Exploring Cocrystals Of Imatinib: Synthesis, Characterization, And In Vitro Evaluation

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Abstract
The limited efficacy of Imatinib as an anticancer agent is attributed to its significantly low solubility and its bioavailability issues. To prepare the cocrystals of Imatinib (IMB) using a cocrystallization techniques with the goal of improving the drug's physicochemical characteristics and bioavailability for myeloid leukaemia, some types of acute lymphoblastic leukaemia, and gastrointestinal stromal tumors. The preparations utilised the mechanochemical technique for two cocrystals of IMB with Theobromine (IMTH), and Alpha-ketoglutaric acid (IMKG). They were further characterised using a spectroscopic and thermoanalytical method. The DSC, PXRD, and FTIT techniques were used to characterize the newly obtained pure crystal forms. The crystal structure determination was done through PXRD, which revealed the presence of a triclinic crystal system having P-1 space groups. Allresults indicated that IMTH cocrystals possess better solubility and dissolution rate than parent drug. Thus, cocrystallization Thus, cocrystallization extends the scope of the existing preformulation choices prior to the pure API form to improve bioavailability and permeability.

Keywords: Cocrystals; Coformers; Anti-Cancer; Solubility; Bioavailability

1. Introduction

Imatinib, a chemotherapeutic drug, is useful in the treatment of diseases such chronic myeloid leukemia and gastrointestinal stromal tumors can be effectively treated with the chemotherapeutic agent drug imatinib (Su et al., 2022). Imatinib (IMB), a tyrosine kinase inhibitor and a new class of rationally designed targeted chemotherapeutic drug molecule andis regarded as standard for cancer treatment (He et al., 2020). It is an anti-leukemic drug approved by the FDA for the management of myeloid leukemia in accelerated phase, chronic phase and blast crisis after unsuccessful interferon therapy(Rawan Nehme et al., 2020; R Nehme et al., 2020). Unfortunately, IMB which is BCS class-2 drug exhibits low aqueous solubility and it is unsuitable to administrate orally(Yang et al., 2020). It is whitish creamy crystalline powder which is optically inactive. Regretfully, due to their poor aqueous, several medicated compounds in the market have inconsistent bioavailability. Consequently, thepharmaceutical industry is making numerous efforts to change these biopharmaceutical properties that they can be used for development. Therefore, cocrystal formation which is oneof the primary solid-state approaches has been used that bring the desired alterations in the physiochemical parameters of a molecule without affecting the pharmacological profile. The co-crystallization is one of the best techniques used to modify the solubility-related parameterof imatinib (IM). Cocrystallization has emerged as a powerful technique in the field of drug development and formulation, offering a versatile tactic to tailor the solubility and bioavailability of low soluble drugs(Srivastava et al., 2022). Cocrystallization offers a solvent-free, easy, environmentally safe, and economically advantageous synthetic derivatization method. It is distinguished from typical organic solvent-based derivatization technologies by its versatile ability to tune the process to produce a product with necessary parameters, such as improved solubility, dissolution, compressibility, stability, and dispersion properties(Kara and Rathnanand, 2022)(P. George et al., 2020).

Co-crystals are homogeneous crystalline substances comprised of two or more molecules in precise stoichiometric ratios held together in a crystal lattice by non-covalent forces(Ross et al., 2016). Co-crystallization tactics itself comprises breaking of existing non-covalent interactions between different constituents of cocrystal(Karimi-Jafari et al., 2018). The main aim of co-crystallization is to construct crystal structure from molecular structure. It plays an vital role in attaining the desired physiochemical attributes in a molecular solid by controlled manipulations of intermolecular interactions. There have been very few attempts were reported for the enhancement of the solubility of imatinib in water, including the development of solid dispersion systems, nanocrystal tablets, and lipid nanoemulsions(Karimi et al., 2020; Moreno-Fuquen et al., 2019; Sharma et al., 2021)

The main drawbacks of the aforementioned strategies, such as instability during storage and a drop in dissolution rate with age, have kept these initiatives from succeeding. The development of a more effective oral dose form of imatinib is

therefore constantly needed. In the present work, imatinib has been co-crystallized co-formers (theobromine and alpha-ketoglutaric acid) to improve the biopharmaceutical parameters(Figure 1).

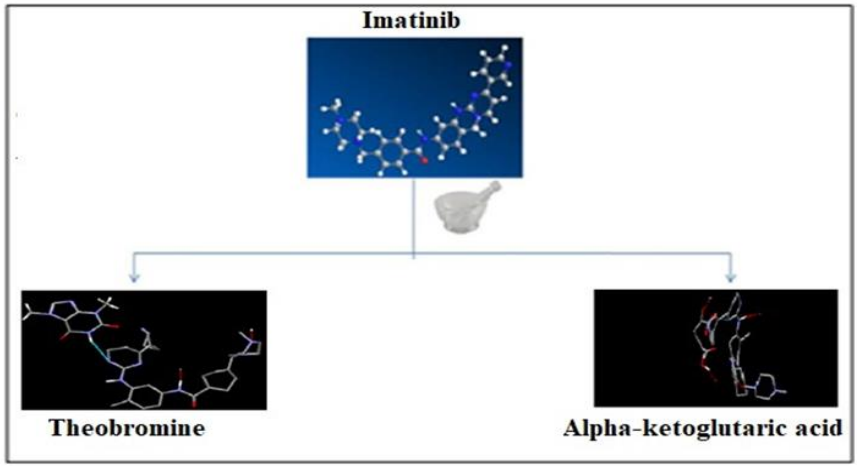


Figure 1: Strategic process for the preparation of Imatinib co-crystals

2. Experimental

Imatinib4-[(4-Methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2- yl)amino] phenyl] benzamide > 99% purity, Molecular weight 588.91 g/mol was received as a Beta Drugs Limited Baddi, Himachal Pradesh. Alpha-ketoglutaric acid (anhydrous) wasobtained from Himedia Labs, India. Theobromine (anhydrous) was received from LobaChemie Pvt. Ltd., Mumbai. Ethanol was purchased from Merk (India) Ltd., Mumbai.

2.1 Designing of Cocrystal

Crystallographic Structure Database (CSD) (version 5.36) was used to explore discrete functional groups present in APIs to design the cocrystals of imatinib using the synthon approach. In order to accomplish this search, ConQuest software (version 1.7) was used. CSDis primarily ascertained by molecule's 3-D shape and polarity. Based on this, we can approximate the possibility of functional m in drugs forming synthons with corresponding functional groups in their coformers.

2.2 Preparation of cocrystals

Cocrystals of IMB with Alpha-ketoglutaric acid (IAA) and Theobromine (ITH) were produced in 1:1 molar ratio by grinding the two phases. Equimolar quantities of IMB (493.63 mg, 1mmol) with theobromine (180.164mg) and IMB (493.63 mg) with Alpha-ketoglutaric acid (146.1 mg,), were triturated with 2 mL of ethanol for approximately 120 minutes were added periodically to enhance the process efficiency. The solid mass thus obtained was overnight dried at room temperature and then stored in desiccators at 25°C/40% RH.

2.3 Differential Scanning Calorimetry (DSC)

Imatinib, coformers (TH and KG), and prepared cocrystals (ITH and IKG) were analyzed using Q20 Calorimeter (TA-Instruments Waters LLC, USA). Indium having melting point of156.6°C and a ΔH of 25.45 J/g served as the calibration control. An aluminum pan was filled with 1-2 mg of sample, and a lid was used to seal the pan. Under a N2 purged conditions (50 $cc.min^{-1}$), the scan was performed in range of 30-350°C operating at 10°C/min of heating rate.

2.4 Hot Stage Microscopy (HSM)

The microscopic changes in crystal geometry that occur by virtue of heating were evaluated by hot stage microscopy (Leica DMLP, Leica, Germany). The microscope was furnished witha cooling stage (LTS350, Linkam) and controlled heating, as well as an imaging system (JVC-Digital camera, VTO 232, and imaging software (Linksys 32), Linkam, England). Thanthe sample were magnified at 10X which further subjected to a temperature gradients of 5and 10 ºC/min, respectively, starting from 40ºC and reaching 350ºC at a rate of 10ºC/min. Images were captured every 10 seconds throughout the entire heating process.

2.5 Powder X-Ray Diffraction (PXRD)

The powder X-Ray diffractograms of IMB, Coformers and its prepared cocrystals were recorded on PAN analytical X'Pert Pro X-ray powder diffractometer (The Netherlands, Holland). The Cu K radiation was observed at an accelerating voltage of 40 kV at current of 45 mA, with 2θ ranging from 5–45° (2), increasing at a scanning speed of $0.00085°s^{-1}$.

2.6 Fourier Transform Infrared Spectroscopy (FTIR)

The spectra were recorded at IR spectrometer (Perkin Elmer, England), KBr pellet method. Quintuplicate scans with a resolution of 4 cm^{-1}, the spectra of drug, conformer and itscorresponding cocrystal were recorded and analysed.

2.7 Crystal Structure Determination from PXRD

Utilizing powder diffraction data, the Reflex plus module of Materials Studio (BIOVIA 7.0) was used to ascertain the crystal structures of co-crystals. Four phases were used to complete the prediction process: indexing, Pawley fitting, structural solution, and Rietveld refinement. In the indexing stage, the proposed unit cells were organized in an X-cell according to their figure of merit, and the crystal class and approximate lattice parameters were deduced from the peak positions in the experimental powder diffraction pattern. An empty unit cell was created after choosing the unit cell with the greatest merit figure(Farooqui et al., 2021).

Pawley fitting and refinement were used to identify the precise lattice and the cell characteristics. The agreement between the predicted and experimental powder patterns was established using the Rwp (weighted Rietveld parameter) value, which was acquired after refinement. This verified the accuracy of the crystal class and the lattice parameters. The space group with the most quality was chosen, and Pawley refining was carried out once more to provide additional Rwp. Motion groups were established when the drug molecule's optimised structure was loaded into the improved unit cell. Reflex Powder solution, which involved Monte Carlo/simulated annealing, was used to obtain the structure. The number of steps in each of the 10 cycles of the simulated annealing was 21,40,100. The calculated and observed diffraction patterns were similar (Guziewski et al., 2020).

2.8 Solubility studies

The solubility studies of IMB and prepared co-crystals (IMTH and IMKG) were performed using water bath shaker. Each sample (about 20mg) was added in excess to 25 ml different conical flasks comprising 5mL of pH 1.2 and phosphate buffer pH 6.8 pre-equilibrated at 37ºC. A horizontal water bath shaker was used to stir the flasks at 200 rpm. After 24 hours of stirring, the samples were taken and filtered through a 0.45-micron filter, and the drug was quantified using a previously reported chromatographic method(Gautam et al., 2019).

2.9 Intrinsic Dissolution Studies

On the United States Pharmacopeia-certified Dissolution Testing Apparatus Lab India DS 8000 (Thane, Maharashtra, India), a dissolution study of the IMB and its prepared co-crystals were carried out for 24 h in pH 6.8 buffer 0.1N HCl (pH 1.2) employing rotating disc method. Gilson mesh sieve (# 80) was used to sifting samples. Fine powder i.e. 100mg of the compound was then compressed in a die cavity about 3-5 minutes at 2000 psi. Further, a base plate was detached from the die to reveal an even, compressed pellet havinga 0.5 cm^2 surface area. The shaft is now put on the stirring drive mechanism of the dissolving apparatus. The dissolution vessel was filled with 900 mL of clean water at 37 °Cand agitated at 100 rpm after the dies were mounted. Aliquots (5 mL) were drawn off with replacement at regular intervals, it is than filtered utilizing 0.45 m membrane filters, and their concentrations were calculated using the predetermined standard curves for the relevant chemicals. Linear regression of the data of drug release vs time per unit surface area was used to compute the intrinsic dissolution rate from the linear part of the graph(Tomar et al., 2020).

3. Result and Discussion:

3.1 Designing of Cocrystals

The initial step to synthesize the cocrystal is its strategically designing which involves the discerning supramolecular chemistry of the functional groups. The supramolecular chemistry can be assessed as intramolecular bond chemistry, such kind of intramolecular interactionsare directed through the geometrical like shape and size as well as chemical factors, such a strategical approach is feasible with the Cambridge structure database (CSD). It is based predominantly on the shape and polarity of molecules and their complementary functional group. CSD provides enough information regarding basic functional moiety that are engaged in supramolecular synthon formation. Synthesis of co-crystals realizes upon the intermolecular interaction between the complementary functionalities present in the parent component and the respective coformer. Based on the potential functional group present inthe parent drug molecules (pyrazine, pyrimidine, secondary amine, and amide) preliminary search for the propensity of the functional group the probability of forming homo and hetero synthons by these functional moieties with the complementary groups of a counter molecule was estimated. By using ConQuest software (Version 1.7). this search was performed. After that selection of the suitable coformers to prepare cocrystals was done on the basis of resultedhits. Amide is the principal functional group present in Imatinib. Therefore, several FDA- approved co-crystal former with a complementary functional group (COOH, CONH, piperidine, pyrimidine, and hydroxide) can be selected for the co-crystallization. Final selections were done on the basis of functionally base on the synthon approach. Thus based upon that three coformer (theobromine and alphaketoglutaric acid,) were selected besides having high solubility and have their own clinical effect. The potential functional moieties ofIMB are pyrazine, amide (-CONH), pyrimidine**(-N-)**, and secondary amine(), [Fig. 1]. Amide is the principal functional group present in Imatinib. Consequently, based on the number of hits obtained, various coformers with high aqueous solubility were attempted to create cocrystals of imatinib.

However, only two cocrystals involving theobromine and alpha-ketoglutaric acid weresuccessfully obtained, while the remaining coformers did not yield satisfactory results. This can be attributed to the influence of other factors that impede cocrystal formation. These internal factors include the strength of interactions, electrostatic behavior, and the ability to engage in homo or hetero intermolecular interactions, as well as proficient packing.

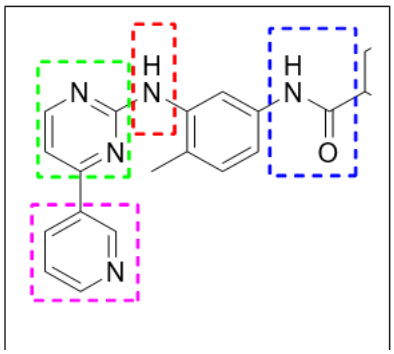
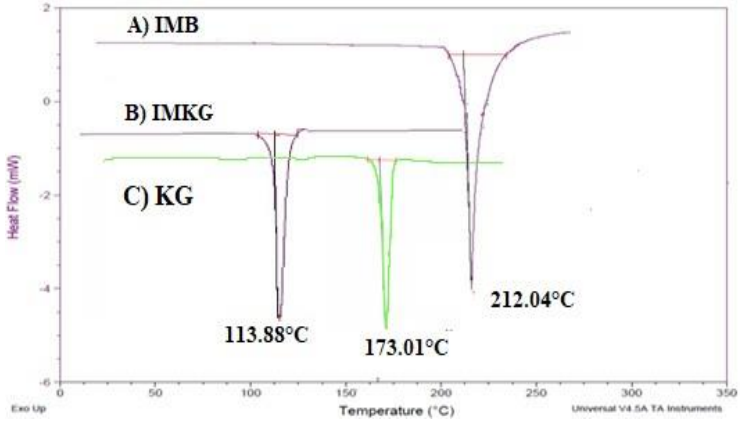
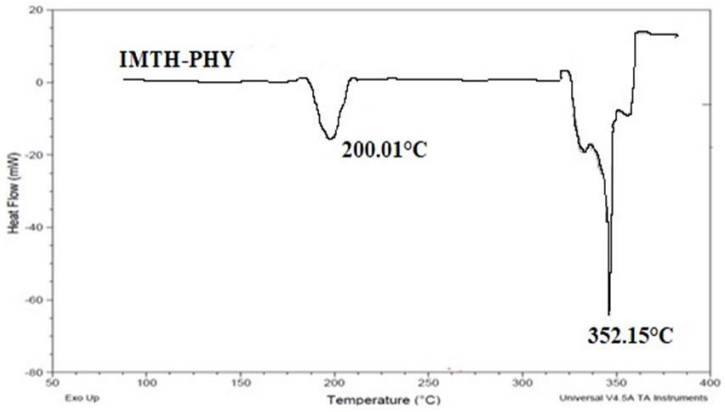


Figure 2: Potential functional groups of Imatinib for CSD hits

3.2 Differential Scanning Calorimetry (DSC)



(a)



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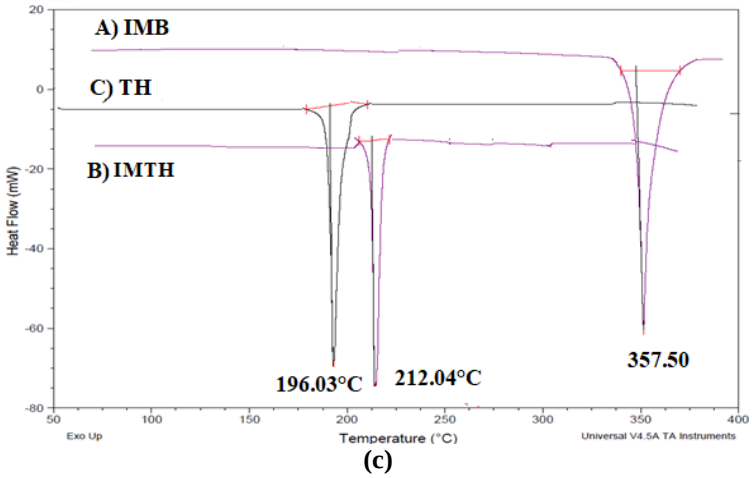

(c)

Figure 3: DSC thermograms of (a) IMTH (b) Physical Mixture of IMB and TH (c)IMKG

Imatinib showed a sharp endotherm transition at 212.04˚C. Whereas, the DSC thermogram of IMTH and IMKG cocrystals revealed single and sharp endothermic transition at 196.03˚C (Figure 3a and 173.01˚C (Figure 3b). They are discrete from the melting endotherms of respective coformers i.e., TH (357.50C) and KG (135.23˚C) and and the reference drug IMB (212.04˚C). This indicates towards formation of new crystalline and pure solid forms. However, the presence of two individual peaks in DSC thermogram of physical mixture (Figure 5.5) showing peaks corresponding to the pure drug molecule (IMB) and the respective coformer (TB), negate the existence of the eutectic(Tomar et al., 2020). Additionally, the apparent sharp melting endotherm disproves the existence of a co- amorphous phase. Besides this, formation of the cocrystals was additionally confirmed by different analytical techniques.

3.3 Hot Stage Microscopy

With the use of hot stage microscopy, the morphological modifications and thermal events that take place throughout the heating tests are clearly examined. This figure displays thedrug and its cocrystals at different temperatures during the heating phase from 30°C to400°C. In case of IMB, it is observed that the crystal gets darker about 122°C and then it is completely melted at 212.04°C. No further changes are observed. In IMSA cocrystal, melting of cocrystal begins near 201.11°C. Similarly, in IMKG melting of cocrystal occurs at 173.32°C with no further changes occurs. In case of IMTB melting occurs 196.03 °C (Figure 4).

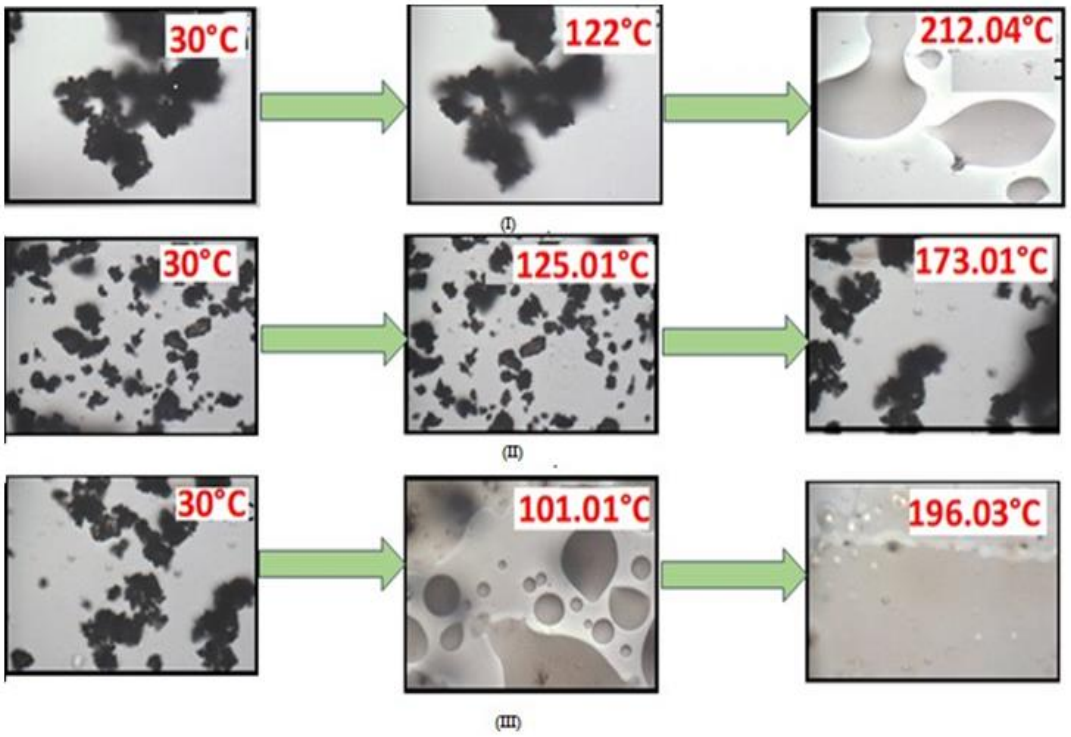

Figure 4: Microscopic images obtained by Hot stage microscopy at different temperatures (I) IMB (II) IMKG (III) IMTH

3.4 Fourier Transform Infrared Spectroscopy

FTIR is a great analytical method for examining changes in the vibrational frequencies of the functional moieties involved in co-crystal formation. The shift in the drug's and co- former's distinctive peaks was detected in FTIR spectra as a result of hydrogen bonding within the corresponding functional group. In FTIR spectrum of IMTH co-crystal, the characteristic carbonyl stretch shifted from 1664cm^{-1} to 1693 cm^{-1}(C=O and N-H stretch) from 3287 cm^{-1}to 3115 cm^{-1}in imatinib whereas C-O bending vibration of TB shifted from 1156 cm^{-1}to 1136 cm^{-1}, suggesting the formation of hydrogen bonding between the carboxamide group of imatinib with carboxylic O-H of TB. Similarly, after formation of (**Figure 5a**) IMKG cocrystal, carboxamide C=O stretch of imatinib shifted from 1664 cm^{-1} to 1652 cm^{-1}, and N-H stretch shifted from 3287 cm^{-1} to 3242 cm^{-1} whereas the KTG carboxamide C=O stretch shifted from1680 cm^{-1} to 1617 cm^{-1}and N-H stretch from 3362 cm^{-1}, 3189 cm^{-1} to 3435 cm^{-1}, 31202cm^{-1} (**Figure 5b**) which confirmed the occurrence of thehydrogen bonding between N-H of KG and C=O of IMB)

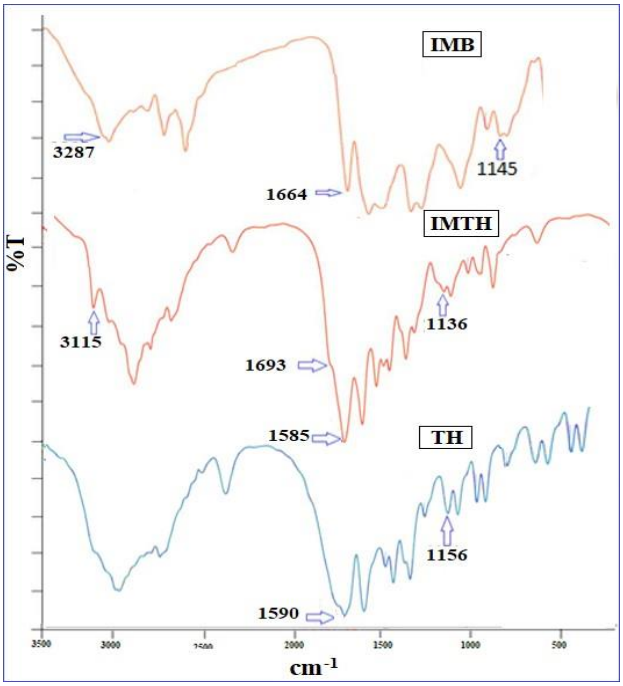

Figure 5 (a): FTIR pattern of imatinib, theobromine and IMTH cocrystal (II) PXRDpattern of imatinib, alpha-ketoglutaric acid, and IMKG cocrystal

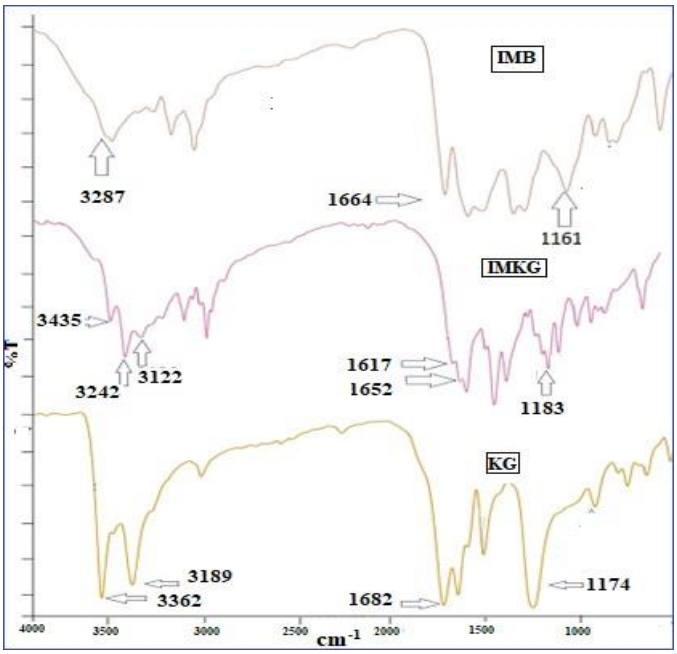

Figure 5 (b) FTIR pattern of imatinib, alpha-ketoglutaric acid, and IMKG cocrystal

3.5 Powder X-ray Diffraction (PXRD)

Analysis and identification of crystallization degrees of starting materials and their prepared crystals are performed by PXRD. In every new crystalline material, there is a unique peak indicating different planes of reflection. Peaks disappearing, appearing in new places, or distorted shape suggest that two solid systems are interacting and creating a new solid systemthat is distinct from the parent solids.

In IMTH cocrystal, some of the peak at 2Θ value of 13.62°, 15.31°, a n d 15.70° has newly appeared and some of the peaks at 2Θ value of 8.23°, 17.68°, and 35.27° in IMB disappeared. Furthermore, the peak at 2Θ value in IMB viz. 12.79°, 17.56°, 18.60°, 19.45° have shifted to 12.99°, 17.27°, 18.85°, 19.93° while the peak at 21.89, 23.27 of TH have shifted to 21.06, 23.96 respectively. The peak at 24.56° of IMB and 24.99° of TH amalgamated to form a peak at 24.17° (100% intensity) in cocrystal (Figure 6 I).

Similarly, in IMKG cocrystal, PXRD pattern (Figure 6 II) shows new peaks at 9.52°, 23.79°, 24.24°, and 19.85° 2Θ. Few peaks at 2Θ value of 8.23°, 10.89°, 16.16°, 17.68° and 26.15° in IMB and at 19.62°, 22.34 in KG have disappeared showing the formation of new crystalline form. Some of the peak in IM at 12.79°, 17.56°, 19.45°, 21.89 have shifted to 12.84°, 17.11°, 19.85°, 21.60° while the peak at 22.34°, 25.99° in ND have shifted to 22.15°, 25.76°(Figure II).

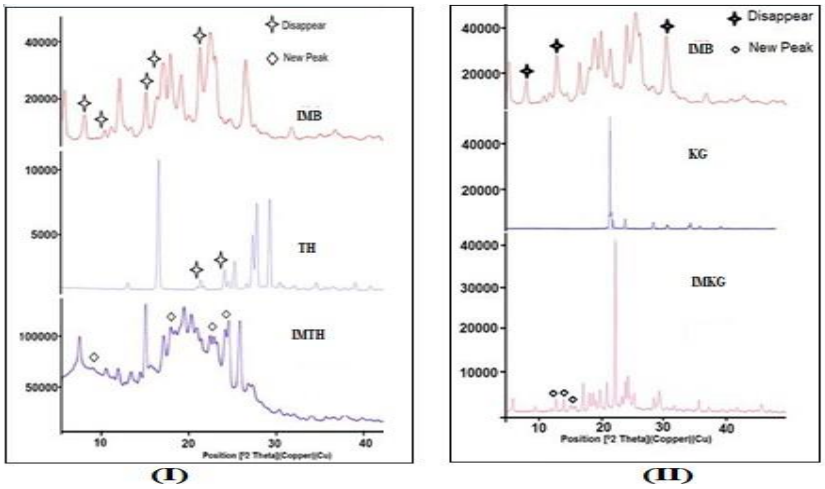

Figure 6: (I): PXRD pattern of imatinib, theobromine and IMTH cocrystal (II) PXRDpattern of imatinib, alpha-ketoglutaric acid, and IMKG cocrystal

3.6 Crystal structure determination from PXRD

Imatinib (IMB) exhibits a triclinic crystal system with a P-1 space group, containing two molecules within each unit cell. In the crystal structure, one IMB molecule forms interaction with two other IMB molecules. Specifically, the -NH group adjacent to the pyrimidine moietyof one IMB molecule attaches to the carbonyl oxygen of the carboxamide moiety (N2) andthe hydroxyl group (OH1) of another IMB molecule. Additionally, the -NH group of the carboxamide group within the same IMB molecule connects to the pyrimidine (N3) and the - NH group (NH7) of another IMB molecule. When co-crystallized, these interactions involving the -NH groups undergo a transformation, replacing the original homomeric synthons with respective heterosynthons formed with the coformer.

IMTH: IMTH co-crystallized in a triclinic crystal system having (P-1) space group, consisting of one molecule of Imatinib linked with one molecule of TB in the unit cell (Figure. 7 b). The asymmetric unit of cocrystals comprises of one molecule theobromine subtended to each other at an angle 21.54°. In pyridine (N5) of imatinib molecule formed hydrogen bond with amine group of theobromine molecule and the imatinib (IMB) molecules connected with intermolecular hydrogen bonds and heteromeric synthon are generated in the crystal lattice by breaking the already existing homosynthons in imatinib (IMB) along with distance 2.227 Å (Figure 7 d). The individual units are attached through the Vander wall forces.

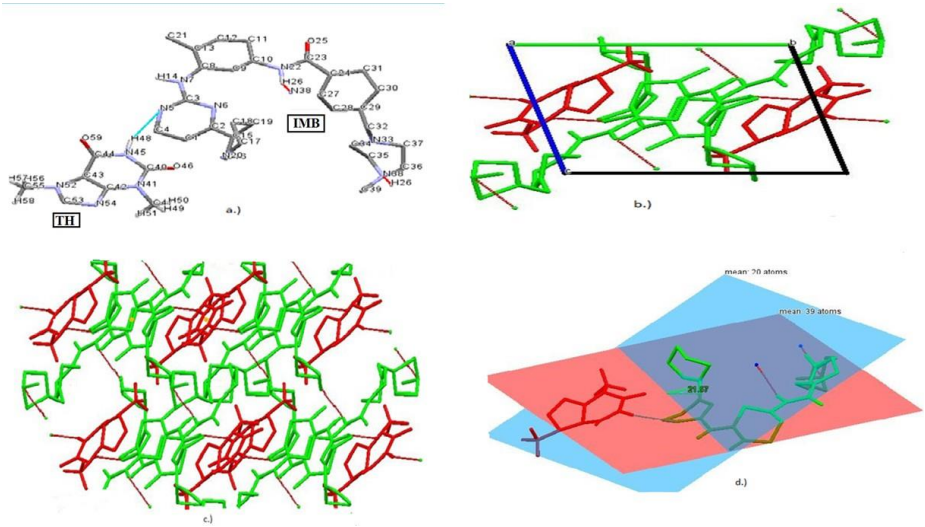

Figure 7: a.) Hydrogen bond interaction, b.) Packing of IMTH in unit cell, c.)arrangement in unit, d.) Angle between two planes

IMKG: PXRD pattern indexing of IMKG yielded triclinic unit cell with P-1 space group (Table 1).

IMKG co-crystallize in a triclinic crystal system with (P-1) space group, consisting of one molecule of Imatinib and one molecule of KTG in the unit cell. The drug and coformer are linked via heterosynthons (Figure 8)**.** The carboxyl functional COOH (O3) of KTG creates hydrogen bond with pyridine nitrogen (N2) of IM causes the intermolecular hydrogen bonding (Figure 8a) with –OH group of alphaketoglutaric acid. The drug molecule incorporated with the coformer and π- stacking of the aromatic function first KTG molecule activated as carboxylate as proton, thus generates the hetero synthon, along with distance1.184 Å, and angle 39.89 Å (Figure 8d).

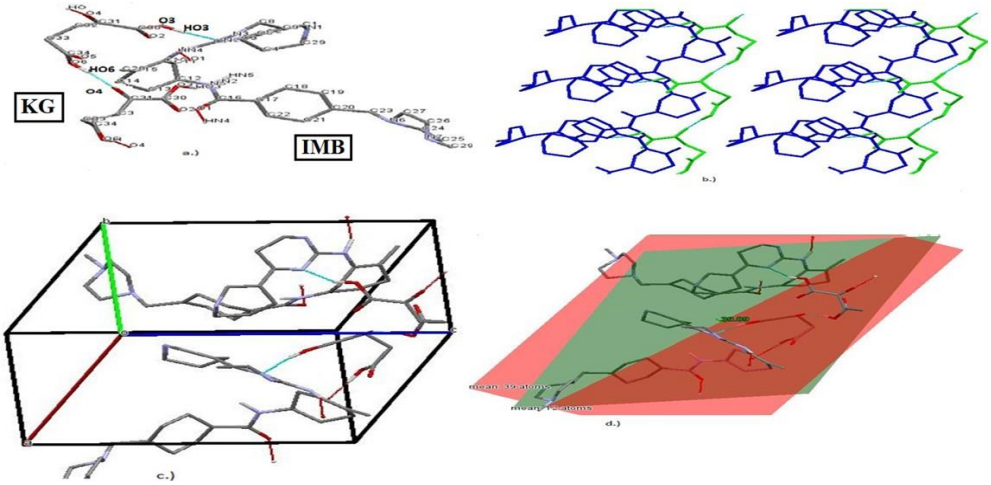

Figure 8 a) Hydrogen bond interaction, b.) Arrangement in unit, c.) Packing of IMKTGin unit cell, d.) Angle between two planes

Table 1: Crystallographic data of Imatinib and co-crystals

Crystallography Parameters	IMTH	IMKG
Molecular formula	C36H39N11O3	C34H37N7O6
Stoichiometry	1:1	1:1
Crystal system	Triclinic	Triclinic
Cell Volumes (A3)	702.042	1030
Space Group	P-1	P-1
Cell Lengths (Aº)	a=9.9597,b=9.7406 c=8.4120	a= 13.73, b=10.13c=13.21
Cell Angles (deg)	α=71.5008 β=113.51 γ=104.76	α=90.4451 β=102.3757
		γ=90.1901
Z value	0	0
Distance Å	2.227	2.081
Angle Å	21.57	39.89
Rwp value	8.12%	12.70%

3.8 Solubility and Dissolution studies

The improved solubility and dissolution rate of cocrystals are influenced by factors such as the arrangement of crystals, their shape, the strength of hydrogen bonds, melting point, and solubility of coformers. These characteristics play a crucial role in enhancing the absorptionof pharmaceuticals. Therefore, assessing solubility and dissolution rate of solids is essential for pharmaceutical development and quality control. To develop an active pharmaceutical ingredient (API), it is necessary to determine the solubility and intrinsic dissolution rate. Consequently, in this study, the solubility and dissolution rate (IDR) of imatinib and its corresponding cocrystals were evaluated in a simulated phosphate buffer (pH 6.8) and 0.1 NHCl solution (pH 1.2) at a temperature of 37 ± 0.5 °C(Figure 9a and 9b). The solubility of the prepared co-crystals (IMTB and IMSA) were found more than pure drug IMB, and the solubility was more in 0.1N HCl (pH 1.2) **as** compare to in phosphate buffer (pH 6.8). The solubility order of cocrystals was observed as IMTH> IMKG > IMB.

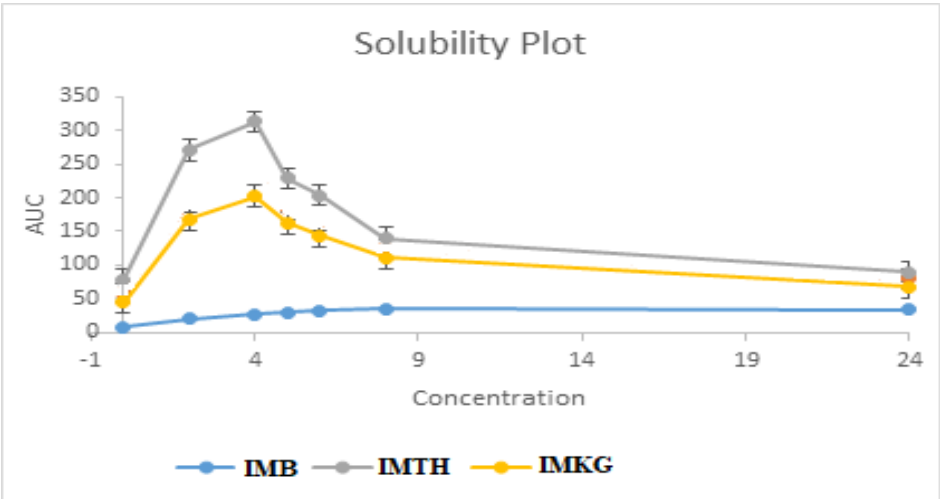

Figure 9: a) Solubility plot of IMB and its respective cocrystals

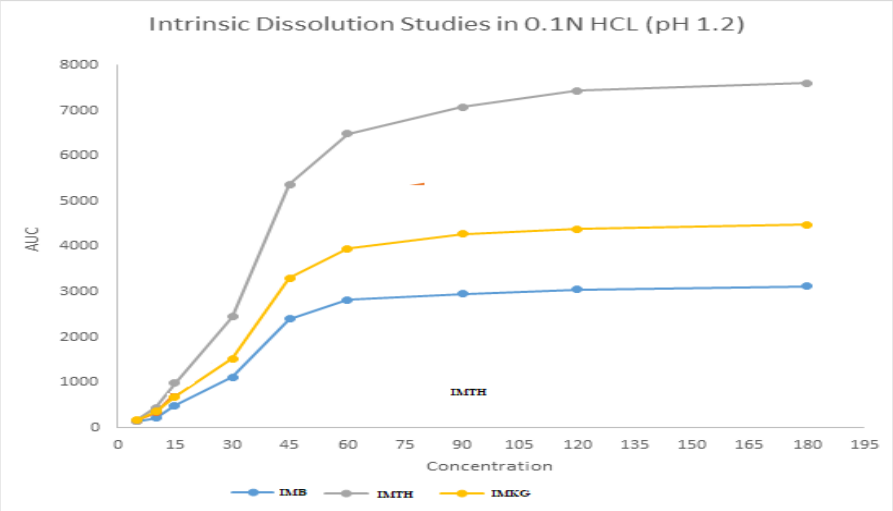

Figure 9: b) Intrinsic Dissolution rate of IMB and prepared cocrystal

4. Conclusion:

The efficiency of imatinib cocrystals in improving biopharmaceutical parameters is the focus of the current investigation. Through the use of DSC, HSM, PXRD, and FTIR, IMB with TH, KG, and solvent assisted grinding technique cocrystals were thoroughly examined. These improvements are influenced by elements such crystal packing, shape, the strength of hydrogen bonds, melting point, and the solubility of coformers. Compared to the drug's pure form, imatinib cocrystals have better solubility and a faster rate of dissolution. The cocrystals'greater solubility and faster rate of dissolution point to the possibility of improved absorption and bioavailability. For the formulation and quality control of the active pharmaceutical ingredient, the measurement of solubility and intrinsic dissolution rate under various pH settings is helpful (API). Overall, the cocrystal method appears promising for improving

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