# *COMPATIBILITY STUDIES OF ATORVASTATIN CALCIUM WITH SELECTED EXCIPIENTS BY MEANS OF THERMAL AND FT-IR SPECTROSCOPIC METHODS FOR THE DEVELOPMENT OF IMMEDIATE RELEASE TABLET*

*A THESIS SUBMITTED TO*

**ASSAM SCIENCE AND TECHNOLOGY UNIVERSITY,**
**GUWAHATI ASSAM**

**IN THE PARTIAL FULFILLMENT OF THE REQUIREMENT**
**FOR THE AWARD OF DEGREE OF**

**MASTER OF PHARMACY (M.PHARM)**
**IN**
**(PHARMACEUTICS)**

**UNDER THE SUPERVISION OF**

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**Assistant Professor,**
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**SUBMITTED BY**

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## ***CERTIFICATE BY THE PRINCIPAL, GIPS***

*This is to certified that the topic incorporated in this thesis entitled, "**COMPATIBILITY STUDIES OF ATORVASTATIN CALCIUM WITH SELECTED EXCIPIENTS BY MEANS OF THERMAL AND FT-IR SPECTROSCOPIC METHODS FOR THE DEVELOPMENT OF IMMEDIATE RELEASE TABLET**" being carried out by **Tushar Kanti Roy** bearing **Roll no:1405211011,Regd no:099205214**, under the direct supervision of Dr. Bipul Nath, M.Pharm, Ph.D, Assistant Professor, GIPS is a bonafied assignment and submitted to **Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), affiliated to Assam Science And Technical University, Jalukbari, Guwahati, Assam Tushar Kanti Roy** in partial fulfilment of the requirement for the award of Degree of Master of Pharmacy (M. Pharm) in Pharmaceutics during the academic session 2015-2016.*

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## CERTIFICATE FROM THE HEAD OF THE DEPARTMENT

This is to certified that the topic incorporated in this one year research based project dissertation entitled "**COMPATIBILITY STUDIES OF ATORVASTATIN CALCIUM WITH SELECTED EXCIPIENTS BY MEANS OF THERMAL AND FT-IR SPECTROSCOPIC METHODS FOR THE DEVELOPMENT OF IMMEDIATE RELEASE TABLET**" being submitted by **Tushar Kanti Roy, Roll No:1405211011, Regd No: *099205214***, in partial fulfillment of the requirement for the award of Degree of Master of Pharmacy (M. Pharm) of **Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), affiliated to Assam Science and Technical University, Guwahati, Assam** is a bonafied assignment which has been carried out in the Department of Pharmaceutics, GIPS during the academic session 2015-2016.

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## *DECLARATION BY THE CANDIDATE*

*I hereby declare that the thesis entitled "**COMPATIBILITY STUDIES OF ATORVASTATIN CALCIUM WITH SELECTED EXCIPIENTS BY MEANS OF THERMAL AND FT-IR SPECTROSCOPIC METHODS FOR THE DEVELOPMENT OF IMMEDIATE RELEASE TABLET** " is a bonafide and genuine research work carried out by me under the direct supervision of **Dr. Bipul Nath**, Assistant Professor, Department of Pharmaceutics, GIPS for the partial fulfilment of the award of degree of Master of Pharmacy in specialization Pharmaceutics.*

*I also declare that the matter embodied in this thesis is an original bonafied research work being submitted solely to GIPS, Assam Science and Technology University and it has not been submitted to any other University or institution for the award of any degree, diploma, or fellowship.*

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*I give special thanks to Dr. Indranil Chanda for extending analytical facilities and Mr. Bipul Sarma, for providing chemicals, instrumental results of my research samples.*

*Last but not the least I am thankful to all my class mates for their support, help and encouragement during my course of study.*

*Finally, I owe to my parents, my mother SWAPNA ROY and my father PRANABENDRA ROY for making me capable of reaching up to this height of education by providing all forms of care, financial support and affection.*

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***Date:*** ***(TUSHAR KANTI ROY)***

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***ABSTRACT***

*The objectives of present investigation is to evaluate the compatibility of Atorvastatin calcium with immediate release excipients and to optimize the tablet which release is best comparable with innovator product by varying different super disintegrants. Various excipients used were sodium starch glycollate, Cross carmellose sodium, Cross-povidone, lactose, Micro crystalline cellulose, mannitol, sodium alurayl sulfate, magnesium stearate, and stearic acid. Thermal characterization of the drug was done by DSC and FT-IR. From the DSC studies, the excipients such as microcrystalline cellulose (Avicel 101), magnesium stearate, mannitol, Sodium lauryl sulfate were found to have physical interactions with Atovastatin. Immidiate release tablet was prepared by direct compression method and its release profile was compared with the marketed IR tablet. The prepared tablet have conform the pharmacopoeial limit for hardness, thickness, friability, weight variation and content uniformity. Formulation F11 containing two super disintegrants have shown the disintegration time less than 25 sec and better dissolution than all other formulations releasing more than 80% of the drug after 20 minutes. Kinetic data reveals that the drug release follows best order by Higuchi model, followed by korsemeyer peppas, zero order and first order mechanisms. The results of accelerated stability studies as per ICH guidelines indicated that the tablet was stable as there were no any significant physical changes after the study.*

## ***PREFACE***

*The work incorporated in this thesis is about studies of drug-excipient compatibility which represent an important phase in the preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutic properties and stability of the dosage form. The present review contains a basic mode of drug degradation, mechanism of drug- excipient interaction like physical, chemical and biopharmaceutical. Different Thermal and Non-thermal method of analysis, Tools and software for incompatibility is also discussed. Once the type of interaction is determined we can take further steps to improve the stability of drug and dosage form. From review, we conclude that consequent use of thermal and non-thermal method provide data for drug- excipient interaction which can further help in selection of excipient for the development of stable dosage form. Excipients present in solid dosage forms are composed of mixture of adjuvants, such as diluents, binders, disintegrants, lubricants, glidants, and surfactants. They permit the efficient manufacturing of capsules and tablets and affect the physical and chemical characteristics of the active ingredients as well as its bioavailability. The incompatibility between drugs and excipients can alter the physicochemical properties of drugs and hence, can have an effect on its efficacy and safety profile. Therefore, drug-excipient interaction study at the initial stage of a formulation development should be treated as an imperative exercise to ensure correct selection of excipients and hereby, increasing the possibility of developing a successful dosage form.*

*Date:* *(TUSHAR KANTI ROY)*

*Place:*

*Contd.....*

## *1. INTRODUCTION OF DRUG-EXCIPIENT COMPATIBILITY STUDIES:*

### 1.1. Drug Excipient Interaction: [1-7]

*Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutic properties and stability of the dosage form. The present review contains a basic mode of drug degradation, mechanism of drug- excipient interaction like physical, chemical and biopharmaceutical. Different Thermal and Non-thermal method of analysis, Tools and software for incompatibility is also discussed. Once the type of interaction is determined we can take further steps to improve the stability of drug and dosage form. From review, we conclude that consequent use of thermal and non-thermal method provide data for drug-excipient interaction which can further help in selection of excipient for the development of stable dosage form.*

*Excipients present in solid dosage forms are composed of mixture of adjuvants, such as diluents, binders, disintegrants, lubricants, glidants, and surfactants. They permit the efficient manufacturing of capsules and tablets and affect the physical and chemical characteristics of the active ingredients as well as its bioavailability. The incompatibility between drugs and excipients can alter the physicochemical properties of drugs and hence, can have an effect on its efficacy and safety profile. Therefore, drug-excipient interaction study at the initial stage of a formulation development should be treated as an imperative exercise to ensure correct selection of excipients and hereby, increasing the possibility of developing a successful dosage form [1, 2]. In particular, the cost and time constraints associated with the process of pharmaceutical product development have made this type of predictability techniques even more desirable. Differential scanning calorimetry (DSC) has been widely used to assess incompatibility between formulation components, because the*

*method is fast and versatile, and requires only a small quantity of sample [1,6]. However, caution needs to be exercised if the results of DSC alone are interpreted. Whenever possible, other techniques such as infrared spectroscopy (IR) and quantitative analysis after storage under stressed conditions should be utilized in conjunction with DSC [6]. As the thermo-analytical methods do not yield direct chemical information, Fourier transform infrared spectroscopic (FT-IR) investigations were used in this work. Oral drug delivery remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be designed by appropriate pharmaceutically acceptable diluent or carrier, which gives rapid rate of drug release and absorption [3,4]. The basic approach used in development of such tablets is the use of superdisintegrants like cross linked polyvinylpyrrolidone or crospovidone (polyplasdone), sodium starch glycolate (SSG), croscarmellose sodium (CCS) etc. As a drug entity reaches the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen.*

*Atorvastatin (ATV), a HMG CoA reductase inhibitor, lipid lowering agent given in the dose ranging from 10-80 mg/day by oral route. After oral administration alone, ATV is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed*

*to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Atorvastatin, a drug with low solubility and high permeability belongs to the Class II in the biopharmaceutics classification system (BCS), in which, dissolution process is the rate-limiting step for the absorption [6, 7]. Hence, it is important to evaluate drug features, such as the presence of polymorphism, stability, and compatibility of the pharmaceutical formulation, since any changes can directly influence its bioavailability. Hence, the objectives of present investigation is to evaluate the compatibility of Atorvastatin with immediate release excipients and to optimize the tablet which release is best comparable with innovator product by varying different super disintegrants.*

*A complete characterization and understanding of physicochemical interactions of an active pharmaceutical ingredient (API) in the dosage forms is an integral part of preformulation stage of new dosage form development as it is most desirable for consistent efficacy, safety and stability of a drug product. In a dosage form, an API comes in direct contact with other components (excipients) of the formulation that facilitate the administration and release of an active component as well as protect it from the environment. Although excipients are pharmacologically inert, they can interact with drugs in the dosage form to affect drug product stability in physical aspects such as organoleptic properties, dissolution slow down or chemically by causing drug degradation. Careful selection of the excipients are required for a robust and effective formulation of dosage forms that make administration easier, improve patient compliance, promote release and bioavailability of the drug and increase its shelf life. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors and is at the fore front of drug product science and technology research. A complete understanding of the physicochemical interactions in dosage forms is expected under quality by design prototype*

*of drug development. The analytical methods into the initial steps of preformulation studies have contributed significantly to early prediction, monitoring and characterization of the API incompatibility to avoid costly material wastage and considerably reduce the time required to arrive at an appropriate product formulation.*

*Compatibility studies are usually aimed at identifying the most common or previously encountered incompatibilities. For example, an incompatibility in dosage form can be identified as any of the following changes: change in color/appearance, loss in mechanical properties (e.g., tablet hardness), changes to dissolution performance, physical form conversion, loss through sublimation, a decrease in potency, and increase in degradation products . The compatibility studies can be carried out in several different modalities with an aim to study the impact of various environmental factors and process parameters, in addition to product composition (Fig.1). Certain aspects of drug-excipient interactions, such as unintended drug-excipient binding, are usually not studied in an excipient compatibility study. This chapter highlights the importance of such interactions and discusses methodologies that can be utilized to study their potential impact on oral bioavailability of a drug. Unintended physicochemical interaction of an excipient with a drug substance in a dosage form can result in the complexation or binding of the drug, resulting in slow and/or incomplete drug release in a dissolution medium. It is important to assess the risk whether such interactions would reduce the bioavailability of a drug from its dosage form. This chapter describes the development of a methodology to assess the biorelevance of the drug release impact of drug-excipient binding interactions using a model compound, brivanib alaninate. This methodology was developed using a combination of modeling and simulation tools as well as experimental data generated in vitro and in vivo.*

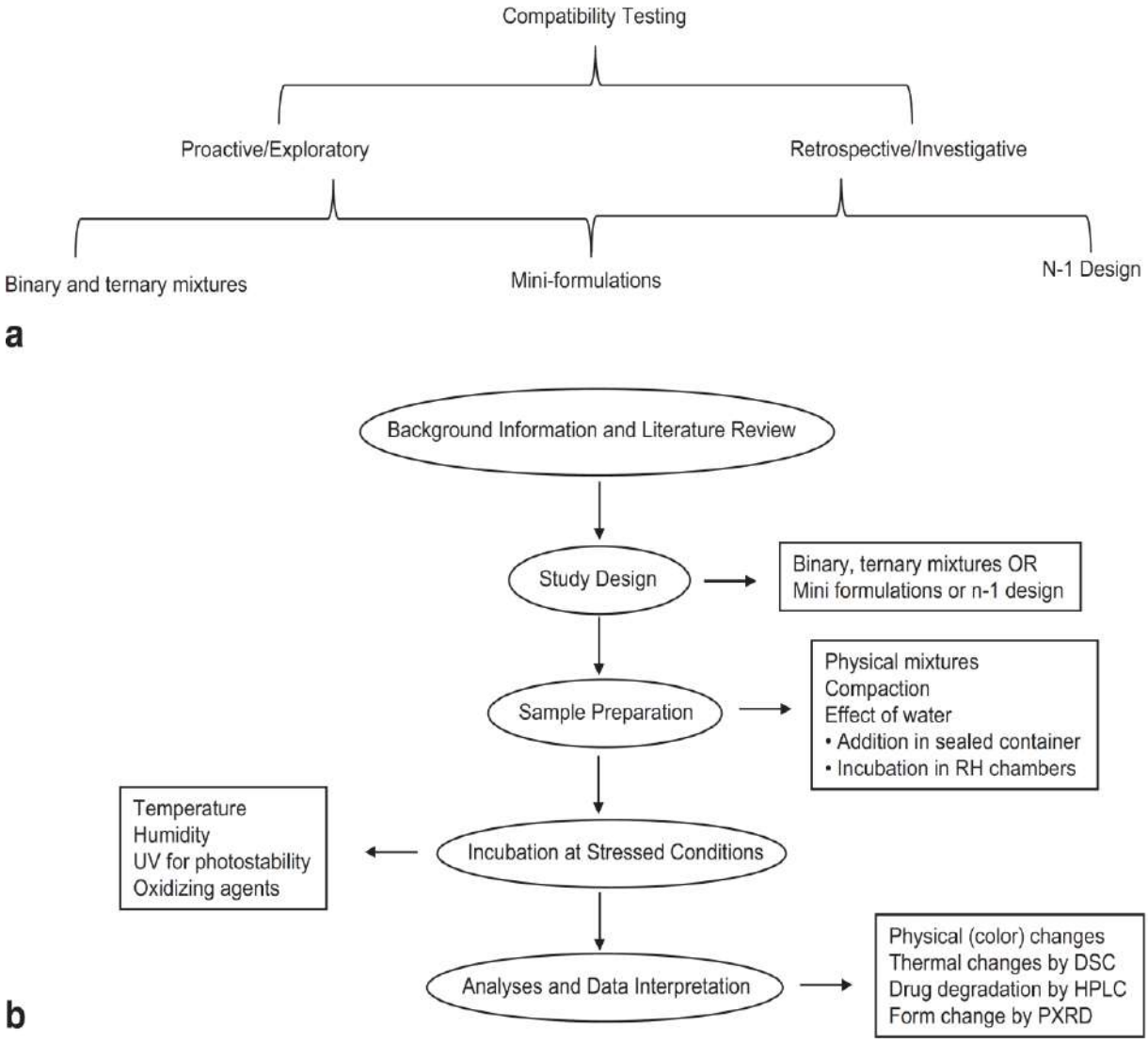


***Fig.1*** *Typical modalities of compatibility testing* ***(a)*** *and the study execution* ***(b)****. Various stages of the compatibility testing are highlighted in ovals and the key decisions and variables involved in each stage are mentioned in square boxes.*

***1.2 Incompatibility:***[2.5.9]

*"Inactivation of drug through either decomposition or loss of drug by its conversion to a less favourable physical or chemical form." When we mix two or more API and / or*

*excipient with each other and if they are antagonistic and affect adversely the safety, therapeutic efficacy, appearance or elegance then they are said to be incompatible.*

### *1.2.1 Importance of drug excipient compatibility:*

- Stability of the dosage form can be maximized. Any physical or chemical interaction *between drug and excipient can affect bioavailability and stability of drug.*
- It helps to avoid the surprise problems. By performing drug excipient compatibility *studies (DECS) we can know the possible reaction before formulating final dosage form.*
- DECS data is essential for IND (investigational new drug) submission. Now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.
- Determine a list of excipient that can be used in final dosage form.
- To reduce associated side effect of drug due to DECS in dosage form.
- To overcome problems associated with incorporation of multiple excipients.

### *1.2.2 Excipients:*[3,4]

***"****Pharmaceutical excipients are substance other than pharmacologically active drug or prodrug in finished dosage form as to impart specific qualities to them.****"***

### *1.2.3 Role of excipient*

- Protect, support or enhance stability of the Formulation.
- Bulk up the formulation in case of potent drug for assisting in formulation of an accurate dosage form.
- Improve patient acceptance.
- Help improve bioavailability of active drug.

- Enhance overall safety and effectiveness of the formulation during its storage and use.

### *1.3 Mode of drug decomposition:*[1,5]

*Medicinal agents invariably have structural features that interact with receptors or facilitate metabolic handling. These predictably confer some degree of liability, making them vulnerable to degradation (and interaction with other materials). They are hydrolysis /dehydration, isomerisation/epimerization decarboxylation, rearrangement and some kinds of polymerization reactions can be generalized into a condition that has been called "thermolytic". These reactions are generally sensitive to temperature and can be accelerated by elevating the temperature under various conditions in the solid state (low and high humidity). Hydrolytic reactions, can be accelerated both by exposure to elevated temperature as and by exposure to different pH values in a broad pH range. Oxidative degradation of pharmaceuticals is generally the result of autoxidation. It is driven by the formation of radicals (via initiators such as transition metals, low levels of peroxides, or molecular oxygen). Photolytic reactions are initiated by the absorption of photons from exposure to various sources of light.*

#### *1.3.1 Common modes of degradation are described below:*

##### *1.3.1.1 Hydrolysis*

*Drugs with functional groups such as esters, amides, lactones may be susceptible to hydrolytic degradation. It is probably the most commonly encountered mode of drug degradation because of the occurrence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions or facilitates microbial growth.*

### *1.3.1.2 Oxidation*

*Oxidative degradation is second only to hydrolysis as a mode of decomposition. In contrast to hydrolysis, oxidative mechanisms are complex, involving removal of an electropositive atom, radical or electron or, conversely, addition of an electronegative moiety. Oxidation reactions can be catalyzed by oxygen, heavy metal ions and light, leading to free radical formation. Free radicals react with oxygen to form peroxy radicals which in turn react with oxidizable compound to generate additional free radicals to fuel further reactions. Aldehydes, alcohols, phenols, alkaloids and unsaturated fats and oils are all susceptible to oxidation.*

### *1.3.1.3 Isomerization*

*Isomerization involves conversion of a chemical into its optical or geometric isomer. Isomers may have different pharmacological or toxicological properties. For example, the activity of levo (L) form of adrenaline is 15-20 times greater than for the dextro (D) form.*

### *1.3.1.4 Photolysis*

*Reactions such as oxidation-reduction, ring alteration and polymerization can be catalyzed or accelerated by exposure to sunlight or artificial light. Energy absorption is greater at lower wavelengths and, as many as drugs absorb UV light; degradation by low wavelength radiation is common. Exposure to light almost invariably leads to discoloration even when chemical transformation is modest or even undetectable.*

### *1.3.1.5 Polymerization*

*Intermolecular reactions can lead to dimeric and higher molecular weight species. Concentrated solutions of ampicillin, an aminopenicillin, progressively form dimer, trimer and ultimately polymeric degradation products. Table 1 lists examples of medicinal agents susceptible to such modes of degradation. Degradation may reflect vulnerability to environmental stresses such as heat, humidity, light or drug–drug interactions. Degradation may also be facilitated or promoted by excipients possessing the requisite functional groups for interaction, or containing residues that catalyze/participate in degradation processes. If excipients are also susceptible to change, this provides additional possibilities for the generation of species that participate in break down processes.*

| Hydrolysis | Oxidation | Isomerization | Photolysis | Polymerization |
|---|---|---|---|---|
| Methyldopa | Calcitonin | Tetracycline | Riboflavin | Ceftazidime |
| Procaine | Ascorbic acid | Vitamin A | Folic acid | Ampicillin |
| Penicillins | isoprenaline | Adrenaline | Nifedipine | |

***Table 1:*** *Modes of degradation of medicinal agents*

### *1.4 Mechanism of drug excipient interaction:*

*Exact mechanism of drug excipients interaction is not clear. However, there are several well documented mechanisms in the literature. Drug excipients interaction occurs more frequently than excipient-excipient interaction. Drugexcipients interaction can either be beneficial or detrimental, which can be simply classified as-*

1. *Physical interactions*
2. *Chemical interactions*

***1.4.1 Physical interactions:*** *Physical interactions are very common in dosage form and also difficult to detect. Physical interactions may or may not involve chemical changes thus permitting the components in the formulation to retain their molecular structure. Physical interactions involve change in a dissolution, solubility, sedimentation rate etc. Physical interactions can be either beneficial or detrimental to the product performance which is dependent on its application. Different physical interactions are as follows,*

***Table 2:*** *Physical Interaction*

| Interaction | Beneficial effect examples | Detrimental effect examples |
|---|---|---|
| Complexation:- Complexing agent binds reversibly with drugs to form complex. Sometimes insoluble complexes are formed which lead to slower dissolution and decreased absorption of drug which is detrimental. Complexing agents can also be used to increase bioavailability of poorly water soluble drugs which is beneficial. | Cyclodextrin is often used to improve bioavailability of poorly water soluble drugs. This increases bioavailability and increases rate and extent of drug dissolution. | Tetracycline formed insoluble complex with calcium carbonate leading to slower dissolution and decreased absorption. |
| Adsorption:- Adsorption of drug by excipient can lead to reduced bioavailability as the drug is not available for dissolution. | Formulation of Indomethacin (NSAID) using kaolin as adsorbent increased its | Cetyl Pyridinium chloride cations get adsorbed on the surface of |

| | | |
|---|---|---|
| Adsorption of drug on excipient surface can assist in increasing surface area of drug available for dissolution which eventually increases bioavailability. | dissolution rate which leads to increase in bioavailability of drug. | magnesium stearate which acts as a lubricant in tablet containing Cetyl Pyridinium chloride. This leads to marked reduction in the antibacterial activity of the drug. |
| Solid dispersion:-<br>This kind of interactions improves the dissolution and bioavailability of hydrophobic drugs.Sometimes solid dispersion interactions can result in slow dissolution of drugs. | Improved dissolution rates of drugs like Piroxicam, Norfloxacin, Nifedipine and Ibuprofen were observed when these drugs were formulated into solid dispersions using Polyethylene glycol of different molecular weights. | Solid dispersion product formed due to interaction between Povidone and Stearic acid in a capsule showed slow dissolution of drugs. |

***1.4.2 Chemical interactions:***

*Active pharmaceutical ingredients and excipients react with each other to form unstable compounds. Several chemical drugs excipient interactions have been reported in*

*literature which is mentioned in literature under heading 2. Generally chemical interactions have a deleterious effect on the formulation hence such kind of interactions must be usually avoided.*

### *1.4.3 Biopharmaceutical interactions:*

*These are the interactions which are observed after administration of the medication. Interaction of medicine with body fluid influences the rate of absorption. All excipients interact in physiological way when they are administered along with active pharmaceutical ingredients, various examples of biopharmaceutical interactions are stated as follows:-*

#### *1.4.3.1 Premature breakdown of enteric coat*

*The enteric coating polymers like cellulose acetate phthalate and hydroxylpropyl cellulose acetate phthalate, are soluble more at basic pH, but antacids raise pH of stomach resulting in breakdown of the enteric coat in stomach and release of active pharmaceutical ingredient in stomach itself, which results in degradation of drug in stomach. In case of NSAID's premature breakdown of enteric coat may cause side effects like gastric bleeding.*

#### *1.4.3.2 Interactions due to adjunct therapy*

*Tetracycline antibiotics form complexes with calcium and magnesium ions which are quite common excipients in various formulations which may be administered along with tetracycline as adjunct therapy the complex so formed is not absorbed from the G.I.T.*

#### *1.4.3.3 Increase in gastrointestinal motility*

*Many of the excipients like sorbitol, xylitol, have tendency to increase the gastrointestinal motility thus reducing the time available for absorption of drugs like metoprolol.*

### *1.4.4 Methods of estimation of drug excipient compatibility*[3-7]

*Formulation scientists have explored various thermal and nonthermal analytical techniques for early prediction of suitable excipients for the dosage forms to minimize or mitigate the untoward reactions (stability issues) which arise from drug–excipient incompatibility. Till date no universally accepted protocol is available for evaluating the compatibility of dru with other components. However, a flurry of reports have appeared in the last decade that highlight the use of analytical tools used in the compatibility screening of APIs in search of suitable excipients. Frequently used analytical techniques for prospective compatibility screening studies include thermal methods such as differential scanning calorimetry, thermo gravimetric analysis, differential thermal analysis, isothermal micro calorimetry, hot stage microscopy and other analytical methods namely powder X-ray diffraction, Fourier transforminfrared spectroscopy, scanning electron microscopy and high performance liquid chromatography. Relatively newer spectroscopic techniques like solid state Nuclear Magnetic Resonance spectroscopy and near Infrared spectroscopy having potential applications in the analysis of pharmaceutical solids, have been extended to study the drug–excipient or drug moisture interactions that may lead to instability of the active principles. These techniques vary in their working principles, mechanical and thermal stress that is applied to the sample, time of analysis and amount of sample required, sensitivity of the technique to minute changes, and the necessity of internal or external standards. Moreover, some of the reported methods for the assessment of compatibility have poor predictive value while a few of them possess time consuming exercise in the pharmaceutical product development. Therefore, combinations of thermal and non-thermal methods are successful in proper identification of incompatibility. Analytical tools for compatibility assessment of APIs*

### *1.4.5 Thermal methods of analyses*

*1. Differential scanning calorimetry (DSC)*

*2. Isothermal microcalorimetry*

***1.4.6 Spectroscopic techniques***

*1. Vibrational spectroscopy*

*2. Powder X-ray diffraction (PXRD)*

***1.4.5 Thermal methods of analyses** :*

*Thermal analysis plays a critical role in compatibility screening studies and has been frequently employed for quick assessment of physicochemical incompatibility. Conventional compatibility testing methods require both multiple sample preparation and long storage times in order to obtain meaningful results. However, the thermal methods offer potential advantages over the conventional isothermal stress testing (IST) techniques. Thermal analysis eliminate the lengthy storage conditions and method development for all the active compounds required during IST and allow for a large number of excipient screening experiments to be performed in a short duration of time. The results obtained from thermal techniques are direct indicators of that excipient which are likely to be compatible, cutting down the conventional compatibility samples to prepare and thus saving the valuable time.*

***1.4.5.1 Differential scanning calorimetry (DSC)***

*DSC represents a leading thermal analysis technique that has been increasingly used for active pharmaceutical ingredient screening of incompatibilities for over 50 years. In this technique, the DSC curves of pure components are compared to the curves obtained from 1:1 physical mixtures. It is assumed that the thermal properties (melting point, change in enthalpy, etc.) of blends are the sum of the individual components if the components are compatible with each other. An absence, a significant shift in the melting of the components or appearance of a new exo/endothermic peak and/or variation in the corresponding*

*enthalpies of reaction in the physical mixture indicates incompatibility. However, slight changes in peak shape height and width are expected due to possible differences in the mixture geometry. DSC stands to benefit over other conventional techniques in requirement of short time of analysis and low sample consumption. It also provides useful indications of the potential problems, so that an excipient can be rejected at an initial stage of product development. If the excipient under consideration is indispensable, the nature of interactions with the active API can be studied in depth. In spite of all the merits, the conclusions based on DSC results alone may be misleading and have to be interpreted carefully.*

***1.4.5.1.1 The DSC Technique:***

- *DSC is used to measure melting temperature, heat of fusion, latent heat of melting, reaction energy and temperature, glass transition temperature, crystalline phase transition temperature and energy, precipitation energy and temperature, denaturization temperatures, oxidation induction times, and specific heat or heat capacity.*
- *DSC measures the amount of energy absorbed or released by a sample when it is heated or cooled, providing quantitative and qualitative data on endothermic (heat absorption) and exothermic (heat evolution) processes.*
- *Only non-corrosive samples can be analyzed in this very sensitive instrument. No organic or other materials containing F, Cl, Br, or I may be submitted for DSC analysis without our knowledge. The customer must either tell us what the material is or at least that it is non-corrosive to metals and assume responsibility for possible replacement of a $3000 DSC cell if a cell is destroyed as a result of the analysis of their sample. Or, you may have us perform such analysis as may be needed to determine what the material is and whether it can be analyzed in the DSC.*

- *The sample is placed in a suitable pan and sits upon a constantan disc on a platform in the DSC cell with a chromel wafer immediately underneath. A chromel-alumel thermocouple under the constantan disc measures the sample temperature. An empty reference pan sits on a symmetric platform with its own underlying chromel wafer and chromel-alumel thermocouple. Heat flow is measured by comparing the difference in temperature across the sample and the reference chromel wafers.*
- *Temperature can range from -120°C to 725°C, though an inert atmosphere is required above 600°C. The temperature is measured with a repeatability of ±0.1°C.*
- *Pans of Al, Cu, Au, Pt, alumina, and graphite are available and need to be chosen to avoid reactions with samples.*
- *Atmospheres: nitrogen, air, oxygen, argon, vacuum, controlled mixed gases.*
- *Calorimetric Specifications:*
  - *Sensitivity: 6 μW/cm*
  - *Precision: 1%*
  - *Baseline noise: ±5 μW*
  - *Baseline stability: 20 μW (ambient to 200°C); 400 μW (ambient to 600°C)*
  - *Maximum power output is 300W*
- *Sample size: from 0.5mg to 100mg.*
- *Samples can be encapsulated in aluminum pans using a pan press*
- *Used to determine the thermal properties of plastics, adhesives, sealants, metal alloys, pharmaceutical materials, waxes, foods, lubricants, oils, catalysts, and fertilizers*

#### *1.4.5.1.2 Applications of Differential Scanning Calorimetry*

- *Metal alloy melting temperatures and heat of fusion.*
- *Metal magnetic or structure transition temperatures and heat of transformation.*

- *Intermetallic phase formation temperatures and exothermal energies.*
- *Oxidation temperature and oxidation energy.*
- *Exothermal energy of polymer cure (as in epoxy adhesives), allows determination of the degree and rate of cure.*
- *Determine the melting behavior of complex organic materials, both temperatures and enthalpies of melting can be used to determine purity of a material.*
- *Measurement of plastic or glassy material glass transition temperatures or softening temperatures, which change dependent upon the temperature history of the polymer or the amount and type of fill material, among other effects.*
- *Determines crystalline to amorphous transition temperatures in polymers and plastics and the energy associated with the transition.*
- *Crystallization and melting temperatures and phase transition energies for inorganic compounds.*
- *Oxidative induction period of an oil or fat.*
- *May be used as one of multiple techniques to identify an unknown material or by itself to confirm that it is the expected material.*
- *Determine the thermal stability of a material.*
- *Determine the reaction kinetics of a material.*
- *TMA can also be used to measure glass transition temperatures, melting temperatures, crystalline phase formation temperatures, and crystalline to amorphous transition temperatures. It is often more sensitive to detecting the transition, but cannot measure the energy of the transition as DSC does. It also may measure the temperature more accurately when sample thermal conductivity is low or its dimensions are large since DSC has to have a higher rate of temperature change commonly to detect the transitions.*

### *1.4.5.2 Isothermal microcalorimetry*

*Isothermal microcalorimetry has proved to be an invaluable tool in the realm of solid state pharmaceutics with its important application in compatibility determination. It works on the principle that all physical and chemical processes are accompanied by a heat exchange within their surroundings. It allows determination of minute amounts of evolved or absorbed heat and heat flow signals in the range of μW are easily detectable. Further, micro reaction calorimeter gives meaningful results without requirement of multiple sample preparations and long storage times. In a typical compatibility experiment, a solution, suspension, or solid mixture of API and excipient is placed in the calorimeter and the thermal activity (heat flow) at a constant temperature is monitored. The basic assumption is that the rate of heat production is proportional to the rate of chemical and/or physical processestaking place in sample. The thermal activity of API and excipient are measured individually, and then the output of the blend is compared to the "non-interaction" curve constructed from the individual components. If an experimentally significant difference is observed, the excipient is considered to be potentially incompatible with the API. Because the signal may be the sum of numerous chemical and physical processes, one should exercise proper caution before attempting to correlate the signal with rate of degradation. Instead, the method should be used as an indicator of potential incompatibility. Applying these simple testing criteria reduces*

*the number of samples that must be screened using time consuming HPLC, X-ray and other methods, thus saving valuable time and effort during the formulation process.*

### *1.4.6 Spectroscopic techniques*

#### *1.4.6.1 Vibrational spectroscopy*

*Fourier Transform Infrared, Raman and near Infrared spectroscopy are sensitive to the structure and the environment of organic compounds. These techniques are not only focused on solid state behavior of APIs and their formulations, but are also used as compatibility screening tool as the vibrational changes serve as probe of potential intermolecular interactions among the components. Thus, pharmaceutical interactions that result in desalting, hydrate formation, dehydration, polymorphic changes or transformation of crystalline to amorphous forms and vice versa during processing can easily be detected with the aid of these spectroscopic techniques. However, the presence of overlapping peaks in the spectra may hinder the analysis. Thus, FT-IR helped in the choice of suitable excipients for a stable formulation. DRIFT (diffuse reflectance infrared Fourier transform infrared spectroscopy) is the most suitable technique of the nondestructive spectroscopic methods and has attracted interest, as the materials are not subjected to thermal or mechanical energy during sample preparation, thereby preventing solid state transformations.*

***1.4.6.2 Powder X-ray diffraction (PXRD)***

*It is a direct measure of the crystal form of a material with atypical output being a plot of intensity vs the diffraction angle (2θ). A crystalline material exhibits unique set of diffraction peaks and the lack of crystalline API peaks when a dosageform is analyzed could indicate that the material is amorphous or that the loading is too low to detect using the parameters chosen. PXRD analysis is of immense help in case of incompatibilities which occur during processes like compression, wet granulation etc. and bring on change in crystallinity /amorphicity and polymorphic forms of API in the presence of excipients with/without adsorbed moisture.*

***1.4.9 Summary***

*Drug-excipient interactions/incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance. Many stability problems encountered during development and post-commercialization can be ascribed to inadequate matching of the ingredients in dosage forms, lack of awareness of the complexities of chemical and physical interactions, or the unheralded presence of a residue in one of the excipients. Many such issues concern low levels of novel entities formed by drug– excipient interactions that pose questions concerning safety or tolerance. Drug-excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and pre-formulation studies. They can complicate and compromise a development programme or the viability of a commercial product. It is possible to reduce the probability of such undesirable and costly scenarios by allying knowledge of the propensity of a drug to undergo degradation reactions with awareness of excipient reactivity and of the residues that they may contain. Thermo analytical and spectroscopic techniques have played a pivotal role in characterization of solid state interactions and early detection of drug–excipient compatibility. The in-depth knowledge and appropriate use of these analytical techniques have brought forth extraction of valuable information concerning the drug–excipient interactions that aid in the selection of appropriate excipients for stable and an efficacious solid dosage form. In Non-thermal method of analysis FTIR gives reliable data for structural conformation. DSC results are not useful if thermal changes are small, it should be confirmed using another non-thermal method. In summary, knowledge of drug–excipient interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality.*

## *2. REVIEW OF LITERATURE:*

- **Raghavendra S.** et al(9) proposed the study on solubility and dissolution properties of any drug are vital determinants of its oral bioavailability. The dissolution rate of poorly soluble, highly permeable (BCS-II) drugs, such as atorvastatin calcium, can be improved by application of the liquisolid (LS) techniques. Different liquisolid compacts were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200 and Explotab were employed as carrier, coating material and disintegrant, respectively. The prepared liquisolid systems were evaluated for their micromeritic properties and possible drug-excipient interactions by Infrared spectra (IR) analysis, differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD).

- **Arunkumar N.** et al(11) developed the solubility and dissolution characteristics of a poorly soluble drug (atorvastatin calcium) using nanosuspension technology. Nanoparticles were characterized in terms of size and morphological characteristics. Saturation solubility and dissolution characteristics were investigated and compared to the commercial drug. Crystallinity of the drug was also evaluated by performing thermal gravimetric analysis (TGA),differential scanning calorimetry (DSC) and

powder X-ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Through this study, it has been shown that the crystalline state of the drug is reduced following particle size reduction and the dissolution rates of amorphous atorvastatin calcium nanoparticles were highly increased in comparison with commercial drug by the enhancement of intrinsic dissolution rate and the reduction of particle size, resulting in an increased specific surface area.

- **Zaheer Z.** et al(17) studied the stability-indicating high-performance liquid chromatographic (HPLC) method of analysis of Atorvastatin Calcium in pharmaceutical dosage form was developed and validated. The chromatographic conditions comprised of a reversed-phase C18 column (250 x 4.6 mm), 5 µ with a mobile phase consisting of a mixture of Methanol: Acetonitrile: Phosphate Buffer solution in the ratio (45:45:10). Flow rate was 1 mL / min. Detection was carried out at 246 nm. The retention time of Atorvastatin was 6.98 min. Atorvastatin Calcium was subjected to acid and alkali hydrolysis, oxidation, photochemical degradation and thermal degradation. The method was validated for precision, recovery, ruggedness and robustness. The drug undergoes degradation under acidic, basic, photochemical and thermal degradation conditions. They found that the method could effectively separate the drug from its degradation product, it can be employed as a stability-indicating one.

- **Vukkum P.** et al(23) developed a rapid, reversed-phase liquid chromatographic method for the quantitative determination of Atorvastatin calcium, its related

substances (12 impurities), and degradation impurities in bulk drugs.The drug substance was subjected to stress studies such as hydrolysis, oxidation, photolysis, and thermal degradation, and considerable degradation was observed in acidic hydrolysis, oxidative, thermal, and photolytic stress conditions.The stressed samples were quantified against a qualified reference standard and the mass balance was found to be close to 99.5% (w/w) when the response of the degradant was considered to be equal to the analyte (i.e. Atorvastatin), which demonstrates the stability-indicating capability of the method. The method was validated in agreement with ICH requirements and developed here was single and shorter (25 min method for the determination of all 12 related impurities of Atorvastatin and its degradation products), with clearly better resolution and higher sensitivity than the European (85 min method for the determination of six impurities) and United States pharmacopeia (115 min and 55 min, two different methods for the determination of six related substances).

- **Zelko R.** et al(25) studied the compatibility of metronidazole with different pharmaceutical excipients (hydroxypropyl methylcellulose, poly(ethylene oxide), microcrystalline cellulose, dicalcium phosphate dihydrate, and anhydrous dicalcium phosphate) using differential scanning calorimetry and diffuse reflectance spectroscopy. Dicalcium phosphate dehydrate was the only excipient that showed interaction with metronidazole even before storage. Changes referring to a possible transition to dihydrate form were observed in the thermal curves of anhydrous dicalcium phosphate after four weeks of storage. Although dicalcium phosphate dihydrate can be replaced by the anhydrous form in pharmaceutical formulations, the observed transition might negatively influence the stability of dosage forms.

- **Gutch P.K.** et al(29) the compatibility of 2-PAM chloride with a number of commonly used excipients by using thermoanalytical technique viz., differential scanning calorimetry (DSC) and thermogravimetry/differential thermogravimetry (TG/DTG) used in pharmaceutical formulation. The TG and DSC both results demonstrated that polyvinyl alcohol, polyacrylamide, microcrestline cellulose, hydroxypropyl cellulose, cellulose acetate, ethyl cellulose found to be compatible with 2-PAM chloride and chosen for the preparation of antidote against chemical warfare agents.

- **Cides L.C.S.** et al (14) studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). Isothermal and non-isothermal methods were employed to determine kinetic data of decomposition process. The physical chemical properties and compatibilities of several commonly used pharmaceutical excipients (glycolate starch, microcrystalline cellulose, stearate, lactose and Plasdone®) with glimepiride were evaluated using thermoanalytical methods. The 1:1 physical mixtures of these excipients with glimepiride showed physical interaction of the drug with Mg stearate, lactose and Plasdone ® . On the other hand, IR results did not evidence any chemical modifications. From isothermal experiments, activation energy (*E*a) can be obtained from slope of ln*t vs.* 1/*T* at a constant conversion level. The average value of this energy was 123 kJ mol–1 . For non-isothermal method *E*a can be obtained from plot of logarithms of heating rates, as a function of inverse of temperature, resulting a value of 157 and 150 kJ mol –1 , respectively, in air and N2 atmosphere, from the first stage of thermal decomposition.

- **Freitas M.N.** et al(20) studied the Osmotically controlled and oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. We apply the thermal methods and IR spectroscopy to study compatibility between atenolol and several excipients usually found in the osmotic systems formulations (Polyethylene oxide, *MW* 3350, 100000, 200000 and 5000000; HPMC K4000, magnesium stearate and cellulose acetate. Cellulose acetate, HPMC K4000 and magnesium stearate have essentially no interaction with atenolol otherwise all Polyethylene oxide excipients modifies significantly the drug melting point indicating some extend of interaction.

- **Stulzer H.K.** et al studied possible interactions between CAP and excipients in tablets formulations, differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis completed by X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR) were used for compatibility studies. A possible drug-excipient interaction was observed with magnesium stearate by DSC technique. CAP is an antihypertensive drug currently being administered in tablet form and was the first commercially available angiotensine-converting enzyme (ACE) inhibitor

- **Laszcz M.** et al performed the Differential scanning calorimetry and thermogravimetric analysis with the support of X-ray powder diffraction and infrared spectroscopy were used as screening techniques for the compatibility testing of imatinib mesylate, with following excipients: magnesium stearate, polyvinylpyrrolidone, microcrystalline cellulose. In order to maximize the probability

of interactions 1:1 (by mass) drug: excipient binary mixtures were analysed and compared to individual components. Additionally an influence of storage at temperatures of 25 and 40°C on physico-chemical stability on drug – excipient binary mixtures was investigated. The largest visible changes were observed in the DSC curves of imatinib mesylate – magnesium stearate mixtures.

- **Filho R. O. C.** et al proposed a formulation of nifedipine tablets which were conditioned in amber-colored glass containers and placed in a climatized room at 40°C and relative humidity of 75% for 180 days. Differential scanning calorimetry (DSC) and thermogravimetry (TG) were used in order to evaluate the thermal properties of nifedipine, the excipients and two well-known nifedipine degradation products. The results demonstrated that there is no evidence on the interaction between nifedipine and excipients, or degradation products.

- **Freire F.D.** et al (16)proposed a formulation of Chlorpropamide belongs to the compounds having sulfonylurea group and is widely used as an oral antidiabetic agent. In this work differential scanning calorimetry (DSC) was used during pre-formulation of chlorpropamide tablets to determine the drug-excipients compatibility. The DSC curves of chlorpropamide and binary mixtures with excipients (sodium croscarmellose, sodium lauryl sulfate, microcrystalline cellulose, magnesium stearate and calcium carbonate) showed that chlorpropamide exhibited interaction with magnesium stearate and sodium lauryl sulfate. The binary mixtures of chlorpropamide– magnesium stearate presented a single endothermic process at 96–108 _C and chlorpropamide–sodium lauryl sulfate showed a wide endotherm at 99–120 _C.

- **Oliveira P.R.** et al(26) have developed the thermal characterization and compatibility studies of norfloxacin for extended release tablets The development of extended release tablets improves the patients' comfort and compliance, resulting in lower discontinuation of the therapy; with consequently decrease in bacterial resistance. In the present work, the thermal behavior of NFX was investigated using TG and DSC techniques. Isothermal and non-isothermal methods were employed to determine kinetic data of decomposition process. Compatibility studies between NFX and pharmaceutical excipients, including three hydrophilic polymers were carried out in order to develop a new formulation of NFX to obtain extended release tablets with an approved quality.

- **Peres-Filho M.J.** et al(32) performed Thermoanalytical investigation of olanzapine compatibility with excipients used in solid oral dosage forms. During preformulation studies of pharmaceutical solid dosage forms, thermal analysis techniques are very useful to detect physical or chemical incompatibilities between the drug and adjuvants of interest that might interfere with efficacy and safety of the final drug product. Differential scanning calorimetry (DSC) and thermogravimetry (TG) are useful tools for this purpose. The aim of this study was to investigate the thermoanalytical behavior of olanzapine (OLZ) when mixed with several excipients commonly used in solid dosage forms such as microcrystalline cellulose, croscarmellose, dicalcium phosphate dehydrate (DCPD), lactose, magnesium stearate, and povidone. Following DSC and TG analyses, powder X-ray diffraction tests were carried out. Thermoanalytical methods showed evidence of interaction between OLZ and magnesium stearate, lactose, and povidone. These results can be useful during the selection of excipients for pharmaceutical formulation development.

- **Gohel M.C.** et al(37) performed Compatibility study of quetiapine fumarate with widely used sustained release excipients. The drug-excipient compatibility study of quetiapine fumarate, with widely used sustained release excipients, was carried out employing differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR). The selected excipients were HPMC K100M, sodium alginate, xanthan gum, Eudragit RSPO, hydrogenated castor oil, carnauba wax, and PEO WSR 303. Equal proportion of drug and excipients was utilized in the interaction study. FT-IR spectra indicated the absence of interaction between drug and excipients. The DSC curve showed a sharp endothermic melting peak at 173.26 _C for quetiapine fumarate. Post melting interaction was observed for carnauba wax, Eudragit RSPO, and hydrogenated castor oil probably due to solubilization of drug in the melted excipient. No interaction was observed for other excipients. The physical mixtures stored at 30 ± 2 _C/65 ± 5% RH did not show any significant degradation of the drug. The concept of systemically conducted preformulation studies will facilitate dossier submission to the drug control authority.

- **Singh A.V.** et al(33) performed Synthesis, characterization, and compatibility study of acetylated starch with lamivudine. In this study, highly substituted starch acetate was prepared by reaction with native moth bean starch and acetic anhydride. Physicochemical characterization of this modified starch was done using scanning electron microscopy, X-ray diffraction, and thermogravimetric analysis. Their formation was confirmed by titrimetric analysis and highest degree of substitution was observed with a value of 2.35. The synthesized modified starch was further

studied for compatibility with model drug lamivudine using differential scanning calorimetry and isothermal stress testing for its controlled release tablet formulation.

- **Tita Dumitru** et al(27) performed compatibility of the acetylsalicylic acid (ASA), an non steroidal anti-inflammatory drug, with pharmaceutical excipients of common use including diluents, binders, disintegrants, lubricants and solubilising agents. In order to investigate the possible interactions between ASA and eleven excipients differential scanning calorimetry (DSC) and thermogravimetry/ derivative thermogravimetry analysis completed by Fourier transform infrared spectroscopy (FT-IR) and X-ray powder diffraction were used for compatibility study. The DSC has proven to be, among the selected analytical techniques, the most sensitive and specific in assessing the compatibility. The samples, as physical mixtures, were prepared by mixing the analyte and excipients in a proportion of 1:1 (w:w). On the basis of thermal results (especially DSC), confirmed by FT-IR and X-ray analysis, a possible chemical interaction was found between the ASA with polyvinylpyrrolidone K30 (PVP) and magnesium stearate, respectively a possible physical interaction with colloidal silicon dioxide and stearic acid (Ac. St.).

### *3.1 AIM AND OBJECTIVES:*

*The aim of the present investigation is to evaluate the thermal stability and compatibility of Atorvastatin calcium(AT) with common pharmaceutical excipients, used in the solid dosage form, by thermo analytical technique (DSC), with support of Fourier*

*transformed infrared (FT-IR). Further, the excipients found compatible were used in the development of immediate release tablet formulations.*

### *3.2 NEED OF THE STUDY:*

*The thermal techniques of analysis will be used to assess the compatibility between Atorvastatin Calcium (AT) and some excipients used in the development of immediate released formulations. This study is a part of a systematic study undertaken to find and optimizes a general method of detecting the drug–excipient interactions, with the aim of predicting rapidly and assuring the long-term stability of pharmaceutical product and speeding up its marketing. The thermal properties of AT and its physical association as binary mixtures with some common excipients will be evaluated by FT-IR, differential scanning calorimetry. FT-IR spectroscopy will be used as complementary techniques to adequately implement and assist in interpretation of the thermal results. Based on their frequent use in preformulations nine different excipients: starch; microcrystalline cellulose, Sodium starch glycolate, colloidal silicon dioxide; lactose (anhydrous); polyvinylpyrrolidone; magnesium stearate and talc will be blended with AT. The samples were prepared by mixing the analyte and excipients in a proportion of 1:1(w:w).*

*Studies of drug–excipient compatibility represent an important phase in the preformulation stage for the development of all dosage forms. In fact potential physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety. Thermal analysis (TA) is a rapid analytical technique commonly used for evaluating drug–excipient interactions through the appearance, shift or disappearance of endo- or exothermal effects and/or variations in the relevant enthalpy values.*

*Differential scanning calorimetry (DSC) has been widely used to assess incompatibility between formulation components, because the method is fast and versatile, and requires only a small quantity of sample. However, caution needs to be exercised if the results of DSC alone are interpreted. Whenever possible, other techniques such as infrared spectroscopy (IR) and quantitative analysis after storage under stressed conditions should be utilized in conjunction with DSC. As the thermo-analytical methods do not yield direct chemical information, Fourier transform infrared spectroscopic (FT-IR) investigations will be used in this work.*

## *4. DRUG PROFILE:*

### *4.1 ATORVASTATIN CALCIUM:*

Atorvastatin is in a group of drugs called HMG CoA reductase inhibitors, or "statins." Atorvastatin reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL)

and triglycerides in the blood, while increasing levels of "good" cholesterol (high-density lipoprotein, or HDL).Atorvastatin is used to treat high cholesterol, and to lower the risk of stroke, heart attack, or other heart complications in people with type 2 diabetes, coronary heart disease, or other risk factors. Atorvastatin is used in adults and children who are at least 10 years old.

### *4.1.1. Chemistry:*

*Atrovastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is* $(C_{33}H_{34}FN_2O_5)2Ca \bullet 3H_2O$ *and its molecular weight is 1209.42. Its structural formula is:*

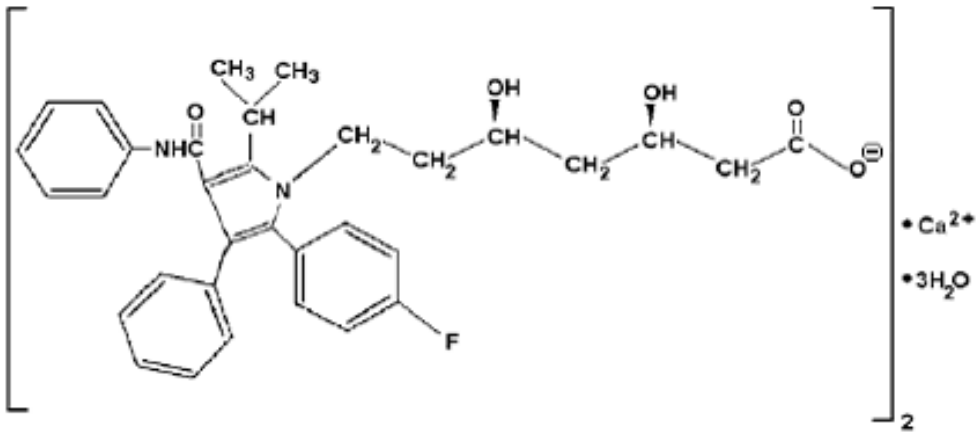


***Fig: Chemical Structure of Atorvastatin Calcium***

### *4.1.2 Physiochemical Characterization:*

*Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol. Biological half-life of the drug Atorvastatin Calcium is 14 hours*

### *4.1.3Pharmacodynamic Properties:*

*Atorvastatin inhibits HMG-CoA reductase and impedes the formation of mevalonic acid, which is a rate-limiting step in the biosynthesis of cholesterol. The resulting effect is a reduction in intracellular cholesterol leading to an increase in the number of low density lipoprotein (LDL)-receptors and increase in LDL-cholesterol clearance from plasma. HMG-CoA reductase inhibitors may also lower plasma cholesterol levels by decreasing hepatic production of very low density lipoprotein (VLDL)- and LDL-cholesterol.*

*Atorvastatin inhibited cholesterol synthesis by 50% in human liver-derived cell line (Hep-G2) at a concentration of 73 nmol/L. Atorvastatin 80 mg/day reduced fasting plasma mevalonic acid levels by 59% in patients with heterozygous familial hypercholesterolaemia.*

*Patients with hypertriglyceridaemia receiving atorvastatin either 20 or 80 mg/day for 4 weeks experienced significant reductions in plasma levels of total cholesterol, triglycerides and apolipoproteins B, C-II, C-III and E.*

*Two indirect mechanisms have been suggested to explain the reduction in triglycéride levels with atorvastatin. Firstly, marked inhibition of cholesterol synthesis would impair the assembly and secretion of VLDL particles, of which cholesterol is an essential component, therefore causing reductions in triglyceride levels. Secondly, reductions in hepatocyte cholesterol levels caused by substantial inhibition of cholesterol synthesis would lead to*

*increases in LDL-receptor expression and hence increased binding of VLDL particles and LDL, resulting in the reduction of both cholesterol and triglyceride levels.*

*There is some evidence that atorvastatin, like other drugs of its class, may have antiatherogenic effects. The drug inhibits smooth muscle cell proliferation and/or migration. Compared with untreated controls, atorvastatin 2.5 mg/kg significantly reduced rabbit atherosclerotic lesion size by 67%. Furthermore, in patients with hyperlipidaemia, atorvastatin 80 mg/day reduced plasma viscosity by 10%, factor VII activity by 8%, red blood cell sedimentation rate by 33% and arachidonic acid-induced whole blood aggregation by 11%.*

***4.1.4 Pharmacokinetic Properties:***

*Multiple daily doses of atorvastatin 2.5 to 80mg produced steady-state maximum plasma concentrations ($C_{max}$) of 1.95 to 252 µg/L within 2 to 4 hours after administration and area under the plasma concentration-time curve (AUC) values of 25.2 to 1293 |Ug/L · h. The drug has an absolute bioavailability of 12%. Atorvastatin is ≥98% protein-bound in plasma and has a mean elimination half-life of about 14 hours, but as a result of active metabolites the half-life of HMG-CoA reductase inhibition is 20 to 30 hours. Less than 2% of the parent drug and metabolites are excreted renally.*

*Atorvastatin Cmax and AUC values may be prolonged in patients with hepatic impairment. Renal impairment had no effect on atorvastatin pharmacokinetic parameters. Although some accumulation was evident in the elderly, this did not produce clinically significant changes in lipid reduction.*

***4.1.5 Therapeutic Efficacy:***

*Currently, results of studies investigating the potential benefits of atorvastatin on mortality and morbidity in patients with or without coronary heart disease are not available.*

*Therefore, clinical evaluation of atorvastatin at this time is based on lipid-lowering effects, a surrogate marker of clinical efficacy.*

*In placebo-controlled dose-response studies in patients with primary hypercholesterolaemia, atorvastatin 10 to 80 mg/day produced 35 to 61% reductions in LDL-cholesterol levels. 90% of the maximum observed reduction in LDL-cholesterol levels was attained after 2 weeks of treatment. In patients with hypertriglyceridaemia, atorvastatin 5,20 or 80 mg/day reduced triglyceride levels by 26 to 46%, LDL-cholesterol levels by 17 to 41% and total cholesterol levels by 20 to 43%.*

*In large double-blind trials of 1 year's duration involving patients with hypercholesterolaemia, reductions in total cholesterol, LDL-cholesterol, apolipoprotein B and triglyceride levels were significantly greater with atorvastatin 10 to 20 mg/day than with lovastatin 20 to 40 mg/day, pravastatin 20 to 40 mg/day or simvastatin 10 to 20 mg/day. Atorvastatin, lovastatin, pravastatin and simvastatin all raised HDL-cholesterol levels by 7 to 10%. A greater number of patients tended to reach US National Cholesterol Education Program (NCEP) LDL-cholesterol goals with atorvastatin than with lovastatin, pravastatin or simvastatin. As a result, fewer patients receiving atorvastatin than these other agents tended to require upward dosage titration after 16 weeks of treatment.*

*In one study, the combination of atorvastatin 10 mg/day and colestipol 20 g/day tended to produce larger reductions in LDL-cholesterol levels and smaller reductions in triglyceride levels than atorvastatin 10 mg/day monotherapy, in patients with primary hypercholesterolaemia.*

*In patients with combined hyperlipidaemia (elevated LDL-cholesterol and triglyceride levels), atorvastatin 10 mg/day produced larger reductions in total cholesterol and LDL-cholesterol than fenofibrate 100mg 3 times daily or nicotinic acid (niacin) 100 to 1000mg 3*

*times daily. However, smaller reductions in triglyceride levels and more modest increases in high density lipoprotein (HDL)-cholesterol levels were achieved with atorvastatin than with both fenofibrate and nicotinic acid.*

*Atorvastatin 10 to 20 mg/day caused a greater reduction in triglyceride levels than simvastatin 10 to 20 mg/day in patients with raised cholesterol and triglyceride levels secondary to non-insulin-dependent diabetes mellitus (NIDDM).*

***4.1.6 Tolerability***

*Atorvastatin has been generally well tolerated in clinical studies of up to 52 weeks' duration. Like other HMG-CoA reductase inhibitors, gastrointestinal effects (including flatulence, dyspepsia, constipation and abdominal pain) are the most frequently reported adverse events associated with atorvastatin. In total, <2% of 2502 patients withdrew from treatment with atorvastatin in clinical trials because of adverse events. In comparative trials, atorvastatin had a similar adverse event profile to that of lovastatin, pravastatin and simvastatin.*

*Hepatic dysfunction (raised serum aspartate or alanine aminotransferase levels) and myopathy (myalgia and abnormal creatine phosphokinase levels >10 times the normal limit) are the most serious tolerability concerns associated with HMG-CoA reductase inhibitors. To date, myopathy has not yet been reported with atorvastatin, although the drug has not been used as extensively as other HMG-CoA reductase inhibitors. 3% of the atorvastatin group (n=132) in one study reported myalgia, but no patients had persistent increases in creatine phosphokinase levels >10 times the normal limit.*

*Elevated serum transaminase levels were reported in 0.2, 0.6, 0.6 and 2.3% of patients receiving atorvastatin 10, 20,40 and 80 mg/day, respectively. In patients receiving*

*atorvastatin in clinical trials, the total incidence of persistent elevations in serum transaminases was 0.7%. After 52 weeks of treatment in a large study, the incidence of abnormal transaminase levels was similar with atorvastatin and lovastatin. Pancreatitis was reported in 1 of 1135 patients receiving atorvastatin in 3 trials.*

***4.1.7 Dosage and Administration***

*10 to 80 mg/day may be used to reduce the raised lipid levels in patients with primary hypercholesterolaemia (heterozygous familial, homozygous familial or nonfamilial) or combined dyslipidaemia*

*The dosage of atorvastatin should be adjusted according to response. Atorvastatin may be taken at any time of day with or without food. In patients with hepatic insufficiency dosage reductions may be required. The drug is contraindicated in patients with active hepatic disease or unexplained persistent elevations in serum transaminases.*

*Concomitant use of atorvastatin with cyclosporin, nicotinic acid, fibric acid derivatives, erythromycin or azole antifungals is likely to increase the risk of adverse events (e.g. myopathy or rhabdomyolysis), and these combinations should be avoided where possible.*

***4.1.7.1Usual Adult Dose for Prevention of Cardiovascular Disease:***

*Initial dose: 10 mg to 80 mg orally once a day.*

*The initial dosage of atorvastatin recommended for this patient in the prevention of cardiovascular disease is 10 mg to 80 mg orally once a day. The dose may be administered at any time of the day without regard for meals.*

*Dose adjustments should be made at intervals of 2 to 4 weeks..*

*Studies have demonstrated that treatment with atorvastatin is associated with significant reductions in the risk of cardiovascular endpoints and stroke in various patient populations for both primary and secondary prevention.*

*For primary prevention, atorvastatin treatment was effective in hypertensive patients with normal or mildly elevated cholesterol levels as well as in patients with type II diabetes. Patients had relatively low cholesterol levels at baseline in both trials; however, treatment with this medicine still resulted in significant reductions in cardiovascular outcomes and stroke.*

*For secondary prevention, intensive lipid lowering therapy with atorvastatin 80 mg/day was associated with significant incremental clinical benefit beyond therapy with 10 mg/day in patients with stable coronary heart disease. It was also shown to significantly reduce the risk of clinical outcomes in coronary heart disease patients versus usual medical care.*

***4.1.7.2Usual Adult Dose for Hyperlipidemia:***

*Initial dose: 10, 20 or 40 mg orally once a day. The 40 mg starting dose is recommended for patients who require a reduction in LDL-cholesterol of more than 45%.*

*Dose adjustments should be made at intervals of 2 to 4 weeks.*

*Maintenance dose: 10 to 80 mg orally once a day.*

***4.1.7.3 Usual Pediatric Dose for Heterozygous Familial Hypercholesterolemia:***

*10 to 17 years:*

*10 mg per day (max dose is 20 mg per day). Adjustments should be made at intervals of 4 weeks or more*

## *5. MATERIALS AND EXPERIMENTAL*

***Table: 5.1. Materials (Chemicals and reagents):***

| SL NO | Material | Source |
|---|---|---|
| 1 | Atorvastatin Calcium | Yerrow chem., Mumbai-37 |
| 2 | Cros carmelose (NaCMC) | Himedia,Mumbai-86 |
| 3 | Carbopol 940 | Balaji,Drugs, Mumbai-37 |
| 4 | Avicel 101(MCC) | Balaji,Drugs, Mumbai-37 |
| 5 | Microcrystalline Cellulose(MCC) | Balaji,Drugs, Mumbai-37 |
| 6 | Sodium Starch Glycolate | Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018 |
| 7 | Collidal Silicondioxide | Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018 |
| 8 | Hydroxypropyl methyl cellulose(HPMC) | Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018 |
| 9 | Stearic Acid | Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018 |
| 10 | Magnesium stearate | Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018 |
| 11 | Lactose | Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018 |
| 12 | Talc | Changshu Yangyuan chemical, china |
| 13 | Eudragit L100 | Changshu Yangyuan chemical, china |
| 14 | PVP K30 | Changshu Yangyuan chemical, china |

| | | |
|---|---|---|
| 15 | Conc Hydrochloric acid | Balaji,Drugs, Mumbai-37 |

| | | |
|---|---|---|
| 16 | Sodium dihydrogen phosphate | Balaji,Drugs, Mumbai-37 |
| 17 | Potassium dihydrogen phosphate | Balaji,Drugs, Mumbai-37 |
| 18 | Sodium hydroxide | Balaji,Drugs, Mumbai-37 |
| 19 | Acetone | Changshu Yangyuan chemical, china |
| 20 | Methanol | Changshu Yangyuan chemical, china |
| 21 | Isopropyl alcohol | Balaji,Drugs, Mumbai-37 |

***5.2. Instruments and equipments***

| Sl no | Instrument | Company name |
|---|---|---|
| 1 | Digital weighing balance | Denver Instrument |
| 2 | UV Visible spectrophotometer | Shimadju,Model no:UV 1800 240V |
| 3 | Tablet compression machine (I.P/B.P/U.S.P. standard) | Shakti,9001:2000 Company |
| 4 | Hardness tester | Rolex Tablet hardness tester |
| 5 | Friability tester | Rochi friabiliter |
| 6 | Dissolution test apparatus | Libinda,DS 8000 |
| 7 | FT-IR | Bruker Model no:10059736 |

| | | |
|---|---|---|
| 8 | Melting point determination | Macroscientific works10A/UA,Janwahar Nagar, Delhi-11007 |
| 9 | Hot air oven | International commercial Traders,18,Kolkata-700001 |
| 10 | Bulk density apparatus | Rolex |
| 11 | Viscometer | Brookfield viscometer DV-E viscometer |
| 12 | Texture Analyzer | Stable Microsystem, Model:TA-XT Express |
| 13 | DSC instrument | Parkin Elmer |

***5.3 Experimental (Preformulation studies of drug and excipients):***

***5.3.1 Preparation of products and storage conditions:***

*Binary component mixtures in 1:1 mass ratio were prepared in a porcelain mortar. The original components were investigated by means of DSC and FT-IR methods. The mixtures were investigated immediately after the preparation and after accelerated storage period (40 ◦C/75% RH/ 3 months). The composition of various binary mixtures for drug-excipients compatibility studies were as follows: ATV Calcium; ATV Calcium : SSG 1:1; ATV: CCS 1:1; ATV: CP 1:1; ATV Calcium : Lactose 1:1; ATV Calcium : MCC 1:1; ATV: Sodium lauryl sulfate 1:3; ATV Calcium : Mannitol 1:1; ATV Calcium : Magnesium stearate 1:0.5; ATV Calcium: Stearic acid 1:1.*

***5.3.2 Physicochemical characterisation of the drug:***

*The pure drug was characterised for its identity, purity and organoleptic properties by FT-IR, UV analysis, melting point determination and visual observations.*

**(a) Organoleptic Properties**

*The organoleptic properties of the drug sample were evaluated for its state, colour, odour and taste.*

***5.3.3. Solubility determination:***

*A minute quantity of the drug sample was taken in a test tube and solubility of the drug was determined by dissolving the drug in 1 ml of various solvent like water,0.1 M HCL, methanol, ethanol, phosphate buffer, Acetone etc.*

***5.3.4. Melting point determination**:*

*It was placed a little of drug sample in a dry capillary tube of 1-mm internal diameter forming a column about 3 mm high. Heat the melting-point apparatus to a temperature 5-10 °C below the expected temperature of melting and adjust the heating so that the temperature in the chamber rises about 1 °C per minute. Introduce the capillary tube into the melting point apparatus, and noted the temperature when the drug substance becomes completely melted to liquid state; this is considered to be the melting point.*

***5.3.5. FT-IR spectroscopy study[29]:***

*This was carried out to find out the compatibility between the drug Atorvastatin Calcium and the polymer Magnesium Stearate, Lactose,Stearic Acid 10 mg of the sample were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at10 kg/cm$^2$ using a hydraulic press. The pellet was kept into the sample holder and scanned from 400 cm-1 to 4000 cm-1 in Bruker FT-IR spectrophotometer. Samples were prepared for drug Atorvastatin Calcium , polymer*

*Magnesium Stearate, Lactose,Stearic Acid, sodium CMC, carbopol 934 and physical mixture of drug and polymer. The spectra obtained were compared and interpreted for the functional group peaks.*

***5.3.6. Differential scanning calorimetry(DSC) study[29-30]:***

*Differential scanning calorimetry (DSC) of the bulk drug Atorvastatin Calcium and the excipient were performed using (Parkin Elmer) for measurement of the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. About 6-7 mg of the individual components or drug-excipients combinations were weighed in aluminium DSC pans and hermetically sealed capsules were prepared with aluminum lids. An initial ramp was used to jump the temperature to 40ºC and then a constant heating rate of 10 ºC/min was used up to 300 ºC under nitrogen atmosphere.*

***5.3.7. UV analysis of the drug:***

***5.3.7.1. Determination of absorption maxima (λmax) in water:***

*10 mg of Atorvastatin Calcium was weighed accurately and dissolved in 10 ml water in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with water. The resulting solution was labelled as standard working Solution. 0 .4 ml of the working solution was withdrawn and diluted up to 10 ml with water in 10 ml volumetric flask. The spectrum of this solution was run in 200 to 400 nm range in UV-visible spectrophotometer. The λ max of the Atorvastatin Calcium was found to be 238 nm.*

***5.3.7.2. Preparation of standard calibration curve in water:***

*From above standard working solution, 0.2 ml, 0.4 ml, 0.6 ml and 0.8 ml, 1ml, 1.2 was withdrawn and diluted up to 10 ml with water in 10 ml volumetric flask to get concentration of 2 µg/ml, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of*

*each solution was measured by UV-visible spectrophotometer at 238 nm using water as blank.*

***5.3.7.3. Preparation of standard calibration in 0.1 M HCL:***

*10 mg of Atorvastatin Calcium was weighed accurately and dissolved in 10 ml of 0.1M HCL buffer ($p^H$ 1.2) in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with pH 1.2 0.1 M HCL buffer. The resulting solution was labelled as standard working Solution. From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml, 1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with pH 1.2 0.1M HCL buffer in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 289 nm using the pH 1.2 0.1M HCL buffer as blank.*

***5.3.7.4. Preparation of standard calibration curve in phosphate buffer pH 6.8:***

*10 mg of Atorvastatin Calcium was weighed accurately and dissolved in 10 ml of distilled water in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with water. The resulting solution was labelled as standard working Solution. From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml, 1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with water in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 239 nm using water as blank*

***5.3.7.5. Preparation of standard calibration in phosphate buffer pH 7.4:***

*10 mg of Atorvastatin Calcium was weighed accurately and dissolved in 10 ml of pH 7.4 phosphate buffer in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with pH 6.8 phosphate buffer. The resulting solution was labelled as standard working Solution From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml,1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with pH 6.8 phosphate buffer in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 238 nm using the pH 6.8 phosphate buffers as blank.*

***5.3.7.6. Saturation Solubility determination[27]:***

*The Solubility of the selected drug was determined in distilled water, 0.1M HCL,Phosphate buffer pH 6.8 by the following procedure: Excess amount of drug was taken and dissolved in a measured amount of solution of each Solvent in a volumetric flask to get a saturated solution. The solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. After 24 hour the solution was sonicated for 30 min & the resultant solution was centrifuged to separate supernatant then withdrawn the supernatant and successively diluted and analyzed concentration of Atorvastatin Calcium by UV (Ultraviolet) Spectrophotometer at 238 nm.*

***5.3.8. Preparation of Immediate release tablet of ATV by direct compression:***

*The weighed quantity of ATV was screened through sieve no. #40. The various excipients were accurately weighed and screened separately using sieve no. # 40. The immediate release tablets were prepared by direct compression method using the formula shown in Table 1. Different ratios of superdisintegrants, fixed amount of diluents, glidants*

*were passed through Sieve No.60 and mixed in mortar with a pestle to obtain uniform mixing. The blended powder was compressed into tablets weighing appprox. 150 mg on a single punch tablet machine (Cadmach, Ahmadabad) using a flat-faced non-beveled punch and die set of 8-mm diameter* [10, 12].

**5.3.9. Pre-compression parameters:**

**5.3.9.1.Bulk density:**

It is a ratio of mass of powder to bulk volume. It is expressed in gm/ml and is given by the formula [8, 10]: Bulk density=M/Vo

Where, M = mass of the powder, Vo = bulk volume of the powder

**5.3.9.2.Tapped density :**

It is a ratio of mass of powder to tapped volume. Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by [8, 10]:

Tapped density=M/Vt

Where, M = mass of the powder

Vt = final tapping volume of the powder

**5.3.9.3. Angle of repose (θ) :**

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was then calculated using following equation [5, 10]:

Angle of repose $\theta = \tan^{-1}(h/r)$

Where, h=height of the pile

r=radius of the pile

**5.3.9.4. Compressibilty index (Carr's index):**

Compressibility index is used as an important parameter to determine the flow behaviour of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics.

Carr's index is determined by employing following formula [5]:

Carr's Index= [(TD-BD)x100]/ TD

**5.3.9.5.Hausner's Ratio:**

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material [5, 15]. Hausner's ratio = TD/BD

*Physical evaluation of the matrix tablets*

*The thickness, hardness, weight uniformity and friability were determined in a similar manner as stated for conventional oral tablets in the accredited pharmacopoeia [8, 13].*

***5.3.9.6. Determination of Drug Content:***

*20 tablets from each formulation were finely powdered and a portion equal to 10 mg ATV was transferred to a 100 ml volumetric flask, dissolved in phosphate buffer (pH 6.8). Then the volume was made up with buffer and shaken for 10 minutes to ensure complete solubility of drug. The mixture was centrifuged and 10 mL of the supernatant liquid was diluted 20 times with buffer and the absorbance was determined spectrophotometrically using a UV spectrometer (UV-Visible, Perkin-Elmer, USA) at 243 nm [15].*

***5.3.9.7. Disintegration test:***

*Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. Disintegration test was carried out using tablet disintegration test apparatus (Electrolab, India) using distilled water without disk at room temperature (37±2$^{o}$C). The time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds* [10, 15].

***5.3.9.8. In-vitro drug release studies:***

*In vitro dissolution studies for all the tablets were carried out using USP type II Dissolution apparatus (Electrolab, Mumbai, India). The dissolution medium used was 900 ml, mixture of phosphate buffer solution pH 6.8 and water (1:1) used as dissolution medium. The tablets containing 20 mg of ATV were weighed and then introduced into the dissolution medium. 1 ml aliquots were withdrawn at every 1 hour and replaced by 1 ml of fresh dissolution media (37ºC). The medium was stirred at 50 rpm using paddle at 37±0.5$^{o}$C. The samples were collected, filtered through Whatman filter paper (0.45um) and analyzed after suitable dilution (if required) at 243 nm using UV-visible spectrophotometer against phosphate buffer (pH 6.8) as blank* [13, 14].

***5.3.9.9. Kinetic evaluation of release data:***

*The dissolution data from various batches of tablets were subjected to release kinetic study by fitting in to various postulated kinetic models. Drug dissolution from solid dosage form has been described by kinetic models in which the dissolved amount of drug (Q) is compared to the drug content (%) function of the test time (t). The analytical and kinetic models of the Q versus t commonly used are Zero order, First order, Higuchi and Korsmeyer-Peppas model to study the possible release mechanism* [14, 16].

***5.3.9.10. Stability studies:***

*The stability studies were conducted by storing the optimized tablets at 40 ± 2ºC/75 ± 5% RH in stability chamber for 45 days. The samples were withdrawn after 45 days and analyzed for various physical tests and drug release study* [5, 15].

## *6. RESULT AND DISSCUSSION:*

### *6.1. Preformulation study Atorvastatin Calcium*

### *6.1.1. Organoleptic properties:*

| | |
|---|---|
| *1. Nature* | *Crystalline white powder* |
| *2. Color* | *White powder* |
| *3. Odor* | *characteristic.* |
| *4. Taste* | *Slightly Bitter taste* |

*5. Solubility-*

| | |
|---|---|
| *In water* | *Slightly Soluble.* |
| *In acetone* | *Freely Soluble.* |
| *In methanol* | *Freely Soluble.* |
| *In ethanol* | *Slightly Soluble.* |
| *In phosphate buffer $P^H$ 6.8* | *Sparingly soluble.* |
| *In phosphate buffer $P^H$ 7.4* | *Slightly Soluble.* |

*From the solubility study of the drug it has been seen that the drug is soluble in polar solvent so it can be concluded that the drug is polar.*

### *6.1.2. Melting point determination:*

*The melting point of the drug sample was found to be $176^0C$, which matched the melting point as reported in official pharmacopoeia (I.P). This reveals that drug sample is retaining the desired property of purity.*

### *6.2. Drugs Polymer Interaction Study by FT-IR spectrophotometer:*

*FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drug Atrovastatin Calcium and the polymers Stearic Acid,Lactose used for the preparation of tablets. The FT-IR was performed for drug, polymer and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies at wavelength between 400 cm-1 to 4000cm-1 is shown Table. From the FT-IR study it is clearly understood the identical FT-IR bands were also present in the drug-polymer physical mixture as like that of the drug. This confirms that there are no drug-excipient interactions present.*

*The principal infra-red absorption peaks of pure ATV calcium shows characteristics peaks belonging at 1577.77, 1649, 1550, 1217.38, 1317.0, 3363 $cm^{-1}$ corresponding to aromatic secondary N-H vibrations, C=O, C=C, C-O, C-N and O-H stretching of aromatic ring respectively* ***(Figure 2)****. The identical peaks of N-H vibrations, C==O, C=C, C-O, C-N and O-H stretching were also appeared in the spectra of physical mixture of drug with SLS, mannitol, magnesium stearate , and all other excipients found compatible in DSC studies. FT-IR-spectra of drug and its physical mixture with above excipients are exactly same, and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.*

***Table: 6.2.1 IR interpretation of drug, Stearic Acid and physical mixture of drug-Stearic Acid:***

| Sl No | Interpretatation | IR absorption bands (cm-1) | | |
|---|---|---|---|---|
| | | Drug | Stearic Acid | Drug+Stearic Acid |
| 1 | C-H(Aromatic) | ---- | 2955.17 | 2915.92 |
| 2 | C-H | ---- | 2871.51 | 2848.16 |
| 3 | S=O | 1216.17 | 1187.11 | 1216.01 |
| 4 | C-O | 1372.13 | 1310.25 | 1316.20 |
| 5 | C=N | 1649.11 | 1695.77 | ----- |
| 6 | C-N | 1242.05 | 1226.48 | ----- |
| 7 | C-C | 810.27 | 934.13 | 842.26 |
| 8 | N-H | 3363.08 | ----- | 1650.14 |
| 9 | O-H | 1062.49 | 1270.51 | ----- |

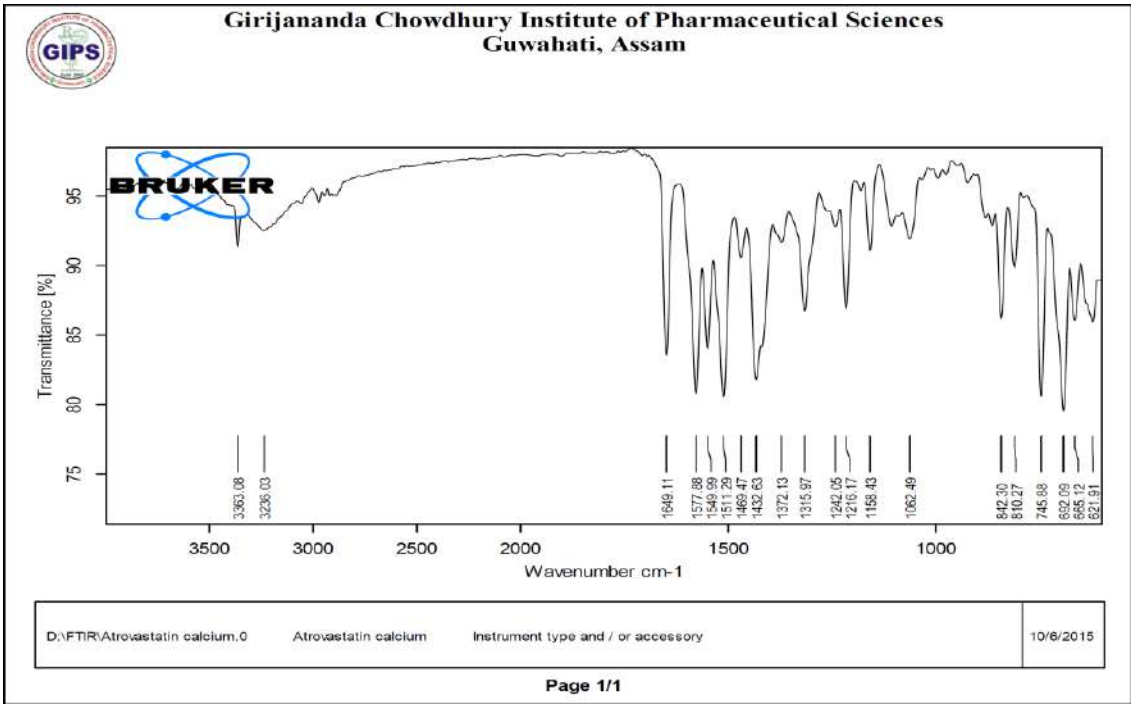


*Fig: 6.2.1.1. IR spectrum of Atorvastatin Calcium*

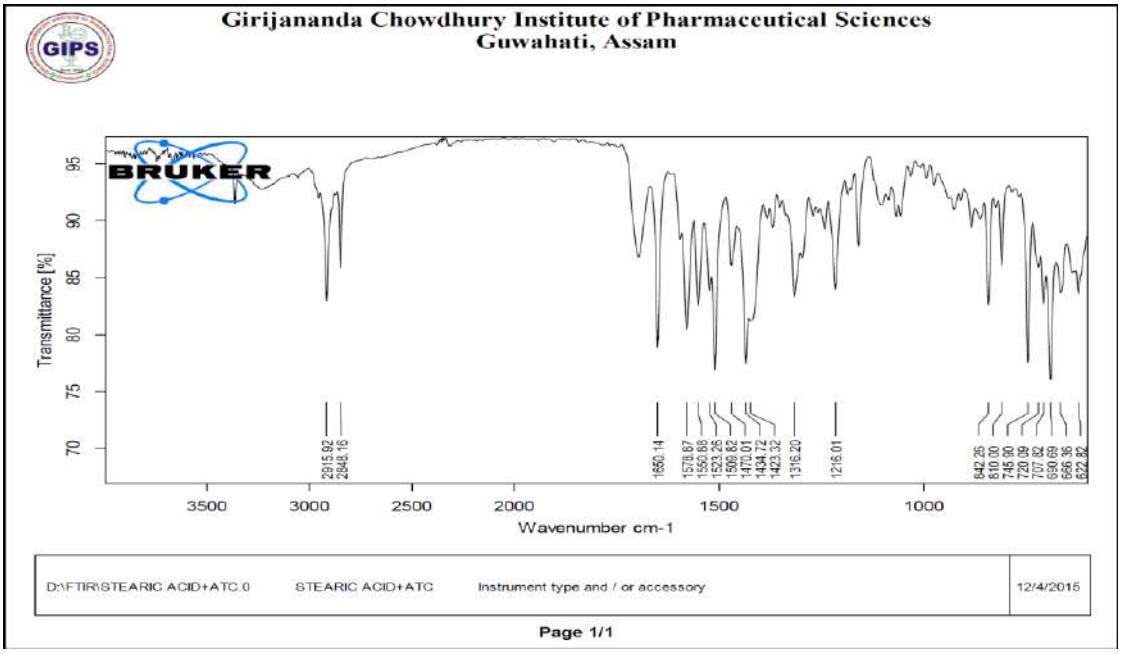


*Fig: 6.2.1.2. IR spectrum of the mixture of Atorvastatin Calcium and Stearic Acid.*

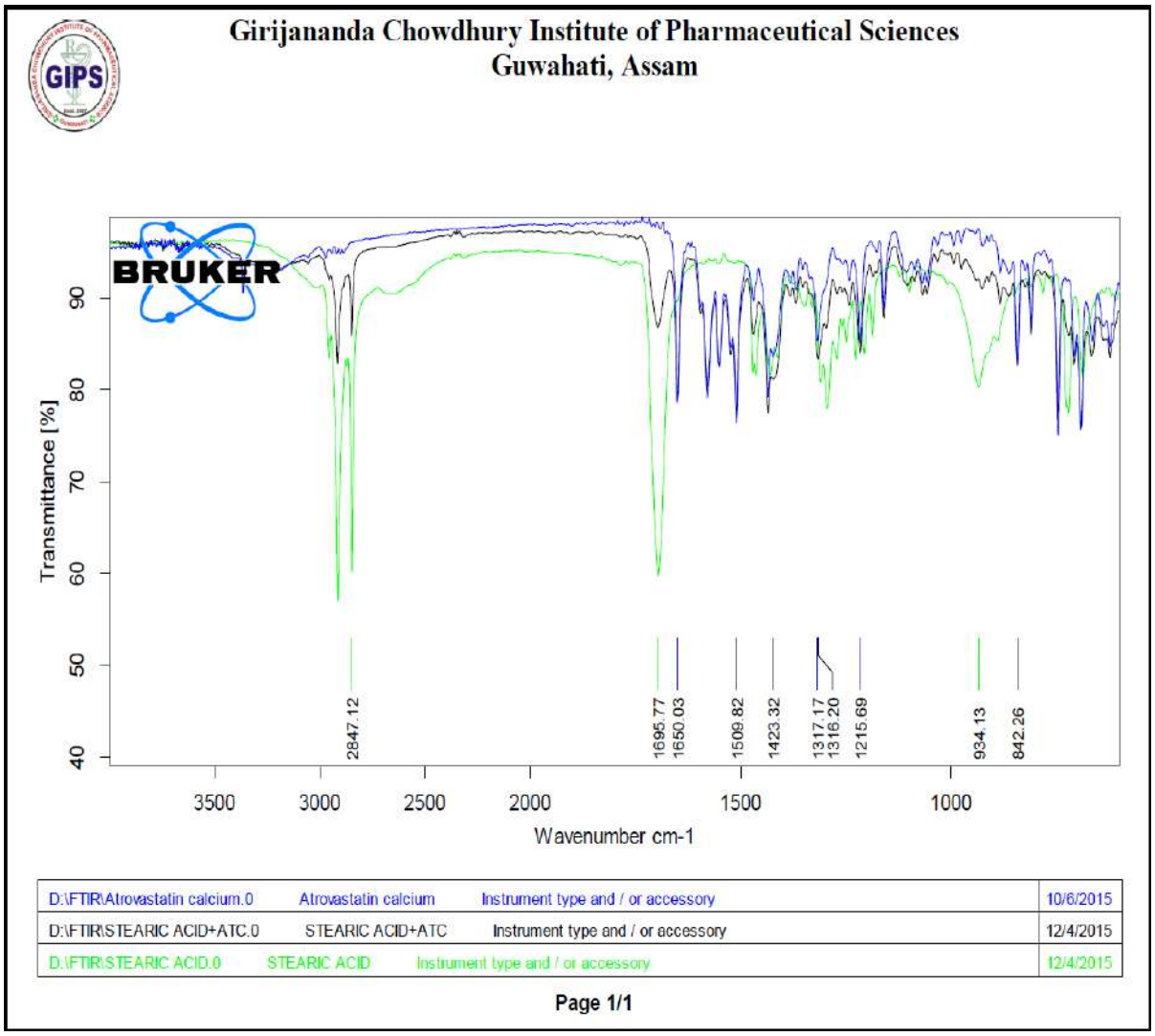


***Fig: 6.2.1.3 IR spectrum of the drug, Stearic Acid, mixture of drug and stesaric acid.***

***Table: 6.2.2. IR interpretation of drug, Lactose and physical mixture of drug-Lactose.***

| Sl No | Interpretation | IR absorption bands (cm-1) | | |
|---|---|---|---|---|
| | | Drug | Lactose | Drug+Lactose |
| 1 | C-H(Aromatic) | ---- | 2917.47 | ----- |
| 2 | S=O | 1216.17 | 1166.77 | 1068.57 |
| 3 | C-O | 1372.13 | 1338.81 | 1317.44 |
| 4 | C=N | 1649.11 | ---- | 1550.86 |
| 5 | C-N | 1242.05 | 1139.95 | 1031.59 |
| 6 | C-C | 810.27 | 875.15 | 810.00 |
| 7 | N-H | 3363.08 | ----- | 1650.27 |
| 8 | O-H | 1062.49 | 1017.97 | 1031.59 |

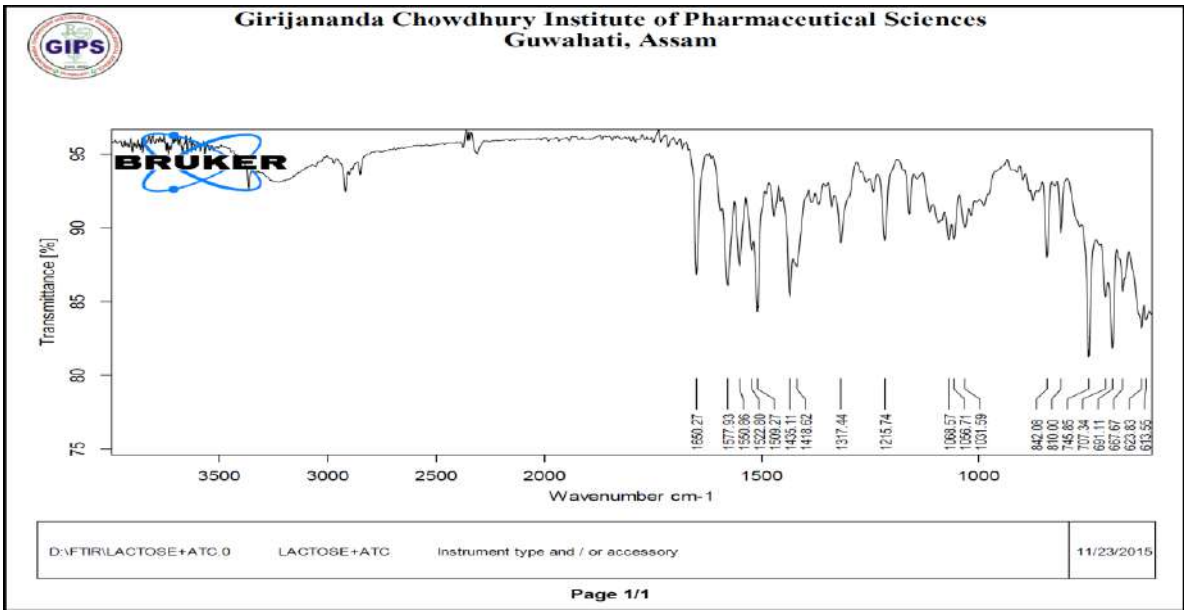


*Fig: 6.2.2.1. IR Spectrum of the mixture of Atorvastatin Calcium and Lactose*

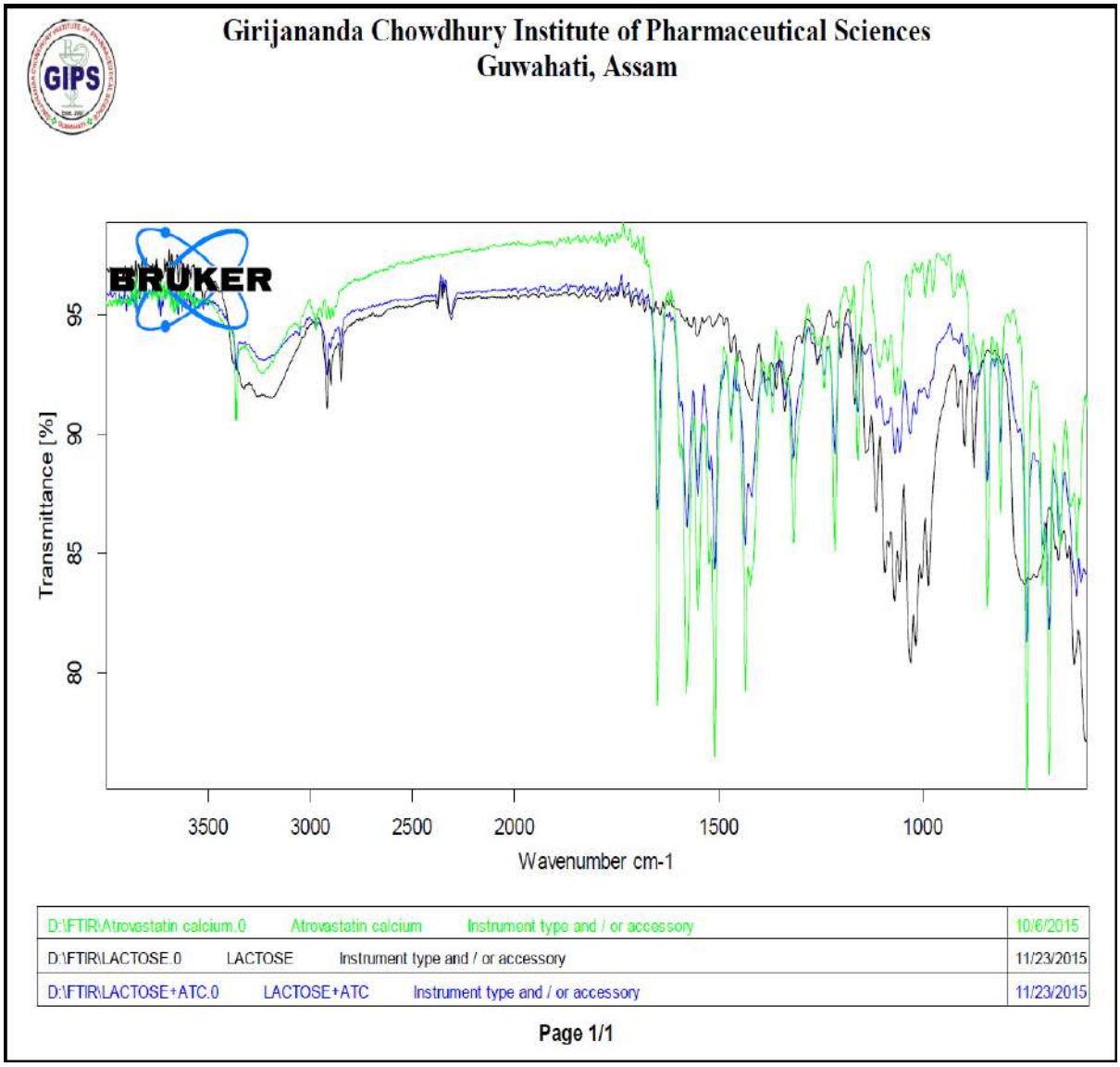


***Fig: 6.2.2.2. IR spectrum of the drug, Lactose, mixture of drug and Lactose.***

***Table: 6.2.3.IR interpretation of drug, Magnesium Stearate and physical mixture of drug-Magnesium Stearate***

| **Sl No** | **Interpretation** | **IR absorption bands (cm-1)** | | |
|---|---|---|---|---|
| | | **Drug** | **Magnesium Stearate** | **Drug+Magnesium Stearate** |
| 1 | C-H(Aromatic) | ---- | 2956.76 | 2916.82 |
| 2 | C-H | ---- | 2916.49 | 2849.87 |
| 3 | S=O | 1216.17 | 1211.99 | 1215.43 |
| 4 | C-O | 1372.13 | 1319.38 | 1317.85 |
| 5 | C=N | 1649.11 | 1633.02 | 1649.99 |
| 6 | C-N | 1242.05 | 1112.96 | ---- |
| 7 | C-C | 810.27 | 883.16 | 842.14 |
| 8 | N-H | 3363.08 | 1573.35 | 1577.08 |
| 9 | O-H | 1062.49 | 1232.98 | ---- |

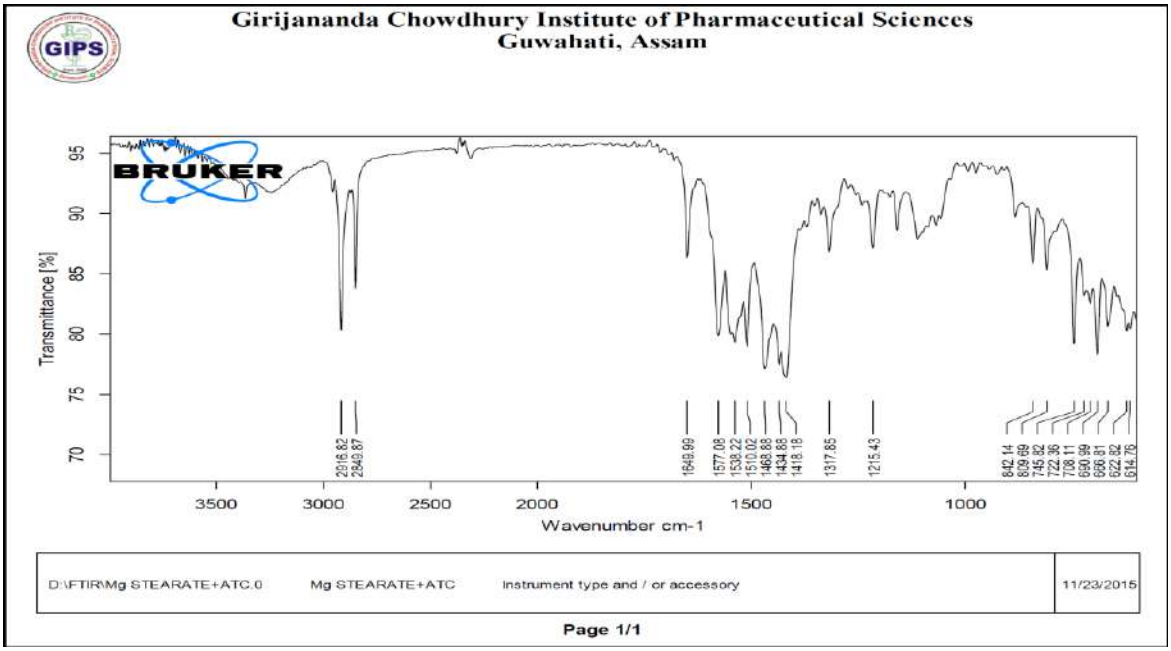


***Fig: 6.2.3.1. IR Spectrum of the mixture of Atorvastatin Calcium and Magnesium Stearate***

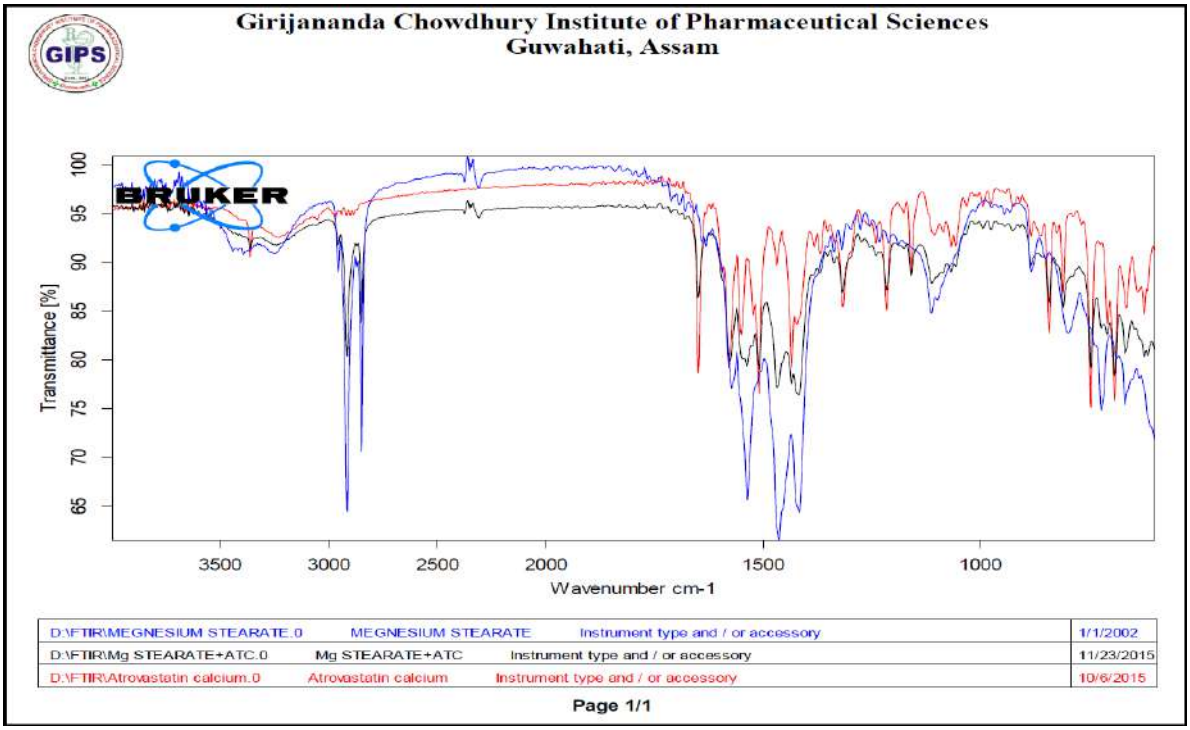


***Fig: 6.2.3.2. IR spectrum of the drug, Magnesium stearate, mixture of drug and Magnesium stearate.***

***Table: 6.2.4.IR interpretation of drug, Croscarmellose and physical mixture of drug-Croscarmellose sodium***

| **Sl No** | **Interpretation** | **IR absorption bands (cm-1)** | | |
|---|---|---|---|---|
| | | **Drug** | **Croscarmellose sodium** | **Drug+ Croscarmellose sodium** |
| 1 | C-H (Aromatic) | ---- | ---- | ---- |
| 2 | C-H | ---- | ---- | ---- |
| 3 | S=O | 1215.61 | 1211.99 | 1215.43 |
| 4 | C-O | 1317.14 | 1319.38 | 1317.85 |
| 5 | C=N | 1649.11 | 1633.02 | 1649.99 |
| 6 | C-N | 1242.05 | 1112.96 | ---- |
| 7 | C-C | 830.22 | 841.94 | 842.14 |
| 8 | N-H | 3363.08 | 1573.35 | 1577.08 |
| 9 | O-H | 1062.49 | 1232.98 | ---- |

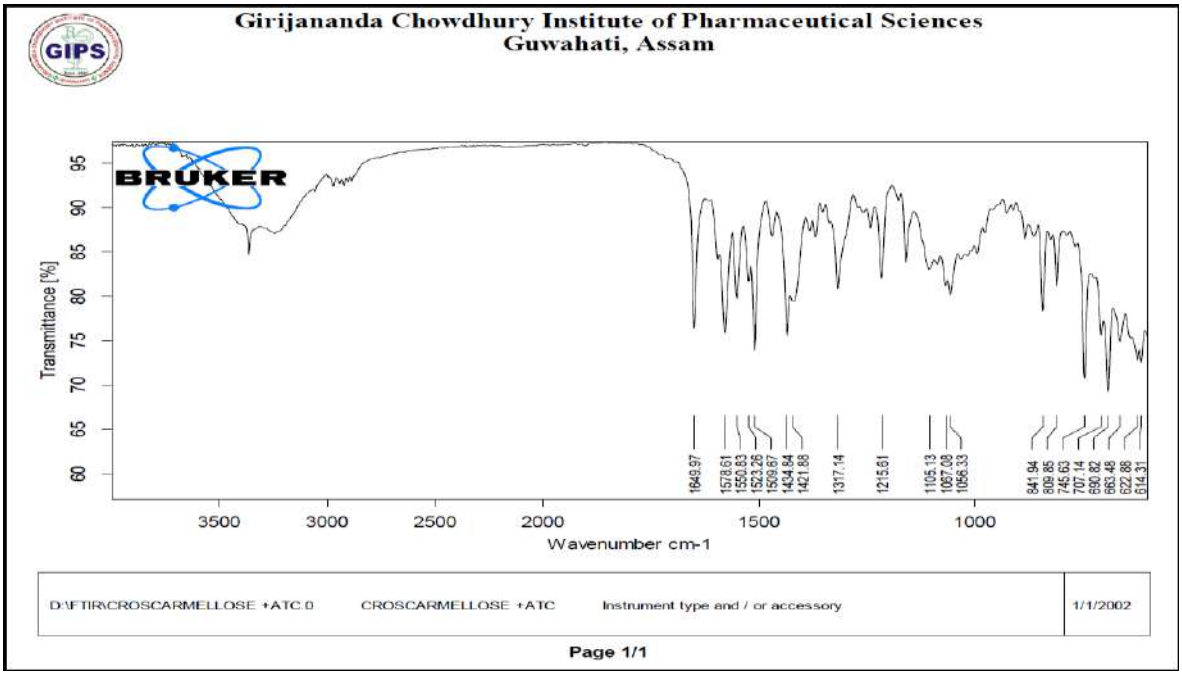


*Fig: 6.2.4.1. IR spectrum of the mixture of drug and Croscarmellose sodium*

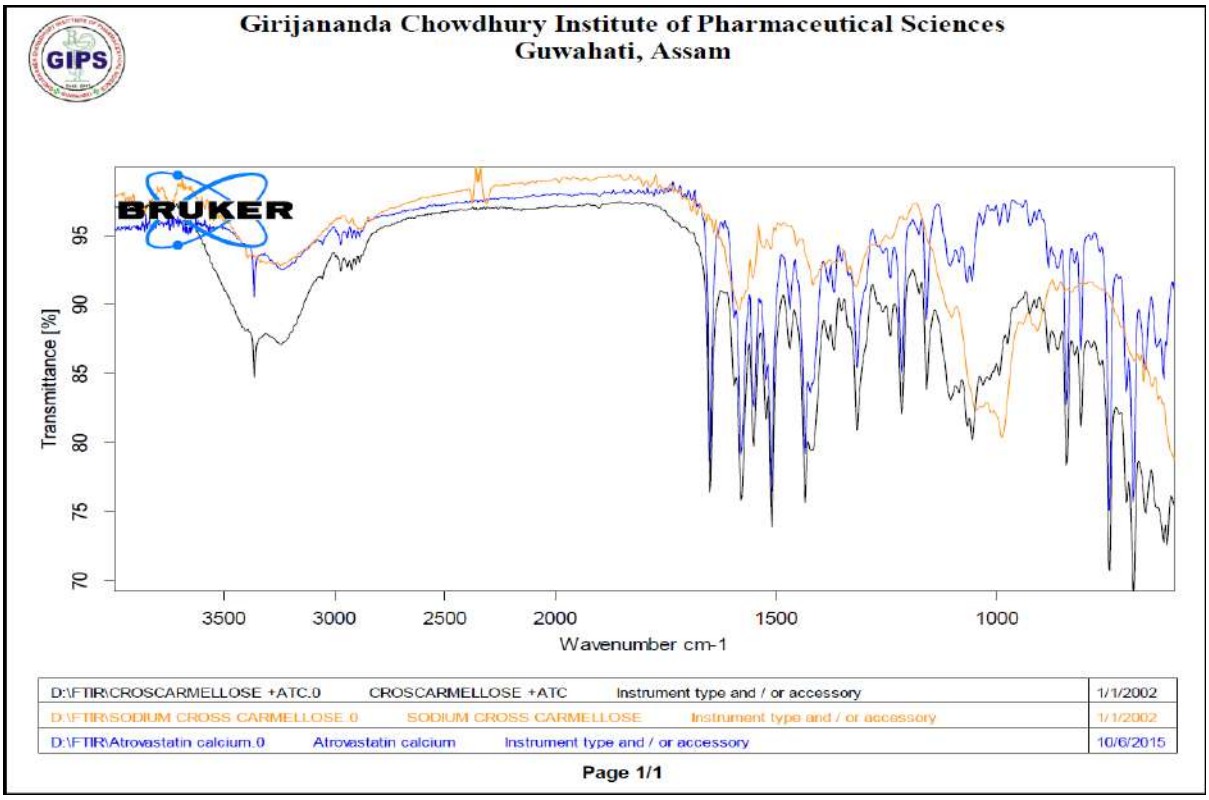


*Fig: 6.2.4.2. IR spectrum of the drug, Croscarmellose sodium, mixture of drug and Croscarmellose sodium.*

***Table: 6.2.5.IR interpretation of drug, EudragitL100 and physical mixture of drug-EudragitL100***

| **Sl No** | **Interpretation** | **IR absorption bands (cm-1)** | | |
|---|---|---|---|---|
| | | **Drug** | **EudragitL100** | **Drug+ EudragitL100** |
| 1 | C-H(Aromatic) | ---- | 2991.20 | 2948.49 |
| 2 | C-H | ---- | 2991.20 | 2991.20 |
| 3 | S=O | 1216.17 | 1211.99 | 1215.43 |
| 4 | C-O | 1388.41 | 1319.38 | 1317.85 |
| 5 | C=N | 1649.11 | 1633.02 | 1649.99 |
| 6 | C-N | 1242.05 | 1156.24 | ---- |
| 7 | C-C | 837.80 | 883.16 | 842.14 |
| 8 | N-H | 3471.06 | 1573.35 | 1577.08 |
| 9 | O-H | 1062.49 | 1232.98 | 1253.29 |

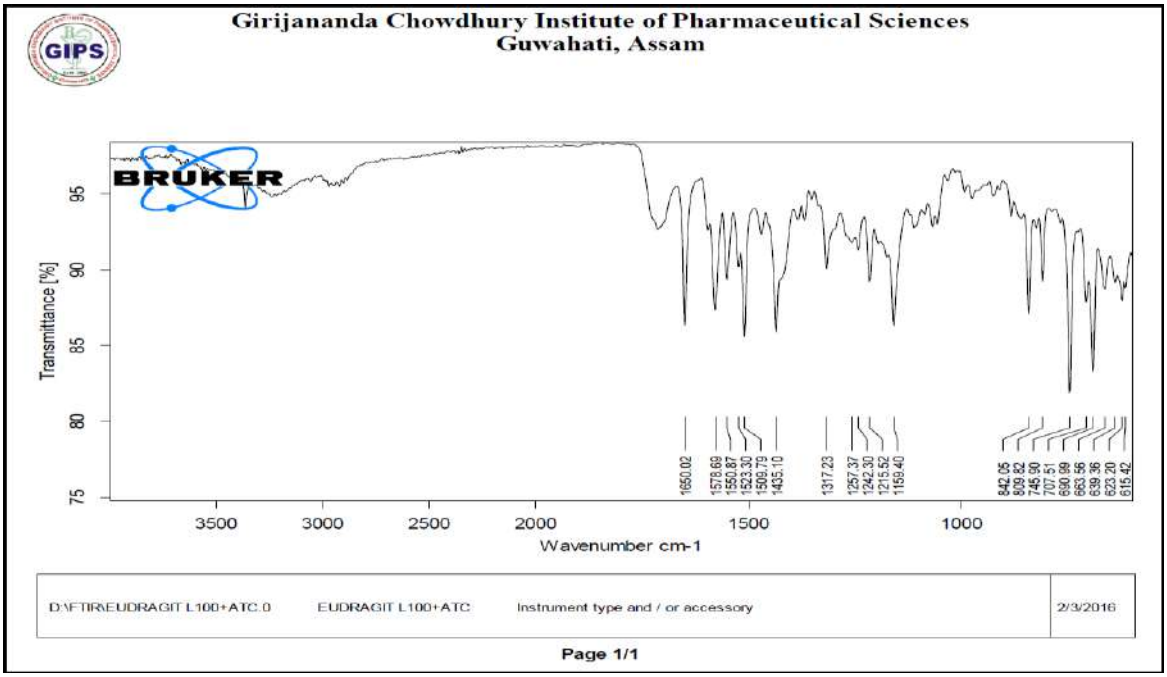


***Fig: 6.2.5.1. IR spectrum of the mixture of drug and EudragitL100.***

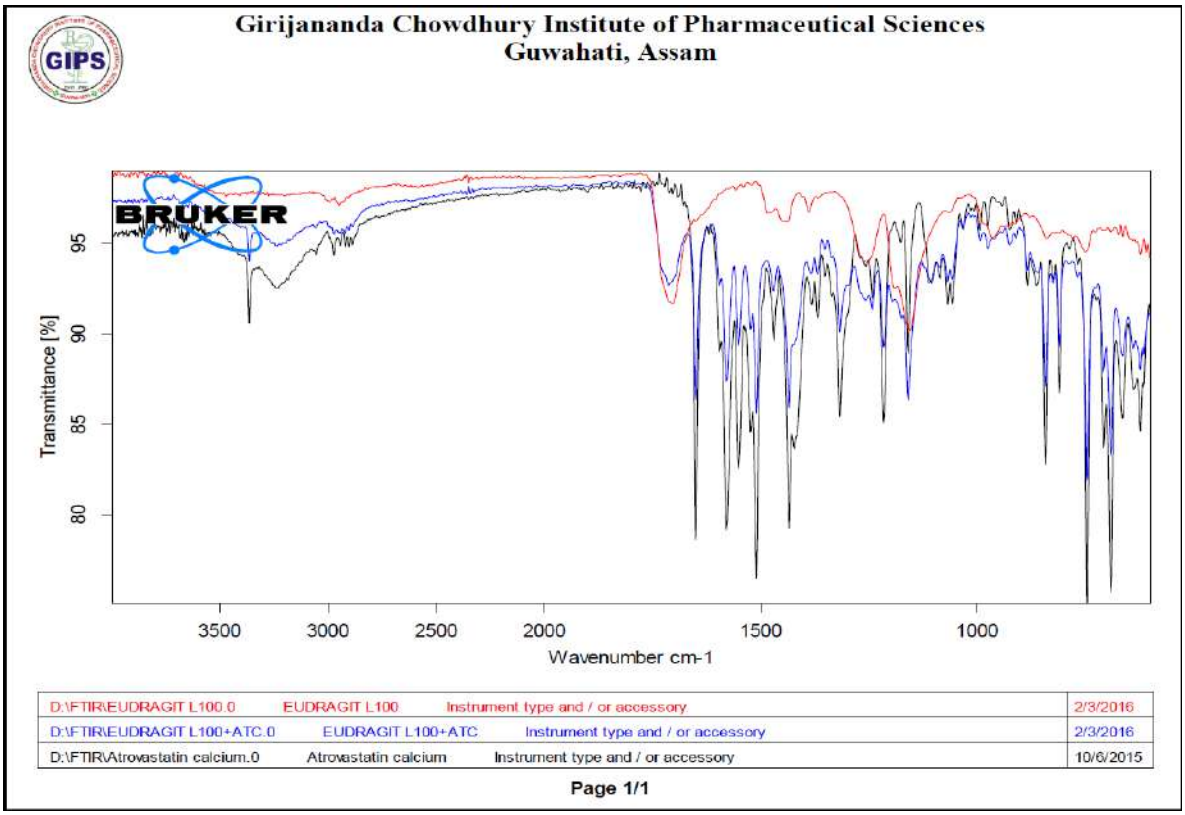


***Fig: 6.2.5.2. IR spectrum of the drug, EudragitL100 , mixture of drug and EudragitL100.***

***Table: 6.2.6.IR interpretation of drug, HPMCK4M and physical mixture of drug-HPMCK4M***

| **Sl No** | **Interpretation** | **IR absorption bands (cm-1)** | | |
|---|---|---|---|---|
| | | **Drug** | **HPMCK4M** | **Drug+ HPMCK4M** |
| 1 | C-H(Aromatic) | ---- | 2882.48 | 2836.01 |
| 2 | C-H | ---- | 2865.09 | 2916.96 |
| 3 | S=O | ---- | 1215.59 | 1215.43 |
| 4 | C-O | 1317.32 | 1319.38 | 1314.88 |
| 5 | C=N | 1650.49 | 1677.43 | 1669.03 |
| 6 | C-N | 1242.05 | 1112.96 | ---- |
| 7 | C-C | 810.27 | 883.16 | 842.14 |
| 8 | N-H | 3363.08 | 1573.35 | 1577.08 |
| 9 | O-H | 1032.56 | 1218.52 | 1215.61 |

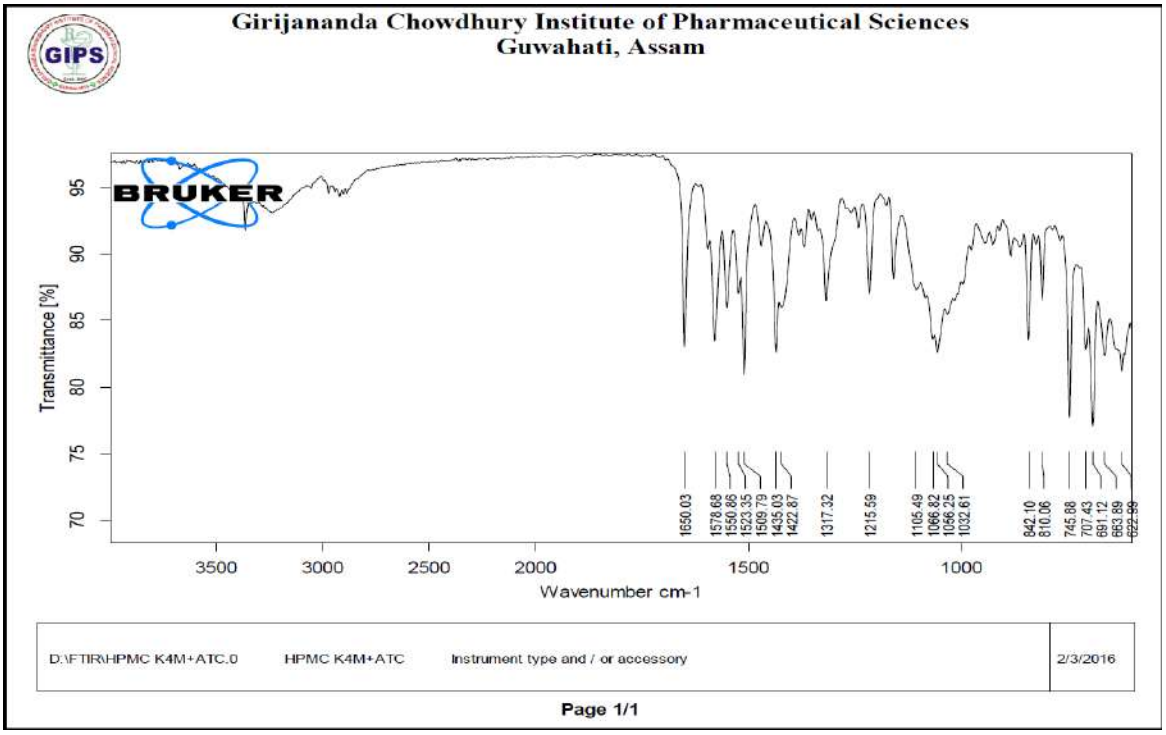


*Fig: 6.2.6.1. IR spectrum of the mixture of drug and HPMCK4M.*

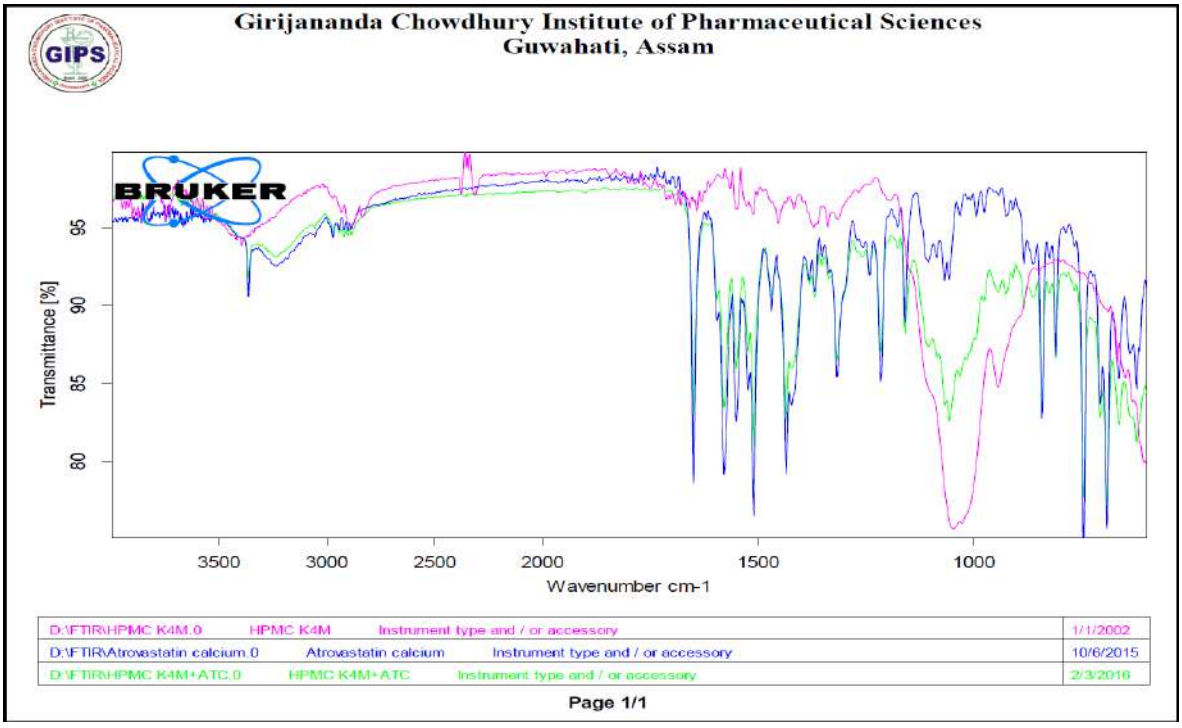


*Fig: 6.2.6.2. IR spectrum of the drug, HPMCK4M , mixture of drug and HPMCK4M.*

***Table: 6.2.7. IR interpretation of drug, Sodium starch glycolate and physical mixture of drug- Sodium starch glycolate***

| **Sl No** | **Interpretation** | **IR absorption bands (cm-1)** | | |
|---|---|---|---|---|
| | | **Drug** | **Sodium starch glycolate** | **Drug+ Sodium starch glycolate** |
| 1 | C-H(Aromatic) | ---- | 2918.83 | 2922.76 |
| 2 | C-H | ---- | 2851.77 | 2836.45 |
| 3 | S=O | 1217.76 | 1211.23 | 1215.72 |
| 4 | C-O | 1313.78 | 1366.87 | 1355.43 |
| 5 | C=N | 1675.59 | 1632.09 | 1649.67 |
| 6 | C-N | 1267.05 | 12.56 | ---- |
| 7 | C-C | 823.66 | 876.54 | 842.14 |
| 8 | N-H | 3363.08 | 1573.35 | 1577.08 |
| 9 | O-H | 1052.49 | 1272.98 | ---- |

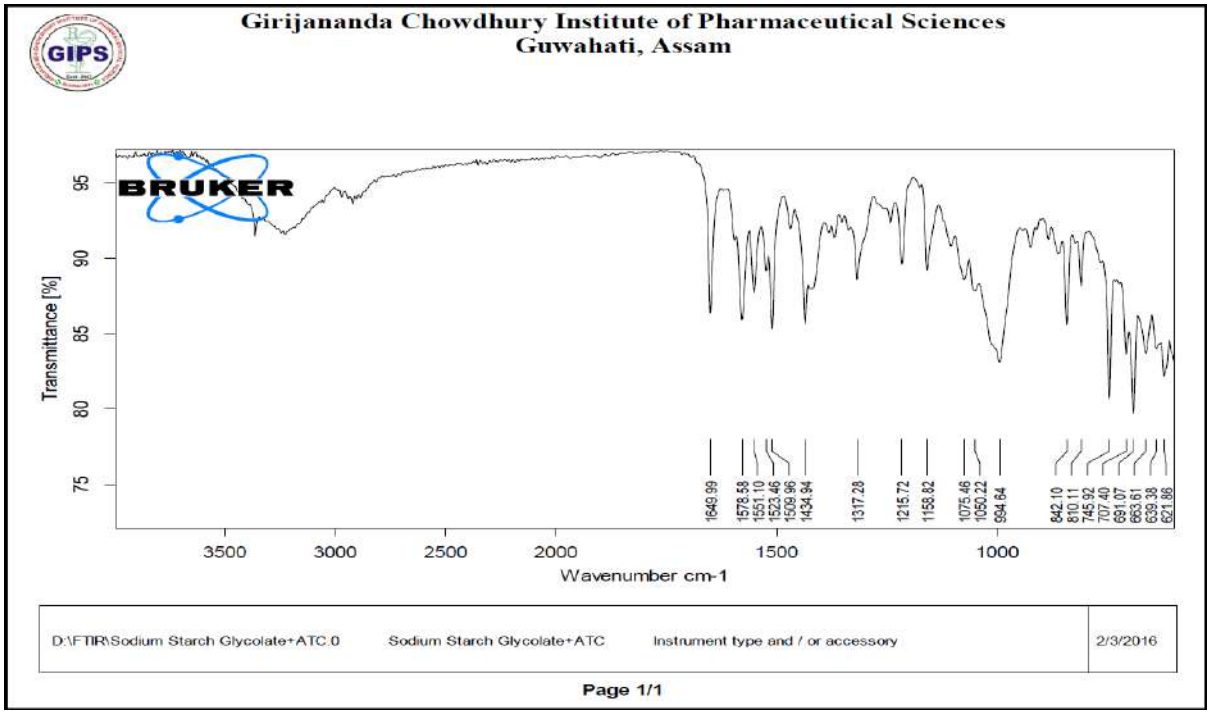


*Fig: 6.2.7.1. IR spectrum of the mixture of drug and Sodium starch glycolate.*

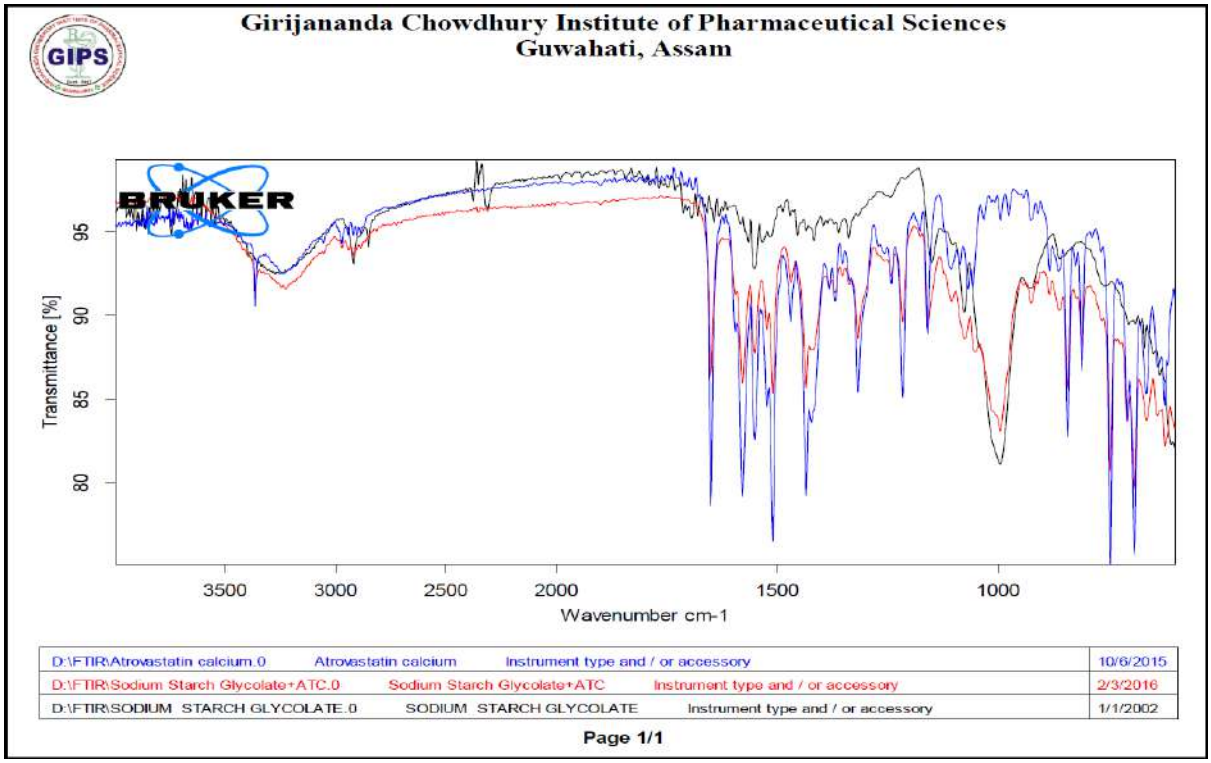


***Fig: 6.2.7.2. IR spectrum of the drug, Sodium starch glycolate, mixture of drug and Sodium starch glycolate.***

***Table: 6.2.8. IR interpretation of drug, PVPK30 and physical mixture of drug- PVPK30***

| Sl No | Interpretation | IR absorption bands (cm-1) | | |
|---|---|---|---|---|
| | | Drug | Pvpk30 | Drug+ pvpk30 |
| 1 | C-H(Aromatic) | ---- | 2950.50 | 2965.98 |
| 2 | C-H | ---- | 2947.67 | 2844.23 |
| 3 | S=O | 1217.19 | 1251.90 | 1215.43 |
| 4 | C-O | 1372.12 | 1339.38 | 1317.85 |
| 5 | C=N | 1649.16 | 1633.02 | 1649.99 |
| 6 | C-N | 1251.90 | 1122.75 | ---- |
| 7 | C-C | 840.95 | 867.56 | 8834.98 |
| 8 | N-H | 3393.08 | 1533.35 | 1577.08 |
| 9 | O-H | 1092.49 | 1232.98 | ---- |

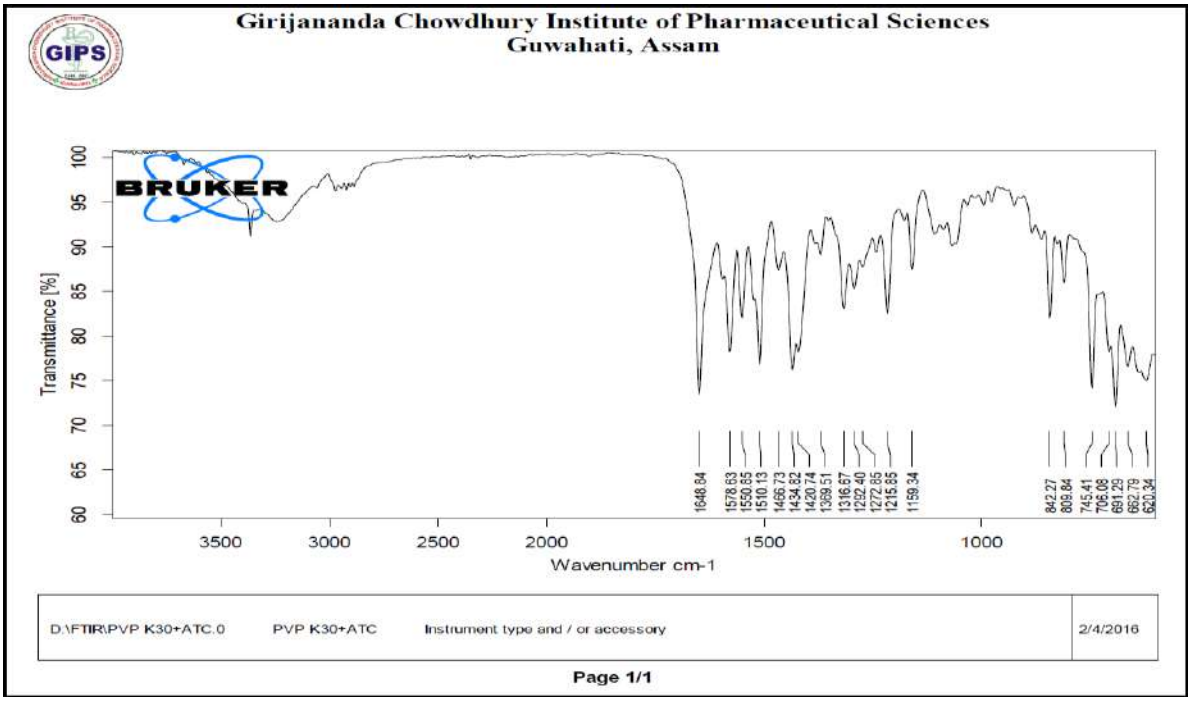


***Fig: 6.2.8.1. IR spectrum of the mixture of drug and pvpk30.***

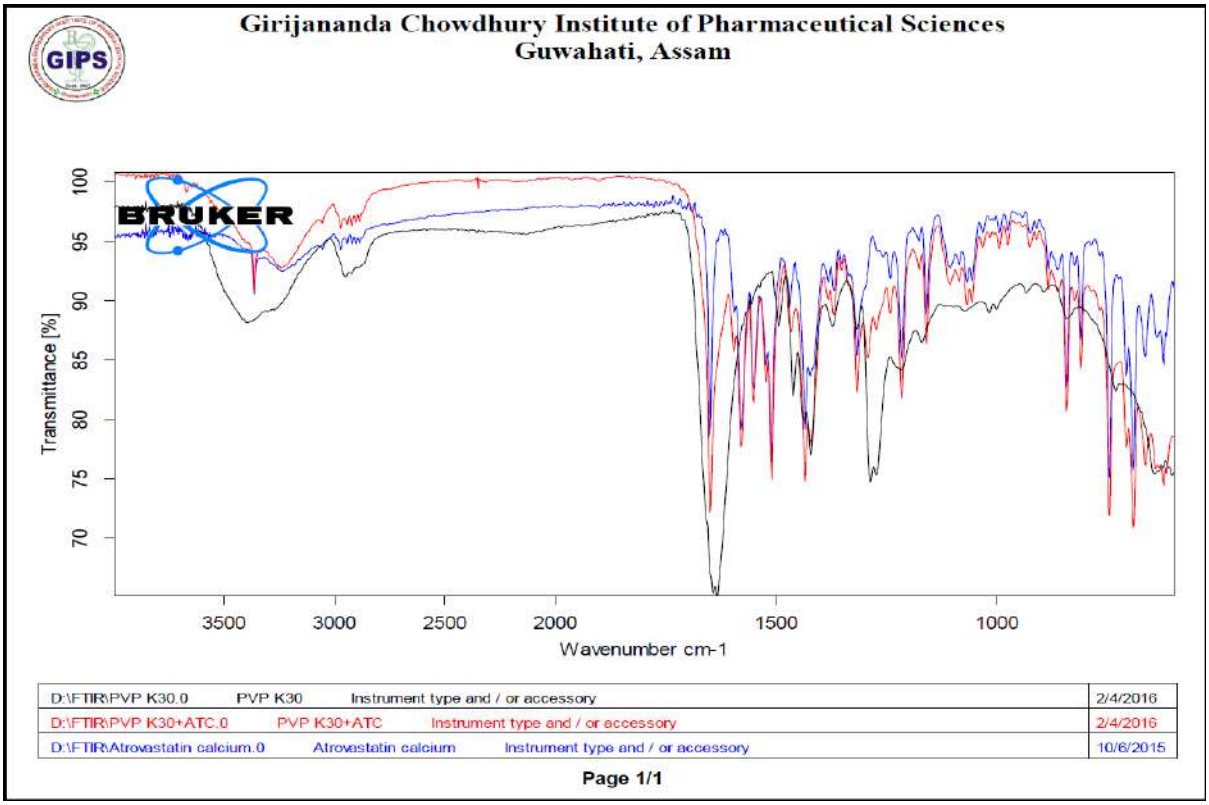


***Fig: 6.2.8.2. IR spectrum of the drug, PVPK30, mixture of drug and PVPK30.***

### *6.3. DSC study:*

*DSC studies of the pure drug and excipient were carried out to determine if there was any interaction between the drug and the excipient. The thermo gram of pure Atrovastatin Calcium shows a sharp endothermic peak at 153°C. The melting temperature, T* onset, *is defined by the extrapolated beginning of the curve, being defined by the point of intersection of the tangent with the point of maximum slope, on the principal side of the peak with the base line extrapolated.*

***Table 1 Thermoanalytical data of DSC of Atorvastatin calcium and excipients***

| Sample | $T_{onset}$ (fusion)/$^{o}$C | $T_{peak}$ (fusion)/$^{o}$C | ΔHfusion/J g-1 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Atorvastatin Calcium (Drug) | 134.46 | 153.05 | 74.0427 |
| Lactose | 209.70 | 216.08 | 142.28 |
| Magnesium Stereate | 92.09 | 107.08 | 149.15 |
| Stearic Acid | 56.14 | 62.01 | 187.17 |
| Microcrystalline cellulose | 328.56 | 347.61 | 44.3379 |
| Crospovidone | 49.34 | 89.39 | 344.49 |
| Sodium Starch Glycolate | 50.11 | 79.34 | 74.40 |
| Cross Carmellose Sodium | 47.65 | 86.62 | 322.27 |
| HPMC K4M | 49.64 | 74.35 | 109.80 |
| Eudragit L100 | 207.84 | 235.01 | 73.37 |

***Table 2: Thermoanalytical data of DSC of drug-excipient physical mixtures***

| Drug+Excipients | $T_{onset}$ (fusion)/$^{o}$C | $T_{peak}$ (fusion)/$^{o}$C | ΔHfusion/J g-1 |
|---|---|---|---|
| Drug + Lactose | 202.33 | 207.01 | 58.8503 |
| Drug + Magnesium Stereate | 102.15 | 114.25 | 890.862 |
| Drug + Stearic Acid | 55.65 | 61.36 | 149.75 |
| Drug +Microcrystalline cellulose | 200.30 | 236.96 | 58.7159 |
| Drug + Crospovidone | 49.34 | 89.39 | 344.49 |
| Drug + Sodium Starch Glycolate | 50.11 | 79.34 | 74.40 |
| Drug + Cross Carmellose Sodium | 47.65 | 86.62 | 322.27 |
| Drug + HPMC K4M | 49.64 | 74.35 | 109.80 |
| Drug + Eudragit L100 | 207.84 | 235.01 | 73.37 |

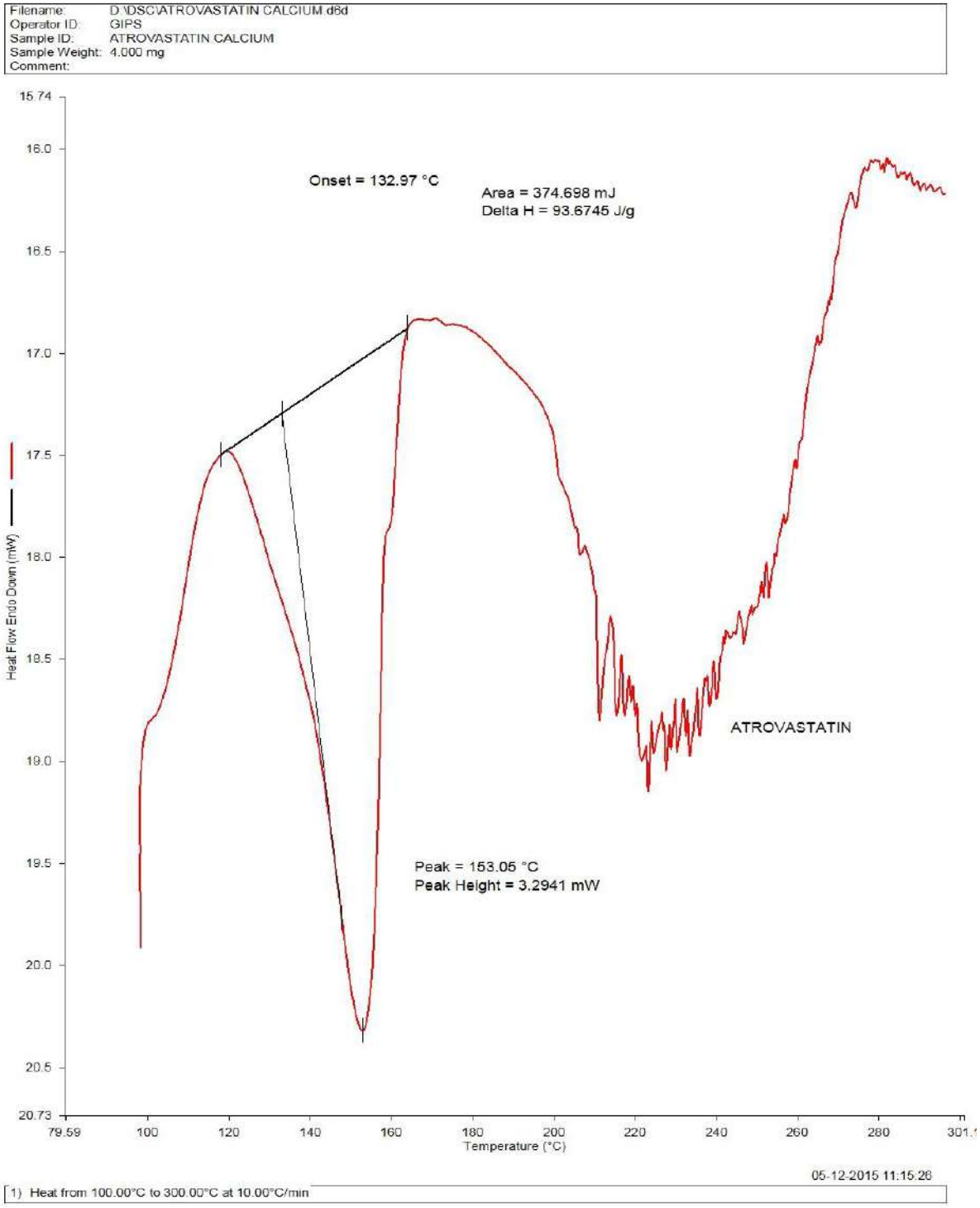


***Fig: 6.3.1. DSC thermogram of Atorvastatin Calcium***

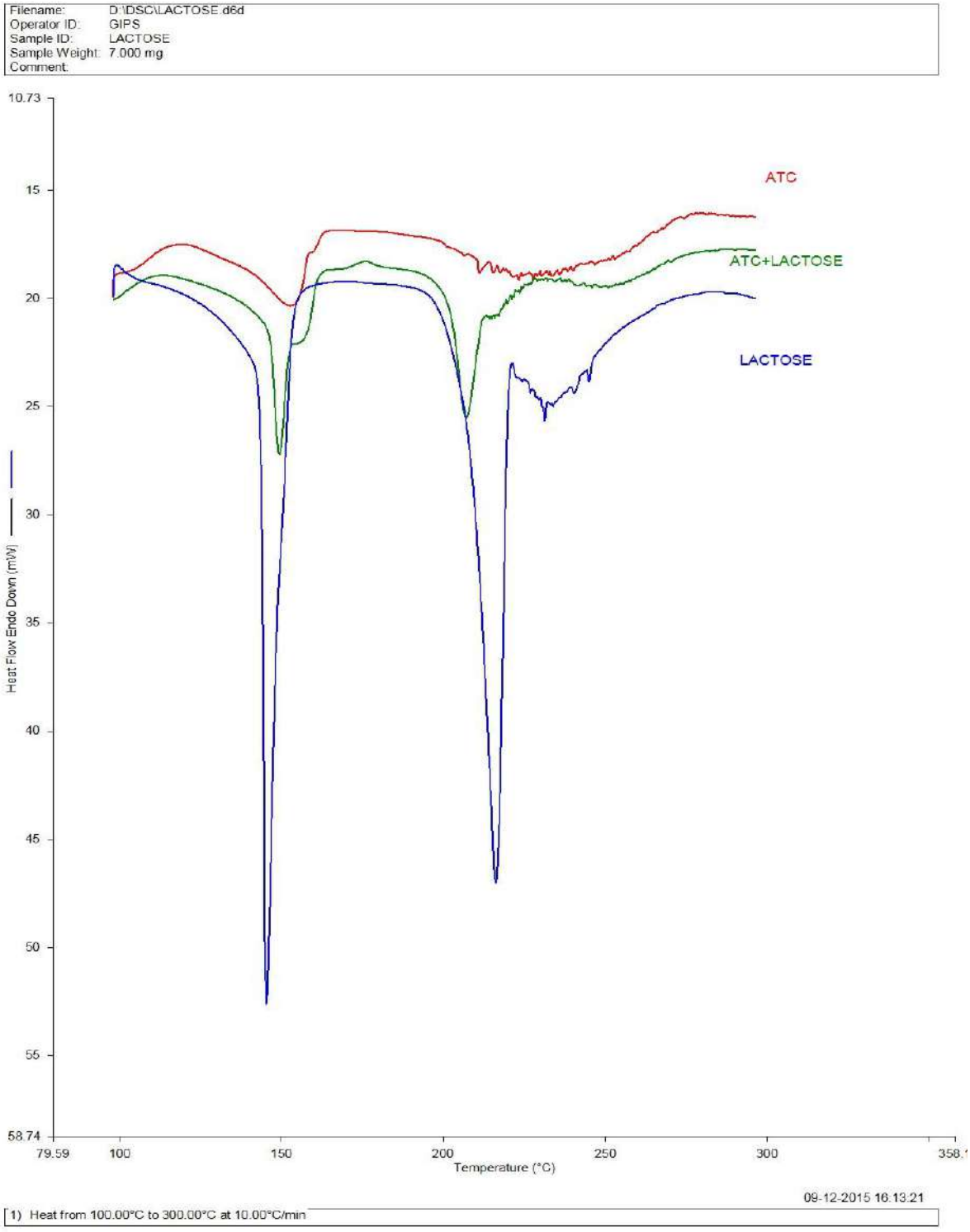


***Fig: 6.3.2. DSC thermo gram of the drug, Lactose and Mixture of drug and Lactose.***

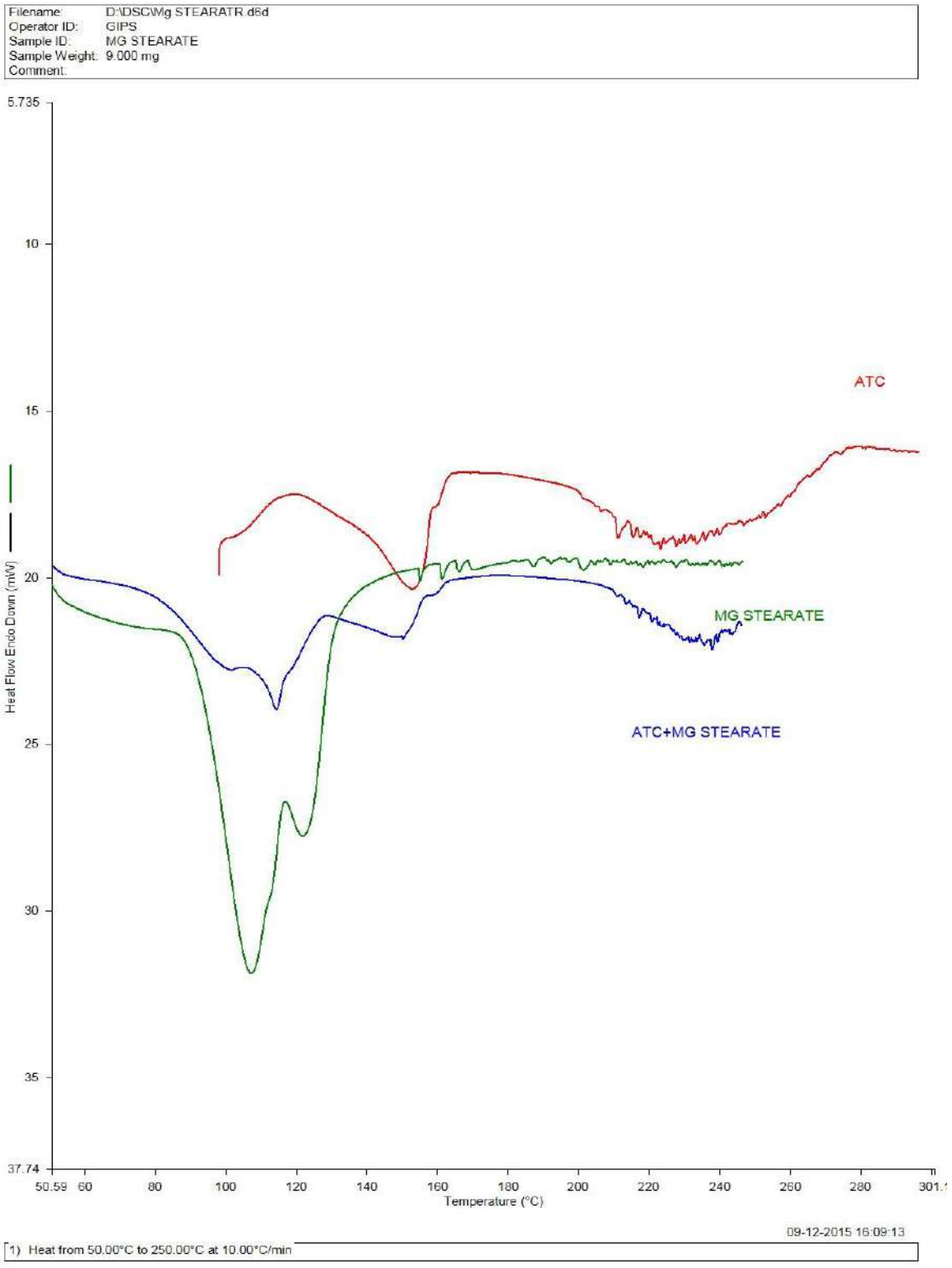


***Fig: 6.3.3. DSC thermo gram of the drug, Magnesium Stearate and Mixture of drug and Magnesium Stearate.***

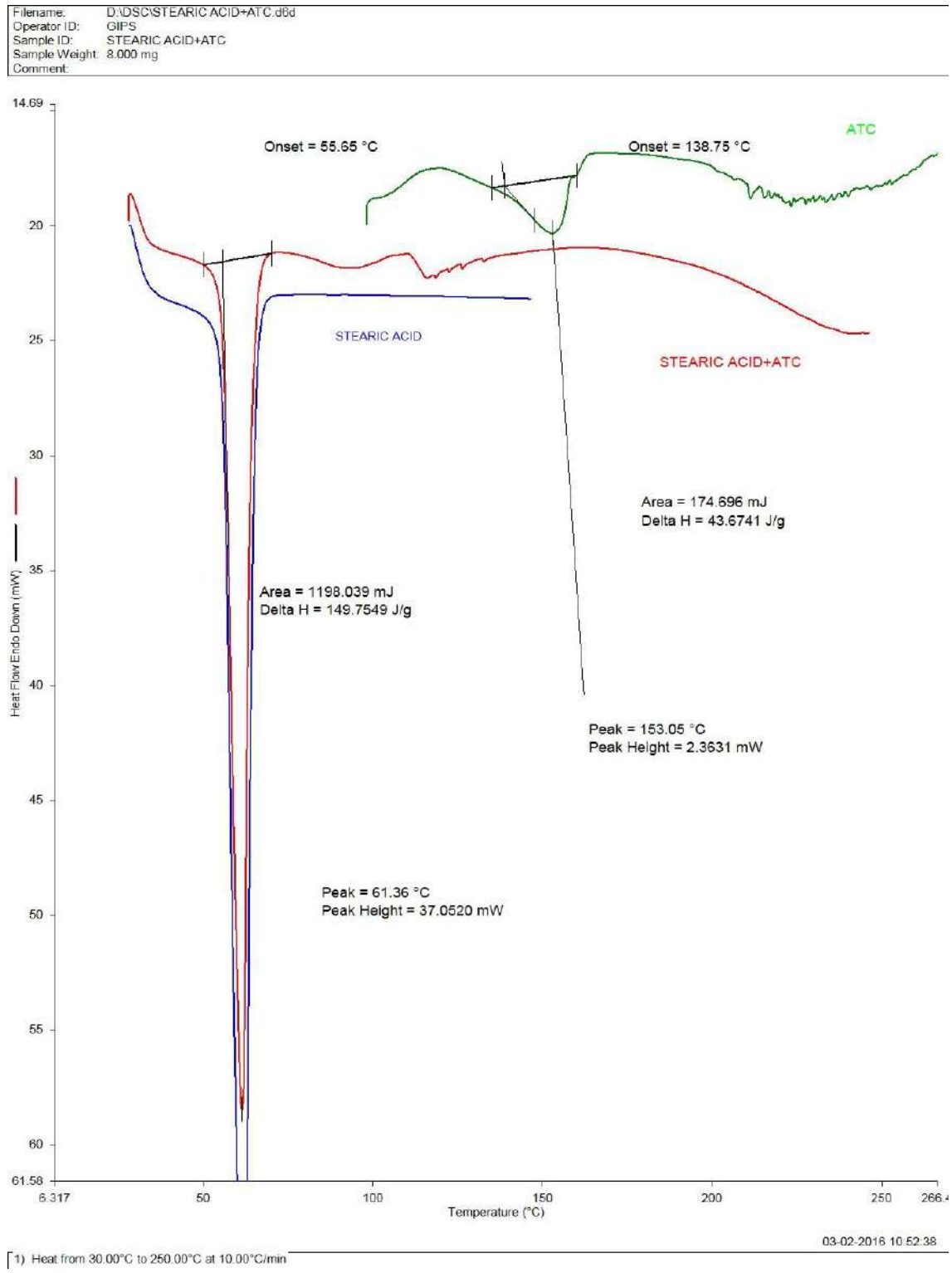


***Fig: 6.3.4. DSC thermo gram of the drug, Stearic acid and Mixture of drug and Stearic acid.***

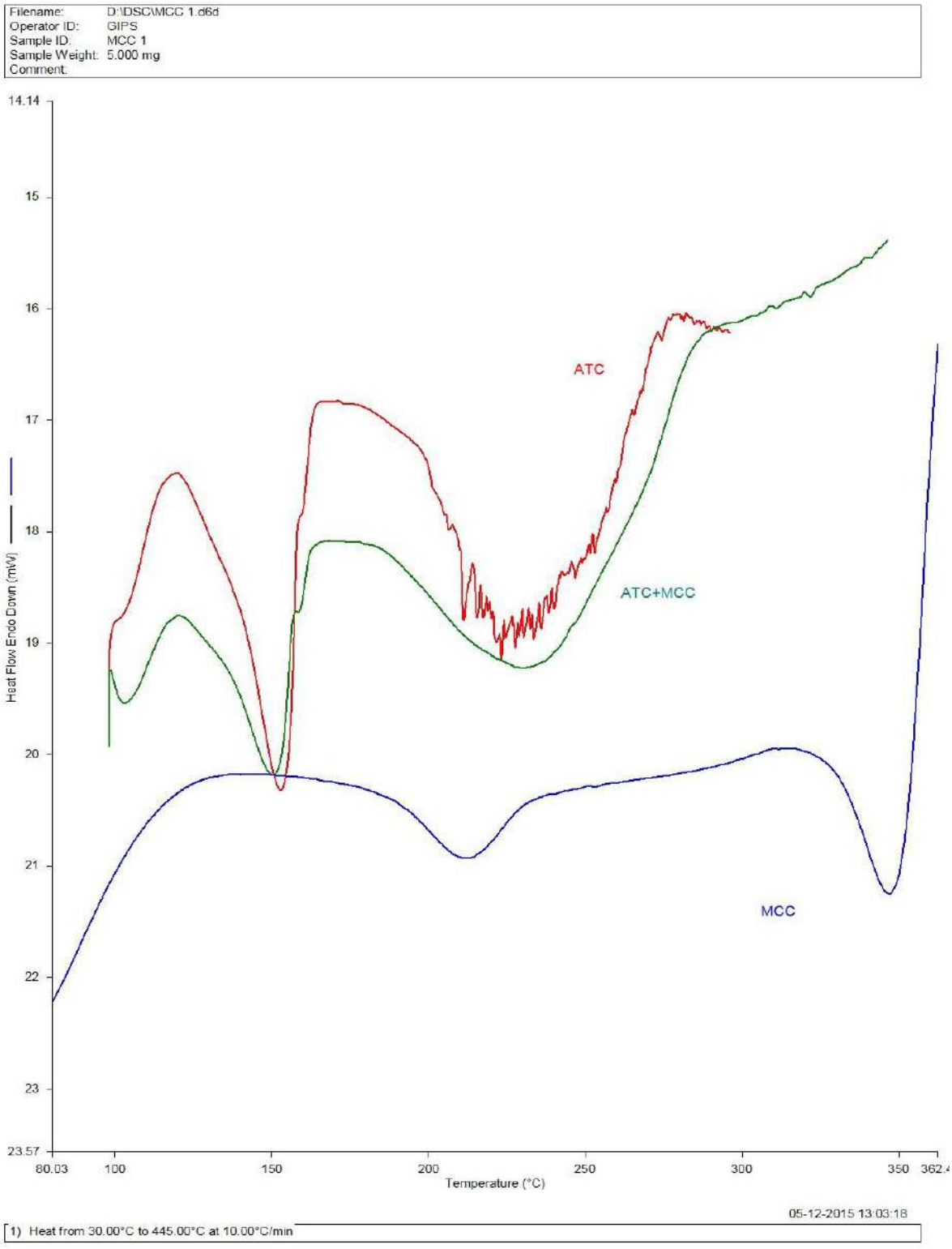


***Fig: 6.3.5. DSC thermo gram of the drug, Microcrystalline cellulose and Mixture of drug and Microcrystalline cellulose.***

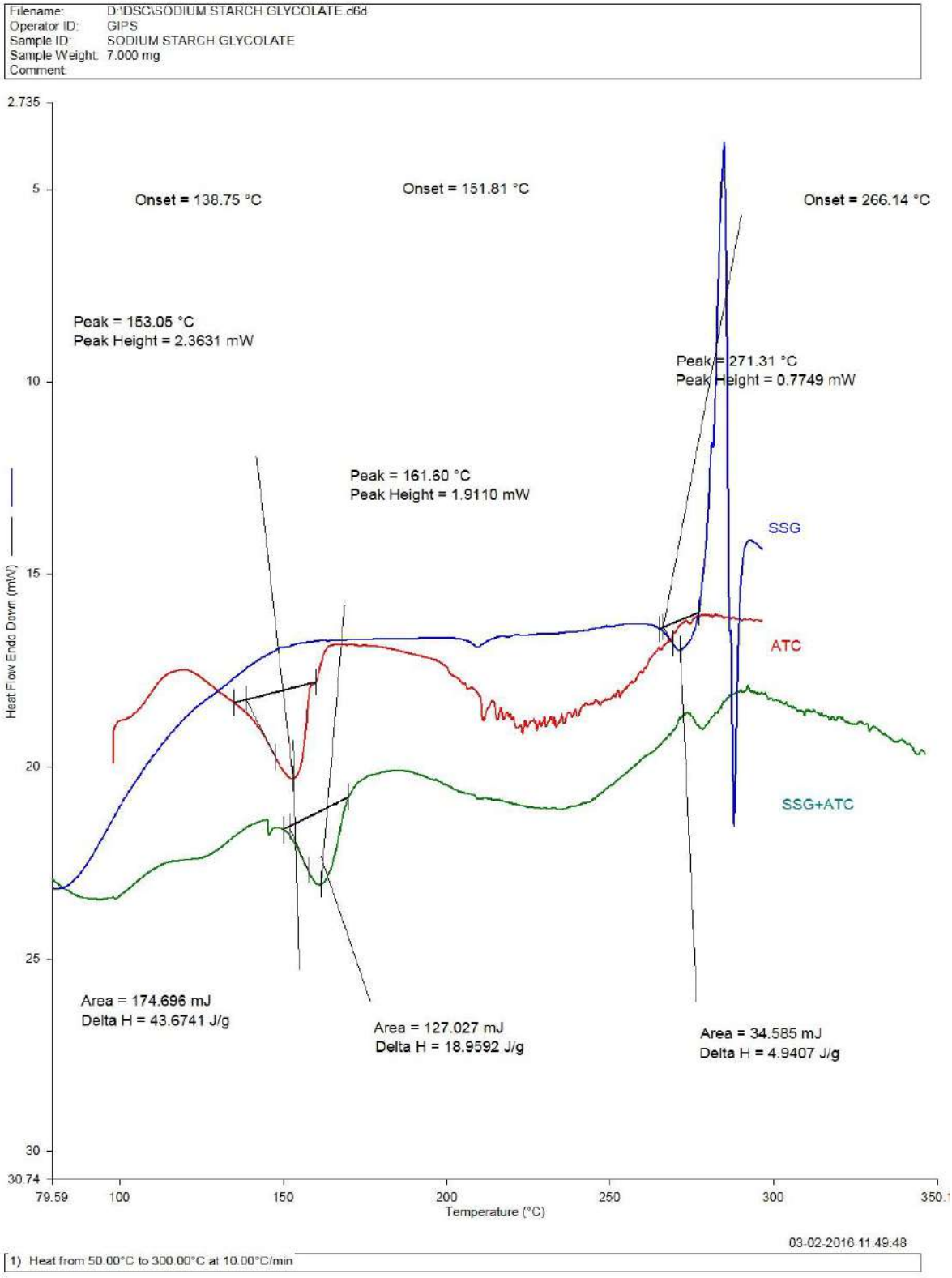


***Fig: 6.3.6. DSC thermo gram of the drug, Sodium starch glycolate and Mixture of drug and Sodium starch glycolate***

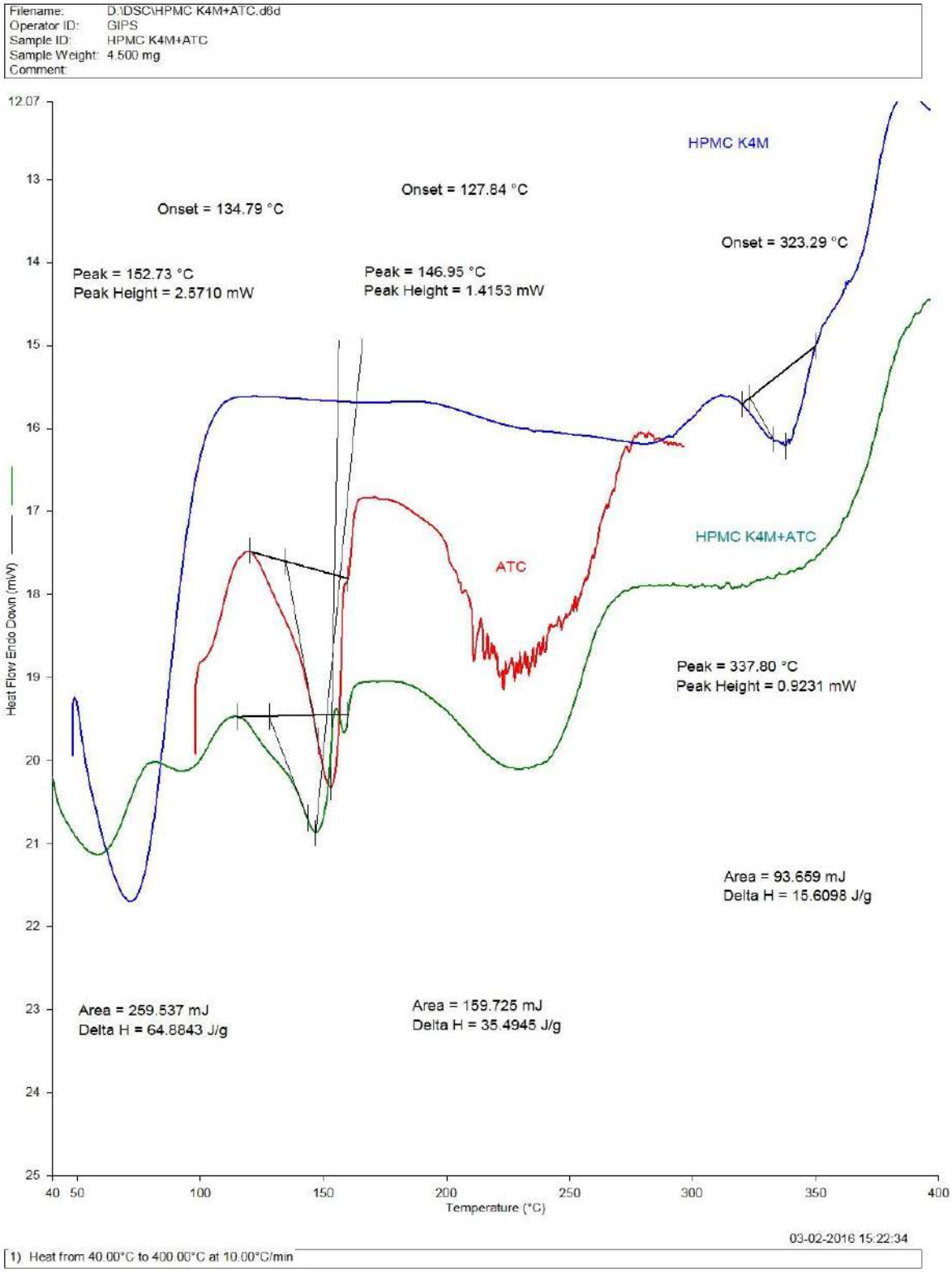


***Fig: 6.3.7. DSC thermo gram of the drug, HPMCK4M and Mixture of drug and HPMCK4M***

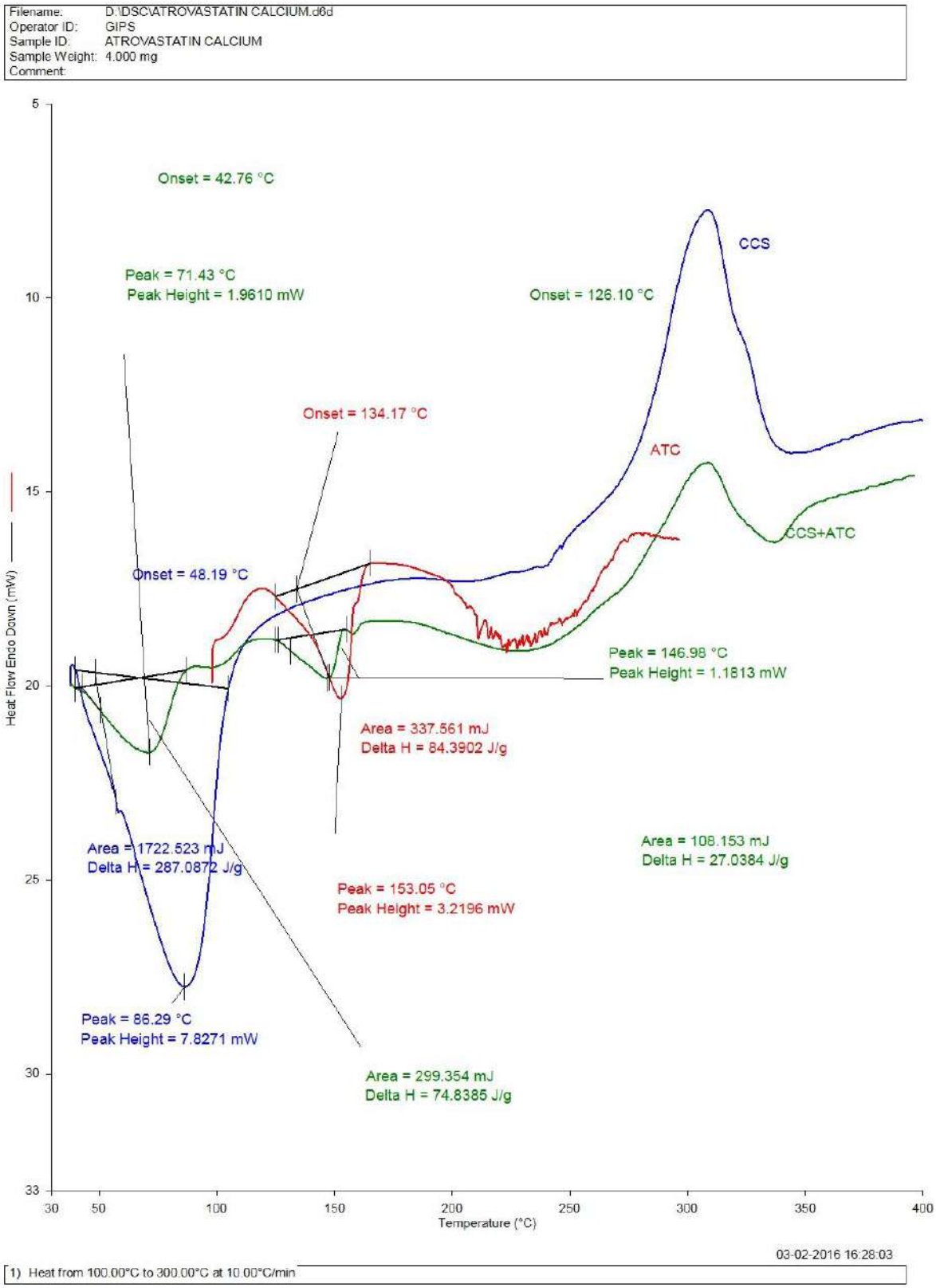


***Fig: 6.3.8. DSC thermo gram of the drug, Croscarmellose Sodium and Mixture of drug and Croscarmellose Sodium***

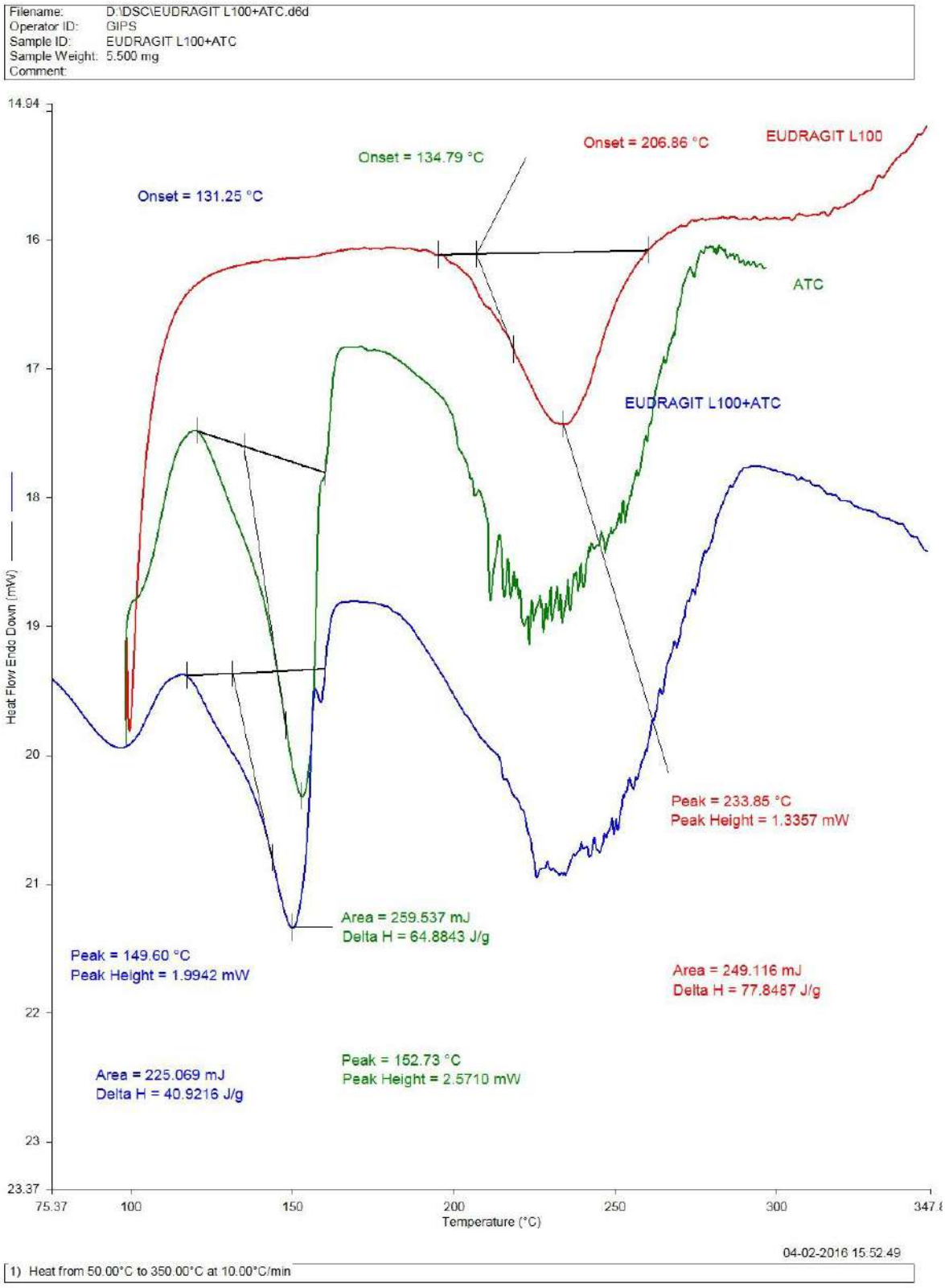


***Fig: 6.3.9. DSC thermo gram of the drug, EudragitL100 and Mixture of drug and EudragitL100***

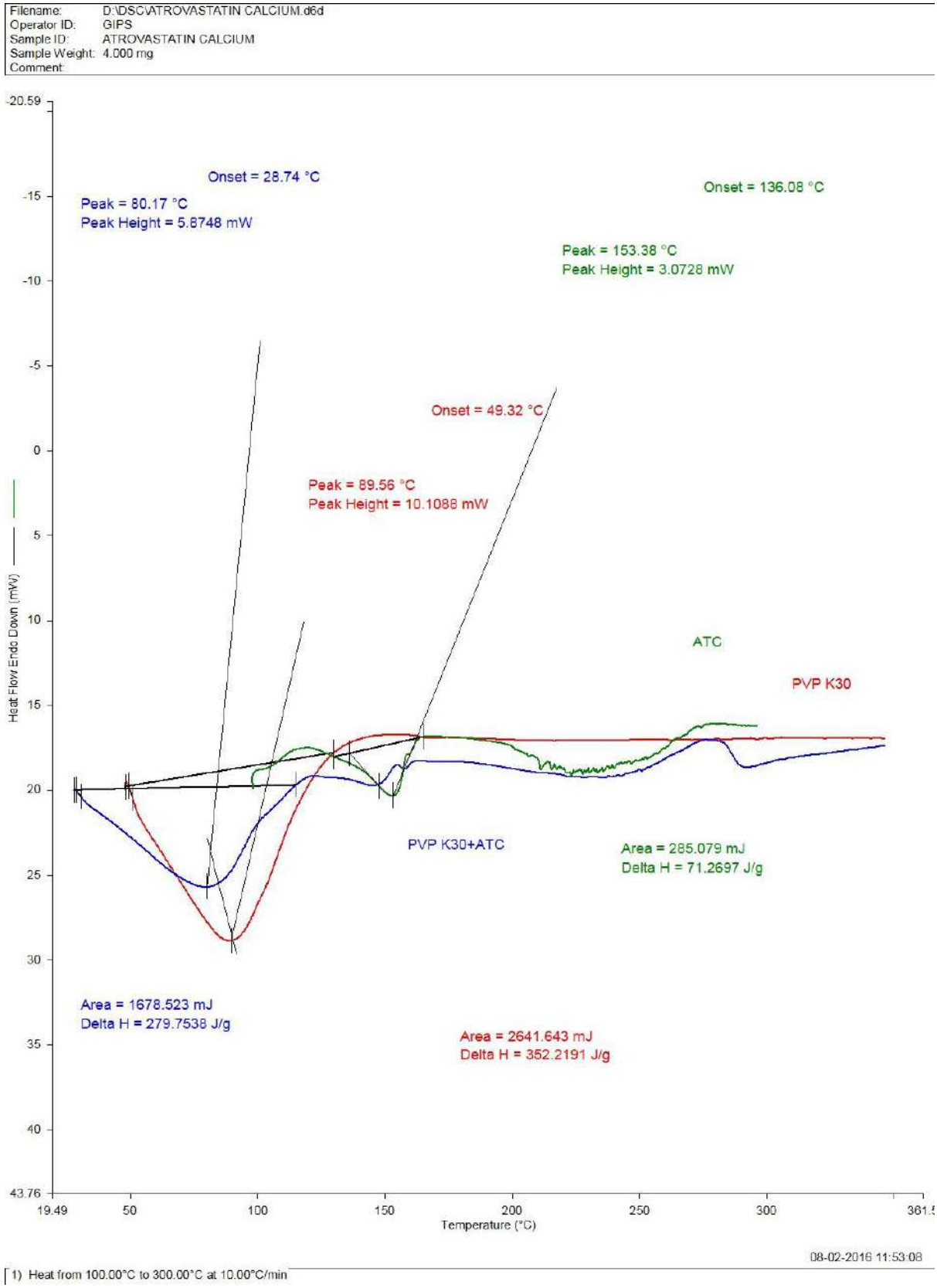


***Fig: 6.3.10. DSC thermo gram of the drug, pvpk30 and Mixture of drug and pvpk30***

### *6.3.11 Thermal characterization of ATV*

*DSC curve of ATV shows an endothermic event whose melting $T_{onset}$ was 153.05 °C and Tpeak was 132.97 °C (ΔH 93.674 J g-1). Then another endothermic event is observed which can be attributed to a phase transition characteristic of this polymorph with the following decomposition there of around 190-250 ° C. The melting peak of ATV according to Zhang (2009) happened to 158.8°C and enthalpy of 86.85 J $g^{-1}$[51]. The melting peak of atorvastatin when disappeared, or decreased in intensity in drug-excipient binary mixtures, it was confirmed to be physical interaction. DSC curve of atorvastatin+lactose shows only the characteristic endothermic peaks of lactose. According to the literature[51], lactose melting at 144 °C prior to the melting of ATV which promotes the solubility of ATV into the lactose and subsequent disappearance of the peak temperature of ATV. Therefore, there is no interaction with lactose. DSC curve of ATV+mannitol cause the disappearance of the melting peak characteristic of ATV or appearance of only peak of the excipient. Thus, it suggests interactions which may be physical or chemical. This was further reconfirmed by FT-IR studies. From the DSC studies, the excipients such as microcrystalline cellulose, magnesium stearate, mannitol, sodium lauryl sulfate were found to have physical interactions with ATV.*

### *6.4 UV analysis of drug:*

***6.4.1. Preparation of standard calibration curve:***

*Standard calibration curve for the drug Atrovastatin Calcium were done separately in water, pH 1.2 acidic buffers and pH (6.8, 7.4) phosphate buffer. Tables 6.6. to 6.8 show the concentrations of pantoprazole sodium sesquihydrate in pH 1.2 acidic and pH (6.8, 7.4) phosphate buffers and the respective absorbance. The Figures 6.6 to 6.8 shows the calibration curves of Atrovastatin Calcium in pH 1.2 acidic buffers and pH (6.8, 7.4) phosphate buffer respectively.*

***6.4.2. Spectrophotometric data for standard calibration curve of Atorvastatin Calcium in distilled water:***

| Sl no | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.0276 |
| 3 | 4 | 0.0393 |
| 4 | 6 | 0.0707 |
| 5 | 8 | 0.0891 |
| 6 | 10 | 0.1454 |
| 7 | 12 | 0.1765 |

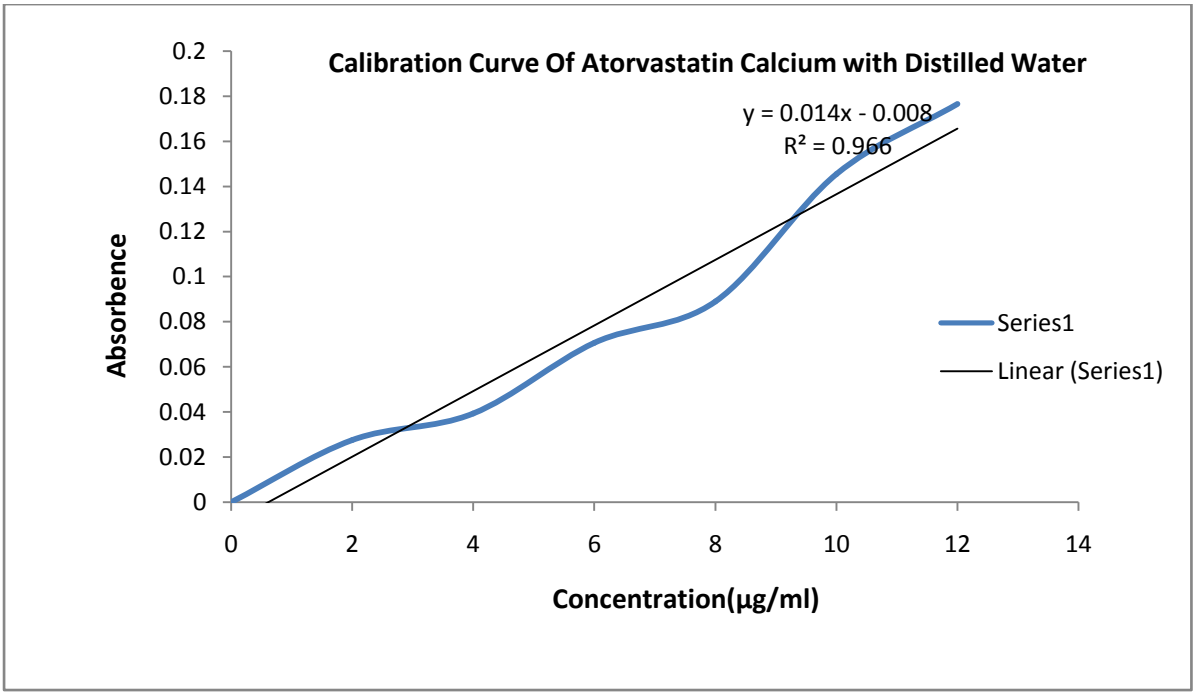


*Fig: 6.4.3. Standard calibration curve of Atorvastatin Calcium in water.*

### *6.4.4. Preparation of standard calibration curve in 0.1M HCL (pH 1.2)*

| Sl No | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.0422 |
| 3 | 4 | 0.0765 |
| 4 | 6 | 0.0973 |
| 5 | 8 | 0.1344 |
| 6 | 10 | 0.1856 |
| 7 | 12 | 0.2458 |

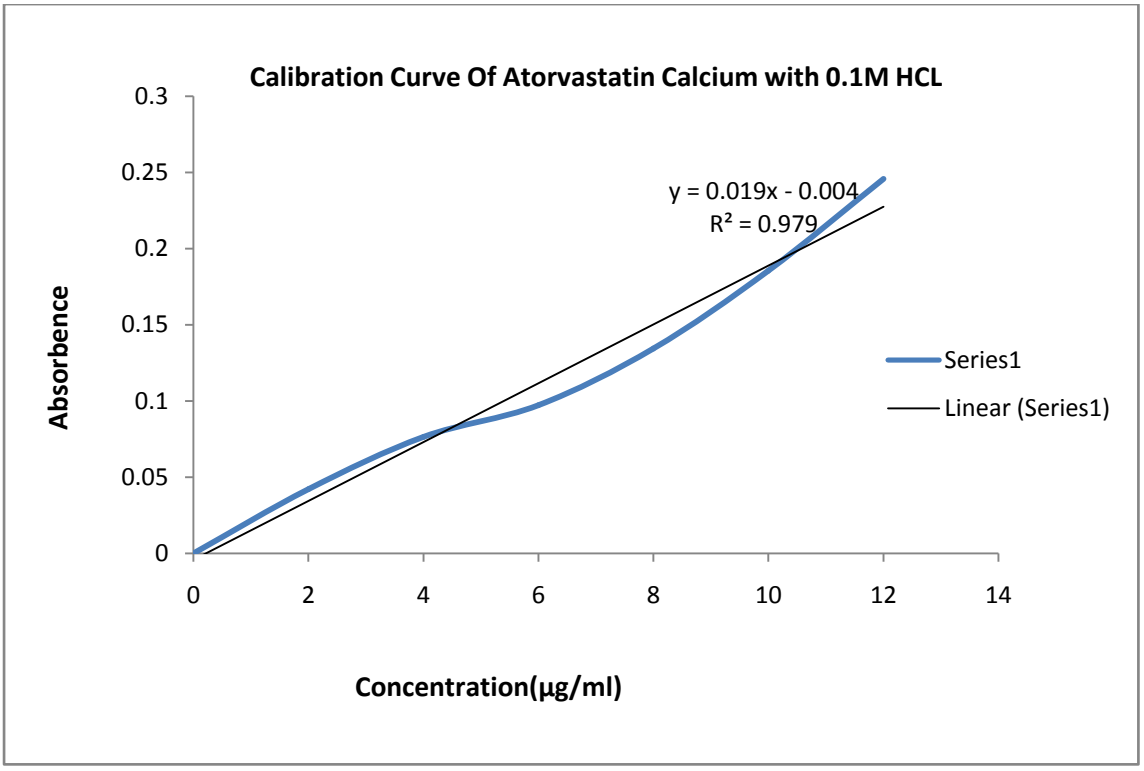


*Fig: 6.4.5 Standard calibration curve of Atorvastatin Calcium in 0.1 M HCL.*

***6.4.6. Preparation of standard calibration curve of Atorvastatin Calcium in phosphate buffer pH= 6.8***

| Sl no | Concentration(µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.0248 |
| 3 | 4 | 0.0643 |
| 4 | 6 | 0.0969 |
| 5 | 8 | 0.1178 |
| 6 | 10 | 0.1449 |

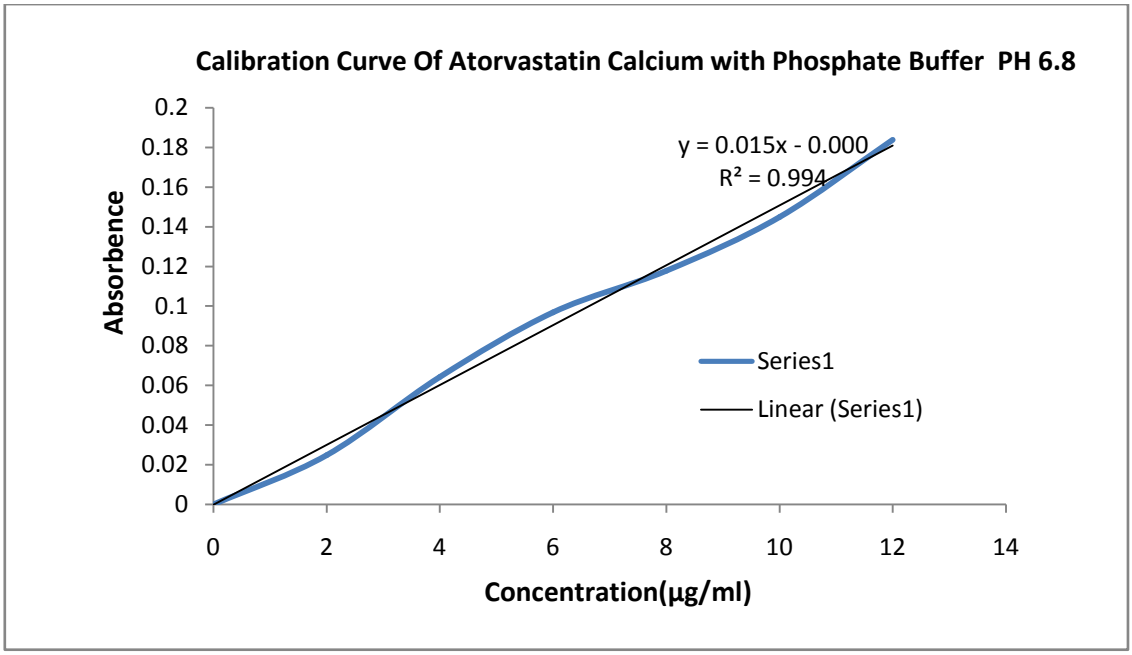


*Fig: 6.4.7. Standard curve of Atorvastatin Calcium in phosphate buffer pH 6.8*

***6.4.8. Preparation of standard calibration curve of Atorvastatin Calcium in phosphate buffer pH =7.4***

| Sl No | Concentration(µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.1367 |
| 3 | 4 | 0.1876 |
| 4 | 6 | 0.2478 |
| 5 | 8 | 0.2936 |
| 6 | 10 | 0.3367 |
| 7 | 12 | 0.3829 |

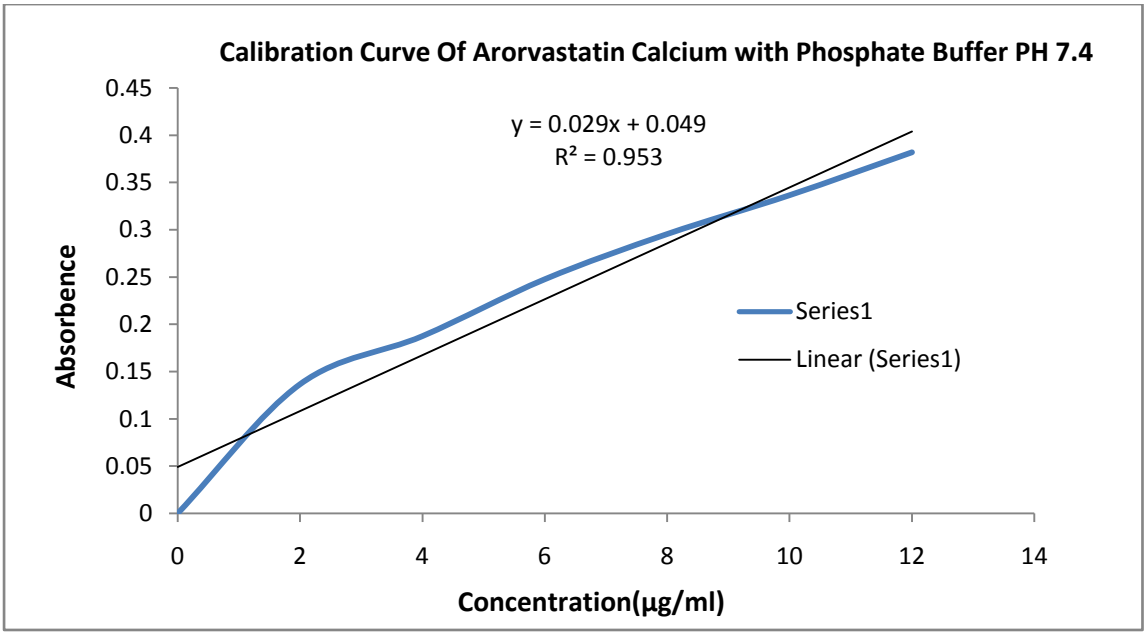


***Fig: 6.4.9 Standard curve of Atorvastatin Calcium in phosphate buffer pH 7.4***

### *6.4.10. Saturation solubility:*

*The saturation solubility of the drug sample was determined in various solvent like water, 0.1M HCL, phosphate buffer pH6.8 and phosphate buffer pH7.4 found to be 70.05 mg/ml, 35.9 mg/ml, 51.2mg/ml and 48.8 mg/ml.*

***Table: 6.3.11 Saturation solubility data***

| Sl no | Solvent used | Absorbance | Saturation solubility(mg/ml) |
|---|---|---|---|
| 1 | Water | 0.1882 | 70.05 |
| 2 | 0.1M HCL pH 1.2 | 0.1325 | 35.9 |
| 3 | Phosphate buffer pH 6.8 | 0.1537 | 51.2 |
| 4 | Phosphate buffer pH 7.4 | 0.3321 | 48.8 |

### *6.5.1Evaluation of pre-compression properties :*

*Immediate release tablet of ATV were successfully prepared by direct compression method using superdisintgrant like croscarmellose soudium and varying the grades of microcrystalline cellulose, as per formulation table* ***(Table no. 1)****. The directly compressible powder blend was evaluated for parameters like bulk density, tapped density, compressibility index, and angle of repose, Hausner ratio as shown in* ***Table 2****. The bulk density of the powder was in the range of 0.33 to 0.52 gm/ml; the tapped density was in the range of 0.47 to 0.67gm/ml, which indicates that the powder was not bulky. The angle of repose of the formulations with lactose in larger quantity was in the range of 21º to 25º, which indicated good flow of the powder. The Carr's index was found to be in the range of 22 to 30 indicating moderate to fairer compressibility of the tablet blend. The Hausner ratio lays in the range 0.758 to 0.814 confirming good flow characteristics for direct compression tablets.*

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atorvastatin Calcium | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 | 20.70 |
| Sodium Starch Glycollate | ---- | ---- | ---- | 4 | 6 | 8 | ---- | ---- | ---- | ---- | 8 | 8 |
| Cross Carmellose Sodium | 4 | 6 | 8 | ---- | ---- | ---- | ---- | ---- | ---- | 8 | 8 | ---- |
| Cross Povidone | ---- | ---- | ---- | ---- | ---- | ---- | 4 | 6 | 8 | 8 | ---- | 8 |
| Sodium Lauryl Sulphate | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Anhydrous Lactose | 110.8 | 108.8 | 106.8 | 110.8 | 108.8 | 106.8 | 110.8 | 108.8 | 106.8 | 98.8 | 98.8 | 98.8 |
| Saccharin sodium | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Stearic Acid | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

***Table 1: Composition of various batches of atorvastatin Immidiate release tablets***

***Table. 2. Physical properties of directly compressible powder blend***

| ***Formulation Code*** | **Angle of Repose (degree)◦** | ***Tapped Density (g/cm$^3$)*** | ***Bulk Density (gm/cm$^3$)*** | ***Hausner ratio*** | ***Compressi-bility Index (%)*** |
|---|---|---|---|---|---|
| *F-1* | *21.88±1.10* | *0.435±1.21* | *0.543±0.06* | *0.801±0.21* | *24.82±0.02* |
| *F-2* | *23.76±0.05* | *0.414±1.12* | *0.546±0.04* | *0.758±0.18* | *31.88v0.05* |
| *F-3* | *24.32±0.21* | *0.455±1.24* | *0.567±1.09* | *0.802±0.10* | *24.61±0.02* |
| *F-4* | *22.66±0.24* | *0.476±1.11* | *0.597±0.07* | *0.797±0.08* | *25.42±0.06* |
| *F-5* | *23.98±0.31* | *0.422±1.30* | *0.518±0.03* | *0.814±0.09* | *22.74±0.01* |
| *F-6* | *24.12±0.08* | *0.458±1.18* | *0.562±0.08* | *0.814±1.10* | *22.70±0.04* |
| *F-7* | *23.50±0.18* | *0.436±1.10* | *0.564±1.10* | *0.773±1.05* | *29.35±0.06* |
| *F-8* | *23.61±0.14* | *0.421±1.07* | *0.548±1.13* | *0.768±1.07* | *30.16±0.02* |
| *F-9* | *25.34±0.11* | *0.431±1.03* | *0.553±1.14* | *0.779±1.10* | *28.30±0.08* |
| *F-10* | *24.78±0.07* | *0.464±1.12* | *0.578±0.09* | *0.802±1.02* | *24.56±0.03* |
| *F-11* | *24.08±0.15* | *0.430±1.04* | *0.558±0.06* | *0.770±0.91* | *28.57±0.05* |
| *F-12* | *25.30±0.13* | *0.453±1.21* | *0.578±1.10* | *0.783±0.88* | *27.59±0.06* |

***6.5.2. Evaluation of post-compression properties:***

*All the batches of tablets (F1-F12) were evaluated for various post compression properties such as hardness, thickness,friability, weight variation, content uniformity as shown in* ***Table 3****. The tablets were compressed at the average weight of 150 mg. The weight variation of all batches in the ranges of 147±0.34 to 154±0.34 mg. The pharmacopoeial limit for percent deviation in weight variation for 100 mg tablet is ±7.5%. The average percent deviation for all tablets was found to be within the limit and hence it passes the weight variation test. The tablets thickness was 3.5±0.03 to 3.8±0.03 mm. The tablets hardness was 3.5±0.15 to 4.1±0.13 kg/cm$^2$.*

***Table 3. Physical properties of various batches of immediate release tablets***

| Batch Code | Thickness (mm) | Hardness ($kg/cm^2$) | Friability (%) | Weight Variation (mg) | Drug Content (%) | DT(sec) |
|---|---|---|---|---|---|---|
| F1 | 3.5±0.03 | 3.5±0.15 | 0.68±0.23 | 148±0.45 | 98.67±0.05 | 45±0.04 |
| F2 | 3.8±0.06 | 3.4±0.16 | 0.57±0.28 | 147±0.34 | 96.54±0.03 | 40±0.06 |
| F3 | 3.6±0.04 | 3.5±0.13 | 0.54±0.31 | 151±0.08 | 98.45±0.02 | 35±0.03 |
| F4 | 3.5±0.02 | 3.6±0.16 | 0.72±0.38 | 150±0.25 | 96.08±0.04 | 34±0.01 |
| F5 | 3.8±0.05 | 3.8±0.12 | 0.64±0.21 | 148±0.56 | 97.32±0.03 | 30±0.06 |
| F6 | 3.5±0.05 | 4.0±0.10 | 0.52±0.25 | 149±0.65 | 96.54±0.04 | 28±0.03 |
| F7 | 3.8±0.02 | 4.1±0.13 | 0.54±0.28 | 152±0.60 | 97.81±0.06 | 46±0.02 |
| F8 | 3.7±0.04 | 4.2±0.08 | 0.65±0.18 | 154±0.34 | 98.74±0.03 | 41±0.06 |
| F9 | 3.8±0.05 | 4.0±0.12 | 0.63±0.11 | 151±0.71 | 95.56±0.07 | 38±0.02 |
| F10 | 3.8±0.03 | 3.6±0.13 | 0.69±0.24 | 153±.46 | 96.71±0.03 | 28±0.10 |
| F11 | 3.6±0.05 | 3.5±0.08 | 0.75±0.21 | 148±.05 | 98.10±0.02 | 24±0.19 |
| F12 | 3.8±0.03 | 3.8±0.10 | 0.72±0.16 | 150±0.90 | 96.72±0.05 | 34±0.12 |

***6.6. In-vitro drug release behavior of prepared tablets***

*The in-vitro dissolution profiles of all formulations are depicted in* ***Figure 6.6 (a), (b), (c) and (d).*** *Release a data revealed that formulation F1, F2 and F3 released 72.3%, 74.37%*

*and 76.50% drug respectively within 20 minutes. Formulation F4, F5 and F6 released 71.2%, 73.37% and 74.7% drug respectively within 20 minutes. Formulation F7, F8 and F9 released 67.17%, 69.30% and 71.21% drug respectively within 20 minutes. Results also reveals that the batches F10, F11 and F12 released 72.4%, 82.7% , 77.8% and 72.4% of drug within 20 minutes demonstrating the immediate release pattern. Among all the formulations F3 containing cross carmellose sodium, F6 containing sodium starch glycollate and F12 containing 1:1 ratio of CCS:SSG, F11 containing 1:1 ratio of CCS: cross povidone have shown increased drug release in 20 minutes as compared to CP. Formulation F11have shown the disintegration time less than 25 sec and better dissolution than all other formulations. Hence, formulation F11 is considered to be the best formulation among the other formulations containing mixture of two super disintegrants.*

***Table 4: In-vitro drug release profile of various batches of tablets***

| Time (Min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | MKT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 42.6 | 49.8 | 54.2 | 41.5 | 43.2 | 46.7 | 49.7 | 52.4 | 54.6 | 46.1 | 52.4 | 49.2 | 56.4 |
| 10 | 57.8 | 59.1 | 61.7 | 58.4 | 60.1 | 62.5 | 59.1 | 62.4 | 64.7 | 56.8 | 62.6 | 58.2 | 67.8 |
| 15 | 64.3 | 66.6 | 68.4 | 66.9 | 68.4 | 68.4 | 63.1 | 66.1 | 67.4 | 63.1 | 71.5 | 67.4 | 74.6 |
| 20 | 72.3 | 74.87 | 76.5 | 71.2 | 73.37 | 74.7 | 67.17 | 69.3 | 71.21 | 72.4 | 82.7 | 77.8 | 81.2 |
| 25 | 95.8 | 96.5 | 98.8 | 87.6 | 89.5 | 91.6 | 73.6 | 76.1 | 78.6 | 85.1 | 98.2 | 87.6 | 97.8 |
| 30 | 96.1 | 97.4 | 98.8 | 94.2 | 96.1 | 97.8 | 86.6 | 89.7 | 92.6 | 91.7 | 98.8 | 94.6 | 98.8 |

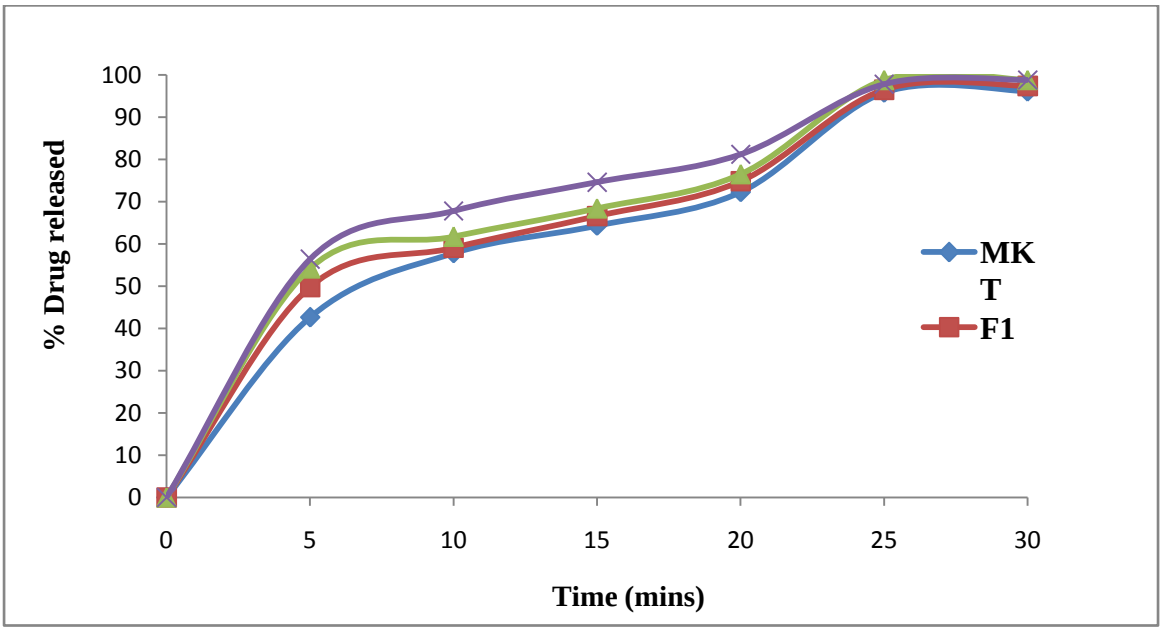


***Figure 6.6 (a) : In vitro drug release rate curve for different immediate release tablets in pH 6.8 containing different proportion of super disintegrants . Marketed (-♦-), F1 (-■-), F2 (-▲-), F3 (-¥-) showing release of drug from prepared formulations.***

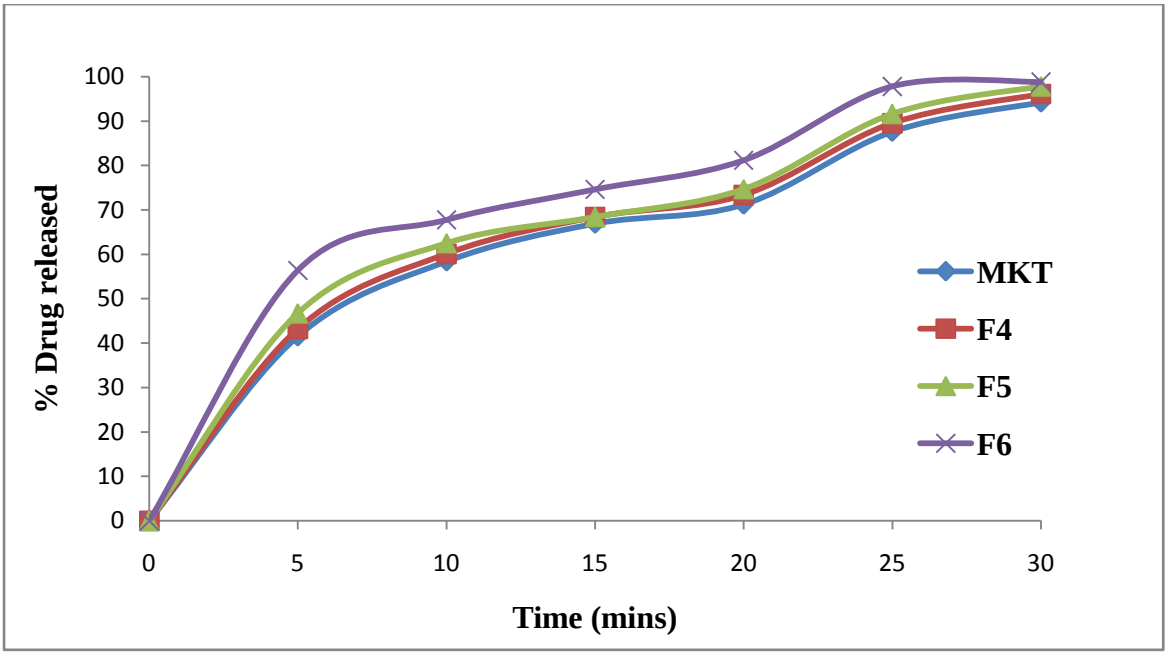


***Figure 6.6 (b) : In vitro drug release rate curve for different immediate release tablets containing different proportion of super disintegrants . Marketed (-♦-), F4 (-■-), F5 (-▲-), F6 (-¥-) showing release of drug from prepared formulations in pH 6.8.***

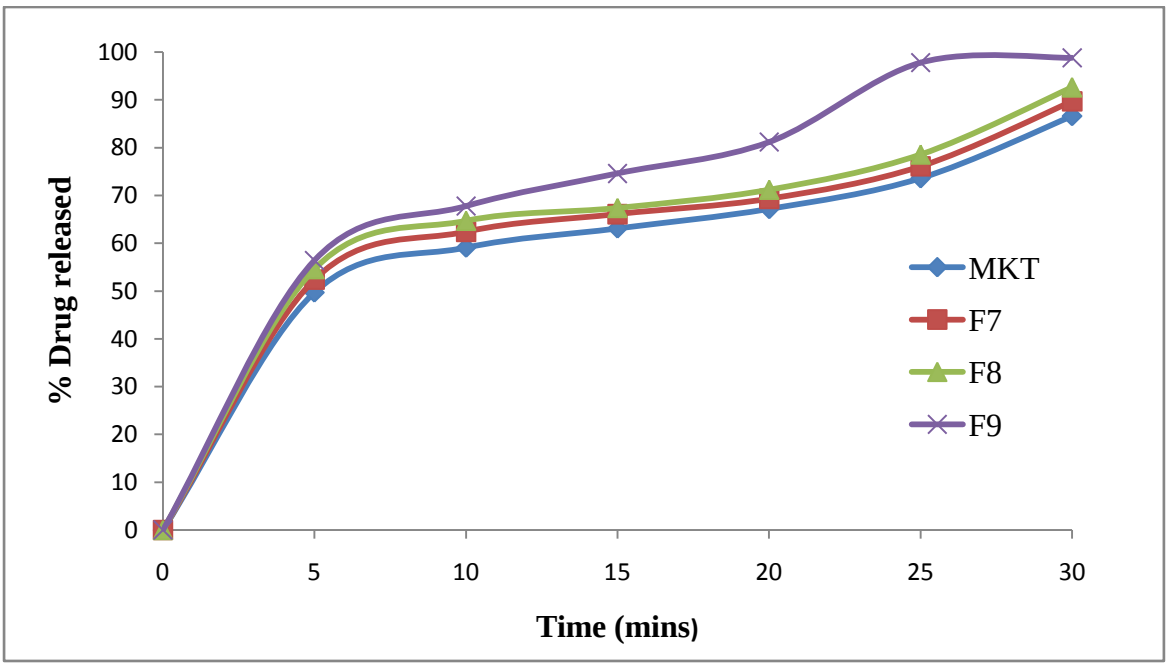


***Figure 6.6 (c) : In vitro drug release rate curve for different immediate release tablets containing different proportion of super disintegrants . Marketed (-♦-), F7 (-■-), F8 (-▲-), F9 (-¥-) showing release of drug from prepared formulations in pH 6.8***

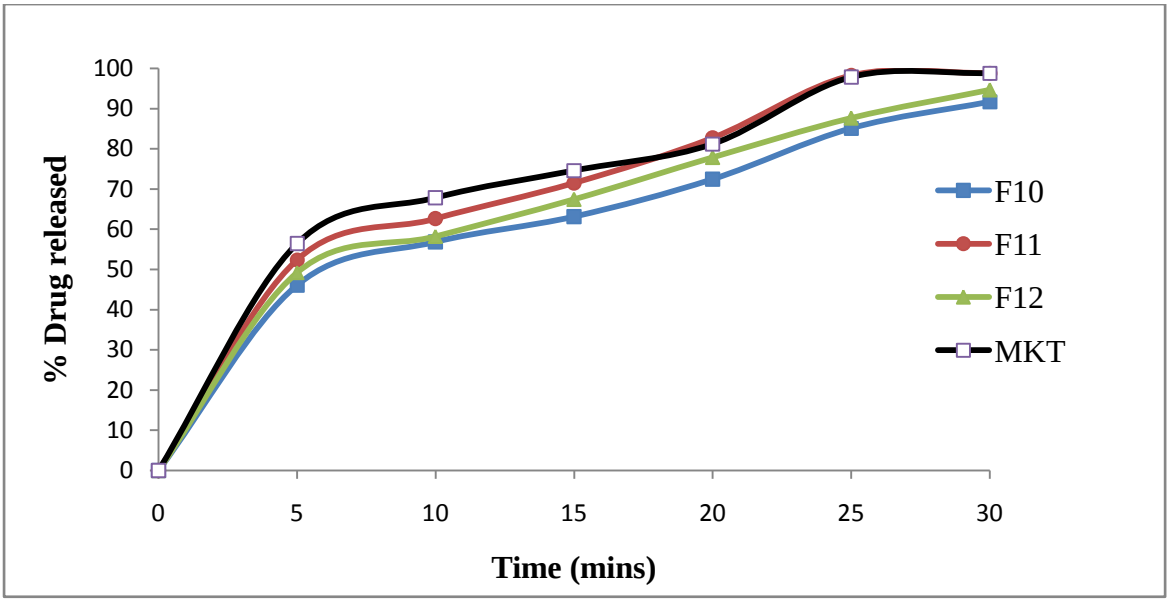


***Figure 6.6 (d) : In vitro drug release rate curve for different immediate release tablets containing different proportion of super disintegrants . Marketed (-□-), F10 (-■-), F11 (-●-), F12 (-▲-) showing release of drug from prepared formulations in pH 6.8.***

### *6.6.1. Drug Release mechanism:*

*The results of in-vitro release data after kinetic evaluation are presented in* ***Table 5****. Kinetic evaluation of the release data reveals that the* $r^2$ *value of optimized batch F11for zero order and first order were obtained as 0.853 and 0.866 respectively. Based on the results it was confirmed that the optimized formulation followed first order release. However, the highest co-relation of F11 was found in Higuchi's model as evidenced by linearity closer* $R^2$ *value (0.982) indicating that drug release from the immediate release tablets occurs through diffusion process. The in-vitro release data was further fitted to Krosmeyer-Peppas model which is generally used to analyze the release mechanism when more than one type of release phenomenon is operational. Good linearity was observed with high 'r' values. The value of release exponent 'n' is an indicative of release mechanism. The value of 'n' obtained for the optimized formulation F11 was found to be 0.4 suggesting probable release by case-I transport. The results of accelerated stability studies as per ICH guidelines indicated that the*

*tablets did not show any significant physical changes (color change, friability and hardness), assay and dissolution characteristics during the study period.*

***6.6.2 Zero Order release kinetics:***

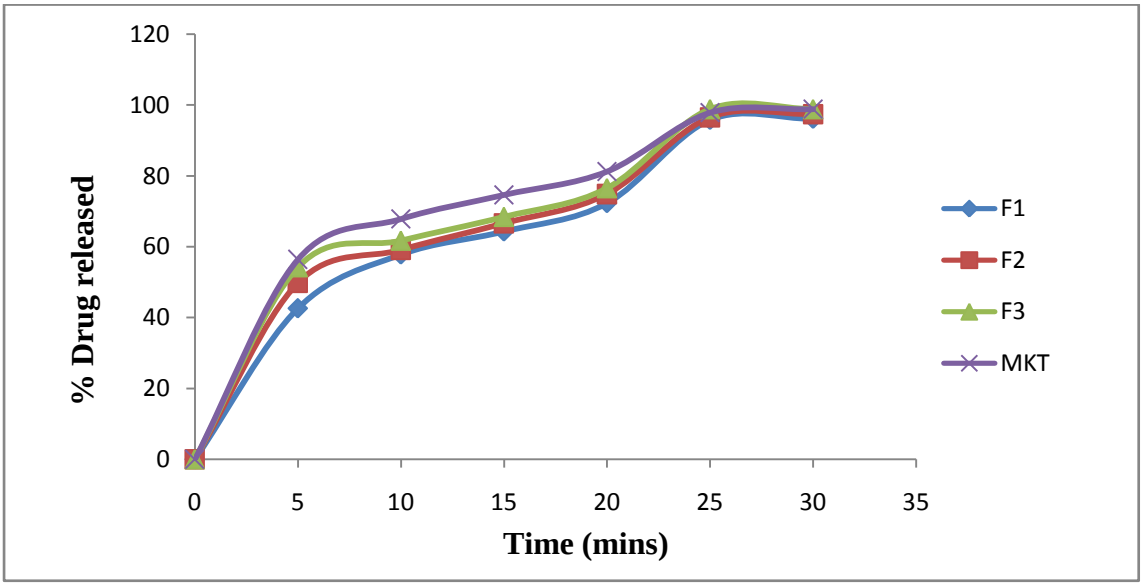


***Figure 6.6.2.1: In-vitro drug release profile of F1, F2, F3 and Marketed drug for Zero Order release kinetics***

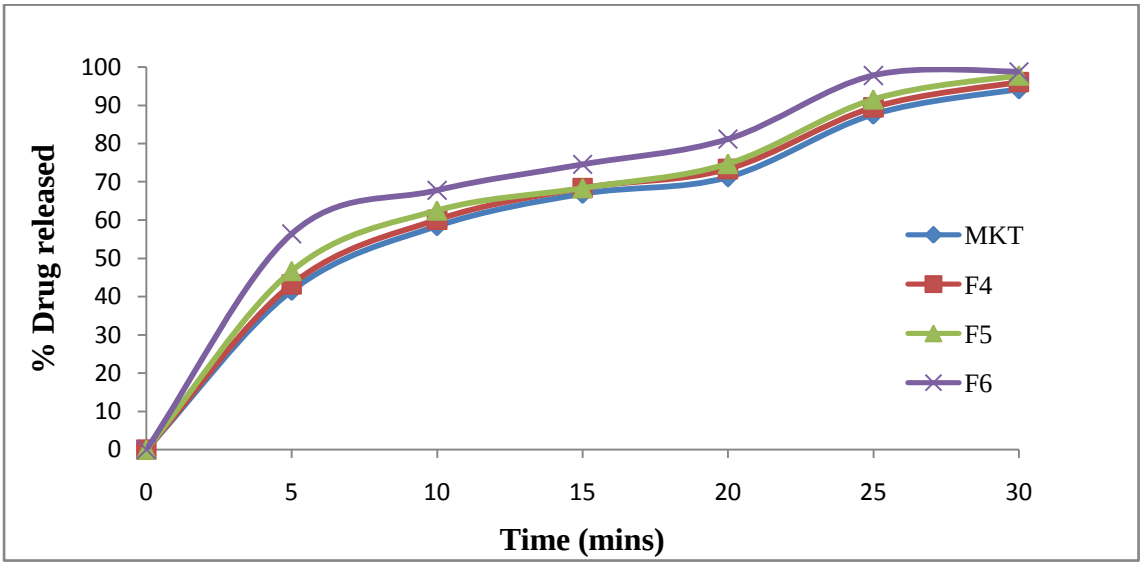


***Figure 6.6.2.2: In-vitro drug release profile of F4, F5, F6 and Marketed drug for Zero Order release kinetics***

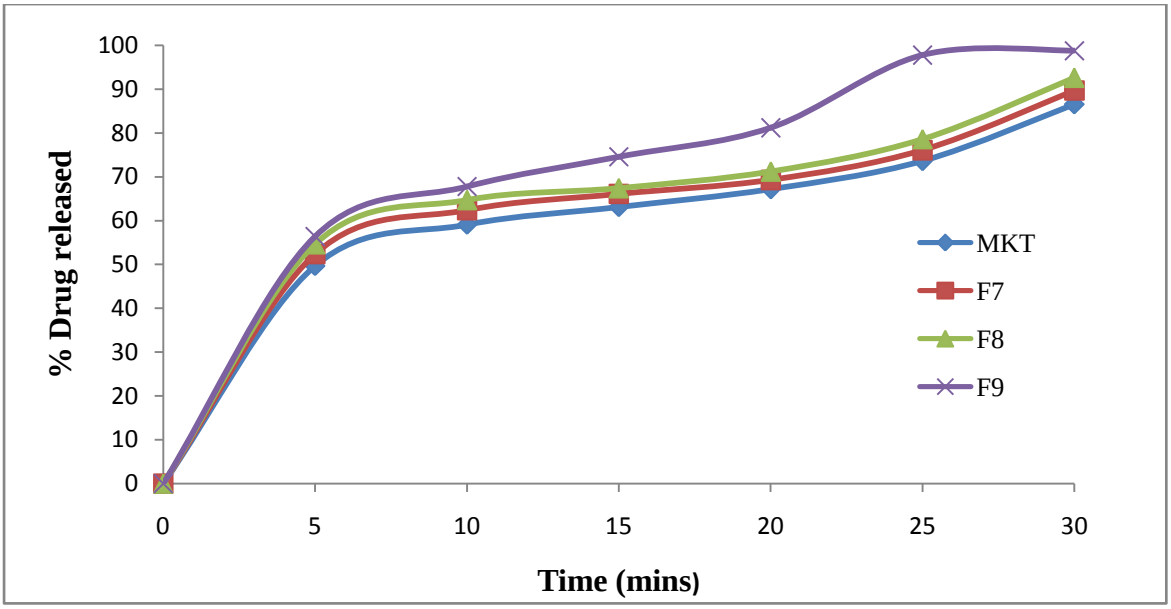


*Figure 6.6.2.3: In-vitro drug release profile of F7, F8, F9 and Marketed drug for Zero Order release kinetics*

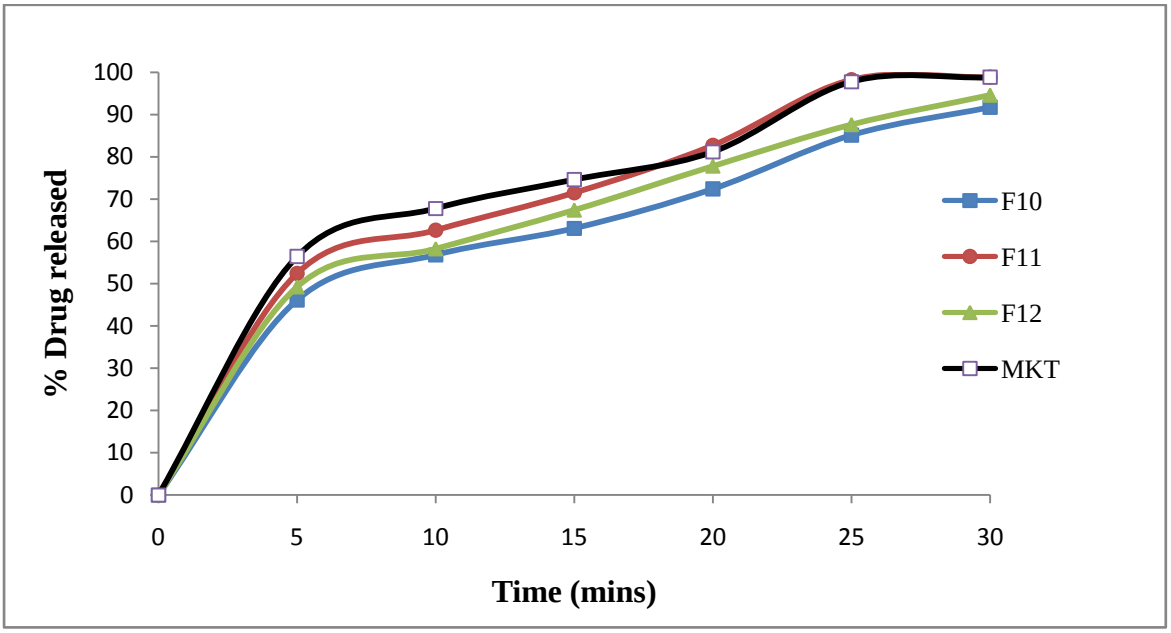


*Figure 6.6.2.4: In-vitro drug release profile of F10, F11, F12 and Marketed drug for Zero Order release kinetics*

***6.6.3. First Order Model:***

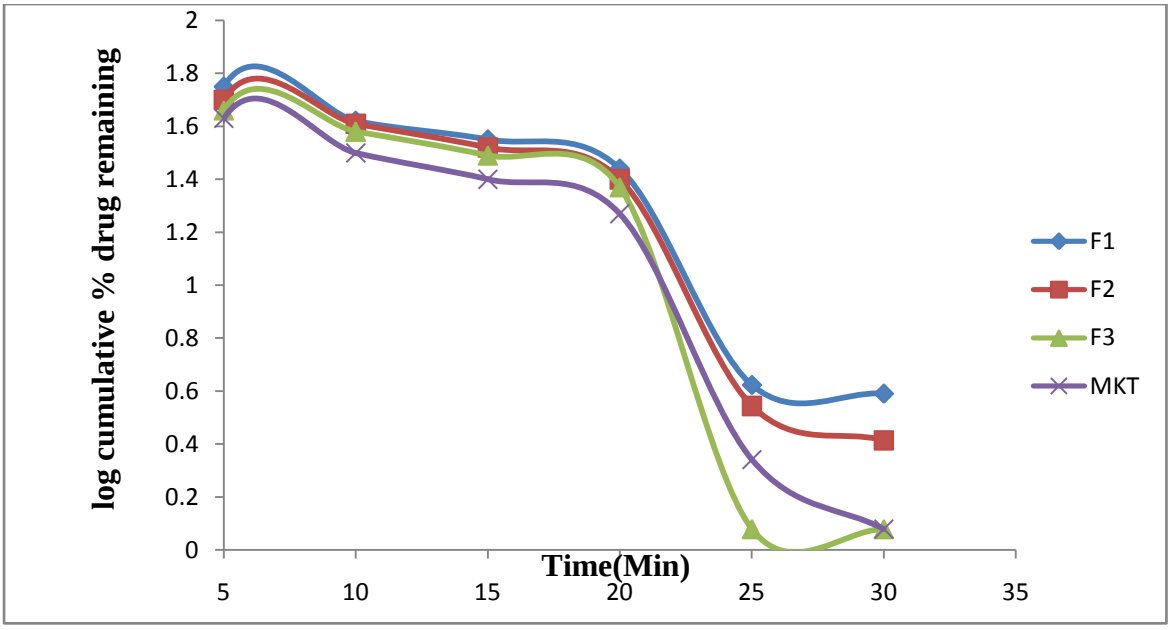


***Figure 6.6.3.1: In-vitro drug release profile of F1, F2, F3 and Marketed drug for 1st Order release kinetics***

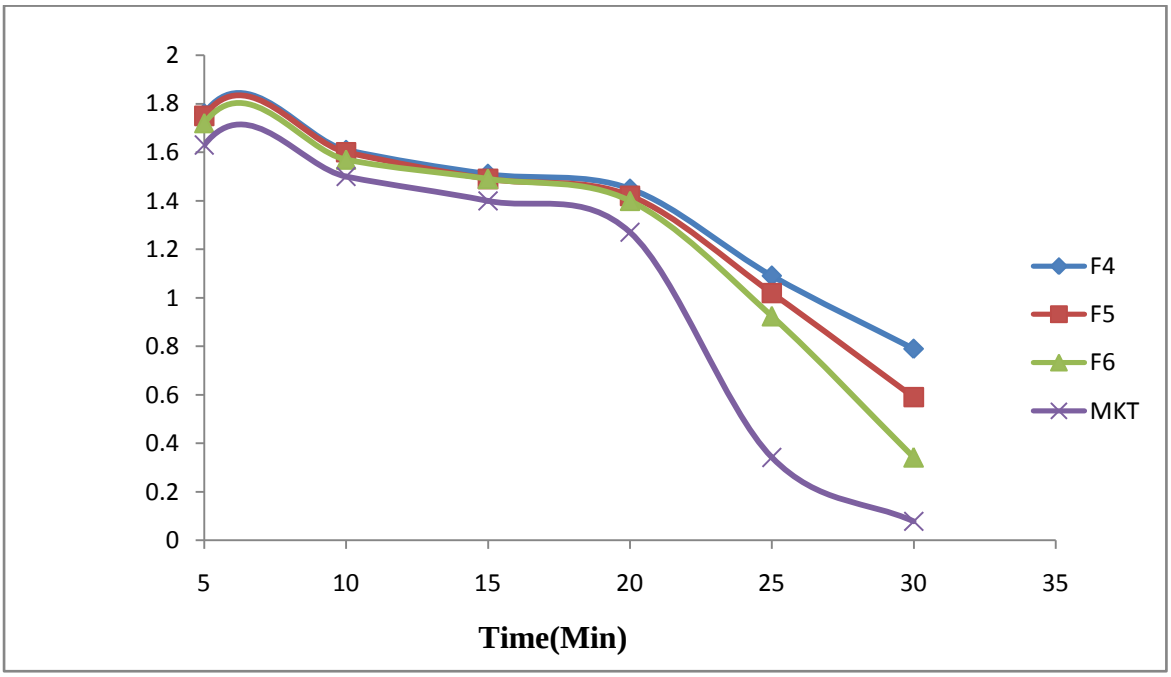


***Figure 6.6.3.2: In-vitro drug release profile of F4, F5, F6 and Marketed drug for 1st Order release kinetics***

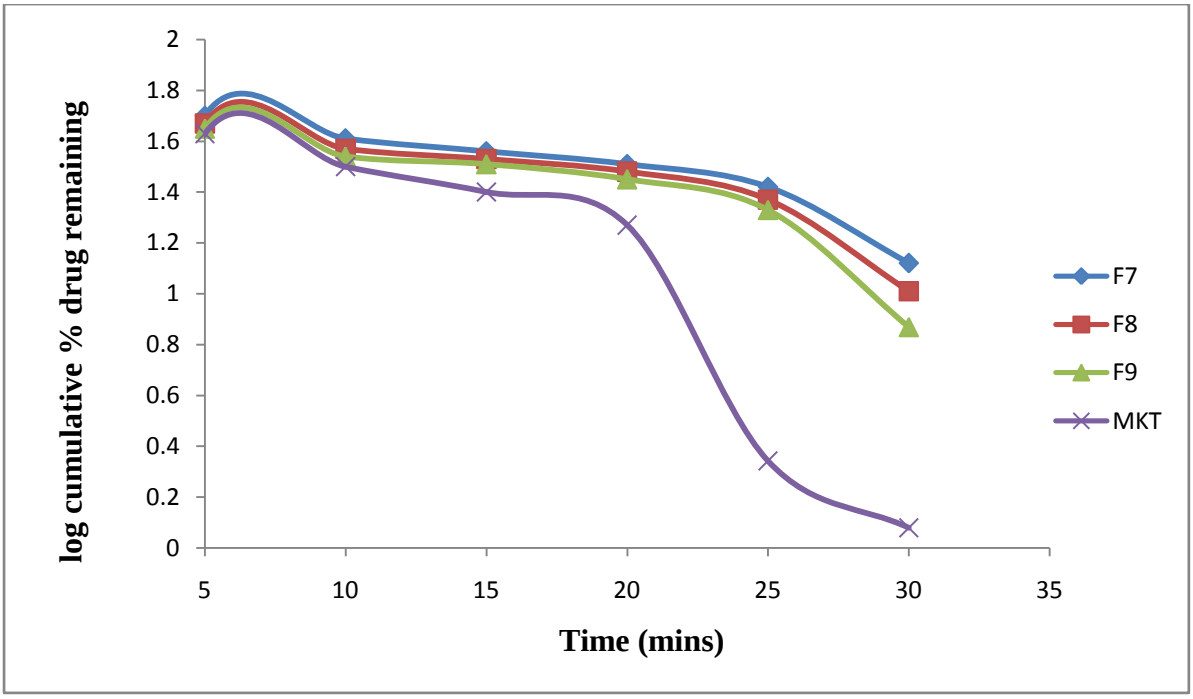


***Figure 6.6.3.3: In-vitro drug release profile of F7, F8, F9 and Marketed drug for 1st Order release kinetics***

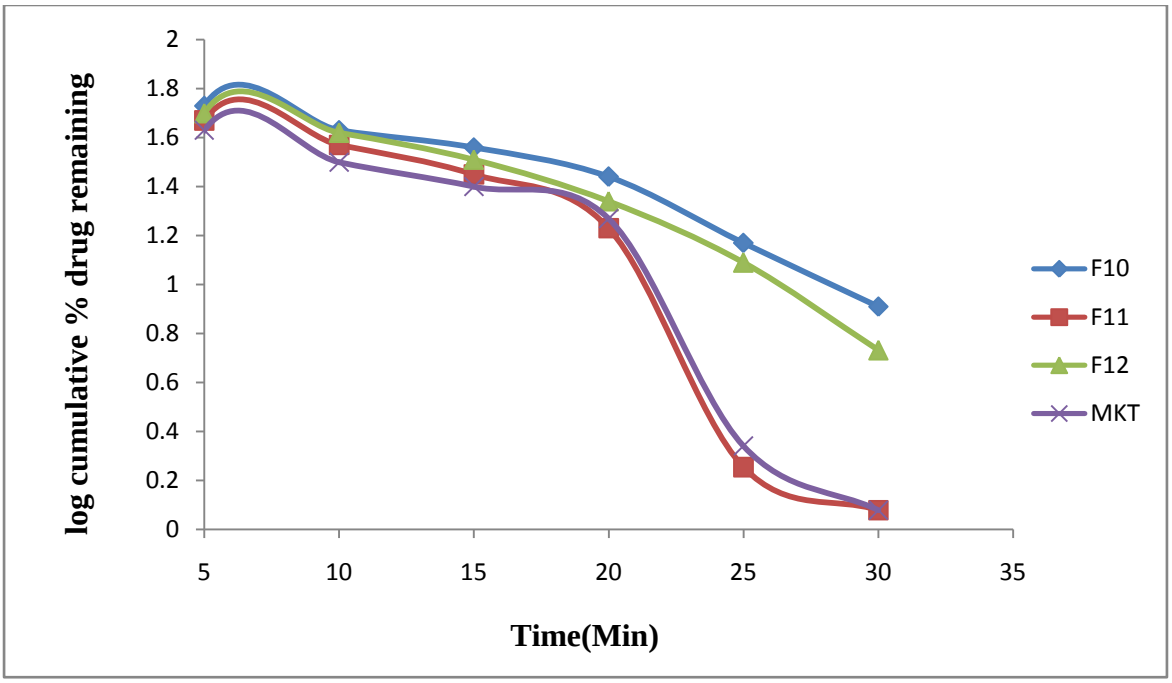


***Figure 6.6.3.4: In-vitro drug release profile of F10, F11, F12 and Marketed drug for 1st Order release kinetics***

***6.6.4.Higuchi model:***

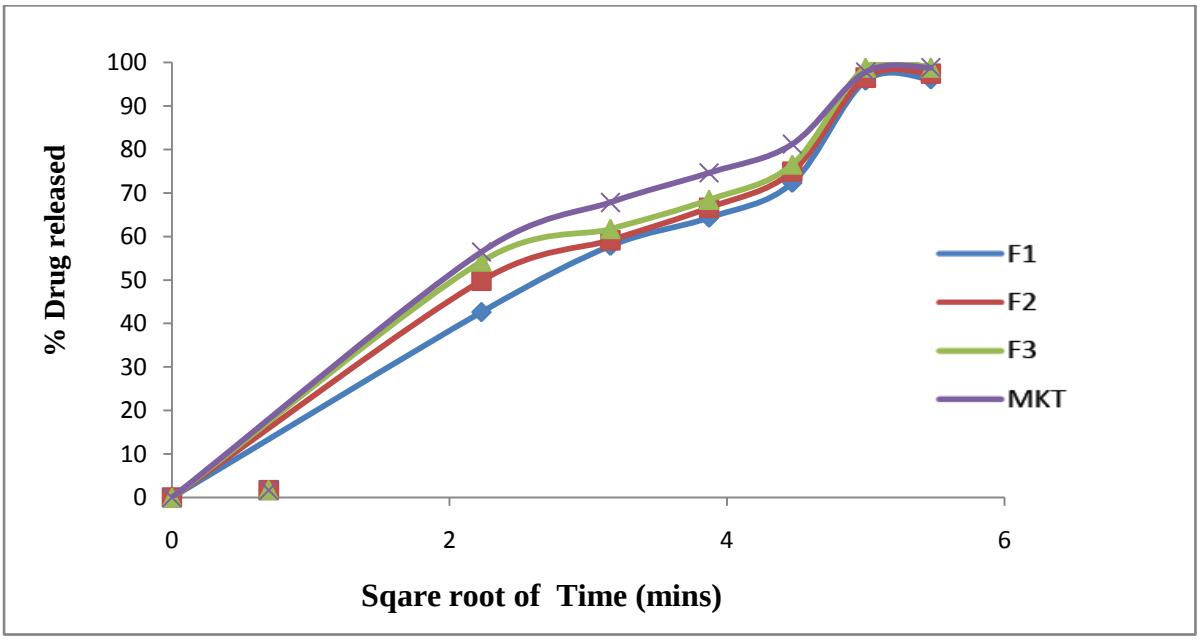


*Figure 6.6.4.1: In-vitro drug release profile of F1, F2, F3 and Marketed drug for Higuchi model release kinetics*

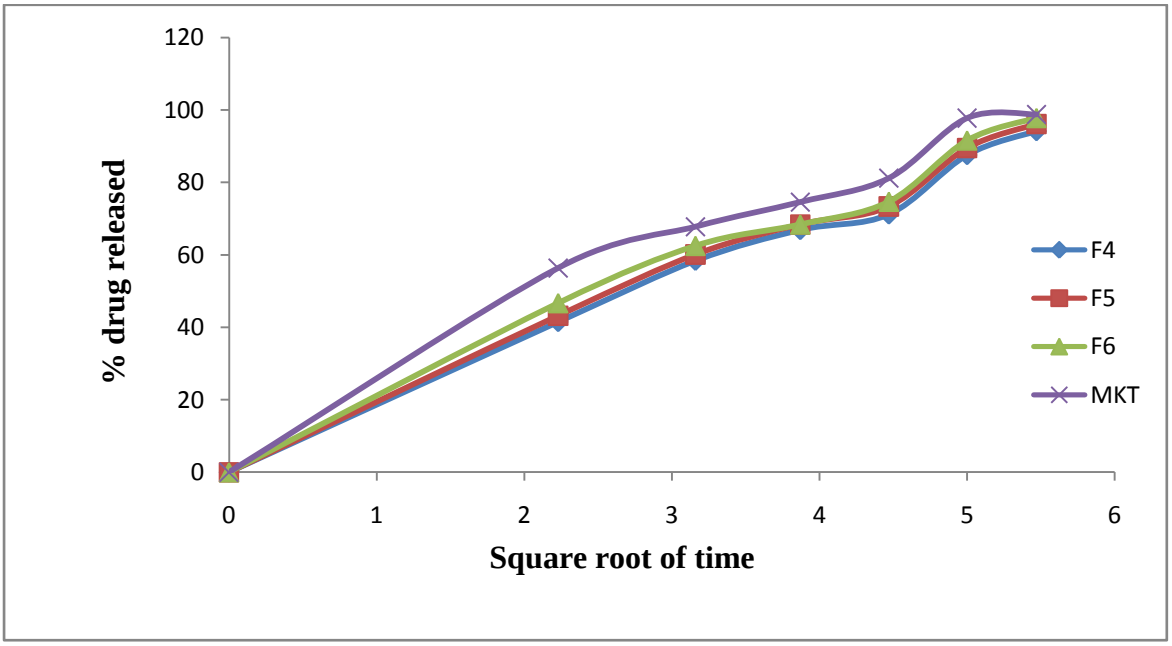


*Figure 6.6.4.2: In-vitro drug release profile of F4, F5, F6 and Marketed drug for Higuchi model release kinetics*

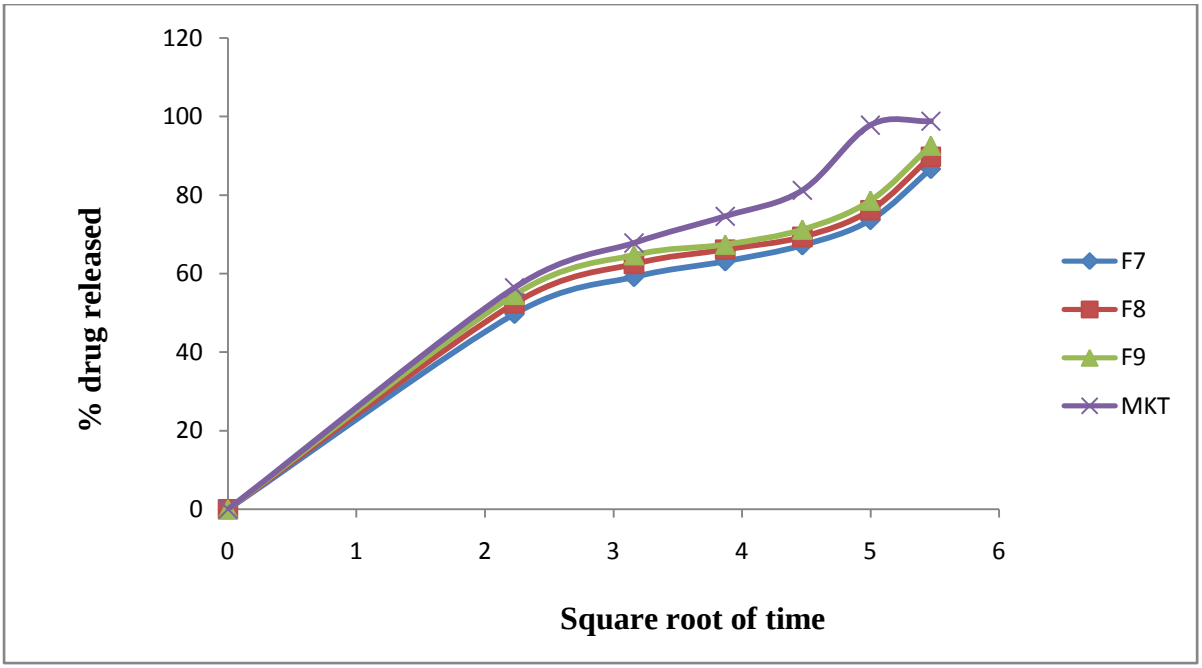


*Figure 6.6.4.3: In-vitro drug release profile of F7, F8, F9 and Marketed drug for Higuchi model release kinetics*

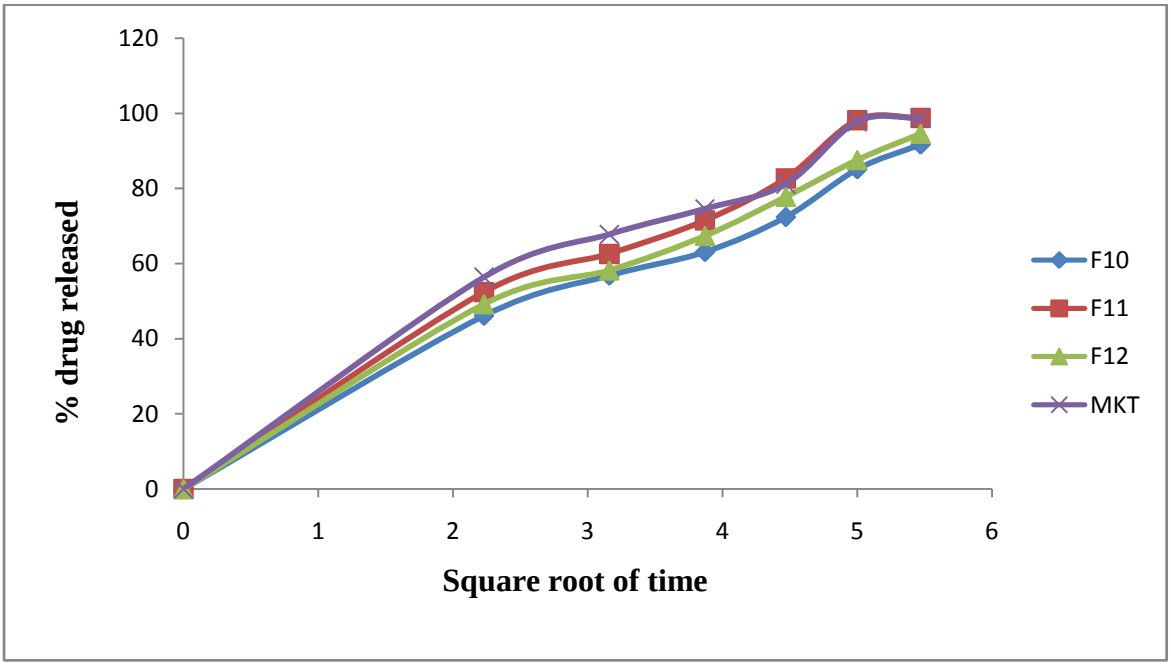


*Figure 6.6.4.4: In-vitro drug release profile of F10, F11, F12 and Marketed drug for Higuchi model release kinetics*

*6.6.5 Korsemeyer-Peppas Model:*

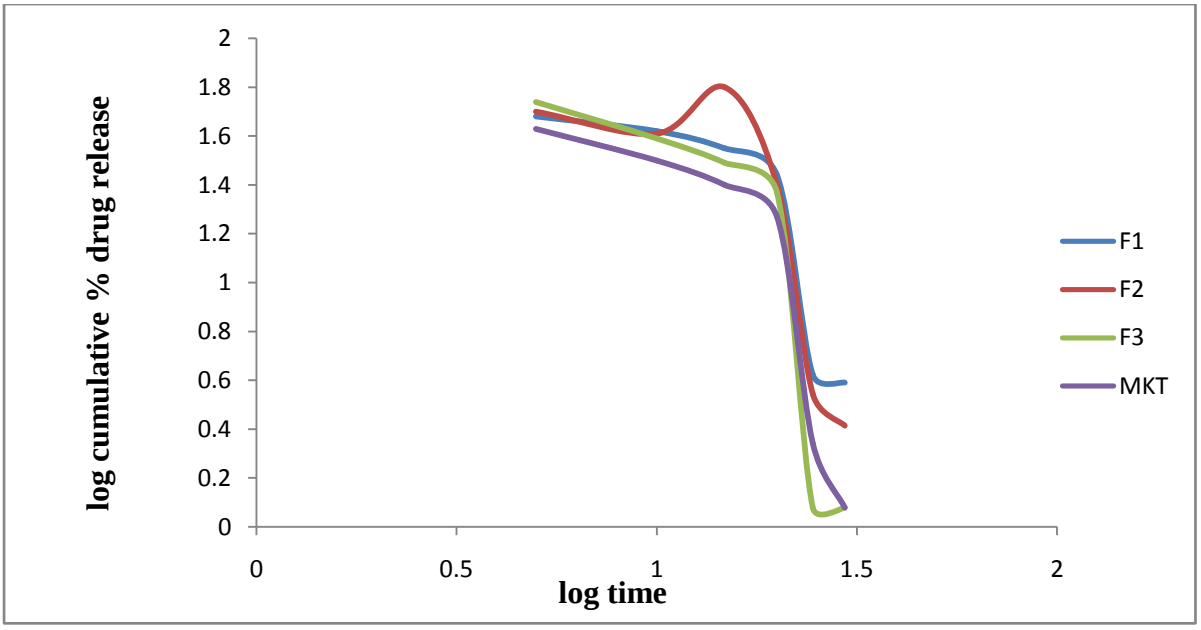


*Figure 6.6.5.1: In-vitro drug release profile of F1, F2, F3 and Marketed drug for Korsemeyer-Peppas model release kinetics*

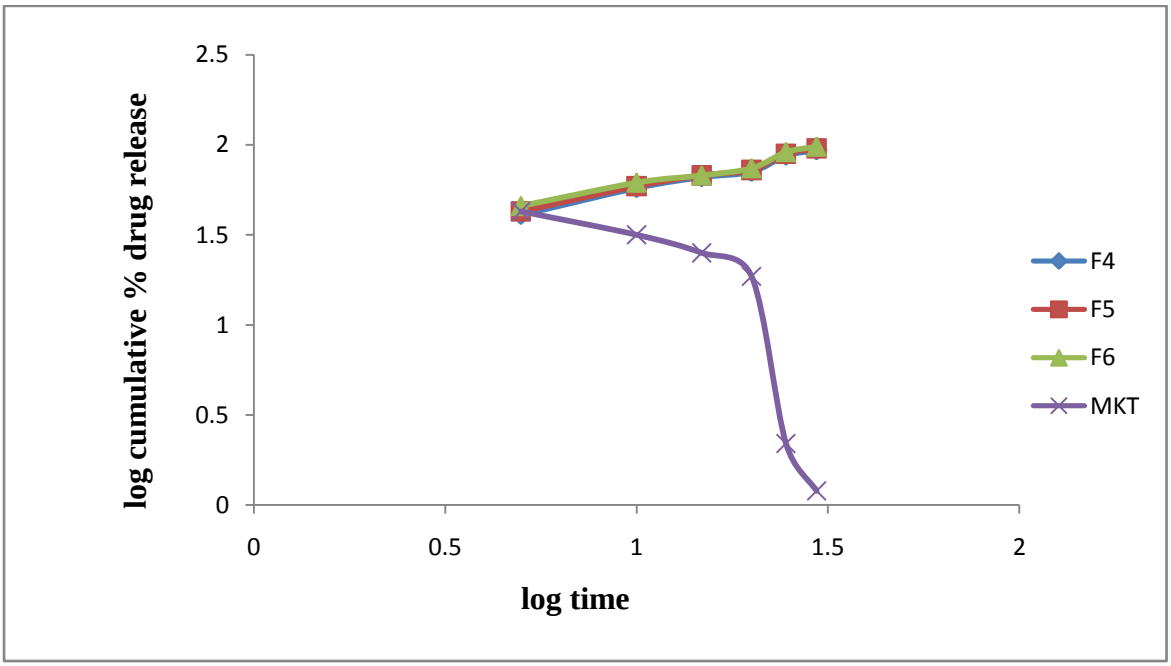


*Figure 6.6.5.2: In-vitro drug release profile of F4, F5, F6 and Marketed drug for Korsemeyer-Peppas model release kinetics*

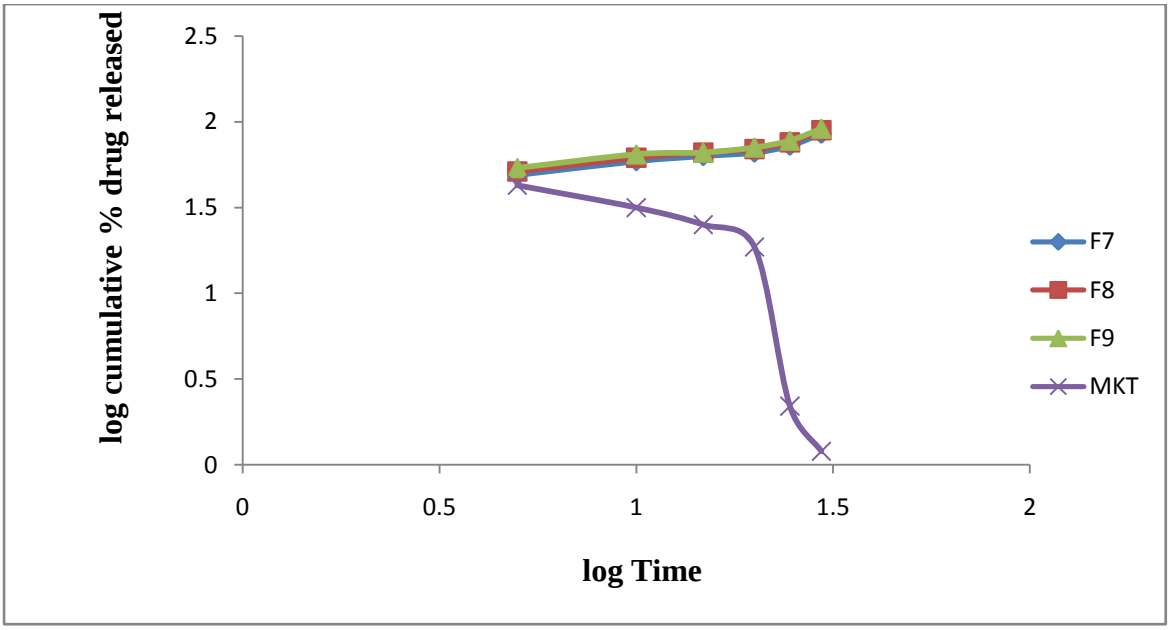


*Figure 6.6.5.3: In-vitro drug release profile of F7, F8, F9 and Marketed drug for Korsemeyer-Peppas model release kinetics*

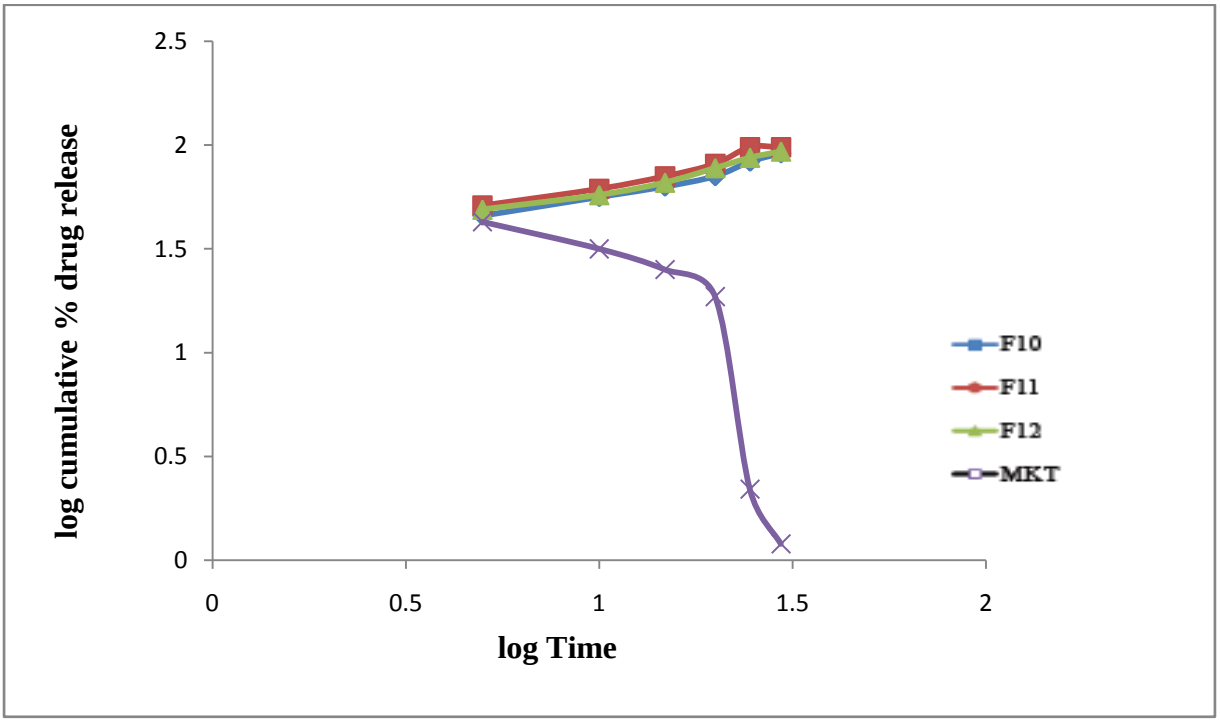


*Figure 6.6.5.4: In-vitro drug release profile of F10, F11, F12 and Marketed drug for Korsemeyer-Peppas model release kinetics*

***Table 5. Kinetic model evaluation of in-vitro release data***

| *Formulation code* | *Zero order* | | *1st order* | | *Higuchi* | | *Korsemeyer peppas* | |
|---|---|---|---|---|---|---|---|---|
| | $K_0$ | $R^2$ | $K_1$ | $R^2$ | $K_H$ | $R^2$ | *n* | $R^2$ |
| *MKT* | *2.804* | *0.808* | *0.064* | *0.856* | *19.18* | *0.076* | *-1.88* | *0.674* |
| *F1* | *2.922* | *0.899* | *0.050* | *0.844* | *18.51* | *0.978* | *-1.41* | *0.641* |
| *F2* | *2.866* | *0.869* | *0.055* | *0.853* | *18.63* | *0.971* | *-1.62* | *0.577* |
| *F3* | *2.860* | *0.844* | *0.071* | *0.791* | *18.90* | *0.962* | *-2.16* | *0.646* |
| *F4* | *2.768* | *0.887* | *0.037* | *0.919* | *16.82* | *0.990* | *0.453* | *0.980* |
| *F5* | *2.815* | *0.882* | *0.043* | *0.894* | *17.15* | *0.990* | *0.441* | *0.979* |
| *F6* | *2.824* | *0.868* | *0.051* | *0.851* | *17.29* | *0.985* | *0.414* | *0.968* |
| *F7* | *2.254* | *0.773* | *0.020* | *0.861* | *14.32* | *0.945* | *0.274* | *0.927* |
| *F8* | *2.310* | *0.758* | *0.022* | *0.827* | *14.76* | *0.936* | *0.264* | *0.921* |
| *F9* | *2.373* | *0.754* | *0.026* | *0.727* | *15.17* | *0.933* | *0.258* | *0.898* |
| *F10* | *2.633* | *0.867* | *0.032* | *0.930* | *16.14* | *0.985* | *0.381* | *0.966* |
| *F11* | *2.915* | *0.853* | *0.069* | *0.866* | *17.98* | *0.982* | *0.383* | *0.961* |
| *F12* | *2.715* | *0.857* | *0.037* | *0.930* | *16.74* | *0.986* | *0.373* | *0.967* |

## *7. CONCLUSION*

*From the study it is concluded that, ATV Calcium found compatible with selected excipients and incompatible with mannitol, Magnesium stearate, MCC. So, DSC and FT-IR was successful tool to screen the interactions with ATV and immediate release tablet can be developed by direct compression method. All formulations were found to be satisfactory when evaluated for thickness, weight uniformity, hardness, friability, drug content uniformity, and disintegration time and in-vitro drug release. Formulation* ***F11*** *containing two super disintegrants have shown the disintegration time less than 25 sec and better dissolution than all other formulations releasing more than 80% of the drug after 20 minutes. Evaluation of the release kinetic data reveals that tablets containing 1:1 ration of two super disintegrants (CCS:SSG) exhibit Higuchi spherical matrix release indicating that drug release from the tablet was diffusion controlled followed by case I transport. Stability study revealed that, the selected formulation F11 was stable over the period of three months of stability study.*

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formulations were found to be satisfactory when evaluated for thickness, weight uniformity, hardness, friability, drug content uniformity, disintegration time and in-vitro drug release. Formulation F11 containing two super disintegrants have shown the disintegration time less than 25 sec and better dissolution than all other formulations releasing more than 80% of the drug after 20 minutes. Evaluation of the release kinetic data reveals that tablets containing 1:1 ration of two super disintegrants (CCS:SSG) exhibit Higuchi spherical matrix release indicating that drug release from the tablet was diffusion controlled followed by case I transport. Stability study revealed that, the selected formulation F11 was stable over the period of three months of stability study.

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