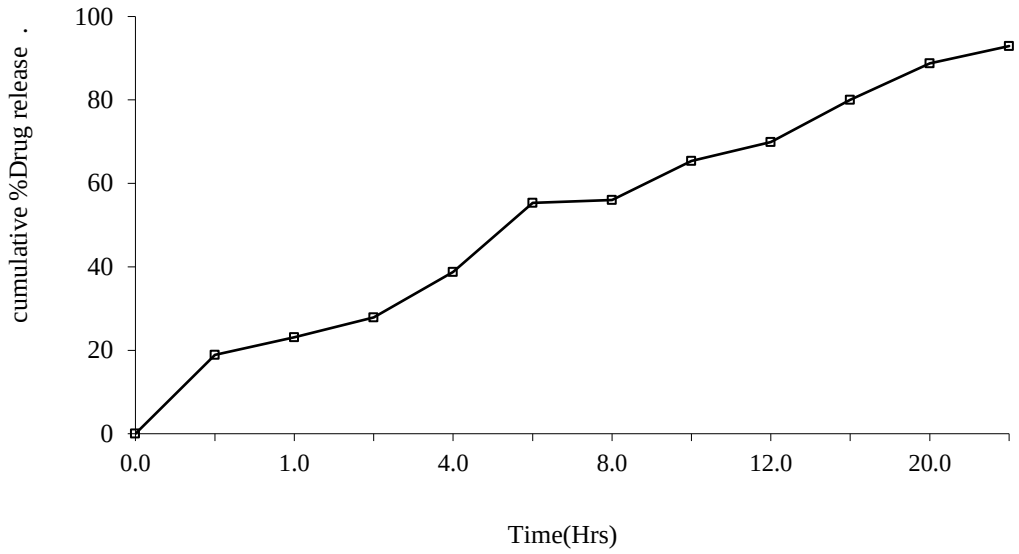


Fig: 24 Zero order release profile of formulation F5

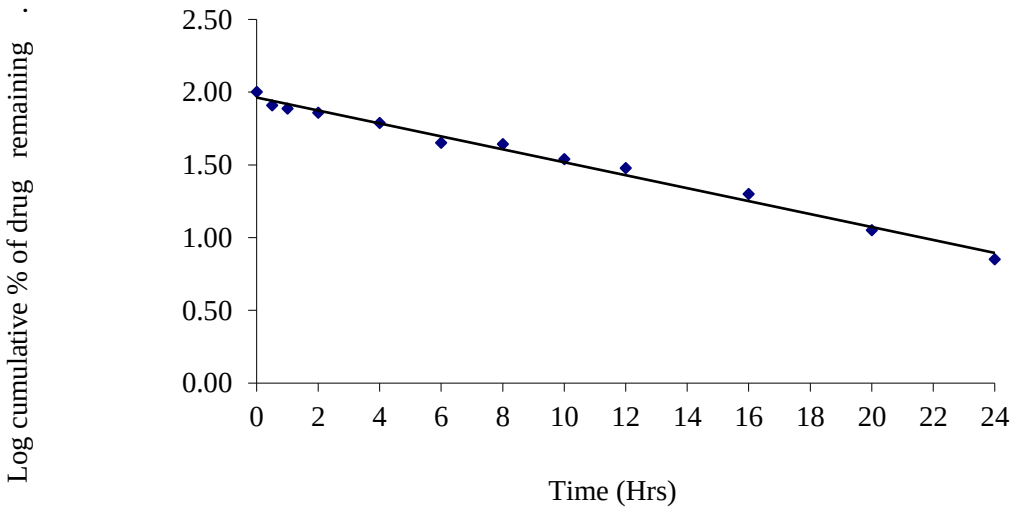


Fig: 25 First order release profile of formulation F5

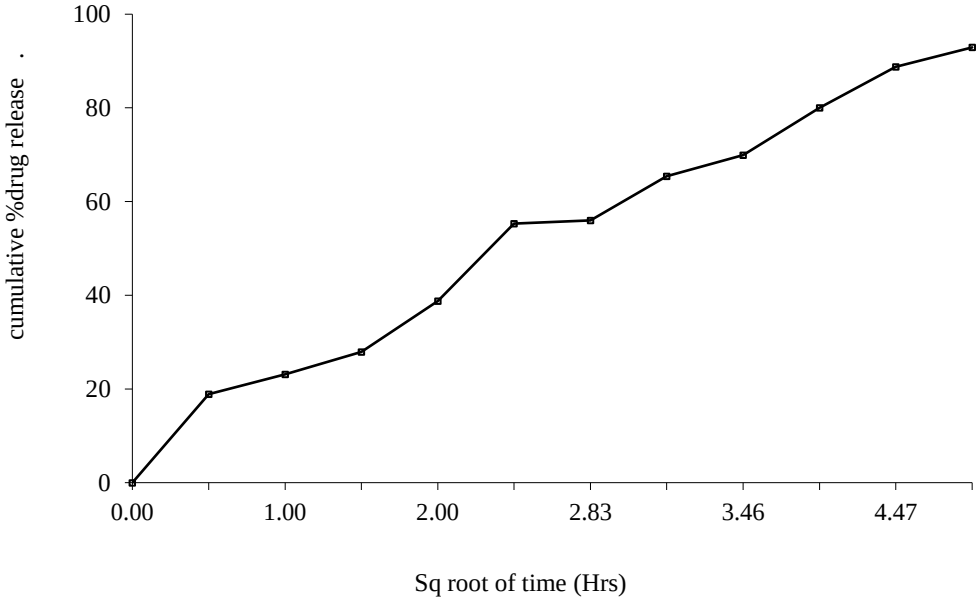


Fig: 26 Higuchi release profile of formulation F-5

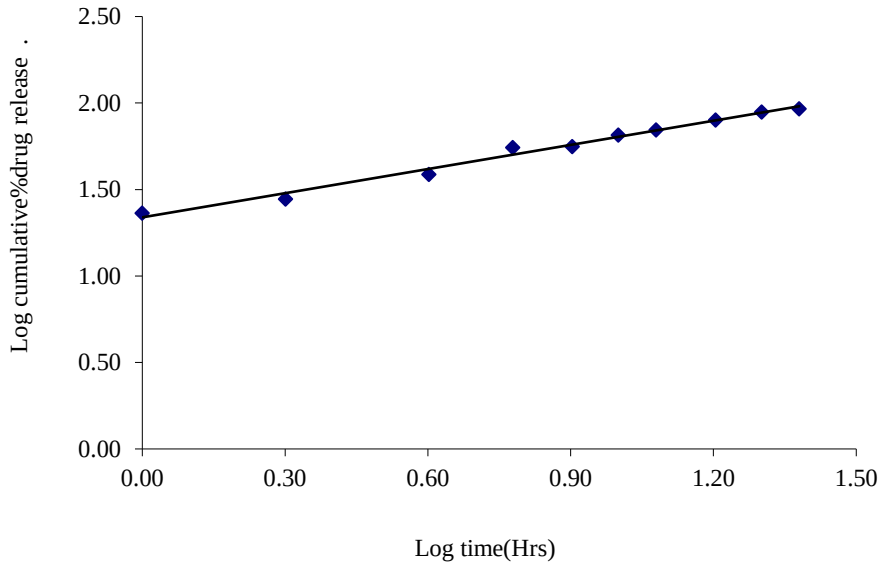


Fig: 27 Koresmeyer release profile of formulation F5

Table: 14

In vitro dissolution profile of formulation F6

Sl No	Time (hrs)	**Absorbance (nm)**	***Cumulative percentage of drug released**
1	0	0.0000	0.000
2	0.5	0.0151	17.819±0.80
3	1	0.0195	20.738±0.55
4	2	0.0280	34.230±0.48
5	4	0.0350	38.061±0.55
6	6	0.0472	51.693±0.65
7	8	0.0525	56.654±0.48
8	10	0.0605	64.630±0.35
9	12	0.0681	77.170±0.90
10	16	0.0694	77.702±0.15
11	20	0.0744	85.357±0.20
12	24	0.0812	94.023±0.10

*Average of three value

± Standard deviations

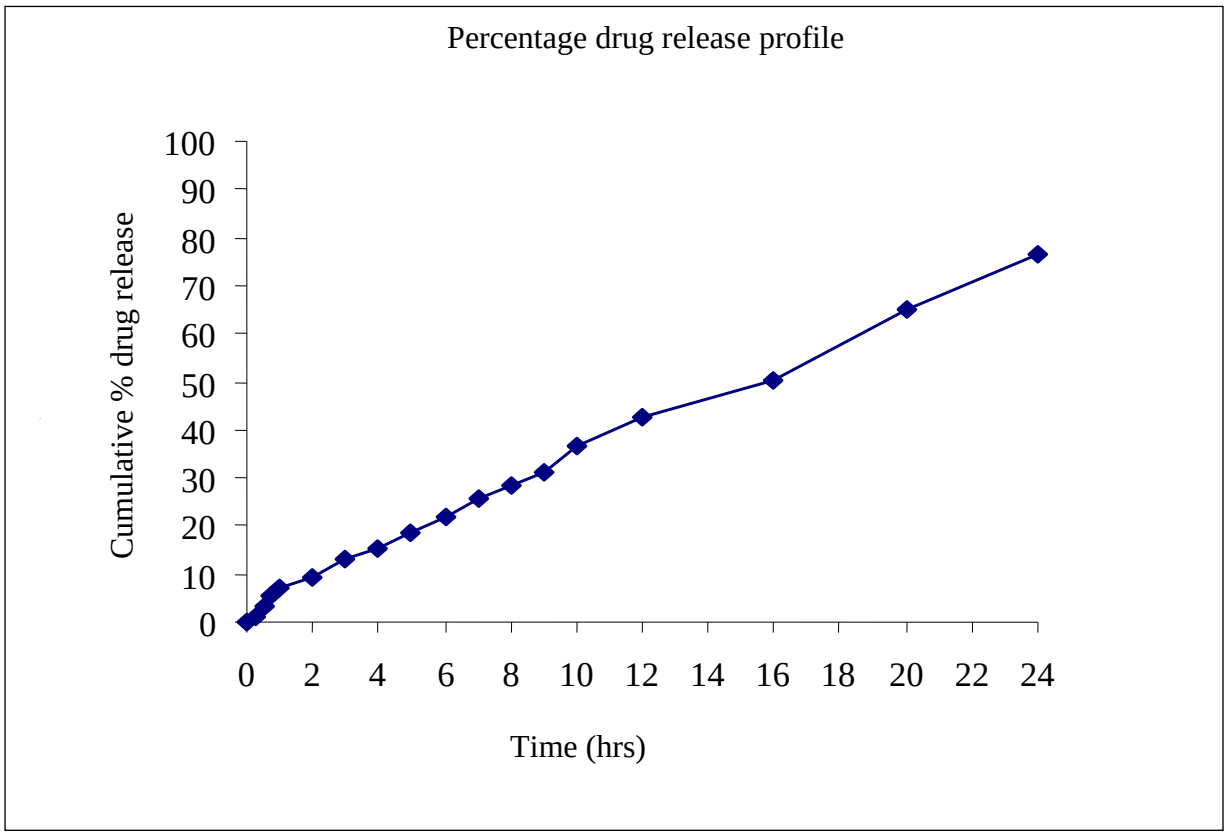


Fig: 28 In vitro drug release profile of formulation FS-6

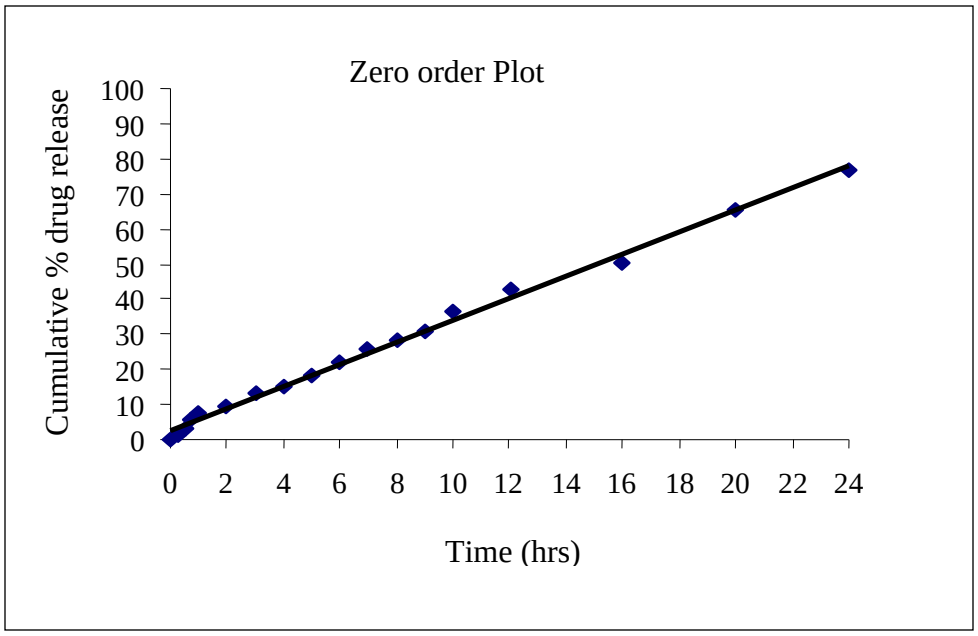


Fig: 29 Zero order release profile of formulation F6

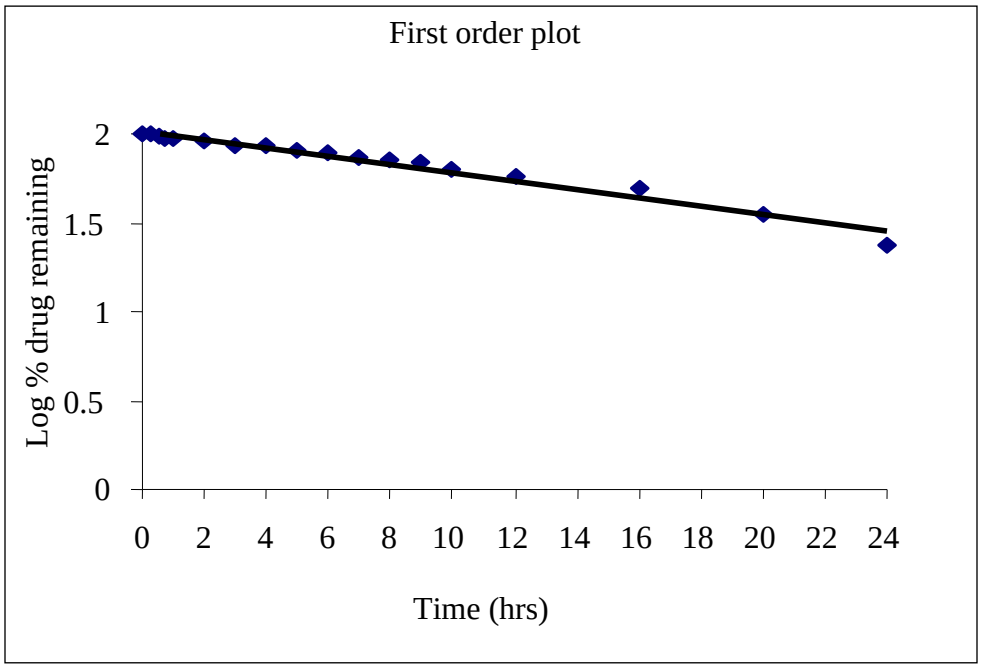


Fig: 30 First order release profile of formulation F6

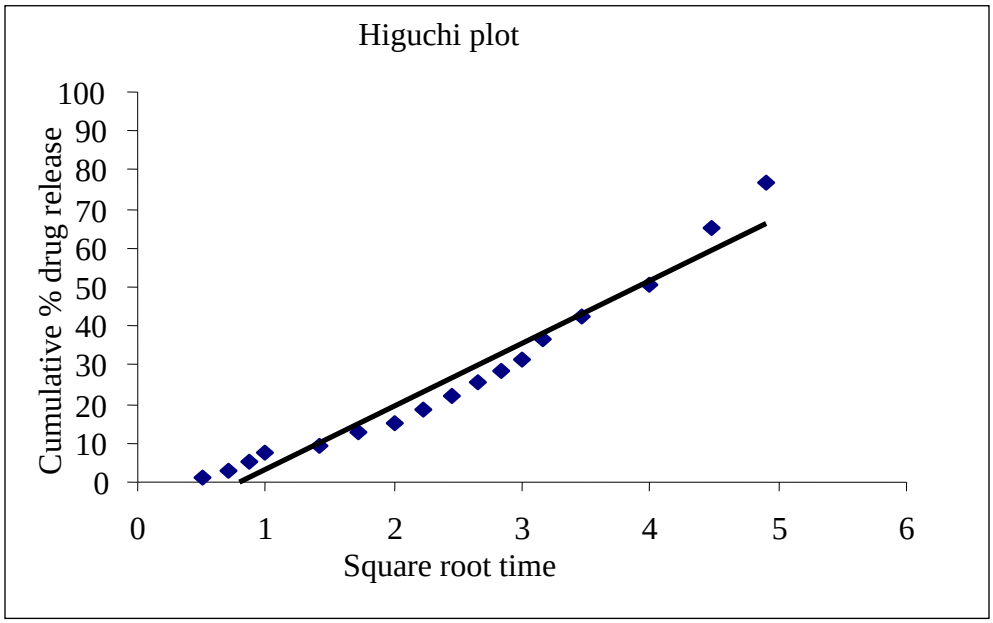


Fig: 31 Higuchi profile of formulation F6

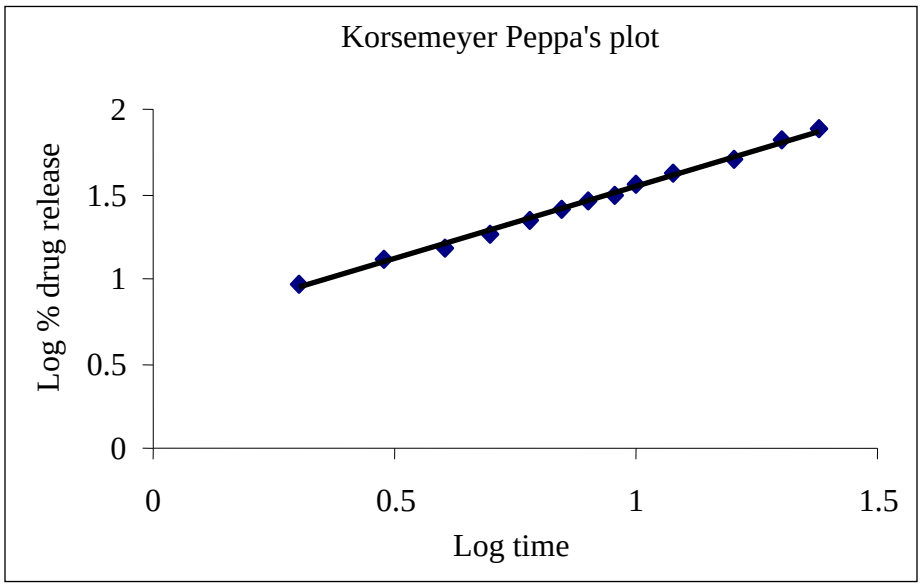


Fig: 32 Korsemeyer profile of formulation F6

The cumulative percentage drug release from the formulations F1, F2, F3, F4, F5, and F6 were found to be 97.91±0.65%, 98.61±0.80%, 87.34±0.65%, 91.02±0.10%, 92.91 ±0.53%, 94.02±0.10% respectively. It was observed that all the formulation had been showing sustained release of the drug. In general, it can be observed from figures that better release of the drug was seen from all the formulations. From results of *in vitro* dissolution studies, it can be concluded that the formulation F-2 (with Guargum) & F-6 (with SCMC) had better-sustained release than the other formulations with the same polymers.

Among all the formulation, F2 shows highest drug release (98.61%) in 16 hrs; whereas the drug release from other formulations was slow. This shows that Guargum is less permeable. The release rate of the drug could be extended by varying the polymer concentration. The data clearly indicate the drug release can be effectively controlled by varying the polymer and its ratio.

Table: 15

Kinetic data obtained from different formulations

Formulation	**Zero order**	**First order**	**Higuchi**	**koresmeyer**
F1	0.9439	0.9747	0.9596	0.9260
F2	0.9260	0.9705	0.9883	0.9899
F3	0.9134	0.9817	0.9816	0.9661
F4	0.8656	0.9804	0.9842	0.9874
F5	0.8978	0.9895	0.9922	0.9875
F6	0.977	0.9865	0.9917	0.7176

The kinetic data for all the formulations is shown in Table: 15. In order to understand the complex mechanism of drug release from the tablets, the *in vitro* Lamivudine release data were fitted to Korsmeyer-peppa's release model and interpretation of release exponent values (n) enlightens us in understanding the release mechanism from the dosage form. The regression coefficients obtained for first order

kinetics were found to be R^2 = 0.9705 to 0.9895, indicating that drug released from all the formulations followed first order kinetics. Based on these release exponent values we can say that the formulations exhibited non-fickian transport. The linearity of the plots indicates that the release process is diffusion-controlled.

Stability studies: The stability studies were performed according to ICH guidelines for 3 months and the results of the various physicochemical evaluations & dissolution studies were found to be stable in the storage period.

9.0 CONCLUSION

From the observations of the said work it could be concluded that slow and controlled release of Lamivudine for more than 12 hours was obtained by using of natural (guar gum) and more than 24 hrs by using semi synthetic polymers (sodium carboxy methyl cellulose). Both the polymers were successful in the formation of matrix and at the same time it is effective in retarding the drug release. The drug release follows first-order kinetics. The mechanism of drug release was diffusion coupled with erosion. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. The *In vitro* studies suggest that a controlled release matrix tablet of Lamivudine with a natural polymer matrix would be promising for therapy of AIDS by minimizing the side effects of the synthetic polymers. A further detailed study in human subjects will through more light on their efficacy and compliance.

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