FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF LAMIVUDINE

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DEPARTMENT OF PHARMACEUTICS
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CERTIFICATE

This is to certify that the dissertation entitled**, "FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF LAMIVUDINE."** Submitted by **Mr. T.PRAKASH** in the Department of Pharmaceutics, Madurai Medical College, Madurai – 20, in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by him, under the guidance and supervision of **Prof. Mr. A. Abdul Hasan Sathali**, **M.Pharm.,(Ph.D)** Professor and Head, in the Department of Pharmaceutics, Madurai Medical College, Madurai-20,during the academic year 2011 – 2012.

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I wish him success in all his endeavors.

Place: Madurai

Date: **(Prof. Mr. A. Abdul Hasan Sathali)**

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CONTENTS

CHAPTER-I

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Should next generation drugs are predominantly protein or peptide based, tablets may no longer may be the dominant format give the difficulty of dosing such moiety. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that50% of the population is affected

by this problem, which results in a high incidence of noncompliance and ineffective therapy. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way. Less frequently, they are designed to be absorbed through the buccal and esophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from fast dispersing formulations may be even greater than that observed for standard dosage forms.

The concept of Mouth Dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in

the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. FDDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets.

Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. FDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Taste-masking is of critical importance in the formulation of an acceptable FDDT.

Traditional tablet formulations generally do not address the issue of taste masking, because it isassumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups and chewable tablets simply contain flavors, sugars and other sweeteners to overwhelm or complement the bitter taste of the drug. Current methods of taste masking in fast dissolving/ drug particles. FDTs are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well. The primary methods of taste-masking include

adsorption onto or complexation with carriers and spray coating of solid dosage forms, which increase consumer choice, for the reason of rapid disintegrate/dissolve in oral cavity within seconds and swallowed without the need of water or chewing. As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism.

Fast dissolving drug delivery can be achieved various techniques like direct compression, wet granulation, compression moulding, volatization and freeze – drying. They involve different mechanisms like use of high amounts of hydrophilic disintegrating agents which allow the dosage forms to disintegrate quickly in the patient's mouth on contact with saliva.

CHAPTER-II

FAST DISSOLVING TABLETS - A REVIEW

DEFINITION

A fast dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water. The fast disintegrating tablets are synonymous with fast dissolving tablets; melt in mouth tablets, rapimelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.

DIFFICULTIES WITH EXISTING ORAL DOSAGE FORM

Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration. Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia. Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult. Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications cost of products is main factor as parenteral formulations are most costly and discomfort.

SALIENT FEATURES OF MOUTH DISSOLVING DRUG DELIVERY SYSTEM

DESIRED CRITERIA FOR MOUTH DISSOLVING DRUG DELIVERY SYSTEM

Mouth Dissolving Tablet should-Not require water to swallow, but it should dissolve or disintegrate in the mouth within matter of seconds. Be compatible with taste masking Be portable without fragility concern. Have a pleasing mouth feel. Leave minimal or no residue in the mouth after oral administration. Exhibit low sensivity to environmental condition as humidity and temperature. Be manufactured using conventional processing and packaging equipment at low cost. Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients. Convenience of administration and accurate dosing as compared to liquids. No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water. Good mouth feel property of MDDS helps to change the basic view of medication as “bitter pill”, particularly for pediatric patients. Rapid dissolution and absorption of drug, which may produce rapid onset of action. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, and in such cases bioavailability of drugs in increased. Ability to provide advantages of liquid medication in the form of solid preparation. Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

IDEAL CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEM

Mouth-feel - Mouth-feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly

soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can an improved mouth-feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth-feel by reducing the "dryness" of a product. Hygroscopicity - Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity, which calls for specialized product packaging. Friability - In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel off blister packing. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets, such as Wowtab by Yamanouchi-Shadlee and Dura Solve by CIMA labs.

Excipients balance the properties of the actives in fast-melting tablets. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

BULKING MATERIALS:

Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

EMULSIFYING AGENTS:

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

LUBRICANTS:

Lubricants, though not essential excipirnts, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

FLAVOURS AND SWEETENERS:

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame,

sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

SUPER DISINTEGRANTS:

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

ADVANTAGES:

Effective in lower concentrations Less effect on compressibility and flowability More effective intragranularly

Some super disintegrants are:

1) **Sodium Starch Glycolate (Explotab, primogel**) used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: Rapid and extensive swelling with minimal gelling.

Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking

2) **Cross-linked Povidone (crospovidone) (Kollidone**) used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

Mechanism of Action: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants.

3) Low-substituted hydroxyl propyl cellulose, which is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration capacity. Recommended concentration 1-5%

4) Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium:

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation

Gas producing disintegrants

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Care should be taken during tab letting, particularly on moisture level. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates. In many instances lower concentration can be used with gas producing disintegrants than are required by other

disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide.

Conventional Technique Used In The Preparation Of MFDTS.

- Freeze drying technique
- Tablet molding technique
- Spray drying technique
- Direct compression technique
- Sublimation technique
- Mass extrusion technique

Freeze Drying Technology (Zydis Technology)

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth.

The drug is entrapped in a water soluble matrix whichis freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless. Corveleyn and Remon investigated the influence of various formulation and process parameters on the characteristics of rapidly disintegrating

tablets in lyophilized form using hydrochlorthiazide as a model drug. They have concluded that maltodxtrins are useful in the formulation of fast dissolving tablets made by freeze-drying. Lyophilization is relatively expensive and time consuming manufacturing process. Other drawback includes fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition.

Tablet Molding

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

Spray Drying

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. This technique is based on a particulate support matrix, which isprepared by spray drying an aqueous

composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets.

Direct Compression Method

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

Sublimation Technique

The basis of this technique is to add inert solid ingredients that volatilize readily, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.

Mass-Extrusion (Mass-Extrusion)

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even

segments using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking

PATENTED TECHNOLOGIES OF FDTs [20]

Currently, four fast-dissolving/disintegrating technologies have reached the U.S. market:

- Zydis (R.P. Scherer, Inc.)
,
- WOWTAB (Yamanouchi Pharma Technologies, Inc.)
- ,
- OraSolv (Cima Labs, Inc.).
- DuraSolv (Cima Labs, Inc.).
- Three others are available outside the U.S. :
- FlashDose (Fuisz Technologies, Ltd.),
- Flashtab (Prographarm Group),
- OraQuick (KV Pharmaceutical Co., Inc.).

Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These forms a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the

manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

Limitations

- The amount of drug could be incorporated should generally be less than 400mg for insoluble drugs and less that 60mg for soluble drugs.
- The particle size of the insoluble drugs should not be less than 50μm and not more than 200μm to prevent sedimentation during processing.

Advantages

- Buccal pharyngeal and gastric regions are all areas of absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism.
- The zydis formulation self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

Disadvantages

- The process of freeze-drying is a relatively expensive manufacturing process.
- The formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses.
- It has poor stability at higher temperatures and humidities.

- The freeze-drying is time consuming process
- It has poor physical resistance
- Loading of high dose of water-soluble drugs is not possible

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Advantages

- Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabletting.
- The Durasolv product is thus produced in a faster and in more effective manner.

Disadvantages

- It is not compatible with larger doses of active ingredients because the formulation is subjected to high pressures on compaction.
- The drug powder coating may fractured during compaction, exposing the bitter tasting drug to patient's taste buds.

Orasolv Technology

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral

dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Advantages

- The Orosolv formulations are not very hygroscopic
- The formulation can accommodate high doses.
- It also provides a distinct, pleasant sensation of effervescence in the mouth.

Disadvantages

- A weaker and more brittle tablet in comparison with conventional tablets.
- Poor mechanical strength.
- The cost of fast dissolving tablets is higher than the cost of standard tablets made by direct compression
- Manufacturing requires a controlled environment at low relative humidity.

Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

Advantages

- Offers Superior mouthfeel due to the smooth melt action
- It is suitable for both conventional bottle and blister packaging

- Bit more stable to the environment than the zydis and orasolv.

Flash Dose Technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self-binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion- spheronisation. All the processing utilized conventional tabletting technology.

Oraquick Technology

The Oraquick fast dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its micro sphere technology, known as Micro Mask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to

achieve significant mechanical strength without disrupting taste-masking Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

Each technology has a different mechanism, and each fast-dissolving/disintegrating dosage form varies regarding the following:

- Mechanical strength of final product;
- Drug and dosage form stability;
- Mouth feel;
- Taste;
- Rate of dissolution of drug formulation in saliva;
- Swallow ability;
- Rate of absorption from the saliva solution; and
- Overall bioavailability.

CHAPTER-III

LITERATURE REVIEW

Viral Shah *et al.,* 2011, Formulation and Evaluation of Mouth Dissolving Tablets of Metaclopramide Hcl by Direct compression technique. The tablets were prepared by direct compressed method using crospovidone, croscarmallose sodium and sodium starch glycolate and superdisintegrant. Tablets containing crospovidone showed better disintegration character along with rapid release.

Vineet Bhardwaj *et al.,* 2010, Formulation and Evaluation of Fast Dissolving Tablet of Amlodopine besylate using different superdisintegrants and camphor as sublimating agent. The tablets were prepared by direct compression method. Different concentrations (2% 4% 5% 6%) of super disintegrants such as Ac-Di-sol, Sodium starch glycolate, kollidon-CL were used as superdisintegrant, camphor was used as sublimating agent. The result concluded that the formulation containing 6% croscarmallose sodium has greater release rate and faster disintegration time than other formulations.

Vikram Chopra *et al.,* 2009, Formulation, Evaluation and Comparison of Fast Dissolving Tablet of Nimesulide by using Crospovidone as superdisintegrant. Fast dissolving tablets of nimesulide were prepared by using crospovidone as superdisintegrant (crospovidone) was used in different concentration to formulate fast dissolving tablets of nimesulide and optimized batch was compared with marketed formulation. It can be concluded in the research study that the disintegration of nimesulide can be enhanced by direct compression technique with addition of crospovidone.

Vijay Tiwari *et al.,* 2010, Preparation and Evaluation of Fast Dissolving Tablets of Celecoxib. Fast dissolving dosage from proves its significance for enhancing the

bioavailability of water insoluble drug by increasing its dissolution and solubility. The inclusion of solid dispersion process as a step of preparation of fast dissolving tablets have a synergistic effect on bioavailability of final dosage form by its contribution in improvement of solubility profile. It proves that the concentration of superdisintegrants plays a major role in release profile of fast dissolving tablets.

Uday S Rangole *et al.,* 2008, Formulation and *In Vitro* Evaluation of rapidly disintegrating tablets using Hydrochlorthiazide as model drug. The tablets were prepared by direct compression method using 2%, 3%, 4%, 5% of superdisintegrants like croscarmallose sodium and crospovidone. The tablets containing 4% crospovidone gave fast disintegration and highest dissolution rates.

Suhas M. Kakade *et al.,* 2010, Formulation and Evaluation of Mouth Dissolving Tablets of Losartan potassium by Direct Compression Method. The mouth dissolving tablets were prepared by direct compression method using disintegrants like ployplasdone XL 10, croscarmallose sodium and explotab in different concentrations. The relative efficacy of different superdisintegrants to improve dissolution rate of tablets is in the order of ployplasdoneXL 10 > croscarmallose sodium > Explotab.

Sridhar B.K. *et al.,* 2010, Formulation and Evaluation of Fast dissolving / Disintegrating tablets of Isoxsuprine Hcl. The tablets were prepared by direct compression method using crospovidone, croscarmallose sodium and sodium starch glycolate as superdisintegrants at various levels. The formulation containing 5% croscarmallose sodium showed complete release of drug within 4 minutes than other formulations.

Shirshand S.B. *et al.,* 2010, Formulation design and Optimization of Fast Disintegranting Lorazepam Tablets by Effervescent Method". The tablets were prepared by effervescent method with a view to enhance patient compliance. A 3^2 full factorial design was applied to

investigate the combined effect of two formulation variables: amount of crospovidone and mixture of sodium- bi- carbonate, citric acid and tartaric acid on *in vitro* dispersion time. Crospovidone 2 to 8% w/w was used as superdisintegrant and mixture of sodium- bi-carbonate, citric acid and tartaric acid (6 to 18% w/w) was used as effervescent material along with directly compressible mannitol. The formulation containing 8% w/w of Crospovidone 18% w/w mixture of sodium- bi- carbonate, citric acid and tartaric acid was found to be promising.

Sharma vijay *et al.,* 2011, Formulation and Evaluation of Mouth Dissolving Tablets of Cefixime. The tablets were prepared using different concentrations of disintegrants by direct compression method. crospovidone, croscarmallose and sodium starch glycolate and Kyron T-314 were the superdisintegrants used. The formulation containing 7.5% of crospovidone was concluded as best formulation based on wetting time, disintegration time and dissolution data.

Shailendra Kumar singh *et al.,* 2009, Fast Distintegrating Combination Tablets of Omeprazole and Domperidone. The tablets were prepared using mannitol as diluent and sodium saccharin as sweetening agent along with three different levels of disintegrant. Kollidon- Cl, Ac-Di-sol , and sodium starch glycolate are the superdisintegrants used. The formulation containing Ac-Di-sol (CCS) 10 mg disintegrated fast.

Senthilnathan B. *et al.,* 2011, Formulation devolepment of Venlafaxine Hcl Orodispersible Tablet. The tablets were prepared by direct compression method using crospovidone, croscarmallose sodium and sodium starch glycolate as superdisintegrants. Formulation containing 10% crospovidone was found to demonstrate desirable properties and optimized drug release.

Sandhya Jaiswal *et al.,* 2011, Formulation and Evaluation of Mouth Dissolving Tablets of Atenolol. The tablets were prepared by direct compression method using crospovidone, croscarmallose and sodium starch glycolate in different ratio with directly compressible mannitol. The formulation containing 4% w/w of crospovidone emerged as over all best formulation with good disintegration time and highest release rate profile than other formulations.

Sachin B.S Mahamuni *et al.,* 2009, Formulation and Evaluation of Fast Dissolving Tablets of promethazine Hcl Masked Bitter Taste. Taste masked granules were prepared by extrusion method using Eudragit E-100. Fast Dissolving Tablets were prepared by direct compression using crospovidone, croscarmallose sodium and sodium starch glycolate as superdisintregrants a mixture of excipients containing optimized level of microcrystalline cellulose and starch. Tablets containing 5% crospovidone showed the highest improvement in disintegration and dissolution rate. It was concluded that compelxation of promethazine Hcl with Eudragit E- 100 masks its bitter taste as well as improved its dissolution profile.

Ravi Kumar *et al.,* 2009, Formulation and Evaluation of Mouth Dissolving Tablets of Fenofibrate using sublimation technique. The mouth dissolving tablets of fenofibrate were prepared by sublimation technique using menthol, camphor, ammonium bicarbonate and thymol as sublimating agent. The wetting time was observed to be very fast. The total drug from optimized batch was found to be released within first ten minutes of dissolutions study. The prepared tablets were found to provide benefits in terms of patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect and good stability.

Rampure. M.V. *et al.,* 2010, Formulation and Evaluation of Orodispersible Tablets of Alfuzosin. The tablets were prepared by sublimation method using camphor as sublimating agent along with varying concentrations of croscarmallose sodium, crospovidone, sodium

starch glycolate in 2 to 10% w/w. The formulation containing 10% w/w of crospovidone and 30% w/w of camphor emerged as overall best formulation based on drug release characteristics.

Rampure M.V. *et al.*, 2011, Formulation and design of Rapidly Disintegrating Phenobarbitone Tablets by direct compression method. The formulation containing 8% w/w of crospovidone and 15% w/w of microcrystalline cellulose emerged as overall best formulations based on *in vitro* dispersion time and drug release compared to conventional commercial tablet.

Raghavendra Rao N.G. *et al.*, 2009, Formulation and Evaluation of Fast Dissolving Chlorthalidone Tablets.The fast dissolving chlorthalidone tablets were prepared by direct compression using co-grinding and solid dispersion methods by using chlorthalidone.The tablet formulation containing Poly vinyl pyrrolidone - 12 solid dispersion showed maximum drug release than Poly vinyl pyrrolidone -12 by co-grinding method. Results concluded that using solid dispersion of the drug with the hydrophilic carrier Poly vinyl pyrrolidone can enhance the dissolution rate of chlorthalidone tablets.

Raghavendra Rao N.G *et al.*, 2010, Formulation and design of Fast Dissolving Tablets of felodipine using novel coprocessed superdisintegrants. The novel co-processed superdisintegrants were developed by solvent evaporation method using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2, and 1:3) for use in fast dissolving tablets. The fast dissolving tablets were prepared by direct compression in method. The results concluded that formulation containing (1:1 mixture of crospovidone and sodium starch glycolate) has best drug release and dispersion time than other formulations.

Padmavathi Y. *et al.,* 2011, Development of Fixed Dose Combination Dispersible Tablets containing Stavudine, Lamivudine and Nevirapine for pediatric applications. Dispersible tablets were prepared by direct compression method and formulated using different superdisntegrants like croscarmallose sodium, crospovidone, sodium starch glycolate at different concentration levels. The effect of superdisintegrant on dispersion time, drug content and *invitro* release has been studied. The formulation containing croscarmallose sodium showed good drug release of all the three drugs when compared to formulation containing sodium starch glycolate and crospovidone.

Neena Bedi *et al.,* 2009, Formulation and Evaluation of Mouth Dissolving Tablets of Oxcarbazepine. The mouth dissolving tablets were prepared by two different technologies, direct compression method and solid dispersion technique. Tablets produced by direct compression method containing crospovione as a superdisintegrant and aspartame as sweetener. Solid dispersions of oxcarbazepine with poly vinyl pyrrolidone K-30 and polyethylene glycol 6000 in different weight ratio. Solid dispersion with polyvinyl pyrrolidone K30 in 1:2 ratios of drug carrier showed maximum drug release. It was concluded that solid dispersion technology can be used as better alternative to the direct compression method for the formulation of mouth dissolving tablets especially for drugs having poor solubility.

Narayanan *et al.,* 2011, Formulation and Evaluation of Olanzapine as Orodispersible Drug Delivery System by using β-cyclodextrin and superdisintegrants are used to enhance the solubility of drug. The drug is complexed with polymer and tablets are formed in direct compression in method. The superdisintegrants crospovidone, croscarmallose sodium, sodium starch glycolate are used for formulation in 2 to 5% concentration. The orodispersible tablet prepared by using croscarmallose sodium (AC-Di-Sol) as superdisintegrant showed

faster relase of drug than both control formulation and formulations prepared with other super superdisintegrants.

Nagendra Kumar D. *et al.,* 2010, Formulation design of Fast Dissolving Tablets of Fexofenadine Hcl by sublimation method. Fast dissolving tablets of fexofenadine were prepared by sublimation method using camphor as sublimating agent. Crospovidone and croscarmallose sodium were used as superdisintegrants. The study concludes that formulation containing 8% w/w crospovidone and 30% w/w camphor as best formulation based on release characteristics and *invitro* dispersion time.

Margret Chandira M. *et al.,* 2010 "Formulation and Evaluation of Mouth Dissolving Tablets of Etoricoxib. The mouth dissolving tablets of etoricoxib were prepared by direct compression method using primogel, kollidone, Ac–Di-sol, L-hydroxypropyl methylcellulose, L-hydorxypropylcellulose as superdisintegrants in different concentration like 4% to8%.The results conclude that formulation containing 8% L-hydorxypropylcellulose showed minimum disintegration time, wetting time and drug release.The results showed that disintegration time increased in the manner of L-hydorxypropylcellulose < kollidone < Ac– Di-sol < primogel < L-hydroxypropyl methylcellulose.

Khole *et al.,* 2011, Development and Evaluation of Melt in Mouth Tablets by Sublimation Technique. Solid dispersion of the drug Rizatriptan benzoate and taste masking β-Cycodextrins prepared. Tablets were formulated by direct compression. The tablets prepared using sublimating agents were porous in nature and showed faster disintegration and dissolution which is the major aim.

Kawtikwar. P.S. *et al.,* 2009, Formulation and Optimization of Fast Dissolving Tablet containing Tizanidine Hcl. Eudragit E- 100 is used as a taste masking agent. The granules

were prepared by mass extrusion technique. There superdisintegrants sodium starch glycolate, croscarmallose sodium and crospovidone were used. It was concluded that fast dissolving tablets of Tizanidine Hcl can be successfully prepared by superdisintegrants addition and sublimation method and superdisintegrant method was found to be superior to that of sublimation method.

Jain C.P. *et al.,* 2009, Formulation and Evaluation of Fast Dissolving Tablets of valsartan. The fast dissolving tablets of valsartan were prepared using different superdisintegrants by direct compression method. It was concluded that the fast dissolving tablets of valsartan containing crospovidone is most acceptable.

Indhumathi D. *et al.,* 2011, Formulation and Evaluation of Orodispersible tablet of Fluoxetine using super disintegrants. The tablets were prepared by wet granulation method using crospovidone, pregelatinized starch, croscarmallose sodium and sodium starch glycolate as superdisintegrants. It was found and concluded that crospovidone at a concentration of 5% w/w showed maximum *in vitro* dissolution profile and hence it emerged as overall best formulation the *in vitro* drug release of superdisintegrants was in the order of crospovidone > pregelatinized starch > croscarmallose sodium > sodium starch glycolate .

Harish Chander *et al.,* 2011, Formulation and Evaluation of Fast Dissolving Tablets of Ramipril. The fast dissolving tablets were prepared by direct compression technique (effervescent) with sodium bicarbonate, mannitol, and polyvinyl pyrrolidone. Citric acid in different ratios of sodium bicarbonate: Mannitol. In conclusion, overall results suggests that fast dissolving tablets the containing sodium bicarboinate and mannitol in ratio of 1:3 showed best result in terms of percentage drug release, compressibility index, hardness and disintegration time.

Gupta S.C *et al.,* 2011, Formulation and Evaluation of Mouth Dissolving Tablets of Dicyclomine Hcl with enhanced bioavailability.The mouth dissolving tablets were prepared by direct compression method using D-mannitol as diluents, crospovidone as a superdisintegrants and aspartame as a sweetener. It was concluded that the formulation containing crospovidone as the best formulation with rapid disintegration time and higher release rate than other formulations.

Gohil *et al.,* 2011, Formulation and Characterization of Bambuterol Hcl Fast Dissolving Tablet using various superdisintegrants. The tablets were prepared with four disintegrants sodium starch glycolate, crospovidone, croscarmallose sodium and pregelatinized starch by direct compression method. The maximum increase in dissolutions rate was observed with 12% crospovidone amongst the superdisintegrants. The order of enhancement of dissolution rate with various disintegrants was found to be crospovidone > croscarmallose sodium > sodium starch glycolate > pregelatinized starch.

Gnanaprakash K. *et al.,* 2009, Formulation and Evaluation of Fast Dissolving Tablets of Valdecoxcib. The fast dissolving tablets of valdecoxib were prepared with some carriers (polymers) and superdisintegrants such as polyvinyl pyrrolidone (PVP), sodium carboxy methyl cellulose; crospovidone and β-cyclodextrin in different proportions of 5%, 10% and 15% by direct compression method. The formulation containing 15% crospovidone prepared using mannitol and aspartame were found to have maximum release at the end of 10 minutes.

Ganesh Kumar Gudas *et al.,* 2010, Formulation and Evaluation of Fast Dissolving Tablets of Chlorpromazine Hcl. The tablets were prepared with five superdisintegrants namely sodium starch glycolate, croscarmallose sodium and crospovidone, L-hydroxypropylcellulose and pregelatinized starch. The tablets were prepared by direct impression method. The maximum increase in dissolution rate was observed with 5% crospovidone amongst the super

disintegrants. The order of enhancement of dissolution rate is crospovidone > croscarmallose sodium > sodium starch glycolate > L- hydroxypropylcellulose > pregelatinized starch.

Diensh Mohan S. *et al.,* 2010, Formulation and Evaluation of Salbutamol Sulphate Fast Dissolving Tablet. The tablets were prepared by direct compression method using superdisintegrants such as primojel, kollidon CL, L- Hydroxypropylcellulose. The effectiveness of super disintegrants was found to be in the order of kollidon CL > Primojel > L-Hydroxy propyl cellulose.

Deshpande K.B. *et al.,* 2011, Formulation and Evaluation of Orodispersible Tablets of Propranolol Hcl. The main objective of the present work is to develop orodispersible tablets of propranolol Hcl to improve bioavailability, disintegration time, dissolution efficiency and patient compliance. The formulation containing 4% crospovidone is considered as the best formulation in all parameters.

Debijit Bhowmik *et al.,* 2009, Design and characterisation of Fast Dissolving Tablets of Telmisartan. The tablets were prepared by direct compression method using crospovidone, croscarmallose sodium and sodium starch glycolate as superdisintegrants at different levels (5%, 7.5% and 10%). The formulation containing 10% crospovidone was found to be promising than other formulations with minimum disintegration time and maximum dissolution rate.

Chandrasekar patro *et al.,* 2011, Formulation and Evaluation of Cetrizine Hcl Mouth Fast Dissolving Tablets. The tablets were prepared by direct compression methods using crospovidone, croscarmallose and sodium starch glycolate in different concentration as superdisintegrants. The results indicate that formulation containing 5% croscarmallose sodium was found to be optimized with maximum drug release and minimum disintegration time.

Chandira. M *et al.,* 2011, Formulation and Evaluation of Fast Dissolving Tablets of Rupatidine fumarate. The fast dissolving tablets of rupatidine fumarate were prepared by direct compression method using mannitol, microcrystalline cellulose as filler croscarmallose sodium, crospovidone, sodium starch glycolate as superdisintegrants at different concentrations (2-5%). In conclusion with increase in concentration of superdisintegrant, the disintegration time decreases in order of croscarmallose sodium > crospovidone > sodium starch glycolate.

Basawarj S. patil *et al.,* 2011, Formulation and Evaluation of Granisetron Hcl by Direct Compression Method. The Fast Dissolving Tablets of granisetron Hcl were prepared by direct compression method. Effect of super disintegrates (such as crospovidone, croscarmallose sodium and sodium starch glycolate) on wetting time, dispersion time, and stability parameters were studied.The formulation containing crospovidone as superdistegrant showed highest dissolution rate.

Basawaraj S. patil *et al.,* 2011, Formulation and Evaluation of Fast Dissolving Candesartan Cilexetil Tablets. The fast dissolving tablets were prepared by direct compression method using croscarmallose sodium and crospovidone as disintegrants. The effect of superdisintegrants on wetting time, *in vitro* dispersion time and stability parameter has been studied. The present work revealed that the superdisintegrant crospovidone showed better disintegrating and dissolution property than sodium starch glycolate in formulation of fast dissolving tablets .

Aravind K. Singh *et al.,* 2010, Development and Evaluations of Fast Disintegrating Tablets of Salbutamol sulphate by superdisintegranting agents. The fast dissolving tablet is formulated using Ac-di-sol, polyplasdone and primogel as super disintegrants. While microcrystalline cellulose and mannitol were used as diluents. Direct compression is the

technique used. It was concluded that with increase in concentration of superdisintegrants, the disintegration time decreases in Ac- Di-sol and poly plasdone XL, while increases in primogel due to formation of viscous plug on swelling.

Althaf *et al.,* 2011, Formulation and Evaluation of Oral Fast Dissolving Tablets of Sildenafil Citrate. The Mouth Dissolving Tablets were prepared by wet granulation and direct compression method by super disintegrant addition. Crospovidone and croscarmallose sodium are used as superdisintegrants in different concentrations. Croscarmallose in the concentration of 5% showed minimum disintegration time and wetting time as compared to other formulations. The results showed that disintegration time increased with the type of superdisintegrant.

Aiman A. Obaidat *et al.,* 2010, Development and Evaluation of Fast Dissolving Tablets of Meloxicam- ß-Cyclodexrin complex prepared by direct compression. A complex of meloxicam with ß-Cd was prepared by spray drying and then compressed in the term of tablets by direct compression using various levels of three types disintegrants crospovidone, croscarmallose sodium and sodium starch glycolate. Co-spray dried mannitol were and as diluents. Formulation containing 6% of croscarmallose sodium, as superdisintegrant showed shortest disintegration time and higher release rate than other formulations. It was concluded that complexation of melaxicam with ß-Cd provides greatest drug release.

CHAPTER-IV

AIM OF THE WORK

The aim of present work is to formulate and evaluate Fast Dissolving Tablets of Lamivudine to prevent MTCT (Mother to Child Transmission) of HIV virus in perinatal infants.

Lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R, cis)-4-amino-1-(2-hydroxymethyl-1-3, 3-oxathiolan-5-yl)-(IH)-pyrimidin-2-one.The solubility of lamivudine is approximately 70mg/ml in water at 20ºc (Narasimharao *et al*., 2011).

Rationale behind the devolepment of Fast Dissolving Tablets of Lamivudine (30mg)

MTCT is typically addressed by suppression of virus in mother or by limiting child's exposure to the various body fluids during child birth, for example by utilizing caesarian section birth. However, in addition to potential exposure to HIV in utero and during birth, new borns may also face continued exposure to HIV through breast feeding. Thus an alternative approach to reduce incidents of MTCT of HIV is to administer a single entity anti-retiroviral drug to the new born. While anti-retiroviral "cocktails" may be used to treat adult patients with HIV/AIDS, such drug combinations may not be necessary or desirable for preventing MTCT of virus in perinatal infants. First, the maturity of the virus in the newborn is typically less than in infected adults. That is, the virus in perinatal children has no time or oppurtunity to mutate and devolep drug resistance. Thus, treatment with single antiretiroviral entities may effectively reduce the

MTCT without need to rely on multicomponent anti-retiroviral cocktails. Further significant toxicities are associated with antiviral drug cocktails, which may cause undesirable side effects upon administration to the developing physiology of the perinatal or infants (Adeyeye *et al*., 2011).

CHAPTER-V

PLAN OF WORK

PART I

1. Determination of λmax for Lamivudine.

2. Calibration of Lamivudine.

PART-II

1. Preformulation evaluations

a) Differential Scanning Colorimetry (DSC) Studies

b) Fourier Transmission Infra-Red (FT-IR) Studies

PART-III

1. Precompression evaluations of all the formulations

PART -IV

1. Formulation of Fast Dissolving Tablets of Lamivudine using various superdisintegrants at different ratios by direct compression method

PART-V

1. Post compression evaluations for tablets of all formulations.

CHAPTER-VI

MATERIALS AND EQUIPMENTS

MATERIALS	SUPPLIERS
Lamivudine	Strides Acrolabs, Bangalore, India.
Sodium starch glycolate	Octis Research Lab, Uttarkhand, India.
Crospovidone	Octis Research Lab, Uttarkhand, India.
Croscarmellose sodium	Octis Research Lab, Uttarkhand, India
Microcrystalline cellulose	High purity laboratory chemicals, Mumbai, India.
Mannitol	Universal Scientific Appliances, Madurai, India.
Saccharin sodium	Universal Scientific Appliances, Madurai,India.
Magnesium stearate	Universal Scientific Appliances, Madurai, India
Talc	Universal Scientific Appliances, Madurai. India

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A & D Company HR 200, Japan.
Single Punch Tablet Compression Machine	Cadmach, Ahmedabad, India.
UV- Visible Spectrophotometer	Shimadzu, Japan.
Digital Tablet Dissolution Test Apparatus	Disso 2000, Lab India, New Mumbai, India.
Friability Test Apparatus	Indian Equipment Corporation, Mumbai,
Hot Air Oven	Rands Instruments, Chennai, India.
Disintegration Test Apparutus	Rolex, India.
Tablets hardness tester (Monsanto)	Pravin Enterprises, Bangalore, India.
Vernier Caliper	Linker, India.
Differential Scanning Calorimeter	T.A.Instrument, USA.

CHAPTER-VII

DRUG PROFILE

Name:

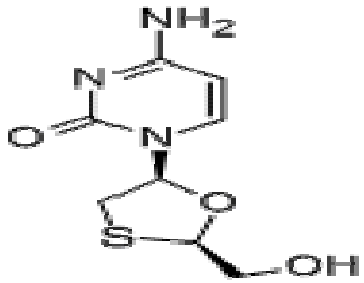
Lamivudine

Description:

A Reverse transcriptase inhibitor and zalcitabine analog in which a sulphur atom replaces the 3' carbon o the pentose ring. It is used to treat HumanImmunodeficiency Virus Type 1 (HIV-1) and hepatitis-B (HBV).

Molecular weight: 229.256

Structure:



Chemical Formula: $C_8H_{11}N_3O_3S$

IUPAC Name: 4-amino-1-[(2R,5S)-2-(hydroxymethl)-1,3-oxathiolan-5yl]-1,2-dihydropyrimidin-2-one

Indication: For the treatment of HIV infection and chronic hepatitis-B (HBV)

Pharmaco-dynamics:

Lamivudine is a nucleoside reverse transcriptase inhibitor(NRTI) with activity against Human Imunodeficiency Virus Type 1 (HIV1) and hepatitis-B (HBV).Lamivudine is phosphorylated to active metabolites that compete for incorporation in to viral DNA. They inhibit the HIV reverse transcriptase enzyme completely and act as a chain terminater 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 growth is terminated.

Mechanism of action:

Lamivudine is asynthetic nucleoside analogue and is phosphorylated intracellularly to its active 5'-triphosphate metabolite,lamivudine triphosphate (L-TP).This nucleosid analogue is incorporated into viral DNA by HIV reverse transcriptase and HBV polymerase,resulting in DNA chain termination.

Absorption:

Lamivudine is rapidly absorbed after oral administration in HIV infected patients.

Bioavailability: 86% ± 16% for tablet and 87% ± 13%

Protein binding: 36%

Metabolism: The only metabolite of lamivudine is trans-sulfoxide.

Route of elimination: Lamivudine is excreted unchanged in urine and, also is excreted in human breast milk.

Half life: 5 to 7 hrs

Clearance: Renal clearance = 280.4 ± 75.2 ml / min [HIV – infected patients given a single dose IV ranging from 0.25 to 8mg/kg]

Melting point: 160 to162°c.

Solubility: 7mg/ml in water at 20°c

Dosage:

HIV – 300mg as single or two divided doses.

HBV – 100mg OD

HIV – Infants and children

Over 3 months of age and weighing less than 14kg or in those unable to swallow oral solution – 4mg/kg b.i.d to a maximum of 300mg.

Weighing 14 to 21 kg – Tablet in a dose of 75mg b.i.d.

Weighing 21to 30 kg – 7mg in morning and 150mg at night.

Over 30 kg – 150mg b.i.d.

Dosage reduction is needed in HIV patients of 3 months age and weighing not less than 30kg with moderate to severe renal impairment

i.e., CC below 50ml/min.

CC below 30 to 49ml/min – 4mg first dose and then 4mg/kg O.D

CC 15 to 29ml/min -4mg/kg first dose and then 2.6mg/kg O.D

CC 5 to 14ml/min – 4mg/kg first dose and then 1.3mg/kg O.D

CC less than 5ml/min -1.3mg/kg first dose and then 0.7mg/kgO.D

Chronic Hep-B in children between 2 to 17 years – 3mg/kg O.D to maximum of 100mg.

CHAPTER-VIII

CROSPOVIDONE

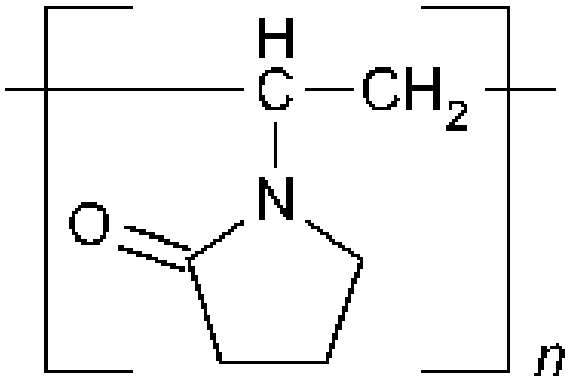
Synonyms:

- Cross linked Povidone.
- Kollidon.
- Polyplasdone.
- Polyvinylpoly pyrrolidone.
- 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer.

Chemical Structure:



Empirical formula:

$(C6H9NO)_n$

Molecular Weight:

>1 000 000

Functional category:

Tablet disintegrant.

Application in Pharmaceutical formulation:

- Tablet disintegrant and dissolution agent.
- Solubility enhancer for poorly soluble drug.

Description:

Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odourless, hygroscopic powder.

Stability and storage condition:

Crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. (Hand book of Pharmaceutical excipients-5th edition, 214-216)

CROSCARMELLOSE SODIUM

Synonyms:

- Ac-Di-Sol.
- Cross linked carboxymethylcellulose sodium.
- Explocel.
- Modified cellulose gum.
- Primellose.
- Solutab.
- Vivasol.

Chemical Name:

Cross linked carboxy methyl ether Cellulose sodium salt.

Functional Category:

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation:

Disintegrating agent for tablets and capsules.

Description:

-White or grayish white powder.

-Odourless and tasteless.

-Insoluble in water. Practically insoluble in acetone, ethanol and toluene .

Pharmacopoeial Specifications:

pH (1% w/v dispersion) 5.0–7.0

Loss on drying ≤10%

Heavy metals ≤10 ppm

Sodium chloride and sodium glycolate ≤ 0.5%

Sulfated ash 14.0–28.0%

Settling volume 10.0–30.0 ml

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.

Density (bulk): 0.529 g/cm3

Density (tapped): 0.819 g/cm3

Density (true): 1.543 g/cm3

Stability and Storage Conditions:

Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Handling Precautions:

Croscarmellose sodium may be irritant to the eyes; eye protection is recommended (Hand book of Pharmaceutical excipients-5th edition, 211-213).

SODIUM STARCH GLYCOLATE

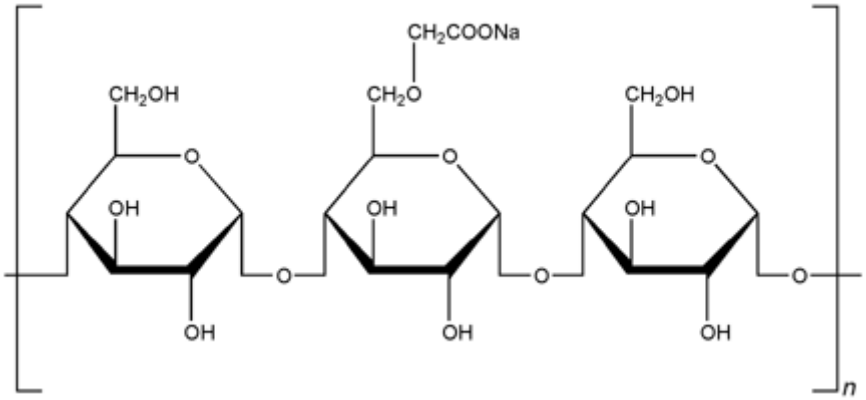
Synonyms:

- Explosol.
- Explotab.
- Primojel.
- Starch carboxymethyl ether, sodium salt.
- Tablo.
- Vivastar P.

Chemical Name:

Sodium carboxymethyl starch.

Chemical structure:



Functional Category:

Tablet and capsule disintegrant.

Application in Pharmaceutical Formulation:

- Sodium starch glycolate is used as a disintegrant in capsule and tablet formulations.
- Sodium starch glycolate is also used as a suspending vehicle.

Description

- Sodium starch glycolate is a white to off-white, odorless, tasteless, free flowing powder
- It does not melt, but chars at approximately 200^{o}C
- It is sparingly soluble in ethanol (95%) but practically insoluble in water.

Pharmacopoeial Specifications:

- Specific surface area: 0.24m2/g;
- Swelling capacity: In water, sodium starch glycolate swells to up to 300 times its volume.
- Viscosity (dynamic): 4200 mPa s (200 cP) for a 4% w/v aqueous dispersion.
- Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

Stability and Storage Conditions:

Sodium starch glycolate should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Handling Precautions:

Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. .(Hand book of Pharmaceutical excipients-5th edition)

MAGNESIUM STEARATE

Synonyms:

- Magnesium octadecanoat.
- Octadecanoic acid, magnesium salt.
- Stearic acid, magnesium salt.

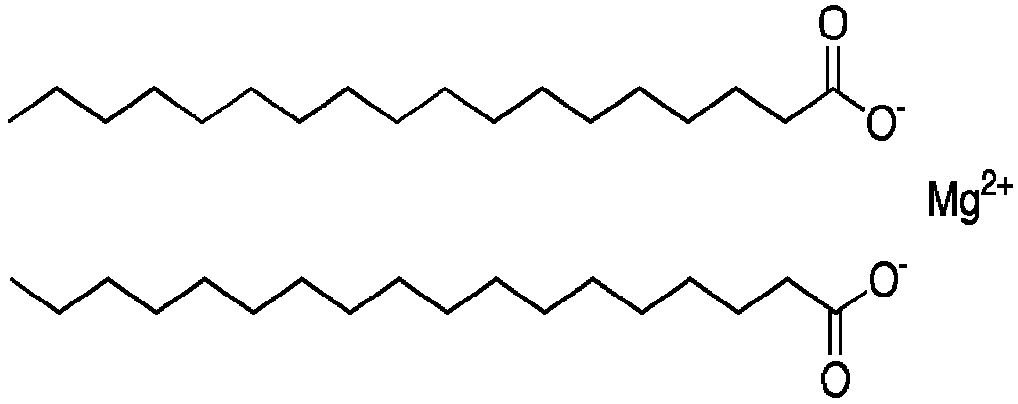
Chemical Name:

Octadecanoic acid magnesium salt.

Structural Formula:

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

Molecular Structure:



Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ & 591.34

Functional Category:

Tablet and capsule lubricant.

Application in Pharmaceutical Formulation:

- Lubricant in capsule and tablet formulation.(0.25% to 0.25%).
- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.

- It is also used in barrier creams.

Description:

- Magnesium stearate is a very fine, light white powder.
- Faint odour.
- Characteristic taste.
- Greasy to the touch and readily adheres to the skin.

Pharmacopoeial Specifications:

Freezing point	5538C
Nickel	45 ppm
Cadmium	43 ppm
Loss on drying	46.0%
Chloride	40.1%
Sulfate	41.0%
Lead	410 ppm

Stability and Storage Conditions:

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

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety:

Oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Handling Precautions:

- Eye protection and gloves are recommended.

-Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. .(Hand book of Pharmaceutical excipients-5th edition,430-433)

MANNITOL

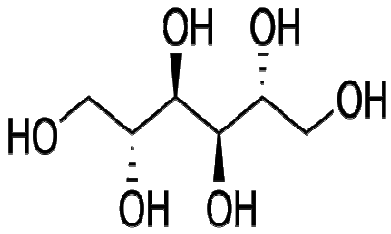
Synonyms:

- Cordycepic acid.
- Manna sugar.
- D-Mannite.
- Pearlitol.

Chemical Name:

D-Mannitol.

Chemical structure:



Empirical Formula and Molecular Weight:

$C_6H_{14}O_6$ & 182.17

Functional Category:

- Diluent.
- Sweetening agent.
- Tonicity agent.

Application in Pharmaceutical Formulation:

- Mannitol is widely used in pharmaceutical formulations and food products.
- It is used as diluents (10–90% w/w) in tablet formulations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations.
- Plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulation.
- It is used as a carrier in dry powder inhalers.
- It is also used as diluents in rapidly dispersing oral dosage forms.
- It is used in food applications as a bulking agent.

Description:

- Mannitol is a white, odorless, crystalline powder, or free-flowing granules.
- It has a sweet taste.
- Microscopically, it appears as orthorhombic needles when crystallized from alcohol.
- Mannitol shows polymorphism.
- **Pharmacopoeial Specifications:**
- Density (bulk):0.430 g/cm3.
- Density (tapped):0.734 g/cm3.
- Density (true): 1.514 g/cm3.
- Dissociation constant: pKa = 13.5 at 188C.
- Flowability: powder is cohesive, granules are free flowing.

- Melting point: 166–168^{o}C
- Loss on drying: 40.3%

Stability and Storage Conditions:

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

Incompatibilities:

- Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.
- Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.
- Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Handling Precautions:

Mannitol may be irritant to the eyes; eye protection is recommended. . (Hand book of Pharmaceutical excipients-5th edition,449-453)

MICROCRYSTALLINE CELLULOSE

Synonyms:

- Avicel PH.
- Celex.
- Celphere.
- Ceolus KG.
- Ethispheres.
- Fibrocel.
- Pharmacel.
- Tabulose.

- Vivapur.

Chemical Name:

Cellulose.

Empirical Formula:

$(C_6H_{10}O_5)$ n

Molecular Weight:

36 000

Functional Category:

- Adsorbent.
- Suspending agent, Tablet and capsule diluents, tablet disintegrant.

Application in Pharmaceutical Formulation:

- Microcrystalline cellulose is used as a binder/diluent in oral tablet and capsule formulations.
- Microcrystalline cellulose is used as a lubricant and disintegrant agent in tablet formulation.
- Microcrystalline cellulose is also used in cosmetics and food products.

Description:

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

Use Concentration (%)

- Adsorbent: 20–90
- Antiadherent: 5–20
- Capsule binder/diluent: 20–90
- Tablet disintegrant : 5–15
- Tablet binder/diluents: 20–90

Pharmacopoeial Specifications:

- pH: 5.0–7.0
- Loss on drying: 47.0%
- Residue on ignition: 40.05%
- Sulfated ash: 40.1%
- Heavy metals: 410 ppm

Typical Properties:

- Density (tapped):0.478 g/cm3,
- Density (true): 1.512–1.668 g/cm3
- Flowability: 1.41 g/s for Emcocel 90M.
- Melting point: chars at 260–2708C.
- Microcrystalline cellulose is hygroscopic.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Handling Precautions:

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. .(Hand book of Pharmaceutical excipients-5th edition132-135,)

SACCHARIN SODIUM

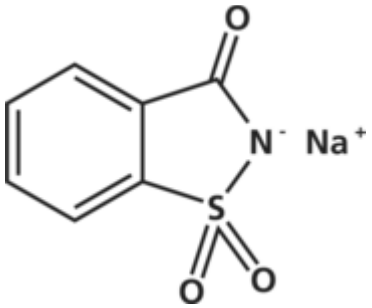
Synonyms:

1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt; Crystallose E954; sodium o-benzosulfimide; soluble gluside; soluble saccharin; sucaryl sodium.

Chemical Name;

1,2-Benzisothiazol-3(2H)-one 1,1-dioxide, sodium salt for the dihydrate for the anhydrous material.

Chemical structure:



Empirical Formula and Molecular Weight:

C7H4NNaO3S 205.16

Functional Category:

Sweetening agent.

Application in Pharmaceutical Formulation:

Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes; It is also used in vitamin preparations.

Uses of saccharin sodium

- Dental paste/gel 0.12–0.3%
- IM/IV injections 0.9%
- Oral solution 0.075–0.6%

Description:

Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic aftertaste that at normal levels of use can be detected by approximately 25% of the population. Saccharin sodium can contain variable amounts of water.

Pharmacopoeial Specification:

- Water 415.0%
- Arsenic 42 ppm
- Selenium 40.003%
- Heavy metals 420 ppm
- Assay (anhydrous basis) 99.0–101.0%

- **Typical Properties**:
- Acidity/alkalinity: pH = 6.6 (10% w/v aqueous solution)
- Density (bulk):0.8–1.1 g/cm3
- Density (particle): 1.70 g/cm3
- Density (tapped): 0.9–1.2 g/cm3
- Moisture content: 14.5% w/w water;
- Solvent Solubility at 208C
- Specific surface area: 0.25m2/g

Stability and Storage Conditions:

Saccharin sodium is stable under the normal range of conditions employed in formulations. Saccharin sodium should be stored in a well-closed container in a cool, dry place.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. .(Hand book of Pharmaceutican excipients-5th edition)

TALC

Synonyms:

Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite, Superiore.

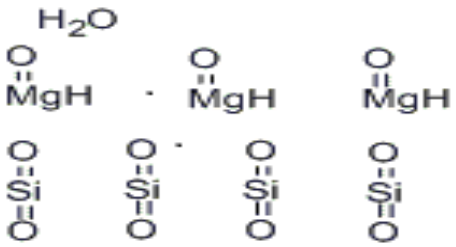
Chemical Name:

Talc

Empirical Formula:

$Mg_6(Si_2O_5)_4(OH)_4$.

Chemical Structure:



Functional Category:

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

Applications in Pharmaceutical Formulations:

- Lubricant and diluents.
- Dissolution retardant in the development of controlled-release products.
- An adsorbant.
- Dusting powder.

- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Dusting powder: 90.0–99.0%

Glidant and tablet lubricant: 1.0–10.0%

Tablet and capsule diluents: 5.0–30.0%

Description:

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

Pharmacopoeial Specifications:

- Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.
- Hardness (Mohs): 1.0–1.5
- Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.
- Specific gravity: 2.7–2.8
- Specific surface area: 2.41–2.42m2/g

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Handling Precautions:

Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. In the UK, the occupational exposure limit for talc is 1 mg/m3 of

respirable dust long-term (8-hour TWA).Eye protection, gloves, and a respirator are recommended (Handbook of Pharmaceutical excipients- 5th edition, 641-643).

CHAPTER- IX

EXPERIMENTAL DETAILS

1. CALIBRATION OF LAMIVUDINE

An accurately weighed quantity of 100mg lamivudine pure drug is taken in a 100ml standard flask. It is mixed with sufficient quantity of distilled water and shaken well until the drug is completely dissolved. From this, 10ml of the solution is pipetted out and made up to 100ml with distilled water. From this 5,10,15,20 and 25ml of solutions are pipetted out in separate standard flasks and the volume is made up to 100ml with distilled water. The absorbance is measured at 271nm in UV-Spectrophotometer.

2. PREFORMULATION EVALUATIONS

a) Differential Scanning Calorimetry (DSC) Studies

DSC analysis **(**DSC200 TA instruments, USA**)** of samples are carried out by heating the samples under nitrogen atmosphere on an aluminium pan at a heating rate of 10°C / min, over the temperature range 5 - 200 $^{\circ}$C and a nitrogen gas flow of 20 lb / cm^2.

b) Fourier Transmission Infra-Red (FT-IR) Studies

The studies are performed to check the compatability of drug and excipients used in the formulation in order to prevent degradation by interaction. FT-IR spectra (Spectrum RX -1 Perkin-Elmer, German) for the drug and various physical mixtures are obtained in a FT-IR spectroscopy in the transmission mode with a wave number region 4000 – 400 cm^{-1}.KBr pellets are prepared gently by mixing 1mg sample powder with 100mg KBr.

3. FORMULATION OF FAST DISSOLVING TABLETS OF LAMIVUDINE

The Fast dissolving tablets of lamivudine were prepared by direct compression method. Three different superdisintegrants are used namely

- Croscarmallose sodium
- Sodium starch glycolate
- Crospovidone

Fifteen formulations were prepared using different superdisintegrants for each of five formulations, in a concentration ranging from 2% to 10% (2, 4, 6, 8 &10). An accurately weighed quantity of drug, superdisintegrants & microcrystalline cellulose are taken in a glass mortar and ground well, the other excipients like mannitol, sodium saccharin, magnesium stearate and talc are added in an order and mixed well to ensure thorough mixing of all ingredients. Then the powder is analysed for flow properties like

- Angle of repose
- Bulk density
- Tapped density
- Compressibility Index
- Hausner's ratio

The total powder blend is weighed individually for fifty tablets for each formulation, as per the calculations derived from the drug content of the powder blend. Then the individually weighed powders are compressed in the tablet compressing machine.

4. PRECOMPRESSION EVALUATIONS FOR THE POWDER BLEND

The prepared blend was evaluated by following tests.

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

a. Angle of repose

Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug- excipient blend is allowed to flow through the funnel freely on the surface of a paper. The diameter of the powder cone is measured and angle of repose is calculated using the following equation (Amrutkar *et al .,* 2010)

$$\text{Tan } \theta = h/r$$

Where

h = height of the cone

r = radius of the cone

b. Bulk density

Apparent bulk density is determined by pouring a weighed quantity of blend in to a graduated cylinder and measuring the volume and weight. (Vijay Tiwari *et al.,* 2010)

$$\text{Bulk Density} = \frac{\text{Weight of the powder}}{\text{Volume of packing}}$$

c. Tapped Density

The tapped density is determined by placing a graduated cylinder, containing a known mass of drug - excipients blend. The cylinder is tapped on a flat surface from a height of 10cm at 2 seconds intervals. The tapping is continued until no further change in volume is noted (Suhas M.Kakade *et al.,* 2010)

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

d. Compressibility Index

The compressibility index of the blend is determined by carr's compressibility index. (Gnanaprakash *et al.,* 2010)

$$\text{Carr's compressibility index} = \frac{\text{Tapped density-bulk density}}{\text{Tapped density}} \times 100$$

.

e. Hausner's ratio

Hausner's ratio is determined by the following formula: (Debijit Bhoumik *et al.,* 2009)

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

5. POST COMPRESSION EVALUATION

a. Hardness

The hardness of the tablets is an indication of its strength measuring the force required to break the tablet across tests it. The force is measured in kg and hardness of about 3-5kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of ten tablets from each formulation was determined by using mansanto hardness tester. (Kolhe *et al.,* 2011)

b. Thickness

Thickness of the tablets is determined by using vernier calliper. (Althaf *et al.,* 2011)

c. Diameter

The diameter of the tablets is determined by using vernier calliper.(Ravikumar *et al.,* 2009)

d. Drug content

Five tablets from each batch are weighed and powdered, 10mg equivalent of the powder is taken and diluted with 10ml of distilled water and the volume is made up to 100 ml. From this 10ml of the solution is taken and the volume is made up to 100ml with distilled water. The absorbance of the solution is measured using UV-Spectrophotometer at 271 nm. (C.P Jain *et al.,* 2009)

e. Weight variation test

Twenty tablets are taken and their weight is determined individually and collectively on a digital weighing balance the average weight of one tablet is determined from the collective weight. (P.S Kwtikwar *et al.,* 2009)

USP specification for the uniformity of weight

S.NO.	AVERAGE WEIGHT (mg)	MAXIMUM % DIFFERENCE ALLOWED
1	130 or less	10%
2	130-324 mg	7.5%
3	More than 324 mg	5%

f. Friability

Friability is the loss of weight of tablet in the container due to removal of particles from surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of tablets.20 tablets from each formulation are employed for finding the friability of tablets. The tablets are weighed and placed in roche friabilator. That is rotated at 25 rpm for 4 min. The tablets are dusted and weighed again .The percentage of weight loss is calculated again using the formula (Harish chander *et al.,* 2011).

$$\text{Percentage friability} = \frac{\text{Initial weight- final weight}}{\text{Initial weight}} \times 100$$

g. Wetting time and Water absorption ratio

For determination wetting time and water absorption ratio, a piece of tissue paper is folded twice and placed in a small petridish (having internal diameter of 5 cm) containing 6 ml of water .a small quantity of amaranth red dye is added to the water. A

tablet is placed on the paper and the time required for the complete wetting is measured .The wetted tablet is then weighed (M.V Rampure *et al.,* 2010**)**. The water absorption ratio 'R' is determined using the equation

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where,

W_a =Weight of the tablet after water absorption.

W_b = Weight of the tablet before water absorption.

h. Disintegration test

The disintegration test is performed using an USP disintegration apparatus with distilled water at 27± 0.5℃ .the time reported to obtain complete disintegration of 6 tablets are recorded and average is reported (Viral shah *et al.,* 2011).

i. Dissolution Studies

The release rate of the formulated Lamivudine tablets are characterized using USP type 2(Paddle) at 50rpm, 900ml of distilled water is used as dissolution medium.10mlof samples are withdrawn from the dissolution medium and replace with 10ml of blank media. The samples are withdrawn at 5,10,15,30 and 45 mins, and analysed using UV-Spectrophotometer. Results of the dissolution rate are recorded **(**K.Prakash *et al.,*2008).

CHAPTER-X

RESULTS AND DISCUSSION

1. CALIBRATION OF LAMIVUDINE

The λ_{max} of Lamivudine was determined by scanning the 10µg / ml solution of drug using UV-Spectrophotometer and was found to be 271nm.The absorbance of the solution 5 to 25 µg/ml was measured in UV-Spectrophotometer at 271nm.(Table-1). The linear correlation was found to be 0.9995(Distilled water) (Fig- 1)

2. PREFOFORMULATION EVALUATIONS

a) Differential Scanning Calorimetry (DSC) Studies

DSC experiments are carried out in order to characterise the physical state of drugs in formulation. The thermograms of pure drug exhibit the single isothermic peak at 177.4°c. In thermogram of physical mixture of drug with excipients, the drug peaks were shifted to lower temperature with reduced intensity which may due to baseline shift. Baseline shift are caused by changes in sample weight or specific heat of sample.(Fig- 5 to 10)

b) Fourier Transmission Infra –Red (FT-IR) Studies

Before formulation, preformulation study was carried out by comparing FT-IR spectra of pure Lamivudine and its physical mixture with superdisintegrants using Fourier Transmission Infrared spectrophotometer. There was no difference in their spectra. It was observed that the drug remained intact in the presence of superdisintegrants. (Fig -11 to 15)

3. FORMULATION OF FAST DISSOLVING TABLETS OF LAMIVUDINE

The individually weighed powder blends of each formulation were compressed in to tablets in a single punch tablet compressing machine. Fifty tablets for each formulation were obtained. The tablets were white in colour and round in shape. The contents for tablets of each formulation were shown in Table -02

4. PRECOMPRESSION EVALUATIONS FOR THE POWDER BLEND

Precompression evaluations were done to ensure the flow properties of the powder blend .Good flow properties of the powder blend will yield the tablets of desired quality and ease the tableting process. So it was mandatory to assess the flowability of the blend before compression. The various precompression evaluations were as follows

- Angle of repose
- Bulk density
- Tapped density
- Compressibility Index
- Hausner's ratio

a. Angle of repose

The angle of repose was used for the measurement of frictional force in a loose powder which in turn will influence the flow properties of the powder blend. The angle repose of all the formulations ranges from 30˚.06' to 30˚ .72'.It was evident from the results, that the powder blends of all formulations posses' good flow

properties. The results of angle of repose for all the formulations were summarised in Table – 03 (Amrutkar*et al*., 2010).

b. Bulk density

The bulk density was determined to assess the free flowing property of the powder blend. The bulk density of all formulations ranges from 0.3368g/cm^3 to 0.3916g/cm^3. The results indicate that the powder blends of all fifteen formulations were having good flow properties. The results were summarised in Table-03(Vijay Tiwari *et al*., 2010).

c. Tapped density

The tapped densities of all fifteen formulations were determined to analyse the powder blends for their free flowing property. The tapped density of all the formulations ranges from 0.4436g/cm^3 to 0.4663g/cm^3. From the results, it was inferred that the powder blend of all formulations posses good flow properties. The results of all the formulations were summarised in Table -03(Suhas M. Kakade *et al*., 2010).

d. Compressibility Index

The compressibility index was the simplest method to measure the free flowing of powder blends of all formulations. The ease with which a material was induced to flow was given by compressibility index. The compressibility index of all the formulations ranges from 15.9 to 24.14.The results indicate that the powder blend of all formulations possess good flow properties. The results of all formulations were summarised in Table -03 (K.Gnanaprakash*et al*., 2009).

e. Hausner's ratio

The Hausner's ratio was an indirect index of ease of powder to flow. The Hausner's ratio for powder blends of all fifteen formulations ranges from 1.18 to 1.31.It was observed from the results that the powder blends of all formulations have good flow properties except for formulations (F1, F4, F5) .The results were summarised in Table – 03.

Hausner's ratio

< 1.25 – Good flow property

>1.25 – poor flow property (Debijit Bhowmik *et al.,* 2009)

It was evident from the results of the precompression studies, that the powder blends of all fifteen formulations posses good flow properties, which were within the standard limits and were qualified for compression into Tablets.

5. POST COMPRESSION EVALUATIONS

The tablets obtained after compression were evaluated on various parameters to determine their quality and to ensure that the resultant product meets all necessary criteria's required for the fast dissolving tablets.

a. Hardness

The hardness for tablets determines the resistance of the tablets to abrasion or breakage under conditions of storage, transformation and handling before usage. The hardness for tablets of all the fifteen formulations was found to be $3kg/cm^3$.The results indicate that the tablets of all formulations have uniform hardness, which in

turn protect them from mechanical damage .The results were summarised in Table -04 (Kolhe *et al*., 2011).

b. Thickness

The thickness of tablets gives appearance, prevents damage from external forces and ensures uniform die filling of the powder blends. The thickness for Tablets of all fifteen formulations was found to be 3mm.The results indicate that the Tablets of all formulations were of uniform size. The results were summarised in Table -04 (Althaf *et al .,* 2011).

c. Diameter

The diameter was measured to ensure the uniformity in size and shape of the Tablets. The diameter of all fifteen formulations was found to be 8mm.The results indicate that the Tablets of all batches were of uniform size and shape. The results were summarised in Table -04. (Ravikumar *et al .,* 2009)

d. Drug content

The drug content of the tablets was estimated to ensure that all the tablets of a formulation contains the therapeutic dosage of the active ingredient meant for the particular dosage form. The drug contents for tablets of all the formulations ranges from 95.74% to 97.16%.The results indicate that the contents for tablets of all formulations were uniform and contains therapeutic dose of the active ingredient. The results were summarised in Table -04 (C.P Jain *et al*., 2009).

e. Weight variation test

The weight variation test was carried out to ensure that the tablets of each formulation were of uniform weight, which in turn will indicate the uniform distribution of contents of the powder blends of each formulations. The weight variation for tablets of all formulations was found to be within the range of ±7.5%. The results indicate that all tablets of each formulation were of uniform weight. The results were shown in Table-04 (P.S Kawtikwar *et al.,* 2009)

f. Friability test

The friability test was carried out to ensure the mechanical strength of tablets to avoid the loss of the external surface of the tablets during the process of packing, handling, transit, and storage. Friability below 1% was an indication of good mechanical resistance. The results indicate that the friability for tablets of all formulations were below 1%and hence passes the test. The results were summarised in Table -04 (Harish Chander *et al.,* 2011).

g. Wetting time and Water absorption ratio

The wetting time and water absorption ratio indicates the capacity of the superdisintegrants to absorb water and completely wet the tablet at the earliest time possible, which were the significant characteristics of fast dissolving tablets. The minimum wetting time and maximum water absorption ratio will enable faster disintegration of the tablets, which were the prime important criteria for fast dissolving tablets. The wetting time for formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15 were found to be 15, 90, 103, 36, 151, 70, 74, 88, 57, 100, 74, 30, 25, 24, 19 seconds respectively .The results indicates that the wetting

time and water absorption ratio of all tablets were within the limits. The results were summarwase-04 (M.V Rampure *et al*., 2010).

h. Disintegration time

The disintegration time was the time taken by the tablet to break down in to small particles, in the presence of aqueous medium. It varies with type and concentration of the superdisintegrants incorporated in the formulation. As the name implies disintegration time were the prime most criteria for fast dissolving tablets, which should be less than 30 secs to 3 minutes as per the standards. The disintegration time for formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15 was found to be 623, 173, 179, 42.6, 311, 217, 91, 171, 120, 150, 72, 87, 29, 21, 4 respectively. The results indicate that the disintegration time for tablets of all formulations are within the limits except for formulations(F1, F5, F6,) were within the permissible limits, which indicate that the Tablets of all formulations disintegrate quickly. The results were summarised in Table -04 (Viral shah *et al*., 2011).

i. Dissolution studies

The dissolution studies were performed to evaluate the release profile of the drug, which relates the percentage of drug release from its dosage form with the function of time. The superdisintegrants were added to the solid dosage formulations to enhance the disintegration time and thereby enhancing the faster release of active drug from its dosage form, which ultimately results in enhanced rates of absorption and bioavailability of the drug. The desired quality of fast dissolving tablets was to have a maximum release of therapeutic dose at a very minimal time period. The maximum drug release at a time period of five minutes is noted for all the formulations. The drug release for tablets of all formulations ranges from 19.27 to

97.19. The results indicate that the drug release of all the formulations were found to be above 80% in five minutes except for formulations (F1 and F2).The release rate of the three superdisintegrants were in the order of Crospovidone>Sodium Starch Glycolate>Croscarmallose. The results were summarised in Table -04. (K. Prakash *et al*., 2008).The graphical representation for the release rates of formulations containing three superdisintegrants are as shown in Fig-2, 3, & 4.

From the results obtained from the post compression studies of tablets of all fifteen formulations, the formulation fifteen with concentration of 10% Crospovidone was found to be the best formulation with a disintegration time of 4secs, wetting time of 19secs and drug release of 97.19±0.28 which was the highest of all formulations .The results were summarised in Table -04 (K.Prakash *et al* 2008)

TABLE-01 CALIBRATION OF LAMIVUDINE

S.No	Concentration(µg/ml)	Absorbance at 271nm (Avg ± S.D)
1	5	0.197 ± 0.0045
2	10	0.423 ± 0.004
3	15	0.611 ± 0.0024
4	20	0.804 ± 0.005
5	25	1.005 ± 0.0076
		r^2=0.9995

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Lamivudine	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Croscarmallose sodium	4	8	12	16	20	-	-	-	-	-	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	4	8	12	16	20	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	-	-	4	8	12	16	20
Mannitol(27.5%)	55	55	55	55	55	55	55	55	55	55	55	55	55	55	55
Magnesium stearate(2%)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Sodium Sacharrin(5%)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc(0.5%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Micro Crystalline Cellulose	96	92	88	84	80	96	92	88	84	80	96	92	88	84	80
Total weight of tablet	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

TABLE -02 FORMULATION OF FAST DISSOLVING TABLETS OF LAMIVUDINE

Formulation code	Angle of repose(°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index(%)	Hausner's ratio	Drug content (%)
F1	30.50	0.3368	0.4440	24.14	1.31	96.92
F2	31.40	0.3614	0.4436	18.53	1.22	96.69
F3	30.69	0.3760	0.4655	19.22	1.23	96.92
F4	30.54	0.3624	0.4660	22.23	1.28	96.45
F5	30.25	0.3621	0.4656	22.22	1.28	96.69
F6	30.66	0.3906	0.4650	16	1.19	96.21
F7	30.56	0.3760	0.4444	15.39	1.18	96.69
F8	30.54	0.3913	0.4658	15.99	1.19	95.98
F9	30.46	0.3916	0.4663	16	1.19	96.92
F10	30.72	0.3915	0.4661	16	1.19	96.21
F11	30.72	0.3914	0.4659	15.9	1.19	96.45
F12	30.43	0.3914	0.4660	16	1.19	96.92
F13	30.59	0.3915	0.4661	16	1.19	96.21
F14	30.52	0.3913	0.4659	16	1.19	96.21
F15	30.06	0.3914	0.4660	16	1.19	96.69

TABLE 03 PRECOMPRESSION EVALUATIONS

Formulation code	Hardness ($kg/cm^{3)}$	Thickness (mm)	Diameter (mm)	Drug content (%)	Weight variation(mg)	Friability (%)	Wetting time (sec)	Water absorption ratio in (%)	Disintegration time (sec)	% drug release in 5 minutes
F1	3	3	8	95.74	184.1 -214.04	0.51	15	75.22	623	19.27±0.56
F2	3	3	8	96.21	184.47-214.27	0.72	90	113	173	77.60±0.76
F3	3	3	8	96.69	185.04-214.84	0.55	103	131	179	88.55±0.50
F4	3	3	8	96.21	184.5 - 214.5	0.56	36	144	42.6	95.34±0.64
F5	3	3	8	97.16	184.26-214.12	0.53	151	59.6	311	83.06±0.42
F6	3	3	8	95.98	185.06-215.06	0.71	70	86.3	217	95.98±0.67
F7	3	3	8	96.21	184.82-214.78	0.54	74	110.8	91	90.71±0.66
F8	3	3	8	96.45	184.7 -214.64	0.52	88	119.8	171	93.24±0.28
F9	3	3	8	96.21	184.63-204.49	0.52	57	105.9	120	92.26±0.43
F10	3	3	8	96.69	185 -214.98	0.66	100	110.3	150	93.06±0.29
F11	3	3	8	95.74	184.76-214.72	0.65	74	129.6	72	90.21±0.24
F12	3	3	8	96.45	184.92-214.9	0.66	30	108.7	87	92.41±0.15
F13	3	3	8	95.74	184.88-214.86	0.48	25	107.5	29	93.37±0.18
F14	3	3	8	96.21	184.85-214.81	0.50	24	126	21	96.24±0.15
F15	3	3	8	96.69	184.88-214.86	0.70	19	129.6	4	97.19±0.28

TABLE -04 POST COMPRESSION EVALUATIONS OF FAST DISSOLVING TABLETS OF LAMIVUDINE

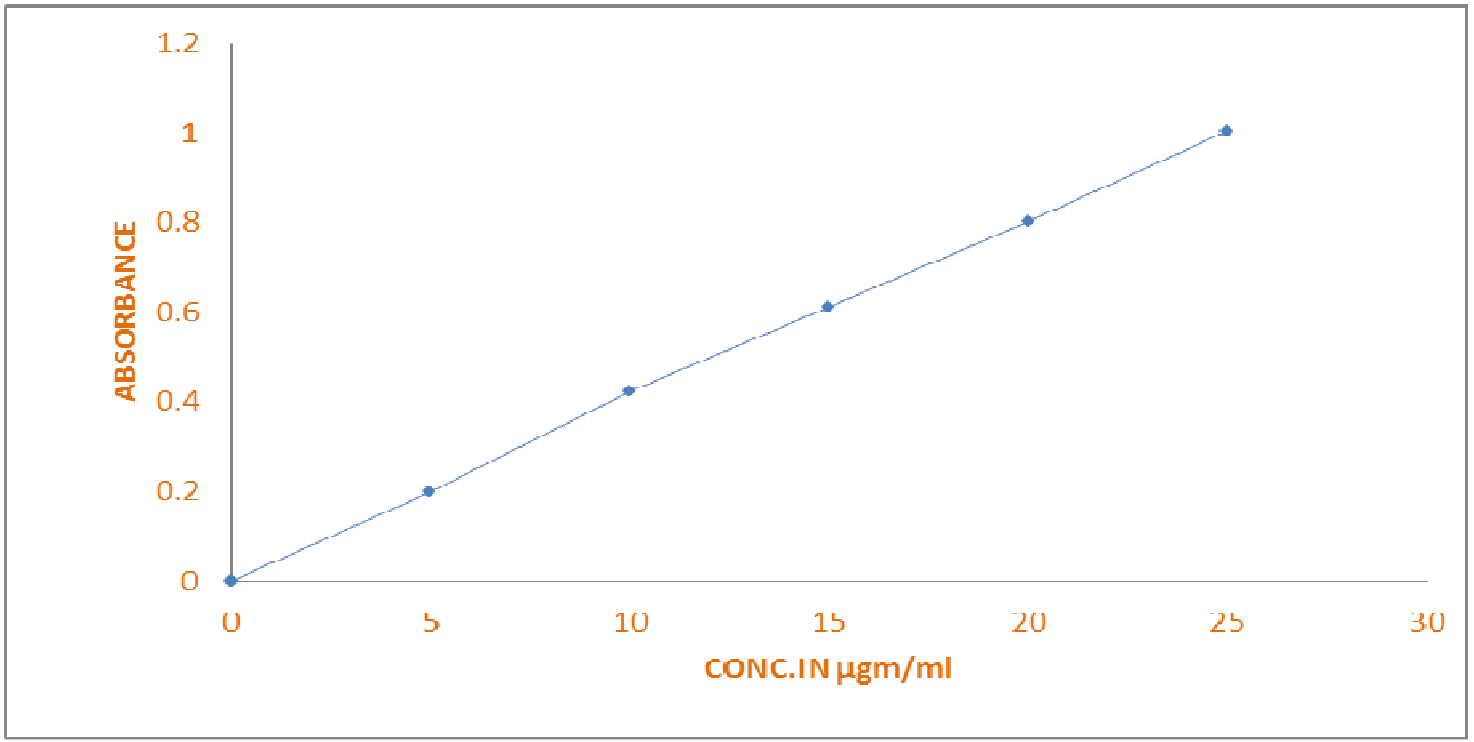


Fig 1 Calibration of lamivudine

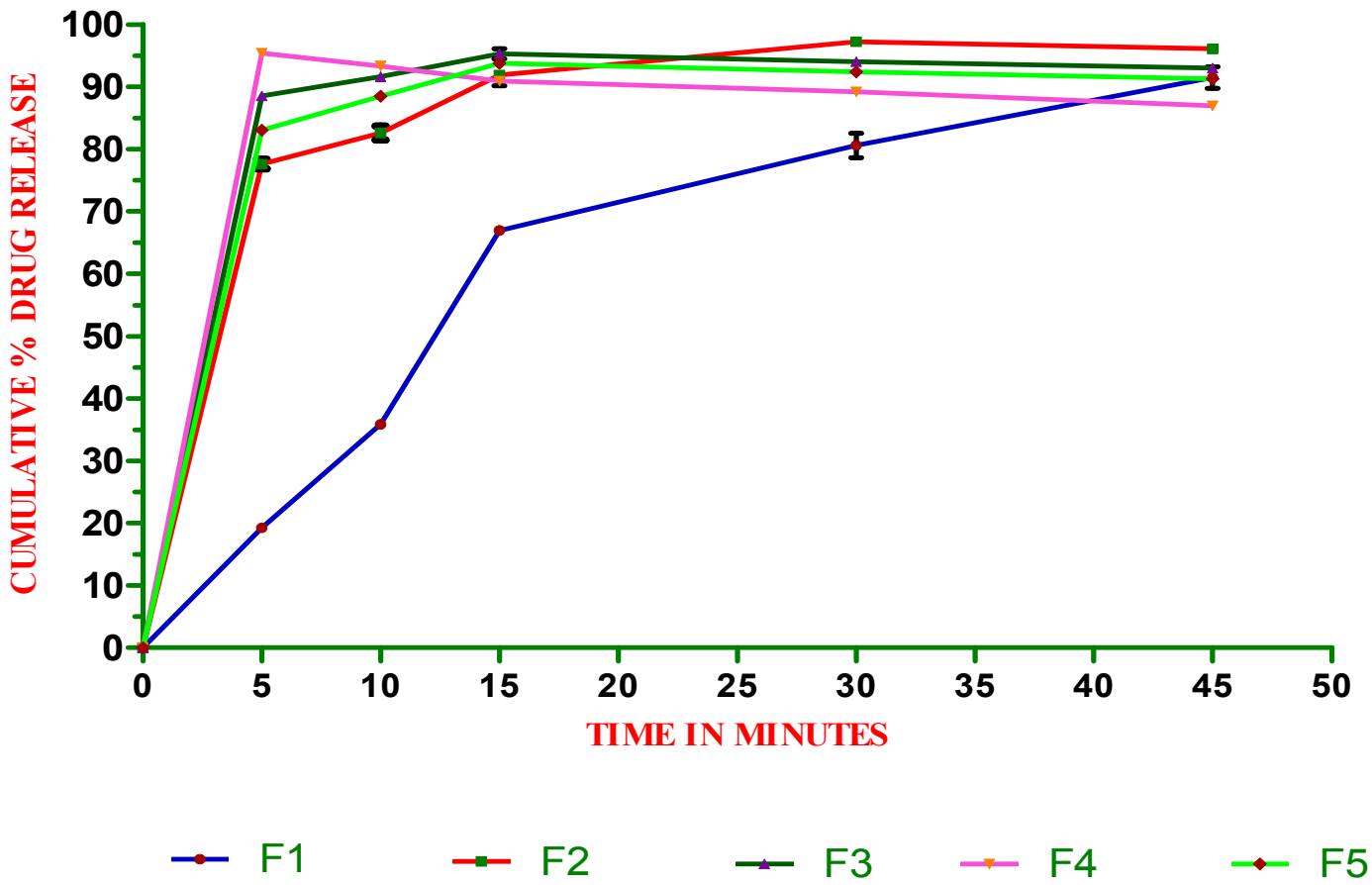


Fig 2 COMPARISON OF INVITRO RELEASE PROFILE OF LAMIVUDINE CONTAINING DIFFERENT PERCENTAGES OF CROSCARMALOSE SODIUM AS DISINTEGRAN

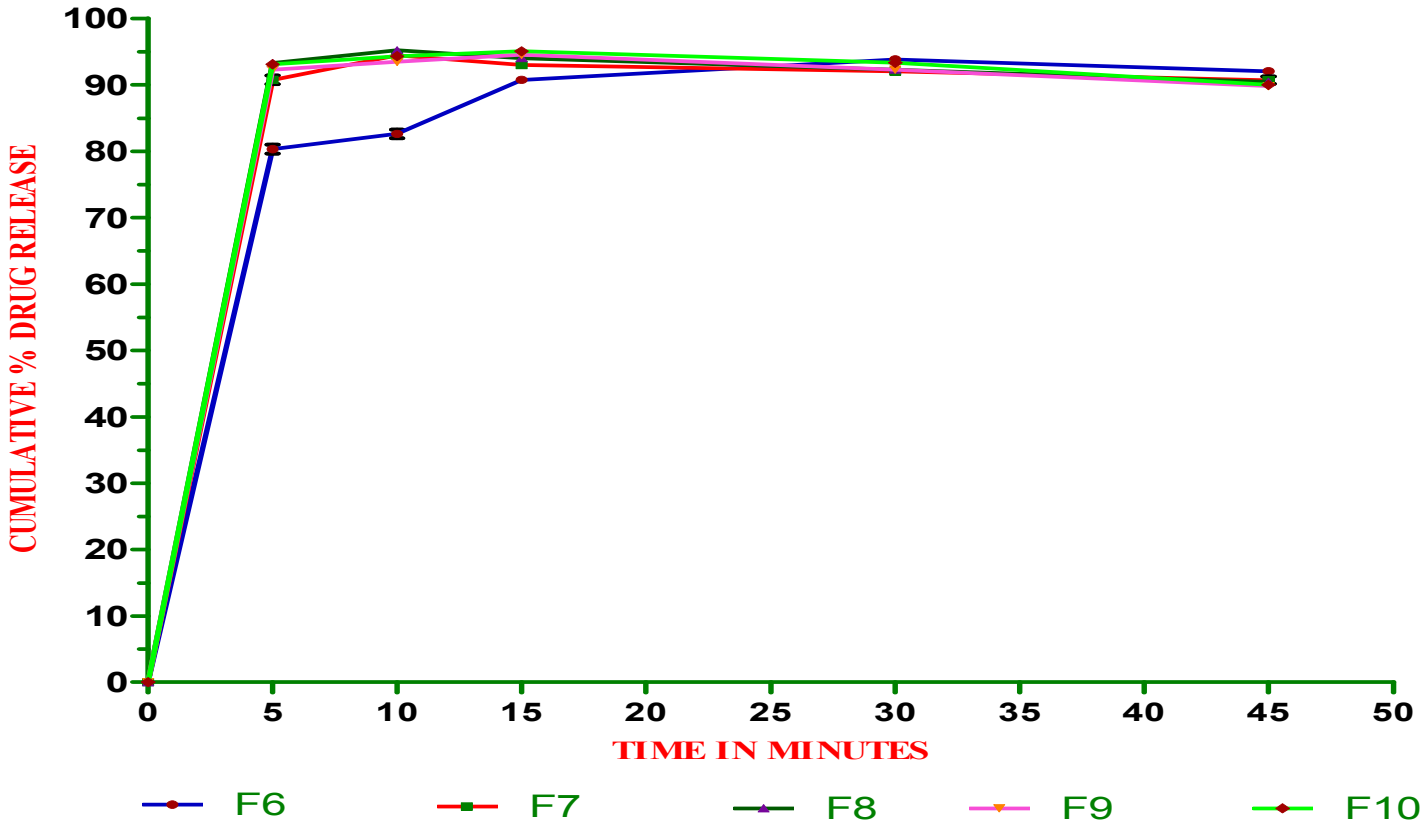


Fig 3 COMPARISON OF INVITRO RELEASE PROFILE OF LAMIVUDINE CONTAINING DIFFERENT PERCENTAGES OF SODIUM STARCH GLYCOLATE AS DISINTEGRANT

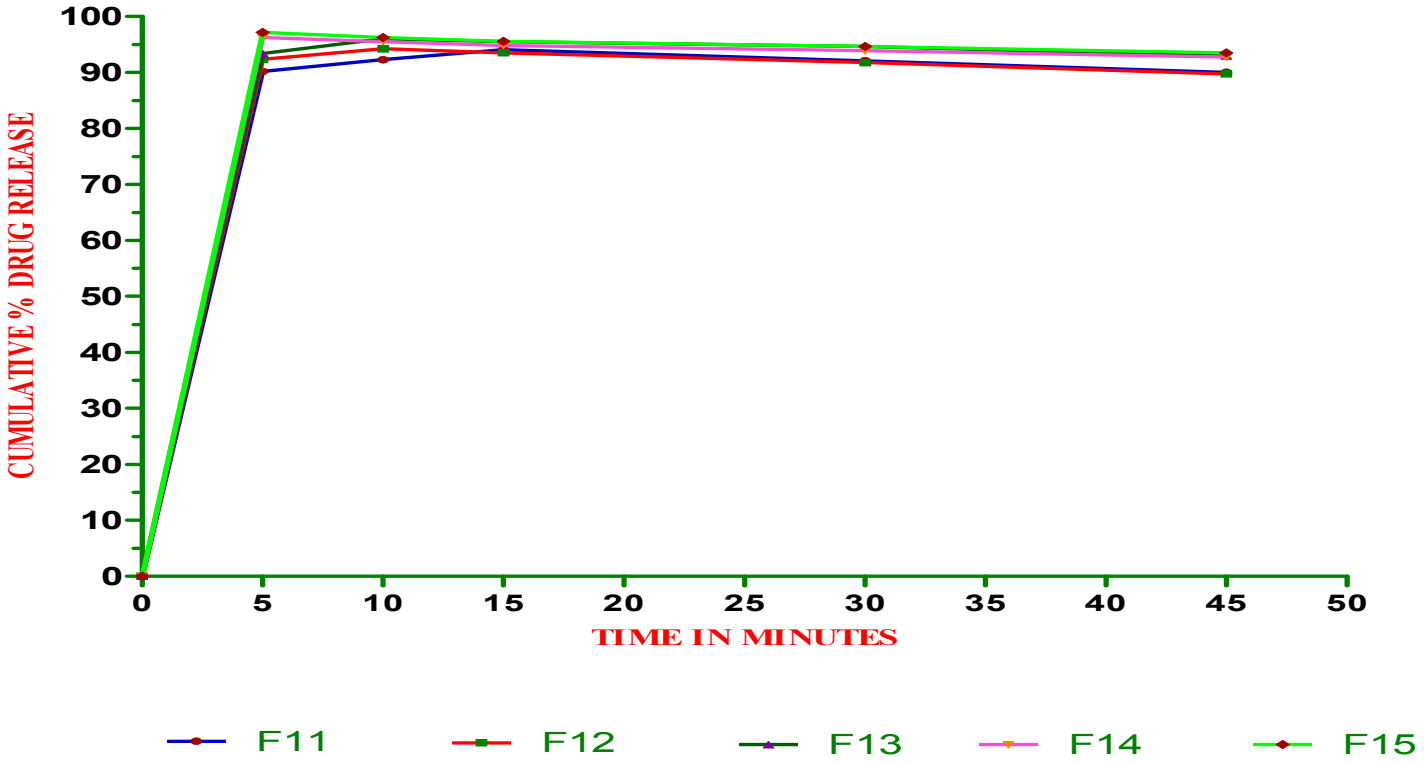


Fig 4 COMPARISON OF INVITRO RELEASE PROFILE OF LAMIVUDINE CONTAINING DIFFERENT PERCENTAGES OF CROSPOVIDONE AS DISINTEGRANT

DSC

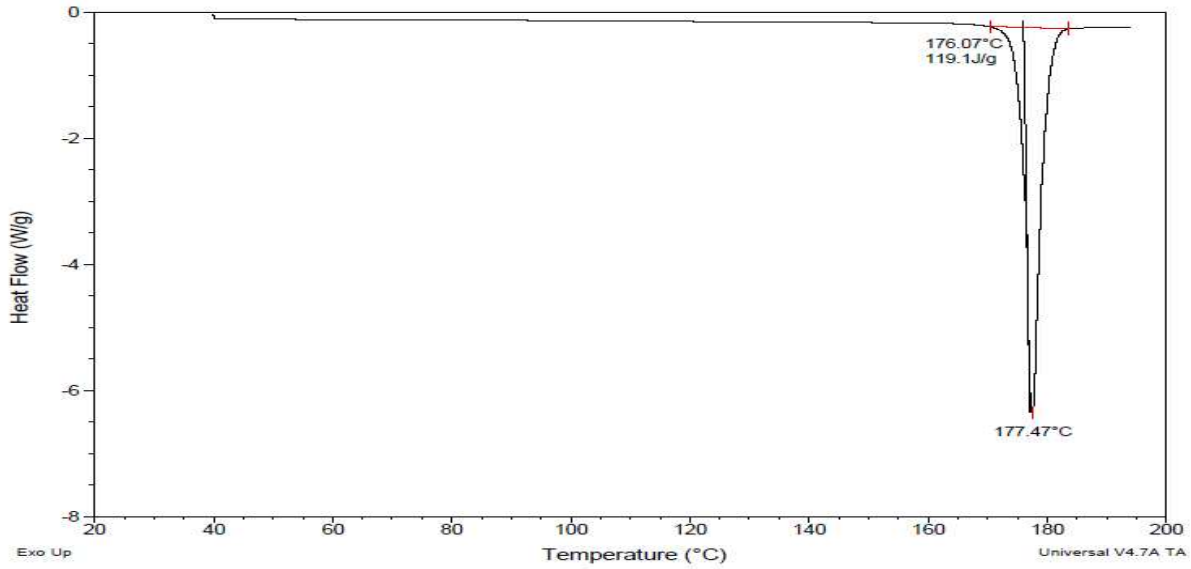


Fig – 5 DSC Thermogram of Lamivudine

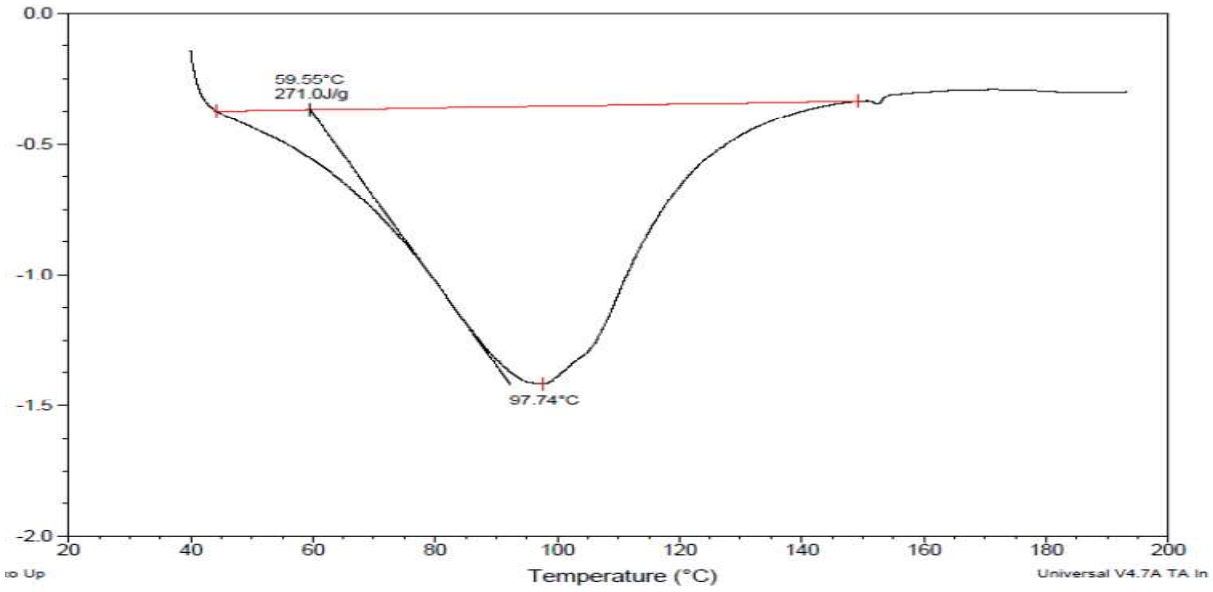


Fig – 6 DSC Thermogram of Croscarmallose sodium

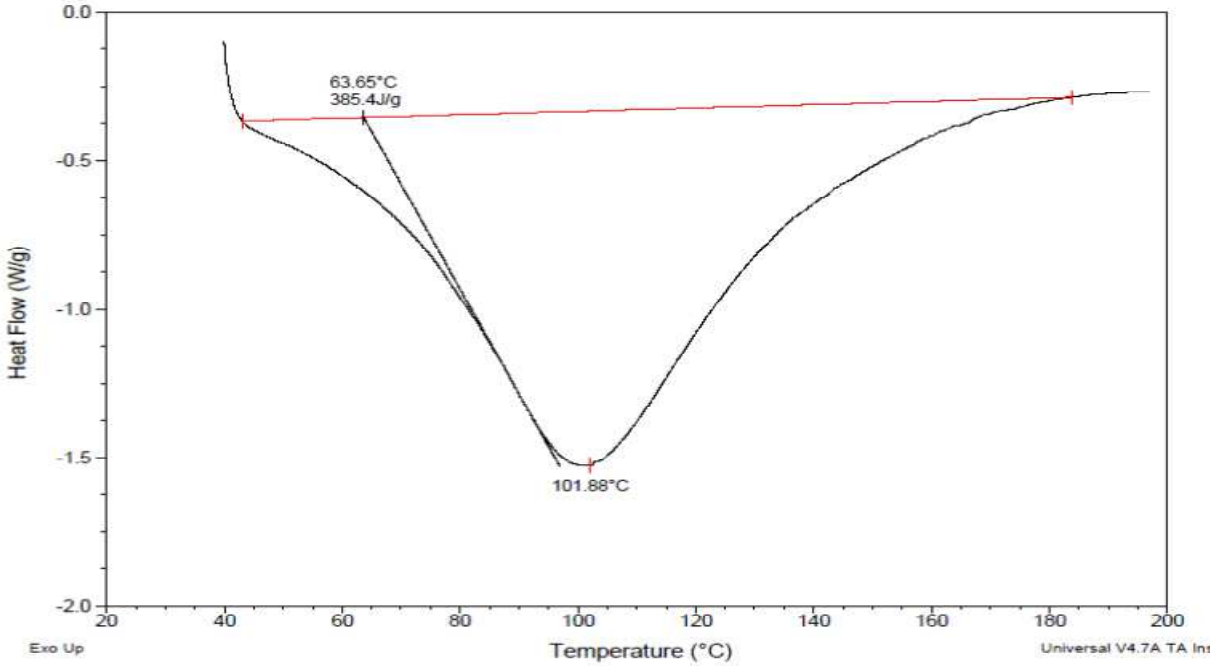


Fig – 7 DSC Thermogram of Sodium starch glycolate

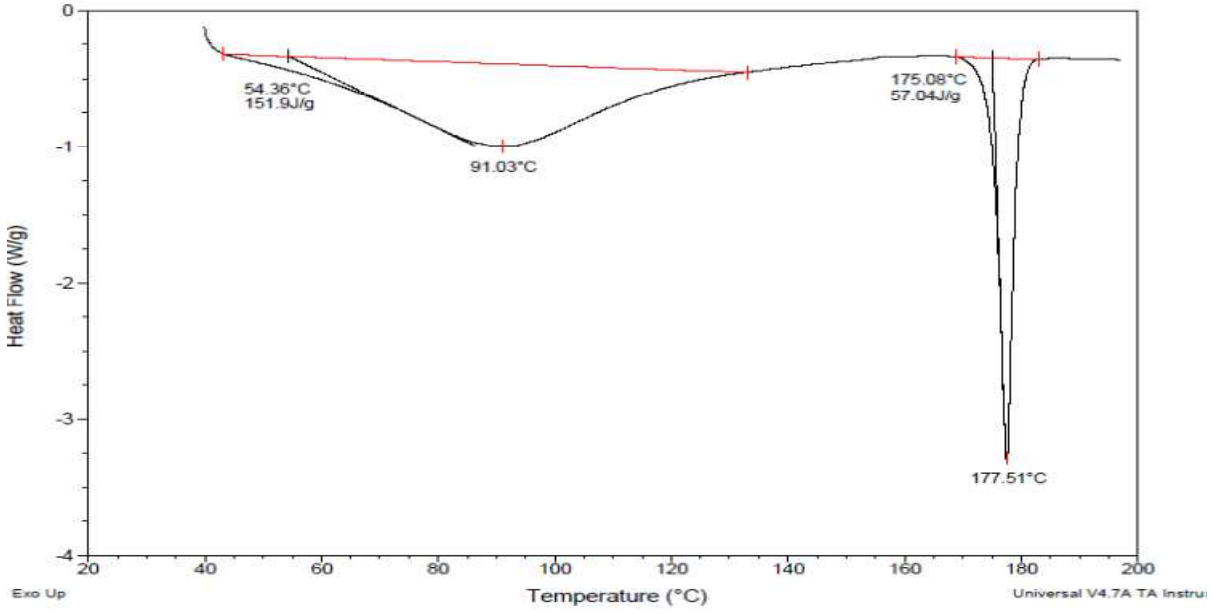


Fig – 8 DSC Thermogram of Lamivudine + Sodium starch glycolate

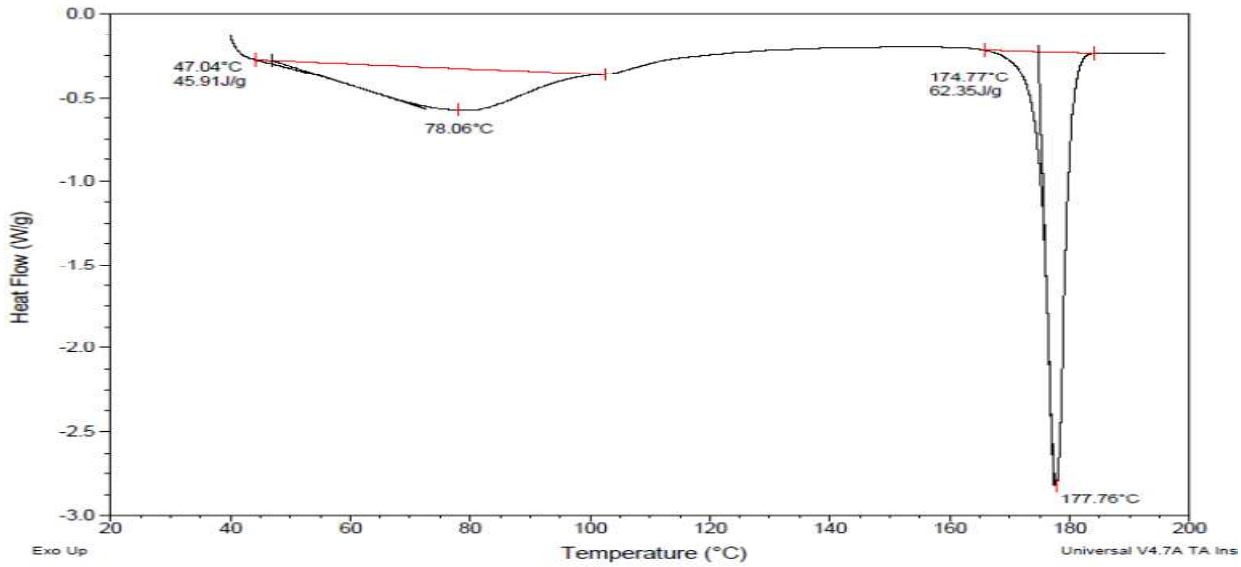


Fig – 9 DSC Thermogram of Lamivudine+ Croscarmallose sodium

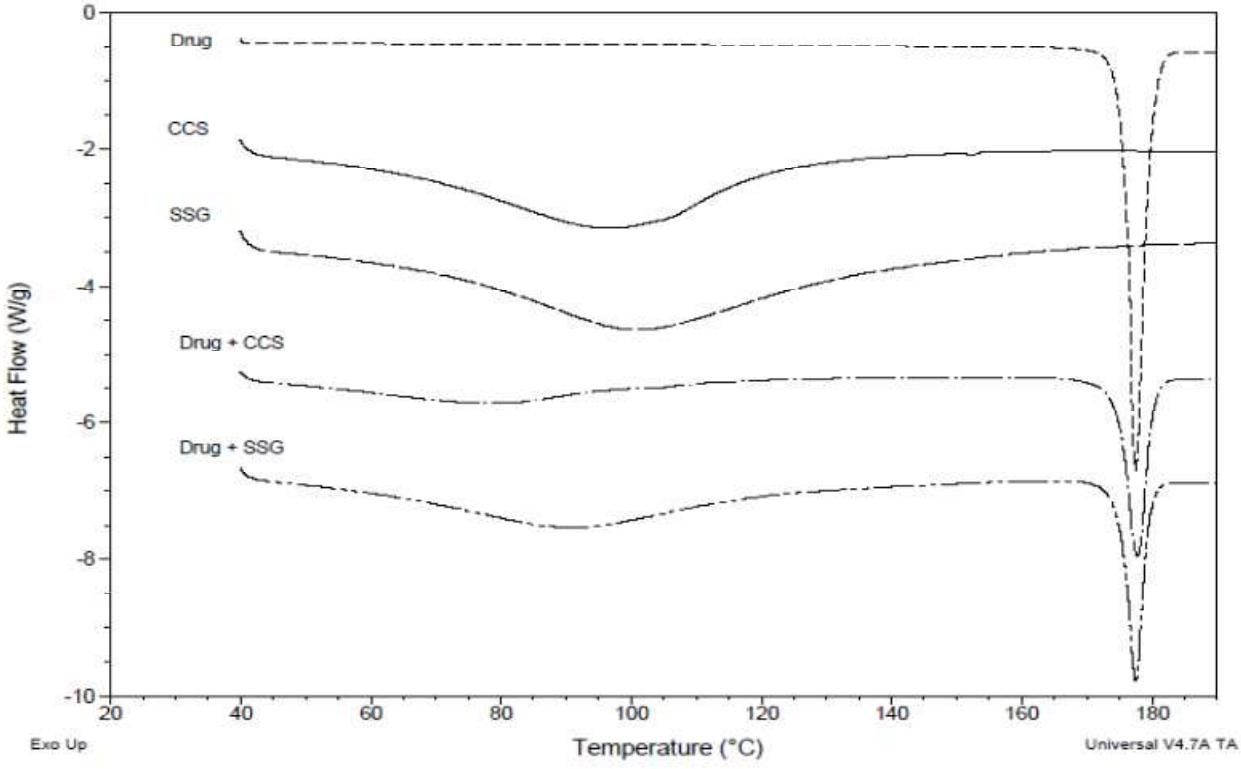


Fig – 10 DSC Thermogram of Overlay of drug and various superdisintegrants

FT- IR

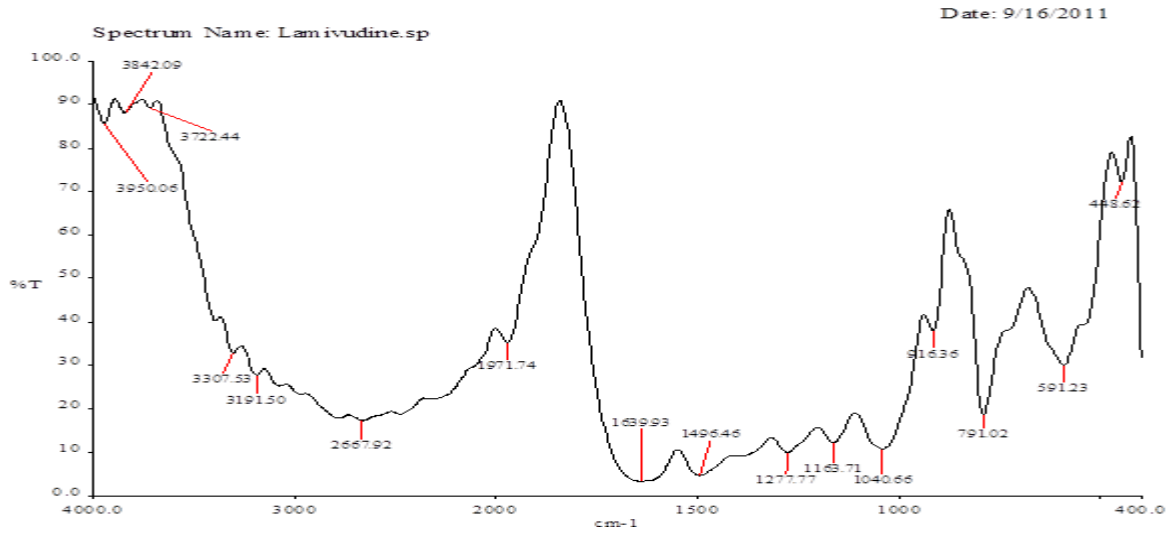


Fig- 11 FT-IR Spectrum of Lamivudine

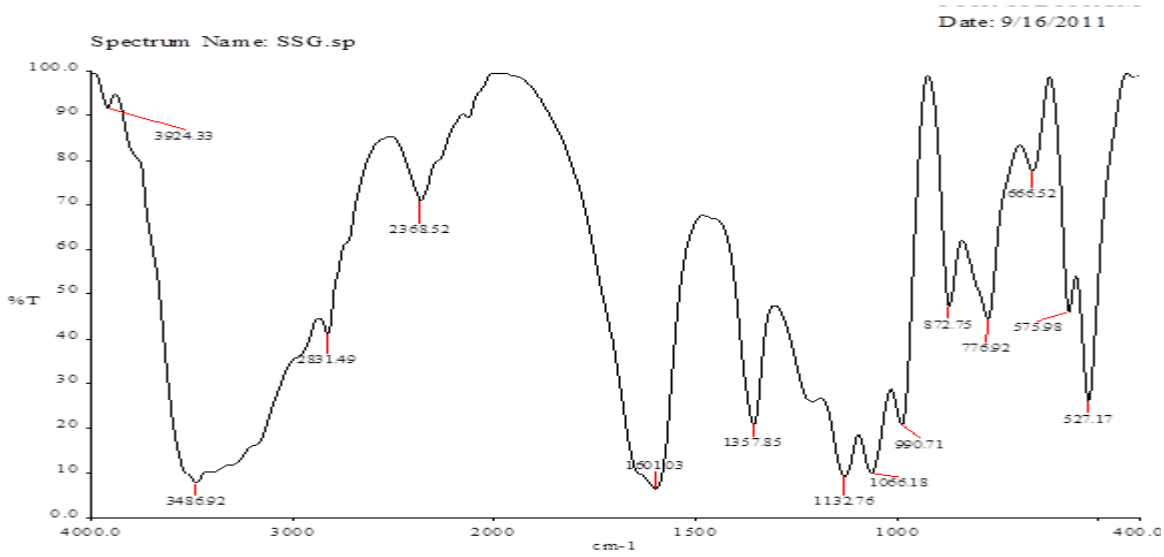


Fig- 12 FT-IR Spectrum of Sodium starch glycolate

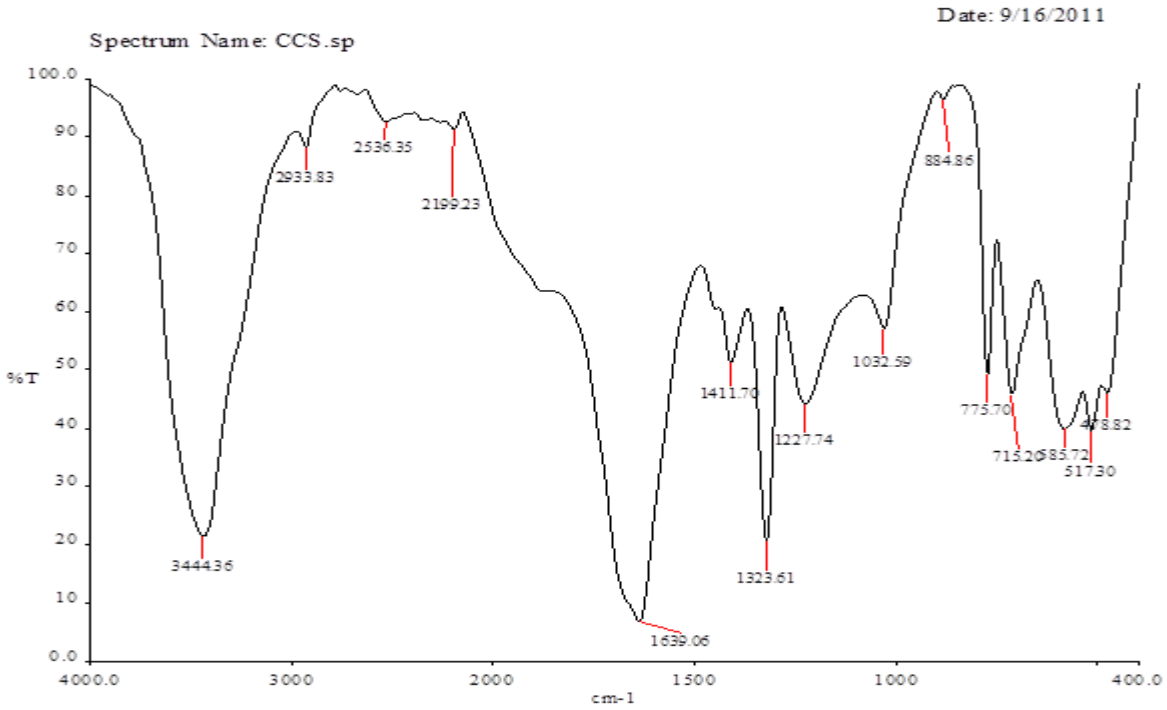


Fig- 13 FT-IR Spectrum of Croscarmallose sodium

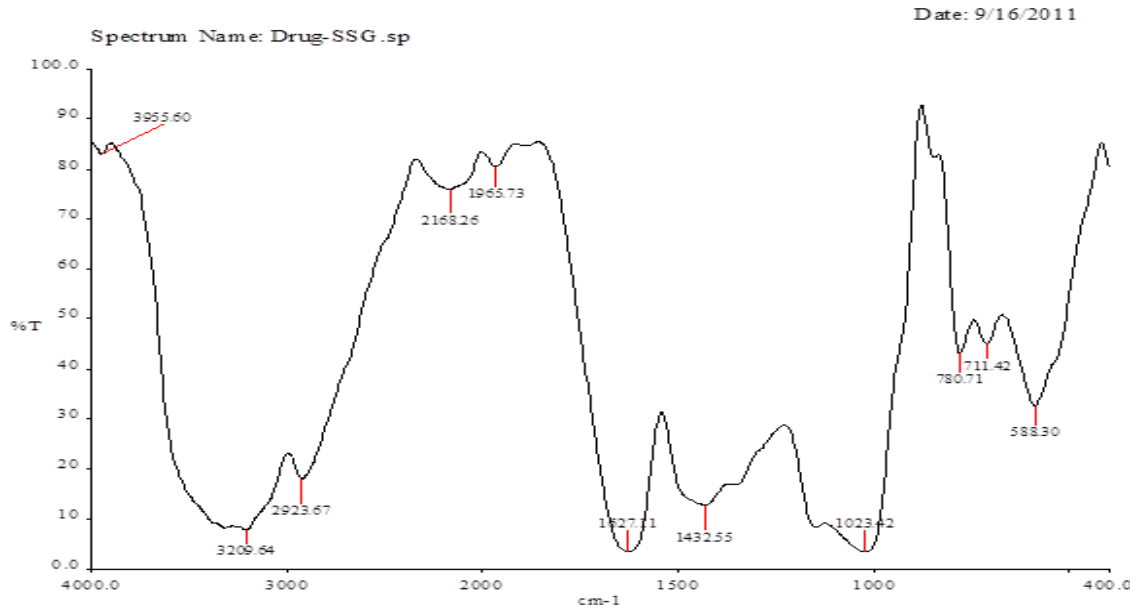


Fig- 14 FT-IR Spectrum of Lamivudine + SSG

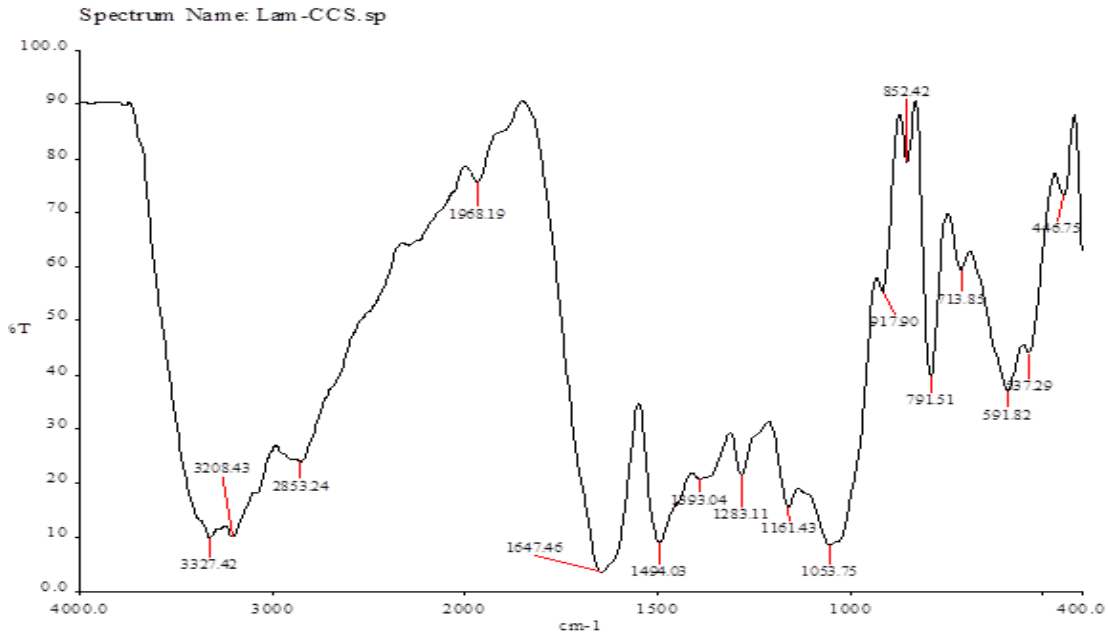


Fig- 15 FT-IR Spectrum of lamivudine + CCS

CHAPTER-XI

SUMMARY AND CONCLUSION

- The purpose of the study was to formulate and evaluate Fast Dissolving Tablets of Lamivudine.
- The results of Differential Scanning calorimetry(DSC) and Fourier Transmission Infra-Red spectroscopy confirm that both drug and excipients are compatible with each other and and are devoid of interactions.
- The results of precompression studies like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio reveals that the prepared powder blends of all formulations possess good flow properties.
- The tablets were prepared by direct compression method using superdisintegrants like Croscarmallose (F1 to F5), Sodium starch glycolate(F6 to F10), Crospovidone(F11 to F15) in different concentrations of 2%,4%,6%,8% and 10%.Mannitol is used as both binder and sweetener, sodium saccharin for additional taste masking and Microcrystalline cellulose as diluent. The tablets obtained were of uniform shape and size.
- The prepared tablets were subjected to post compression evaluations and the results indicate that

➢ The hardness, thickness and diameters of all the tablets are uniform, which ensures that all the tablets were of uniform size and shape with good resistance against mechanical damage.

- The tablets of all formulations contains uniform amount of drug, which ensures content uniformity for tablets of all formulations.
- The tablets were within the limits of weight variation test, which in turn indicate uniform distribution of contents of the powder blends of each formulations.
- The friability of all the tablets was found to be < 1%, which indicates the good mechanical resistance.
- The tablets of all formulations were found to have minimum wetting time and maximum water absorption ratio which is the desired characteristic of fast dissolving tablets, which enables faster disintegration of tablets.
- The disintegration time of all tablets were found to be less than three minutes, which ensures faster disintegration except for formulations (F1, F5 and F6).
- The tablets of all the formulations were found to release more than 80% in 5 minutes, which is the desired quality of fast dissolving tablets that helps in faster absorption of the drug and quick onset of therapeutic effect except for formulations (F1 & F2). The dissolution pattern of various disintegrants used in the formulation was found to be in the order of Crospovidone > Sodium starch glycolate > Croscarmallose sodium.

CONCLUSION

It was concluded, that lamivudine can be successfully formulated as fast dissolving tablets using various superdisintegrants in different concentrations by direct compression method. The formulation containing 10% of crospovidone as superdisintegrant was found to be outstanding than other formulations in terms of disintegration time and rate of dissolution.

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