COMPATIBILITY STUDIES OF GLIMEPIRIDE WITH SELECTED EXCIPIENTS FOR THE DEVELOPMENT OF EXTENDED RELEASE FORMULATIONS

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This is to certified that the topic incorporated in this one year research based project dissertation entitled"**COMPATIBILITY STUDIES OF GLIMEPIRIDE WITH SELECTED EXCIPIENTS FOR THE DEVELOPMENT OF EXTENDED RELEASE FORMULATIONS**" being submitted by **Satyabrat Sarma, Roll No:1405211009,Regd No:099005214**,in partial fulfilment 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 under the direct supervision and guidance of Dr. Bipul Nath, Asstt. Professsor , Department of Pharmaceutics, GIPS during the academic session 2015-2016.

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DECLARATION BY THE CANDIDATE

*I hereby declare that the topic incorporated in this thesis entitled "**COMPATIBILITY STUDIES OF GLIMEPIRIDE WITH SELECTED EXCIPIENTS FOR THE DEVELOPMENT OF EXTENDED RELEASE FORMULATIONS**" is a bonafide and genuine research work carried out by me under the supervision of **Dr. Bipul Nath, M.Pharm, PhD, Asstt. Professor,** Girijananda Choudhury Institute of Pharmaceutical Science (GIPS), Hatkhowapara, Azara, Guwahati. The content of this research thesis has not been submitted or consideration for the award of any degree, diploma or fellowship in any other university or institution.*

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PREFACE

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 HPLC and FTIR gives reliable data for structural conformation. SEM and Hot stage microscopy gives limited chemical information. DSC and DTA 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.

Contd.....

CHAPTER 1

1. INTRODCUTION

Compatibility study [1,2]:

Excipients are components of a finished drug product other than the active pharmaceutical ingredient (API) and are added during formulation for a specific purpose. Although listed as inactive ingredients by FDA, excipients generally have well-defined functions in a drug product. As with active ingredients, they may be Small Molecule or complex and may vary in terms of degree of characterization. They may be chemically synthesized or may be either natural source or biotechnology-derived (recombinant). In contrast to active ingredients, minor components of an excipient may have significant impact on its pharmaceutical performance. Depending on the intended use, an excipient in a drug product may be an active ingredient in another drug product.

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, therapeutical 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.

1.1 Extended Release formulations[1,3,4]:

Extended release dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over the extended period of time after administration of a single dose [1, 2]. The objective in designing a sustained release/extended release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. Techniques of thermal and isothermal stress testing (IST) were used to evaluate the compatibility of drug with selected excipients for the development of extended release formulations. 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 [3,4]. 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. As the thermo-analytical methods do not yield direct chemical information, Fourier transform infrared spectroscopic (FT-IR) investigations were also used in this work. The compatibility studies using thermal analysis present advantageous to readily available knowledge of any physical and chemical interactions between drugs and excipients which might give rise to changes in chemical nature, stability, solubility, absorption and therapeutic response of drugs [5, 6]. Thermal techniques have been increasingly used for quick evaluation of possible incompatibility between formulation components through comparison of thermal curves of pure substances with curve obtained from a 1:1 mixture

Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action. It is practically insoluble in water. Soluble in dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride. It also dissolves in

dilute alkali and in dilute acids. Half life is approximately 5 hours following single dose. Completely (100%) absorbed following oral administration. Over 99.5% bound to plasma protein. The highest recommended dose per day is 6-8 mg. Daily doses of glimepiride of more than 6 mg are more effective only in a minority of patients. There is a risk of hypoglycaemia, if starting dose exceeds the daily dose of GLM being taken. Glimepiride is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin [7,8]. The aim of the present investigation was to study compatibility of GLM with selected matrix polymers and to prepare extended release tablets by direct compression method.

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.

1.2 Incompatibility [3]

"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.

1.3 Importance of drug excipient compatibility [5, 6]

- *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.*

1.4 Excipients [7, 8]

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

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.*

2. Mode of drug decomposition [10,11]

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.

2.1. Common modes of degradation are described below: [12,13]

2.1.1 *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.*

2.1.2. Oxidation[14,15,16]

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.

2.1.3. 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.

2.1.4. 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.

2.1.5. 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. 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.

3. 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

3. Biopharmaceutical interactions

3.1 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*

3.2 Chemical interactions: *-*

1. 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.

3.3. 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:-*

3.3.1. 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.

3.3.2. 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.

3.3.3. 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.

4. Methods of estimation of drug excipient compatibility *[1, 13]*

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 drug 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 transform infrared 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

4.1. Thermal methods of analysis

1. Differential scanning calorimetry (DSC)

2. Isothermal micro calorimetry

3. Hot stage microscopy (HSM)

4.2. Spectroscopic techniques

1. Vibrational spectroscopy

2. Powder X-ray diffraction (PXRD).

3. Solid state nuclear magnetic resonance spectroscopy(ss NMR)

4.3. Microscopic technique

1. Scanning electron microscopy (SEM)

4.4. Chromatographic technique

1. High performance liquid chromatography

4.1 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.

4.1.1 Differential scanning calorimetry (DSC) [18, 19,25]

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.

CHAPTER 2

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2. REVIEW OF LITERATURE:[19,16,22,27,28,30,36]

1. Bharate Sonali S et al*[20]*, *proposed that, Studies of active 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 nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety. The present review covers the literature reports of interaction and incompatibilities of commonly used pharmaceutical excipients with different active pharmaceutical ingredients in solid dosage forms. Examples of active drug/excipient interactions, such as transacylation, the Maillard browning reaction, acid base reactions and physical changes are discussed for different active pharmaceutical ingredients belonging to different therapeutic categories* viz *antiviral, anti-inflammatory, antidiabetic, antihypertensive, anti-convulsant, antibiotic, bronchodialator, antimalarial, antiemetic, antiamoebic, antipsychotic, antidepressant, anticancer, anticoagulant and sedative/hypnotic drugs and vitamins. Once the solid-state reactions of a pharmaceutical system are*

understood, the necessary steps can be taken to avoid reactivity and improve the stability of drug substances and products.

2. Ahad Abdul Hindustan, Anand Babu U[31], et al proposed that, develop matrix tablets of Glimepiride with *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone and to study its functionality as a matrix forming agent for sustained release tablet formulations. Mucilage from *Datura stramonium* leaves was extracted, isolated, purified and characterized. Physicochemical properties of the dried powdered mucilage of *Datura stramonium* leaves were studied. Various formulations of Glimepiride *Datura stramonium* leave mucilage and Poly Vinyl Pyrrolidone were prepared. The formulated tablets were tested for mechanical properties, friability, swelling behavior, *in vitro* drug release pattern and the dissolution data was treated with mathematical modeling and the optimized formulation was tested for accelerated stability studies. The formulated tablets were found to have good mechanical properties, good swelling properties. The *in vitro* dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. From this study it was concluded that the dried *Datura stramonium* leaves mucilage and Poly Vinyl Pyrrolidone combination can be used as a matrix forming material for making sustained release matrix tablets.

3. Ali Kamal Attia et al[35] proposed that, the Thermal behavior of some antidiabetic drugs such as pioglitazone hydrochloride (PTZ), rosiglitazone maleate (RGZ), glibenclamide (GBD) and glimepiride (GMP) has been studied. **Methods**: Thermogravimetric analysis (TGA), derivative thermogravimetry (DTG) and differential thermal analysis (DTA) techniques were used to study the thermal behavior of the drugs under investigation. **Results:** Thermal

analysis technique was used to obtain quality control parameters such as melting point 193.13 °C, 122.42 °C, 173.75 °C and 208 °C for PTZ, RGZ, GBD and GMP, respectively. The values of melting point of gave satisfactory results in comparison to that obtained by using the official method. Non-isothermal methods were employed to determine the activation energy values of the first stage of thermal decomposition. Comparison of the activation energy values suggests the following sequence of thermal stability: GMP > GBD > RGZ > PTZ. **Conclusion:** The results obtained are useful for the identification of these compounds and permitted interpretations concerning their thermal decomposition. Thermal stability of pharmaceutical compounds can be studied and compared by using thermal analysis techniques.

4. **Sandhya Pamu., et al[36].** Proposed that, prepare bilayer tablets of Glimepride and Metformin HCL in combination. Metformin hydrochloride and Glimepiride are oral hypoglycemic drug and effectively used in treatment of diabetes mellitus (type-2 diabetes). The main aim of the present study was to formulate Metformin hydrochloride sustained release and Glimepride immediate release matrix tablets as a dosage form by different polymers such as HPMC, Povidone, Lactose Monohydrate, Ethylcellulose, Microcrystalline Cellulose and study the invitro release patterns of the drug. In the present study bilayer tablets Glimepride prepared by direct compression method and Metformin prepared by wet granulation technology. The prepared tablets were evaluated for various physicochemical parameters such as drug-excipient interaction by FTIR,flow properties, hardness, weight variation, friability, and in vitro dissolution studies optimised based on desired sustained release time (16hrs) and acceptable floating properties The FTIR study revealed that there is no drug-excipient interaction. During preformulation it has been observed that there is no

drug- drug and drug excipient interaction, so the excipients which have been selected for the formulation are compatible with the drugs. This system provides zero order or near zero order release for IR layer and SR layer provides Higuchi model.

5. **Prasad Hari Har et al[37],** proposed that, a Glimepiride immediate release tablet formulation for the effective treatment of Type-2 Diabetes mellitus (or) Non-Insulin-Dependent Diabetes Mellitus (or) adult-onset diabetes. Glimepiride is a sulfonylurea antidiabetic drug. Glimepiride acts as an insulin secretagogue. To provide the patients with the most convenient mode of administration, there was a need to develop immediate release dosage form, particularly one that disintegrates rapidly and disperses and helps in enhancing the Bioavailability of the drug. Glimepiride immediate release tablets were formulated by using wet granulation method and povidone k 30, starch as binders, croscarmellose sodium, Sodium Starch Glycolate, Crospovidone as disintegrants, Lactose monohydrate as Diluent and Magnesium stearate as Lubricant. The tablets were evaluated for Pre compression and Post compression Parameters after conducting Preformulation Studies. All the parameters were within the pharmacopoeial limits and the drug disintegration time was less and the Invitro dissolution studies showed that the drug release was fast in Formulation(F2) containing Sodium Starch Glycolate as Super disintegrant and Povidone k 30 as Binder when compared to all other Formulations.

6. **Bhanja satyabrata et al[38].** Proposed that formulation and evaluation of Mucoadhesive buccal tablets containing antidiabetic drug, Glimepiride to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression method. Six formulations were

developed with varying concentrations of polymers like Carbopol 934P, HPMCK4M and Chitosan. The tablets were tested for weight variation, hardness, surface pH, drug Content uniformity, percentage swelling index, bioadhesive strength, *ex-vivo* residence time *in-vitro* drug dissolution study, *In-vitro* drug release kinetic study, *ex-vivo* permeation study and Stability study.

Results: FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The best in-vitro *drug release profile was achieved with the formulation F3 which contains the drug, Carbopol 934p, HPMC K4M and Chitosan in the ratio of 1:3.75:8.75:1.25. The surface pH, bioadhesive strength,* ex-vivo *residence time and swelling index of formulation F3 was found to be 6.80±0.02, 36.3±0.04g, 325min and 289.8±0.52%, respectively. The formulation F3, containing 4 mg of Glimepiride exhibited 6 h sustained drug release i.e. 93.98±0.8% with desired therapeutic concentration. The drug permeation from the formulation F3 was slow and steady and 3.56 mg of Glimepiride could permeate through sheep buccal membrane with a flux of 0.27 mg hr-1 cm-2. The* in-vitro *release kinetics studies reveal that all formulations fits well with zero order kinetics and followed non-Fickian diffusion mechanism*

Conclusion: Hence, it was concluded that the best formulation F3 was suitable for all the evaluation parameters and can be permeated through human buccal mucosa.

7. ***Chowdhury subhadeep et al[39].*** *Proposed that Long term administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin. For this complication atorvastatin calcium can be used to reduce the cardiovascular mortility. The objective of the present study was to evaluate the effects of two factors (amount of carboxymethylcellulose sodium and sodium starch glycolate) on drug release of atorvastatin calcium and glimepiride*

from the tablet in order to optimize the formulation by 2 factor 3 level factorial design. Two independent variables taken were carboxymethylcellulose sodium (10mg, 12.5mg and 15 mg) and sodium starch glycolate (2.5 mg, 5mg and 7.5mg). The evaluated response were percentage release of atorvastatin ca in 60 min (Y1) and percentage release of glimepiride in 60 min (Y2) was taken as the response variables. Drug release was measured in USP 2 (paddle type) apparatus using 900 ml 0.05 M phosphate buffer (pH 6.8) solution at a rotation speed 75 rpm. The dissolution data revealed that amount of carboxymethylcellulose sodium and sodium starch glycolate are very important to achieve optimum formulation. Using responses and resulted statistical equations, optimum formulation was predicted. It shows that sodium starch glycolate has more effect than carboxymethylcellulose sodium on the tablet formulation and formulation with 14.78 mg of carboxymethylcellulose sodium and 7.5 mg of sodium starch glycolate is the optimized formulation. The optimized formulation produced dissolution profiles that were closed to predicted values.

8. ***Reddy Narasimha D et al***[40] *proposed that develop mucoadhesive tablets of Glimepiride and Parecoxib drugs were prepared to achieve controlled plasma level of the drug especially in diabetes mellitus patients with pain therapy. The mucoadhesive tablets were prepared by direct compression technique. The drug- excipient compatibility studies were performed by Fourier Transform Infrared spectroscopy (FTIR). Physicochemical characteristics and in vitro drug dissolution tests were performed. The in vitro drug release pattern and the dissolution data was treated with mathematical modeling Accelerated stability studies were also carried out to the optimized formulation (F-5). The FTIR studies revealed that drugs were compatible with the polymer used. The optimized formulations were found to have good physicochemical and in vitro release properties. The in vitro dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release.*

The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. From this study it was concluded that Glimepiride and Parecoxib combination mucoadhesive Tablets is a good combination for diabetics associated with pain and inflammation.

*9.**Basavaraju . V.D.T. et al**[41] proposed that,the formulation and evaluation of Bilayer matrixtablet that would release Amlodipine Besilate immediately and Glimepiride as extended release. The bilayer matrix tablets were prepared by direct compression method. Extended release layer (Glimepiride) pre compresses on compression machine manually and on the pre compressed layer immediate release layer (Amlodipine Besilate) was loaded and punched on compression machine automatically. Total seven batches wereprepared and powder blends before compressions were subjected for evaluation of flow properties. All the parameters were within the limit showing good flow properties. Data from Preformulation compatability studies suggested that there is no interaction between the excipients and the drug and the same was confirmed from IR Spectroscopy. Weight variation test showed that the weights of all the formulations were within Pharmacopeial limits. Drug content in all the developed formulations was found to be uniform with sufficient hardness confirming a good mechanical strength to them. In vitro dissolution studies had shown a satisfactory drug release from all the formulation. Based on higher invitro release, F2A2 was selected as optimized formulation. The drug release from the optimized formulation was found to follow zero order kinetics for extended release layer and first order release for immediate release layer. The developed formulation was found to be stable during the stability studies of three months.*

10. **A. Mohamed Noha et al**[42] proposed that, the effect of monotherapy with sitagliptin, or its combination with glimepiride in glycemic control, islet cell diameter and its proliferation in type 2 diabetic rats. Rats were fed with a high fat diet followed by injection with a low dose of streptozotocin to induce type 2 diabetes. Then, rats were switched to normal diet and for other 28 days. Monotherapy with sitagliptin did not affect the body weight, while its combination with glimepiride did not induce a significant change. The combination increased the % change in body weight compared to sitagliptin alone. All the treatment regiment enhanced glucose clearance as indicated by a reduction in the area under the curve. Pancreatic immunohistochemistry and morphometric analysis were performed to measure the diameter of islet cells, insulin-positive area and the number of Ki-67 positive nuclei. In sitagliptin group, diameter of large-sized islets was 2-fold greater than those observed in diabetic group. The monotherapy with glimepiride did not change the islet-cell diameter. Further, the combination group showed better glycemic control and greater cell proliferation compared to monotherapies. Consequently, we conclude that the combination therapy of sitagliptin/glimepiride has synergistic effect.

11. ***Ethiraj T et al***[43] *proposed that, Nanosuspension of Glimepiride in order to improve the solubility and bioavailability of poorly water soluble drugs. Nanosuspensions of Glimepiride were developed with different ratios of Urea and PVP combinations by nanoprecipitation technique. Nanoprecipitation method being simple and less sophisticated was optimized for the preparation of nanosuspension. The Fourier transform infrared (FTIR) spectroscopy was used to confirm compatibility and to rule out any possible interactions between drug and carriers. Four formulations (F1, F2, F3 and F4) consisting PVP and urea in the ratios of 1:3 and 1:6 respectively were prepared. All formulations were prepared using poloxamer as*

stabilizer, mixture of drug and acetone as organic phase and distilled water containing carriers as aqueous phase. . Physicochemical characteristics of nanosuspension in terms of size, zeta potential, entrapment efficiency (% EE) and in vitro drug release were found within their acceptable ranges. Differential scanning calorimetry studies provided evidence that enhancement in solubility of drug resulted due to change in crystallinity of drug within the formulation. Data of in vitro release from nanosuspensions were fit in to different equations and kinetic models to explain release kinetics.

12. Bharate. Sonali S. et al[44] *proposed that, Studies of active 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 nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety. The present review covers the literature reports of interaction and incompatibilities of commonly used pharmaceutical excipients with different active pharmaceutical ingredients in solid dosage forms. Examples of active drug/excipient interactions, such as transacylation, the Maillard browning reaction, acid base reactions and physical changes are discussed for different active pharmaceutical ingredients belonging to different therapeutic categories* viz *antiviral, anti-inflammatory, antidiabetic, antihypertensive, anti-convulsant, antibiotic, bronchodialator, antimalarial, antiemetic, antiamoebic, antipsychotic, antidepressant, anticancer, anticoagulant and sedative/hypnotic drugs and vitamins. Once the solid-state reactions of a pharmaceutical system are understood, the necessary steps can be taken to avoid reactivity and improve the stability of drug substances and products.*

13. L. C. S. Cides et al[45] *proposed that the thermal decomposition of glimepiride (sulfonylurea hypoglycemic agent) was 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. 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.*

14. ***Lima Naiana G. P. B. et al[46]*** *proposed that, the evaluate the compatibility of trioxsalen with pharmaceutical excipients used in the solid forms by analytical techniques. Binary mixtures between the trioxsalen and pharmaceutical excipients (namely, magnesium stearate, a-lactose, microcrystalline cellulose 102, pregelatinized starch, mannitol, sodium lauryl sulfate, sodium starch glycolate, and croscarmellose sodium) were examined. The trioxsalen–sodium lauryl sulfate mixture displayed some physical interaction based on the DTA and DSC results, but the FTIR study ruled out any chemical change.*

15. ***Shantikumar S. et al[47]*** *proposed that, the DSC used as a screening technique for assessing the compatibility of sitagliptin with some currently employed pharmaceutical*

excipients. The influence of processing conditions and their effects (simple blending, co-grinding or kneading) on drug stability was evaluated. Sitagliptin showed a sharp endothermic peak at 212.1 _C with an enthalpy change of 131.5 J g-1 indicating melting of drug. Facile transformation of dehydrated sitagliptin to monohydrate form was observed in some mixtures, disappearance of sharp melting endothermic peak of sitagliptin was observed in some mixtures. On the basis of DSC results, sitagliptin was found to be compatible with micro crystalline cellulose, croscarmellose, and pregelatinized starch. Some excipient interaction was observed with magnesium stearate, ascorbic acid, and citric acid. X-ray diffractometry and FT-IR were used as supportive tools in interpreting the DSC results. Overall, the excipients selected were compatible. with the API and the mixtures are stable within the tested conditions. These results would be useful for formulation development of the film coated tablets of sitaglitptin.

16. ***Leandro de O. Porfi´rio et al***[24] *proposed that, this study intends to develop hydroxypropylmethylcellulose films (HPMC) containing AZT and films containing 3TC, and assess the existence of drug/polymer interactions bymeans of thermal analysis techniques [differential scanning calorimetry (DSC) and thermogravimetry (TG)/derivative TG (DTG)], Fourier transform infrared (FTIR) spectroscopy, and X-ray diffraction (XRD), contributing to the optimization of antiretroviral therapy. The films produced showed drying uniformity and drug distribution.DSCcurves indicated that these drugs may be in an amorphous form dispersed in the polymericmatrix. Thermal decomposition profiles obtained in the TG/DTG studies of films containing drugs showed similarities with the curves of their respective physical mixtures. The FTIR spectra showed the characteristic bands conservation of AZT and 3TC isolated in the films with drugs. The results indicate that these drugs did not undergo a process of degradation or chemical interaction with the polymer that would lead*

to the modification or alteration of their chemical structures. XRD studies confirmed that these drugs were homogenously dispersed in the polymeric matrix. These results also showed that there was no drug/polymer incompatibility in HPMC films.

17. ***Lima I´ gor Prado de Barros et al***[34] *proposed that Thermal techniques, such as differential scanning calorimetry (DSC), thermogravimetry (TG), derivate of TG curve, differential thermal analysis, and non-thermal techniques such as fourier transform infrared (FTIR) spectroscopy and X-ray diffractometry (XRD) were used to evaluate the possible interactions between hydroquinone (HQ) and excipients commonly used in semi-solid pharmaceutical forms. The DSC curve of HQ showed a sharp endothermic event between 173 and 179 _C indicating melting point. No evidence of interaction was observed between HQ and cetyl alcohol (CA), cetostearyl alcohol (CTA), disodium ethylenediaminetetraacetate , and decyl oleate. However, based on the thermoanalytical trials, a physical interaction was suspected between HQ and dipropylene glycol (DPG), glycerin (GLY), hydroxypropyl methylcellulose (HPMC), imidazolidinyl urea (IMD), methylparaben (MTP), and propylparaben (PPP). The FTIR results show that for DPG, GLY, HPMC, MTP, and PPP, there were no chemical interactions with HQ at room temperature, but the heating promotes interaction between HQ and HPMC. The FTIR spectra of HQ/IMD show the chemical interaction at room temperature, which was also observed with heating. The XRD results of mixtures between HQ and DPG, HPMC, IMD, MTP, and PPP indicate no interaction between these substances at room temperature, but the heating modifies the HQ crystallinity in these mixtures. All of these methods showed incompatibility between HQ and the excipient IMD.*

18. ***Simone Buarque Tavares Dias et al***[35] *proposed that , polymorphic characterization and compatibility study of clozapine. Different solvatomorphic forms of clozapine were obtained by recrystallization technique. Polymorphic characterization was performed using optical microscopy, SEM, intrinsic dissolution, and thermal analysis. Compatibility studies of clozapine:excipients were performed by TG and DSC techniques. The polymorphic characterization obtained by analytical and thermal techniques showed the formation of a solvatomorphic form of clozapine (clozapine monohydrate) when recrystallized in aqueous solvents and in alkaline medium. The polymorphic form (clozapine anhydrate) showed higher intrinsic dissolution rate compared to solvatomorphic form (clozapine monohydrate). All industrial batches of clozapine presented in anhydrate form. The DSC/TG data demonstrated similar melting peaks for 2 polymorphic forms, but desolvation peaks characteristic of monohydrate form was observed in clozapine monohydrate. Studies of binary mixtures showed no incompatibilities between clozapine and excipients, except for clozapine:lactose which can reduce the stability of bulk and tablets of clozapine. Tablets of clozapine presented the same thermal analysis profile of clozapine:lactose but did not contribute in decreasing shelf life of clozapine tablets before 24 months of storage.*

19. ***Rui Gao et al*** [37] *proposed that, the drugexcipient compatibility of binary mixtures (BMs) (1:1 BMs, w/w), initially by differential scanning calorimetry (DSC), and subsequently, by complementary techniques such as X-ray powder diffraction (XRPD) and high performance liquid chromatography (HPLC) if there was any evidence of interaction. The samples were stored under accelerated stability conditions (40 _C at 75 % relative humidity). The DSC curves of estradiol and the BMs with excipients (corn starch, lactose, xanthan gum, microcrystalline cellulose, magnesium stearate, dibasic calcium phosphate, and talc) were obtained. The results show that estradiol was compatible with all the selected excipients. XRPD and HPLC analysis were instrumental in interpreting the DSC results and excluding*

relevant pharmaceutical incompatibilities in all cases. Overall, the compatibility of the selected excipients with estradiol was successfully evaluated using a combination of thermal and spectroscopic methods, and the formulations developed using the compatible excipients were found to be stable.

20. ***I´ gor Prado de Barros Lima et al***[36] *proposed that The analysis of the FTIR spectra of TRET/excipient binary mixture (BM) was also conducted by a method of Pearson's correlation, which calculated the difference between the theoretical and experimental FTIR spectra. The TRET, excipients and BM were heated at 200 _C to be analyzed by FTIR and XRD. The physical interactions suggested were mainly observed in the results obtained by thermal techniques with TRET/ MTP, TRET/PPP, TRET/CA, and TRET/CTA, but in the TRET/IMD, the FTIR technique shows that there was chemical interaction between these components. The heating of samples changed the chemical structure of the TRET in the TRET/CTA, as well as changed the crystallinity of the TRET in the TRET/MTP and TRET/PPP BM. SEM microphotograph of the mixtures showed no adhesive interfaces in mixtures suggesting that no intense physical interactions between these pharmaceutical raw materials at room temperature.*

CHAPTER 3

AIM AND OBJECTIVES*:*

The aim of the present investigation is to evaluate the compatibility of glimepiride with common pharmaceutical excipients, used in the solid dosage form, by means of DSC and Fourier transformed infrared (FT-IR) study for the development of extended release formulations.

NEED OF THE STUDY:*[21,25,27]*

The thermal techniques of analysis will be used to assess the compatibility between glimepiride and some excipients used in the development of extended 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 and its physical association as binary mixtures with some common excipients will be evaluated by FT-IR, differential scanning calorimetry. FT-IR spectroscopy and X-ray powder diffraction (XRPD) 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 the drug. 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.

CHAPTER 4

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3. DRUG PROFILE:[35,38]

3.1 Glimepiride dgug profile:

The products contain the active ingredient glimepiride and are indicated for the treatment of a type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group.

Glimepiride acts mainly by stimulating insulin release from pancreatic β-cells. As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic β-cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extra-pancreatic effects also postulated for other sulphonylureas.

Glimepiride acts at ATP-sensitive potassium channels (KATP) on pancreatic β-cells to promote insulin release. It binds to 65 kD protein on β-cells, which appears to be a part of the same sulphonylurea receptor that bind glibenclamide. Glimepiride after oral administration lowers blood glucose 3.5 times more potently than glibenclamide. It may be used in non-insulin dependent diabetes mellitus.

3.2Chemistry:

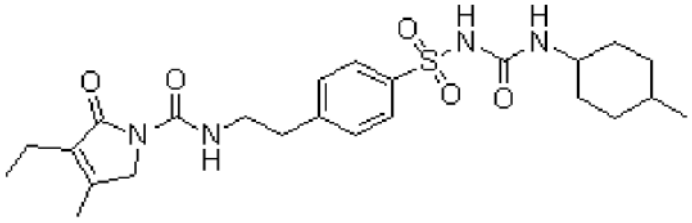
INN: Glimepiride

Chemical Name: 1) H*-pyrrole-1-carboxamide, 3 -ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(trans-4-methylcyclohexyl) amino] carbonyl] amino] sulfonyl] phenyl] ethyl]-2-oxo-*

trans-*,2)* *1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl] phenyl]sulphonyl]-3-(*trans*-4-methylcyclohexyl) urea.*

Molecular Formula: C24H34N4O5S

Structure:



Molecular Weight: 490.62

Glimepiride is a white or almost white powder with a melting point of 205.0 to 208.0°C. It is practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride and very slightly soluble in methanol. Glimepiride exhibits polymorphism. Glimepiride is a trans-isomer. Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. An appropriate specification is provided for the active substance glimepiride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Appropriate proof of structure has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Acceptable certificates of analysis have been provided for all reference standards used. Batch analysis data are provided and comply with the proposed specification. Appropriate stability data have been generated to support the proposed retest period.

3.3. Pharmacokinetics: *[38]*

2-mg oral tablet of glimepiride Gastrointestinal absorption is complete, with no interference from meals. Significant absorption can occur within one hour, and distribution is throughout the body, 99.5% bound to plasma protein. Metabolism is by oxidative biotransformation. Excretion in the urine is 65%, and the remainder is excreted in the feces.

3.4..Drug-Drug Interactions:[8,39]

Nonsteroidal anti-inflammatory drugs (such as salicylates), sulfonamides , chloramphenicol , coumadin and probenecid) may potentiate the hypoglycemic action of glimepiride. Thiazides , other diuretics , phothiazides, thyroid products, oral contraceptives, and phenytoin tend to produce hyperglycemia .

3..5.Contraindications:

Sulfonylurea Glimepiride (Glimer) is indicated to treat type 2 diabetes mellitus ; its mode of action is to increase insulin production by the pancreas. It is not used for type 1 diabetes because in type 1 diabetes the pancreas is not able to produce insulin.Its use is contraindicated in patients with hypersensitivity to glimepiride or other sulfonylureas, and during pregnancy.

3.6.Side Effects

Sulfonylurea Side effects from taking glimepiride include gastrointestinal tract (GI) disturbances, occasional allergic reactions, and rarely blood production disorders including thrombocytopenia, leukopenia, and hemolytic anemia. In the initial weeks of treatment, the risk of hypoglycemia may be increased. Alcohol consumption and exposure to sunlight should be restricted because they can worsen side effects.

3.7.Uses:

Sulfonylurea Glimepiride (Glimer) is indicated to treat type 2 diabetes mellitus. Glimepiride is a medium- to long-acting sulfonylurea antidiabetic drug. It is marketed as GLEAM by

Franco Indian Pharmaceuticals,K- GLIM-1 by BLUE CROSS , Glucoryl by Alkem Lab PVT LTD , Amaryl by Sanofi-Aventis , GLIMPID by Ranbaxy Laboratories (Cardiovascular) and GLIMY by Dr.Reddy's Labs .

3.8 Dose:

It is administered orally dose of Tablet 1, 2, and 4 mg .Usual Adult Dose for Diabetes Type 2

Initial dose:

1 to 2 mg orally once a day. Maintenance dose: 1 to 4 mg orally once a day. Glimepiride should be administered with breakfast or the first main meal. Maximum recommended dose is 8 mg per day.

Usual Geriatric Dose for Diabetes Type 2 Initial dose: *1 mg orally once a day. Maintenance dose: 1 to 4 mg orally once a day.*

Usual Pediatric Dose for Diabetes Type 2 >8 years :

Initial dose: 1 to 2 mg orally once a day. Maintenance dose: 1 to 4 mg orally once a day. Glimepiride should be administered with breakfast or the first main meal. Maximum recommended dose is 8 mg per day.

Renal Dose Adjustments CrCl < 30 mL/min: Initial dose: *1 mg orally once a day. Maintenance dose: 1 to 4 mg orally once a day.*

Liver Dose Adjustments :*After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1 or 2 week intervals. Glimepiride should be used with caution in patients with hepatic insufficiency.*

3.9..Storage:

Store the medicine in a closed container at room temperature, away from heat, Moisture, and direct light.

CHAPTER 5

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4. MATERIALS AND METHODS[34,9,41]

4.1.Chemicals and reagents:

SL NO	*Material*	*Source*
1	*Glimepiride*	*Yerrow chem., Mumbai-37*
2	*HPMC K4M*	*Himedia,Mumbai-86*
3	*Ehtyl cellulose*	*Balaji,Drugs, Mumbai-37*
4	*Lactose*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
5	*Sodium hydroxide*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
6	*Hydrochloric acid*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
7	*Potassium dihydrogen phosphate*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
8	*Sodium dihydrogen phosphate*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
9	*Magnessium stearate*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
11	*Microcrystalline cellulose 101*	
12	*Ethanol*	*Changshu Yangyuan chemical, china*
13	*Acetone*	*Changshu Yangyuan chemical, china*

14	*Methanol*	*Changshu Yangyuan chemical, china*
15	*Sodium starch glycolate*	*Merc specialist pvt ltd,shiv sagar estate, Mumbai-400018*
16	*Sodium crosecarmellose*	*Himedia,Mumbai-86*
17	*Steric acid*	*Balaji,Drugs, Mumbai-37*
18	*Monobasic potassium phosphate*	*Balaji,Drugs, Mumbai-37*
19	*Dibasic sodium phosphate*	*Balaji,Drugs, Mumbai-37*
20	*PVK30*	*Balaji,Drugs, Mumbai-37*
21	*Calcium Carbonate*	*Balaji,Drugs, Mumbai-37*

4.2.Instruments

Sl no	***Instrument***	***Company name***
1	*Digital weighing balance*	*Denver Instrument*
2	*UV Visible spectrophotometer*	*Shimadju,Model no:UV 1800 240V*
3	*FT-IR*	*Bruker Model no:10059736*
4	*DSC*	
5	*Tablet compression machine (I.P/B.P/U.S.P. standard)*	*Shakti,9001:2000 Company*
6	*Hardness tester*	*Rolex Tablet hardness tester*
7	*Friability tester*	*Rochi friabiliter*
8	*Dissolution test apparatus*	*Libinda,DS 8000*
9	*Melting point determination*	*Macroscientific works10A/UA,Janwahar Nagar, Delhi-11007*
10	*Hot air oven*	*International commercial Traders,18,Kolkata-700001*
11	*Bulk density apparatus*	*Rolex*
12	*Viscometer*	*Brookfield viscometer DV-E viscometer*
13	*Texture Analyzer*	*Stable Microsystem,Model:TA-XT Express*

4.3. Preformulation studies of drug and excipients:

4.3.1.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 various solvent like water,0.1 N HCL, methanol, ethanol, phosphate buffer, Acetone etc.

4.3.2. Melting point determination[47]:

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.

4.3. 3.FT-Infrared spectroscopy study[29]:

This was carried out to find out the compatibility between the drug glimepiride and the various excipients like hydroxypropylmethylecelulose, ethyl cellulose,lactose, microcrystalline cellulose101, sodium starch glycolate, sodium crosscarmellose, magnesium stearate, steric acid etc. 10 mg of the sample and 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 onto the sample holder and scanned from 400 cm-1 to 4000 cm-1 in Brooker FT-IR spectrophotometer. Samples were prepared for drug 4 and physical mixture of drug and excipients. The spectra obtained were compared and interpreted for the functional group peaks.

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

Differential scanning calorimetry (DSC) of the bulk drug glimepiride and the excipients and also the mixture of drug excipients of 1:1 ratio was performed using BRUKER DSC 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 aluminum 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.

4.3.5.Viscosity determination[31-33:]

The viscosity of the polymer were determined by preparing carbopol 0.5% w/v in 50 ml water, sodium CMC 0.5% in 50 water, sodium alginate 0.5% w/v in 50 ml water, chitosan 0.5%w/v in 50 ml glacial acetic acid . The viscosities of prepared polymeric solution were

determined by using Brookfield viscometer. At 25 spindle and 1,5,10,50 rpm were selected and for determining the viscosity.

UV ANALYSIS OF THE DRUG:

4.4.1. Determination of absorption maxima (λmax) in water :

10 mg of glimepiride 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 glimepiride was found to be 279 nm.

4.4.2. 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, 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 water as blank.

4.4.3. Preparation of standard calibration in 0.1 N HCL:

10 mg of glimepiride was weighed accurately and dissolved in 10 ml of 0.1N 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 N 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 0.1N 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 279 nm using the pH 1.2 0.1N HCL buffer as blank.

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

10 mg of glimepiride was weighed accurately and dissolved in 10 ml of phosphate buffer pH 6.8 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 289 nm using phosphate buffer pH 6.8 as blank.

4.4.5.Preparation of standard caliberation in phosphate buffer pH 7.4 :

10 mg of glimepiride 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 7.4 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 7.4 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 279 nm using the pH 7.4 phosphate buffer as blank.

4.4.5.Preparation of standard caliberation in phosphate buffer pH 7.8 :

10 mg of glimepiride was weighed accurately and dissolved in 10 ml of pH 7.8 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 7.4 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 7.8 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 279 nm using the pH 7.8 phosphate buffer as blank.

4.4.7.Saturation Solubility determination[47]:

The Solubility of the selected drug was determined in distilled water,0.1N HCL,Phosphate buffer PH 6.8 in 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 sonicate for 30 min & the resultant solution was centrifuged to separate supernatant then withdrawn the supernatant and successively diluted and analyzed concentration of pantoprazole by U. V. (Ultraviolet) Spectrophotometer at 279 nm.

5.1. Pre compression parameters:[14-17]

5.1.1.Bulk density (Db)[14]:

Accurately weighed powder was carefully transferred into graduated measuring cylinder. The power bed was then made uniform and the volume occupied by the powder was noted as per the graduation marks on the cylinder as ml.It is expressed in gm/ml and is calculated using the following formula.

$$Db = M/V_b$$

Where, M - Mass of the powder

Vb - Bulk volume of the powder

5.1.2.Tapped density (Dt)[15]:

It is the ratio of total mass of powder to the tapped volume of powder. The graduated measuring cylinder containing accurately weighed powder was manually tapped for 50 times. Volume occupied by the powder was noted. It is expressed in gram/ml and is calculated by following formula.

$$Dt = M/Vt$$

Where, M - Mass of the powder

Vt - Tapped volume of the powder

5.1.3.Compressibility index (I) and Hausner's ratio[16]:

Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula.

$$I = Dt - Db/Dt \times 100$$

Where, Dt – Tapped density of the powder

Db – Bulk density of the powder

Hausner's ratio= $D_t/D_b = V_b/V_t$

5.1.4. Angle of repose (θ)[17]:

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of pantoprazole powder were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula.

Angle of repose (θ) = tan-1 (h/r)
Where, h – Height of the pile in cm
r – Radius of the pile

CHAPTER 6

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6. RESULT AND DISSCUSSION:

6.1.Preformulation study of Glimepiride:

6.1.1. Organoleptic properties:

1. Nature	*A white powder*
2. Color	*white powder*
3. Odor	*odourless.*

4. Taste	*tasteless*
5. Solubility-	
In water	*Insoluble.*
In acetone	*Insoluble.*
In methanol	*Insoluble.*
In ethanol	*Soluble.*
In phosphate buffer P^H 6.8	*Sparingly soluble.*
In phosphate buffer P^H 7.8	*Sparingly soluble.*
In DMSO water	*Soluble*

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

6.1.2. Melting point determination:

The melting point of the drug sample was found to be 215^0, which matched the melting point as reported in official pharmacopoeia (B.P). This reveals that drug sample is retaining the desired property of purity.

6.1.3. Drugs Excipients Interaction Study by FTIR spectrophotometer

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

Table: 6.1.3.1. IR interpretation of drug, lactose and physical mixture of drug-lactose:

Sl No	*Interpretatation*	*IR absorption bands (cm-1)*		
		Drug	***Lactose***	***Drug+Lactose***
1	*C-H(Aromatic)*	*2977.33*	*----*	*2946.17*
2	*C-H*	*2943.16*	*2868.90*	*2917.72*
3	*S=O*	*1079.61*	*----*	*1070*
4	*C-O*	*1344.19*	*1318*	*1391*
5	*C=N*	*1539.78*	*----*	*1586*
6	*C-N*	*1455.97*	*1419*	*1452*
7	*C-C*	*1357.97*	*1576&1644*	*1359*
8	*N-H*	*----*	*3350.79*	*____*
9	*O-H*	*----*	*3254.70*	*____*

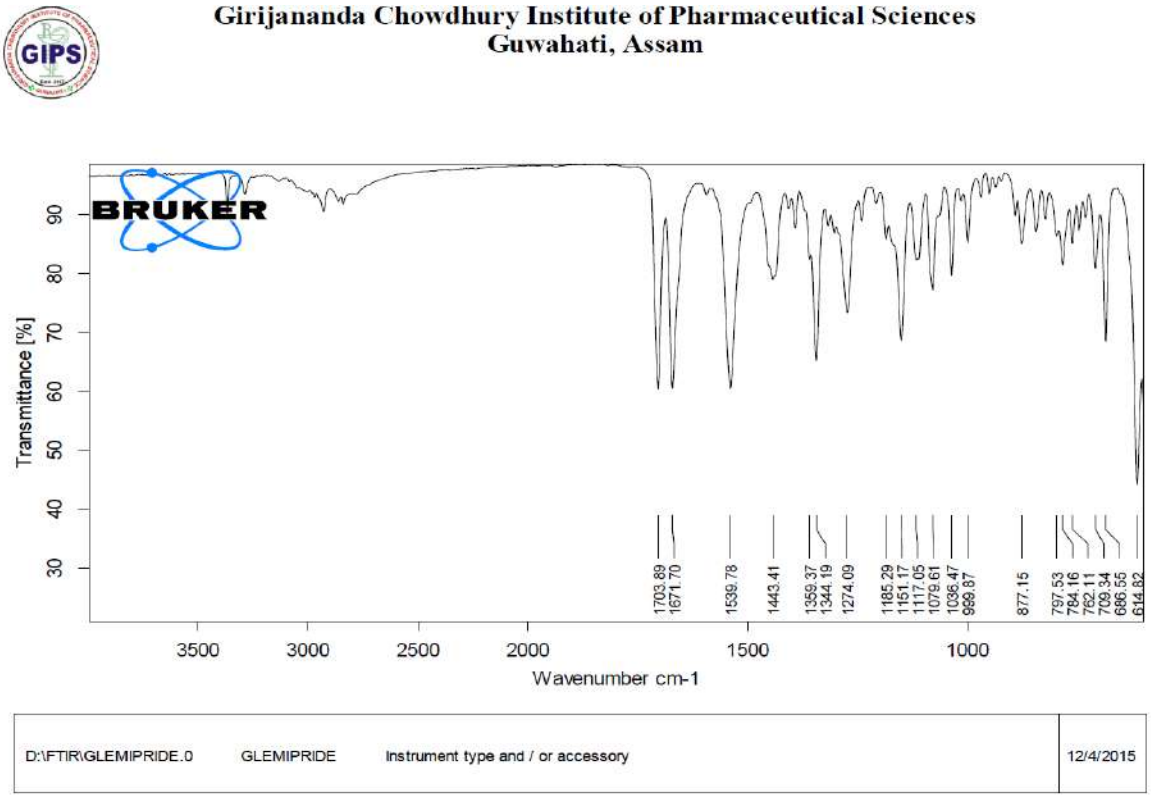


Fig: 6.1.3.1. IR spectrum of GLIMEPIRIDE

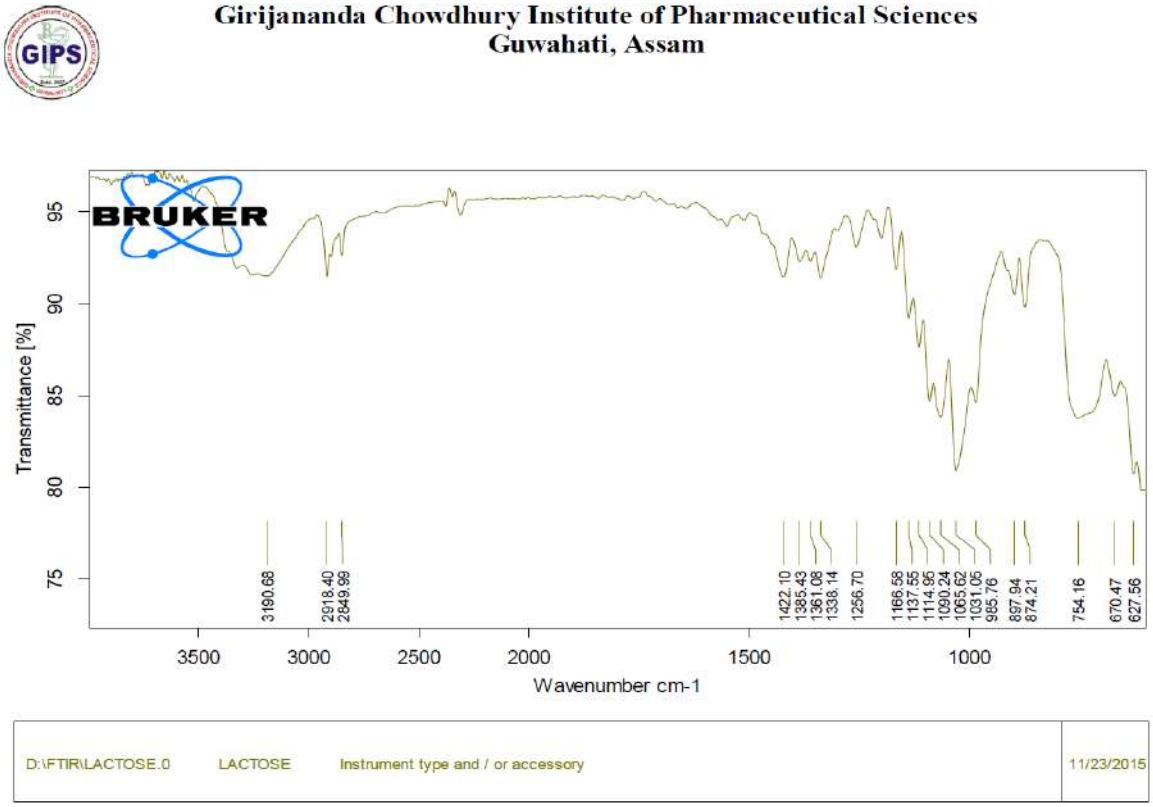


Fig: 6.1.3.2. IR spectrum of Lactose

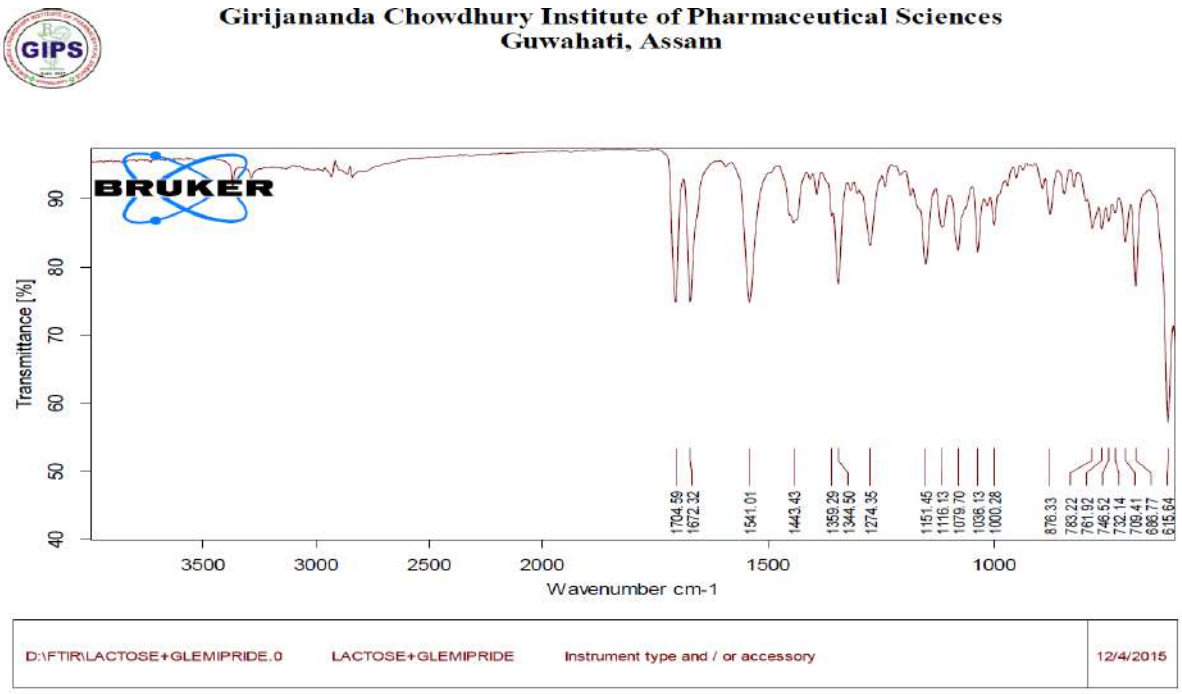


Fig: 6.1.3.3. IR spectrum of the mixture of Glimepiride and Lactose.

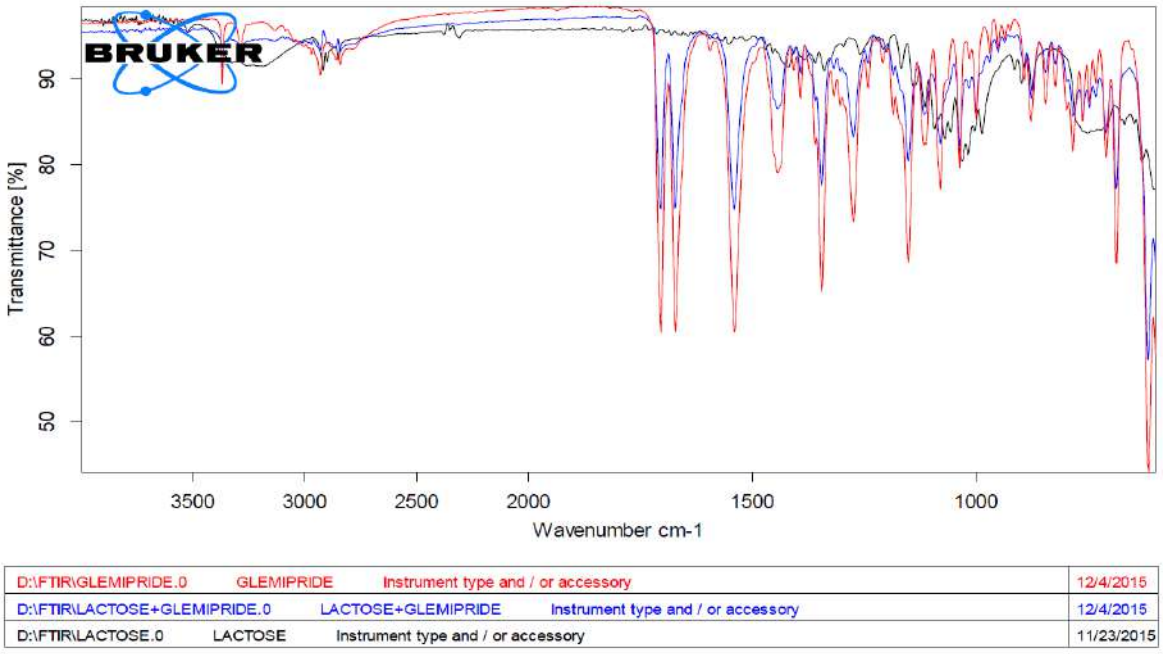


Fig: 6.1.3.4. IR spectrum of the mixture of Glimepiride and Lactose.+ Glimepiride

Table: 6.1.3.2. IR interpretation of drug, HPMC K4M and physical mixture of drug-HPMC K4M.

Sl No	***Interpretation***	***IR absorption bands (cm-1)***		
		Drug	***HPMCK4M***	***Drug+HPMCK4M***
1	*O-H*	-----	*3252.55*	-----
2	*C-H*	*2943.16*	*2923.47*	----
3	*C-O*	*1380.77*	*1730.55*	----
4	*C=N*	*1586.05*	*1593.48*	*1586.54*
5	*C-C*	*1357.97*	*1354.91*	*1360.01*
6	*C-N*	*1455.97*	*1402.05*	*1427.88*
7	*C-H(Aromatic)*	*2977.33*	------	-----

8	*S=O*	*1070.98*	*------*	*-----*

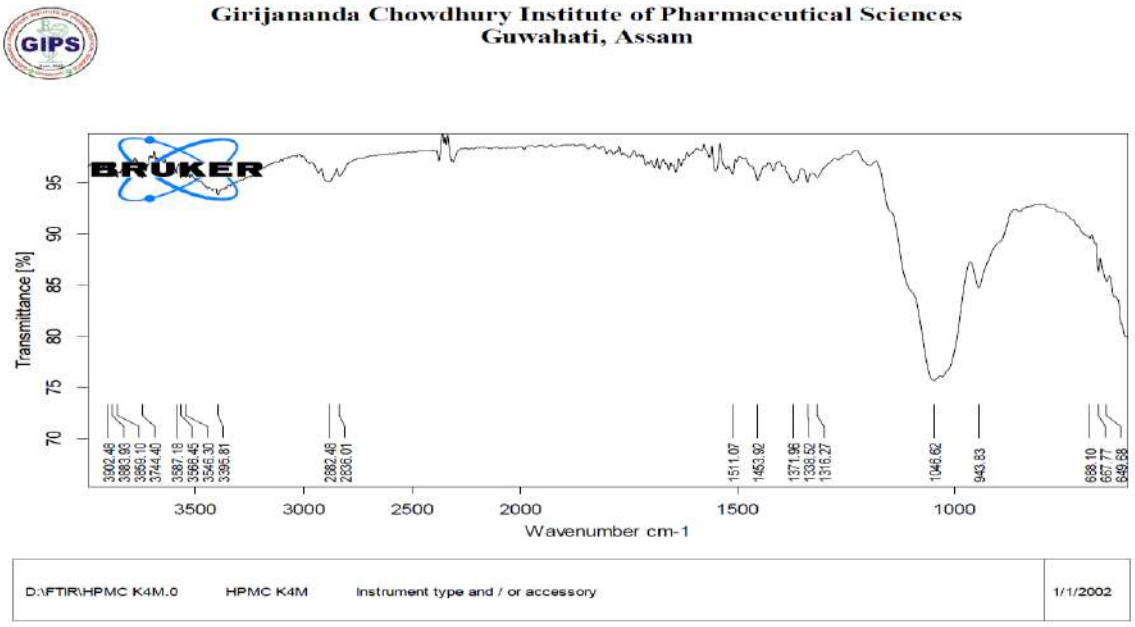


Fig: 6.1.3.2.1. IR Spectrum of HPMC K4M

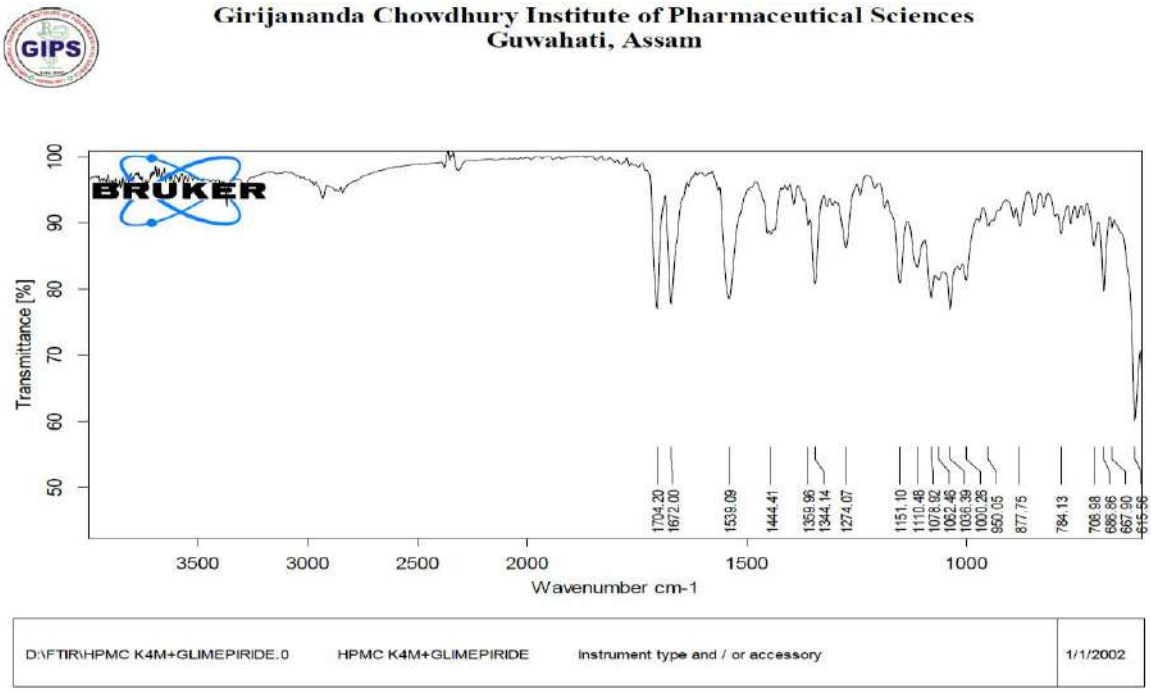


Fig: 6.1.3.2.2. IR Spectrum of the mixture of Glimepiride and HPMC K4M

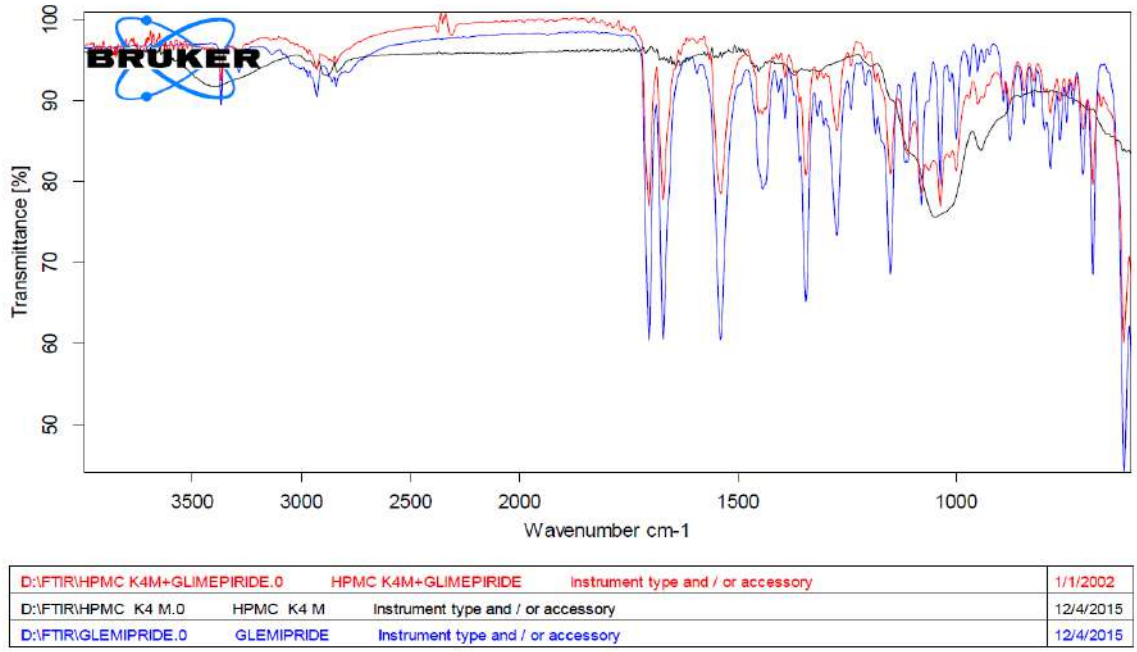


Fig: 6.2.3.IR interpretation of drug, Glimepiride and physical mixture of drug-glimepiride overlap.

Table: 6.1.3.3. IR interpretation of drugMCC and physical mixture of drug-MCC.

Sl No	***Interpretation***	***IR absorption bands (cm-1)***		
		Drug	***MCC***	***Drug+MCC***
1	*C-H(Aromatic)*	*2977.33*	----	*2820*
2	*C-H*	*2943.16*	*3010*	*3130*
3	*S=O*	*1070.98*	----	*1037*
4	*C-O*	*1380.77*	*1703*	*1704*
5	*C=N*	*1586.05*	----	*1520*
6	*C-N*	*1455.97*	----	*1428*
7	*C-C*	*1357.97*	*1413.04*	*1300*
8	*N-H*	----	-----	----
9	*O-H*	----	*2938.13*	*3302*

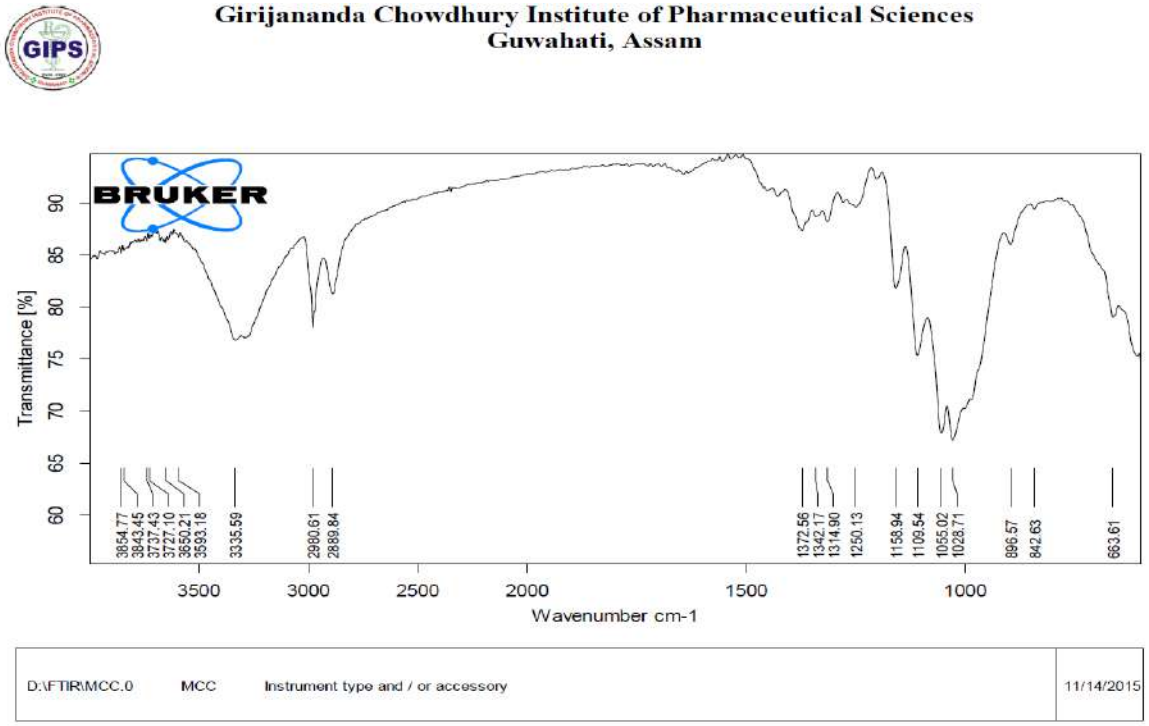


Fig: 6.3.3.1. IR Spectrum of MCC.

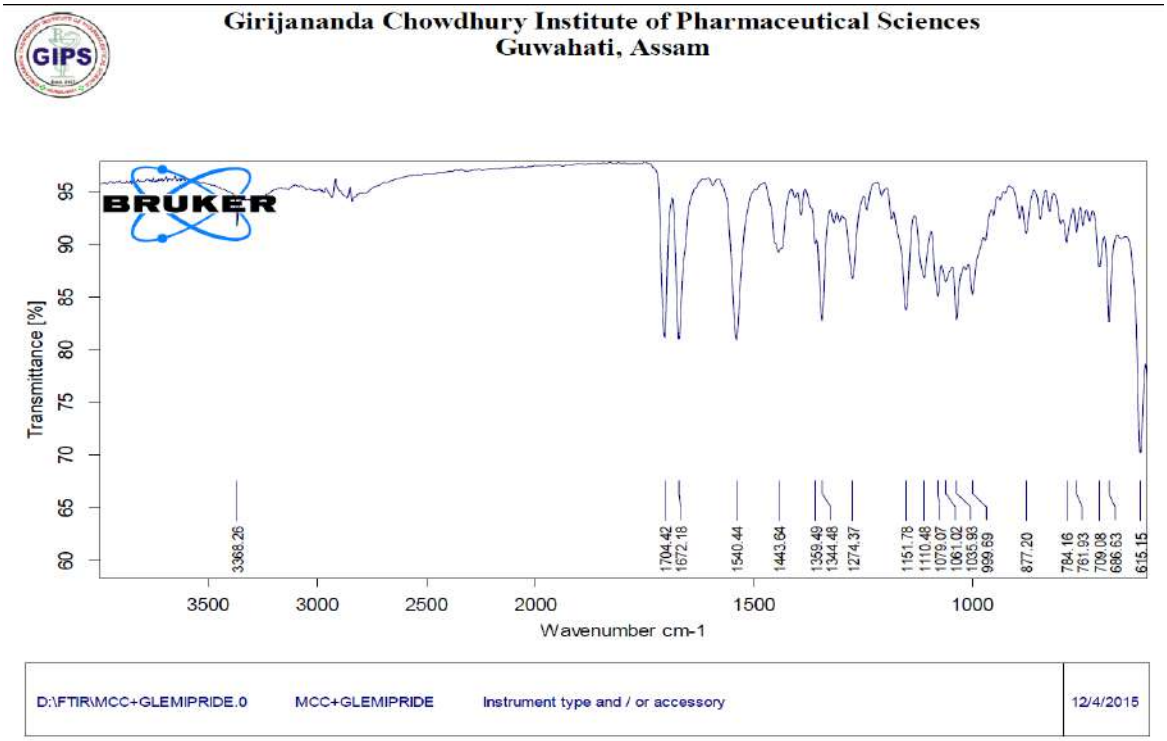


Fig: 6.3.3.2. IR Spectrum of Glimepiride+ MCC

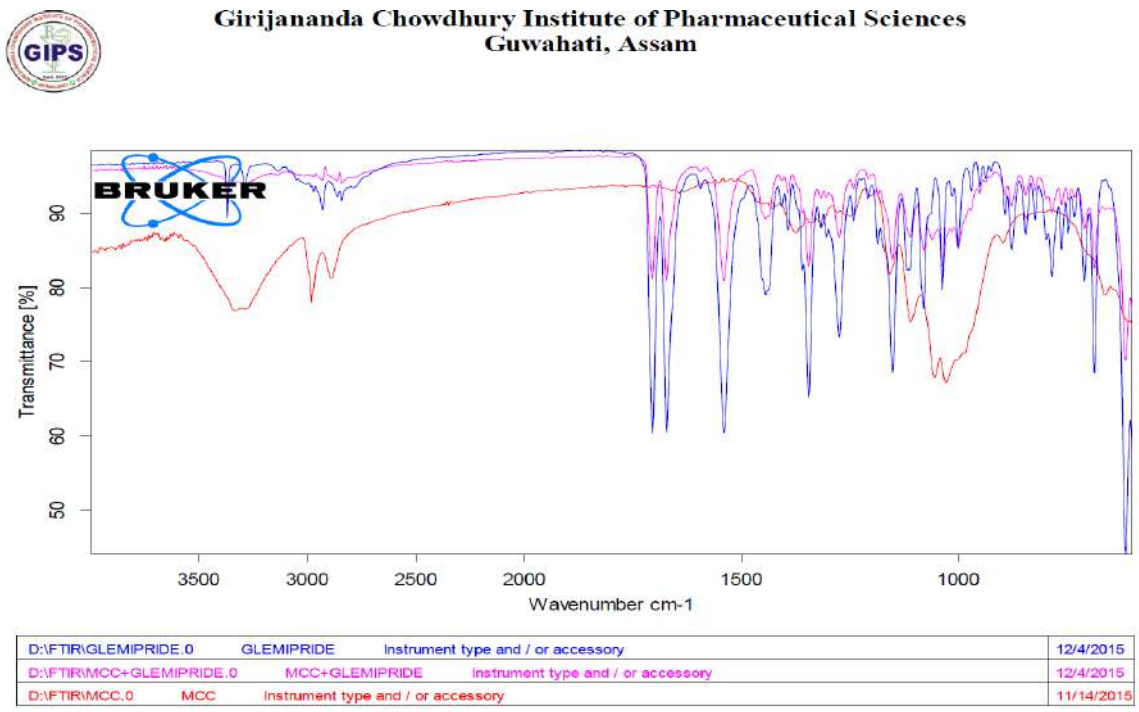


Fig: 6.3.3.3. IR Spectrum of Glimepiride,Glimepiride+ MCC overlap

Table:6.3.4. IR interpretation of drug, Magnesium sterate and physical mixture of drug-Magnesium sterate

Sl No	*Interpretation*	*IR absorption bands (cm-1)*		
		Drug	*, Magnesium sterate*	*Drug+, Magnesium sterate*
1	*C-H(Aromatic)*	*2977.33*		*----*
2	*C-H*	*2943.16*	*2934*	*2930*
3	*S=O*	*1070.98*		*1070.43*
4	*C-O*	*1380.77*	*1319*	*1301*
5	*C=N*	*1586.05*	*-----*	*1586.32*
6	*C-N*	*1455.97*	*-----*	*-----*
7	*C-C*	*1357.97*	*1409*	*------*

8	*N-H*	-----		-----
9	*O-H*	-----	*3380*	-----
10	*C=O*	-----	*1627*	-----

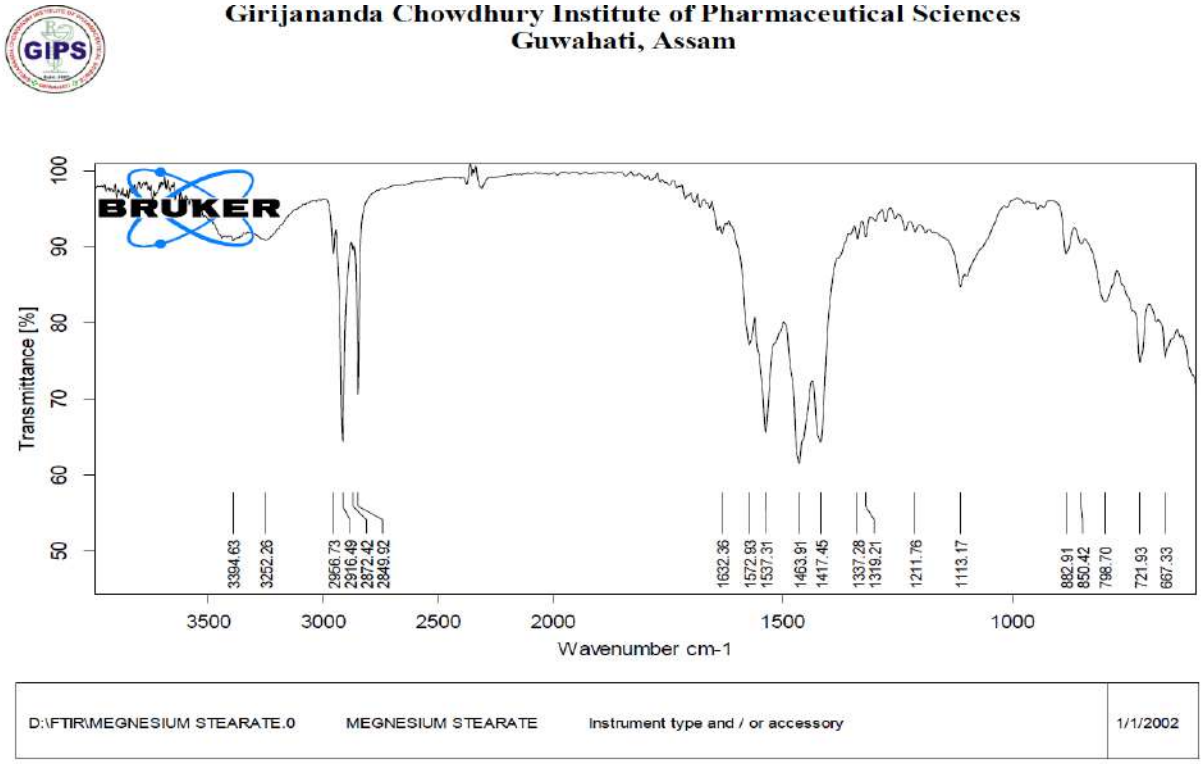


Fig: 6.3.4.1. IR spectrum of Megnesium state

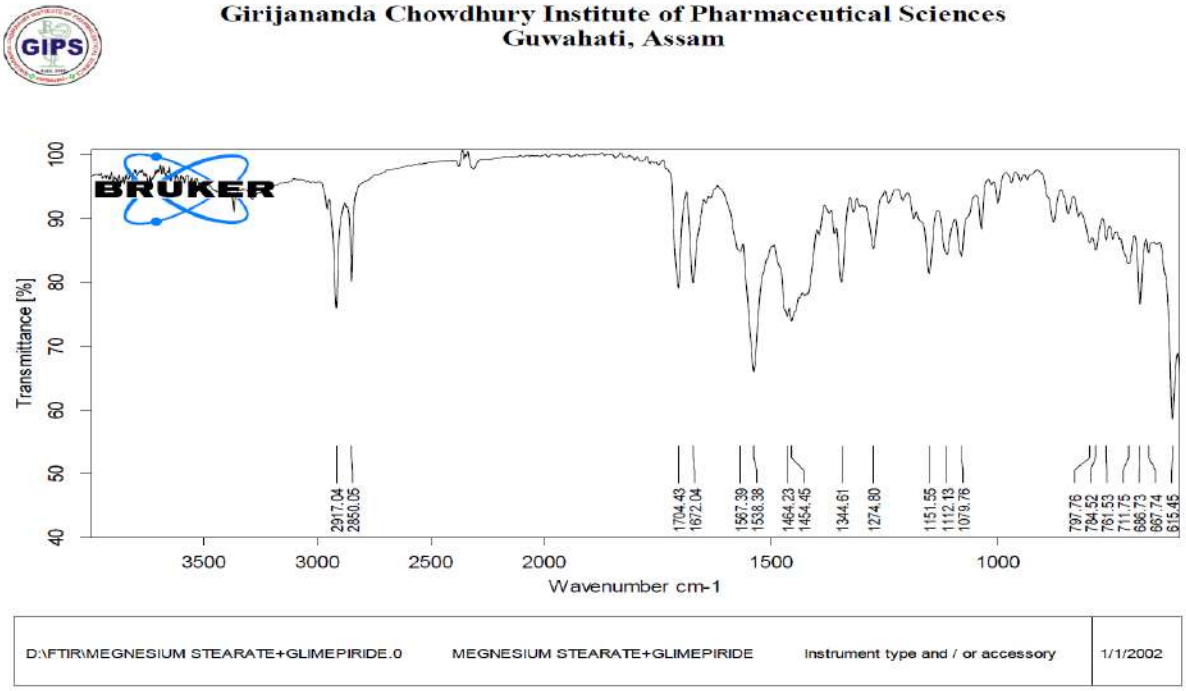


Fig: 6.3.4.2. IR spectrum of the mixture of Glimepiride+ magnesium starate

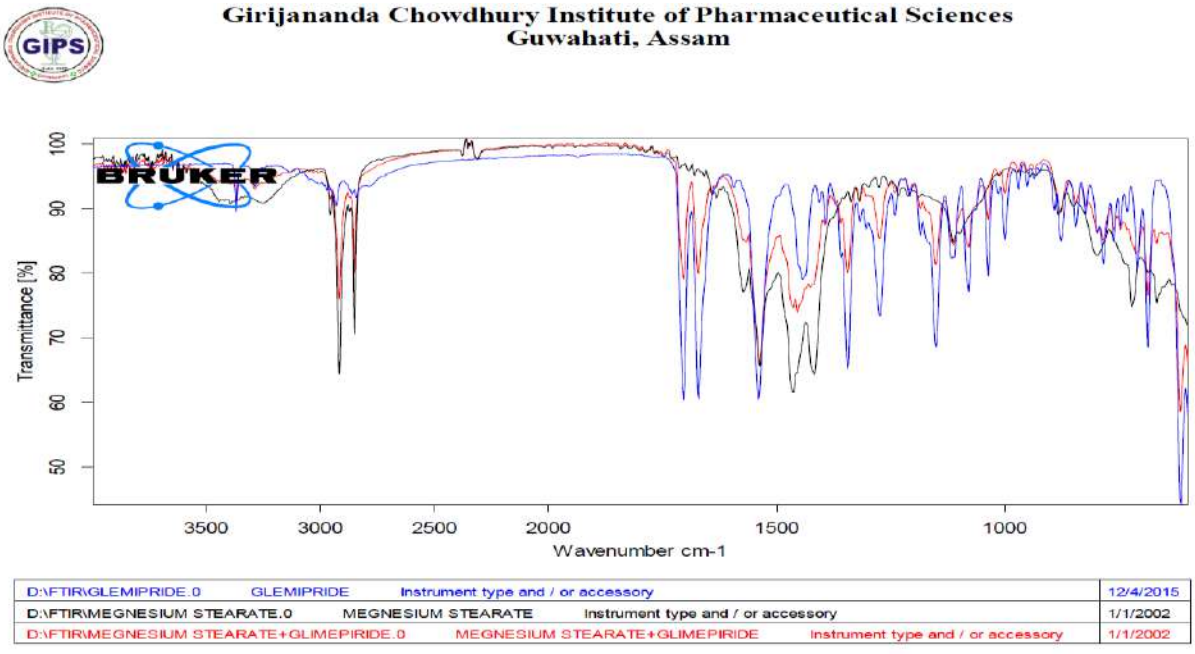


Fig: 6.3.4.3. IR spectrum of the mixture ofGlimepiride, Glimepiride+ magnesium starate overlap.

Table: 6.3.5. IR interpretation of drug, Steric acid and physical mixture of drug-steric acid

Sl. No	*Interpretation*	*IR absorption bands (cm-1)*		
		Drug	*Steric acid*	*Drug+Steric acid*
1	*O-H*	*-----*	*3252.55*	*-----*
2	*C-H*	*2943.16*	*2923.47*	*----*
3	*C-O*	*1380.77*	*1730.55*	*----*
4	*C=N*	*1586.05*	*1593.48*	*1586.54*
5	*C-C*	*1357.97*	*1354.91*	*1360.01*
6	*C-N*	*1455.97*	*1402.05*	*1427.88*
7	*C-H(Aromatic)*	*2977.33*	*------*	*-----*
8	*S=O*	*1070.98*	*------*	*-----*

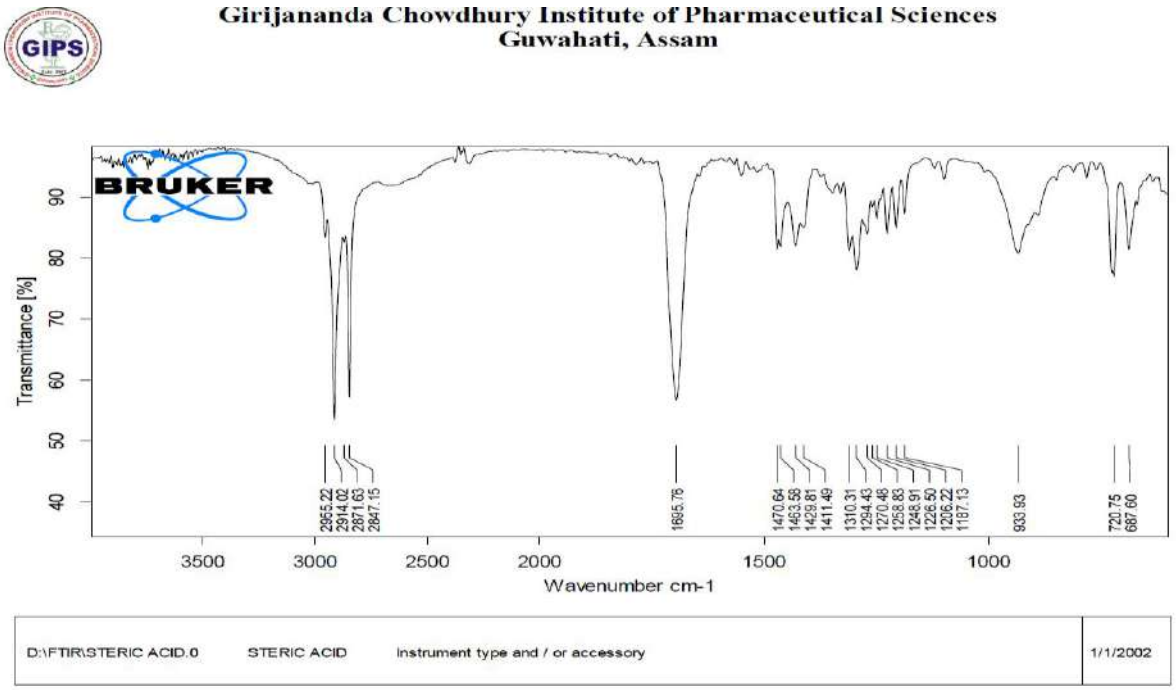


Fig: 6.3.5.1. IR spectrum of stearic acid

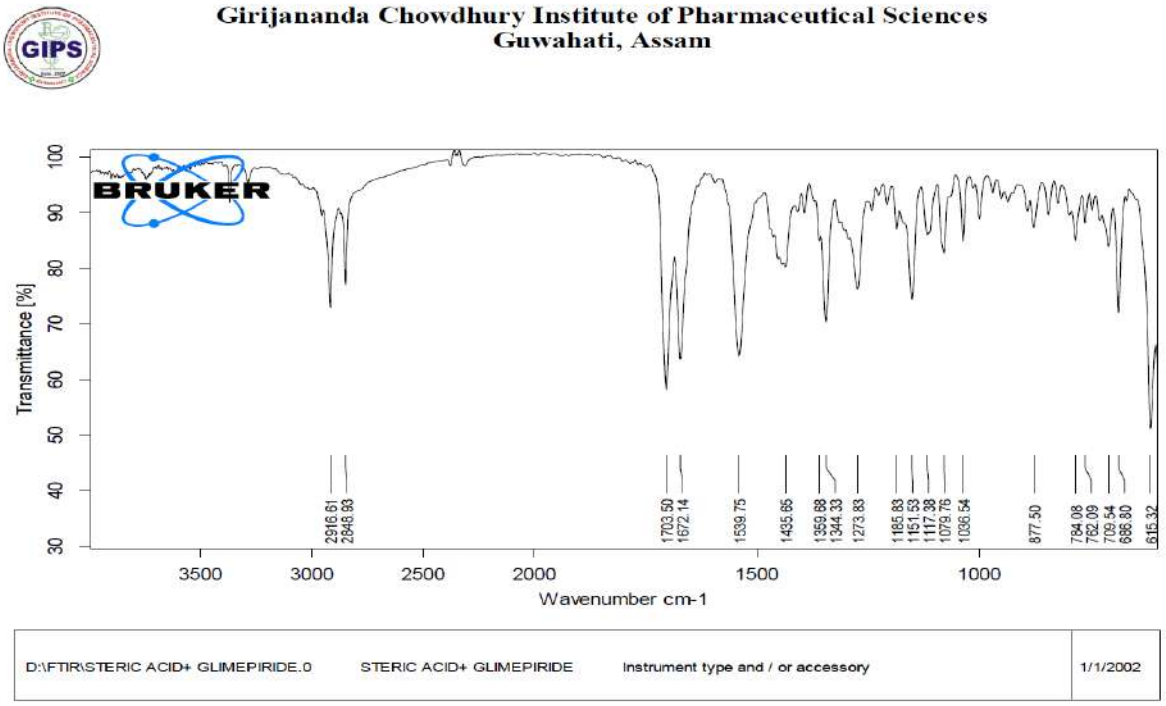


Fig: 6.3.5.2. IR spectrum of Glimepiride + steric acid

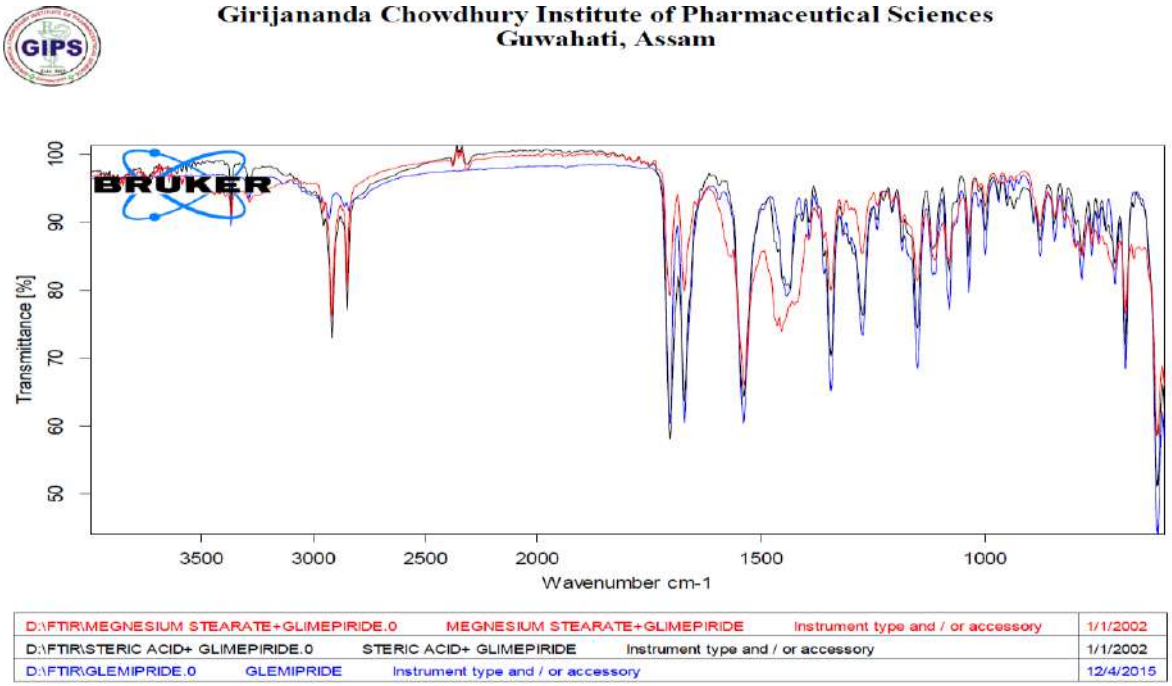


Fig: 6.3.5.3. IR spectrum ofGlimepiride, Glimepiride + steric acid overlap

Table: 6.3.6. IR interpretation of drug, Sodium cross carmellose and physical mixture of drug- Sodium cross carmellose

Sl No	*Interpretation*	*IR absorption bands (cm-1)*		
		Drug	*Sodium cross carmellose*	*Drug+ Sodium cross carmellose*
1	*O-H*	-----	*3252.55*	-----
2	*C-H*	*2943.16*	*2923.47*	----
3	*C-O*	*1380.77*	*1730.55*	----
4	*C=N*	*1586.05*	*1593.48*	*1586.54*
5	*C-C*	*1357.97*	*1354.91*	*1360.01*
6	*C-N*	*1455.97*	*1402.05*	*1427.88*
7	*C-H(Aromatic)*	*2977.33*	------	-----
8	*S=O*	*1070.98*	------	-----

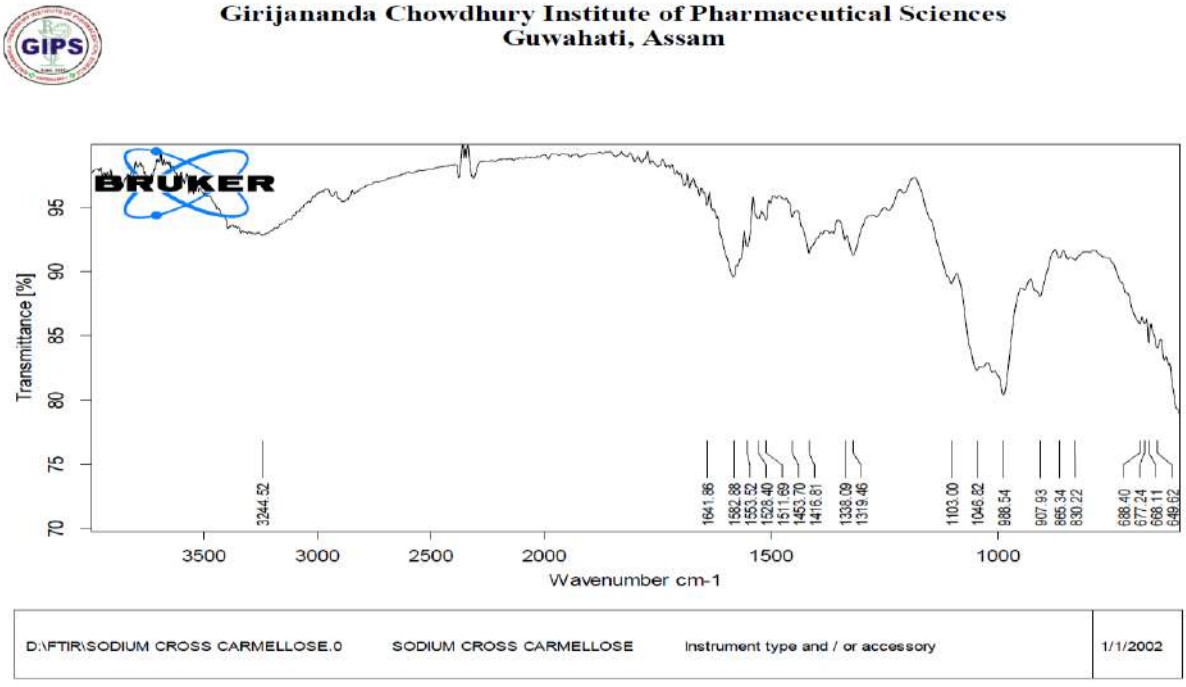


Fig: 6.3.6.1. IR spectrum of Sodium cross carmellose

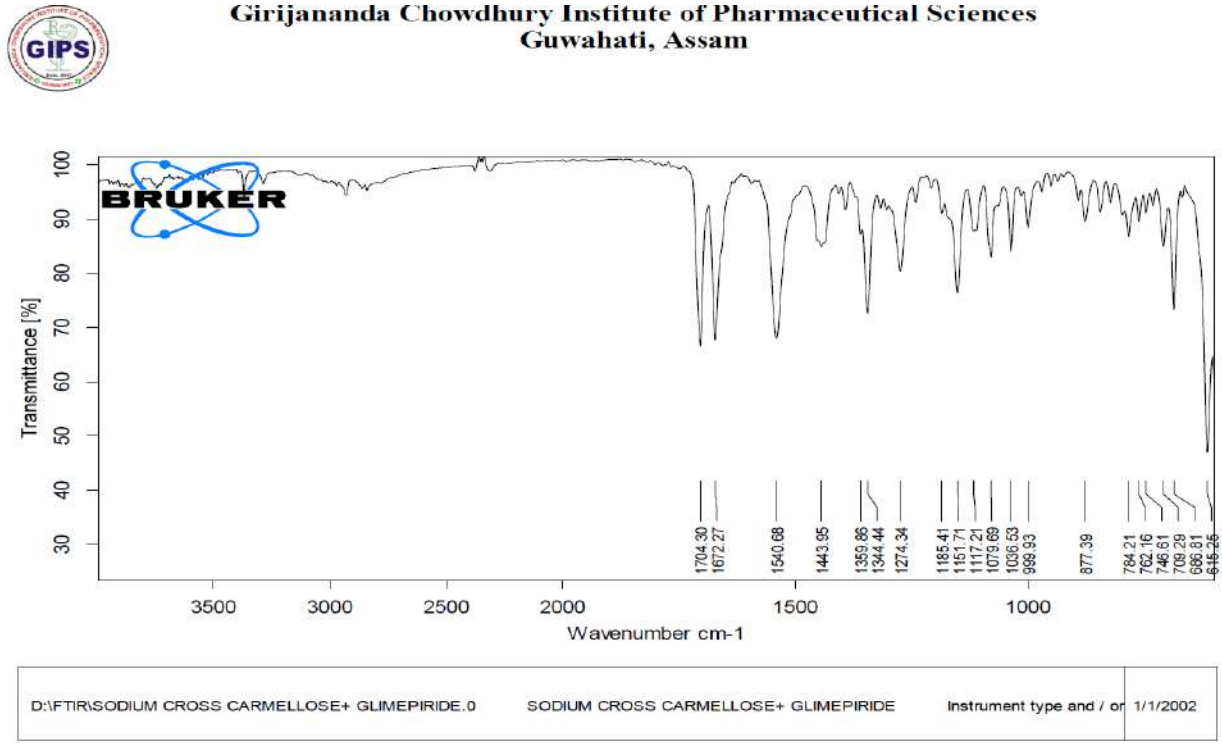


Fig: 6.3.6.2. IR spectrum of mixture of Glimepiride Sodium cross carmillose

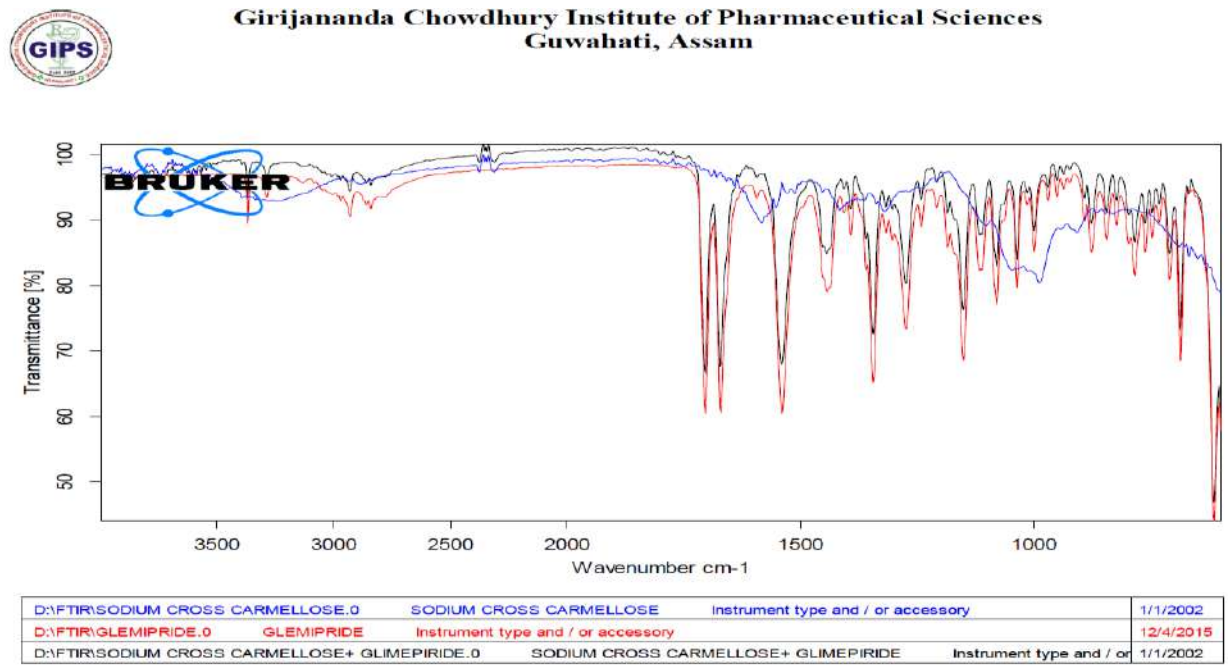


Fig: 6.3.6.3 IR spectrum of mixture of Glimepiride Sodium cross carmillose ang Glimepiride

Table: 6.3.7. 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 e***
1	*O-H*	*-----*	*3252.55*	*-----*
2	*C-H*	*2943.16*	*2923.47*	*----*
3	*C-O*	*1380.77*	*1730.55*	*----*
4	*C=N*	*1586.05*	*1593.48*	*1586.54*
5	*C-C*	*1357.97*	*1354.91*	*1360.01*
6	*C-N*	*1455.97*	*1402.05*	*1427.88*
7	*C-H(Aromatic)*	*2977.33*	*------*	*-----*
8	*S=O*	*1070.98*	*------*	*-----*

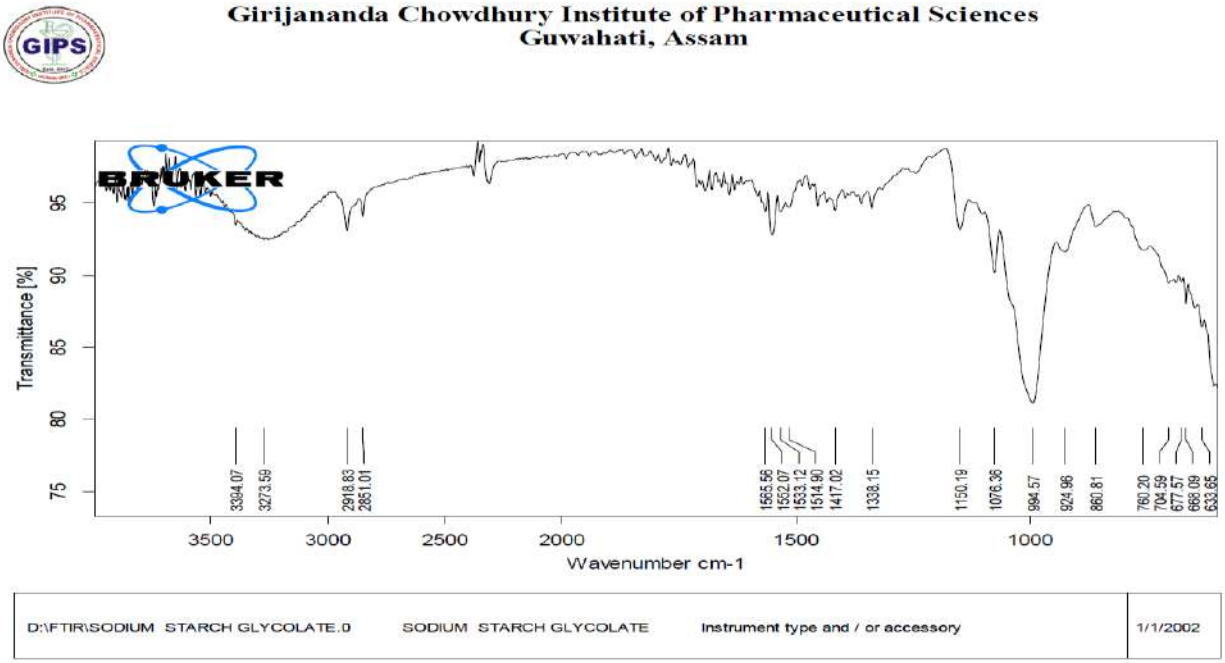


Fig: 6.3.7.1. IR spectrum of Sodium starch glycolate

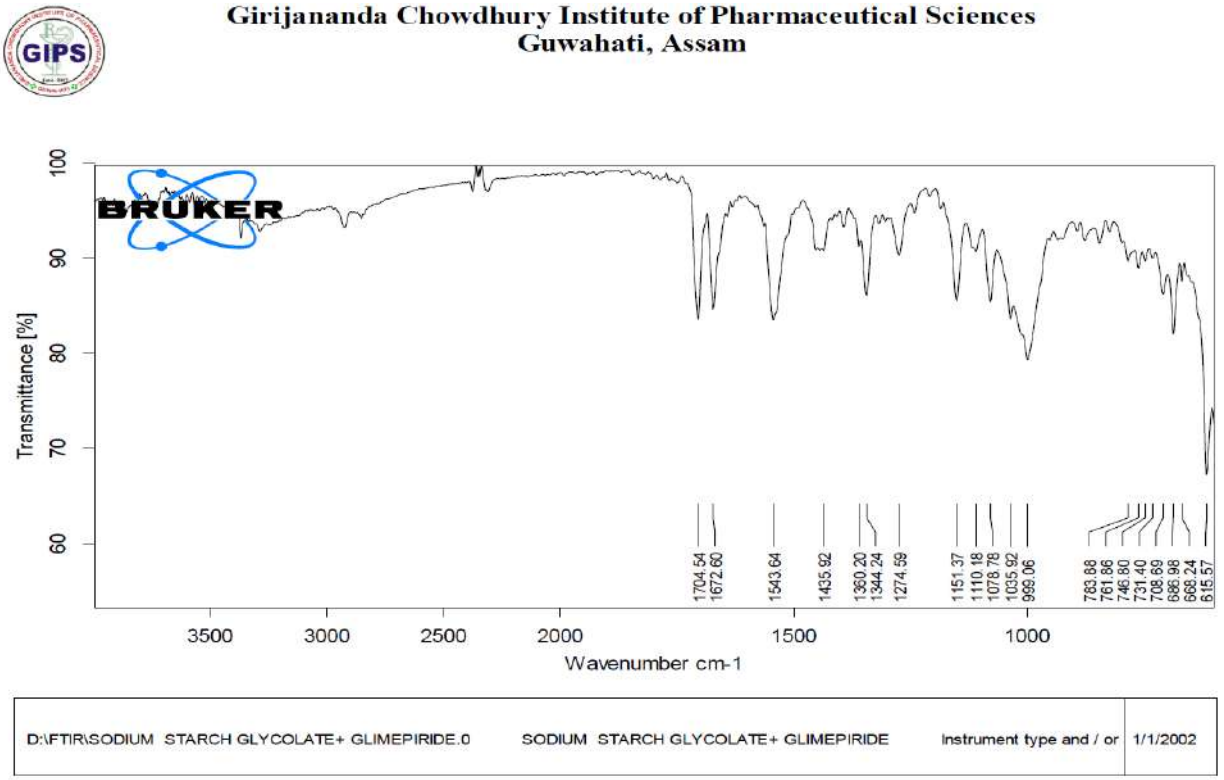


Fig: 6.3.7.2. IR spectrum of mixture of Glimepiride Sodium starch glycolate

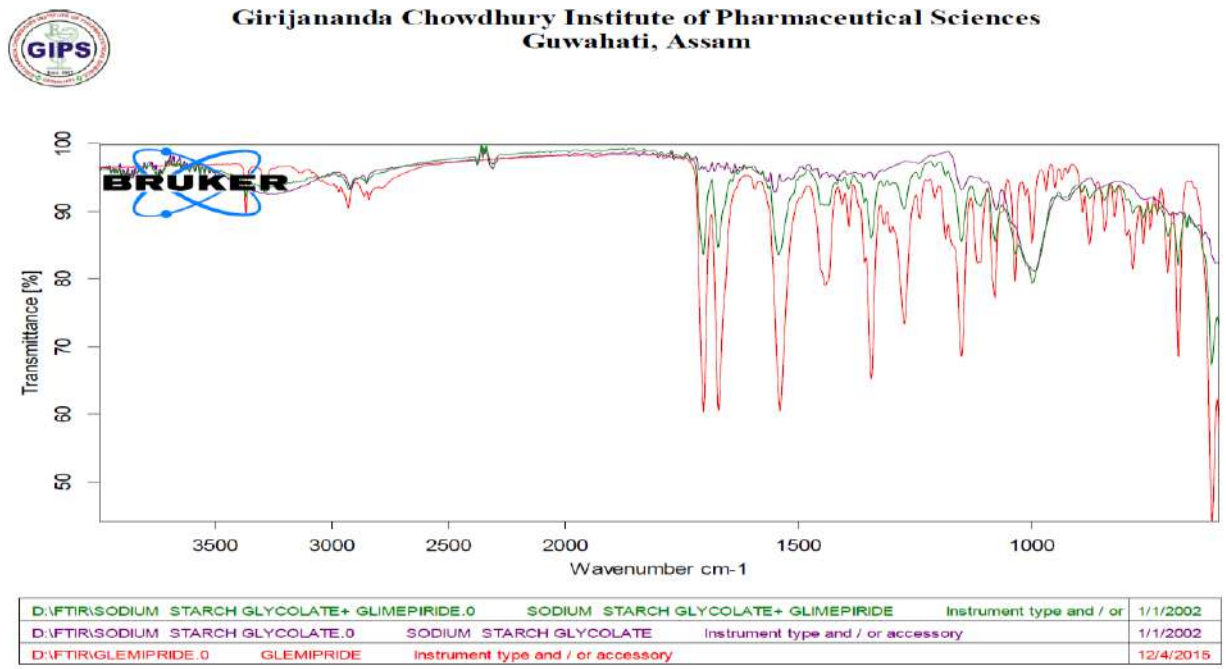


Fig: 6.3.7.3. IR spectrum of mixture of Glimepiride Sodium starch glycolate ang Glimepiride

6.3.2. DSC study[40,54]:

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 glimepiride shows a sharp endothermic peak at 216°C , which corresponds to its melting point. The tomogram of glimepiride with variuos excipient sharp endothermic peak at 156.18^{0}c,161.61^{0}c,156.52^{0}c,122.19^{0}c (fig:7.1.4.2 to 7.1.4.6) respectively, due to the presence of pantoprazole. Thus, the thermal data did not reveal any interaction between the drug and the excipients used for the prototype formulation development.

Table 6.3.2.1 Thermoanalytical data of DSC of GLIMEPIRIDE and excipients

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

Glimepiride (Drug)	*213.89*	*216.33*	*119.31*
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*
HPMC K4M	*49.64*	*74.35*	*109.80*
Sodium Cross Carmillose	*47.65*	*86.62*	*322.27*
Sodium Starch Glycolate	*50.11*	*79.34*	*74.40*
Ethyl Cellulose	*171.38*	*183.29*	*5.109*

Table 6.3.2.2 Thermoanalytical data of drug excipients physical mixture

Drug+Excipients	***T_{onset} (fusion)/^{o}C***	***T_{peak} (fusion)/^{o}C***	***ΔHfusion/J g-1***
Glimepiride+ Lactose	*193.91*	*195.46*	*132.82*
Glimepiride+ Magnesium Stereate	*213.02*	*114.25*	*890.862*
Glimepiride+ HPMC K4M	*212*	*215.22*	*201.604*
Glimepiride+ Microcrystalline cellulose	*213.02*	*216.19*	*73.40*
Glimepiride + Seric Acid	*192.64*	*193.56*	*26.65*
Glimepiride + Sodium cross carmillose	*21162*	*214.18*	*97.42*

Glimepiride + Sodium Starch Glycolate	*210.64*	*213.06*	*68.97*
Glimepiride + Ethyl Cellulose	*206.42*	*211.46*	*54.31*
Glimepiride +$CaCO_3$	*208.45*	*216.46*	*57.4*

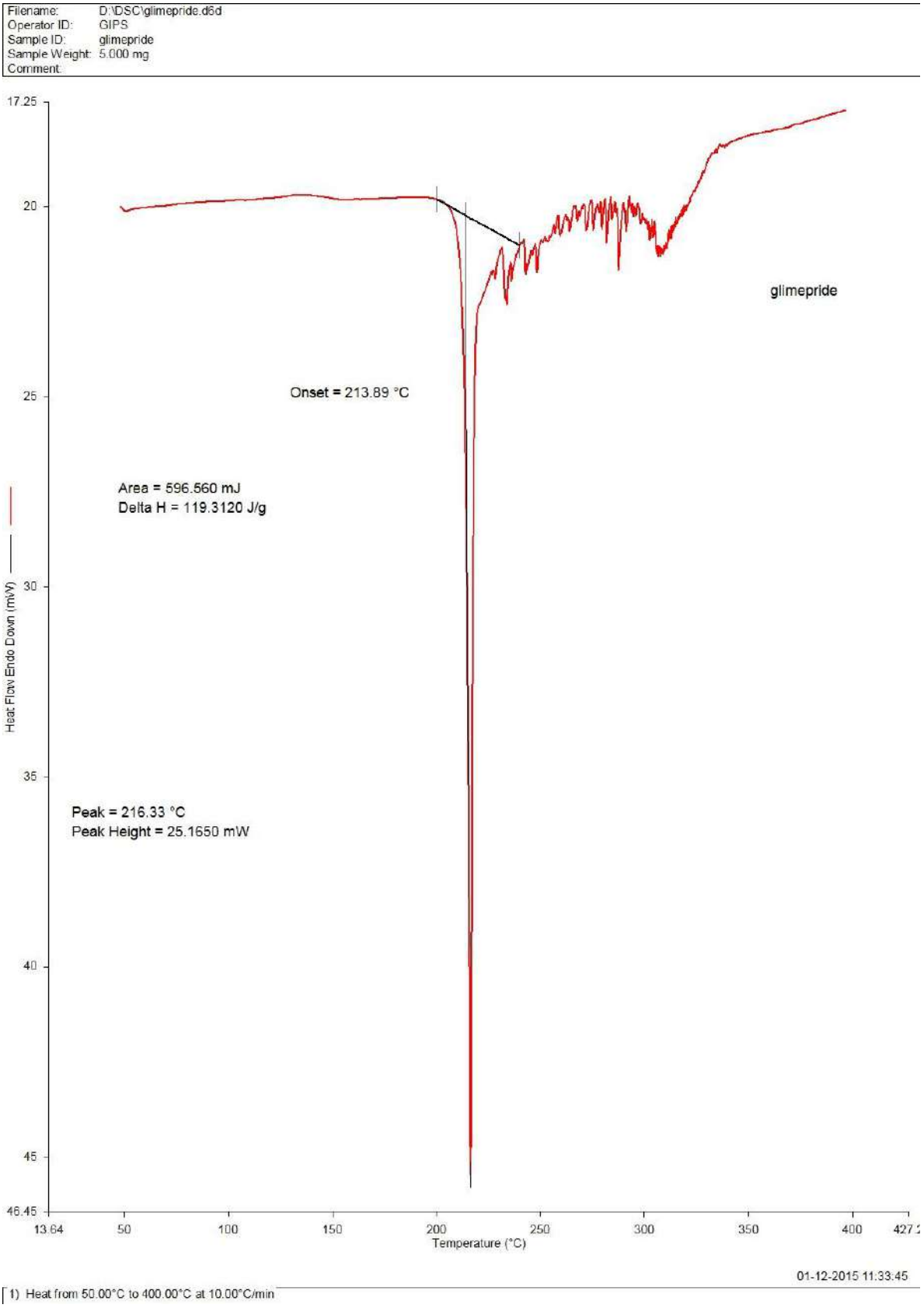


Fig: 6.3.2.1 DSC thermogram of Glimepiride

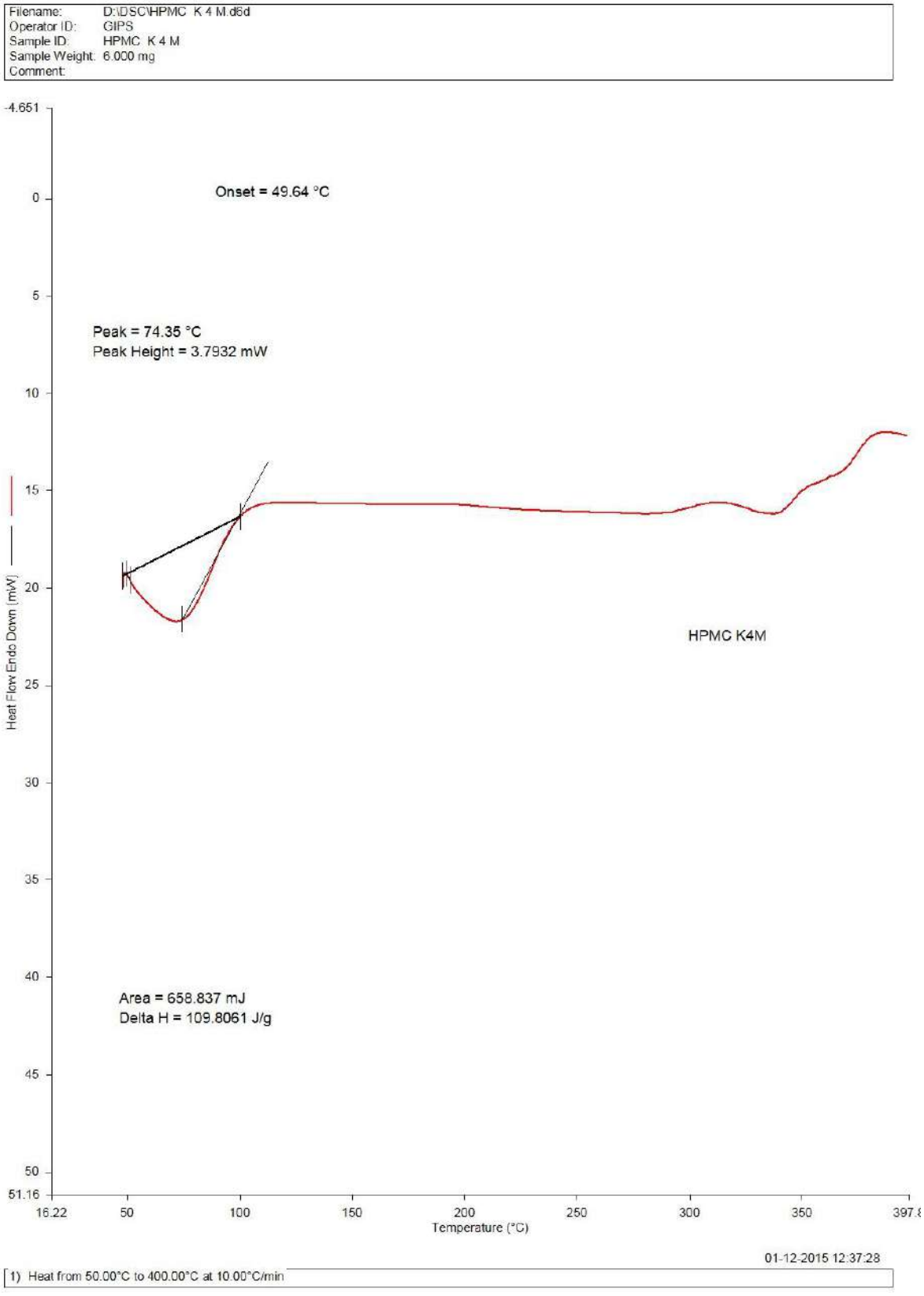


Fig: 6.3.2.2 DSC thermo gram of HPMC K4M

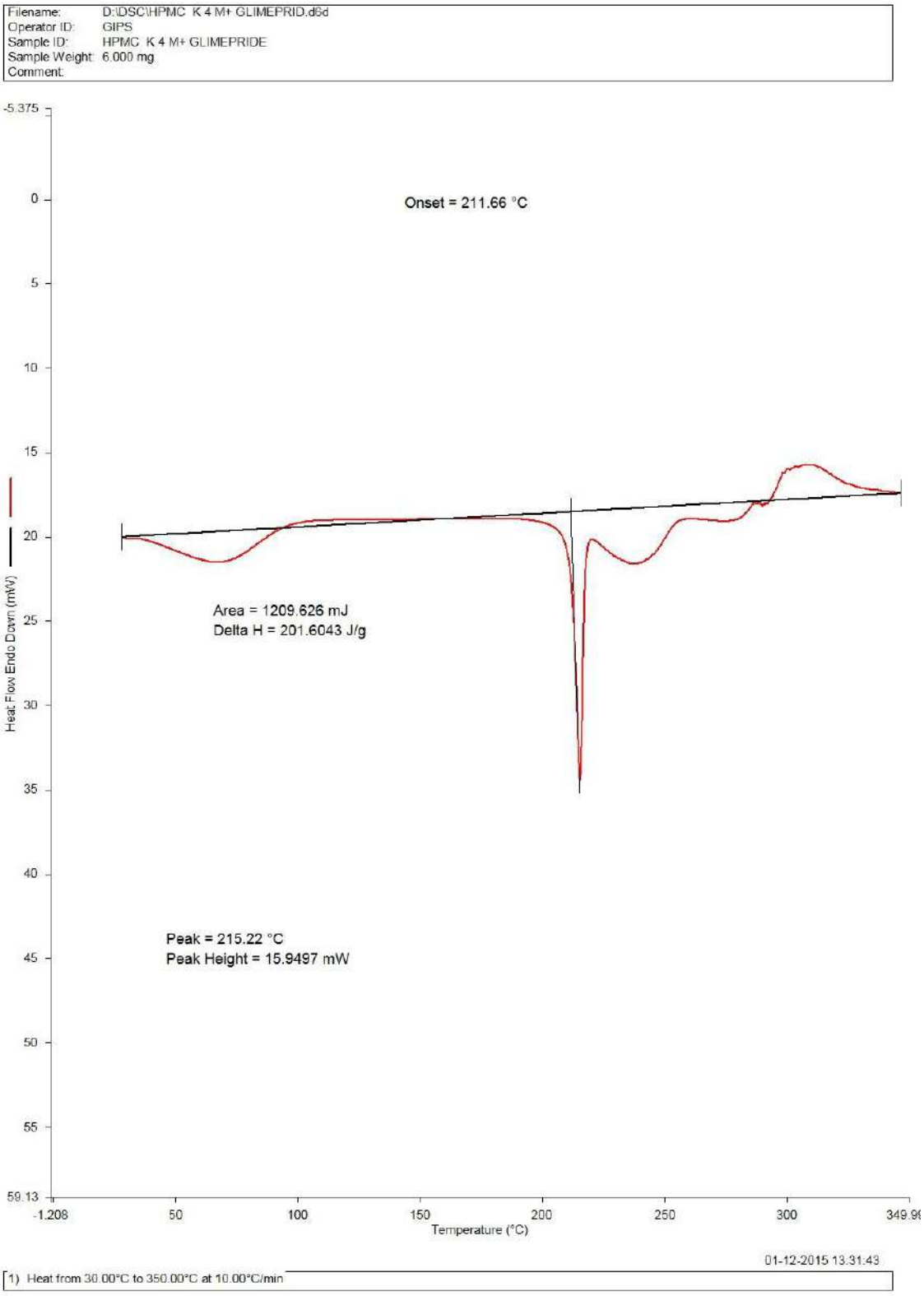


Fig: 6.3.2.3. DSC thermo gram of the mixture of Glimepiride and HPMC K4M.

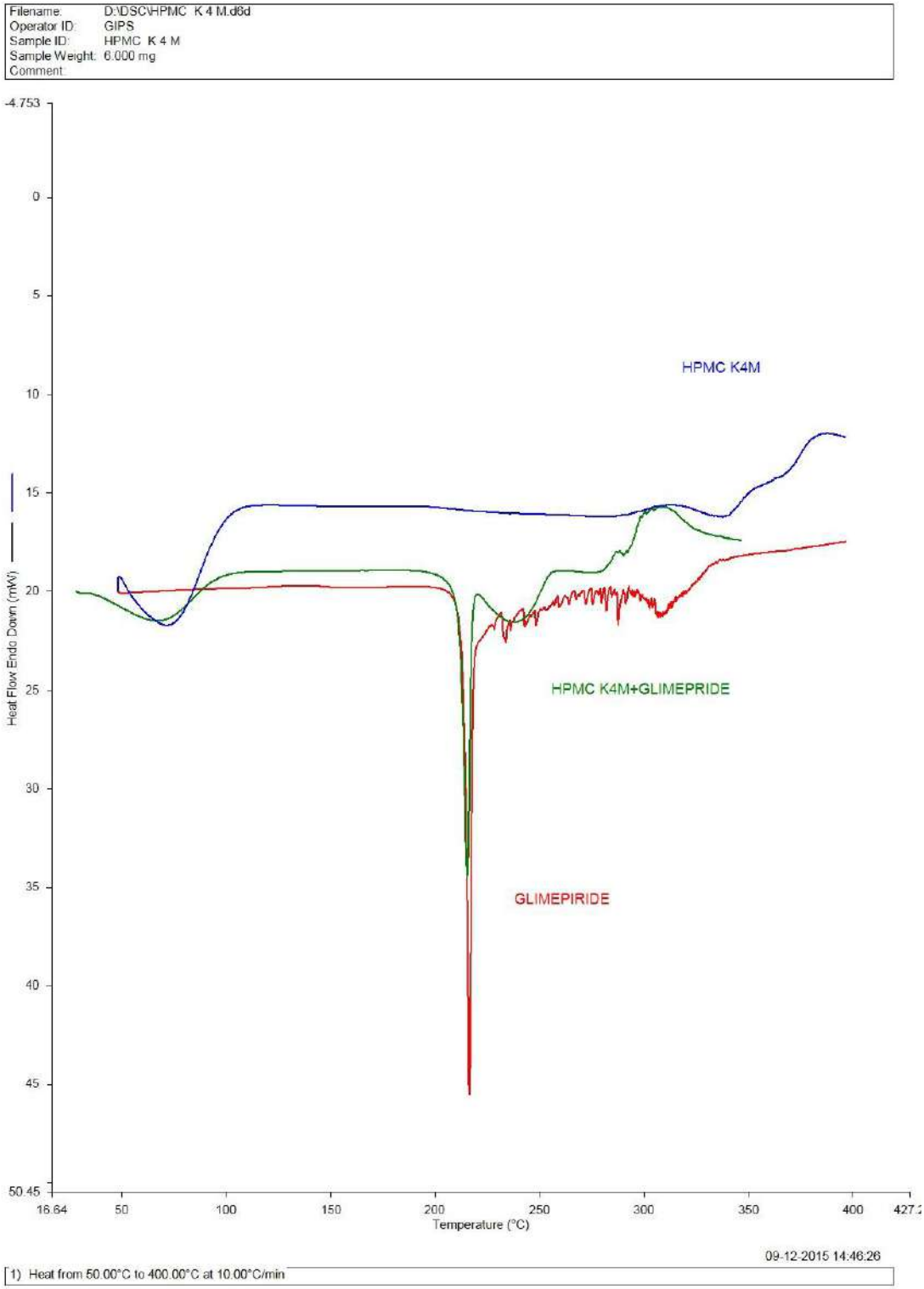


Fig: 6.3.2.4 DSC thermo gram of the mixture of Glimepiride and HPMC K4M overlap.

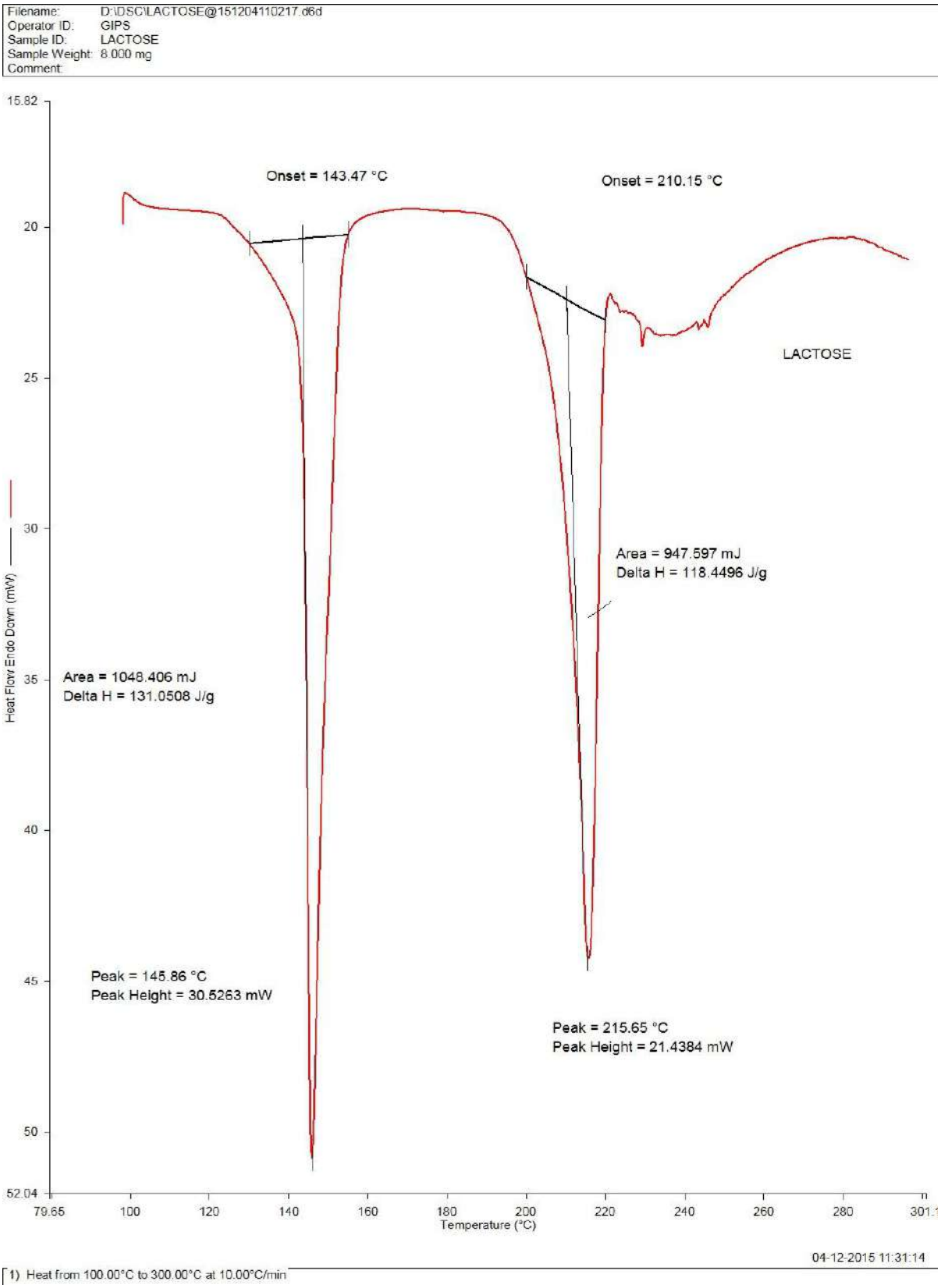


Fig: 6.3.2.5 DSC thermo gram of the Lactose

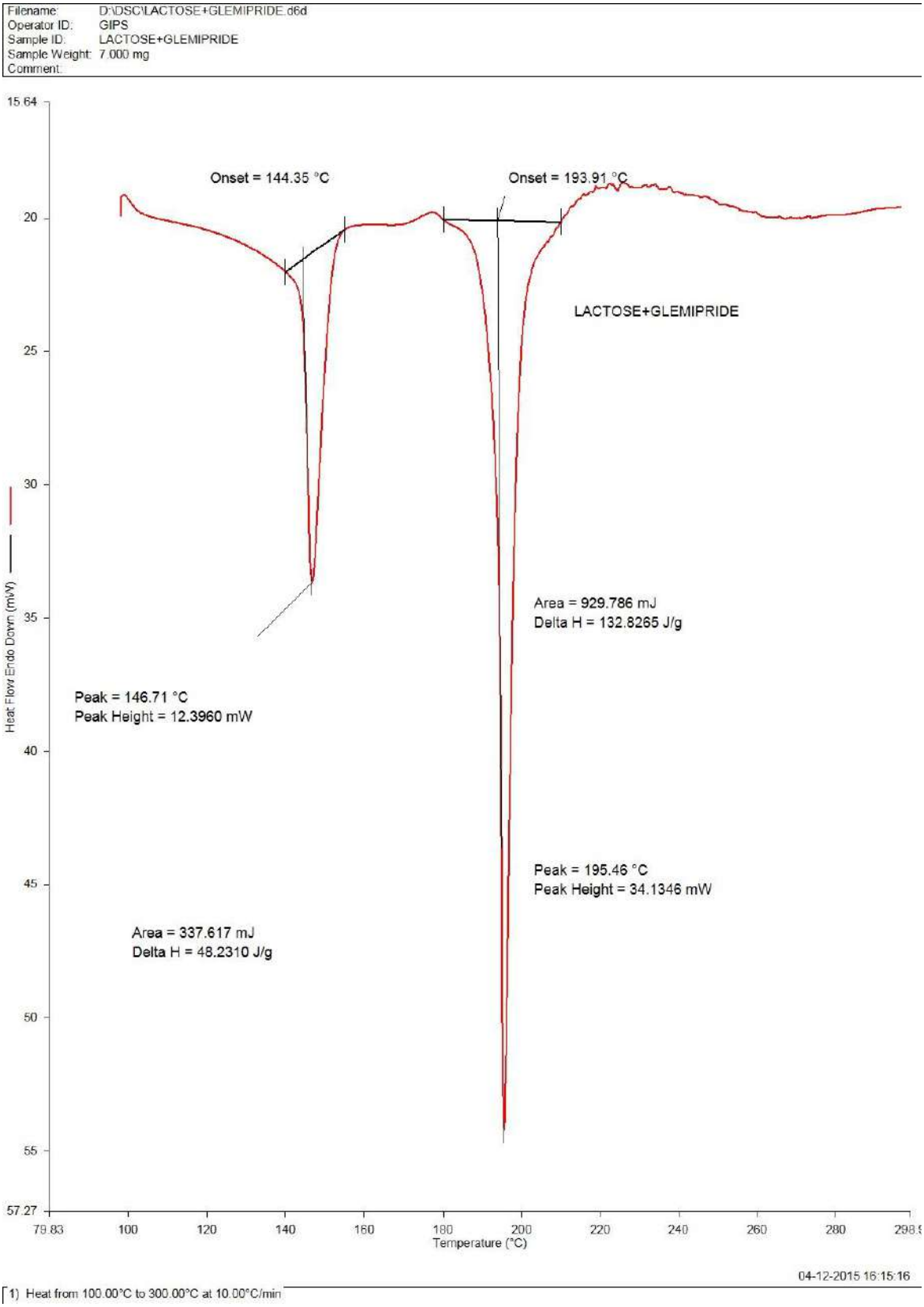
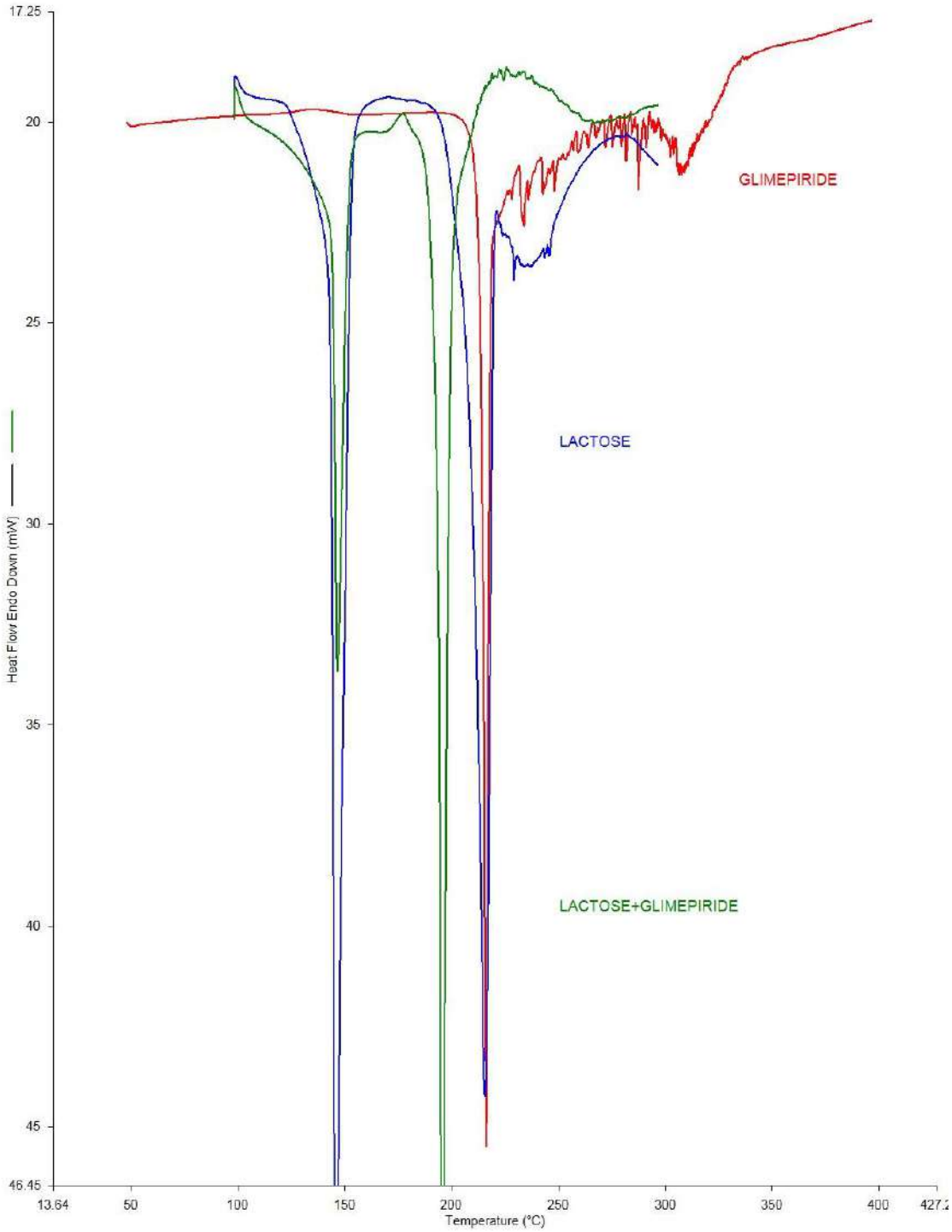


Fig: 6.3.2.6. DSC thermo gram of the mixture of Lactose and glimepiride

Filename: D:\DSC\LACTOSE+GLEMIPRIDE.d6d
Operator ID: GIPS
Sample ID: LACTOSE+GLEMIPRIDE
Sample Weight: 7.000 mg
Comment:



09-12-2015 14:51:20

1) Heat from 100.00°C to 300.00°C at 10.00°C/min

Fig: 6.3.2.7. DSC thermo gram of the mixture of Lactose and glimepiride overlap

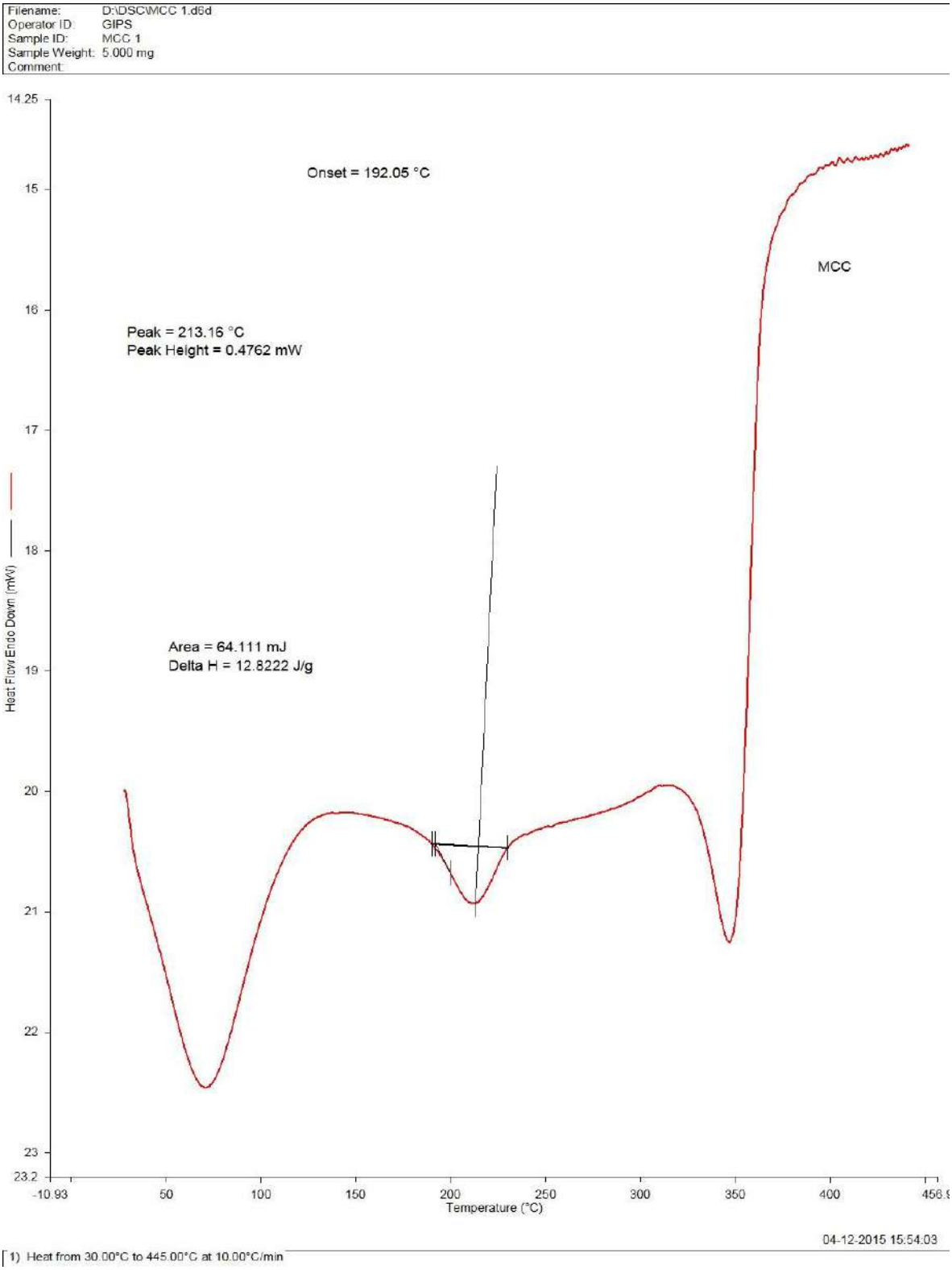


Fig: 6.3.2.8. DSC thermo gram of MCC

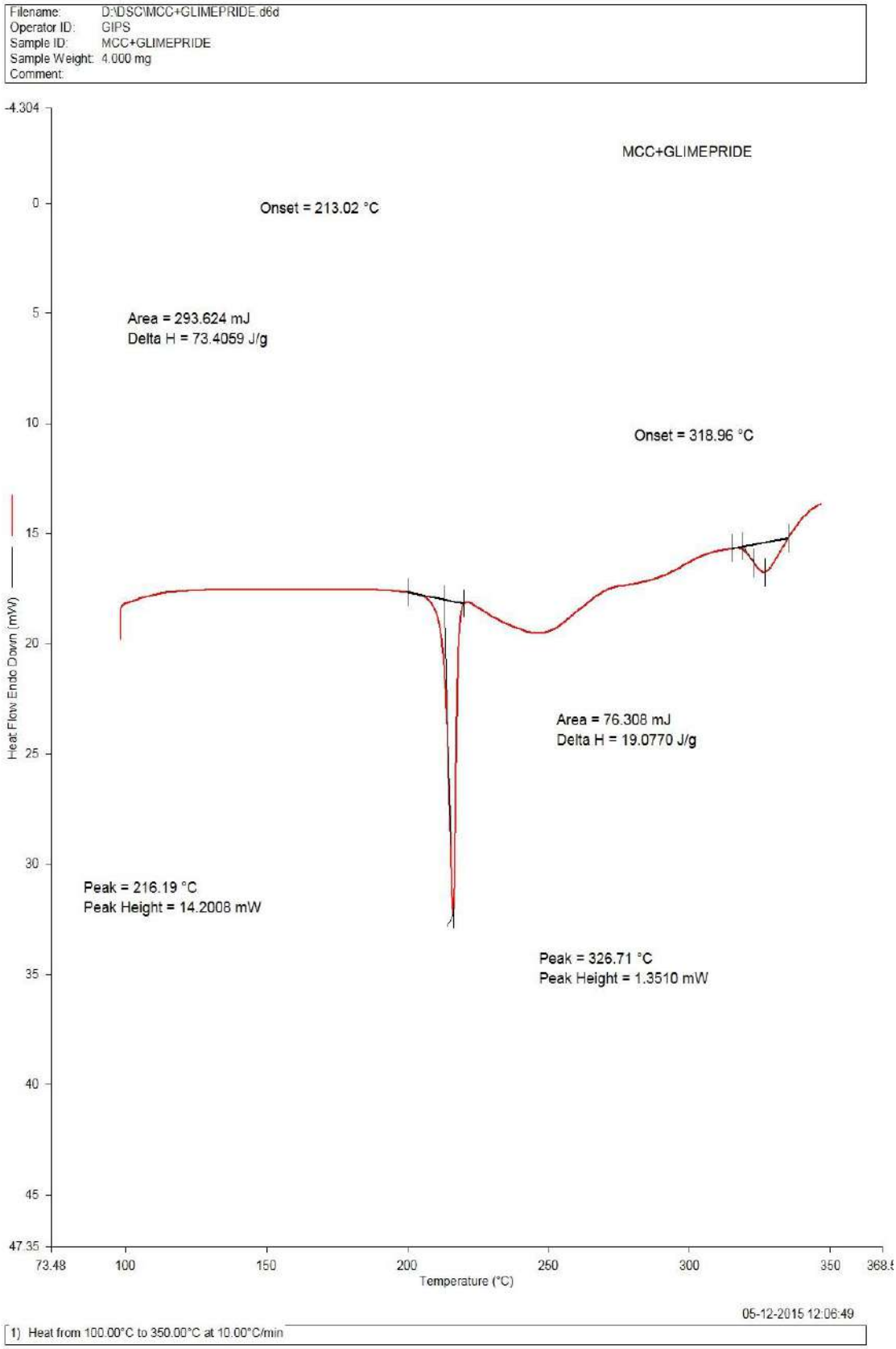


Fig: 6.3.2.9 DSC thermo gram of mixture of Glimepiride + MCC

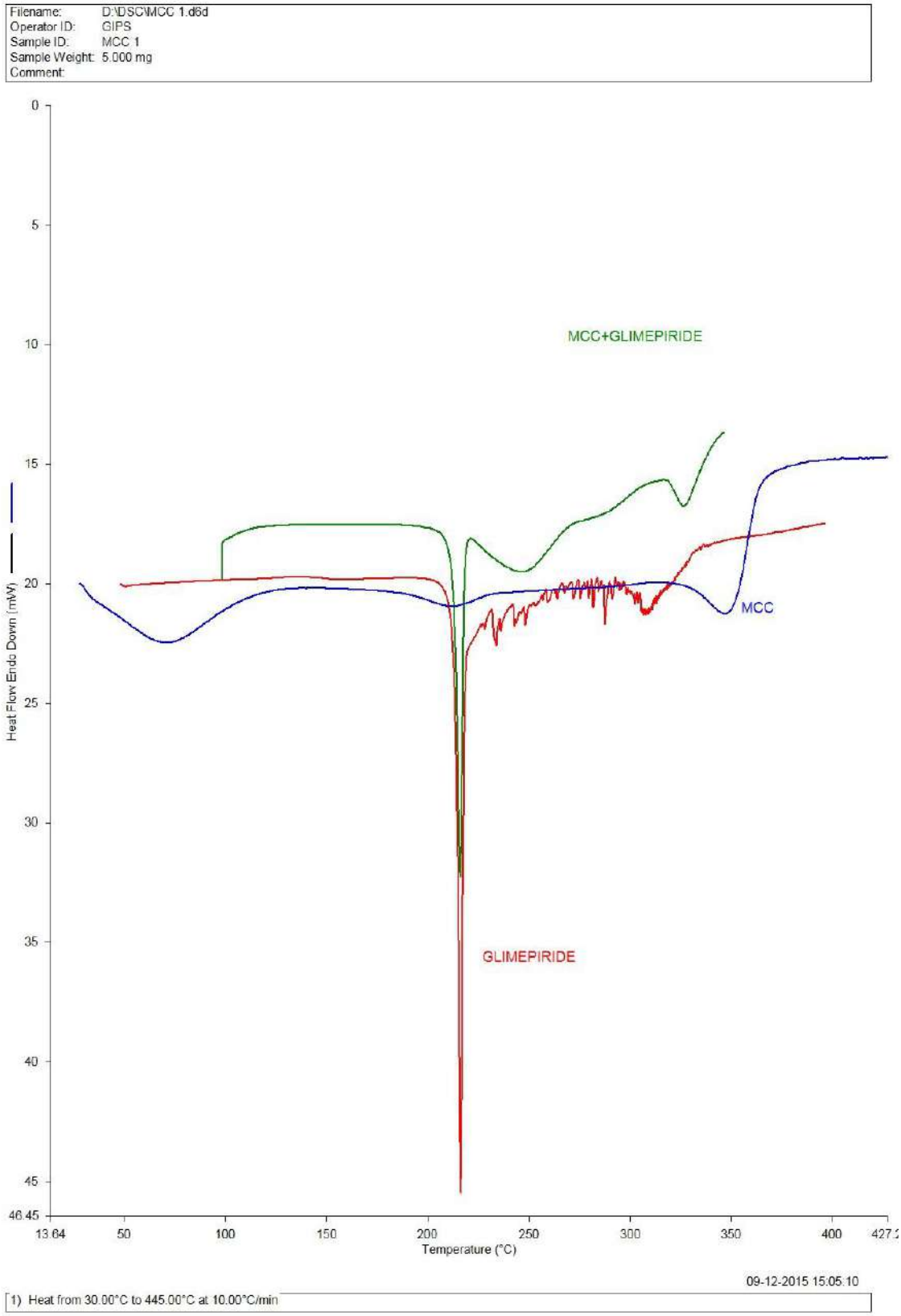


Fig: 6.3.2.10 DSC thermo gram of mixture of Glimepiride + MCC overlap

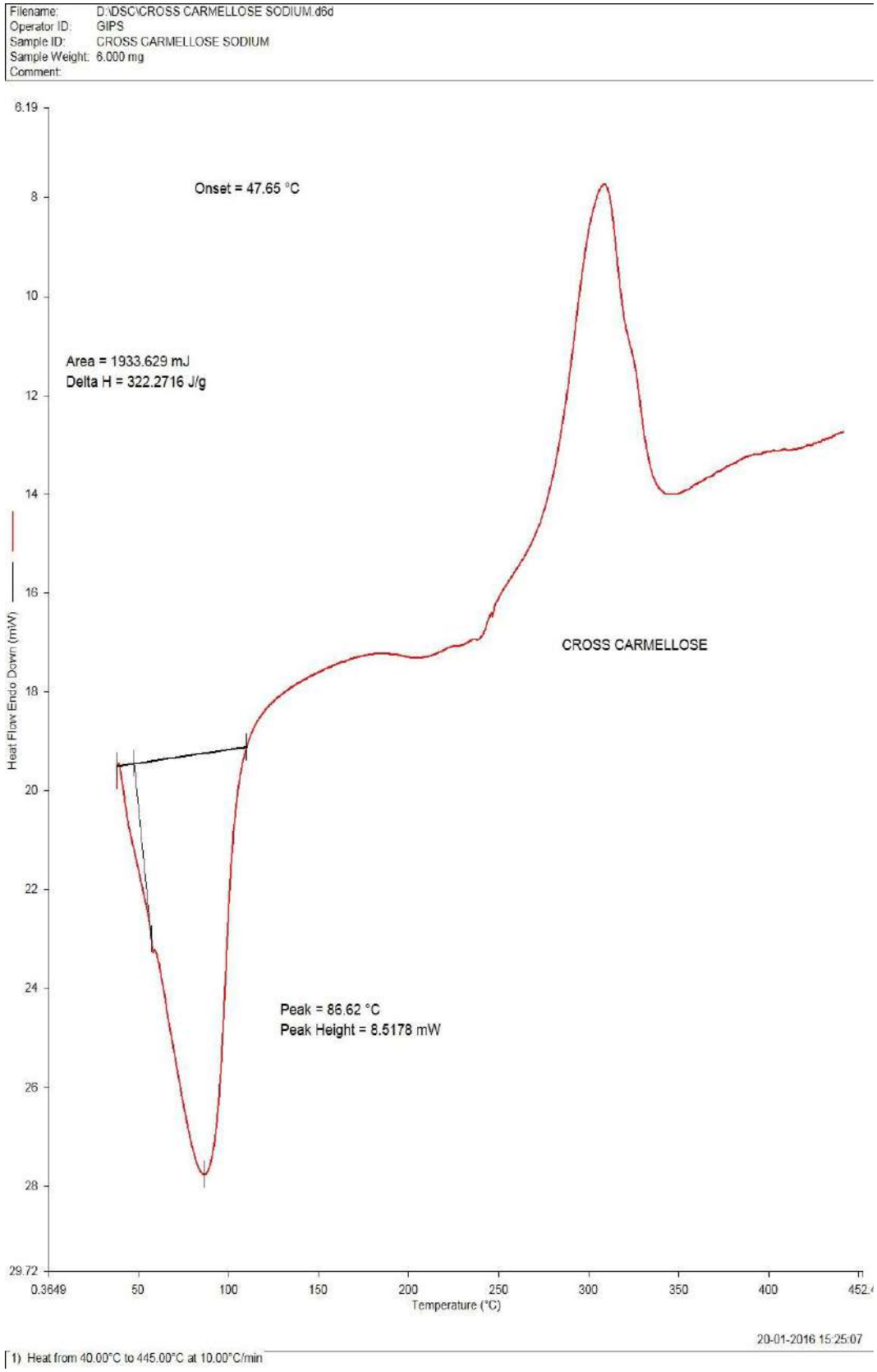


Fig.6.3.2.11. DSC thermo gram of Cross Carmillose Sodium

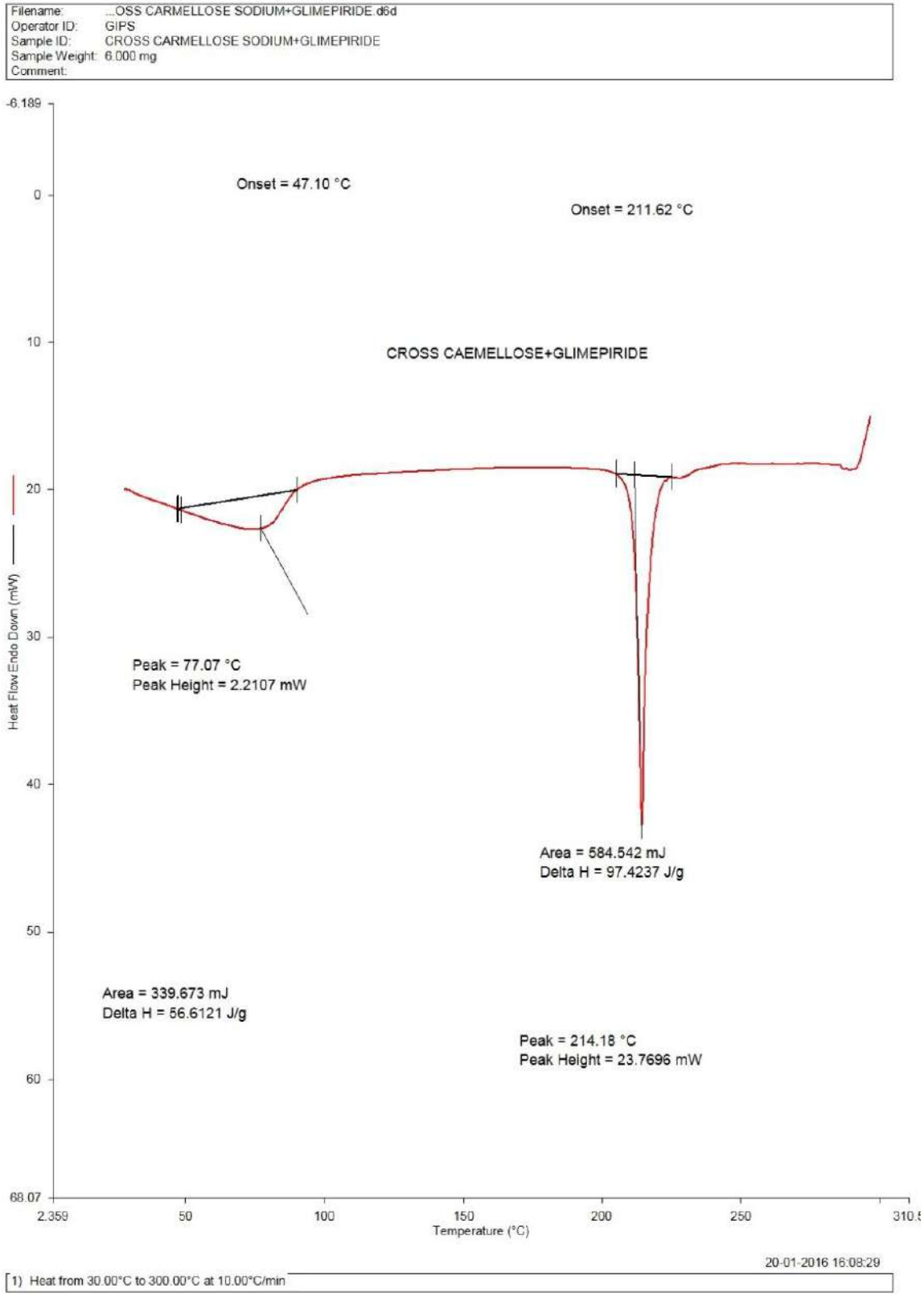
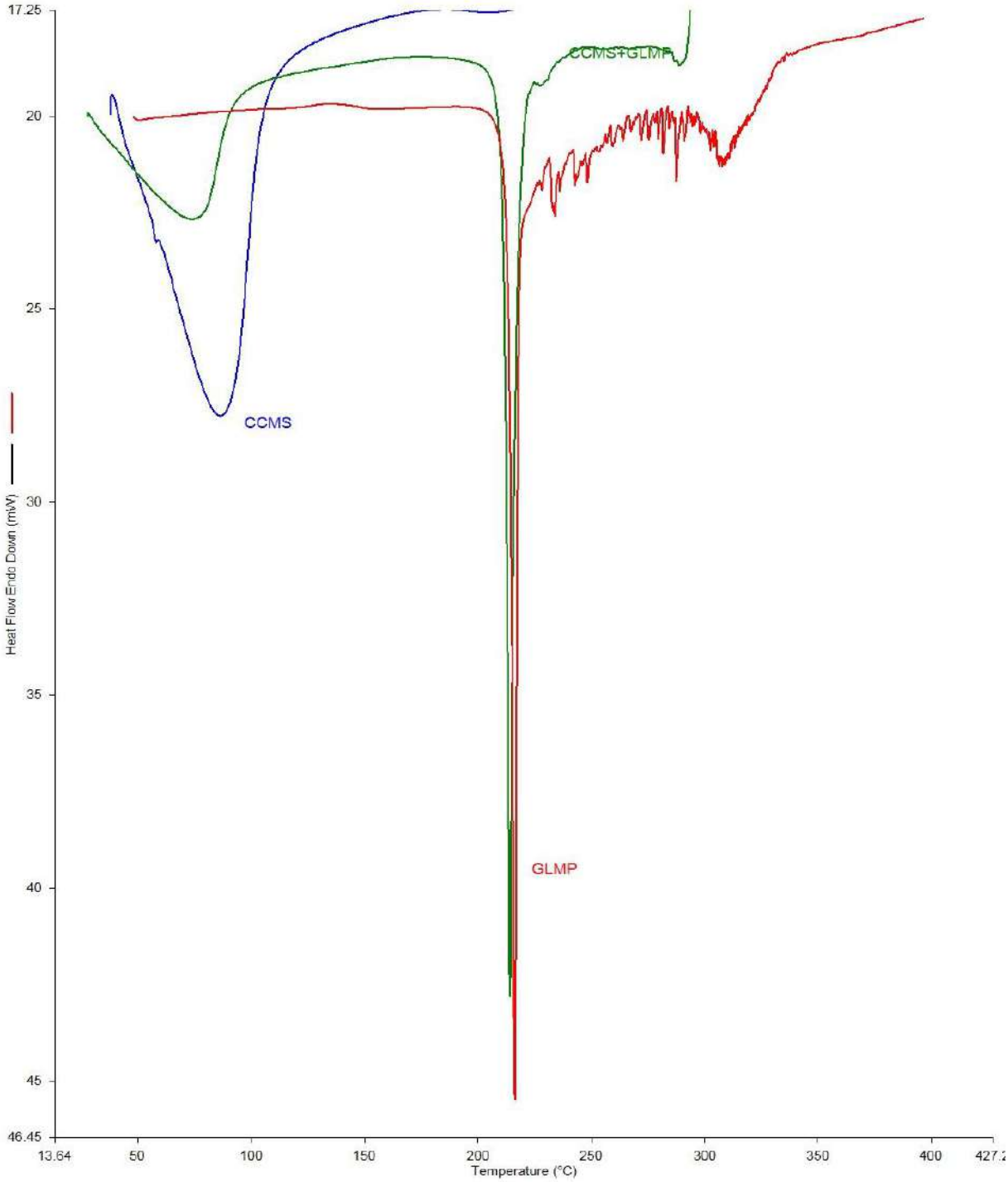


Fig.6.3.2.12. DSC thermo gram of Cross Carmillose Sodium +Glimepiride

Filename: D:\DSC\glimepride.d6d
Operator ID: GIPS
Sample ID: glimepride
Sample Weight: 5.000 mg
Comment:



03-05-2016 13:59:03

1) Heat from 50.00°C to 400.00°C at 10.00°C/min

Fig: 6.3.2.13 DSC thermo gram of the mixture of Cross carmillose Sodium and glimepiride overlap

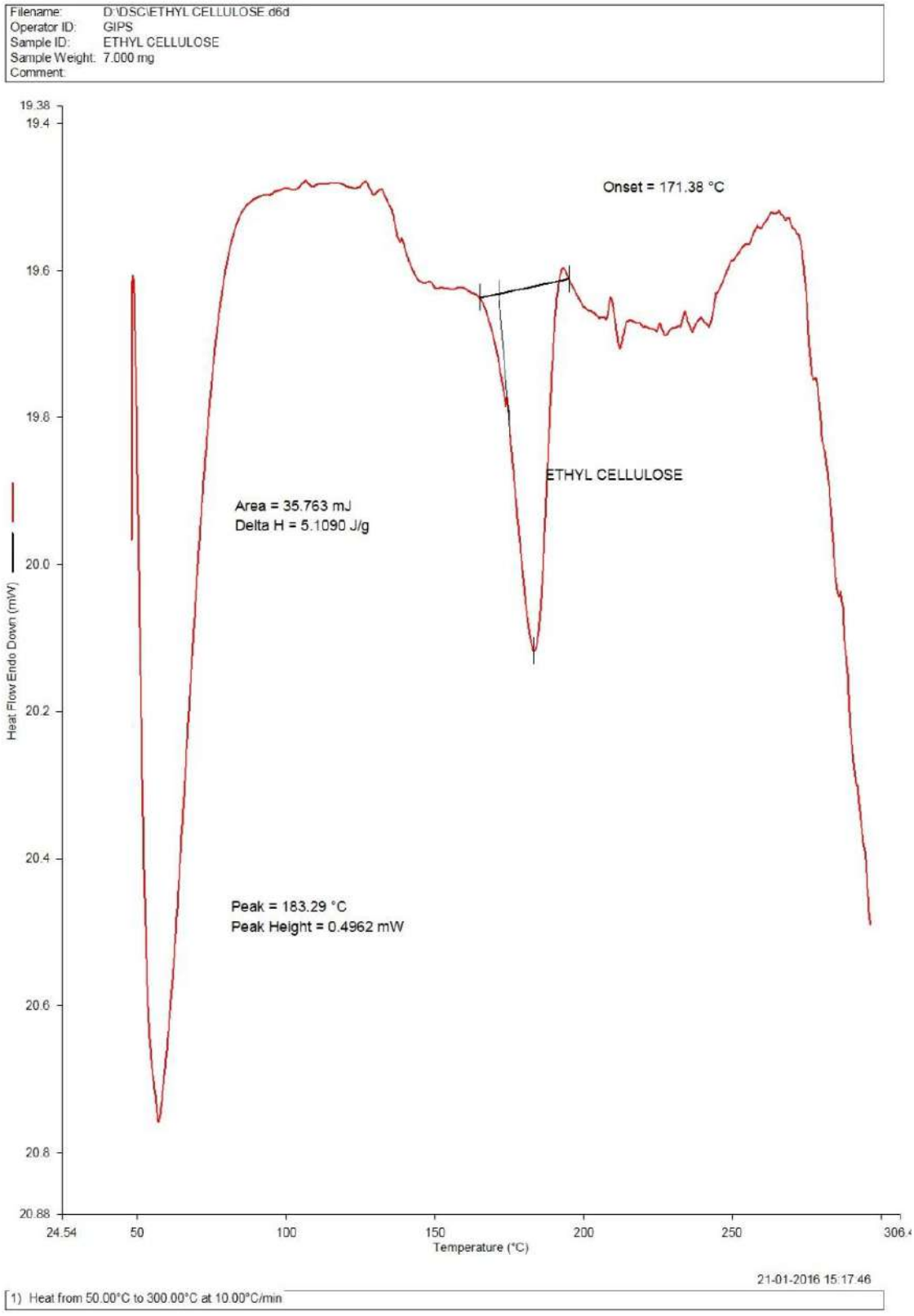


Fig. 6.3.2.14 DSC thermo gram of Ethyl Cellouse

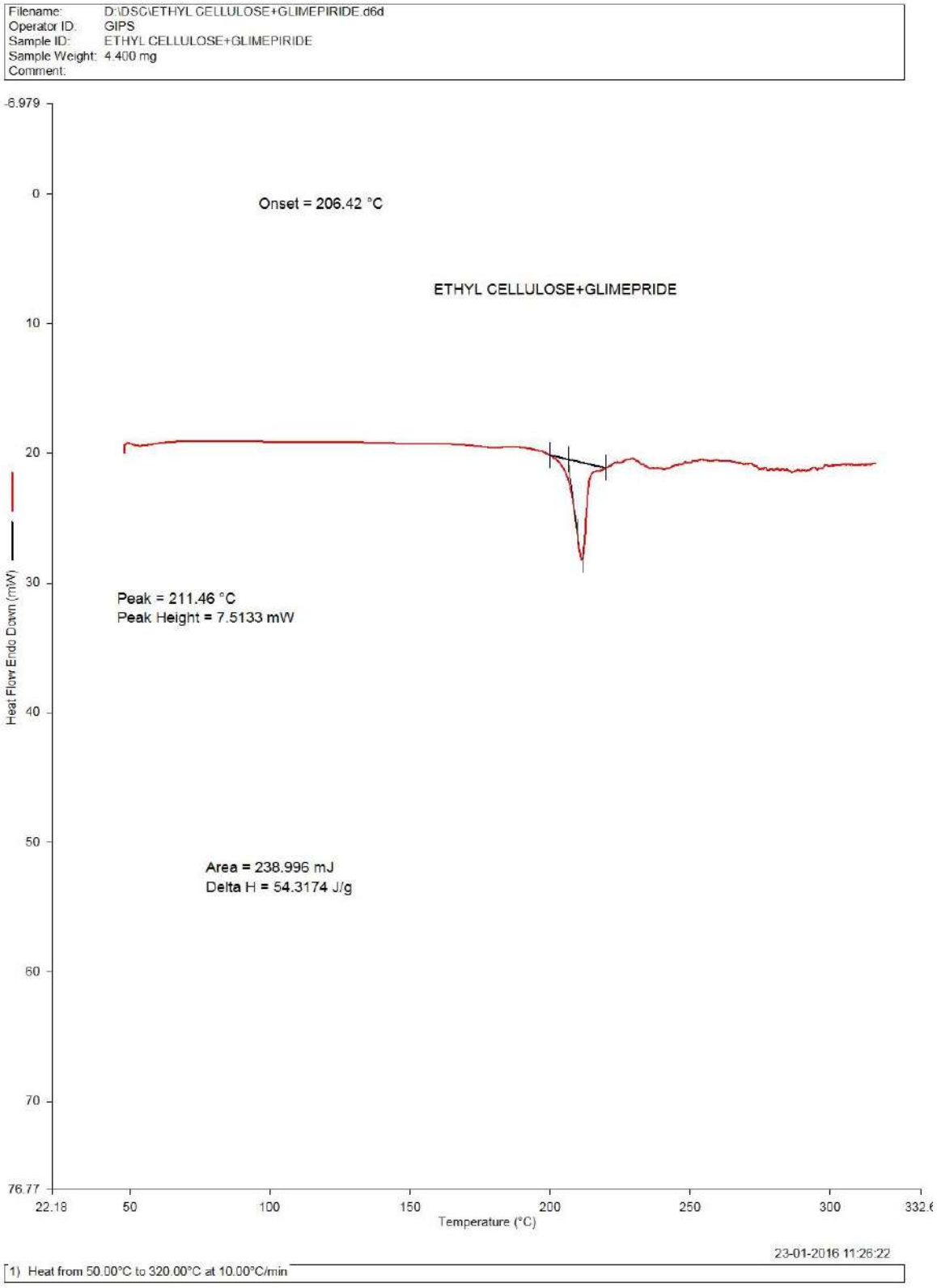


Fig.6.3.2.15. DSC thermo gram of Ethyl Cellouse +Glimepiride

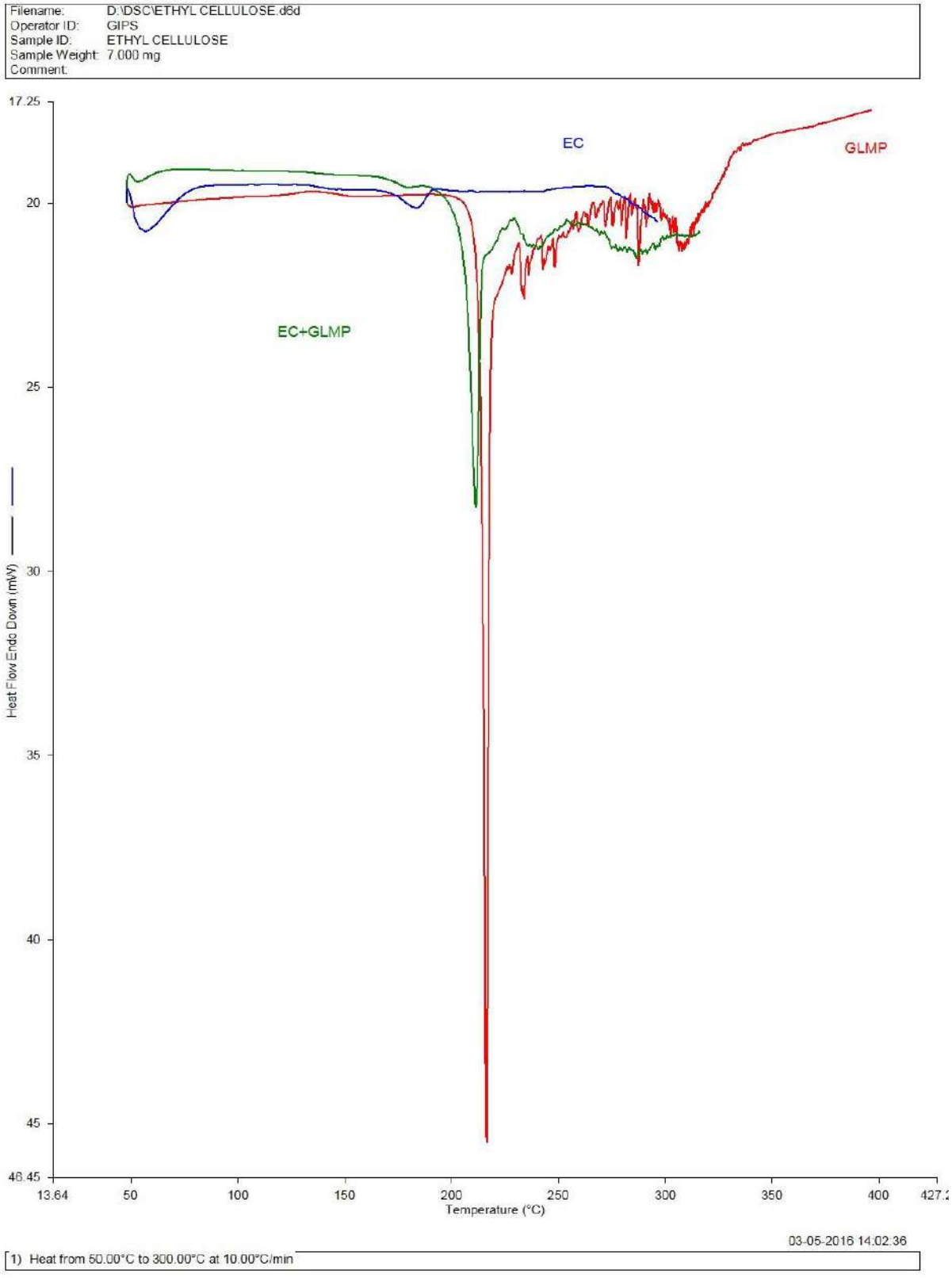


Fig.6.3.2.16.DSC thermo gram of the mixture of Ethyl Cellulose and glimepiride overlap

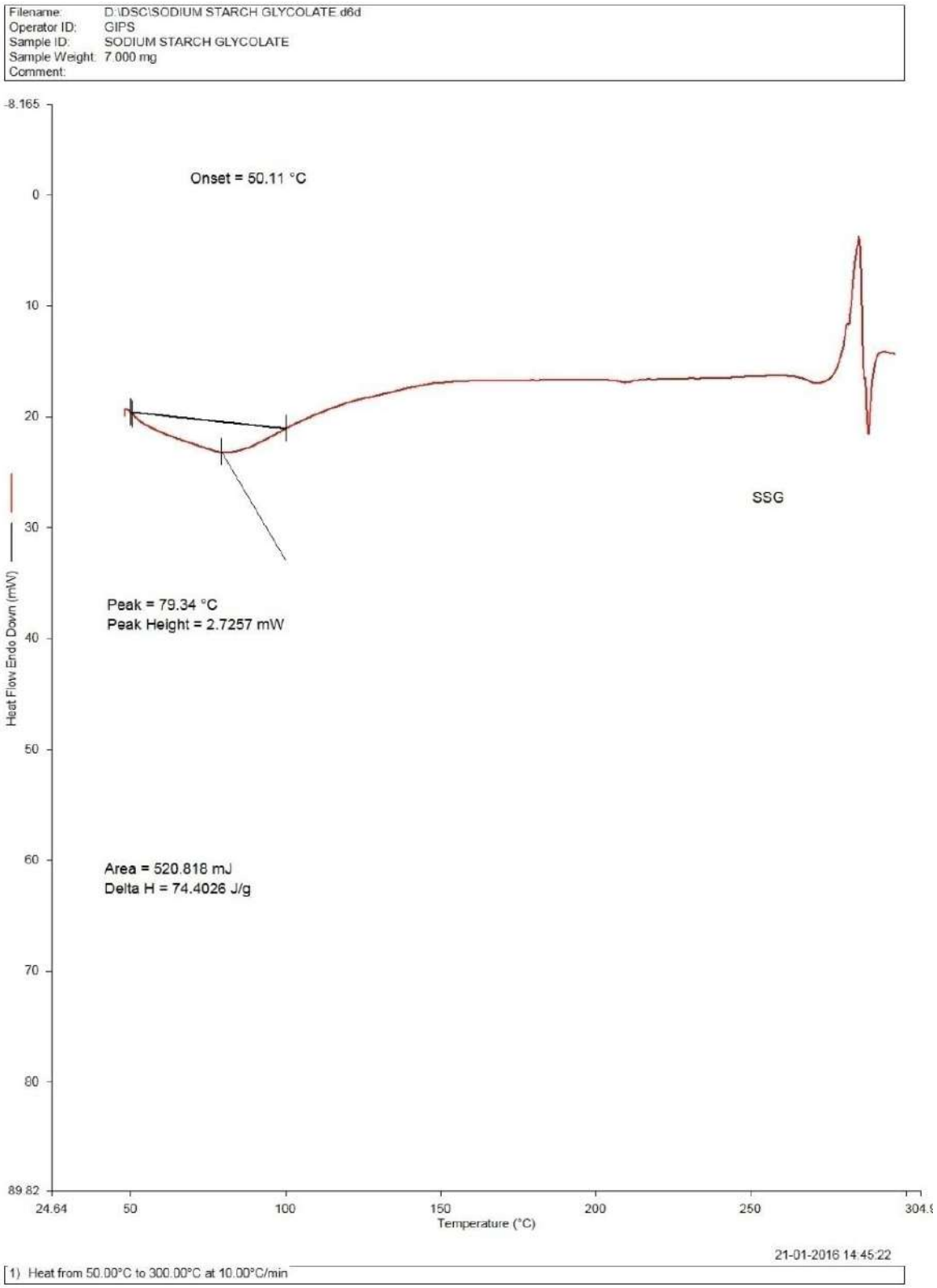


Fig:6.3.2.17. DSC thermo gram of Sodium Starch Glycolate

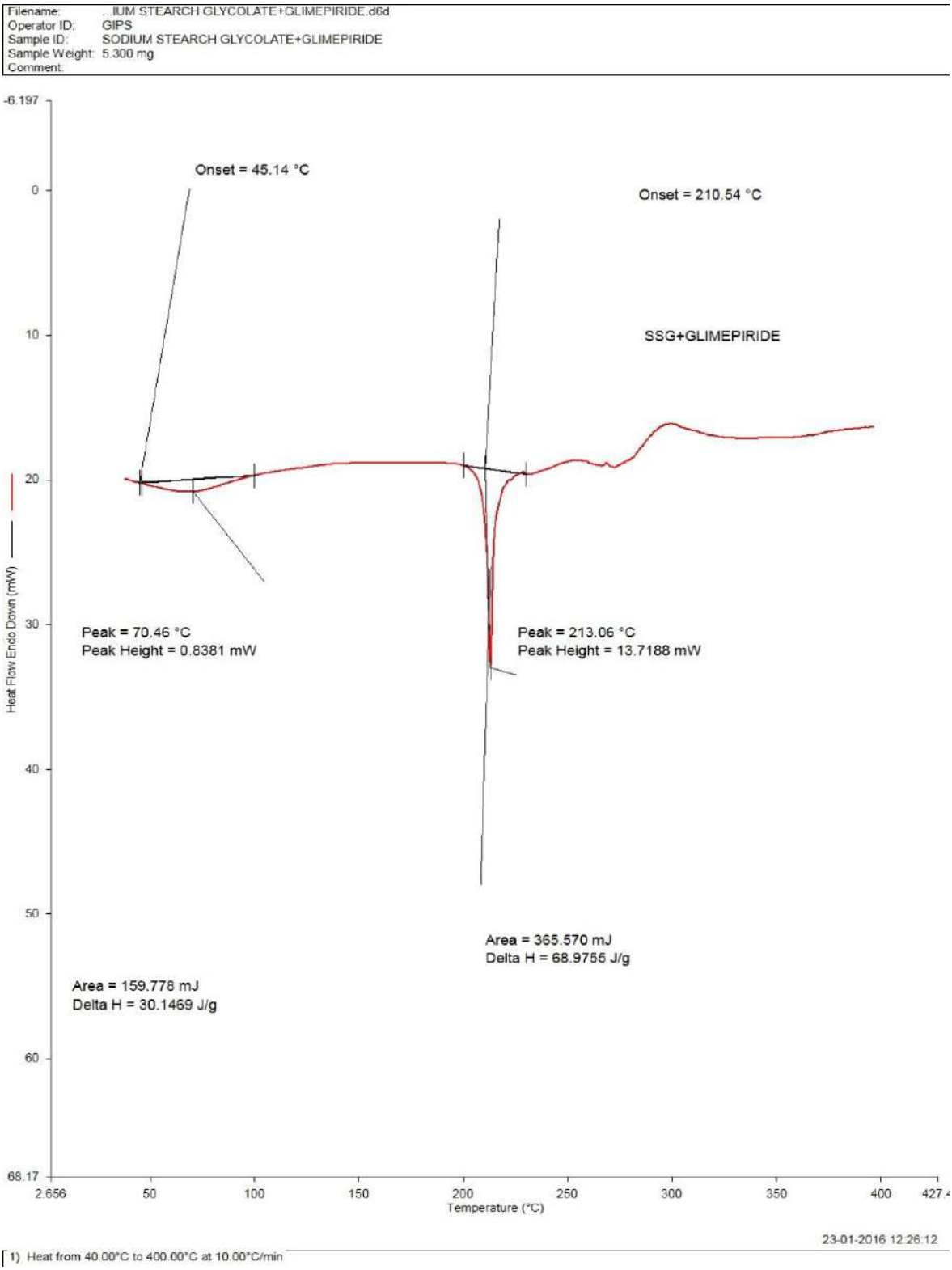
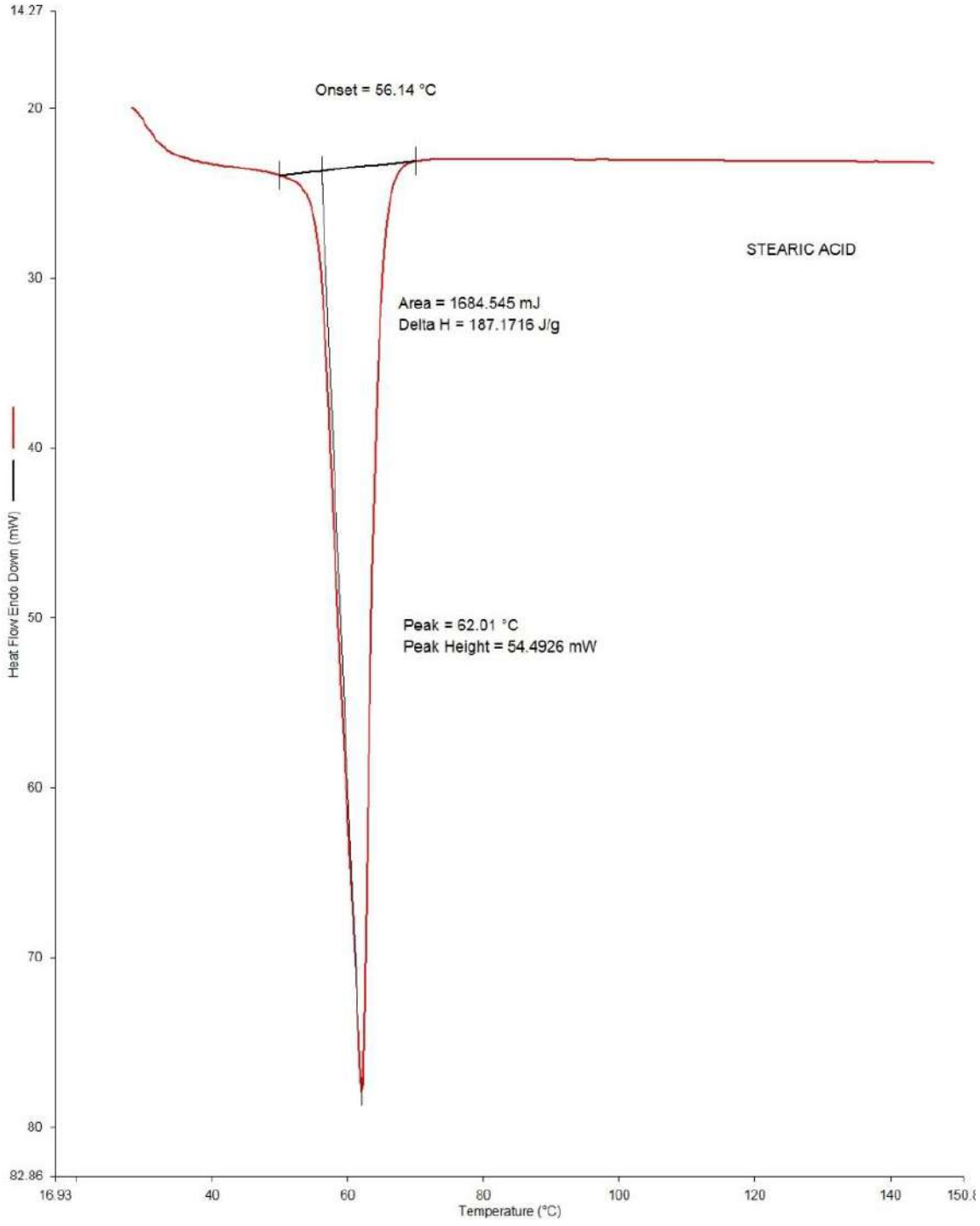


Fig 6.3.2.18.. DSC thermo gram of mixture of Glimepiride + Sodium Starch Glycolate

Filename:	D:\DSC\stearic acid.d6d
Operator ID:	GIPS
Sample ID:	stearic acid
Sample Weight:	9.000 mg
Comment:	



19-01-2016 12:40:02

1) Heat from 30.00°C to 150.00°C at 10.00°C/min

Fig:6.3.2.19 DSC thermo gram of Staric Acid

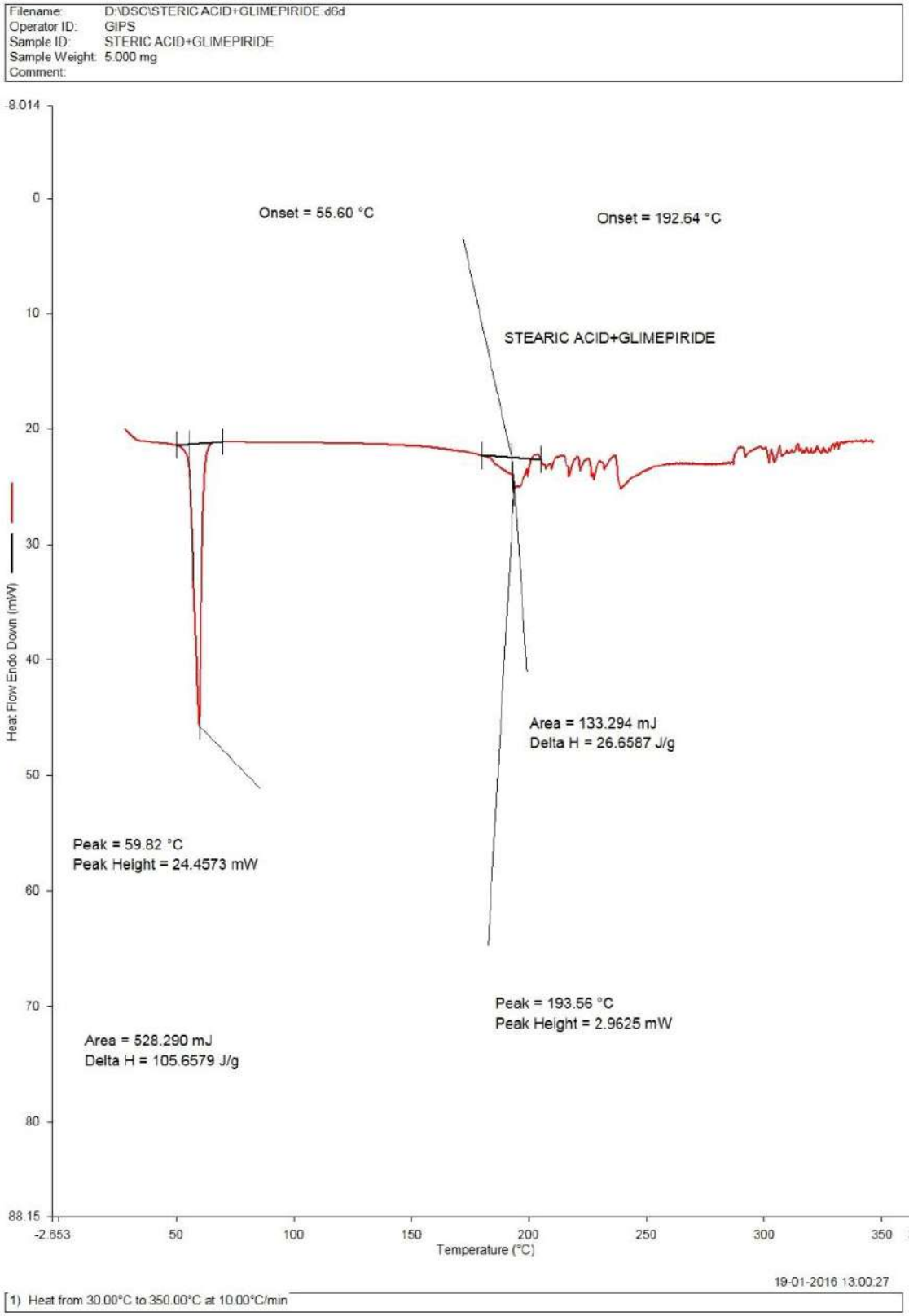


Fig:6.3.2.20. DSC thermo gram of mixture of Glimepiride + Staric Acid

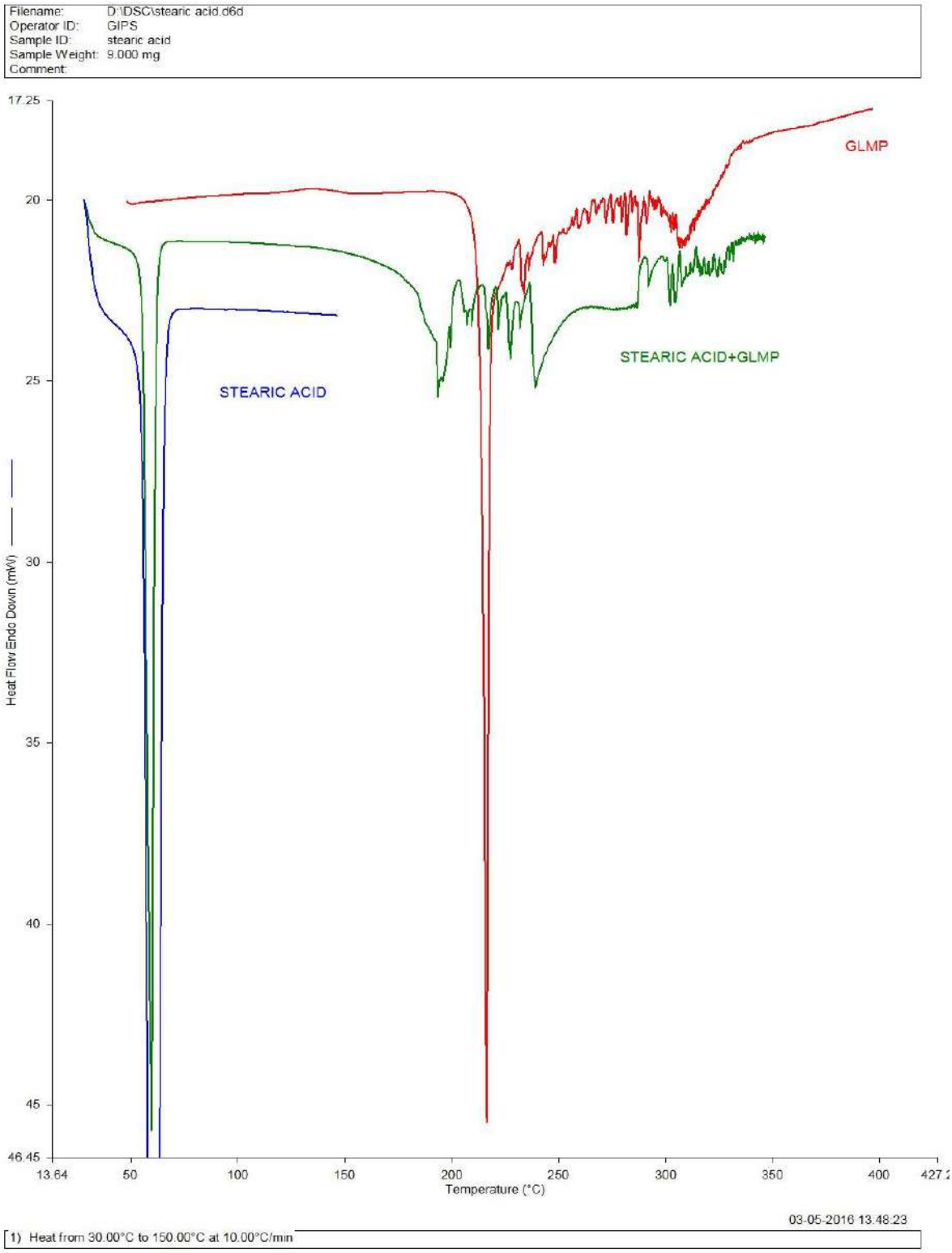


Fig.6.3.2.21 DSC thermo gram of the mixture of Staric Acid and glimepiride overlap

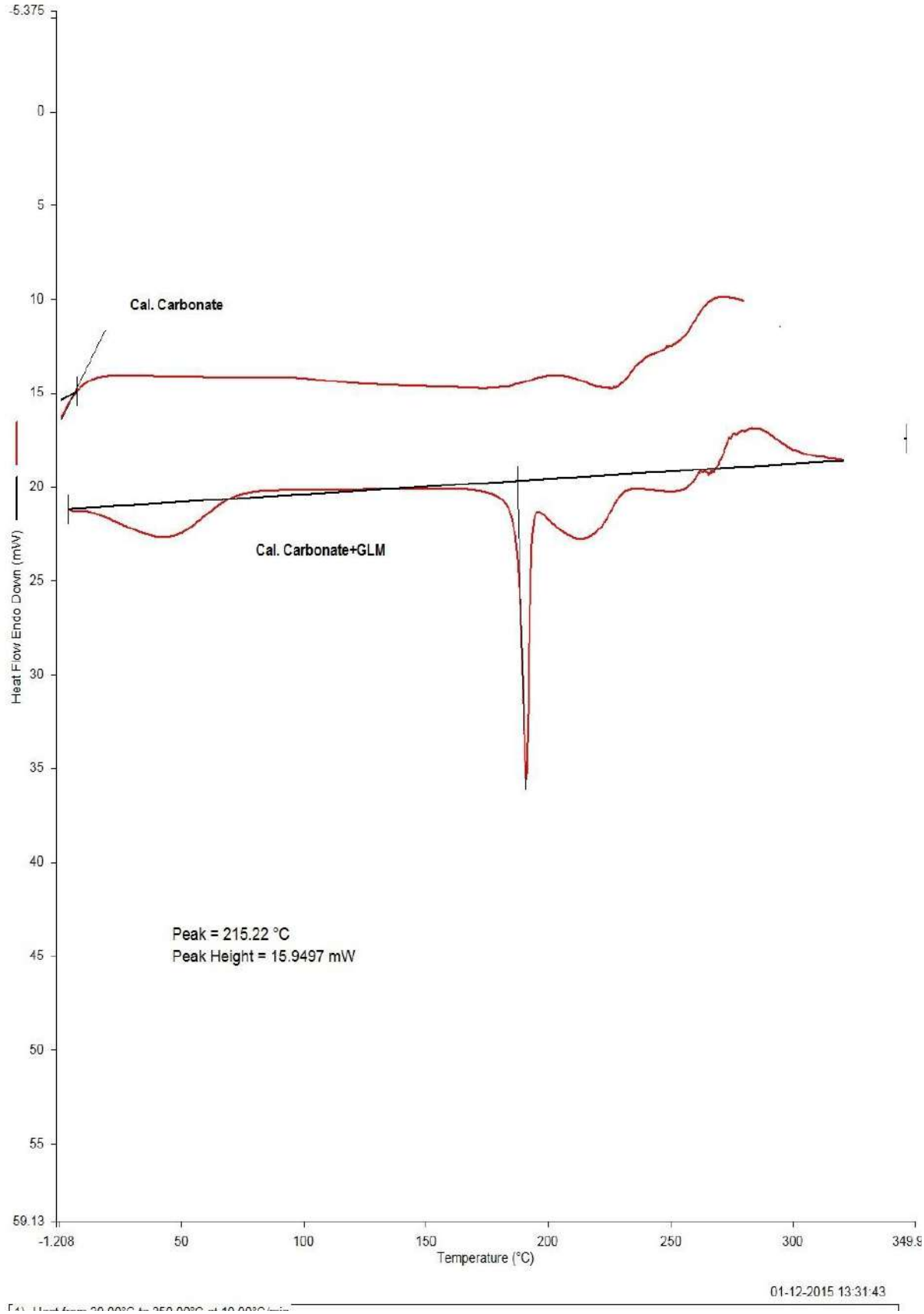


Figure 6.3.2.22. DSC thermogram of GLM and physical mixture with Calcium carbonate.

6.3.3.UV ANALYSIS OF DRUG:

Preparation of standard calibration curve[46,47,49] :

Standard graph for the drug Glimepiride were done separately in water, pH 1.2 acidic buffer and pH (6.8,7.4 and 7.8) phosphate buffer. Tables 7.1.6.1 to 7.1.6.5 show the concentrations of glimepiride in pH 1.2 acidic and pH (6.8,7.4,7.8) phosphate buffers and the respective absorbance. The Figures 7.1.6.1 to 7.1.6.4 show the calibration curves of glimepiride in pH 1.2 acidic buffer and pH (6.8,7.4,7.8) phosphate buffer respectively.

Table 6.3.3.1. Spectrophotometric data for standard calibration curve of Glimepiride in water:

Sl no	***Concentration (µg/ml)***	***Absorbance***
1	*0*	*0*
2	*2*	*0.0665*
3	*4*	*0.1449*
4	*6*	*0.2163*
5	*8*	*0.2775*
6	*10*	*0.3738*

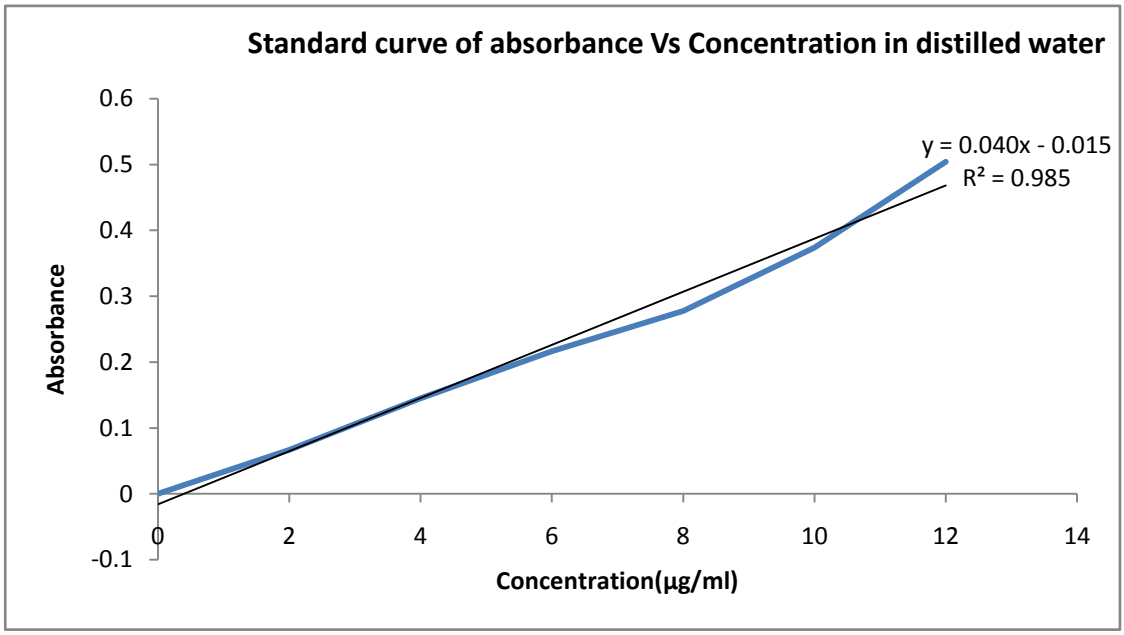


Fig: 6.3.3.1. Standard curve of Glimepiride in water.

6.3.3.2. Preparation of standard Curve in 0.1N HCL:

Sl No	*Concentration (µg/ml)*	*Absorbance*
1	*0*	*0*
2	*2*	*0.0892*
3	*4*	*0.1517*
4	*6*	*0.2241*
5	*8*	*0.2773*
6	*10*	*0.3765*

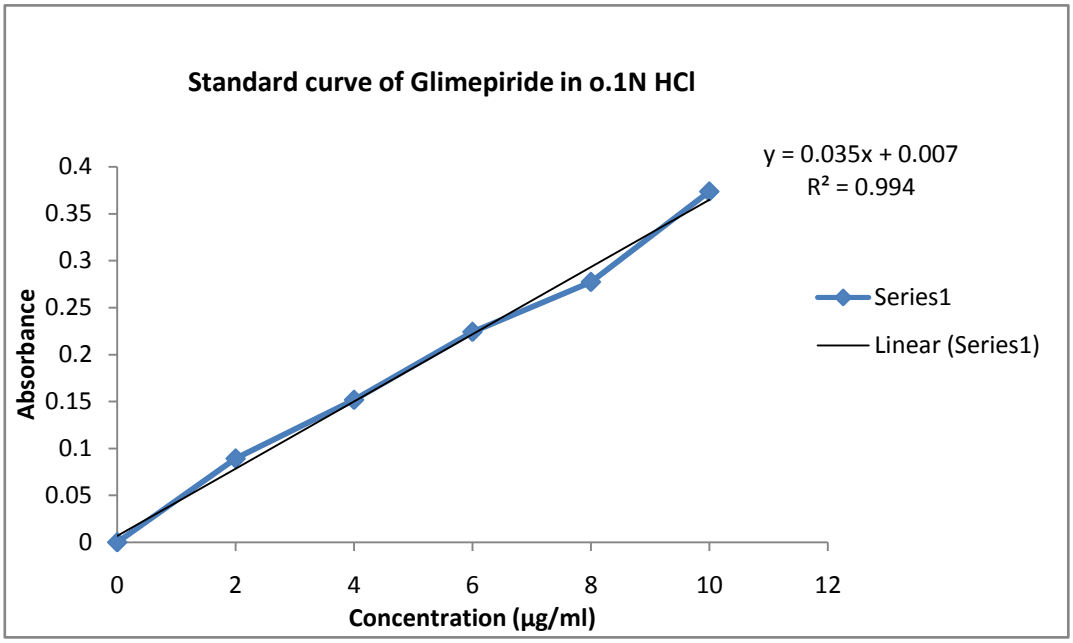


Fig: 6.3.3.2.. Standard curve of Glimepiride in 0.1 N HCL.

6.3.3.3. Preparation of Standard Curve of Glimepiride in Phosphate buffer pH= 6.8

Sl no	*Concentration(µg/ml)*	*Absorbance*
1	*0*	*0*
2	*2*	*0.1402*
3	*4*	*0.1970*
4	*6*	*0.2446*
5	*8*	*0.2780*
6	*10*	*0.3447*

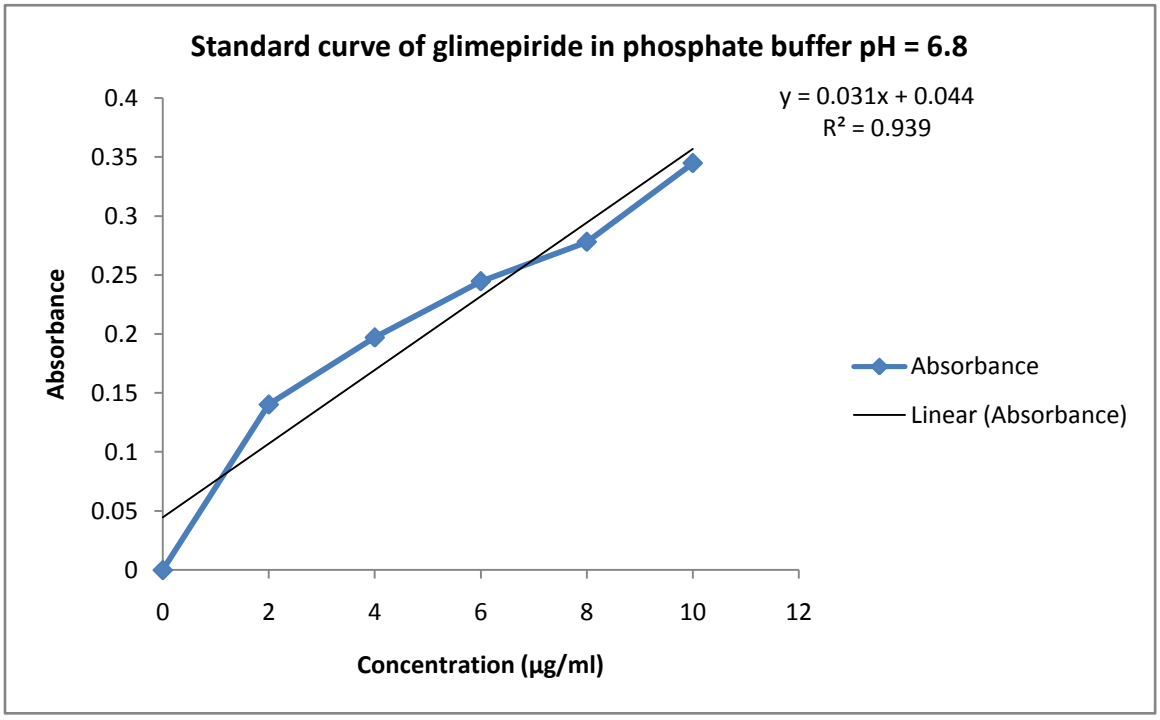


Fig: 6.3.3.4 Standard curve of Glimepiride in phosphate buffer pH = 6.8

Table. 6.3.3.5. Standard Curve of Glimepiride in Phosphate Buffer pH =7.4

Sl No	*Concentration(µg/ml)*	*Absorbance*
1	*0*	*0*
2	*2*	*0.0927*
3	*4*	*0.1703*
4	*6*	*0.2722*
5	*8*	*0.2781*

6	*10*	*0.4179*

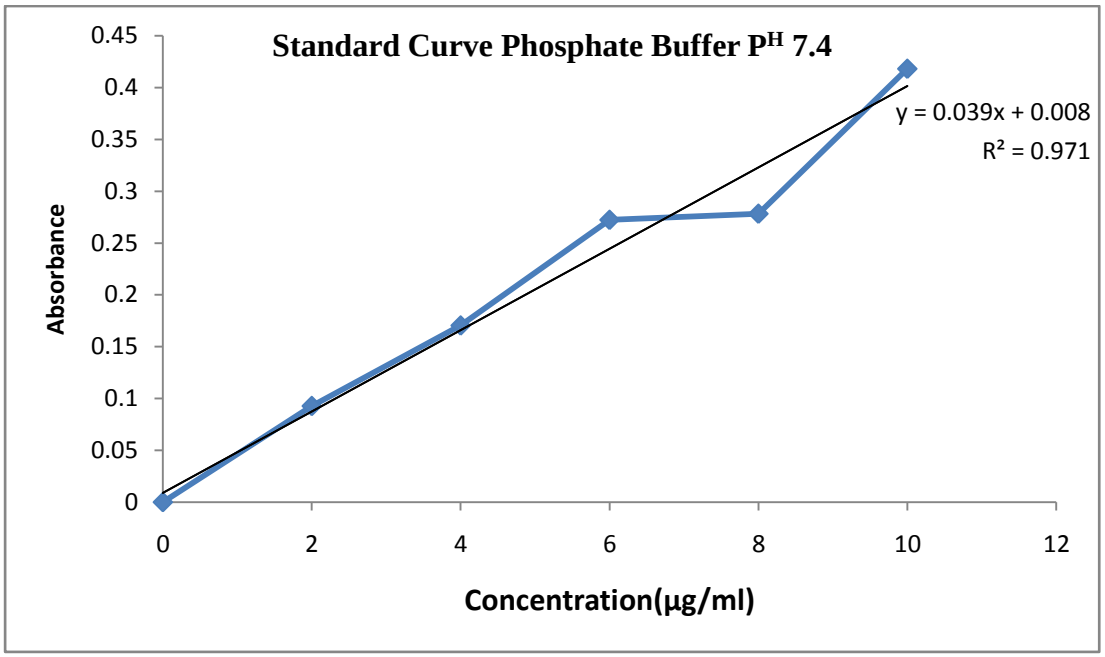


Fig: 6.3.3.5 Standard curve of glimepiride phosphate buffer p^H 7.4

Table:6.3.3.6 Standard curve of glimepiride phosphate buffer p^H 7.8

Sl No	***Concentration(µg/ml)***	***Absorbance***
1	*0*	*0*
2	*2*	*0.0827*

3	*4*	*0.1503*
4	*6*	*0.1822*
5	*8*	*0.2481*
6	*10*	*0.3679*

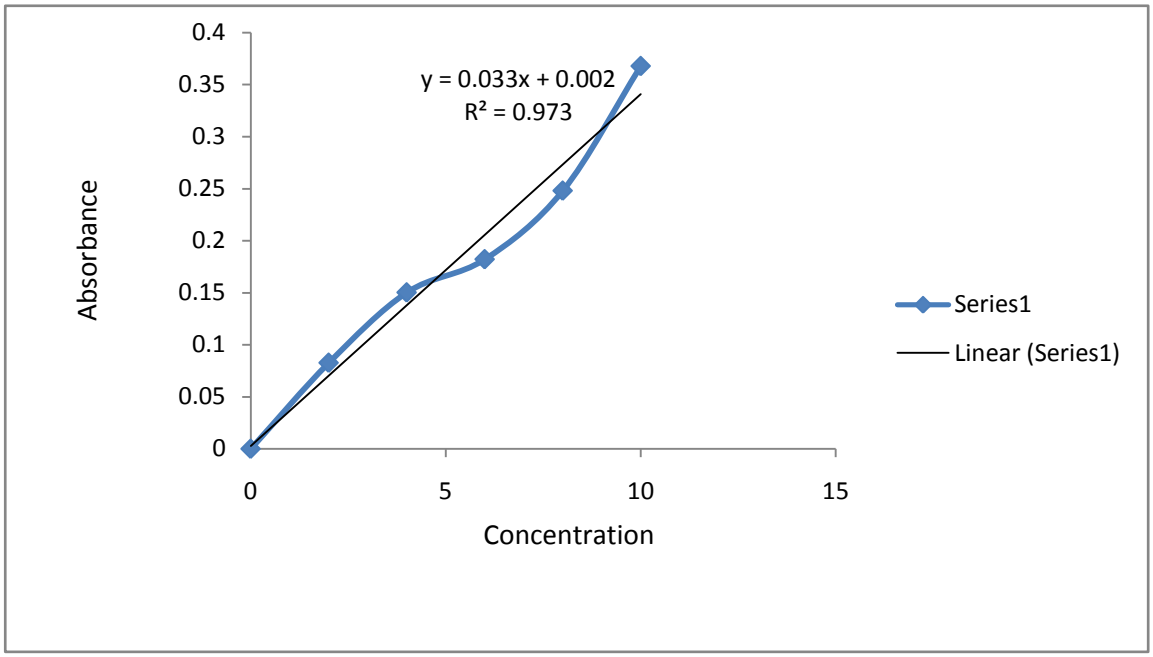


Fig:6.3.3.6 Standard curve of glimepiride phosphate buffer p^H 7.8

6. 4. Saturation solubility:

The saturation solubility of the drug sample was determined in various solvent like water, 0.1N HCL, phosphate buffer pH6.8 and found to be 976 mg/ml, 104.7 mg/ml, 1.774 mg/ml.

Table 6.3.4.Saturation solubility data

Sl no	***Solvent used***	***Absorbance***	***Saturation solubility(mg/ml)***

1	*Water*	*0.3754*	*79.5*
2	*Phosphate buffer pH 6.8*	*0.0495*	*83.2*
3	*Phosphate buffer pH 7.4*	*0.3736*	*91.4*
4	*Phosphate buffer pH 7.8*	*0.6976*	*65.6*

6.5 Pre-compressional evaluations:

Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio and Car's index .Results of all the pre-compressional parameters performed on granules for formulations shown in bellow.

Table 1. Different formulations of tablet

Ingredients (mg)	***Coded Formulations***							
	F-1 (mg)	***F-2 (mg)***	***F-3 (mg)***	***F-4 (mg)***	***F-5 (mg)***	***F-6 (mg)***	***F-7 (mg)***	***F-8 (mg)***
Glimepiride	*6*	*6*	*6*	*6*	*6*	*6*	*6*	*6*
PVP K30	*10*	*10*	*10*	*10*	*10*	*10*	*10*	*10*
Microcrystalline cellulose	*30*	*30*	*30*	*30*	*30*	*30*	*45*	*15*
HPMC K4M	*22.5*	*30*	*37.5*	*45*	*52.5*	*60*	*60*	*60*

Calcium carbonate	*78.5*	*71.0*	*63.5*	*56.0*	*48.5*	*41.0*	*29.0*	*59.0*
Stearic acid	*3*	*3*	*3*	*3*	*3*	*3*	*3*	*3*
Total weight	*150*	*150*	*150*	*150*	*150*	*150*	*150*	*150*

Table 2. Pre compression parameters

Formulation code	**Angle of repose (θ^0)**	***Tapped density (g/cm^3)***	***Bulk density (g/cm^3)***	***Hausner ratio***	***Carr's index (%)***
F-1	*15.12*	*0.440*	*0.456*	*0.964*	*3.63*
F-2	*16.35*	*0.445*	*0.476*	*0.934*	*6.96*
F-3	*17.86*	*0.449*	*0.487*	*0.921*	*8.46*
F-4	*18.52*	*0.451*	*0.472*	*0.955*	*4.65*
F-5	*16.77*	*0.454*	*0.498*	*0.911*	*9.69*
F-6	*17.15*	*0.453*	*0.477*	*0.949*	*5.29*
F-7	*19.16*	*0.460*	*0.486*	*0.946*	*5.65*
F-8	*16.69*	*0.463*	*0.496*	*0.933*	*7.12*

The results of Hausner's ratio were found to be lesser than 1.25 which indicates better flow properties. The results of angle of repose (<30) indicates good flow properties of the powder. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

Table 3. Post compressional evaluations:

The results of physical evaluation of tablets were given bellow:

FORMULATION CODE	***THICKNESS (mm)***	***HARDNESS (kg/cm^2)***	***FRIABILITY (%)***	***% WEIGHT VARIATION***	***% OF DRUG CONTENT***
F-1	*3.321±0.05*	*2.3±0.06*	*0.40±0.02*	*0.24*	*91.27*
F-2	*3.045±0.04*	*2.3±0.02*	*0.46±0.06*	*0.56*	*96.59*
F-3	*3.012±0.01*	*2.3±0.04*	*0.53±0.02*	*0.12*	*99.21*
F-4	*3.564±0.06*	*2.3±0.04*	*0.26±0.08*	*1.34*	*97.62*
F-5	*3.875±0.07*	*2.3±0.07*	*0.33±0.03*	*1.57*	*91.53*
F-6	*3.964±0.03*	*2.3±0.01*	*0.46±0.01*	*1.05*	*93.19*
F-7	*3.854±0.03*	*2.3±0.03*	*0.19±0.05*	*1.36*	*94.69*
F-8	*3.210±0.05*	*2.3±0.06*	*0.39±0.02*	*0.89*	*90.56*

The tablets of different batches were found uniform with respect to hardness within the range of 3.20±0.40 to 4.00±0.55 kg/cm2. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. Results of friability test were also has been found within limit. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 250 mg is ±5% and all the formulations were found to comply with the specifications given in I.P. for weight variationtest. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 90%. All the tablet formulations showed acceptable pharmaco technical properties.

In - vitro drug release study[52,56]:

The results of in-vitro release study of tablets were interpreted with the kinetic models these are given bellow:

For successful extended release of drugs, either soluble or insoluble it is essential that polymer hydration and surface gel layer formation are quick and consistent to prevent tablet disintegration and premature drug release. The dissolution rate profile of all the six formulations showed that a higher amount of HPMC K4M in tablet composition resulted in reduced drug release ***(Table 4).*** *Formulation F-2 having a composition of 20.0 % w/w HPMC K4M gave a predetermined release for 6 hrs. than all other formulations. So it was concluded that formulation F-2 was the optimized batch because its drug release profile* ***(Figure 5)*** *shows drug release for six hours in predetermined rate. At higher percentage of HPMC in tablets, when in contact with release medium, HPMC may swell and form a thick gel, thus may decrease the size of the pores present in the tablet and further reducing the drug release. The drug release profile of various tablets was shown in* ***Figure 3****. Formulation F-2 which showed promising results, were subjected to stability studies at ambient room*

conditions for 3 months. After 3 months, extended release tablets did not show any change in physical appearance or drug content.

Release data revealed that optimized batch F2 follow zero-order drug release followed by Higuchi spherical matrix release as good linearity (R^2) was observed with both these models ***(Table 5).*** *However, the best linearity (R^2 = 0.998) was obtained in Korse-Mayer peppas models. The release exponent n was 0.797, which appears to indicate a coupling of the diffusion and erosion mechanism so-called non-Fickian or anomalous diffusion and may indicate that the drug release is controlled by more than one process*

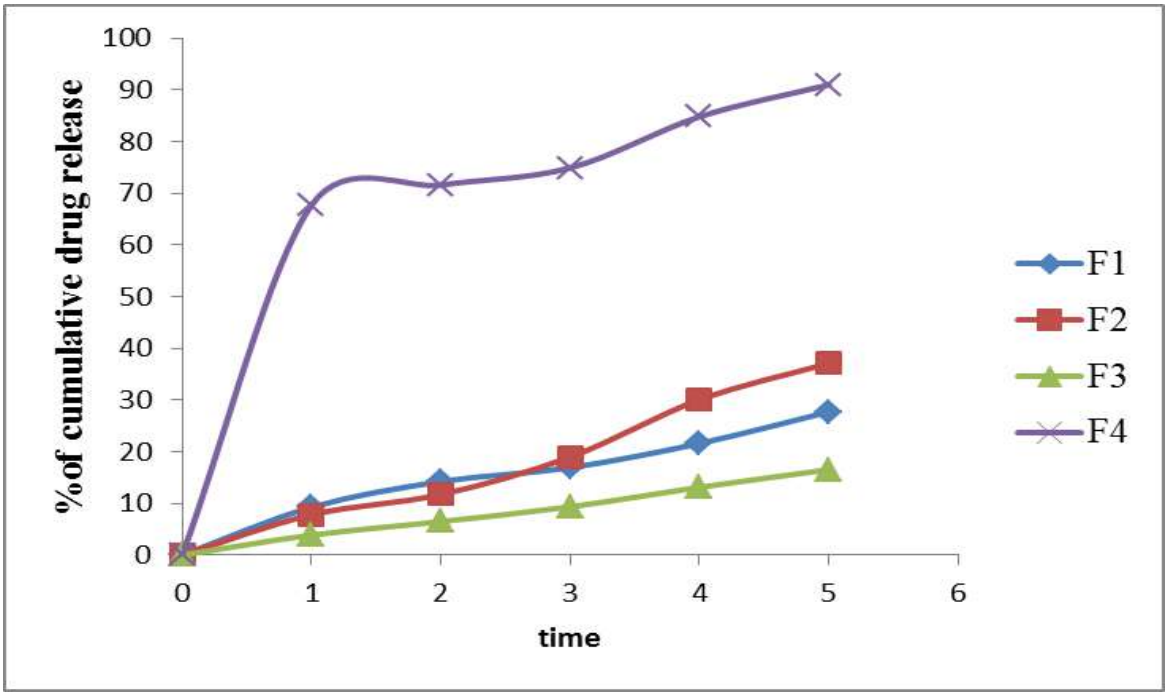
Table 5. In-vitro drug release data of various batches of formulations

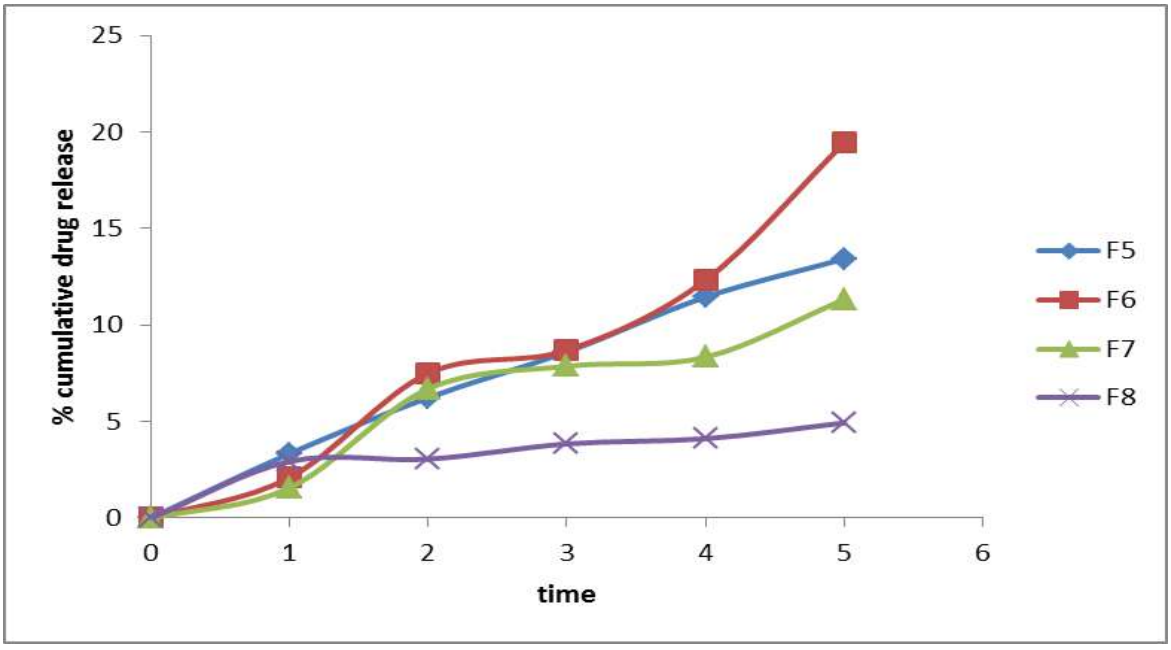
Time in hrs.	***% Cumulative drug release***							
	F-1	***F-2***	***F-3***	***F-4***	***F-5***	***F-6***	***F-7***	***F-8***
1	*9.25*	*7.81*	*3.87*	*7.43*	*6.47*	*7.3*	*1.57*	*2.98*
2	*14.24*	*11.73*	*6.49*	*7.66*	*6.24*	*7.5*	*6.7*	*3.06*
3	*16.92*	*10.62*	*7.21*	*13.41*	*8.61*	*8.7*	*7.8*	*3.5*
4	*21.60*	*30.05*	*13.12*	*17.63*	*9.8*	*12.33*	*8.01*	*4.12*

5	*27.71*	*37.11*	*13.33*	*19.96*	*10.5*	*25.83*	*11.33*	*4.94*
6	*34.27*	*38.56*	*16.76*	*20.30*	*11.93*	*31.39*	*25.28*	*7.05*
12	*98.66*	*94.77*	*83.29*	*91.33*	*106.55*	*87.19*	*96.32*	*99.84*

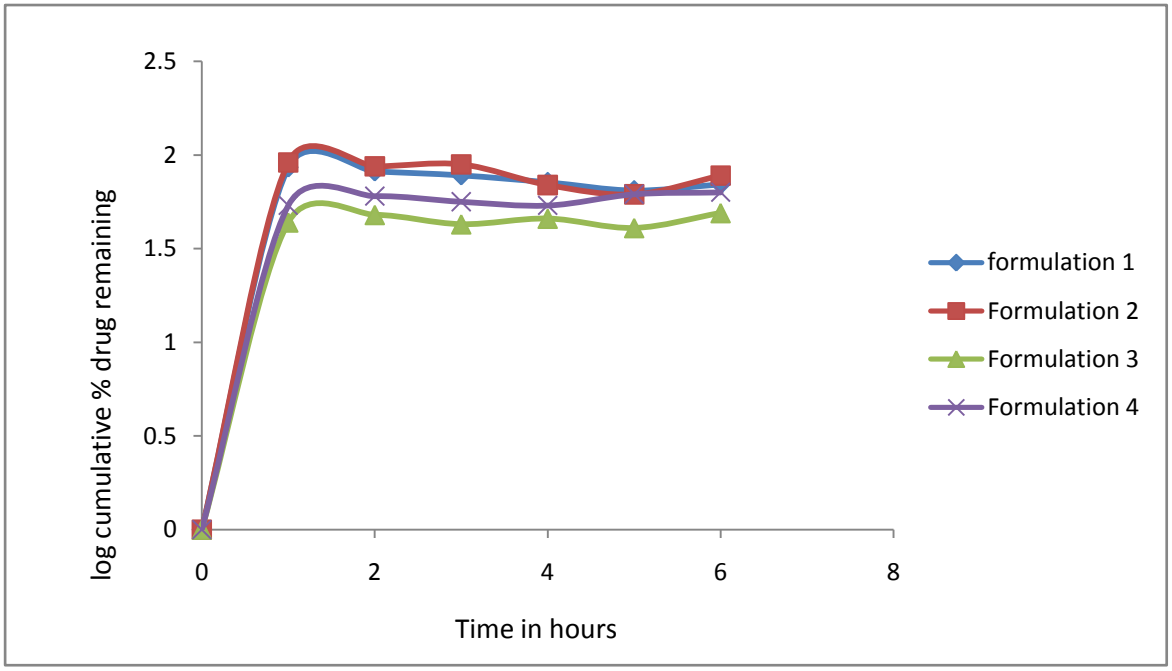
In-vitro drug Release kinetic data for evaluation of drug release mechanism

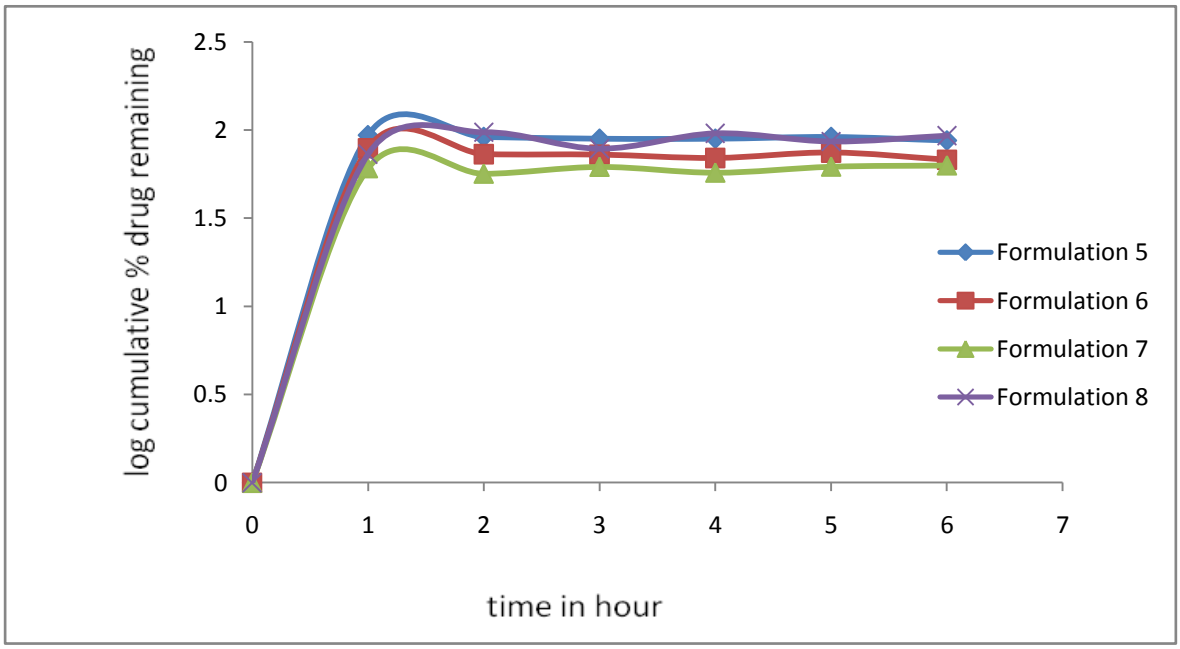
For the Zero Order release kinetics



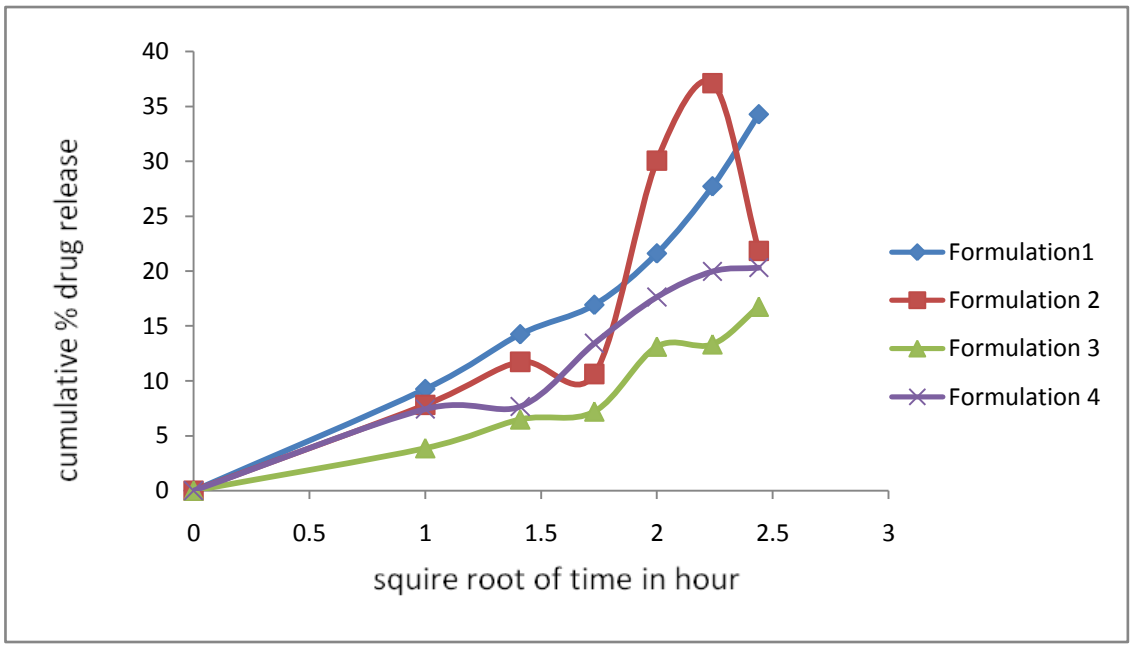


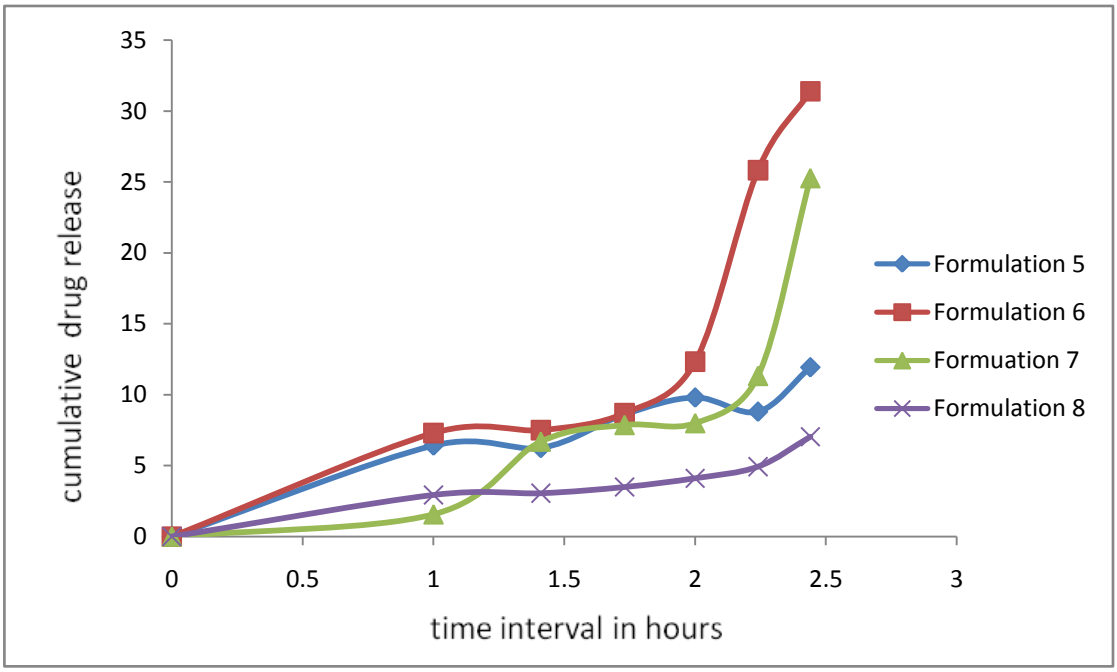
First Order kinetic Model



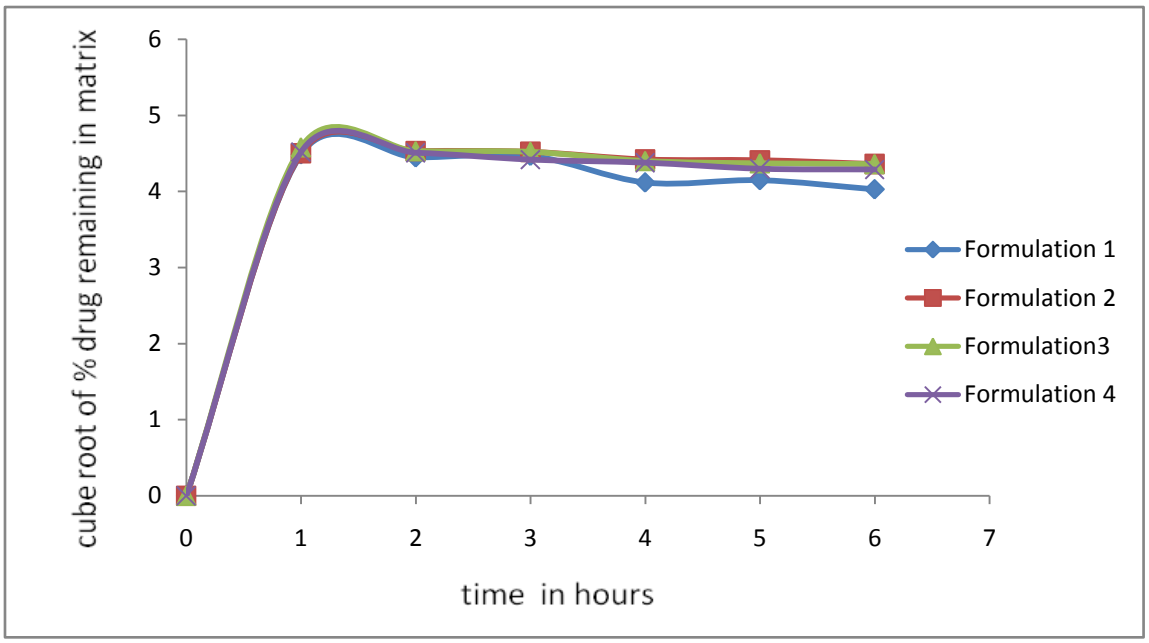


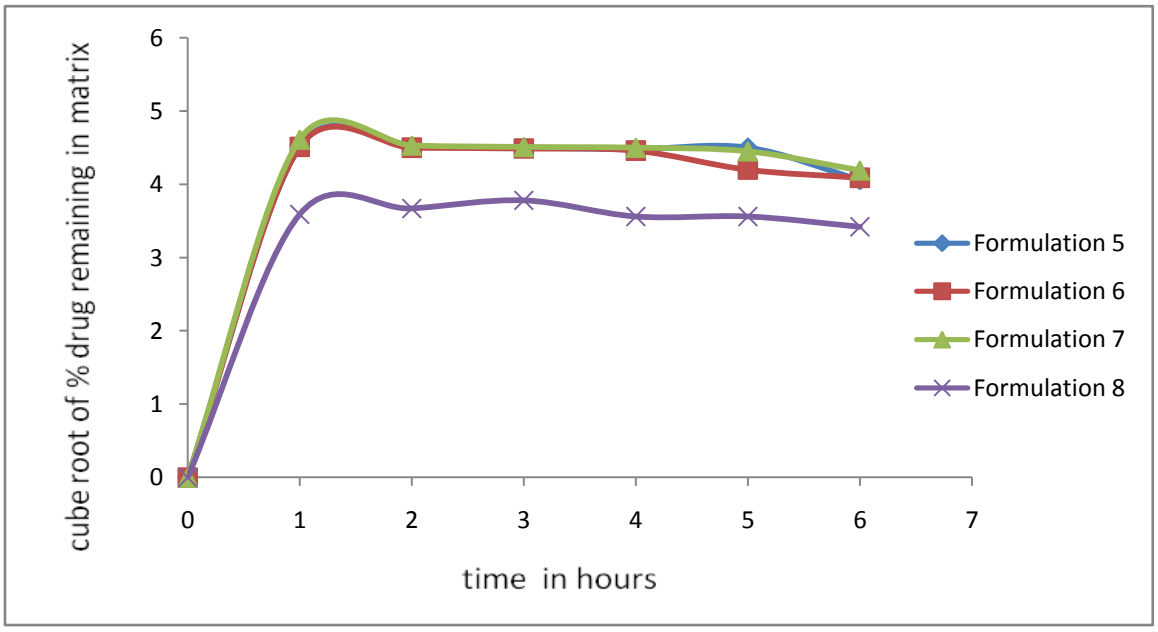
Higuchi model





Hixson –crowell model


cube root of % drug remaining in matrix
0
1
2
3
4
5
6
7
time in hours
Formulation 1
Formulation 2
Formulation3
Formulation 4


cube root of % drug remaining in matrix
0
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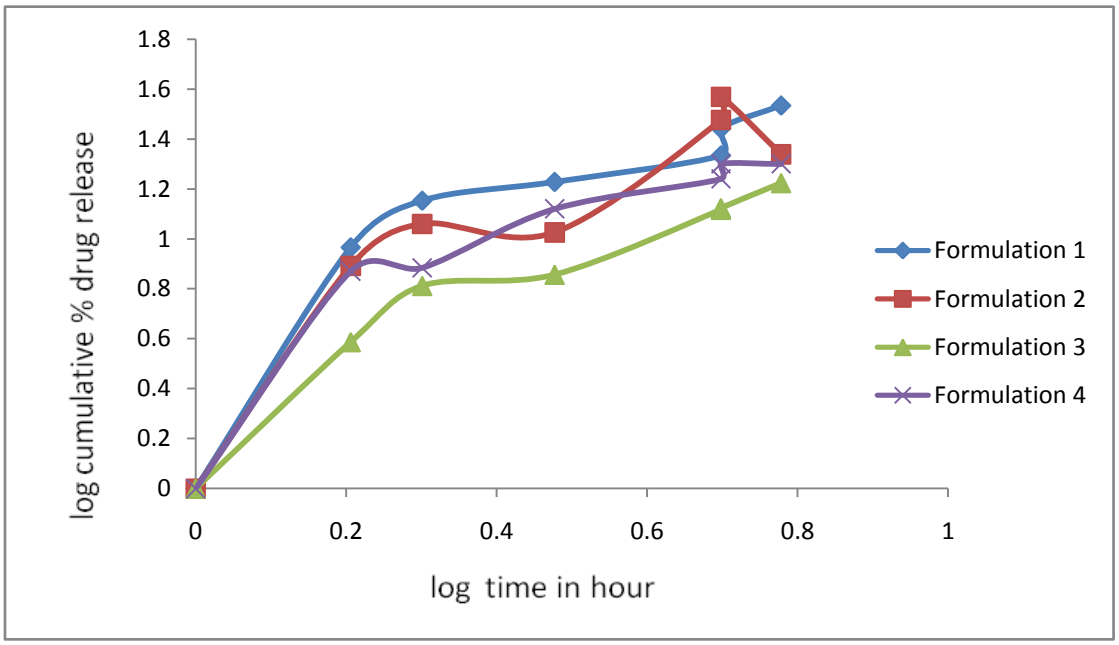
6
7
time in hours
Formulation 5
Formulation 6
Formulation 7
Formulation 8

Korsemeyer-Peppas Model



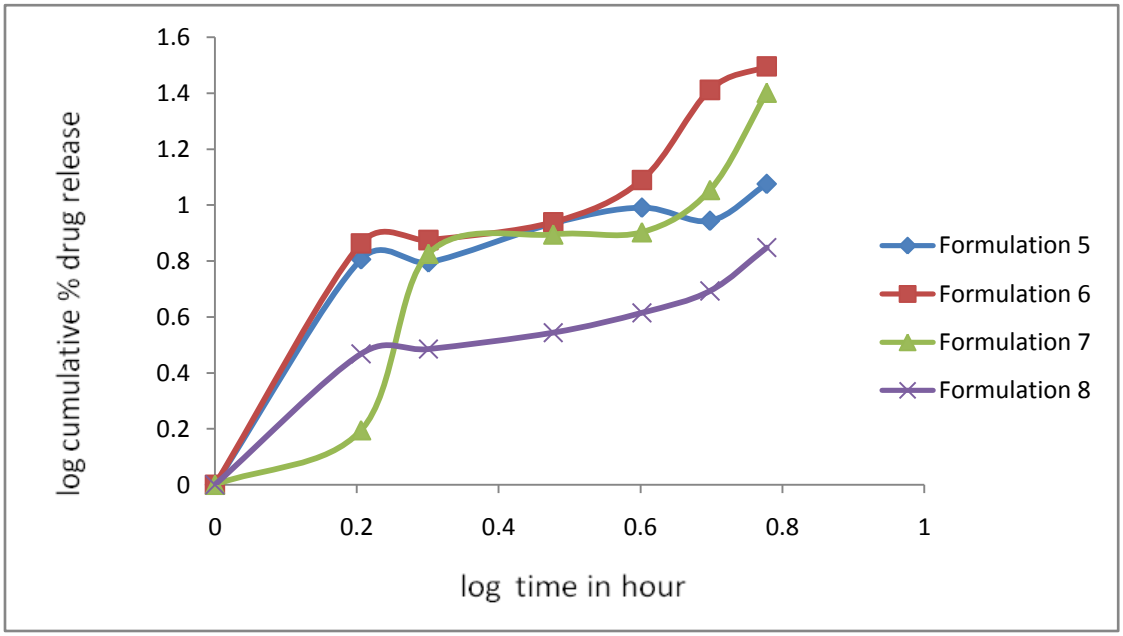


Table 6. Release kinetic data for evaluation of drug release mechanism

FA Code	*Zero order*		*First Order*		*Higuchi Model*		*Hixson – crowell model*		*Korsemeyer-Peppas Model*	
	K_0	R^2	K_1	R^2	K_H	R^2	K_3	R^2	*n*	R^2
F1	*4.862*	*0.982*	*0.027*	*0.963*	*16.59*	*0.941*	*0.101*	*0.841*	*0.66*	*0.936*
F2	*6.834*	*0.958*	*0.026*	*0.506*	*16.90*	*0.986*	*0.33*	*0.796*	*0.797*	*0.998*
F3	*2.990*	*0.950*	*0.012*	*0.938*	*8.944*	*0.928*	*0.048*	*0.925*	*0.820*	*0.951*
F4	*3.530*	*0.928*	*0.015*	*0.949*	*10.51*	*0.930*	*0.053*	*0.959*	*0.652*	*0.891*
F5	*2.473*	*0.828*	*0.004*	*0.584*	*3.56*	*0.797*	*0.067*	*0.482*	*0.332*	*0.779*
F6	*4.449*	*0.837*	*0.028*	*0.836*	*16.82*	*0.746*	*0.086*	*0.789*	*0.821*	*0.722*
F7	*2.536*	*0.771*	*0.023*	*0.820*	*12.59*	*0.701*	*0.067*	*0.756*	*0.292*	*0.891*
F8	*0.756*	*0.863*	*0.004*	*0.716*	*2.52*	*0.762*	*0.016*	*0.950*	*0.436*	*0.758*

Drug release study [62,63,65]

The kinetic data of all the formulations are graphically represented in above. In order to determine the mechanism of drug release form the formulations , the in-vitro dissolution data was fitted to Zero order, First order, Higuchi plot and Korsemeyerpeppa's plot was drawn for optimized formula and interpretation of release exponent value (n) was calculated.. Based on that we have confirmed that the optimized formulation followed first order release.

Higuchi's model was applied to the in-vitro release data, linearity was obtained with high 'r' value indicating that drug release from the sustained-release tablets through diffusion. 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.

CHAPTER 7

CONCLUSION[61,62,64]:

The extended drug delivery system is a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They have been used in-vivo to protect the drug entity in the systemic circulation ,restrict asses of drug to the site of action with enhance therapeutic benefit, with minimizing side effect.

The results of pre-formulation study showed that the glimepiride was soluble n Ethanol and DMSO water, springly soluble in pH 7.4,7.8 and 0.1N HCl. The FT-IR studies confirm the compatibility drug with the excipients used in the formulation . In case of the DSC study ,the results showed the utility of thermal analysis as a rapid and convenient method of screening drug candidate and some excipients during pre-formulation studies, because it permits the ascertainment of excipients compatibility or demonstration of drug-excipient interaction or incompatibility. In this study it was possible to observe the interactions of the Glimepiride with magnesium stearate and lactose. It has been revealed that excipient such as HPMC K4M with polyvinyl pyrrolidone as binder, $CaCO_3$ as filler can be used with direct compression method for versatile extended release technologies. Formulation F-2 having a composition of 20.0 % w/w HPMC K4M gave a predetermined release for 6 hrs than all other formulations. Release study clearly indicates that release rate from the matrix is dependent upon factors including polymer type and level; drug solubility and dose; polymer to drug ratio; filler type and level; particle size of drug and polymer and the porosity and shape of matrix. The optimized formulation was stable after 45 days accelerated stability

study as there were no significant changes in drug content, physicochemical parameters and extended release pattern.

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