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Drug–Excipients Compatibility Studies in Pharmaceutical Formulation Development: A Systematic Evaluation Using Physicochemical and Spectroscopic Techniques

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Abstract

Drug–excipients compatibility is a critical aspect of pharmaceutical formulation development because interactions between the active pharmaceutical ingredient and formulation excipients may affect the stability, safety, efficacy and quality of the final dosage form. The present study aimed to evaluate the compatibility of Afatinib dimaleate with selected pharmaceutical excipients intended for the development of gastro retentive drug delivery system. Physical mixtures of the drug and excipients were prepared and evaluated using Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The results were compared with those of the pure drug to identify potential physicochemical interactions. FTIR spectra analysed for changes in characteristic functional group peaks, while DSC thermograms were evaluated for changes in melting behavior and thermal events. XRD analysis was performed to assess changes in the crystalline nature of the drug. The results demonstrated no significant interaction between Afatinib dimaleate and the investigated excipients. Based on the findings Lactose monohydrate, Microcrystalline Cellulose, Colloidal silicon dioxide, Polyox WSR 303, Methocel E15 and Magnesium Stearate were considered suitable for further formulation development. These compatibility studies provide essential preformulation information for the rational design and development of a stable pharmaceutical dosage form.

Keywords: Afatinib Dimaleate, Assessment of Drug–Excipients Compatibility, Investigation of Drug–Excipients Interactions, Drug–Excipients compatibility

1. Introduction:

Afatinib Dimaleate is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [1]Afatinib is developed to irreversibly inhibit the tyrosine kinase auto-phosphorylation of the EGFR receptor family with down-regulation of signaling. The applicant proposed indication for afatinib is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. FDA has determined that the clinical trial data only supports the indication for the first line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test[2]it's a second-generation targeted drug created by Boehringer Ingelheim in Germany. It is potent & irreversible dual inhibitor between tyrosine kinase & human EGFR (Epidermal Growth Factor Receptor) erbB-2 (HER2) [3].It had been first irreversible ErbB family blocker & new category of orally administered tiny molecules (TKIs) tyrosine kinase inhibitors that can affect all members of ErbB family, including EGFR. Afatinib binds to EGFR permanently, blocking cancer cells' signal pathway and preventing tumor growth, in contrast to first-generation reversible EGFR TKI [4,5].Lung cancer remains the most frequently diagnosed malignancy worldwide, accounting for approximately 12.8 % of the global cancer cases and demonstrates high morbidity and mortality rate (19.1 %). Among the Asian population, lung cancer is the most prevalent disorder, with an incidence rate of 16.5 % and a mortality rate of 21.7 %[6]

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for the majority of diagnosed cases. The development of molecularly targeted therapies has substantially improved treatment outcomes in patients harboring specific oncogenic alterations [7]. Among these therapies, afatinib dimaleate is an orally administered, irreversible tyrosine kinase inhibitor that targets members of the ErbB receptor family, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2) and ErbB4, while also inhibiting transphosphorylation of ErbB3.[8]

Gastro-retentive drug delivery systems (GRDDS) have emerged as an important approach for prolonging the residence time of orally administered dosage forms within the

stomach. These systems are designed to remain in the gastric region for an extended period through mechanisms such as floating, swelling, mucoadhesion, high-density retention, or combinations thereof. Prolonged gastric residence may provide several potential advantages, including sustained drug release, improved utilization of the absorption window, reduced fluctuations in plasma drug concentration, and improved therapeutic performance for appropriately selected drug candidates [9,10,11]

The development of a gastro-retentive formulation of afatinib dimaleate therefore represents an interesting formulation strategy that warrants systematic investigation. A successful GRDDS requires careful optimization of formulation variables, including polymer type and concentration, matrix-forming characteristics, swelling behavior, buoyancy, drug-release kinetics, mechanical integrity, and gastrointestinal compatibility. In addition, the influence of formulation composition on the physicochemical stability and release characteristics of afatinib dimaleate must be comprehensively evaluated.[10,12]

Despite the therapeutic importance of afatinib, there remains a need for systematic investigation of advanced oral delivery approaches capable of controlling its gastrointestinal residence and drug-release characteristics. The application of gastro-retentive technology may provide an opportunity to modulate drug release and gastrointestinal residence through rational formulation design. However, the suitability of such an approach should be established experimentally through comprehensive preformulation, formulation, in-vitro characterization, and, where appropriate, pharmacokinetic evaluation. [10,13]

Therefore, the present study aimed to develop and optimize a gastro-retentive drug delivery system containing afatinib dimaleate through a systematic evaluation of drug–excipients compatibility using Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetric (DSC), X-ray diffraction (XRD), and other appropriate analytical techniques. The study further focused on assessing the formulation characteristics, gastric-retention-related properties, in-vitro drug-release behaviour, release kinetics, and stability of the developed formulations. The optimized formulation was subsequently evaluated to establish its potential as a stable and effective controlled oral delivery system for afatinib dimaleate and to determine whether gastro-retentive technology could offer meaningful pharmaceutical advantages over conventional oral drug delivery.

2. MATERIALS AND METHODS

Materials

Hetero Labs Ltd. in Hyderabad, India, provided a gift sample of Afatinib dimaleate. Polyox WSR and Methocel E5 gift sample received from Colorcon Pvt ltd and Lactose monohydrate, Microcrystalline cellulose, Crospovidone, Colloidal silicon dioxide and Magnesium stearate were acquired from suitable excipient source to initiate the studies. The remaining substances were all of laboratory quality.

Table no:1

S.NO	Inactive Ingredients	Category	Function
1	Afatinib Dimaleate	API	Active Pharmaceutical Ingredient
2	Lactose Monohydrate (Supertab 11SD)	Diluent	Filler; increases bulk and improves tablet manufacturability
3	Microcrystalline Cellulose (MCCPH102)	Diluent / Dry binder	Filler and compression aid; improves tablet compatibility
4	Crospovidone	Super Disintegrant	Promotes water uptake and disintegration/dispersion
5	Colloidal silicon dioxide	Glidant	Improves powder flow and reduces interparticle friction
6	Polyox WSR 303	Hydrophilic	Matrix-forming and drug-release-
7	Methocel E5	Hydrophilic	Matrix-forming and drug-release-
8	Magnesium stearate	Lubricant	Reduces friction during compression

Table no: 1. Composition and Functional Roles of Afatinib Dimaleate and Selected Excipients Used in the Formulation

Polyox™ WSR was selected as the primary hydrophilic matrix-forming polymers for development of the gastro-retentive drug delivery system. Polyethylene oxide has been shown to be an excellent mucoadhesive polymer. Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to water based formulations to provide improved viscosity stability. Polyethylene oxide polymers incorporated to provide controlled

hydration, swelling, and gel-layer formation following exposure to gastrointestinal fluid. The hydrated polymeric matrix was expected to provide resistance to rapid matrix disintegration and regulate drug release through a combination of diffusion and polymer-chain relaxation/erosion mechanisms. [14]

Methocel™ E5 is type 2906 category and hydroxy propoxy content of the compound has limited with the nominal viscosity of 5 mPas. It is an odourless and tasteless, white or creamy white fibrous or granular powder. The key functional category is rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent. [14]

Lactose monohydrate and microcrystalline cellulose were incorporated as diluent and compression-supporting excipients to obtain the desired tablet weight, manufacturability, and mechanical properties. Microcrystalline cellulose may additionally contribute to matrix structure and influence liquid penetration into the compact. Crospovidone was incorporated as a superdisintegrant to enhance liquid uptake and promote dispersion of formulation components; its concentration was carefully considered because excessive incorporation may adversely affect prolonged matrix integrity and controlled drug release. [14]

Colloidal silicon dioxide was used as a glidant to improve powder flow properties and facilitate uniform die filling during compression. Magnesium stearate was incorporated as a lubricant to minimize friction between the tablet formulation and compression tooling and to facilitate tablet ejection. The concentration of magnesium stearate was controlled because excessive lubrication may alter wettability and potentially influence drug-release behavior. [14]

3. Preparation of Drug–Excipients mixtures

Drug–excipients compatibility studies were performed as an integral part of the preformulation investigation to identify any potential physical or chemical interactions between afatinib dimaleate and the excipients selected for development of the gastro-retentive drug delivery system.

Afatinib dimaleate was individually mixed with each selected excipients, namely lactose monohydrate, microcrystalline cellulose, Crospovidone, colloidal silicon dioxide, Polyox™ WSR, Methocel™ E5, and magnesium stearate. Binary physical mixtures were

prepared using a predetermined drug-to-excipients ratio representative of the intended formulation. For preliminary compatibility screening, an exaggerated drug-to-excipients ratio may be employed to increase the probability of detecting potential interactions. The selected ratio should be scientifically justified and clearly reported.

The required quantities of afatinib dimaleate and individual excipients were accurately weighed and thoroughly blended using a suitable mixing procedure to obtain homogeneous physical mixtures and initial evaluation carried out using obtained homogeneous physical blend and one set of samples kept in clear glass vials at 40°C/75%RH up to 3 months' evaluation studies.

The prepared mixture blend as well as 3M 40°C/75%RH condition sample were subjected to initial characterization using Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Where appropriate, X-ray diffraction (XRD) was employed to investigate possible changes in the crystalline state of the drug.

Any significant change in characteristic FTIR bands, thermal behaviour, crystalline characteristics, assay or degradation profile relative to the drug reference was considered an indication requiring further investigation rather than being interpreted as definitive incompatibility based on a single analytical technique. The overall compatibility decision was therefore based on the combined evidence obtained from spectroscopic, thermal, solid-state, and chemical stability assessments.

4.Compatibility Study Techniques:

A. Physical Observation:

A preliminary physical compatibility assessment was performed to identify any visible changes in afatinib dimaleate and its physical mixtures with the selected excipients. The drug and drug–excipient mixtures were visually examined before and after storage condition-3M 40°C/75%RH condition. The samples were evaluated for changes in colour, odour, physical appearance, agglomeration and liquefaction.

The colour and appearance of the samples were examined under suitable lighting conditions and compared with the corresponding initial observations. Any change in colour, such as darkening, yellowing, or discoloration, was recorded as a potential indication of

physical or chemical instability. The samples were also examined for the development of an unusual or characteristic odour that was not present initially.

The physical state of each mixture was assessed for changes such as caking, lump formation, surface alteration or loss of powder characteristics. Particular attention was given to the formation of agglomerates, which may indicate moisture uptake, interaction between formulation components or changes in powder characteristics. The samples were gently inspected for evidence of clumping or formation of cohesive masses.

Liquefaction or partial liquefaction of the powder mixtures was also monitored because it may indicate moisture absorption, eutectic formation or other physicochemical interactions between the drug and excipients. Any visible change observed during the study was documented and compared with the untreated reference sample of afatinib dimaleate.

The physical observations were considered as a preliminary screening assessment of the samples of Initial and 3M 40°C/75%RH condition and were interpreted together with instrumental compatibility studies, including FTIR and DSC and, where applicable, PXRD and chromatographic stability analysis. Absence of significant changes in colour, odour, appearance, agglomeration or liquefaction provided preliminary evidence of physical compatibility; however, the absence of visible changes alone was not considered sufficient to establish complete drug–excipients compatibility in the following table no-1.

Table no: 2

S.No	Sample	Ratio	Observation	Storage condition
			Initial	40°C/75%RH 3 Months
1	Afatinib dimaleate	-	Yellowcolor powder	Yellow color powder
2	Afatinib dimaleate and lactose monohydrate	1:10	Light yellow color powder	Light yellow color powder
3	Afatinib dimaleate and microcrystalline Cellulose	1:10	Light yellow color powder	Light yellow color powder
4	Afatinib dimaleate and crospovidone	1:01	Light yellow color powder	Light yellow color powder
5	Afatinib dimaleate and colloidal silicon dioxide	1:00.3	Light yellow color powder	Light yellow color powder
6	Afatinib dimaleate and Polyox WSR303	1:05	Light yellow color powder	Light yellow color powder
7	Afatinib dimaleate and Methocel E5/E15	1:05	Light yellow color powder	Light yellow color powder
8	Afatinib dimaleate and magnesium stearate	1:0.3	Light yellow color powder	Light yellow color powder

Table no: 2. Physical compatibility of API-Excipients in 40°C/75%RH/3 Months

Table -3

Condition	40°C/75%RH/3 Months –Closed condition					
Sample/Attributes	Colour	Odour	Appearance	Agglomeration	Liquefaction	Inference
Afatinib dimaleate	No change	No change	Free-flowing powder	Absent	Absent	Stable
API + Lactose	No change	No change	Uniform powder	Absent	Absent	Compatible

API + MCC	No change	No change	Uniform powder	Absent	Absent	Compatible
API + Crospovidone	No change	No change	Uniform powder	Absent	Absent	Compatible
API + Colloidal silicon dioxide	No change	No change	Uniform powder	Absent	Absent	Compatible
API + Polyox WSR 303	No change	No change	Uniform powder	Absent	Absent	Compatible
API + Methocel E5	No change	No change	Uniform powder	Absent	Absent	Compatible
API + Magnesium stearate	No change	No change	Uniform powder	Absent	Absent	Compatible

Table no: 3. Preformulation study of a drug-excipients in 40°C/75%RH/3 Months.

B. FTIR Study

Fourier-transform infrared (FTIR) spectroscopy was employed as a preliminary analytical tool to investigate potential chemical interactions between afatinib dimaleate and the selected pharmaceutical excipients used in the development of the gastro-retentive drug delivery system. The FTIR spectra of pure afatinib dimaleate, individual excipients, and their corresponding physical mixtures were recorded under identical experimental conditions over an appropriate mid-infrared spectral range. [15,16]

The spectrum of pure afatinib dimaleate was initially analyzed to identify its characteristic absorption bands corresponding to the principal functional groups present in the drug molecule. The spectra obtained for the individual excipients were subsequently recorded to establish their characteristic infrared absorption profiles. The spectra of the drug–excipient physical mixtures were then compared with those of the pure drug and corresponding excipients.[15,16,17]

The compatibility assessment was based primarily on the retention of the characteristic absorption bands of afatinib dimaleate in the physical mixtures. Particular attention was given to changes in peak position, peak intensity, peak shape, and bandwidth. The disappearance of a characteristic drug peak, substantial displacement of an absorption

band, marked alteration in peak intensity or shape, or appearance of a new absorption band may indicate a possible interaction and should therefore be evaluated in conjunction with complementary techniques such as DSC and PXRD rather than being considered conclusive evidence of incompatibility based on FTIR alone.[15,17]

C. Differential Scanning Calorimetry (DSC) Study

Differential scanning calorimetry (DSC) was employed to investigate the thermal behavior of afatinib dimaleate and to assess potential thermal interactions between the drug and selected pharmaceutical excipients. DSC thermograms of pure afatinib dimaleate, individual excipients and the corresponding drug–excipient physical mixtures were recorded under controlled experimental conditions using a calibrated differential scanning calorimeter. [18,20]

The thermal profile of pure afatinib dimaleate was initially characterized by evaluating its characteristic thermal events, including the onset temperature, peak temperature, and enthalpy associated with the principal endothermic or exothermic transitions. The thermograms of the individual excipients were subsequently analyzed to identify their respective thermal events. The thermograms of the drug–excipient mixtures were then compared with those of the pure drug and corresponding excipients. [18,20,21]

The compatibility assessment was based on changes in the characteristic thermal behavior of afatinib dimaleate, including significant displacement or disappearance of its characteristic thermal transition, development of new thermal events, or substantial changes in peak shape, onset temperature, peak temperature, or enthalpy. The retention of the characteristic thermal event of afatinib dimaleate in the physical mixtures, without the appearance of significant additional thermal events indicative of an interaction, was considered supportive evidence of thermal compatibility. [19, 21]

Particular attention was given to the thermal behavior of afatinib dimaleate in combination with Polyox™ WSR and Methocel™ E5, as these polymers serve as the principal matrix-forming components of the proposed gastro-retentive drug delivery system. Any shift or reduction in the intensity of the drug's characteristic thermal transition was interpreted cautiously; as such changes may arise from dilution effects, physical mixing and alterations in crystallinity, polymorphic transformations, or overlapping thermal events

involving the drug and excipients. Therefore, DSC results were not considered independently conclusive for establishing chemical compatibility and were interpreted in conjunction with FTIR, PXRD, and, where appropriate, stability-indicating chromatographic data to provide a comprehensive assessment of drug–excipient compatibility. [18, 22]

D. X-Ray Diffraction (XRD)

Powder X-ray diffraction (PXRD) analysis was performed to characterize the solid-state properties of afatinib dimaleate and to investigate whether interaction with the selected excipients resulted in changes in the crystalline structure of the drug. Diffractograms of pure afatinib dimaleate, selected individual excipients, and drug–excipient physical mixtures were obtained under controlled instrumental conditions using an appropriate X-ray diffraction measurement protocol. [18,23]

The diffraction pattern of pure afatinib dimaleate was initially examined to identify its characteristic diffraction peaks and establish the baseline crystalline profile of the drug. The diffraction patterns of the physical mixtures were subsequently compared with that of the pure drug with respect to the position, intensity and relative characteristics of the principal diffraction peaks.[23,25]

Retention of the characteristic diffraction peaks of afatinib dimaleate in the physical mixtures, without the appearance of additional peaks indicative of a new crystalline phase, was considered supportive evidence that the drug's crystalline structure was substantially preserved. However, changes in peak position, intensity, broadening, disappearance of characteristic reflections or the appearance of new diffraction peaks were carefully evaluated for potential alterations in the solid-state characteristics. A reduction in peak intensity was interpreted cautiously, as it may occur simply due to dilution of the drug with excipients, while peak broadening or loss of intensity may also result from partial amorphization, reduced crystallite size, preferred orientation or other physical effects. Therefore, such PXRD changes were not considered conclusive evidence of chemical incompatibility and were subjected to further evaluation using complementary analytical techniques. [24–26]

The PXRD findings were therefore interpreted in conjunction with FTIR and DSC results to provide a comprehensive assessment of drug–excipient compatibility. Particular emphasis was placed on the physical mixtures containing Polyox™ WSR and Methocel™ E5

to determine whether incorporation of the hydrophilic polymers produced any substantial alteration in the solid-state characteristics of afatinib dimaleate.

5. Results and Discussion

The study results and discussion are presented the below to ensure the nature of study and selection of excipients of the proposed formulation.

A. FTIR STUDY

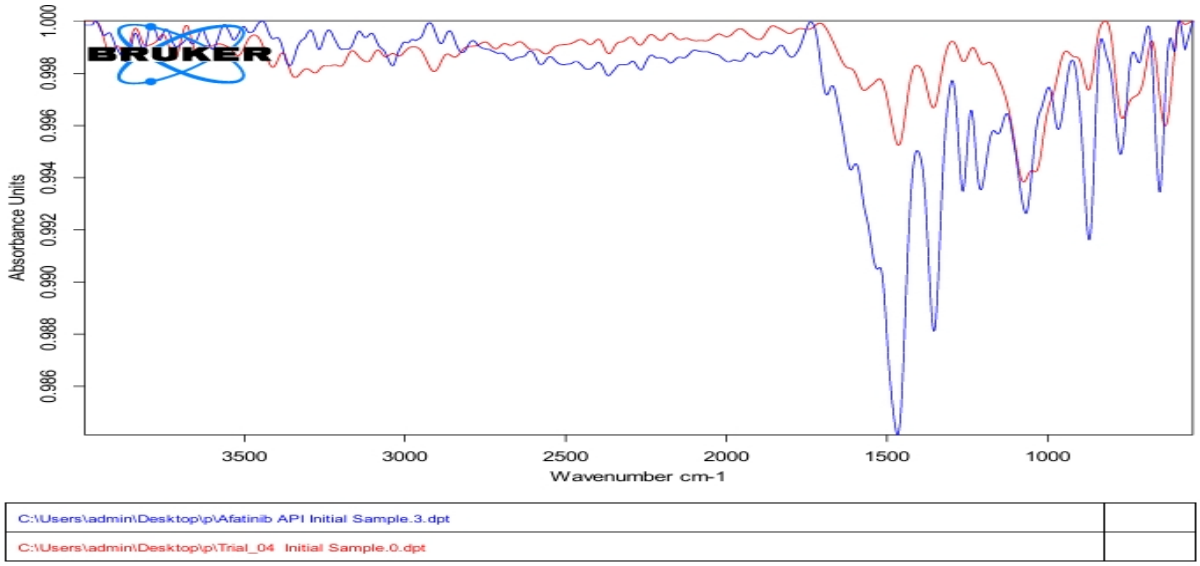


Fig no: 1. Figure X. Comparative FTIR Spectra of Afatinib Dimaleate API and Trial-04 Formulation

FTIR analysis was performed to identify the characteristic functional groups of afatinib dimaleate and to evaluate possible drug–excipient interactions. The afatinib dimaleate spectrum showed characteristic peaks at approximately 3320 cm^{-1} (N–H stretching), 3030 cm^{-1} (aromatic C–H stretching), and 1685–1690 cm^{-1} (C=O stretching). Peaks around 1640–1650 cm^{-1} were associated with conjugated C=C/C=O vibrations, while bands at 1495–1500 and 1455–1460 cm^{-1} corresponded mainly to aromatic ring vibrations. The peaks at approximately 1350–1360 cm^{-1}, 1260–1270 cm^{-1}, and 1065–1070 cm^{-1} were attributed to C–N, C–O–C, and C–O stretching vibrations, respectively. Additional characteristic peaks were observed in the fingerprint region.

Importantly, the major characteristic peaks of afatinib dimaleate were retained in the Trial-04 formulation, although some changes in peak intensity were observed. No prominent new peaks or major shifts in the characteristic bands were detected, suggesting the absence of significant chemical interaction between afatinib dimaleate and the formulation excipients. Thus, the FTIR results provided supportive evidence of drug–excipient compatibility.

B. DSC STUDY

Differential Scanning Calorimetry study was carried out to check the changes in the proposed formulation. The results are presented as below

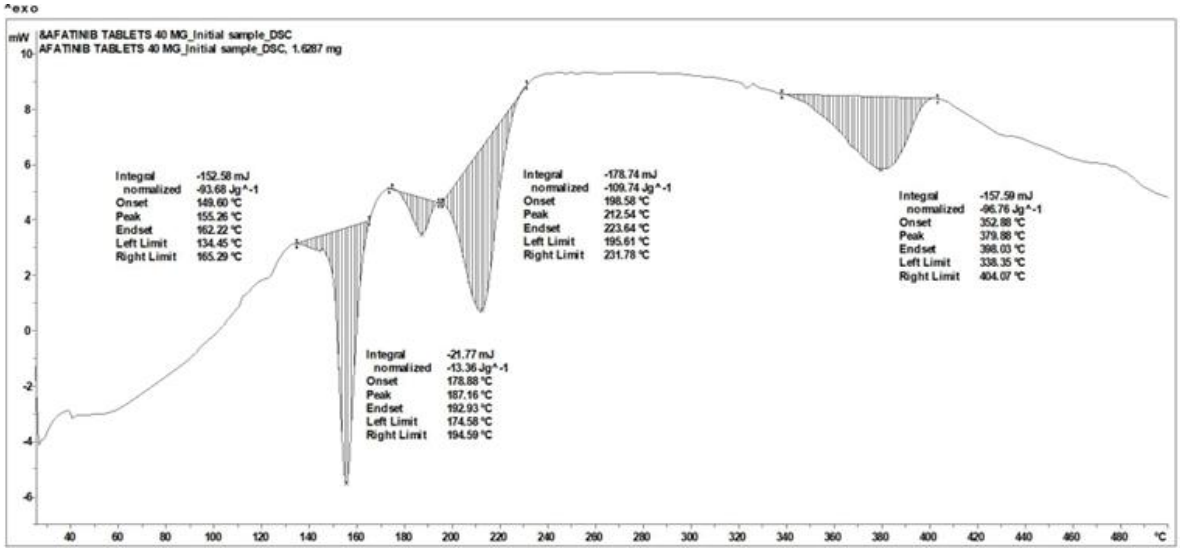


Fig no: 2. Differential Scanning Calorimetry (DSC) Thermogram of Afatinib Dimaleate Tablets (40 mg) – Initial Sample

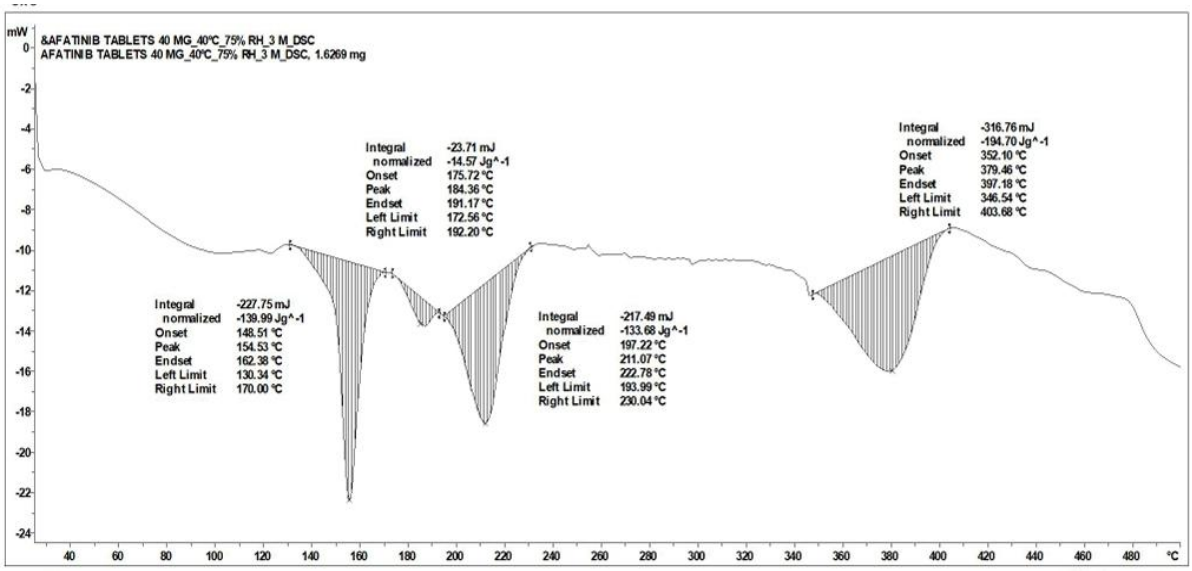


Fig no: 3. DSC Thermogram of Afatinib Dimaleate 40 mg Tablets After Storage at 40°C/75% RH for 3 Months

Both samples were analyzed using the same method: 25–500°C, heating rate 30 K/min, under N_2 at 60 mL/min**,** with approximately 1.63 mg sample.

Table: 4

Thermal event	Initial sample	40°C/75% RH, 3M	Change in peak
Event 1	**155.26°C**	**154.53°C**	−0.73°C
Event 2	**187.16°C**	**184.36°C**	−2.80°C
Event 3	**212.54°C**	**211.07°C**	−1.47°C
Event 4	**379.88°C**	**379.46°C**	−0.42°C

Table no: 4. Comparison of DSC Thermal Events of Afatinib Dimaleate Tablets Before and After Storage at 40°C/75% RH for 3 Months

Differential scanning calorimetry (DSC) was performed to evaluate the thermal behavior and possible solid-state changes of Afatinib tablets before and after storage under accelerated stability conditions. The initial Afatinib tablet sample exhibited a prominent thermal event with an onset temperature of 149.60°C, peak temperature of 155.26°C and end set temperature of 162.22°C. After storage at 40°C/75% RH for 3 months, the corresponding thermal event was observed at an onset temperature of 148.51°C, peak temperature of 154.53°C and endset temperature of 162.38°C.

The peak temperature therefore showed only a minor shift of approximately 0.73°C after storage, while the endset temperature remained comparable. Additional thermal transitions observed in the initial sample at 187.16°C and 212.54°C were also present in the stability sample at 184.36°C and 211.07°C, respectively. The high-temperature transition was similarly maintained, with peak temperatures of 379.88°C and 379.46°C for the initial and stability samples, respectively.

C. XRD STUDY

The overlay shows that both the initial Afatinib API and the Trial-04 sample exhibitdistinct diffraction peaks, indicating that crystalline material is present in both samples.

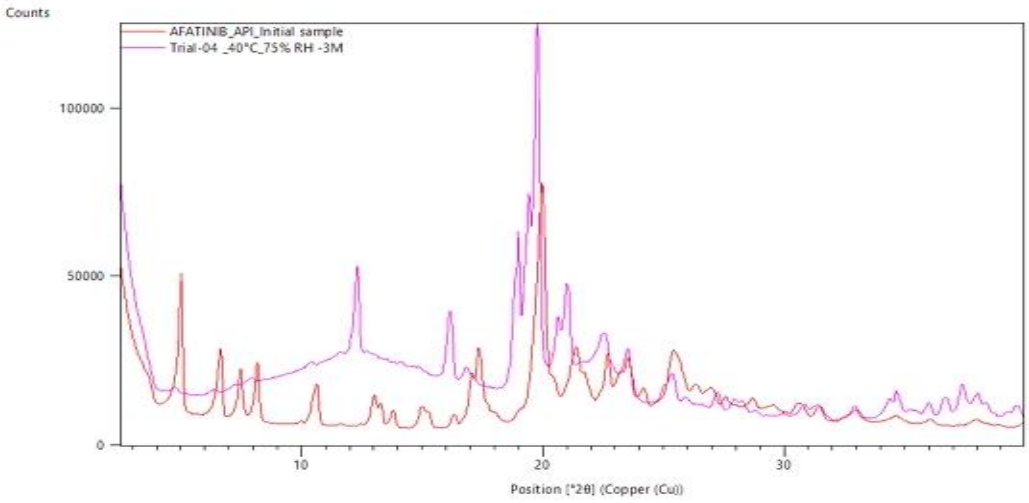


Fig no:4. Comparative PXRD Patterns of Afatinib Dimaleate API and Trial-04 Formulation After Storage at 40°C/75% RH for 3 Months

PXRD analysis was performed to evaluate the crystalline nature and solid-state stability of afatinib dimaleate in the optimized formulation. The PXRD pattern of the afatinib dimaleate API exhibited several sharp and distinct diffraction peaks over the investigated 2θ range, confirming its crystalline nature. The Trial-04 formulation stored at 40°C/75% RH for 3 months retained the major characteristic diffraction reflections of the drug, particularly in the low- and medium-angle regions, although differences in relative peak intensity were observed. No prominent new diffraction peaks or substantial changes in the overall diffraction pattern were evident. The observed variations in peak intensity were interpreted

cautiously because they may result from dilution by excipients, preferred orientation, particle-size effects or changes in the degree of crystallinity. Overall, the retention of the major diffraction reflections after storage indicated that the crystalline structure of afatinib dimaleate was substantially maintained, providing supportive evidence of the solid-state stability of the optimized formulation.

6. Conclusion

The present study evaluated the compatibility of Afatinib dimaleate with selected pharmaceutical excipients intended for the development of Gastro retentive drug delivery. Drug–excipient mixtures were investigated using complementary analytical techniques including FTIR, DS, and XRD, together with physical and stability observations. The characteristic spectral and thermal properties of the drug were substantially retained in mixtures containing afatinib dimaleate indicating their suitability for further formulation development.The findings demonstrate that the importance of systematic drug–excipient compatibility studies during preformulation and provide a scientific basis for the rational selection of excipients for the development of a stable and effective pharmaceutical dosage form.

7. Acknowledgments:

I gratefully acknowledge Hetero Labs Ltd., Hyderabad, India, for providing Afatinib dimaleate as a gift sample. I sincerely thank Colorcon Pvt. Ltd. for providing Polyox™ WSR and Methocel™ E5 as gift samples. I also extend my sincere gratitude to the Department of Pharmacy, Annamalai University, Chidambaram, for providing the required excipient samples. I further acknowledge the respective suppliers for providing the pharmaceutical excipients and laboratory-grade chemicals used in this study.

8. Conflict of Interest:

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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