INFLUENCE OF NATURAL AND SYNTHETIC POLYMERS ON FORMULATION AND EVALUATION OF LAMIVUDINE MATRIX TABLETS

DISSERTATION

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CERTIFICATE

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Constitutes the original work carried out by

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1.

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INTRODUCTION

For many decades, treatment of acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as drug carriers.

Drug may be administered by variety of routes but oral administration is adopted wherever possible. It is safest, easiest, and most economical route of drug administration. Amongst drugs that are administered orally solid oral dosage forms i.e. tablets and capsules, represent the preferred class of products. Out of the two oral solid dosage forms, the tablets have number of advantages like tamper proof, low cost, and speed of manufacturing (direct compression), ease of administration, patient compliance, and flexibility in formulation etc.

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Since there is increase in cost and compliance involved in the development and marketing of new drug entities, this has forced most of the pharmaceutical industries to focus their attention on the development of sustained / controlled / prolonged system.

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repos itory dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems from which

therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities.

Controlled release also denotes systems which can provide some control whether this be of a temporal or spatial nature or both for drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time[6].

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system. This is illustrated in the following figure-1[7].

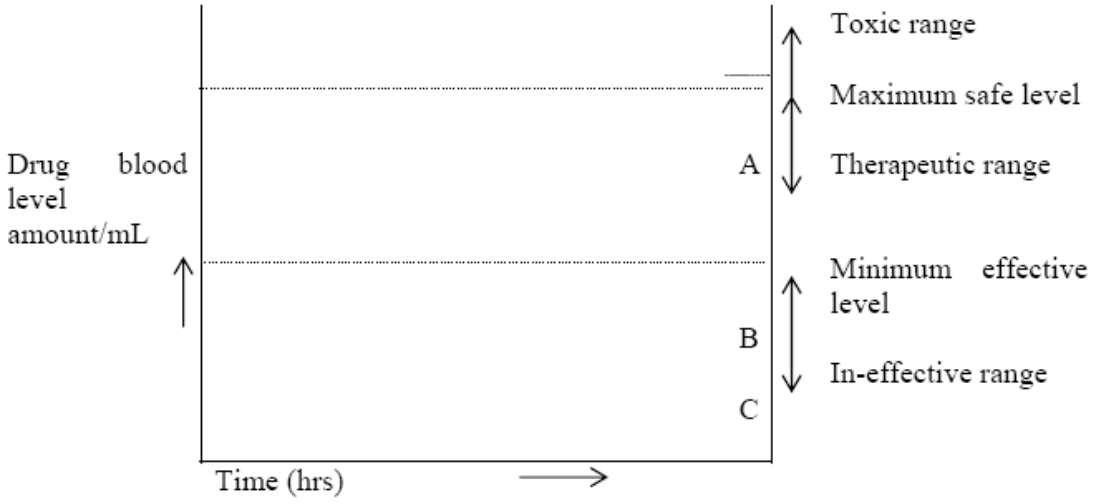


Figure-1: Drug blood levels Versus Time Profiles showing the Relationship between Controlled Release (A), Prolonged Release (B) and Conventional Release (C) Drug Delivery.

The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

1.1 Advantages of Sustained Release Dosage Forms:

1. The frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient as well.
4. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
5. Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
6. The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
7. The total amount of drug administered can be reduced, thus:
    - Maximizing availability with minimum dose;
    - Minimize or eliminate local side effects;
    - Minimize or eliminate systemic side effects;
    - Minimize drug accumulation with chronic dosing.
8. Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

9. Improve efficiency in treatment.

- Cure or control condition more promptly;
- Improve control of condition i.e., reduce fluctuation in drug level;
- Improve bioavailability of some drugs;
- Make use of special effects; e.g. sustained release aspirin for morning relief of arthritis by dosing before bed-time.

10. Economy.

1.2 Disadvantages of Sustained Release Formulations:

1. Administration of sustained release medication does not permit the prompt termination of therapy.

2. Flexibility in adjustment of dosage regimen is limited.

3. Controlled release forms are designed for normal population i.e. on the basis of average drug biologic half-lives.

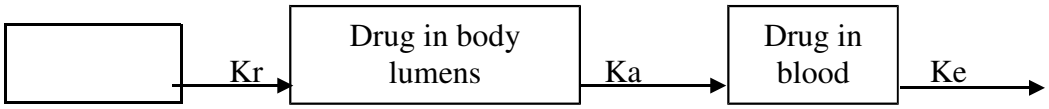
4. Economic factors must also be assessed, since more costly process and equipment are involved in manufacturing of many controlled release dosage forms.

1.3 GENERAL PRINCIPLE OF CONTROLLED – RELEASE SYSTEMS

The concept of controlled release systems is to deliver a constant supply of the active ingredient by continuous release for a certain period of time, an amount of the drug equivalent to that eliminate by the body.

The following model has shown the three major processes involved in controlled-release systems in

Figure -2.



Tablets, Capsules, Transdermal patches, Inserts, Implants, etc.

GIT, Skin surface, Oral cavity, Vagina, Rectum, etc.

Release Absorption Elimination

The kinetics of drug release will be dependent on the specific prolonged action mechanism utilized in manufacturing the controlled release system. Calculations of amount of drug needed in the sustained release component can be accomplished in a following relationship.

Rate of drug input =Rate of drug output[8] ---------- (1)

1. If it is considered that elimination is generally first order process, then

Rate of drug output = $D\ Ke$ ---------- (2)

When D is the maintenance dose, Ke is the first order rate constant of elimination.

The value of Ke can be obtained if the biological half-life drug is known

$Ke = 0.693/t_{1/2}$ - ---------- (3)

Therefore, the rate of drug out put after administering a single dose, D, can be calculated from equation.

$$\text{Rate of drug out put} = \frac{0.693\ (D)}{t_{1/2}} \quad \text{---------- (4)}$$

Substitute for Eq – 4 in Eq – 1, we have

$$\text{Rate of drug input} = \frac{0.693\ (D)}{t_{1/2}} \quad \text{---------- (5)}$$

Thus, in order to calculate the amount of drug needed in the sustained component to represent the dose require for administration at every T hr of dosing intervals, we can multiply Eq-5 by

$$\text{Amount of drug needed in the sustained component} = \frac{0.693(D)T}{t_{1/2}} \quad \text{---------- (6)}$$

1.3.1 Release Rate and Dose Consideration[9]

Conventional dosage forms include solutions, capsules, tablets, emulsions, etc. These dosage forms can be considered to release their active ingredients into an absorption pool immediately.

$$\text{Dosage form} \xrightarrow[\text{Drug Release}]{K_r} \text{Absorption pool} \xrightarrow[\text{absorption}]{K_a} \text{Target area} \xrightarrow[\text{elimination}]{K_e}$$

Where,

K_r = First order rate constant for drug release.

K_a = First order rate constant for drug absorption.

K_e = First order rate constant for overall drug elimination.

- For immediate release dosage forms $K_r >>> K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.
- For non-immediate release dosage forms, $K_r <<< K_a$, that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to

$$\text{Dosage form} \xrightarrow{K_r} \text{Target area} \xrightarrow{K_e}$$

Thus, the effort to develop a delivery system that release drug slowly must be directed primarily at altering the release rate by affecting the value of K_r. The ideal goal in designing a controlled-release system is to deliver drug to the desired site at a rate according to needs of the body, i.e. a self-regulated system based on feedback control but this is a difficult assignment.

1.4 Terminology[10]:

Controlled drug delivery or modified release delivery systems may be defined as follows:-

1.4.1 Controlled – Release formulation:

The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systemically, for a specific period of time.

1.4.2 Repeat action preparations:

A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose. The main advantage is that it provides the convenience of supplying additional dose(s) without the need of re-administration. It has disadvantage that the blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy.

1.4.3 Extended-Release formulations:

Extended-Release formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. This helps avoid the side effects associated with high concentration.

1.4.4 Delayed release preparations:

The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic p^H of the gastric fluid.

1.4.5 Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

1.4.6 Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug with in organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

1.5 PHYSICO-CHEMICAL FACTORS INFLUENCING ORAL CONTROLLED RELEASE DOSAGE FORM[11]:

1.5.1 Dose size:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1 gm is considered maximal.

1.5.2 Ionization, pKa and aqueous solubility:

The pH partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues therefore it is important to note the relationship between pKa of the compound and its absorptive environment. For many compounds the site of maximum absorption will also be the area in which the drug is least soluble. For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For dissolution of diffusion controlled forms, much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

1.5.3 Partition coefficient:

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Further more partitioning effects apply equally to diffusion through polymer membranes

1.5.4 Drug Stability:

Drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine However, such a strategy would be detrimental for drugs that either are unstable in the small intestine or undergo extensive gut wall metabolism, as pointed out in the decreased bioavailability of some anticholinergic drugs from controlled /sustained release formulations.

1.5.5 Protein Binding :

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part

recirculated and not eliminated, drug protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Levine has shown that quarternary ammonium compounds bind to mucin in the GIT. Drug bound to mucin may act as depot and act as a sustained release product.

1.6 BIOLOGICAL FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM:

1.6.1 Biological Half Life:

Therapeutic compounds with short half-lives are excellent candidates for controlled release preparations. Drug with very short half-life will require excessively large amounts of drug in each dosage unit to maintain controlled effects, thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half lives, generally greater than 8 hours are generally not used in controlled release dosage forms since their effect is already sustained and also GI transit time is 8-12 hrs.

Drugs with short half-lives require frequent dosing in order to minimize fluctuations in blood levels accompanying conventional oral dosage regimens. Therefore controlled release dosage forms would appear very desirable for drugs.

Infact sustained release formulations of prednisolone sodium phosphate, a methyl prednisolone have been shown to be equally effective as conventional tablets, offering no advantages over the latter.

1.6.2 Absorption:

The characteristics of absorption of a drug can greatly affect its suitability as a controlled release product. Assuming the transit time of most drugs and devices in the absorptive regions before release is complete. The absorption rate constant is an apparent rate constant. It should in actuality be the release rate constant of the drug from dosage form.

1.6.3 Metabolism:

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems.

TABLE 1

Classification of Sustained/Controlled Release Systems[12]

Type of system	Rate-control mechanism
Diffusion controlled	
➢ Reservoir system	Diffusion through membrane
➢ Monolithic system	
Water penetration controlled	
➢ Osmotic system	- transport of water through semipermeable membrane
➢ Swelling system	- water penetration into glossy polymer
Chemical controlled	
➢ Monolithic system	**-** Surface erosion or bulk erosion
➢ Pendant system	**-** Hydrolysis of pendent group and diffusion from bulk polymer
➢ Ion exchange resins	-Exchange of acidic or basic drugs with the ions present on resins.
Regulated system	
➢ Magnetic, Ultrasound	**-** External application of magnetic field or ultrasound to device

Oral sustained release products have gained importance because of the technological advances, which help achieve zero order release rate of the therapeutic substances. It is not possible to get an ideal sustained effect where the drug is given orally because the rate processes are influenced grossly by a number of factors viz.[13]

- Variations in pH of the gastro-intestinal tract
- Gastric motility
- Nature of fluid
- Fluid volume and content of gastrointestinal tract
- Health and disease
- In-vivo dissolution rate and consequence bioavailability.

In the recent years, considerable attention has been focused on the development of controlled drug delivery systems for convenience and ambulatory patient compliance, which is a problem normally, associated with some class of drug such as nonsteroidal anti-inflammatory, anti-hypertensive, anti-asthmatic and antipyretic drugs. Among all the methods, matrix dissolution controlled using swellable hydrophilic gums have been extensively investigated.[14]

Polymers are used to control the release of drugs from different dosage forms administered orally.[14] An ideal matrix formulation should contain polymers and diluents at amount as little as possible as well as releasing its content in a sustained release profile over a reasonable length of time and preferably with a zero order kinetics.[15]

Controlled release systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors. In case of sustained release dosage forms the release of the active agents, although, is lower than in the conventional formulations, however it is still substantially

affected by the external environments into which it is going to be released. Extended release dosage forms are those due to special technology of the preparation provides, soon after a single dose administration, therapeutic drug level maintained for 8-12 hours; while long or prolong action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half-live.[16]

However, the release behavior is inherently non-linear in nature, with continuously diminishing release rate due to diffusional resistant and / or a decrease in effective area at the diffusion front. With the growing need for optimization therapy, matrix system providing programmable rate of delivery other than the typical first order delivery, are becoming more important. For this reason, constant rate delivery has been one of the primary targets of controlled release system, especially for drug with a narrow therapeutic index. Considerable efforts have been made and are being continued to develop new drug concepts in order to achieve zero-order or near to zero-order release kinetics. To alter the kinetics of drug release from inherent non-linear behavior, scientists have exploited the use of some matrices with erosion, diffusion and swelling controlled mechanisms, as well as matrix membrane combination concepts, during research work. [16] Different types of matrices used as oral sustained release drug delivery system i.e. [16]

- Hydrophobic matrix tablets
- Hydrophilic swellable matrix
- Floating type drug delivery system (gastro retentive drug delivery system)
- Complex reservoir or multi layered matrix
- Bioadhasive or mucoadhesive drug delivery system
- Beads
- Pellets
- Microcapsules and micro tablets

Among various technologies available, monolithic matrices continue to be popular because of simplicity in processing technology required, reproducibility and stability of the materials and dosage forms as well as ease of scale-up operation. The main potential disadvantage of the matrix system is the lack of zero-order release kinetics due to time dependent changes in drug depleted matrix surface area and diffusional path length. In order to achieve linear (zero-order) release, various strategies that seek to manipulate tablet structure or geometry have been developed.[17]

Polymers are used to control the release of drugs from different dosage forms administered orally. The value of hydrophilic, polymer based matrix system as carriers for controlled release delivery is well recognized and increasingly demonstrated by the numerous patents, research paper, and U.S. food and drug administration (FDA)-approved matrix based product. In particular, water-soluble cellulose ether [e.g. hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC)], polyethylene oxide, polyvinyl alcohols, carbopol and polysaccharides such as xanthan gum, chitosan, alginic acid, pectin and guar gum have been extensively used.[17]

1.7 Physicochemical factors influencing oral sustained-release dosage form design

1.7.1 Dose Size:

In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

1.7.2 Ionization, pKa, and aqueous solubility:

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubilityof a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

1.7.3 Partition coefficient:

Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.

1.7.4 Stability:

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. [53]

1.8 Drug selection for oral sustained release drug delivery systems [54]

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug from the G. I. tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient.

Table 2: Parameters for drug selection

Parameter	**Preferred value**
Molecular weight/ size	< 1000
Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and through.

Table 3: Pharmacokinetic parameters for drug selection	
Parameter	**Comment**
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

1.8.1 Basic kinetics of controlled drug delivery [55]

In order to establish a basis for discussion of the influence of drug properties and the route of administration on controlled drug delivery, following mechanisms need a fair mention,

- Behavior of drug within its delivery systems
- Behavior of the drug and its delivery system jointly in the body.

The first of the two elements basically deal with the inherent properties of drug molecules, which influence its release from the delivery system. For conventional

systems, the rate-limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastro intestinal wall.

However, in sustained/controlled release product, the release of drug from the dosage form is the rate limiting instead; thus, drug availability is controlled by the kinetics of drug release than absorption.

1.9 TECHNIQUES FOR PREPARATION OF CONTROLLED RELEASE FORMULATION:

1.9.1 BARRIER COATING:

The barrier coating principle can be applied to either beads or granules or to the whole tablet. If barrier coated granules or beads are used, usually one portion of the granules containing the drug is uncoated for the dosage form, and the rest of the granules are coated, whereby different fractions may be done with different numbers of coats in order to get controlled release. The uncoated and coated beads or granules can either be filled in to a hard gelatin capsules or they can be compressed into a tablet. The coating material may be fats, waxes or plastic materials. The release mechanism is generally by diffusion or in some case erosion.

1.9.2 MATRIX EMBEDMENT:

In this method drug is dispersed in a matrix of material, which may be encapsulated in particulate form or compressed into tablets. Release is controlled by a combination of several processes. These include permeation of the matrix by water, leaching of the drug from the matrix or erosion of matrix material.

Three classes of retardant materials are used to prepare matrix tablet formulations.

1) Water insoluble, inert materials, the examples in this class includes polyethelene, polyvinyl chloride, methyl acrylate-methacrylate copolymer, ethyl cellulose.

2) Insoluble, erodible materials, the examples in this class include stearyl alcohol, stearic acid, polyethylene glycol.

3) Hydrophilic materials, the examples in this class include Hydroxy propyl methyl cellulose, sodium CMC, sodium alginate etc., Matrix systems are also called Monolithic devices. In a monolithic device the therapeutic agent is intimately mixed in a rate controlling polymer, and release occurs by diffusion of the agent from the device. Two types of devices can be considered; one in which the active agent is dissolved in the polymer, whereas in the other the active agent is dispersed in the polymer.

1.9.3 Preparation of Matrix devices [8]:

1. Matrix tablets can be prepared by the usual tablet compression method. The polymers as well as the drug are mixed intimately and granulated with a granulating fluid (water or alcohol) and the granules can then be compressed into tablets.

2. Molding: In this procedure the polymer and drug mixture is forced to flow into a closed container having the desired shape by the application of heat and pressure. The closed container is known as the mold. Two types of molding procedure are used.

   a) Compression molding: In this procedure, the polymer and drug mixture is placed in the lower half of a heated mold, the mold is closed, air and excess mixture are forced out and final pressure is applied for the selected time period.

   b) Injection molding: In this procedure, the mixture is first preheated and then forced into a cold mold cavity by means of a hydraulic plunger at pressures ranging between 10,000 psi and 30,000 psi.

3. Extrusion: In this process, polymer is continuously propelled along a screw through regions of high temperature and pressure where it is melted and compacted and finally forced through a die to give the final shape.

4. In this procedure the polymer and drug mixture is dissolved in a suitable solvent to form a viscous solution that is then spread on a flat, non-adhesive surface; then the solvent slowly evaporates. The resultant polymer is then peeled and milled and the granules are then compressed into tablets.

5. Polymerization in Situ: In this procedure a liquid polymer or a prepolymer is used and drug is dispersed in it. By using a polymerizing agent, the monomer drug mixture is polymerized in a suitable mold.

1.10 MECHANISM OF DRUG RELEASE FROM MATRIX DEVICES:

1.10 DISSOLUTION CONTROLLED RELEASE:

Controlled release oral products employing dissolution as the rate limiting step are in principle simplest to prepare. Even if a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier, that has a slow rate of dissolution.

We can assume the dissolution process where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate limiting step. In this case the dissolution process at steady state would be described by the Noyes-Whitney equation.

$dc/dt = K_D A(C_s - C)$ ---------- (1)

dc/dt is the dissolution rate

K_D is the dissolution rate constant
C_s is the saturation solubility of the drug and
C is the concentration of drug in the bulk of the solution.

In relation to diffusion expression that K_D equals D / V.I. Where 'D' is the diffusion coefficient, 'V' is the volume of the dissolution medium and 'I' is the thickness of the unstirred liquid film.

From the above expression it can be seen that the rate of dissolution i.e., availability is approximately proportional to the solubility of the drug in the dissolution media (C_s) provided constant area and diffusional path length are maintained.

This equation predicts constant dissolution rate as long as enough drug is present to maintain C_s constant and provided surface area does not change. For spherical particles the change in area can be related to weight of the particle and substituted in the diffusion equation to give and expression that relates dissolution to the weight remaining (W).

$W_o^{1/3} - W^{1/3} = K^1_D$ ---------- (2)

W_o is the initial weight.

K^1_D is the cube root dissolution expression.

The above equation described dissolution rate of spherical particles when surface area and diffusional path length are changing.

The common forms of dissolution control formulations fall into two categories.

(a) Encapsulation dissolution control.

(b) Matrix dissolution control.

(a)Encapsulation dissolution control:

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in spacetabs or placed in capsules as in spansule products. Since the time required for dissolution of the coat is a function of thickness and aqueous solubility, one can obtain repeat or sustained action by employing a narrow or a wide spectrum of coated articles of varying thickness respectively.

(b)Matrix dissolution control:

This method involve compressing the drug with a slowly dissolving carrier into a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives and the wettability of tablet and particle surface.

1.10.2 DIFFUSION CONTROLLED RELEASE:

Diffusion controlled release products are basically of two types.

a. Encapsulated diffusion control:

In this system water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particles or tablet. The rate of drug release is given by equation.

$Dm/dt = A\ DK\ C / I$ ---------- (3)

A is area

D is diffusion coefficient

K is the partition coefficient of the drug between the membrane and drug core

'I' is the diffusional path length and

C is the concentration difference across the membrane.

An important parameter in the above eqn (3) is the partition coefficient which is defined as the concentration, of the drug in the membrane over the concentration of drug in the core. If the partition coefficient is high, the core will be depleted of drug in a short time so that zero order release will be observed only over a short segment of the time course of drug release.

To obtain a constant drug release rate all the terms in right hand side of the above equation must be held constant.

Methods to develop reservoir type devices include press coating, air suspension coating techniques. Micro encapsulation process is a commonly used procedure to coat the drug particles to be incorporated.

b. Sintering technique:

Sintering means fusion of particles or formations of welded bonds between particles of polymer. Controlled release oral dosage forms were developed by sintering the polymer matrix by exposing to temperature above the glass transition (Tg) point of the polymer or exposing these matrix systems to solvent vapors.

The temperature treatment methods involves the exposure of the dosage form to temperature and the polymer forming the matrix slowly melts and the welded bonds are formed and this results in the controlled release of the active ingredient. However this method may be applied to only those drugs that are resistance to the temperature exposure and this may be limiting factor for many drugs that get degraded at elevated temperatures. Moreover the storage conditions may also affect the drug release from those preparations.

Tablets prepared from insoluble materials are designed to be ingested intact and not to break apart in the GI tract. Various release retardant polymers such as hydrophilic polymers (xanthan gum,rosin gum,locust bean gum etc) and hydrophobic polymers (Eudragits etc.) are widely used to control the drug release from the matrix. When the matrix tablet comes in contact with biological fluids, the hydrophilic polymers swell and form a strong viscous barrier, thus controlling the drug release.

The matrix tablet preparation appears to be a most attractive approach from the process development and scale-up point of view.

1.11 Factors influencing the in vivo performance of sustained release dosage formulations[52]

There are various factors that can influence the performance of a sustained release product. The physiological, biochemical, and pharmacological factors listed below can complicate the evaluation of the suitability of a sustained release dosage formulation.

(a)Physiological

- Prolonged drug absorption
- Variability in GI emptying and motility
- Gastrointestinal blood flow
- Influence of feeding on drug absorption

(b)Pharmacokinetic/ biochemical

- Dose dumping
- First- pass metabolism
- Variability in urinary pH; effect on drug elimination
- Enzyme induction/ inhibition upon multiple dosing

(c)Pharmacological

- Changes in drug effect upon multiple dosing
- Sensitization/ tolerance

1.12 *In vitro* evaluation of sustained release formulations

The data is generated in a well-designed reproducible *in-vitro* test such as dissolution test. The method should be sensitive enough for discriminating any change in formulation parameters and lot-to-lot variations. The key elements for dissolution are:

a) Reproducibility of method
b) Proper choice of media
c) Maintenance of sink conditions
d) Control of solution hydrodynamics
e) Dissolution rate as a function of pH ranging from pH 1 to 8 including several intermediate values preferably as topographic dissolution characterization.
f) Selection of the most discriminating variables (media, pH rotation speed etc.) as the basis for dissolution test and specification.

Ideal *in-vitro* method can be utilized to characterize bio-availability of the sustained release product and can be relied upon to ensure lot-to-lot performance.

1.13 INTRODUCTION OF ANTIVIRAL DRUG

Viruses are obligate intracellular parasites that consist of either double- or single-stranded DNA or RNA enclosed in a protein coat called a capsid. Some viruses also possess a lipid envelope that, like the capsid, may contain antigenic glycoproteins. Most viruses contain or encode enzymes essential for viral replication inside a host cell, and they usurp the metabolic machinery of their host cell. The discovery of novel antiviral inhibitors often is linked to a better understanding of the molecular events in viral replication. The stages of viral replication and the classes of antiviral agents could act at each stage of replication. Effective antiviral agents inhibit virus-specific replicative events or preferentially inhibit virus-directed rather than host cell-directed nucleic acid or protein synthesis. However, host cell molecules that are essential to viral replication also may offer targets for developing new short-term therapies.

Antiviral drugs are classified as following:

- Nonreteroviral drugs

  E.g. Acyclovir, Cidofovir, Famciclovir, Penciclovir, Ganciclovir, Idoxuridine, Amantadine, Interferon, Ribavirin.

- Antireteroviral drugs

  E.g. Lamivudine, Zidovudine, Didanosine, Zalcitabine, Stavudine, Abacavir, Tenofovir, Nevarapine, Efvirenz, Saqnavir, Ritonavir, Indinavir etc.

The population of patient with chronic disease or complications of other disease has recently been increased. These situations necessitate taking drug for a long period and or multiple medicines simultaneously, which can lead to increase in non-compliance. The problem would be worse for drugs with short biological half-life. One method to solve such problems is to find a dosage form capable of releasing the drug gradually. Microencapsulation has been used as one of the methods to deliver drugs in a controlled manner.

Lamivudine is an analogue of cytidine which is FDA-approved drug for clinical use for the treatment of HIV infection, AIDS and AIDS related conditions either alone or in combination with other antiviral agents. Lamivudine is typically administered orally as a capsule, tablet, and as oral solution. Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability of 86% ± 16%, peak serum concentration of lamivudine (Cmax) of 1.5 ± 0.5 mcg/mL and mean elimination half-life (t½) of 5 to 7 hours, thus necessitating frequent administration to maintain constant therapeutic drug levels. Therefore, the objective of the present work is to provide a long acting pharmaceutical composition containing lamivudine in a sustain release matrix formulation, to maintain the blood levels of the active ingredient for a prolonged period of time.

2.0 AIM AND OBJECTIVE

The aim of this research work was to develop and formulate matrix tablet of Lamivudine by using natural and synthetic polymers, in view to improve patient compliance and therapeutic action.

The specific objective of this research includes:

1. Ensuring safety and improving patient compliance as well as the efficacy of the drug; this can be achieved by less frequent dosing and better control of drug plasma levels.
2. Evaluation of the tablets for their hardness, friability, drug content and in vitro dissolution study.
3. Treatment of dissolution data with various mathematical models.

Plan of work:

1. Preformulation studies, to check the compatibility between the drug and the excipients.
2. Design and formulation of matrix tablets of Lamivudine.
3. Evaluation of precompression parameters such as bulk density, tapped density, compressibility index etc.
4. Evaluation of postcompression parameters like thickness, hardness, friability, drug content and in vitro dissolution.
5. To carry out short term stability studies on the most satisfactory formulation.

3.0 REVIEW OF LITERATURE

1. **Abdul S Althaf,** and study of Lamivudine oral sustained release tablets using hydroxyl propyl methyl cellulose and ethyl cellulose as retardant polymers and to study the effect of various mixtures of drug and polymers on the release profile of the formulation. Results concluded that formulation of sustained release tablet of Lamivudine containing 80 mg of hydroxypropyl-methylcellulose E15 (high viscosity grade) and 80 mg of ethylcellulose i.e. formulation F7 can be taken as an ideal or optimized formulation of sustained release tablets for 16 hours release as it fulfills all the requirements for sustained release tablet.[21]
2. **Kar RK et al.**, Design and Characterization of Controlled Release Tablets of Zidovudine by using various proportion of hydrophilic polymer viz Eudragit RS100 and RL 100 along or in combination with hydrophobic polymer ethyl cellulose and revealed that Eudragit Rs100 or RL 100 10% or 20% w/w of tablet preparations were able to sustain the drug release up to 9hours, but 30%, 40% as well as ethyl cellulose combination with 20% and 25% w/w of Eudragit RS100 and RL 100 were able to sustain for 12 hour.[22]
3. **Sunit KS et al**., Developed Microspheres of Stavudine using copolymers synthesized from acrylic and methacrylic acid esters (Eudragit RS 100 and Eudragit RL100) as a retardant material and concluded that the best-fit release kinetics was achieved with Higuchi plot followed by zero order and first order . The release of Stavudine was influenced by the drug to polymer ratio and particle size and was found to be diffusion controlled.[23]
4. **Feleke F et al.**, formulated Oral Floating extended release stavudine hydrophilic matrix tablets by using hydroxy propyl methyl cellulose (HPMC) as a release-modifying polymer. NaHCO3 and Microcrystalline cellulose (MCC) ,grade Avicel PH 101, were used as a floating aid release modifier, respectively and concluded that the release rate was not significantly affected by the levels of $NaHCO_3$, MCC or CF. Nonetheless, optimum region for the desired drug release

REVIEW OF LITRATURE

was obtained which followed first order at 25% MCC level, and Korsemeyer-Peppas model at 40%.[24]

5. **Punna Rao Ravi et al**.,(2007), formulated Lamvudine oral controlled release tablets by using hydroxy propyl methyl cellulose and concluded that release rate of the drug from matrix tablets was dependent on proportion as well as viscosity of HPMC and Lam, which release 20% to 30% of drug in the first hour and extended the release up to 16 to 20 hours, can overcome the disadvantages associated with conventional formulations of Lam.[25]
6. **Sandiip.B.Tiwari et al**.,(2003), they have prepared controlled release matrix tablets of Tramadol Hydrochloride using Hydrogenated vegetable oil, hydroxy propyl methyl cellulose, Ethyl cellulose. They studied the effect of concentration of Hydrophilic (Hydroxy propyl methyl cellulose) and Hydrophobic polymers (Hydrogenated castor oil, Ethyl cellulose) on the release rate of tramadol was studied. Hydrophilic matrix tablets were prepared by wet granulation technique, while Hydrophobic matrix were prepared by melt granulation technique and In-vitro dissolution studies were performed using united states pharmacopeia apparatus type II. They have concluded that hydrophilic matrix of Hydroxy propyl methyl cellulose could not control the tramadol release effectively for more than 12 hours. It is evident from the result that a hydrophobic matrix prepared by HCO is a better system for controlled delivery of a highly water-soluble drug like. Tramadol hydrochloride. The release of coating with water-soluble excipients (HPMC 6 cps and lactose) proved to be useful as a functional coating to control the drug release along with masking the bitter taste of the drug.[26]
7. **Basak S C et al**, Formulated and studied release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. The results of dissolution studies indicated that formulation F-V (drug to polymer 1;1.47), the most successful of the study, exhibited drug release pattern very close to theoretical release profile. Adecrease in release kinetics of the drug was observed on increasing polymeratio. Applying exponential equation, all the formulation tablets (except F-V) showed

8. **K.Raghuram Reddy** et al.,(2003) prepared sustained release matrix tablets of nicorandil using HPMC (hydroxyl propyl methyl cellulose), Eudragit RL 100 and RS 100 and ethyl cellulose, polyvinyl pyrolidine. The tablets were prepared by wet granulation method the results showed that the hydrophilic matrix of HPMC alone could not control the nicorandil release effectively for 24 hours. They observed that the results from matrix tablets prepared with HPMC and granulating agent of hydrophobic polymer (ethyl cellulose 4%w/v) is a better system for once daily sustained release of a highly water soluble drug like nicorandil. Formulations exhibited diffusion dominated drug release.[28]
9. **Nashiru Billa et al**, studied the release of drug from Xanthan gum based sustained release matrix tablets of diclofenac sodium by using xanthan gum, PEG 6000 and concluded that xanthan gum can be used as an effective matrix former, to retard the release of diclofenac sodium for extended period of time.[29]
10. **Corvi MP et al**, Developed Sustained-release matrix tablet formulation of Dehydroepiandrosterene (DHEA) as ternary complex with α-cyclodextrin and glycine by using the influence of the swelling properties of hydroxypropylmethylcellulose (HPMC) and the disintegrating power of Explotab used in combination, as well as the effect of the presence, type and amount of suitable channeling agents (Emcocel and spray –dried lactose, alone or in combination) on drug release behavior from matrix-tablets and concluded that the best performances in terms of drug release was obtained from formulations containing a 75:25 w/w spray-dried lactose: Emcocel combination in the presence of HPMC as matrix-forming polymer, leading to a more than 65% DHEA released at the of the test, a value which was, respectively, 1.9 and 2.7 times higher than those achieved with the corresponding formulations containing spray-dried lactose or Emcocel alone.[30]

REVIEW OF LITRATURE

11. **Jaber E et al**, Formulated sustain release lithium carbonate matrix tablets and studied influence of hydrophilic materials by using different ratios of polymer including carbopol (cp), Sodium carboxy methyl cellulose (SCMC) and hydroxyl propyl methyl cellulose(HPMC) and concluded that release of lithium carbonate from all formulated sustained matrix tablets were generally sustained. Na CMC, CP, and HPMC can, therefore ,be used to modify release rates of LC in hydrophilic matrix tablets.[31]
12. **Rangaswamy M et al**, Formulated Zolpidem tartarate Extended Release Matrix Tablets by using hydrophilic polymers like HPMCK-100M, AVICEL PH-102 with or without HPMC K4M and concluded that developed extended release matrix tablets of Zolpidem tartarate, capable of maintaining a constant plasma concentration throughout the period of 15 hours.[32]
13. **Mutalik Srinivas and Hiremath Doddayya**[33] have worked on formulation and evaluation of chitosan matrix tablets of nifedipine matrix tablets of nifedipine prepared by wet granulation. The *in vitro* studies showed that the mechanism of drug release was dominantly diffusion in all the cases.
14. **Rangaiah KV et al**[34] have studied the *in vitro* drug release rates of sustained release tablets of theophylline prepared by using eudragits (RLPM and RSPM) and (K15M, K100M) as polymers. The drug release was better approximated by first order kinetics.
15. **Carla Sanchez Lafuente et al**, carried out Development of sustained release matrix tablets of didanosine containing methacrylic and ethyl cellulose polymer was carried out by Carla. The combination of these two polymers have suitably modulated the release profile of didanosine.[35]

REVIEW OF LITRATURE

16. **Nath et al**[36] formulated and evaluated sustained release dosage forms of theophylline using combined hydrophobic and hydrophilic matrix. Cetyl alcohol and methyl cellulose were used in different proportions i.e. 2:1, 3:1 and 4:1 along with usual tablet additives, lactose and talc. The matrix component was varied from 20%, 30% and 40% w/w of total weight. The in vitro release data showed that 30% w/w of the total matrix component gave extended release of theophylline for more than 8h. Analysis of drug release rate from the matrix system indicated that the drug was released by anomalous diffusion obeying first order rate kinetics.

17. **Suwannee et al**[37] studied the swelling properties of hydrophilic cellulose matrix using three drugs having different water solubility: indomethacin, theophylline and mannitol. Two swelling parameters: maximum swelling index (V) and apparent diffusion coefficient of water in the matrix (D_w) were calculated from the swelling data. They were used to describe structures and properties of the swollen matrix.
18. **Mukesh C. Gohel and Maulik K. Panchal**[38] **reported** the method for 12h modified release tablets of diltiazem hydrochloride containing cetyl alcohol, alkali-treated guar gum, talc and magnesium stearate. An in vitro dissolution study was carried out in distilled water. To describe the kinetics of drug release from the test formulation, various mathematical models were used. The criterion for selecting the most appropriate model was based on the goodness-of-fit test.
19. **Murali GV et al** have worked on preparation and evaluation of indomethacin-ethyl cellulose polymer matrix systems. Different ratios of indomethacin-ethyl cellulose polymer matrices were prepared by solvent evaporation technique and the drug release from tablets was studied. The drug release was found to follow first order kinetics with diffusion types of release.

20. **Hariharan et al** formulated controlled release matrix tablets of isosorbide dinitrate using different polymers like carbopol, HPMC and eudragits. The influence of variables including polymer types, drug polymer ratio, tablet hardness, etc. on release profile of isosorbide was discussed. Eudragit NE30D and carbopol were found to have excellent retarding property.
21. **Nagoji KEV et al** have worked on release studies of nimesulide from ethyl cellulose and hydroxy propyl methyl cellulose matrices. It was found that drug release from ethyl cellulose matrices was slow when compared to that from combined polymer matrices.
22. **Singh AV , nath LK et al** Evaluation of microwave assisted grafted sago starch as controlled release polymeric carrier. Due to this hardness, friability, drug content and weight variations.
23. **Singh B, Garg B,et al** The cross limked derivative was synthesized with phosphorous oxchloride and sago starch. The formulated release were evaluated for various physical characteristecs.
24. **Kakubari I , Shinkai N , kawakami J et al** , The skin permeability and stability of formoterol fumarate (FF) in matrix patches using the total of 28 matrix patches having similar composition, containing ethylene- vinyl acetate (EVA). FF was found to increase with increasing 1- methonal and NMP contents.
25. **Tsuruta D , S owa J , Tsuruta K et al** , Patch testing showed a positive reaction to TSO (++), gum rosin (++) and wood rosin (++) at 72 h. as TSO includes highly allergenic material, caution should made in applying this topical therapy.
26. **Bhattacharya SS , Mazahir F , Verma A , Ghosh A et al** , Microspheres of xanthan gum (XG) based super absorbent polymer were prepared by water in oil emulsion cross linking method of sustained release of ciprofloxacin hydrochloride(CIPRO). Based on the result this study suggest that CIPRO loaded IPN microsphere were suitable for sustained release application

REVIEW OF LITRATURE

27. **Shiledar RR , Tagalpallewar AA ,Kokare CR et al** , A novel bilayered mucoadhesive buccal patch of zolmitriptan was prepared using xanthan (XG) was mucoadhesive polymer was used as flim – former and polyvinyl alchol (PVA) was incorporate to increase the tensile strength of the patches. In conclusion, XG can be used as a potential drug release modifier and mucoadhesive polymer for successful formulation of zolmitriptan buccal pathches.

DRUG PROFILE

3.1 Drug profile

Lamivudine

Lamivudine (β-L-2',3'-dideoxy-3'-thiacytidine)(LAM),one of the dideoxycytidine analogue Nucleoside Reverse Transcriptase Inhibitors, is the first nucleoside analogue approved to treat chronic HIV infection and AIDS.

Empirical formula: $C_8H_{11}N_3O_3S$

Molecular weight: 229.26amu

Structure:

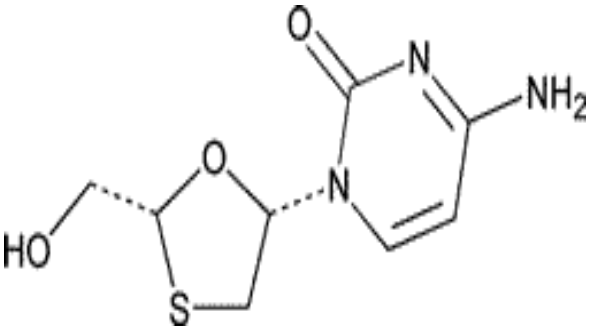


Fig 3:*Structure of lamivudine*

Description: white to off white crystalline powder.

Bulk density: not less than 0.55gm/cc

Melting point: 160-162°c

Solubility: Soluble in water, sparingly soluble in methanol, practically insoluble in acetone.

Chemical name:β-L-2',3'-dideoxy-3'-thiacytidine.

DRUG PROFILE

Pharmacology:

3.1.1 Mechanism of action and resistance

Lamivudine is an analogue of cytidine. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

3.1.2Absorption, Distribution, and Elimination

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in adults is 86% ± 16% for the tablet and 87% ± 13% for the oral solution.

Lamivudine systemic exposure, as measured by the area under the serum drug concentration-time curve (AUC), is not altered when it is administered with food. Lamivudine is widely distributed into total body fluid, the mean apparent volume of distribution (Vd) being approximately 1.3 L/kg following intravenous administration. In pregnant women, lamivudine concentrations in maternal serum, amniotic fluid, umbilical cord and neonatal serum are comparable, indicating that the drug diffuses freely across the placenta. In postpartum women lamivudine is secreted into breast milk. The concentration of lamivudine in cerebrospinal fluid (CSF) is low to modest, being 4 to 8% of serum concentrations in adults and 9 to 17% of serum concentrations in children measured at 2 to 4 hours after the dose. In patients with normal renal function, about 5% of the parent compound is metabolised to the trans-sulphoxide metabolite, which is pharmacologically inactive.

DRUG PROFILE

In patients with renal impairment, the amount of trans-sulphoxide metabolite recovered in the urine increases, presumably as a function of the decreased lamivudine elimination. As approximately 70% of an oral dose is eliminated renally as unchanged drug, the dose needs to be reduced in patients with renal insufficiency. Hepatic impairment does not affect the pharmacokinetics of lamivudine. Systemic clearance following single intravenous doses averages 20 to 25 L/h (approximately 0.3 L/h/kg). The dominant elimination half-life of lamivudine is approximately 5 to 7 hours, and the in vitro intracellular half-life of its active 5'-triphosphate anabolite is 10.5 to 15.5 hours and 17 to 19 hours in HIV-1 and HBV cell lines, respectively.

3.1.3 Adverse effects

Abdominal pain, nausea, vomiting, diarrhoea, insomnia, cough, nasal symptoms, arthralgia, muscle pain, headache, fever, rash, alopecia, malaise, increased creatinine phosphokinase and alanine aminotransferase, peripheral neuropathy. Rarely rhabdomyolysis, pancreatitis, hepatitis. Neutropenia and anaemia (in combination with zidovudine), thrombocytopenia, increases in LFTs. Paronychia. Angioedema, urticaria, and anaphylactoid reaction.

3.1.4 Drug interactions and precautions

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of Lamivudine.

Discontinue use if there is rapid increase in aminotransferase levels, progressive hepatomegaly, or metabolic or lactic acidosis of unknown origin. Discontinue use if clinical signs, symptoms or lab abnormalities suggestive of pancreatitis develop. Hepatomegaly or other risk factors for hepatic impairment. Monitor hepatic function in

chronic hepatitis B patients. Exclude HIV infection prior to hepatitis B therapy. Renal impairment. Pregnancy.

3.1.5 Therapeutic use

Lamivudine has been used for treatment of chronic hepatitis B at a lower dose than for treatment of HIV. It improves the seroconversion of e-antigen positive hepatitis B and also improves histology staging of the liver.

POLYMER PROFILE

3.2 Polymer profile

3.2.1 LOCUST BEAN GUM

Synonyms:

Algaroba, carob bean gum, carob flour, ceratonia gum, ceratonia siliqua, ceratonia siliqua gum, Cheshire gum, locust bean gum.

Chemical Name: Carob gum

Empirical Formula and Molecular Weight:

Ceratonia is a naturally occurring plant material that consists chiefly of a high molecular weight hydrocolloidal polysaccharide, composed of D-galactose and D-mannose units combined through glycosidic linkages, which may be described chemically as galactomannan. The molecular weight is approximately 310 000.

Structural Formula:

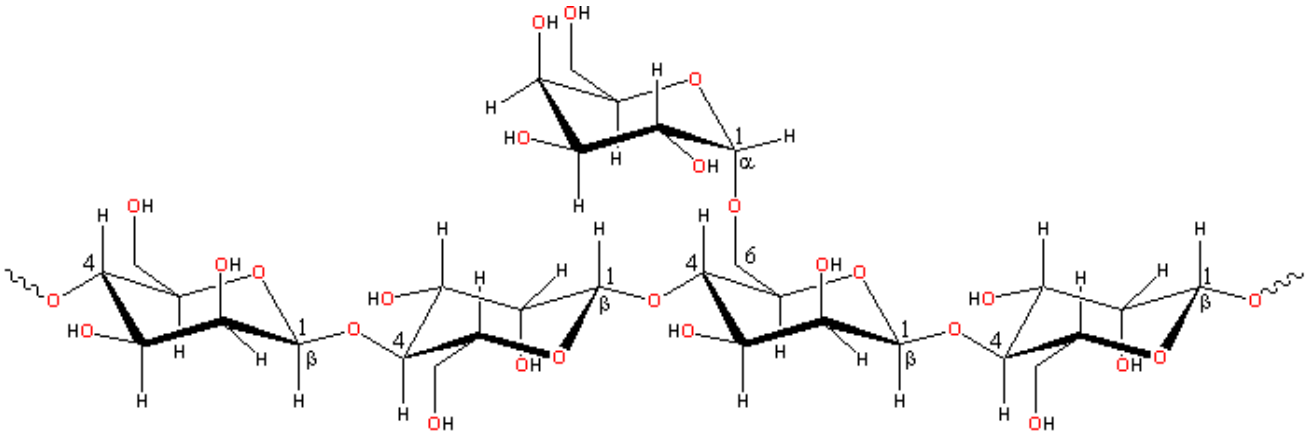


Fig 4: Structure of Locust Bean Gum

POLYMER PROFILE

Functional Category:

Controlled-release agent, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

As a viscosity-increasing agent, ceratonia is said to be five times as effective as starch and twice as effective as tragacanth. Ceratonia has also been used as a tablet binder and is used in oral controlled-release drug delivery systems approved in Europe and the USA. Ceratonia is widely used as a binder, thickening agent, and stabilizing agent in the cosmetics and food industry.

Description:

Ceratonia occurs as a yellow-green or white colored powder. Although odorless and tasteless in the dry powder form, ceratonia acquires a leguminous taste when boiled in water.

Solubility: Ceratonia is dispersible in hot water, forming a sol having a pH 5.4–7.0 that may be converted to a gel by the addition of small amounts of sodium borate. In cold water, ceratonia hydrates very slowly and incompletely.

Stability and Storage Conditions:

The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

The viscosity of xanthan gum solutions is increased in the presence of ceratonia. This interaction is used synergistically in controlled release drug delivery systems.

POLYMER PROFILE

Safety:

Ceratonia is generally regarded as an essentially noncarcinogenic, nontoxic and nonirritant material. Therapeutically, it has been used in oral formulations for the control of vomiting and diarrhea in adults and children.

3.2.2 Polymethacrylates

Both Eudragit RS 100 and Eudragit RL 100

Nonproprietary names

- **USPNF:** Ammonio methacrylate copolymer
- **USPNF:** Methacrylic acid copolymer

Synonyms

Eudragit; Polymeric methacrylates

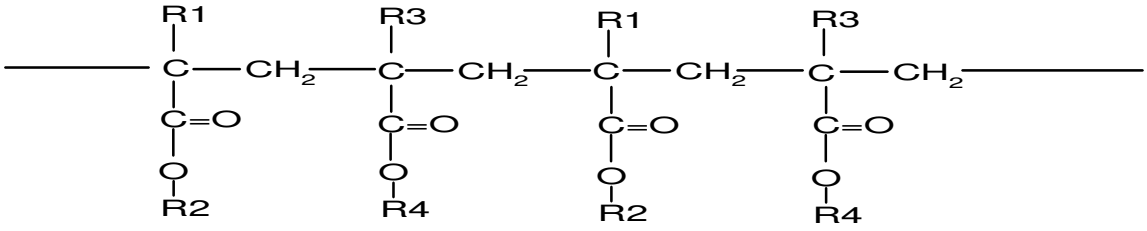
Chemical name

Eudragit RS 100; Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1

Eudragit RL 100; Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2

Eudragit RS and Eudragit RL 100 are also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups.

Structural formula



POLYMER PROFILE

Fig 5: Structure of Eudrgit

Where,

	Eudragit RL	Eudragit RS
R1 =	H	CH_3
R2 =	CH_3	C_2H_5
R3 =	CH_3	CH_3
R4 =	$CH_2CH_2N(CH_3)_3^+CL^-$	$CH_2CH_2N(CH_3)_3^+CL^-$

Functional category

Film-former; tablet binder; tablet diluents.

Typical properties

Alkalinity: 23.9 – 32.3 for Eudragit RL100, 12.1 – 18.3 for Eudragit RS 100

Density: 0.815 – 0.835 gm/cc for Eudragit RL and RS 100

Refractive index: η_D^{20} = 1.38-1.385

Viscosity: ≤ 15 mPa

Solubility: Soluble in acetone, alcohols, dichloromethane and ethyl acetate

Stability and storage conditions: Dry powder polymers forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps although this does not affect the quality of the substance and the clumps can be readily broken up.

POLYMER PROFILE

Applications in pharmaceutical formulation or technology:

- Eudragit RL, RS are used to form water insoluble film coats for sustained release products.
- Eudragit RL films are more permeable than those of Eudragit RS and by mixing the two types together films of varying permeability can be obtained.
- Eudragits are also used to form the matrix layers of transdermal delivery systems.

3.2.3 Rosin Gum

Appearance:- Trans Parent

Colour:-slight yellow,pale yellow,yellow,deep yellow

Softening Point:- slight yellow,pale yellow-76^{0}c

yellow,deep yellow-75^{0}c

Acid value:- slight yellow,pale yellow-166 mins

yellow,deep yellow-165 mins

Alcohol insoluble:- slight yellow,pale yellow-0.03%

yellow,deep yellow- 0.03%

Applications:-Mainly be used as the raw material of adhesives, paints, oil paints, rubber, soaps and paper making industries.

POLYMER PROFILE

3.2.4 Xanthan Gum

Synonyms: Corn sugar gum, Keltrol, Merezan, Polysaccharide B-1459, Rhodigel

Empirical Formula:

It is a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose unit, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

Molecular Weight: 2×10^6

Description: Xanthan gum occurs as a cream or white-colored, odorless, free flowing, and fine powder.

Functional Category: Stabilizing agent, suspending agent, viscosity increasing agent

Applications in Pharmaceutical Formulation:

Xanthan gum is widely used in oral and topical formulations, cosmetics, and food as a suspending and stabilizing agent. It has also been used to prepare sustained release matrix tablets.

Solubility: Practically insoluble in ethanol and ether. It is soluble in cold or warm water.

Stability and Storage Conditions:

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12) and temperature between 10-60 °C. Solutions are also stable in the presence of enzymes, salts, acids and bases.

POLYMER PROFILE

Safety:

Xanthan gum is generally regarded as nontoxic and nonirritant at the levels employed as pharmaceutical excipients.

Incompatibilities: Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, and preservatives since precipitation occurs. It is compatible with most synthetic and natural viscosity increasing agents.

EXCIPIENT PROFILE

3.3 EXCIPIENT PROFILE[45]

3.3.1 MICROCRYSTALLINE CELLULOSE:

Synonyms: Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Tabulose, Vivacel.

Functional Category: Tablet and Capsule diluent, suspending agent, adsorbent, tablet disintegrant.

Applications: As a diluent in tablets (wet granulation and direct compression) and capsule formulation. In addition to its use as a diluent, it also has some lubricant and disintegrant property.

Description: White-colored, odourless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications.

Solubility: Slightly soluble in 5 % w/v NaOH solution, practically insoluble in water, dilute acids and most organic solvents.

Stability: It is a stable, though hygroscopic material.

Storage conditions: The bulk material should be stored in a well-closed container in a cool, dry, place.

Incompatibilities: Incompatible with strong oxidizing agents.

Safety: It is generally regarded as a nontoxic and nonirritant material.

Commercial Grades of Microcrystalline Cellulose

Grade Nominal Mean Particle Size

Avicel PH 102 & 112.....100 μm

Avicel PH 101 & 103.....50 μm

Emocel 50 M.....51 μm

Vivacel 102.....100 μm

Vivacel 12.....180 μm

3.3.2 Magnesium stearate:

Non-proprietary names:

1. BP: Magnesium stearate
2. JP: Magnesium stearate
3. PhEur: Magnesii stearas
4. USPNF: Magnesium stearate

Synonyms:

Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.

Chemical name:

Octadecanoic acid magnesium salt

Structural formula:

$[CH_3(CH_2)_{16}COO]_2Mg$

Molecular weight:

591.34

Functional category:

Tablet and capsule lubricant.

Melting point:

117-150°C

Description:

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

EXCIPIENT PROFILE

Solubility:

It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications:

It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

Stability and storage conditions:

It should be stored in a well closed container in a cool, dry place.

Incompatibilities:

It is incompatible with strong oxidizing agents, strong acids, alkalis and iron salts. It cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

3.3.3 Talc

Non-proprietary names:

1. BP: Purified talc
2. JP: Talc
3. PhEur: Talcum
4. USP: Talc

Synonyms:

Altalc, Luzenac, Luzenac Pharma, Magsil Osmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite and Superiore.

Chemical name:

Talc

EXCIPIENT PROFILE

Structural formula:

$Mg_6(Si_2O_5)_4(OH)_4$

Functional Category:

Anticaking agent, glidant, tablet and capsule diluent and lubricant.

Description:

It is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Solubility:

It is practically insoluble in dilute acids and alkalis, organic solvents and water.

Applications:

It was once widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as dissolution retardant in the development of controlled release products. In topical preparations, it is used as a dusting powder, although it should not be used to dust surgical gloves. It is a natural material; it may frequently contain micro-organisms and should be sterilized when used as a dusting powder. It is additionally used to clarify liquids and is also used mainly for its lubricant properties, in cosmetics and food products.

Stability and storage conditions:

It is a stable material and may be sterilized by heating at 160˚C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in a well closed container in a cool, dry, place.

Incompatibilities:

It is incompatible with quaternary ammonium compounds.

METHODOLOGY

4.0 METHODOLOGY

4.1 Materials used:

TABLE NO. 04

S. No.	INGREDIENTS AND REAGENTS	MANUFACTURER / SUPPLIERS
1.	Lamivudine	Yarrowchem Products,Mumbai
2.	Xanthan Gum	Yarrowchem Products,Mumbai
3.	Locust Bean Gum	Yarrowchem Products,Mumbai
4	Rosin Gum	Leochem, Bangalore
5.	Eudragit RL 100	Leochem, Bangalore
6.	Eudragit RS 100	Leochem, Bangalore
7.	PVP K 30	SD Fine chemicals Ltd. Mumbai
8.	Magnesium Stearate	Loba chemie pvt.ltd, Mumbai
9.	Micro Crystalline cellulose	SD Fine chemicals Ltd. Mumbai
10.	Talc	SD Fine chemicals Ltd. Mumbai

4.2 Instruments used:

TABLE NO. 05

Sr. No.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1.	Digital Balance	Shimadzu ELB 300
2.	Tablet hardness tester	Monsanto tablet hardness tester.
3.	Friability tester	Veego tablet friability test apparatus
4.	Vernier Caliper	Mitutoyo Corporation, Japan
5.	Dissolution apparatus USP XXIII	Electrolab tablet dissolution apparatus
6.	Double beam UV Spectrophoto-meter	labindia - 25 UV/VIS spectrometer, Mumbai.
7.	Rotary tablet punching machine	Shakti Pharmatech Pvt.Ltd, Ahmedabad
8.	pH meter	Hanna Instruments, Japan
9.	FT-IR Spectrophotometer	Perkin Elmer spectrum RX1 FT-IR spectrometer

METHODOLOGY

4.1. DOSE SELECTION

TABLE 6: Pharmacokinetic parameters and its value (for Lamivudine)

Parameters		Value
Bioavailability (F)	:	86%
Plasma half life ($t_{1/2}$)	:	5-6 hrs
Concentration at steady state(Css)	:	0.44mg/ml
Vol. of Distribution (Vd)	:	1.3 L/KG

Theoretical release profile

Calculation of Immediate Release profile Lamivudine:

IRP = Css * V_d /F

Where Css=Concentration at steady state

V_d= Volume of distribution

F= fraction of bio available dose

Calculation of dose

Dose = IRP ([1+0.693t]/ $t_{1/2}$)

Where t=time up to sustain release required

$t_{1/2}$ = half life of drug

4.2. DEVELOPMENT OF ANALYTICAL METHOD OF DRUG

Calibration curve of drug Lamivudine was prepared in phosphate buffer (6.8)

4.2.1. Calibration curve for Lamivudine in phosphate buffer ph 6.8:
4.2.2.

METHODOLOGY

4.2.2.1. Preparation of phosphate buffer pH 6.8:

50ml of the potassium dihydrogen phosphate (0.2M) solution was mixed with 22.4ml of the sodium hydroxide (0.2M) solution in a volumetric flask and then the volume was made up with water up to 200ml.

4.2.2.2. 0.2M potassium dihydrogen phosphate solution

27.218g of potassium dihydrogen phosphate was dissolved in water and diluted it with water to make the volume 1000ml.

4.2.2.3. 0.2N NaOH solution

8g of NaOH was dissolved in 1000ml of water.

4.2.2.4. 0.2M KCl solution

14.91g of KCl was dissolved in water, and diluted it with water to 1000ml.

4.2.3. Determination of λmax of Lamivudine in phosphate buffer(PBS) pH 6.8

A solution of Lamivudine in phosphate buffer pH 6.8 was scanned in UV range between 200 to 350nm (Shimadzu UV-1601 spectrophotometer, Japan). Lamivudine showed maximum absorbance at 270nm in phosphate buffer pH 6.8.

4.2.4. Preparation of calibration curve in PBS pH 6.8:

Weighed quantity of Lamivudine (50mg) was dissolved in little quantity (3-5ml) of methanol and make up the volume 50ml with phosphate buffer pH 6.8 in 50ml volumetric flask (SS I). From SS I, 10ml solution was transferred to 50ml volumetric flask and volume was made up with PBS pH 6.8 (SS II). From SS II, 10ml solution was transferred to 50ml volumetric flask and volume was made up with PBS pH 6.8 (SS III). 0.5, 1.0, 1.5, 2.0 and 2.5ml from SS III were transferred to 10ml volumetric flasks and diluted up to the mark to give 5, 10, 15, 20 and 25µg/ml solutions respectively.

The absorbance of these solutions was determined in UV spectrophotometer at 270 nm and calibration curve was plotted.

METHODOLOGY

4.3 PREPARATION OF MATRIX TABLETS OF LAMIVUDINE:

Tablet formulations were prepared by wet granulation method. 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. Xanthan gum,Rosin gum,Locust bean gum ,Eudragit RL100 and Eudragit RS 100 were mixed with Lamivudine manually and the obtained blend was mixed with Micro crystlline cellulose to form final blend. PVPK 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 were 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. Tablets were compressed using Rotary tablet machine with 10 mm standard concave punch. Tablet weight was (300mg) kept constant as shown in table-7.

TABLE 7: Composition of Factorial Design batchess

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25
LAMIVUDINE (DRUG)	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
ROSIN GUM	60	75	90	105	120	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
LOCUST BEAN GUM	*	*	*	*	*	60	75	90	105	120	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
XANTHAN GUM	*	*	*	*	*	*	*	*	*	*	60	75	90	105	120	*	*	*	*	*	*	*	*	*	*
EUDRAGIT RL-100	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	60	75	90	105	120	*	*	*	*	*
EUDRAGIT RS-100	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	60	75	90	105	120
AVICEL	76	61	46	31	16	76	61	46	31	16	76	61	46	31	16	76	61	46	31	16	76	61	46	31	16
PVPK-30	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
MAGNESIUM STERATE	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
TALC	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Evaluation Parameters

4.4.1 Pre Compression Parameters

1. Bulk density (D_b)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

Where, D_b = Bulk density (gm/cc)

M is the mass of powder (g)

V_o is the bulk volume of powder (cc)

2. Tapped density (D_t)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

Where, D_t = Tapped density (gm/cc)

M is the mass of powder (g)

V_t is the tapped volume of powder (cc)

3. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was

TABLE 08: Relation between the angle of repose θ, and Carr's index I of a powder and its flow characteristics.

CARR'S INDEX (%)	TYPE OF FLOW
5-15	Excellent
12-18	Good
18-23	Fair to possible
23-35	Poor
Extremely poor35-38	Very poor
>40	

4.4.2 Post Compression Parameters

1. Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

2. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

3. Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

4. Weight variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

Table 09: IP standards of uniformity of weight.

Sl.No	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} X\,100$$

Where, PD = Percentage deviation, W_{avg} = Average weight of tablet, $W_{initial}$ = individual weight of tablet.

5. Uniformity of drug content.

Accurately weighed quantity of the powder tablet equivalent to 100mg of the drug was transferred to 100ml volumetric flask. 50ml of buffer solution of pH-6.8 was added. Mix with the aid of ultrasound for 10min, and then the volume was made up to 100ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45µm. 5ml of the filtrate was diluted to 100ml with same buffer solution and examined under U.V Spectrophotometry at 270nm.

Table 10: ***In-vitro*** release study.

Apparatus	:	USP XXIV Dissolution apparatus
Dissolution medium	:	Phosphate buffer pH- 6.8
Temperature	:	37± 0.5 ^{0} C
RPM	:	50
Vol. withdrawn and replaced	:	5ml every 1 hour
λ max	:	270 nm
Blank solution	:	Phosphate buffer pH- 6.8
Duration of study	:	12 hours
900 ml		
Volume of dissolution media	:	

Procedure:

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer, maintained at 37 $\pm$ 0.5^0 c. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 270 nm. The study was performed in triplicate.

4.4.3 Kinetic Analysis of In-Vitro Release Rates of Sustained Release Tablets of Lamivudine[49]

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

1. Zero order kinetics:

Zero order release would be predicted by the following equation:-

$$A_t = A0 - K_0t$$

Where,

A_t = Drug release at time 't'.
A_0 = Initial drug concentration
K_0 = 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^0.

2. First Order Kinetics:

First – order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 - K_t / 2.303$$

Where,

C = Amount of drug remained at time't'.
C_0 = Initial amount of drug.
K = First – order rate constant (hr^{-1}).

When the data is plotted as log 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.

3. Higuchi's model:

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

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

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.
ε = Porosity of the matrix.

τ = Tortuosity.

τ = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes:

$$Q = Kt1^{/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

4. 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 (Korsmeyer equation / Peppa's law 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 characteristics of the drug / polymer system.

N = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get:

$$\text{Log } M_t / M_a = \text{Log } K + n \text{ Log } t$$

release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0. The result of in –vitro drug release study of all the formulation as shown below.

Table 11: Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

S. No.	N Value	Drug release
1.	0.45	Fickian release
2.	0.45 <n <0.89	Non – Fickian release
3.	n> 0.89	Class II transport

4.5 FTIR study

FTIR spectra of the selected formulation were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were checked in the formulation spectra.

4.6 Stability Studies[50]

Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Method: Selected formulations were stored at different storage conditions at elevated temperatures such as 25°C± 2°C / 60% ± 5% RH, 30°C ± 2°C / 65% ±5% RH and 40°C ± 2° / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes, hardness, friability, drug content and percentage drug release.

Table 12: Compatibility studies of Lamivudine with excipients

Sl. No	Excipients	Drug/ excipients ratio	Physical description initial	$30^0C \pm 2^0C$ / 60% ± 5% RH		
				1 week IR study	2 week IR study	3 week IR study
1	**Lamivudine**	--	White amorphous powder	*	*	*
2	**Xanthan Gum**	--	White crystalline powder	*	*	*
3	**Lamivudine + Xanthan Gum**	1:1	White amorphous powder	*	*	*
4	**Lamivudine+Xanthan Gum+Avicel+Magnesium Sterate+Talc**	1:1	White amorphous powder	*	*	*
5	**Rosin gum**		Pale yellow coloured powder	*	*	*
6	**Lamivudine +Rosin Gum**	1:1	Pale yellow coloured Powder	*	*	*

RESULT

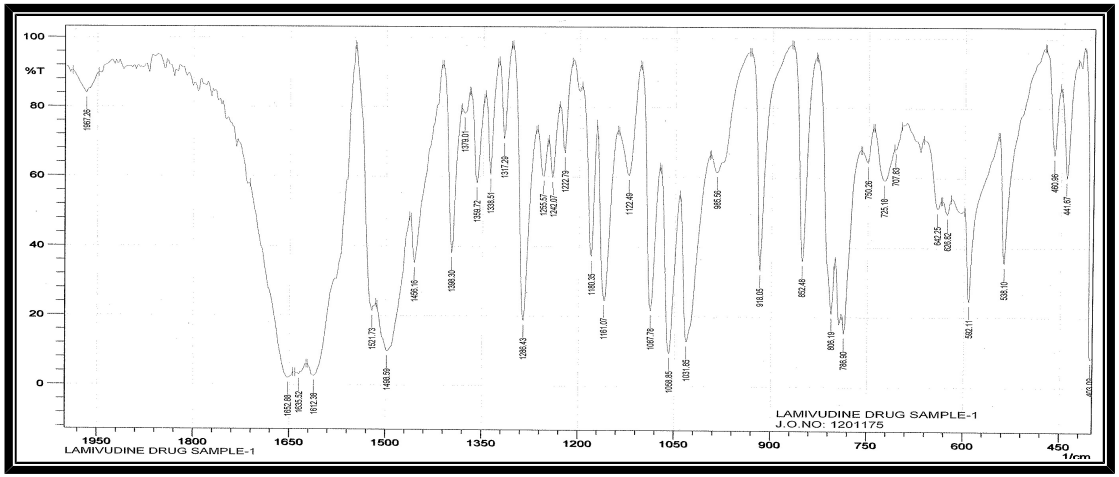
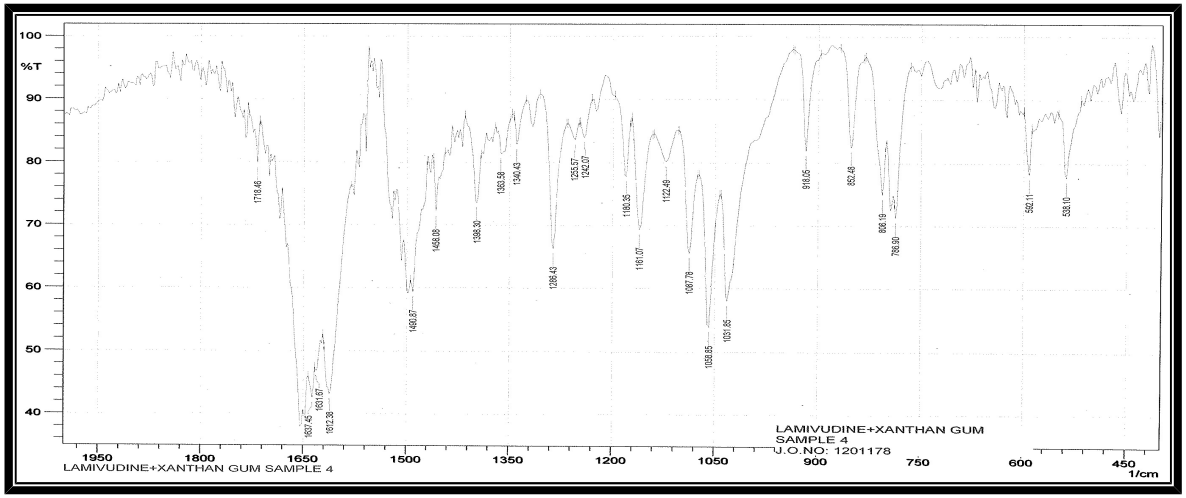


Figure 6: IR Spectram of Lamivudine

Figure 7: IR Spectram of Xanthan Gum



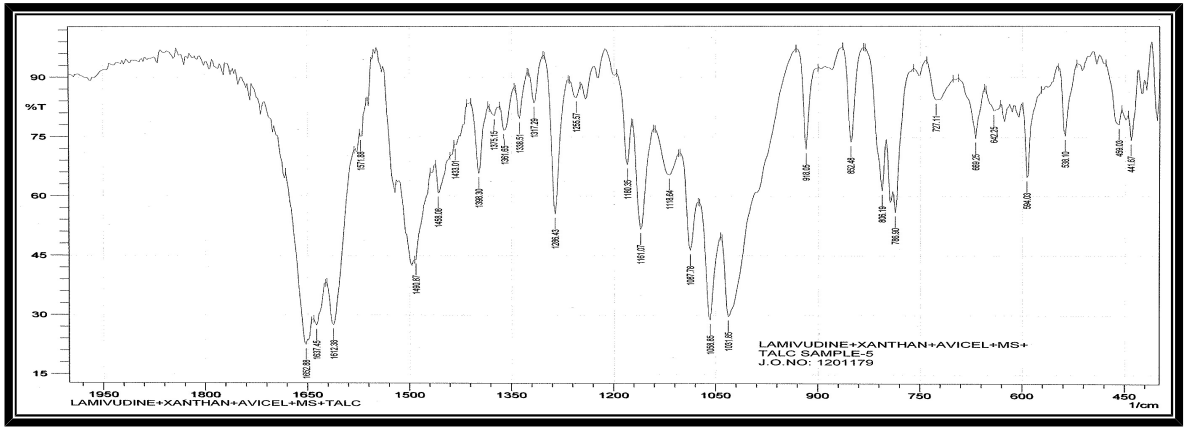
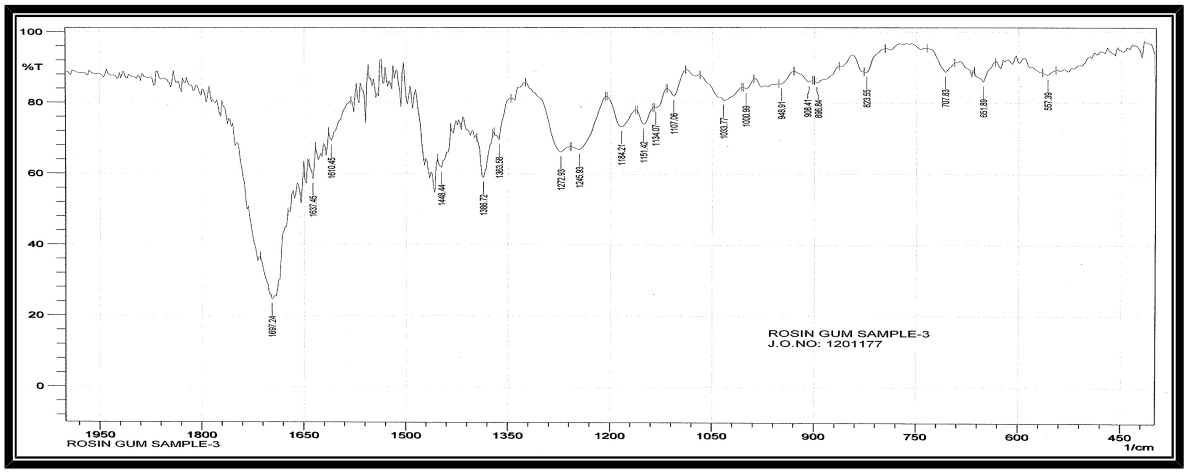


Figure 9: IR Spectram of Formulation F14



RESULT

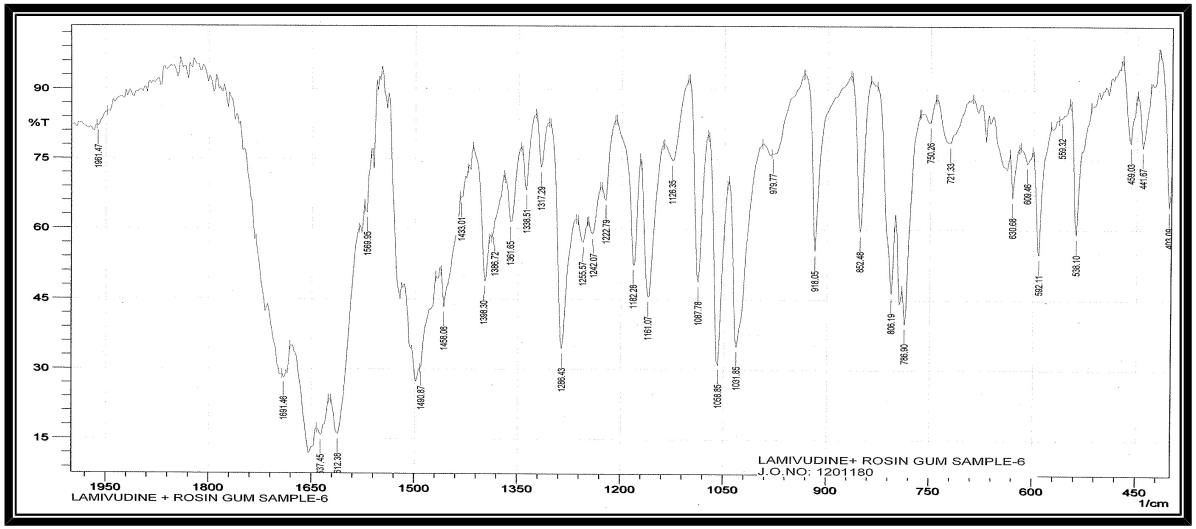


Figure 11: IR Spectram of Lamivudine + Rosin Gum

Table 13: Calibration curve of Lamivudine in Phosphate Buffer solution (pH 6.8)

SI. No	Concentration (µg/ml)	Absorbance
1	5	0.030
2	10	0.051
3	15	0.073
4	20	0.095
5	25	0.123

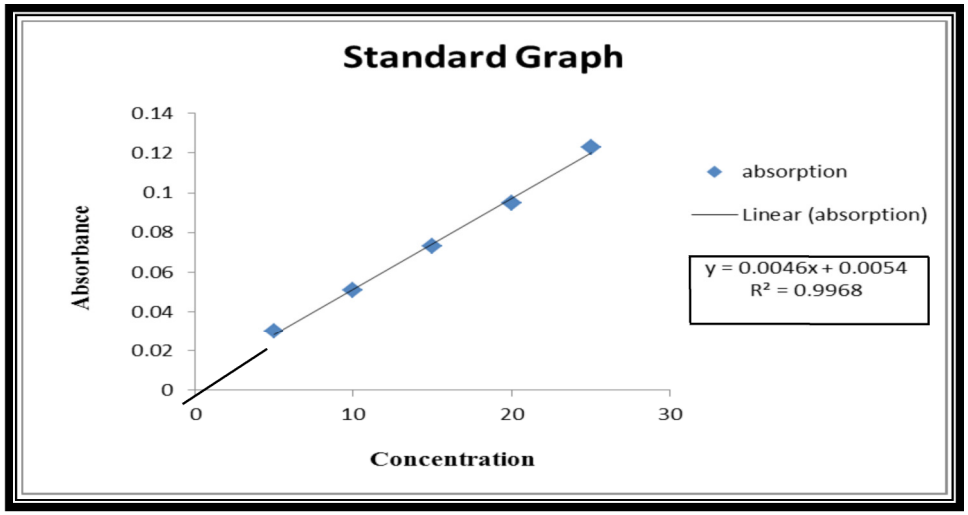


Figure 12: Calibration curve of a Lamivudine in PBS (pH 6.8)

The granular properties like Loose bulk density, Tapped bulk density, Compressibility index and angle of repose, for the batches F1-F25, were determined and the results were reported, as shown in tables 14,15,16,17 and 18.

RESULT

TABLE :14 Granules properties of formulations F1 to F5 of Lamivudine Sustained release Matrix tablets.

Parameters	**Formulation code**				
	F1	F2	F3	F4	F5
Angle of repose	25.22 ± 1.32	27.15 ± 1.41	26.22 ± 1.78	29.45 ± 1.52	28.12 ± 1.57
Loose bulk density (LBD) (g/ml)	0.254 ± 0.005	0.284 ±0.004	0.262 ± 0.003	0.294 ±0.009	0.279 ± 0.006
Tapped bulk density (TBD) (g/ml)	0.273 ± 0.013	0.322 ± 0.011	0.289 ± 0.014	0.235 ± 0.012	0.295 ± 0.016
Compressibility index (%)	8.54 ± 0.75	11.63 ± 1.63	9.71 ± 1.33	10.20 ± 1.48	11.56 ± 0.78

TABLE 15:Granules properties of formulations F6 to F10 of Lamivudine Sustained release Matrix tablets.

Parameters	**Formulation code**				
	F6	F7	F8	F9	F10
Angle of repose	26.12 ± 1.73	31.15 ± 1.38	30.26 ± 1.34	32.35 ± 1.81	28.23±1.72

RESULT

TABLE 16 : Granules properties of formulations F11 to F15 of Lamivudine Sustained release Matrix tablets.

Parameters	Formulation code				
	F11	F12	F13	F14	F15
Angle of repose	25.22 ± 1.32	27.15 ± 1.41	26.22 ± 1.78	27.21±1.54	25.64±1.21
Loose bulk density (LBD) (g/ml)	0.254 ± 0.005	0.284 ±0.004	0.262 ± 0.003	0.254±0.002	0.276±0.006
Tapped bulk density (TBD) (g/ml)	0.273 ± 0.013	0.322 ± 0.011	0.289 ± 0.014	0.276±0.018	0.296±0.012
Compressibility index (%)	8.54 ± 0.75	11.63 ± 1.63	9.71 ± 1.33	10.65±1.44	9.94±1.64

TABLE :17 Granules properties of formulations F16 to F20 of Lamivudine Sustained release Matrix tablets.

Parameters	Formulation code				
	F16	F17	F18	F19	F20
Angle of repose	26.22 ± 1.78	29.45 ± 1.52	28.12 ± 1.57	25.64±1.21	27.51±1.37
Loose bulk density (LBD) (g/ml)	0.262 ± 0.003	0.294 ±0.009	0.279 ± 0.006	0.276±0.006	0.296±0.004
Tapped bulk density (TBD) (g/ml)	0.289 ± 0.014	0.235 ± 0.012	0.295 ± 0.016	0.296±0.012	0.284±0.011

TABLE :18 Granules properties of formulations F21 to F25 of Lamivudine Sustained release Matrix tablets.

Parameters	**Formulation code**				
	F21	F22	F23	F24	F25
Angle of repose	27.15 ± 1.41	26.22 ± 1.78	27.21±1.54	24.19±1.54	25.20±1.71
Loose bulk density (LBD) (g/ml)	0.284 ±0.004	0.262 ± 0.003	0.254±0.002	0.299±0.006	0.324±0.004
Tapped bulk density (TBD) (g/ml)	0.322 ± 0.011	0.289 ± 0.014	0.276±0.018	0.276±0.015	0.295±0.019
Compressibility index (%)	11.63 ± 1.63	9.71 ± 1.33	10.65±1.44	11.23±1.51	10.46±1.31

5.3 POST COMPRESSION PARAMETERS:

TABLE 19: Tablet properties of formulations F1 to F5 of Lamivudine sustained release matrix tablets.

Parameters	**Formulation code**				
	F1	F2	F3	F4	F5
Thickness (mm)	3.38 ± 0.16	3.48 ± 0.18	3.72 ± 0.32	3.85 ± 0.03	3.61 ± 0.16
Hardness (kg/cm^2)	6.2 ± 0.10	6.7 ± 0.24	6.1 ± 0.14	6.4 ± 0.12	6.83 ± 0.35
Friability (%)	0.29 ± 0.13	0.32 ± 0.41	0.34 ± 0.21	0.28 ± 0.12	0.28 ± 0.35
Drug content (%	98.74 ± 0.235	99.08 ± 0.13	98.90 ± 0.132	98.56 ± 0.136	100.8±0.214

Parameters	Formulation code				
	F6	F7	F8	F9	F10
Thickness (mm)	3.41 ± 0.14	3.56 ± 0.12	3.92±0.12	3.92±0.12	3.92±0.12
Friability (%)	0.31 ± 0.21	0.33 ± 0.61	0.32 ± 0.41	0.29 ± 0.12	0.63±0.43
Drug content (%)	98.82±0.241	99.06 ±0.14	99.56±0.172	99.42 ±0.154	98.62±0.19

TABLE 21:Tablet properties of formulations F11 to F15 of Lamivudine sustained release matrix tablets.

Parameters	Formulation code				
	F11	F12	F13	F14	F15
Thickness (mm)	3.72 ± 0.32	3.85 ± 0.03	3.61 ± 0.16	3.41 ± 0.14	3.41 ± 0.14
Hardness(kg/cm^2)	6.1 ± 0.25	6.6 ± 0.12	6.5±0.14	6.1 ± 0.14	6.4 ± 0.12
Friability (%)	0.32 ± 0.41	0.34 ± 0.21	0.28 ± 0.12	0.32 ± 0.41	0.32 ± 0.41
Drug content (%)	99.30 ±0.172	97.90±0.154	99.49 ± 0.13	98.08±0.132	95.32±0.136

TABLE 22: Tablet properties of formulations F16 to F20 of Lamivudine sustained release matrix tablets.

Parameters	Formulation code				
	F16	F17	F18	F19	F20
Thickness (mm)	3.92±0.12	3.92±0.12	3.92±0.12	3.85 ± 0.03	3.56 ±0.12
Hardness (kg/cm^2)	6.1 ± 0.25	6.6 ± 0.12	6.5±0.14	6.1 ± 0.25	6.6 ± 0.12
Friability (%)	0.29 ± 0.12	0.63±0.43	0.33 ± 0.61	0.34 ± 0.21	0.28 ± 0.12
Drug content (%)	97.63 ± 0.13	95.98 ± 0.132	96.59±0.136	97.49±0.14	98.16±0.172

RESULT

TABLE 23:Tablet properties of formulations F20 to F25 of Lamivudine sustained release matrix tablets.

Friability (%)	0.33 ±0.61	0.32 ± 0.41	0.63±0.43	0.28 ± 0.12	0.29 ± 0.12
Drug content (%)	98.16±0.132	95.32 ±0.136	98.59 ± 0.136	99.69 ± 0.14	98.96±0.241

RESULT

TABLE 24:Weight variation for tablet formulations(F-1 to F-10)

Sl. No	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
	Wt	**Wt**	**Wt**	**Wt**	**Wt**	**Wt**	**Wt**	**Wt**	**Wt**	**Wt**

6	298	298	299	295	294	302	298	296	299	297
7	299	295	299	296	297	300	299	299	298	297
8	299	300	296	299	301	300	298	297	294	299
9	298	298	298	302	298	298	300	300	298	297
10	298	301	295	300	302	297	301	301	299	302
Average weight of 10 tablets	297.5	298.2	296.8	298	298.4	299.2	299.1	299	298.5	298.8
% Maximum Positive deviation	0.5	0.9	0.74	1.34	1.20	0.93	0.63	1.67	0.83	1.07
% Minimum Negative deviation	-1.17	-1.07	-0.94	-1.3	-1.47	-0.73	-0.70	-1.0	-1.5	-0.93

RESULT

TABLE 25 :Weight variation for tablet formulations(F-11 to F-20)

Sl. No	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**
	Wt (Mg)	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**
1	298	298	299	295	294	302	298	296	299	297
2	299	295	299	296	297	300	299	299	298	297
3	299	300	296	299	301	300	298	297	294	299
4	298	298	298	302	298	298	300	300	298	297
5	298	301	295	300	302	297	301	301	299	302
6	302	298	298	298	300	297	300	298	296	298
7	294	297	296	297	299	298	298	297	297	300
8	298	299	300	294	296	299	297	299	298	302
9	297	300	302	297	298	300	298	298	302	299

Positive deviation										
% Minimum Negative deviation	-1.40	-1.23	-1.0	-1.20	-1.30	-0.60	-0.63	-0.90	-1.30	-0.63

RESULT

TABLE 26: Weight variation for tablet formulations(F-21 to F-25)

Sl. No	**F21**	**F22**	**F23**	**F24**	**F25**
	Wt (Mg)	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**	**Wt (Mg)**
1	298	301	295	300	302
2	302	298	298	298	300
3	294	297	296	297	299
4	298	299	300	294	296
5	297	300	302	297	298
6	299	301	297	298	294
7	298	297	298	294	298
8	298	298	294	299	299
9	297	300	297	299	299
10	296	299	298	298	298
Average weight of 10 tablets	297.7	299	297.5	297.4	298.3
% Maximum Positive deviation	1.44	0.66	1.51	0.87	1.24
% Minimum Negative	-1.24	-0.66	-1.17	-1.14	-1.44

5.4 DRUG CONTENT UNIFORMITY

Table 27: Drug content uniformity of formulations F1-F25

Tablet formulation	Calculated value (Mg)	Estimated value (Mg)	% Of drug content
F1	150	148.12	98.74
F2	150	148.63	99.08
F3	150	148.35	98.90
F4	150	147.85	98.56
F5	150	150.12	100.8
F6	150	148.23	98.82
F7	150	148.60	99.06
F8	150	149.35	99.56
F9	150	149.14	99.42
F10	150	147.94	98.62
F11	150	148.96	99.30
F12	150	146.85	97.90
F13	150	149.24	99.49
F14	150	147.12	98.08
F15	150	142.98	95.32
F16	150	146.45	97.63
F17	150	143.98	95.98
F18	150	144.89	96.59
F19	150	146.24	97.49
F20	150	147.24	98.16
F21	150	147.25	98.16
F22	150	142.98	95.32
F23	150	144.89	96.59
F24	150	149.54	99.69
F25	150	148.45	98.96

5.5 *IN-VITRO* DISSOLUTION STUDIES

Release studies were carried out in pH 6.8 phosphate buffer (900 ml, 37±0.5 °C, 50 rpm) for 12 hr using the USP XXIV basket apparatus. At predetermined time intervals, 5 ml of sample was withdrawn, suitably diluted and spectrophotometrically assayed for drug concentration at 270 nm.

Table 28: Percentage drug release of formulations F1-F5

Time in hr	Formulations				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	22.5±1.8	15.5±1.3	19±2.1	14.5±2.2	16±2.3
2	31.025±1.9	22.017±1.5	24.52±2.6	19.016±2.6	21.01±2.5
3	34.559±2.3	29.541±1.8	28.548±2.4	23.03±2.4	25.54±2.4
4	36.59±2.4	36.074±1.7	33.08±2.3	29.56±2.4	31.06±2.1
5	55.138±1.7	49.614±2.0	39.616±1.8	33.59±2.1	39.10±2.2
6	80.199±1.2	64.169±2.4	46.16±1.4	43.63±2.4	43.64±1.9
7	95.288±1.3	81.74±2.3	55.2116±2.3	55.18±2.5	47.19±1.5
8	---	96.331±2.5	63.272±2.6	64.23±2.5	59.24±2.3
9	---	---	78.342±2.1	74.30±1.9	64.81±2.4
10	---	---	96.429±2.4	82.38±1.6	79.88±2.5
11	---	---	---	96.97±2.4	89.47±2.4
12	---	---	---	---	96.57±2.1

RESULT

Time in hr	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	17±2.1	14.5±2.3	14.5±2.3	13.5±2.4	15±2.3
2	26.01±1.8	17.01±2.4	17.51±2.4	17.01±2.1	24.51±2.1
3	36.54±1.4	24.03±1.8	24.53±2.1	23.03±2.4	27.04±2.0
4	49.08±1.7	33.56±1.7	30.56±2.6	34.55±1.9	34.57±2.3
5	64.14±1.9	42.09±1.8	39.59±2.2	38.59±1.8	39.61±2.4
6	74.21±2.3	48.14±2.3	42.64±2.0	46.14±1.9	40.65±2.1
7	89.79±2.1	61.69±2.4	49.18±1.9	50.69±2.3	49.70±2.5
8	97.39±2.2	73.76±2.5	61.24±1.9	61.19±2.4	64.75±2.4
9	---	96.84±2.4	71.31±1.8	69.26±2.6	73.32±2.6
10	---	---	84.38±2.3	92.84±2.4	80.90±2.3
11	---	---	97.98±2.4	96.94±2.2	92.49±2.2
12	---	---	---	---	96.10±2.3

RESULT

Table 30: Percentage drug release of formulations F11-F15

Time in hr	Formulations				
	F11	F12	F13	F14	F15
0	0	0	0	0	0
1	17.5±1.9	16±1.8	15.5±2.3	16±2.2	14±2.3
2	24.51±1.8	21.51±1.6	21.51±2.4	21.51±2.1	17.01±2.1

10	---	98.51±2.5	90.94±2.4	84.91±1.9	82.38±2.1
11	---	---	98.54±2.3	91.00±1.7	88.47±2.3
12	---	---	---	98.60±1.8	95.06±1.8

RESULT

Table 31: Percentage drug release of formulations F16-F20

Time in hr	Formulations				
	F16	**F17**	**F18**	**F19**	**F20**
0	0	0	0	0	0
1	17±2.1	17±2.3	16.5±1.8	17.5±2.2	18±2.1
2	28.01±2.2	29.51±2.4	24.51±2.1	23.01±1.9	23.52±2.0
3	38.05±2.4	33.55±2.1	34.04±2.3	31.04±1.8	28.54±2.3
4	49.09±2.3	47.08±2.3	39.58±2.2	39.07±2.3	37.57±1.9
5	79.14±2.0	68.14±2.4	47.12±2.1	47.12±2.4	48.61±1.8
6	89.73±1.9	77.21±2.5	59.17±1.9	60.67±2.1	62.67±1.9
7	95.83±1.4	88.30±2.1	68.24±1.5	67.24±2.3	67.24±2.0
8	---	96.4±1.9	79.32±1.8	79.31±2.1	71.31±2.3
9	---	---	89.40±1.9	81.40±2.3	79.89±2.0
10	---	---	97.00±2.3	88.49±2.0	85.98±2.4
11	---	---	---	95.59±2.1	96.57±2.1
12	---	---	---	---	---

Table 32: Percentage drug release of formulations F21-F25

Time in hr	Formulations				
	F21	**F22**	**F23**	**F24**	**F25**
0	0	0	0	0	0
1	17.5±1.9	17.5±1.8	14±2.1	16.5±1.8	17±2.1
2	28.01±1.4	35.51±1.4	18.51±1.8	21.01±1.9	21.01±1.8
3	49.00±1.7	45.55±1.5	24.03±1.9	31.04±2.1	26.04±1.7
4	63.60±2.3	58.60±1.7	34.06±2.1	35.07±2.0	30.07±2.3
5	74.67±2.1	65.67±1.6	42.10±2.2	40.61±2.2	36.60±2.2
6	88.75±2.4	78.74±2.1	57.14±1.9	45.66±2.3	43.64±2.0
7	96.85±2.1	91.83±2.2	67.21±2.0	59.71±2.4	49.19±2.2
8	---	97.93±1.5	77.78±2.4	70.77±2.6	59.24±2.4
9	---	---	88.37±2.2	77.35±2.3	74.31±2.1
10	---	---	96.96±2.3	88.44±2.1	80.39±2.0
11	---	---	---	96.03±1.9	89.98±1.8
12	---	---	---	---	94.58±2.3

RESULT

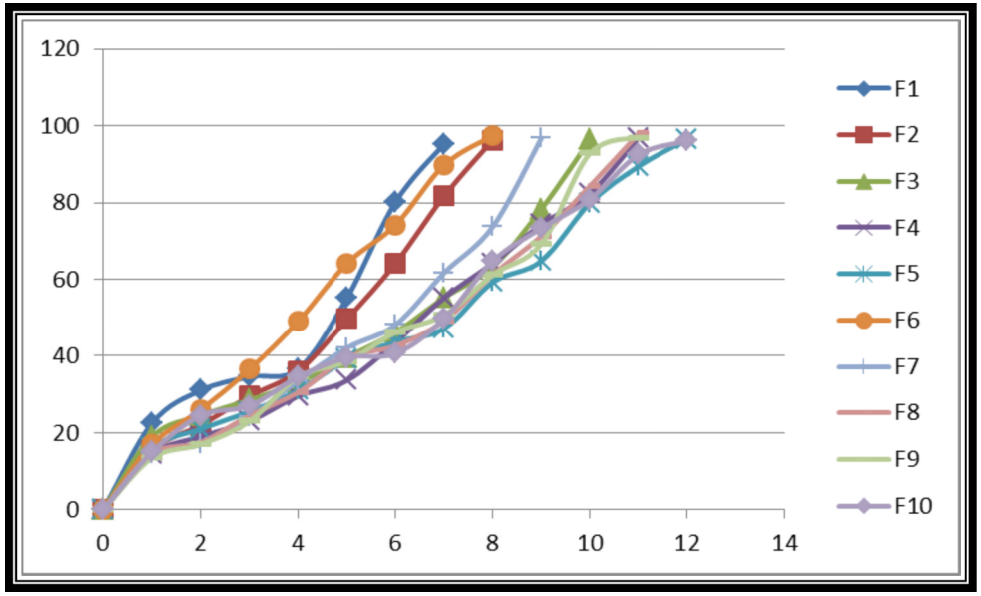


Figure 13:In-vitro dissolution of F1 to F10 formulations

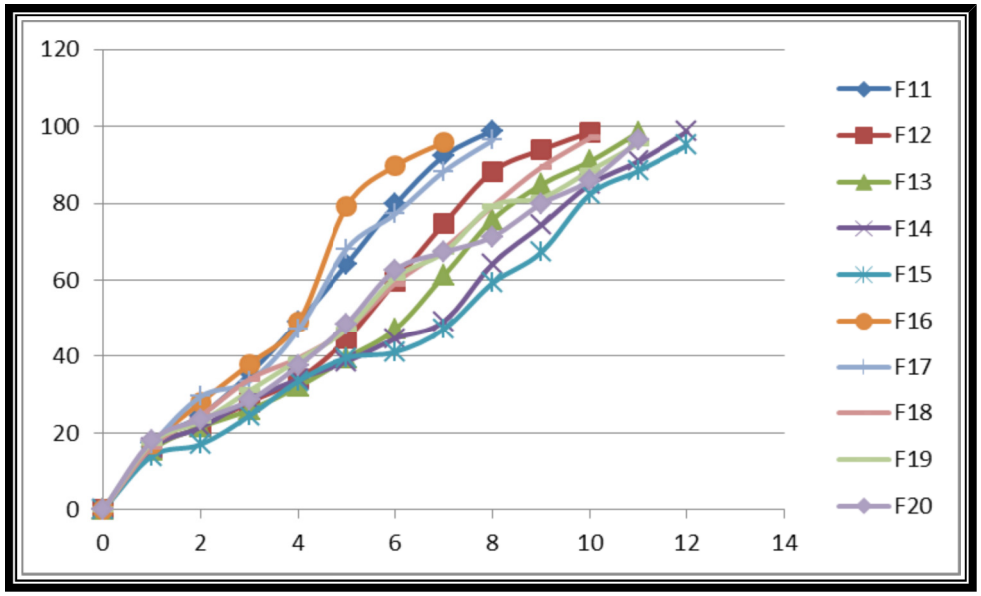


Figure 14: In-vitro dissolution of F11 to F20 formulations

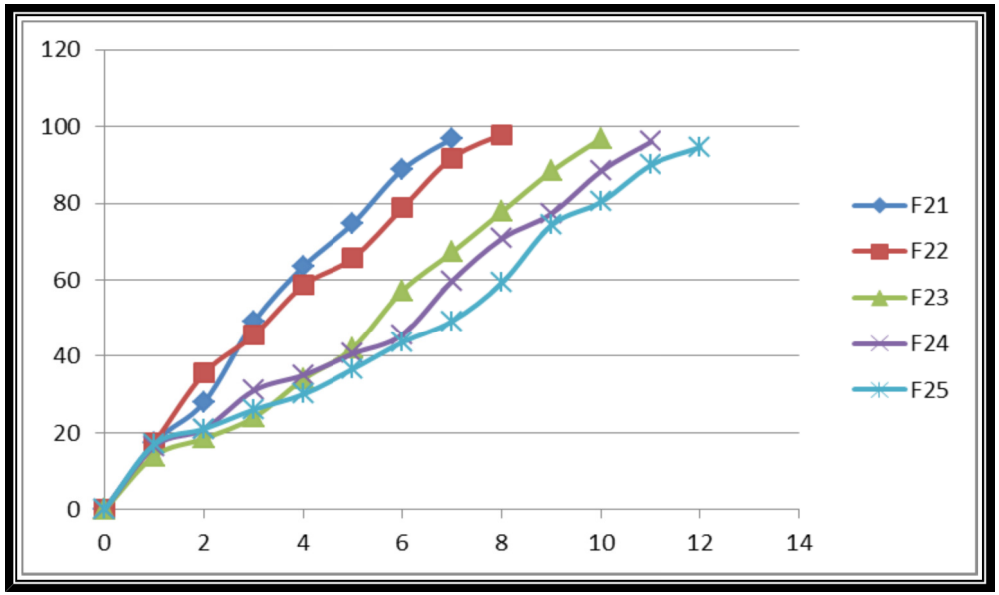


Figure -15: In-vitro dissolution of F21 to F25 formulations

The results of kinetic treatment applied to dissolution profiles of tablets of F5 and F14 were determined and shown as follows

Table 33:Model fitting for formulation F-5(Rosin Gum)

Time(hrs)	%CDR	Log of %drug unreleased	Log time	SQRT	Log%CDR
1	16	1.924279	0	1	1.204119983
2	21.01778	1.897529	0.301029996	1.414213562	1.322585189
3	25.54111	1.871917	0.477121255	1.732050808	1.407239767
4	31.06944	1.838412	0.602059991	2	1.492333426
5	39.10389	1.78459	0.698970004	2.236067977	1.592219963
6	43.64722	1.750915	0.77815125	2.449489743	1.639956588
7	47.19556	1.72267	0.84509804	2.645751311	1.673901144
8	59.24778	1.610151	0.903089987	2.828427125	1.772672082
9	64.81333	1.546378	0.954242509	3	1.811664335
10	79.885	1.30352	1	3.16227766	1.90246524
11	89.47333	1.022291	1.041392685	3.31662479	1.951693601
12	96.57222	0.535013	1.079181246	3.464101615	1.984852215

RESULT

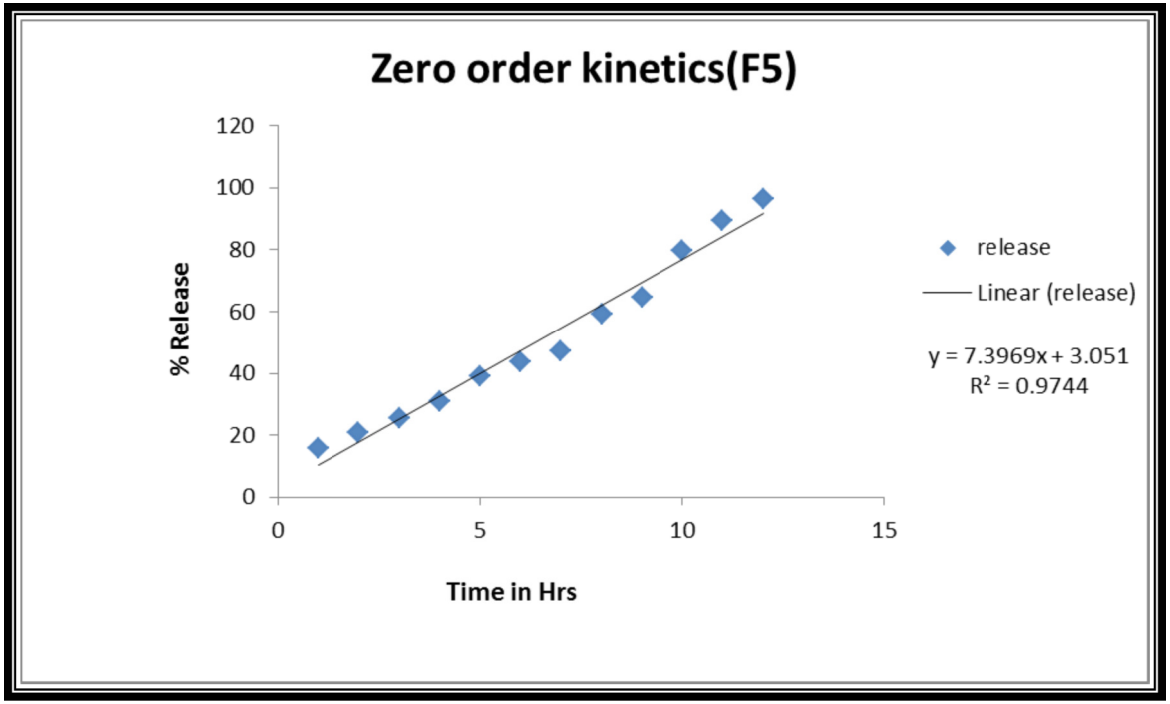


Figure 16:Zero order approximation for the formulation F5

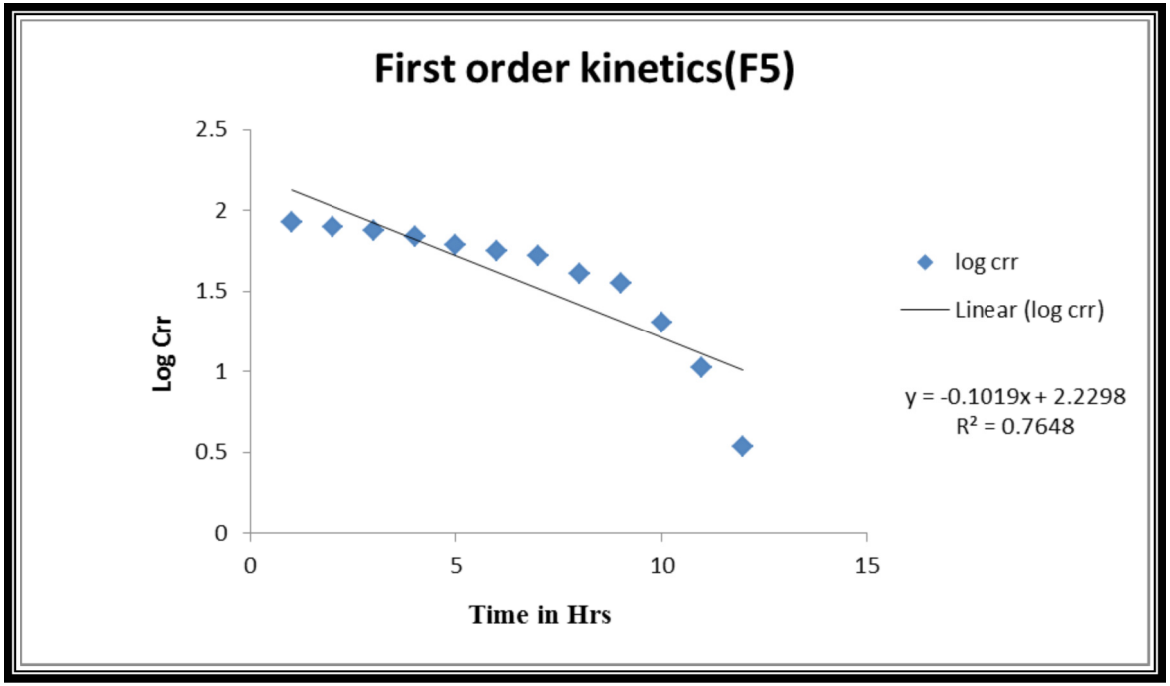
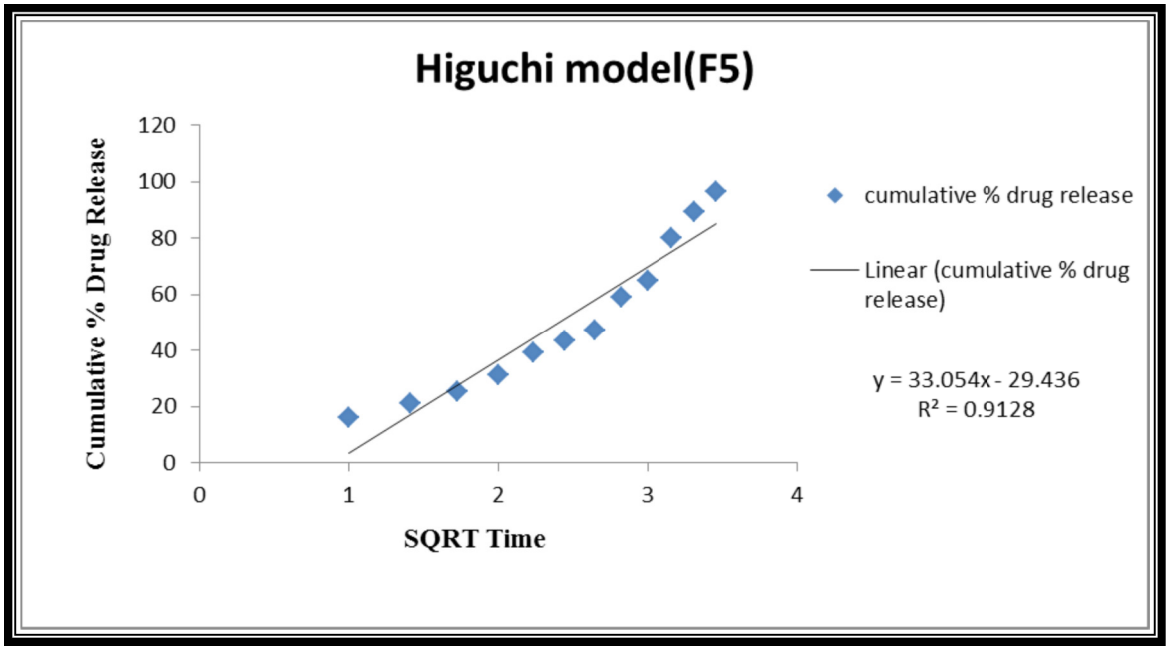


Figure 17 :First order approximation for the formulation F5



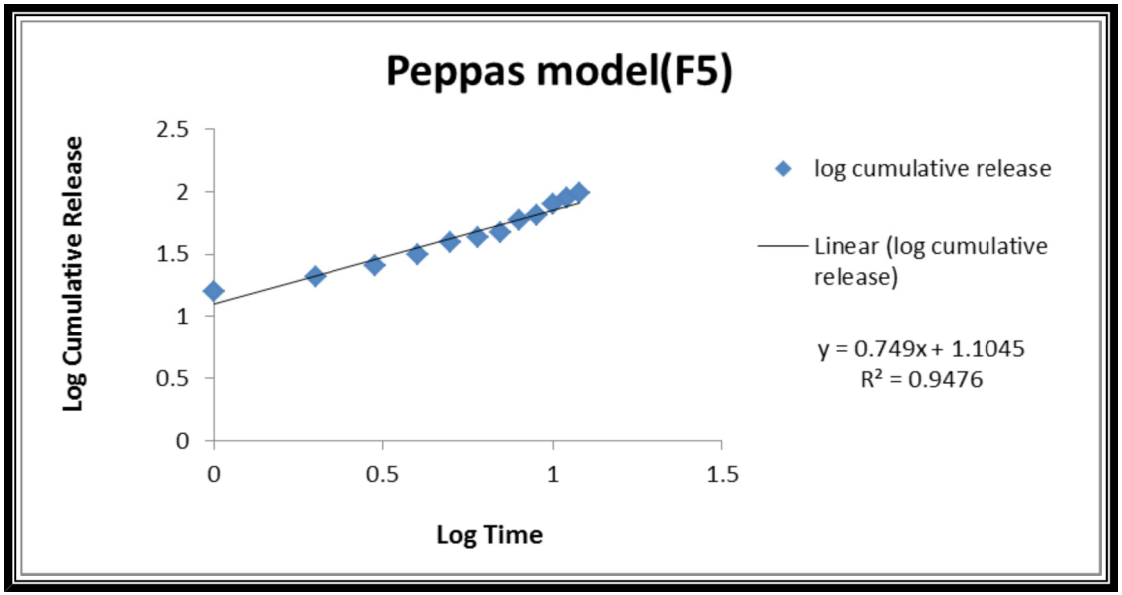


Figure 19 :Korsmeyer-Peppas approximation for the formulation F5

Table 34:Model fitting for formulation F-14(Xanthan Gum)

Time(hrs)	%CDR	Log of %drug unreleased	Log time	SQRT	Log%CDR
1	16	1.924279	0	1	1.204119983
2	21.51778	1.894771	0.301029996	1.414213562	1.332797463
3	28.54167	1.854053	0.477121255	1.732050808	1.455479381
4	34.07333	1.819061	0.602059991	2	1.532414579
5	38.61111	1.78809	0.698970004	2.236067977	1.586712287
6	44.65389	1.743087	0.77815125	2.449489743	1.649859298
7	49.20333	1.705835	0.84509804	2.645751311	1.691994496
8	64.25778	1.553182	0.903089987	2.828427125	1.807925717
9	74.32889	1.409445	0.954242509	3	1.871157647
10	84.91111	1.178657	1	3.16227766	1.928964518
11	91.005	0.954001	1.041392685	3.31662479	1.959065254
12	98.60556	0.144401	1.079181246	3.464101615	1.993901404

RESULT

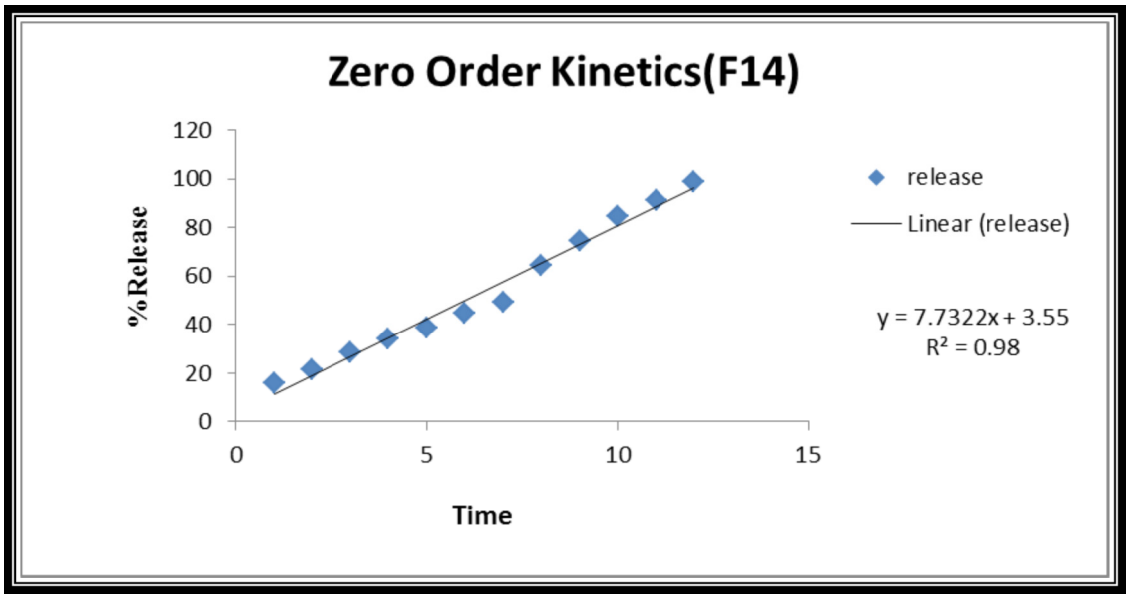
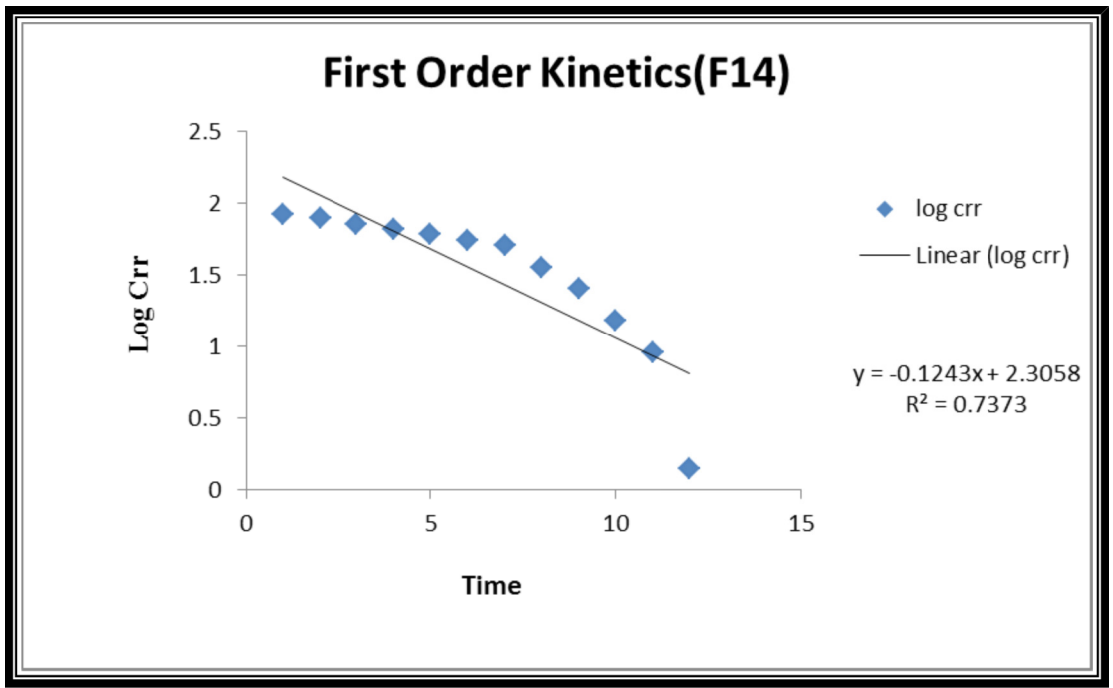


Figure 20 :Zero order approximation for the formulation F14



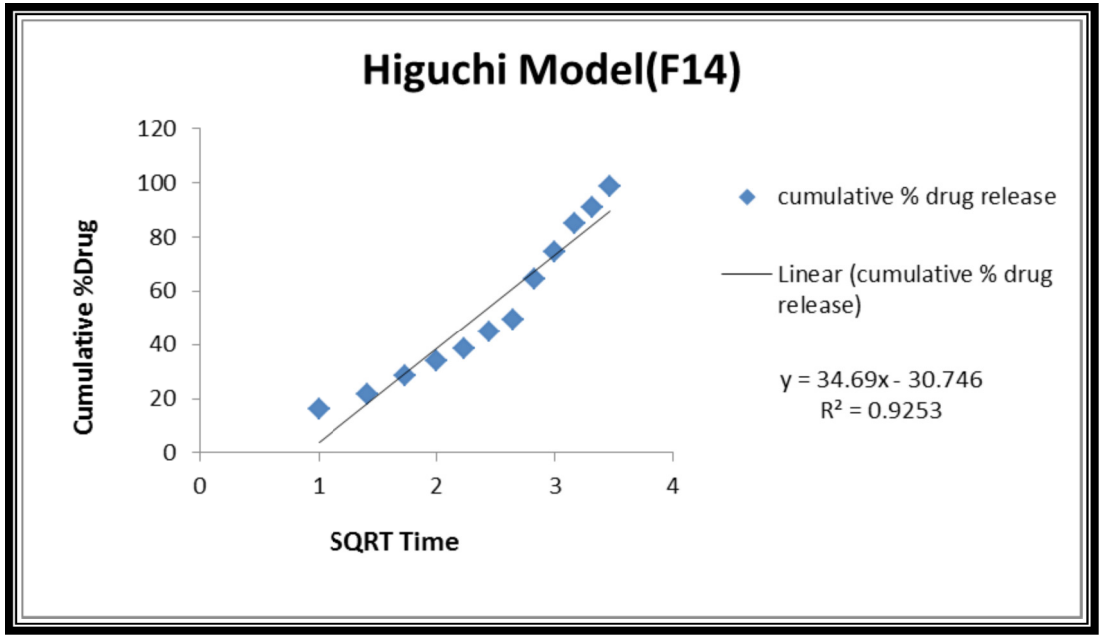


Figure 22 :Higuchi's approximation for the formulation F14

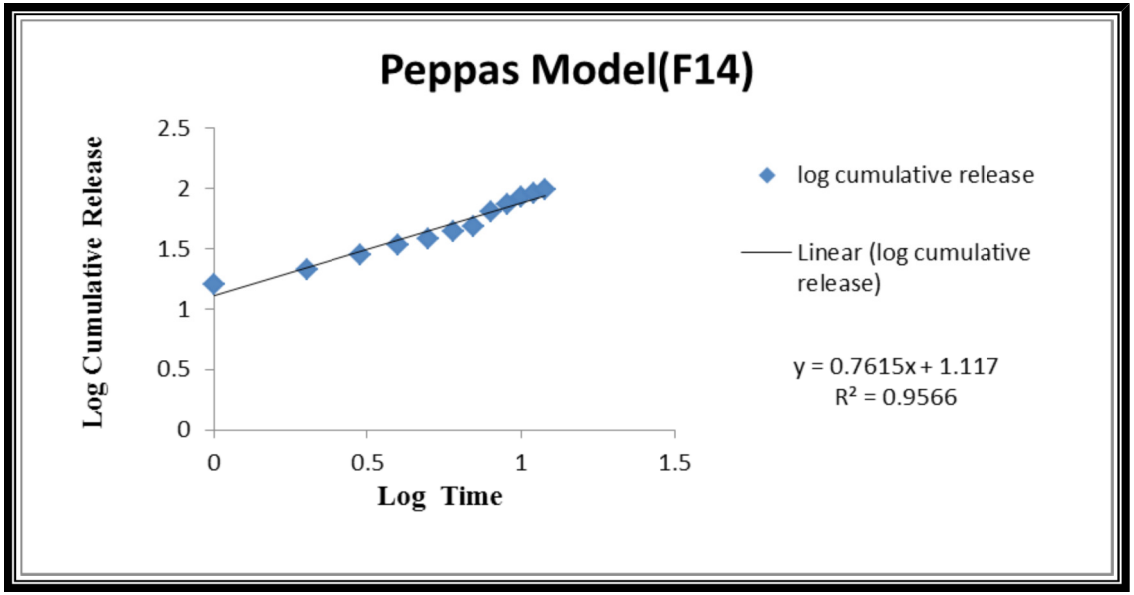


Figure 23: Korsmeyer-Peppas approximation for the formulation F14

Formulations	First order plots•	Higuchi's plots•	Korsmeyer et al's plots□	
Zero order plots▫				
F1	0.8989	0.7293	0.820	0.8459
F2	0.966	0.748	0.9027	0.948
F3	0.9403	0.748	0.8641	0.9097
F4	0.9747	0.7229	0.9097	0.9386
F5	0.9744	0.7648	0.9128	0.9476
F6	0.9956	0.834	0.9688	0.9876
F7				
0.951	0.6463	0.881	0.9324	
F8	0.9676	0.6624	0.9023	0.9473
F9	0.9638	0.6528	0.9046	0.9562
F10	0.9752	0.8124	0.9209	0.9545
F11	0.9908	0.8004	0.9613	0.9758
F12	0.9771	0.6463	0.9332	0.9511
F13	0.9798	0.7708	0.9273	0.9496
F14	0.980	0.7373	0.9253	0.9566
F15	0.9792	0.8209	0.9266	0.9604
F16	0.9684	0.8949	0.9398	0.9720
F17	0.9844	0.8742	0.9601	0.9759
F18	0.9952	0.816	0.9596	0.9838
F19	0.9907	0.896	0.9731	0.9785
F20	0.9887	0.8299	0.9683	0.9688
F21	0.9881	0.8912	0.9398	0.972
F22	0.9908	0.8464	0.9909	0.9937
F23	0.9885	0.8102	0.9414	0.9594
F24	0.9843	0.8112	0.9346	0.9597
F25	0.9769	0.839	0.9163	0.9342

RESULT

▫Zero order equation, $C=K_0 t$. •First order equation, $LogC=logC_o-K_t/2.303$.

•Higuchi's equation, $Q= Kt^{½}$. □Korsmeyer et al's equation, $M_t/M_\alpha= Kt^n$.

5.7 Stability Studies

$25^0C \pm 2^0C$ / 60% ± 5% RH	No change	Physical appearance
$35^0C \pm 2^0C$ / 60% ± 5% RH		
$40^0C \pm 2^0C$ / 60% ± 5% RH		

Table 37: Hardness of optimized formulations after stability studies

No. of days	F5			F14		
	Hardness (Kg/cm^2)*			Hardness (Kg/cm^2)*		
	25^0C / 60% RH	**30^0C / 65% RH**	**40^0C / 75% RH**	**25^0C / 60% RH**	**30^0C / 65% RH**	**40^0C / 75% RH**
0	6.8	6.8	6.8	6.1	6.1	6.1
15	6.8	6.8	6.8	6.1	6.2	6.1
30	6.7	6.7	6.9	6.1	6.2	6.2
45	6.7	6.7	6.7	6.2	6.1	6.2
60	6.6	6.7	6.7	6.2	6.2	6.2
75	6.6	6.6	6.8	6.2	6.2	6.3
90	6.6	6.7	6.8	6.1	6.2	6.3

RESULT

Table 38: Friability of optimized formulations after stability studies

No. of	F5	F14

60	0.30	0.31	0.38	0.34	0.33	0.38
75	0.29	0.29	0.36	0.35	0.35	0.36
90	0.33	0.35	0.40	0.39	0.38	0.41

Table 39: Drug content of optimized formulations after stability studies

No. of days	F5			F14		
	Drug content (mg)			Drug content (mg)		
	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH
0	98.10	98.15	97.78	98.80	98.31	98.22
15	97.15	97.20	97.13	98.20	98.24	98.18
30	97.22	97.17	97.20	98.16	98.17	98.14
45	97.18	97.15	97.18	98.21	97.19	98.26
60	97.11	97.10	97.08	98.15	98.16	97.20
75	97.08	97.12	97.02	98.08	98.09	98.01
90	97.10	97.08	96.91	98.10	98.00	98.55

Table 40: Percentage drug release from optimized formulations after stability studies

No. of days	F5			F14		
	% Drug release			% Drug release		
	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH
0	96.50	96.45	95.20	97.90	98.10	97.94
15	96.26	95.19	96.96	98.09	97.11	97.84
30	96.69	94.55	95.75	97.16	97.94	97.06
45	95.94	94.87	95.17	97.39	97.21	98.11
60	95.77	93.91	96.09	98.22	98.05	96.77
75	94.85	94.37	96.93	97.94	97.83	97.85
90	93.75	95.88	94.65	97.98	96.91	97.62

DISCUSSION

6.0 DISCUSSION

good patient compliance. The main advantage of the oral sustained release dosage form is that it maintains the therapeutic concentration over an extended period of time.

Several new technologies have been developed to overcome the physicochemical and pharmacokinetic characteristic of drugs, while improving the patient compliance. One of these technologies is the matrix type of dosage forms.

6.1 Drug Selection

Lamivudine (β-L-2',3'-dideoxy-3'-thiacytidine)(LAM),one of the dideoxycytidine analogue Nucleoside Reverse Transcriptase Inhibitors, is the first nucleoside analogue approved to treat chronic HIV infection and AIDS. Lamivudine is typically administered orally as a capsule, tablet, and sustained released tablet and as oral solution. Conventional oral formulations of LAM are administered multiple times a day (150 mg per dose) because of its moderate half-life ($t_{1/2}$ = 5-7 hours).Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. Controlled release formulations of LAM can overcome some of these problems. This study, therefore, aims to find out the influence of natural and synthetic polymers on formulation and evaluation of Lamivudine matrix tablet.

processes required, level of reproducibility, stability of the raw materials and dosage form as well as ease of scale up operation, validation and favorable *in-vitro in-vivo* correlation

Classically simple matrix delivery systems exhibit first order or square root of time release kinetics. Matrix tablets are resistant to dose dumping. Due to the simple nature of the formulation and being robust they are unaffected by variations in ingredients. Matrix tablets containing acrylic polymers are common and commercially successful means of prolonging oral drug delivery and hence patient compliance.

6.3 Matrix Tablets

XanthanGum,RosinGum,Locust BeanGum,Eudragit RL100, Eudragit RS100,Avicel,Talc and Magnesium Sterate Were Chosen for the Formulations.Xanthan Gum is a non toxic,hydrophilic nature,cost effective and also reduces the risk of systemic toxicity due to dose dumping.

Rosin Gum also nontoxic, non-allergic hydrophilic nature,cost effective ,and easily available.

Locust Bean Gum also having same properties like Rosin Gum and Xanthan gum but it is costly compare with Xanthan and Rosin Gum

Eudragit RL100 and Eudragit RS100 also non toxic, non allergic, non irritating biocompatible, soluble at pH higher than 6.5.

6.4 Melting Point Determination

Milting point was found to be 160-162°C and it is within the range specified in the official limits.

DISCUSSION

Drug –excipients compatibility studies were carried out at an accelerating condition of $30^0C \pm 2^0C$ / 60%± 5% RH. A small quantity of each mixture was evaluated by FTIR (figure-06,07,08,09,10,11) with the control i.e the pure Lamivudine and the excipient was studied. It was found that all peaks corresponding to different functional groups of pure drug were present in the drug-excipient mixture, this shows the absence of interaction between the drug and excipients listed in Table: 12.

6.6 Flow Properties

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the powders were below 15% and hence they exhibit good flow characteristics.

Values of angle of repose are rarely 20^o and values up to 40^o indicate reasonable flow properties. Above 50^o however the powder flows only with great difficulties. Dynamic angle of repose measurements can be replicated with relative standard deviations of approximately 2%. They are particularly sensitive to changes in particle size distribution and to the moisture content, and they provide a rapid means of monitoring significant batch to batch differences in these respects.

The Carr's Index (Compressibility) of the powders was in the range of 8.54 ± 0.75 to11.63 ± 1.63. The angles of repose of the powders were in the range of 24.19 ± 1.54^0 to 32.35 ± 1.81^0, which indicate a good flow property of the powders. Here the angle of repose was found to be below 40^o this shows that the reasonable flow property of powders.

The punches used to compress the tablets were 10.00mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 6.1 ± 0.14 to 6.83 ± 0.35 Kg/ cm^2. It was within the range of monograph specification.

Thicknesses of the tablets were found to be in the range of 3.38 ±0.16 to 3.92 ± 0.12mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

6.7.2 Weight Variation and Drug Content

Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations twenty tablets were randomly selected and weighed. The results are given in table 24 to 26. The average weights of the tablets were found to be within the prescribed official limits (IP).

Drug content for each of the formulations were estimated. The drug content for all the batches were found to be in the range of 95.32 ± 0.241 to 100.8 ± 0.13 %. The results are given in table 27.

6.7.3 *In-Vitro* Release Study:

In vitro release studies were carried out for all the formulations as per USP XXIV tablet dissolution tester employing basket at 50rpm using 900ml of phosphate buffer of pH 6.8 as dissolution medium. The results were evaluated for 12hrs. As per the results of dissolution study formulations F1,F2,F3,F4,F5,F6,F7,F8,F9,F10,F11,F12,F13,F14,F15, F16,F17,F18,F19,F20,F21,F22,F23,F24andF25 showed 95.288 ± 1.3, 96.331±2.5, 96.429±2.4,96.97±2.4,96.57±2.1, 97.39±2.2,96.84±2.4,97.98±2.4,96.94±2.296.10±2.3, 98.90±2.0,98.51±2.5,98.54±2.3, 98.60±1.8,95.06±1.8,95.83±1.4,96.40±1.9,97.00±2.3,95.59±2.1,96.57±2.1,96.85±2.1,97.93±1.5,96.96±2.3,96.03±1.9,94.58±2.3%

98.60% release within 12hr. Where as in formulation F1 containing 20% of Rosin gum showed 95.28 ± 1.3% of drug release was noted in 7 hours. From the above results it was found that the drug release was sustained with the increase in the polymer concentration. The lamivudine matrix tablets prolonged drug

release for 12 hours or longer would be capable of reducing the frequency of administration and the dose-dependent side effects associated with the repeated administration of conventional lamivudine tablets. No drug polymer interaction was found and lamivudine remained stable over a long period of time.

Formulations F5 and F14 were found to be most promising formulations as they showed sustained release (96.57± 2.1 and 98.60± 1.8%) as well as maintained excellent matrix integrity during the period of study (table 28 to 32 and figure 13-15). Also all other parameters like hardness, thickness, friability, drug content and weight variation for these formulations were within the range. So, formulations F5 and F14 were selected as the optimized formulations.

6.8 Kinetics:

Different models like Zero order, first order, Higuchi's, and Peppas plots were drawn. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, and Peppas plots (figure 16-23 and table 35) for formulation F5 were found to be 0.9744, 0.7648, 0.9128, 0.9476 and for formulation F14 were found to be 0.980, 0.7373, 0.9253, 0.9566. The optimized formulations F5and F14 follows Higuchi's plot since the regression

coefficient is 0.9128 and 0.9253 and plots were also found to be linear, this confirms that the drug release through the matrix was diffusion.

no noticeable incompatibility between the drug and excipients in the selected formulations.

6.10 FTIR Spectroscopy:

Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrum of the pure drug and also no additional peaks were seen in the selected formulations (figure 6,7,8,9,10 and 11). This confirms that no interaction between drug and excipients.

6.11 Stability Study :

Stability studies were carried out on selected formulations (F5 and F14) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content , physical stability, hardness, friability and drug release (table 36-40)for the selected formulations F5 and F14 after 90 days at $25^{o}C \pm 2^{0}C$ / 60% ± 5% RH, $30^{0}C \pm 2^{0}C$ / 65% ±5% RH and $40^{0}C \pm 2^{0}$ / 75% ± 5% RH.

Therefore the main objective of the study to formulate and evaluate the matrix tablets of a model antiviral drug using Rosin gum and xanthan gum as a retardant were achieved.

7.0 CONCLUSION

In this study matrix tablet of Lamivudine was prepared by wet granulation technique, using Rosin gum, Xanthan gum, Locust bean gum, Eudragit RL 100 and Eudragit RS 100 polymers alone as retardant. It was found that increase in the concentration in polymeric ratio decreases the drug release and able to sustain for 12 hours. The formulation F5 and F14 containing 40% of Rosin gum , 35% of Xanthan gum showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release etc. were evaluated for these formulations. Based on these results formulations F5 and F14 were found to be the most promising formulations. The optimized formulations F5 and F14 follows Higuchi's plot since the regression coefficient is 0.9128 and 0.9253 and plots were also found to be linear, this confirms that the drug release through the matrix was diffusion. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 90 days which revealed the stability of the formulations. The results suggest that the developed sustained-release tablets of lamivudine could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of Lamivudine in the management of HIV.

8.0 SUMMARY

The aim of the present work was to formulate and to evaluate the matrix tablets of Lamivudine by wet granulation technique with a view to sustain the drug release and to enhance the stability. Hence frequency of drug administration was reduced and better patient compliance was achieved.

Lamivudine is a freely water soluble drug which is used in the treatment of HIV. In early monotherapy trials, Lamivudine reduced plasma HIV RNA by 70% to 90% and delayed disease progression compared with continued zidovudine therapy. Lamivudine improves the long-term virologic response to stavudine, possibly reflecting the benefits of the M184V mutation. Many large prospective clinical trials have demonstrated potent and durable suppression of viremia and sustained increases in CD4+ cell counts when lamivudine is combined with other nucleoside analogs plus NNRTIs or protease inhibitors. The drug therefore remains a common component of antiretroviral regimens. Based on the drug information and physicochemical properties of drug it was found that, the drug is suitable for developing the sustained release matrix dosage form.

25 different formulations were prepared by wet granulation method using Rosin gum, Xanthan gum, Locust bean gum, Eudragit RL 100 and Eudragit RS 100 as retardant alone with increasing polymer concentration. Talc was used as glidant.

Characterization of the drug was done by Performing the melting point, UV spectroscopy and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all the excipients used in the study. The results showed that there was no drug-excipient interaction. The melting point was found to be 160-162^{0}C and from the UV spectral analysis of the drug solution indicated that λmax value as 270nm.

Pre compression and carr's index of the pure drug indicated that the drug had good flow

SUMMARY

The thickness of the formulations (F1-F25) was in the range of 3.38 ±0.16 to 3.92 ± 0.12mm and the hardness was in the range of 6.1 ± 0.14 to 6.83 ± 0.35 Kg/ cm^2, indicated good mechanical strength of the tablets. Friability and drug content uniformity was found to be within official limits for all the formulations.

The dissolution studies were carried out for 12hrs. As per the result of dissolution study formulation F5 and F14 showed good drug release profile (96.57 ± 2.1 and 98.60 ± 1.8%) and they showed excellent matrix integrity during the period of study, when compare to other formulations.

Based on all these results, formulations F5 and F14 were selected as the optimized formulations with 96.57 ± 2.1 and 98.60 ± 1.8% drug release. The release kinetics was fitted to different mathematical models like Zero order, First order, Higuchi's and Peppas plot. The optimized Formulations F5 and F14 follows Higuchi's plot since the regression coefficient is 0.9128 and 0.9253 and plots were also found to be linear; this confirms that the drug release through the matrix was diffusion.

The drug polymer interaction of the optimized formulations was evaluated by TLC and FTIR. FTIR spectrum of pure drug was compared with that of formulations F5 and F14. All peaks corresponding to the different functional groups of pure drug were present in the formulations which indicate the absence of interaction between the drug and excipients.

The selected formulations (F5 and F14) were subjected for stability studies as per ICH guidelines. Formulations subjected for stability studies were checked for drug content, hardness, friability and physical appearance for 90 days with an interval of 15 days. The formulations were found to be stable as no significant change was observed in the various evaluated parameters of the formulations.

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