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Enhanced solubility and dissolution profile of Poorly Water-Soluble Clotrimazole by Recrystallization/Cocrystallization methods

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Enhanced solubility and dissolution profile of Poorly Water-Soluble Clotrimazole by Co-crystallization/Re-crystallization methods

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Enhanced solubility and dissolution profile of Poorly Water-Soluble Clotrimazole by Recrystallization/Cocrystallization methods

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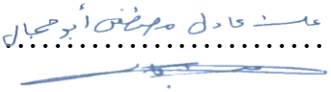
Dedication

To the one who illuminated the path of my life,
from whom I have drawn strength, resilience, and pride in myself
To the everlasting source of tenderness and generosity,
my beloved mother, may God bless her with a long and graceful life
and reward her for her boundless efforts.
To my dear father, the dearest to my heart,
whose support and guidance have always been my compass.
To my cherished brothers and my beloved sister,
whose love and encouragement have been my constant motivation.
To all those who extended a helping hand
in enabling me to complete this study.
And finally,
to my beloved homeland, Palestine**,**
the land that forever inspires my hope and perseverance.

Declaration

I certify that this thesis is submitted for the degree of Master graduation in supplied Industrial Technology is my own research.

Signed: 

Ola Adel Mustafa Abu Jamal

Date: 10/01/2026

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Abstract

Introduction:

Clotrimazole is a widely used antifungal agent classified as a Bio pharmaceutics Classification System (BCS) class II drug, characterized by poor aqueous solubility and consequently limited oral bioavailability. These physicochemical limitations restrict its potential for systemic administration despite its favourable therapeutic profile. The present study aims to enhance the solubility and dissolution behaviour of clotrimazole through solid-state modification using recrystallization and Cocrystallization techniques.

Methodology and results:

Recrystallization was carried out using different organic solvents in an attempt to induce polymorphic transformation and improve solubility. However, the obtained recrystallized forms did not exhibit significant changes in melting point or aqueous solubility compared to the pure drug, and therefore this approach was deemed ineffective.

In contrast, Cocrystallization was performed using various pharmaceutically acceptable co-formers, including Fumaric acid, polyvinyl pyrrolidone, polyvinyl alcohol and Carbomer 940 , employing a mechanical grinding method with different solvents and molar ratios.

The prepared cocrystals were characterized using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetrey (DSC), and melting point analysis to confirm cocrystal formation and investigate intermolecular interactions. Solubility studies were conducted using HPLC analysis. Several cocrystal formulations demonstrated reduced melting points and significantly enhanced aqueous solubility compared to pure clotrimazole, indicating successful modification of the solid-state properties.

In conclusion:

The findings of this study demonstrate that Cocrystallization is an effective and promising strategy for overcoming the solubility limitations of clotrimazole, whereas recrystallization showed no significant benefit. The improved Solubility and dissolution behaviour observed for selected cocrystals highlight their Potential for the development of oral dosage forms with enhanced bioavailability and improved therapeutic performance.

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Abbreviations, Symbols and Terminology:

DSC	differential scanning calorimetrey.
FTIR	Fourier transform infrared.
HPLC	High performance liquid chromatography .
CLT(API)	Clotrimazole .
IPA	Isopropyl alcohol .
CH_3CN	Acetonitrile
CHCL	Chloroform
C_4H_4	Fumaric acid
PVA	Polyvinyl alcohol
Carbomer	Carbomer 940
PVP	Polyvinyl pyrrolidone
M.P	Melting point apparatus.

Chapter One

1. Introduction

1.1 Clotrimazole

Clotrimazole is a lipophilic imidazole derivative classified as a Biopharmaceutical Classification System (BCS) class II drug, characterized by low aqueous solubility and high membrane permeability, which ultimately results in limited oral bioavailability. It is a broad-spectrum antifungal agent extensively used for the treatment of infections caused by Candida albicans and other pathogenic fungi. Since its antifungal activity was first identified in the late 1960s, clotrimazole has been widely formulated for topical administration in various dosage forms (1).

Pharmacologically, clotrimazole belongs to the azole group of synthetic antimycotic agents, which represent the largest class of antifungal drugs currently used in clinical practice. Azoles are further subdivided into imidazoles and triazoles based on their chemical structure, with clotrimazole categorized within the imidazole subclass. Alongside econazole and miconazole, clotrimazole remains a drug of choice for the topical management of dermatophytic infections such as tinea pedis, tinea cruris, and tinea corporis. (8), It is also commonly used in the treatment of vulvovaginal and oropharyngeal candidiasis.

The antifungal mechanism of clotrimazole involves interference with ergosterol biosynthesis, a critical component of the fungal cell membrane. Specifically, clotrimazole inhibits the cytochrome P450-dependent enzyme 14-α-lanosterol demethylase, leading to disruption of membrane integrity and subsequent fungal cell death. (2). Clotrimazole works by inhibiting the growth of individual Candida or fungal cells by altering the permeability of the fungal cell wall. The drug impairs the biosynthesis of ergosterol, a critical component of the fungal cell membrane by inhibiting the P450 enzyme lanosterol 14-alpha demethylase it is may slow fungal growth or result in fungal cell death.

Beyond its antifungal applications, clotrimazole has demonstrated activity against Plasmodium falciparum, particularly chloroquine-resistant strains. This activity is attributed to its ability to form complexes with free heme, thereby inhibiting parasite growth. (3).

The formulation of poor solubility drugs poses significant challenge in pharmaceutical science. Co-crystallization is a technique used to enhance the solubility and other

physiochemical properties of substance particularly active pharmaceutical ingredients (APIs) by forming crystals with second non-covalently bonded molecules called co-former. This process creates a new crystalline structure or co-crystals with improved characteristic like solubility, stability and bioavailability without changing the chemical identify or therapeutic effect of the original molecule, Co-crystals are formed through non-covalent interactions like hydrogen bonding.

Despite its therapeutic potential, clotrimazole exhibits extremely poor water solubility and exists as a crystalline powder that is practically insoluble in water, although it is freely soluble in several organic solvents. This limited aqueous solubility represents a major obstacle to oral and systemic delivery. (4).

Clotrimazole undergoes extensive hepatic metabolism following oral administration, which significantly limits its systemic bioavailability. After absorption from the gastrointestinal tract, clotrimazole is rapidly transported to the liver, where it is subjected to pronounced first-pass metabolism. This extensive hepatic extraction results in very low plasma concentrations of the unchanged parent drug, making oral delivery of clotrimazole clinically challenging (5).

The metabolism of clotrimazole occurs primarily in the liver and is mediated by the cytochrome P450 enzyme system, particularly iso enzymes involved in oxidative biotransformation. Clotrimazole is extensively metabolized through oxidative pathways, including de-alkylation and hydroxylation reactions, leading to the formation of multiple inactive metabolites. These metabolites are subsequently conjugated and eliminated mainly via the biliary route, with minimal amounts excreted in urine (6).

Due to this extensive first-pass hepatic metabolism, the oral bioavailability of clotrimazole is markedly reduced despite its high membrane permeability.

Consequently, clotrimazole is predominantly formulated for topical, vaginal, and oropharyngeal administration rather than systemic oral use. The strong first-pass effect, combined with its poor aqueous solubility and slow dissolution rate, represents a major barrier to the development of effective oral dosage forms.

Improving the solubility and dissolution behaviour of clotrimazole, for example through co-crystallization strategies, may enhance the fraction of drug available for absorption and potentially partially overcome the limitations imposed by first-pass metabolism. Enhanced dissolution could increase the amount of drug reaching systemic circulation, although hepatic metabolism remains a critical factor influencing overall bioavailability.

Clotrimazole is available as suck able tablets (lozenges or troches) intended for local treatment of oropharyngeal candidiasis . These formulations provide prolonged contact with oral mucosa and result in minimal systemic absorption. Although true muco adhesive buccal tablets of clotrimazole are not commercially available .

1.2 Clotrimazol chemical structure

Clotrimazole has the molecular formula C22H17ClN2 and a molecular weight of 344.5 g/mol. The molecule contains an imidazole ring substituted with aromatic phenyl groups, contributing to its lipophilic nature. The presence of nitrogen atoms in the imidazole ring confers weak basicity to the compound. (figure 1) (1).

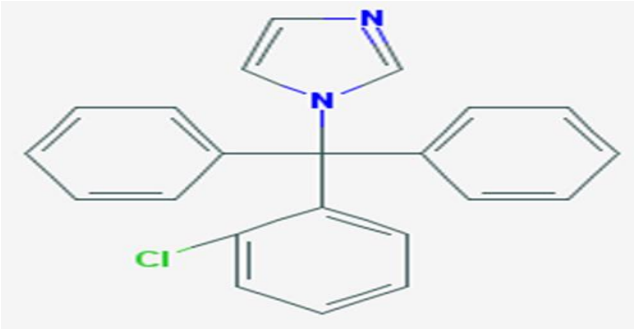


Figure 1.1: The chemical structure of clotrimazole (1).

1.3 Polymorphisms

Polymorphism refers to the ability of a substance to exist in more than one crystalline form while maintaining the same chemical composition. In pharmaceutical development, polymorphism is critically important because different crystal forms may display significant variations in solubility, dissolution rate, stability, and bioavailability (7). The possibility of a drug to have different polymorphous can be checked in the laboratory by the process of recrystallization.

1.3.1 Importance of Polymorphism in Drug Development

Polymorphic behavior is a key factor in pharmaceutical science, as different crystalline forms of the same drug substance can exhibit distinct physical and chemical properties .Such variations may influence drug solubility , dissolution behavior , and long –term stability , which in turn affect bioavailability and clinical performance . In addition, the selected polymorphic form can determine the ease of manufacturing processes, including powder flow, compressibility and overall formulation efficiency (8).

Uncontrolled polymorphic transformations may occur during processing or storage, leading to inconsistencies in product quality and therapeutic outcomes. For this reason, systematic investigation and control of polymorphism during drug development are essential. Identifying and selecting an appropriate crystal form at an early stage helps ensure reproducible manufacturing , product stability and consistent therapeutic efficacy throughout the shelf life of the pharmaceutical product .

1.3.2 Properties of crystal forms

From a thermodynamic perspective, only one polymorphic form is stable under specific conditions, while metastable forms may persist due to kinetic factors. Metastable forms often exhibit higher solubility and dissolution rates, making them desirable for pharmaceutical formulation despite their tendency to convert to the stable form over time (9).

1.4 Re-crystallization

Recrystallization is a conventional technique used to purify crystalline materials and explore polymorphic behavior. The process involves dissolving the drug in a suitable solvent followed by controlled cooling or solvent evaporation to obtain crystalline material with potentially altered physicochemical properties.

1.5 Co-crystallization

Cocrystallization is a solid-state modification approach used to improve the physicochemical properties of poorly water-soluble drugs. Pharmaceutical cocrystals consist of an API and pharmaceutically acceptable coformer bonded through non-covalent interactions, primarily hydrogen bonding. This approach can enhance solubility, dissolution rate, and bioavailability without altering the chemical structure of the API (10).

Co-crystals are solid materials composed of two or more molecular components that interact through non-covalent intermolecular forces, including hydrogen bonding, van der Waals interactions, and π–π stacking. In pharmaceutical sciences, the concept of a supramolecular synthon is central to co-crystal design. A supramolecular synthon refers to a recurring structural motif formed through predictable intermolecular interactions, which can be used as a building block for assembling complex crystal architectures. Crystal engineering aims to identify and manipulate these synthons to design co-crystals with desired physical and chemical properties.

A pharmaceutical co-crystal specifically involves at least one active pharmaceutical ingredient (API) combined with a pharmaceutically acceptable coformer. The coformer is typically non-toxic, pharmacologically inert, and capable of forming strong intermolecular interactions, such as hydrogen bonds, with the API. The formation of pharmaceutical co-crystals allows the modulation of solid-state properties of the API without altering its chemical structure or pharmacological activity.

Co-crystals can significantly enhance physicochemical characteristics such as solubility, dissolution rate, melting point, hygroscopicity, compressibility, and bulk density. By selecting appropriate coformers, it is possible to improve the interactions between the drug molecule and the aqueous environment, thus increasing solubility and bioavailability. Hydrophilic coformers are particularly effective because they facilitate hydrogen bond formation with water molecules, which enhances dissolution.

Beyond improving solubility and dissolution, co-crystallization also offers strategic advantages in pharmaceutical development, including the expansion of solid forms for formulation flexibility and potential intellectual property protection. The choice of coformer, guided by supramolecular synthon concept, allows systematic design of co-crystals with predictable properties. The co-crystal formation process is predominantly driven by hydrogen bonding interactions, which stabilize the crystal lattice and define the overall structure of the resulting solid (11,12).

Discovery of a new co-crystal solid form also offers new opportunities for the exploitation of intellectual property, the most common supra molecular synthons utilized in pharmaceutical co-crystals are shown in Fig.2.

The cocrystal former is chosen so as to increase the water solubility of the complex such as hydrophilic co-crystal formers that lead to enhance the interactions with the surrounding aqueous environment by formation of hydrogen bonds .

A formation of co-crystal itself is believed to be driven also by hydrogen bonding . Fig 2

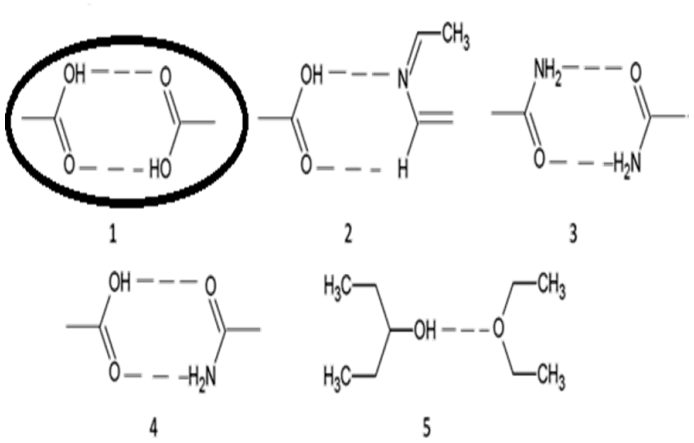


Figure 1.2: Typical hydrogen bonds utilized in crystal engineering (12)

Chapter Two

2.1 Literature Review

Several formulation strategies have been investigated to overcome the poor aqueous solubility and limited oral bioavailability of clotrimazole. One of the earliest approaches involved the formation of inclusion complexes with β-cyclodextrin prepared by spray-drying. This method resulted in a linear increase in clotrimazole solubility as a function of cyclodextrin concentration and produced a noticeable enhancement in the dissolution rate when compared with the pure drug in phosphate buffer solution at pH 7.4 (13).

More recently, novel crystalline adducts of clotrimazole with pharmaceutically acceptable coformers have been developed. These include the preparation of five salts and two cocrystals using carboxylic acids such as adipic acid, maleic acid, caffeic acid, and several hydroxybenzoic acid derivatives. Solubility studies demonstrated significant improvement depending on the selected coformer, with some salt forms showing more than a twenty-fold increase in solubility, while cocrystal systems exhibited moderate but meaningful enhancement compared to untreated clotrimazole in ethanol–water mixtures (14).

Solid dispersion techniques have also been extensively explored to improve the dissolution behavior of clotrimazole. Dispersions prepared with Pluronic F127 using physical mixing and fusion methods showed no chemical interaction between the drug and carrier, while achieving a dramatic improvement in dissolution rate exceeding ninety-fold compared to the crystalline drug. The fusion method, particularly at a 60:40 drug-to-polymer ratio, yielded the most pronounced enhancement (15).

Additional studies employed polyethylene glycol and polyvinylpyrrolidone as hydrophilic carriers to prepare solid dispersions through solvent evaporation. Among the investigated systems, polyvinylpyrrolidone-based dispersions demonstrated superior in vitro drug release and were subsequently incorporated into suppository formulations. These formulations exhibited enhanced antifungal activity and improved drug release profiles compared with suppositories containing the untreated drug (16).

Alternative solid dispersion systems using sugars such as mannitol, fructose, dextrose, and maltose have also been evaluated. Among these carriers, mannitol emerged as the most

effective in improving solubility and dissolution characteristics, highlighting its potential as a hydrophilic carrier for poorly water-soluble drugs like clotrimazole (17).
As a conclusion, no successful method was reported that would suggest the oral formulation of clotrimazole as a consequence of marked in water solubility .

2.2 Problem Statement

A large proportion of active pharmaceutical ingredients currently in use exhibit poor physicochemical properties, particularly low solubility and limited stability. These challenges often complicate drug development and may result in late-stage failure. Enhancing the solubility and bioavailability of poorly water-soluble drugs therefore remains a major challenge in pharmaceutical science. Numerous techniques, including recrystallization, salt and cocrystal formation, micronization, Micellar systems, oil encapsulation, and solid dispersion technologies employing polymers, cyclodextrins, and other additives, have been investigated to address this issue (18).

According to the Biopharmaceutical Classification System, clotrimazole is categorized as a class II drug, characterized by very low aqueous solubility and high membrane permeability. Consequently, its oral administration is associated with variable and unpredictable bioavailability (19).

Although systemic antifungal agents such as Itraconazol and ketoconazole are effective, their clinical use is often limited by hepatotoxic side effects. In contrast, clotrimazole has been reported to exhibit a more favorable hepatic safety profile. However, its poor solubility and slow dissolution rate restrict its potential for systemic application.

Clotrimazole has also demonstrated superior activity against chloroquine-resistant malarial parasites compared to conventional antimalarial drugs. Nevertheless, its poor and erratic oral bioavailability, characterized by delayed peak plasma concentration, underscores the need for strategies aimed at improving its solubility and dissolution properties (20).

In topical applications, clotrimazole is widely used in creams, gels, lozenges, and vaginal formulations. However, rapid removal from the site of application limits therapeutic effectiveness. Enhancing solubility and release rate is therefore critical to achieving rapid and sustained antifungal action (21).

Furthermore, clotrimazole has shown promise in the management of sickle cell disease by inhibiting the Gardos channel and reducing erythrocyte dehydration, further emphasizing the need to improve its bioavailability for systemic use (22).

This thesis investigates design, synthesis and characterization of clotrimazole cocrystals with pharmaceutically acceptable conformers to enhance its solubility and bioavailability. To confirm cocrystal formation and analyze solid-state interactions, advanced analytical techniques such as Differential Scanning Calorimetrey (DSC) and Fourier Transform

Infrared Spectroscopy (FTIR) were employed. DSC was utilized to assess thermal behavior and detect changes in melting points indicative of new crystalline phases, while FTIR was used to identify intermolecular interactions and confirm the presence of hydrogen bonding between clotrimazole and selected conformers.

2.3 Research Objectives

Enhancing the solubility and bioavailability of clotrimazole via Re- crystallization and Co-crystallization technique.
Specific aims :

1. Preparation of clotrimazole crystals by recrystallization an from different polymers and solvents .
2. Preparation of co-crystals of clotrimazole by using different co-formers.
3. Determination of their physical state properties using Melting point , DSC, and FTIR.
4. Evaluation of influence of selected solvents , polymers, and coformers on crystalline modification and solid-state properties.

2.4 Hypothesis

Cocrystallization of clotrimazole with suitable coformers will enhance its aqueous solubility and improve its bioavailability by modifying its physicochemical properties without altering its pharmacological activity. That forming cocrystals of clotrimazole with pharmaceutically acceptable coformers will lead to improved solubility and dissolution rate due to changes in crystal packing and intermolecular interactions. This enhancement in solubility is expected to result in increased oral bioavailability, thereby making the drug more effective at lower doses. There have been a oral antifungal drug systemic treatment of fungal diseases has less side effects on liver than other antifungal drugs and better activity against chloroquine resistant malarial parasites because of its complex forming ability with free heme (20).

Cocrystallization of clotrimazole with suitable pharmaceutically acceptable coformers is expected to enhance its aqueous solubility and improve bioavailability by modifying its physicochemical properties without altering its intrinsic pharmacological activity. Changes in crystal packing and intermolecular interactions are anticipated to result in increased dissolution rate and improved oral absorption. The application of crystal engineering principles is therefore hypothesized to provide an effective platform for optimizing the solid-state properties of clotrimazole and facilitating its pharmaceutical development (23, 24).

Chapter Three

3.1 Instrumentation

The following analytical instruments were utilized during the experimental pr1ocedures:
An analytical balance for precise weighing , a Vortex (VELP) for sample homogenization ,Glass bottles sealed with child proof caps for secure storage . characterization techniques included Fourier transform infrared spectroscopy (FTIR) ,High performance liquid chromatography (HPLC),a Melting point apparatus for determine thermal properties , and Differential scanning calorimetrey (DSC).

3.2 Materials:

Clotrimazole , polyvinyl alcohol , Carbomer 940 ,polyvinyl pyrrolidone (Kollidon 29/30) , Fumaric acid , polyethylene glycol, benzoic acid , isopropyl alcohol , acetonitrile , chloroform , methanol ,purified water .All materials were used as received and when necessary further purified and tested in the Beit Jala Pharmaceutical Company to ensure quality and consistency for experimental applications .

3.3 Re-crystallization methodology

Recrystallization, is accomplished by dissolving the active ingredient in different solvents with or without heating then cooling or evaporating the solvent to obtain a crystal precipitate . changing the solvent in a way to investigate the possibility obtaining polymorphism .
The general steps of the recrystallization process are as follows:

1. Dissolution of the solute: The compound is placed in a beaker, and the appropriate solvent is gradually added. The mixture is heated as needed until the solute completely dissolves, ensuring a homogeneous solution.
2. Controlled cooling: The solution is first allowed to cool to room temperature and then further cooled in an ice bath. Slow cooling promotes the formation of purer and well-defined crystals. The seeding technique can be employed, where a small, pure crystal of the compound is added to provide a nucleation site, facilitating uniform crystal growth.
3. Isolation of crystals: Once the crystals have formed, they are separated from the remaining solution. Vacuum filtration using a Buchner funnel and aspirator is commonly employed to collect the crystals. If crystal formation is insufficient,

gravity filtration can be performed. To remove impurities such as colour contaminants, activated carbon may be added, and the mixture boiled, then filtered through paper before cooling to induce crystallization.

4. Drying and purity assessment: The collected crystals are first dried under vacuum and then transferred to a glass dish to ensure complete drying. The purity of the crystals can be verified by determining their melting point, which provides an indication of crystallinity and absence of impurities (25). See figure 3

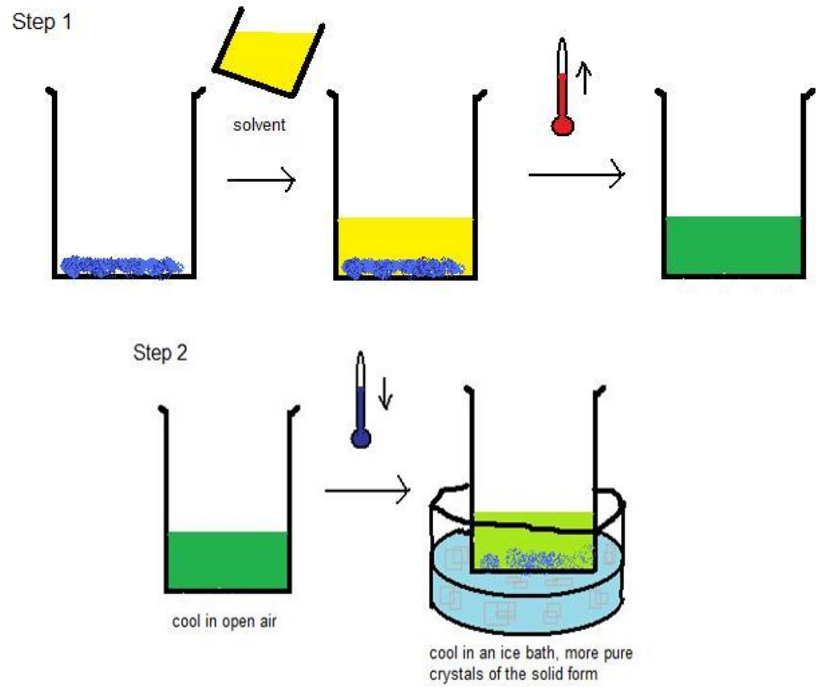


Figure 3.1: The important steps to the recrystallization process.

3.3.1 Re-Crystallization technique

Enhance solubility of clotrimazole via recrystallization technique from different solvents yielding different polymorphic forms .

Clotrimazole dissolved by five different solvents :

Formula 1: 4 gm. of API dissolved in 40 ml of methanol within 2 minutes.

Formula 2: 4 gm. of API dissolved in 40 ml of DMSO (dimethyl sulfoxide) Within 4 minutes.

Formula 3: 4 gm. of API dissolved in 45 ml of ethyl acetate within 3 minutes.

Formula 4: 4 gm. of API dissolved in 20 ml of chloroform within 2 seconds.

Formula 5: 4 gm. of API dissolved in 50 ml of acetone within 3 minutes.

All these cooled in icing path with stirring by the glass rode to enhance crystals then left in open air at room temperature to evaporate to remove all the solvent.

3.3.2 Re-crystal solubility in water technique

The process is:

1. Dissolved 1 gm. crystals of each sample in 100 ml of water.
2. Stirred them over night by stirrer.
3. Filtered all samples by filtered paper.
4. Analysed by HPLC.

3.4 Co-Crystallization methodology

3.4.1 Grinding (mechanical) co-crystal technique

In recent years, significant advancements have been made in the formation of co-crystals using mechanical grinding methods. This approach relies on the application of physical force to a mixture of the active pharmaceutical ingredient (API) and a coformer to promote molecular interactions and phase transformations, resulting in the formation of a new crystalline solid. The grinding method is versatile, rapid, and often preferred due to its simplicity and efficiency.

One widely used variation is liquid-assisted grinding (LAG), which builds upon traditional solvent-free mechanochemical techniques. In LAG, a small quantity of liquid is introduced as an additive to facilitate or control the reactivity of the components. This method has proven effective in screening and producing various solid forms, including inclusion compounds, cocrystals, salts, solvates, and polymorphs. By using stoichiometric ratios of the API and coformer, mechanical agitation—achieved through grinding with a mortar and pestle or in a mechanical mill—induces a transformation from a simple physical mixture into a well-defined co-crystal.

The addition of small amounts of solvent can act as a plasticizer, influencing the kinetics of crystallization and improving the quality of the resulting co-crystals. The mechanical grinding approach provides a controlled and reproducible method for co-crystal formation, making it particularly valuable in the early stages of pharmaceutical development where rapid screening of potential coformers is required.
(26,27).

Advantages of Grinding Cocrystallization:

1. **Enhanced Molecular Mobility and Interaction**

The presence of a minimal quantity of solvent in LAG increases molecular mobility at the solid–solid interface, promoting efficient contact between the active compound and the coformer. This enhanced mobility facilitates the formation of strong intermolecular interactions, such as hydrogen bonding, leading to more reliable and reproducible cocrystal formation.

2. **Faster and More Efficient Cocrystal Formation**

LAG significantly accelerates Cocrystallization kinetics compared to neat grinding. The solvent acts as a reaction mediator, reducing activation energy and enabling rapid nucleation

and growth of the cocrystal phase. As a result, cocrystals are often obtained within a shorter grinding time and with higher conversion efficiency.

3. Improved Phase Purity and Reproducibility

One of the key advantages of LAG is the formation of highly phase-pure cocrystals. The controlled solvent environment minimizes the formation of amorphous phases or incomplete solid-state transformations, leading to improved batch-to-batch reproducibility—an essential requirement for pharmaceutical development.

4. Reduced Dependence on Solubility Constraints

Unlike solution crystallization, LAG does not require full dissolution of the components. The small solvent amount is sufficient to mediate molecular rearrangement without being limited by solubility differences between the components. This makes LAG particularly suitable for systems with poor or mismatched solubility profiles.

5. Selective Polymorph and Solid-Form Control

The choice and amount of solvent used in LAG can influence the resulting solid form, allowing selective control over polymorphism and cocrystal stoichiometry. This tenability provides a strategic advantage in solid-form screening and optimization.

6. Compatibility with Green Chemistry Principles

Although a solvent is used, LAG requires only catalytic quantities, resulting in minimal solvent consumption and waste generation. This offers a balance between enhanced efficiency and environmental sustainability, positioning LAG as a greener alternative to traditional solution-based crystallization methods.

7. Applicability to Thermally Sensitive Compounds

LAG is typically conducted under ambient conditions and does not involve heating, making it suitable for thermally labile compounds that may degrade during melt or solvent evaporation techniques.

Table 3.1: the molecular weight of materials

No,	Material	Molecular weight g/mol
1.	Clotrimazole (API)	344.5
2.	Fumaric acid	116.06
3.	PVP	111.14
4.	Carbomer 940	72.06
5.	PVA	44.6

3.4.1.1 co-crystallization of clotrimazole with Fumaric acid as co-former

Each sample consisting of the active ingredient clotrimazole with Fumaric acid as co-former at different molar ratios ((0.5:1),(1:0.5),(1:1),(1.5:1),(1:1.5),(1:2),(2:1)), and different co-solvent (Isopropyl alcohol ,acetonitrile, chloroform).see table (3.2)

Table 3.2: Clotrimazole and Fumaric acid variable molar ratio /grinding co-crystallization technique

API	Co-former	Solvents
Clotrimazole	Fumaric acid	Isopropyl alcohol Acetonitrile Chloroform

The co-crystals were formed as mentioned in section 3.4.1.1
This procedure was applied for the three solvents chosen and each solvent for seven different molar ratios.

3.4.1.2 co-crystallization of clotrimazole with polyvinyl pyrrolidone as co-former

Each sample consisting of the active ingredient clotrimazole with Polyvinyl pyrrolidone (Kollidon 29/30) as co-former at different molar ratios ((0.5:1),(1:0.5),(1:1),(1.5:1),(1:1.5),(1:2),(2:1)), and different co-solvent (Isopropyl alcohol ,acetonitrile, chloroform).see table (3.3)

Table 3.3: Clotrimazole and Polyvinyl pyrrolidone variable molar ratio /grinding co-crystallization technique

API	Co-former	Solvents
Clotrimazole	Polyvinyl pyrrolidone	Isopropyl alcohol Acetonitrile Chloroform

The co-crystals were formed as mentioned in section 3.4.1.2
This procedure was applied for the three solvents chosen and each solvent for seven different molar ratios.

3.4.1.3 co-crystallization of clotrimazole with polyvinyl alcohol as co-former

Each sample consisting of the active ingredient clotrimazole with polyvinyl alcohol as co-former at different molar ratios ((0.5:1),(1:0.5),(1:1),(1.5:1),(1:1.5),(1:2),(2:1)), and different co-solvent (Isopropyl alcohol ,acetonitrile, chloroform).see table (3.4)

Table 3.4: Clotrimazole and polyvinyl alcohol variable molar ratio /grinding co-crystallization technique

API	Co-former	Solvents
Clotrimazole	polyvinyl alcohol	Isopropyl alcohol Acetonitrile Chloroform

This procedure was applied for the three solvents chosen and each solvent for seven different molar ratios.

The co-crystals were formed as mentioned in section 3.4.1.3

3.4.1.4 co-crystallization of clotrimazole with Carbomer 940 as co-former

Each sample consisting of the active ingredient clotrimazole with Carbomer as co-former at different molar ratios ((0.5:1),(1:0.5),(1:1),(1.5:1),(1:1.5),(1:2),(2:1)), and different co-solvent (Isopropyl alcohol ,acetonitrile, chloroform).see table (3.5)

Table 3.5: Clotrimazole and Carbomer variable molar ratio /grinding co-crystallization technique

API	Co-former	Solvents
Clotrimazole	Carbomer	Isopropyl alcohol Acetonitrile Chloroform

The co-crystals were formed as mentioned in section 3.4.1.4
This procedure was applied for the three solvents chosen and each solvent for seven different molar ratios.

Table 3.6 A: Clotrimazole and coformers for the three solvents chosen and each solvent for seven different molar ratio /grinding co-crystallization technique

Formula #	API : Coformer	Solvent
1-	0.5 API :1.0 Fumaric acid	Isopropyl alcohol
2-	1.0 API :0.5 Fumaric acid	
3-	1.0 API :1.0 Fumaric acid	
4-	1.5 API :1.0 Fumaric acid	
5-	1.0 API :1.5 Fumaric acid	
6-	2.0 API :1.0 Fumaric acid	
7-	1.0 API :2.0 Fumaric acid	
8-	0.5 API :1.0 Fumaric acid	Acetonitrile
9-	1.0 API :0.5 Fumaric acid	
10-	1.0 API :1.0 Fumaric acid	
11-	1.5 API :1.0 Fumaric acid	
12-	1.0 API :1.5 Fumaric acid	
13-	2.0 API :1.0 Fumaric acid	
14-	1.0 API :2.0 Fumaric acid	
15-	0.5 API :1.0 Fumaric acid	Chloroform
16-	1.0 API :0.5 Fumaric acid	
17-	1.0 API :1.0 Fumaric acid	
18-	1.5 API :1.0 Fumaric acid	
19-	1.0 API :1.5 Fumaric acid	
20-	2.0 API :1.0 Fumaric acid	
21-	1.0 API :2.0 Fumaric acid	
22-	0.5 API :1.0 PVP	Isopropyl alcohol
23-	1.0 API :0.5 PVP	
24-	1.0 API :1.0 PVP	
25-	1.5 API :1.0 PVP	
26-	1.0 API :1.5 PVP	
27-	2.0 API :1.0 PVP	
28-	1.0 API :2.0 PVP	
29-	0.5 API :1.0 PVP	Acetonitrile
30-	1.0 API :0.5 PVP	
31-	1.0 API :1.0 PVP	
32-	1.5 API :1.0 PVP	
33-	1.0 API :1.5 PVP	
34-	2.0 API :1.0 PVP	
35-	1.0 API :2.0 PVP	
36-	0.5 API :1.0 PVP	Chloroform
37-	1.0 API :0.5 PVP	
38-	1.0 API :1.0 PVP	
39-	1.5 API :1.0 PVP	
40-	1.0 API :1.5 PVP	
41-	2.0 API :1.0 PVP	
42-	1.0 API :2.0 PVP	
43-	0.5 API :1.0 PVA	Isopropyl alcohol

Table 3.6 B: Clotrimazole and coformers for the three solvents chosen and each solvent for seven different molar ratio /grinding co-crystallization technique

44-	1.0 API :0.5 PVA	
45-	1.0 API :1.0 PVA	
46-	1.5 API :1.0 PVA	
47-	1.0 API :1.5 PVA	
48-	2.0 API :1.0 PVA	
49-	1.0 API :2.0 PVA	
50-	0.5 API :1.0 PVA	Acetonitrile
51-	1.0 API :0.5 PVA	
52-	1.0 API :1.0 PVA	
53-	1.5 API :1.0 PVA	
54-	1.0 API :1.5 PVA	
55-	2.0 API :1.0 PVA	
56-	1.0 API :2.0 PVA	
57-	0.5 API :1.0 PVA	Chloroform
58-	1.0 API :0.5 PVA	
59-	1.0 API :1.0 PVA	
60-	1.5 API :1.0 PVA	
61-	1.0 API :1.5 PVA	
62-	2.0 API :1.0 PVA	
63-	1.0 API :2.0 PVA	
64-	0.5 API :1.0 Carbomer	Isopropyl alcohol
65-	1.0 API :0.5 Carbomer	
66-	1.0 API :1.0 Carbomer	
67-	1.5 API :1.0 Carbomer	
68-	1.0 API :1.5 Carbomer	
69-	2.0 API :1.0 Carbomer	
70-	1.0 API :2.0 Carbomer	
71-	0.5 API :1.0 Carbomer	Acetonitrile
72-	1.0 API :0.5 Carbomer	
73-	1.0 API :1.0 Carbomer	
74-	1.5 API :1.0 Carbomer	
75-	1.0 API :1.5 Carbomer	
76-	2.0 API :1.0 Carbomer	
77-	1.0 API :2.0 Carbomer	
78-	0.5 API :1.0 Carbomer	Chloroform
79	1.0 API :0.5 Carbomer	
80-	1.0 API :1.0 Carbomer	
81-	1.5 API :1.0 Carbomer	
82-	1.0 API :1.5 Carbomer	
83-	2.0 API :1.0 Carbomer	
84-	1.0 API :2.0 Carbomer	

Each formula of the previous preparation was assigned a number as shown in table 3.6.

3.5 Melting point apparatus BUCHI B-545 methodology

1 .Always crush granulated and crystals samples in a mortar and then fill into the M. point capillary to at least 4-6mm. (compared to the height on the attached device).
2. It is probable to set the set point about 5-10 °C below the melting point.
3 . Max point is set automatically 15 °C above the set point
4. If more than one sample to be measured in order to get the average , necessary To fill the capillary tubes with the same height of powder, and that the substance is well compacted in the capillaries.

5. Result of melting point determination can be read either manually or automatically.
6. Compaction in capillary tube is obtained by:
   6.1Knocking the capillary on a hard base
   6.2 Letting the capillary tube drop onto the table through a glass tube approximately 1 meter length for two to three times.
   6.3 Compress sample with the compaction wire.
7. BUCHI B-545 apparatus can perform melting point or melting range.
8. The boiling point can only be determined visually.
   Set point : as from which the adjust temperature program will run down.
   Max point : Maximum temperature to be reached for the current determination .
   This is set automatically at 15 C above the SET POINT but may also be adapted

3.6 Infra-red (IR) spectroscopy methodology

IR involves shining infrared_light through a sample, causing its molecular bonds to vibrate (stretch, bend) at characteristic frequencies, absorbing specific wavelengths. Modern methods use Fourier Transform IR (FTIR) spectrometers that measure all frequencies simultaneously, creating an interferogram decoded by Fourier___transform into a spectrum (transmittance/absorbance vs. wavenumber)**.**

Shimadzu HPLC methodology

Sample taken from each co-crystal 10 mg ,an attempt to dissolve it in 100 ml
Purified water using volumetric flask ,by sonication for 15 minutes . then the
Same solution from each paradigm was filtered by Millipore filter then analysis
By HPLC.

3.7 Differential Scanning Calorimetrey (DSC) methodology

Differential Scanning Calorimetrey (DSC) is a thermo-analytical technique widely employed in pharmaceutical research to investigate the thermal behaviour of materials. This method measures changes in heat flow associated with physical and chemical transformations as a function of temperature. DSC provides both qualitative and quantitative information about endothermic events, where heat is absorbed by the sample, and exothermic events, where heat is released. In addition, it allows for the determination of changes in heat capacity, melting points, crystallization events, and phase transitions. By analysing these thermal properties, researchers can assess the purity, crystallinity, and stability of pharmaceutical compounds and solid-state formulations.

Typical Methodology Steps

1. **Sample Preparation:** Weigh a precise amount of co-crystal sample and load it into a specialized DSC pan, sealing it if necessary. A matched empty pan serves as the reference.
2. **Instrument Setup:** Set the heating/cooling program (rate, temperature range) and purge the cell with an inert gas (like nitrogen) to prevent oxidation.

3. **Calibration:** Calibrate the DSC with known standards (e.g., indium) for temperature and enthalpy accuracy.
4. **Analysis:** Run the sample and reference through the programmed temperature cycle.
5. **Data Interpretation:** Analyze the resulting thermo gram (plot of heat flow vs. temperature/time) to identify transitions (peaks/steps) and calculate associated enthalpy changes (area under the peak) and transition temperatures

Chapter Four

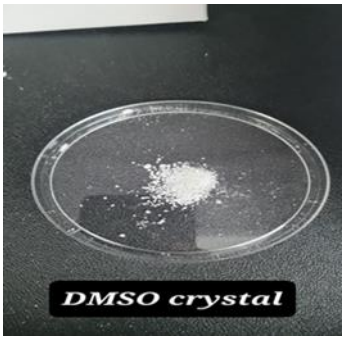
4.1 Recrystallize Results

Pictures of the obtained crystals from recrystallization procedure
Formula 1-5 see section 3.3.1

API

Formula 1

Formula 2



Formula 3

Formula 4

Formula 5

Figure 4.1: Re-crystal samples for different solvents with Clotrimazol

4.1.1 Re-crystal melting point

API melting point is 143 ^{0}c (141-145)
1. API /methanol crystal melting point is 144.6 , 144.8 , 144.7^{0}c.
2. API / DMSO crystal melting point is 144.2 , 144.2 , 144.4 ^{0}c.
3. API / ethyl acetate crystal melting point is 144.7, 144.7 , 145 ^{0}c.
4. API / chloroform crystal melting point is 144.8 , 145 , 145 ^{0}c.
5. API / acetone crystal melting point is 144.7, 144.3, 144.4 ^{0}c.

Compared re-crystals results to clotrimazole no change in the melting point .

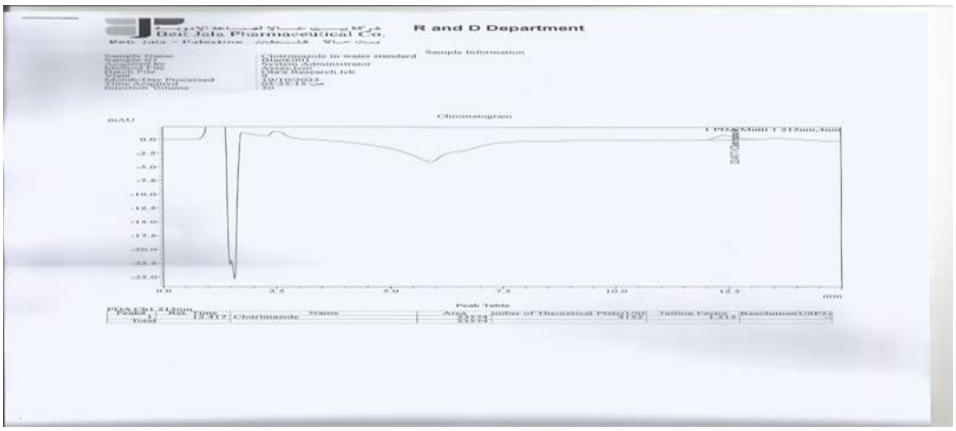
4.1.2 Re-crystal solubility in water

All the crystal samples did not dissolve in water , see picture below

Figure 4.2: Re-crystal for formula (1-5) solubility in water

Table 4.1: Re-crystal solubility in water results

#	Re-crystals	Solubility in water (mg/ml)
	API	0.22
1-	API /methanol	0.017
2-	API / DMSO	0.04
3-	API / ethyl acetate	0.007
4-	API / chloroform	0.005
5-	API / acetone	0.019



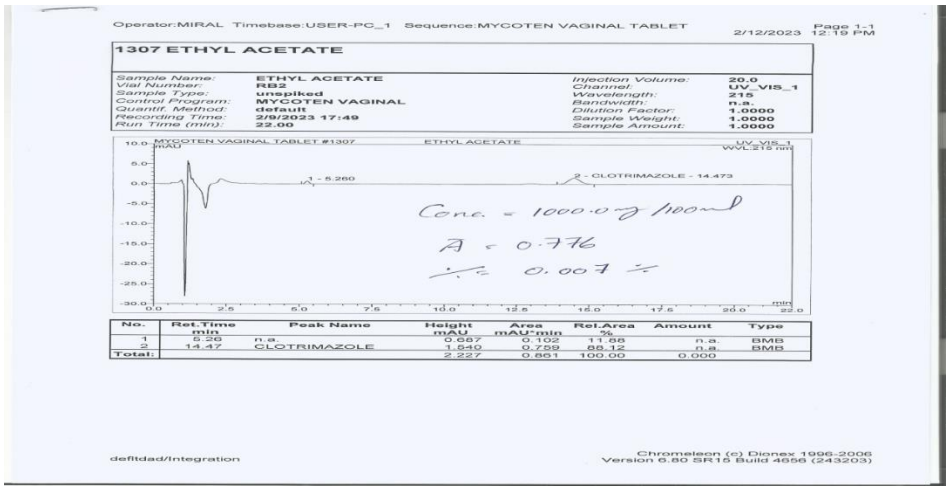


Figure 4.3: Re-crystals solubility in water by HPLC

According to the results, there was no improvement or change in the melting point and the solubility of the crystal samples for all formulas compared to the results of the active ingredient. Accordingly we concluded that method of recrystallization were not beneficial.

4.2 Co-crystals Results:

4.2.1 Macroscopic examination of co-crystals

The co-crystals produced using the grinding method with various co-solvents were evaluated for their macroscopic characteristics. Observations indicated that the crystals exhibited consistent uniformity, well-defined shapes, and a predictable sequence of formation. These features reflect the reproducibility and reliability of the co-crystallization process. Selected co-crystals were photographed to document their morphology and illustrate the visual appearance, as shown in Figure 7.

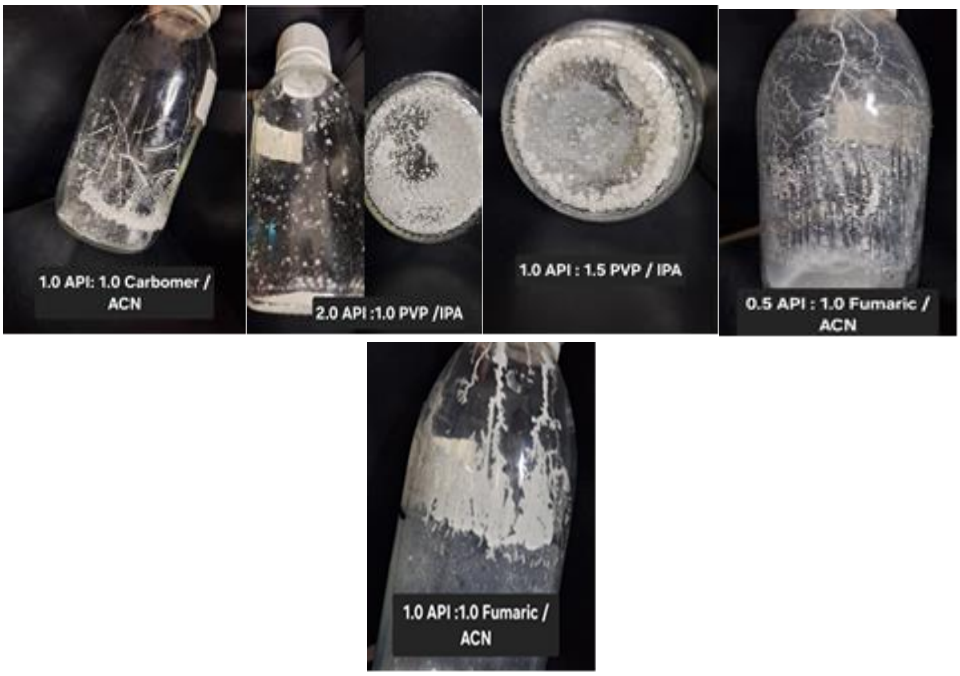


Figure 4.4: co-crystal obtained from each coformer with different solvents /grinding technique

Not all formulas resulted in co-crystal formation as some yielded a non –crystallization powder.

The formulae that yielded crystals, as detected by the naked eye are listed in table 8 with the respect respective melting points.

4.2.2 FTIR analysis of co-crystals

The co-crystals produced using the mechanical grinding method were analyzed using Fourier Transform Infrared (FTIR) spectroscopy to investigate their molecular interactions. Each co-crystal sample was examined individually in its solid state, and the resulting spectra were compared to those of the corresponding pure components. This comparison allowed for the identification of changes in functional group vibrations, providing evidence for the formation of co-crystals and confirming the presence of intermolecular interactions such as hydrogen bonding between the active pharmaceutical ingredient and the coformer.
FTIR analysis performed for formulas in table 8 that yielded lower melting point than the pure material .

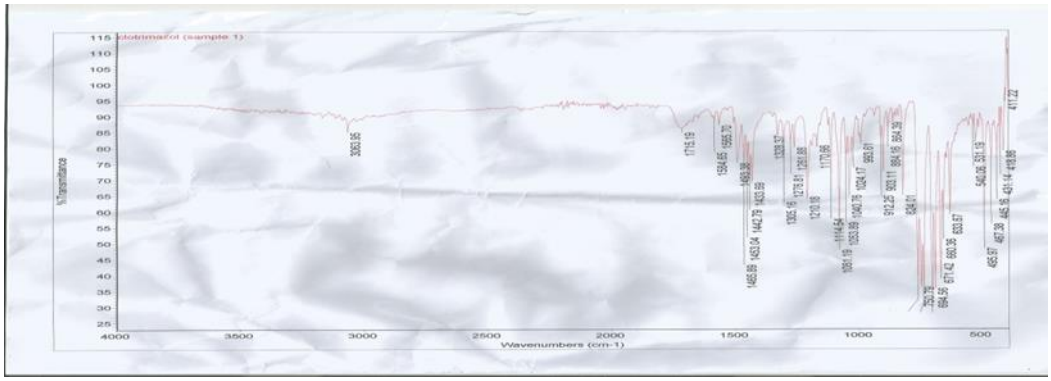


Figure 4:5: FTIR of clotrimazole

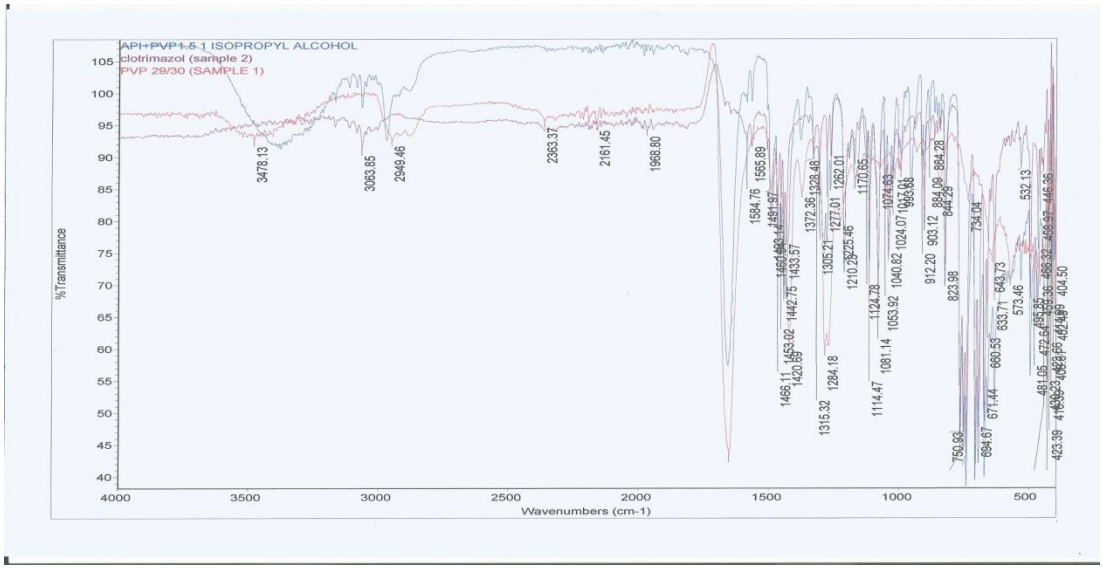


Figure 4.6: FTIR of formula #25

The crystals show much broader, more intense band, indicating hydrogen bonding Hydrogen bonding between PVP and clotrimazole. Shift and broadening of peaks due to molecular interactions .Contribution of isopropyl alcohol causing broad O–H behavior

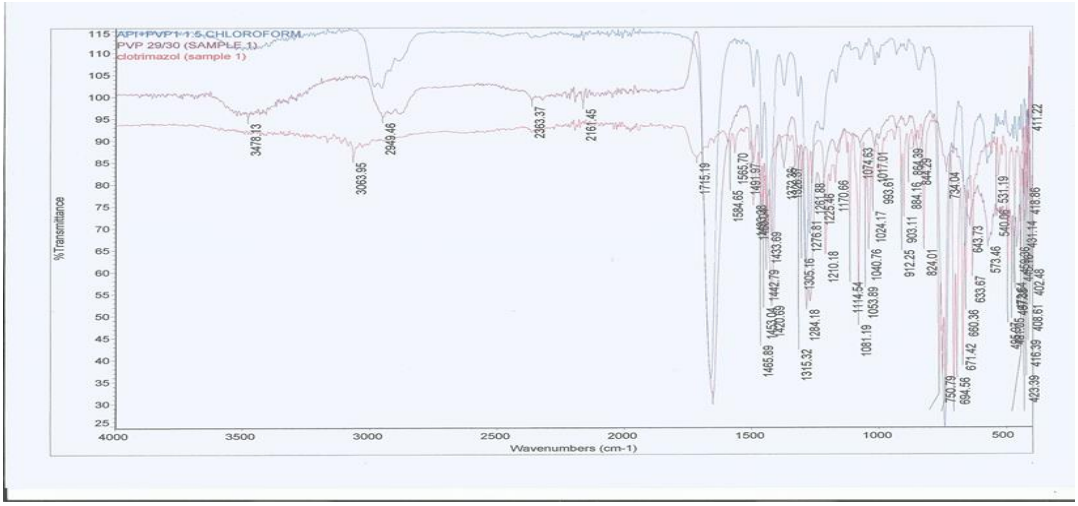


Figure 4.7: FTIR of formula #40

The broad O–H / N–H stretching region (~3200–3500 cm^{-1}) shows noticeable shifts and shape changes , clotrimazole has interacted with PVP (likely via hydrogen bonding) and have become partially or fully amorphous in the sample.

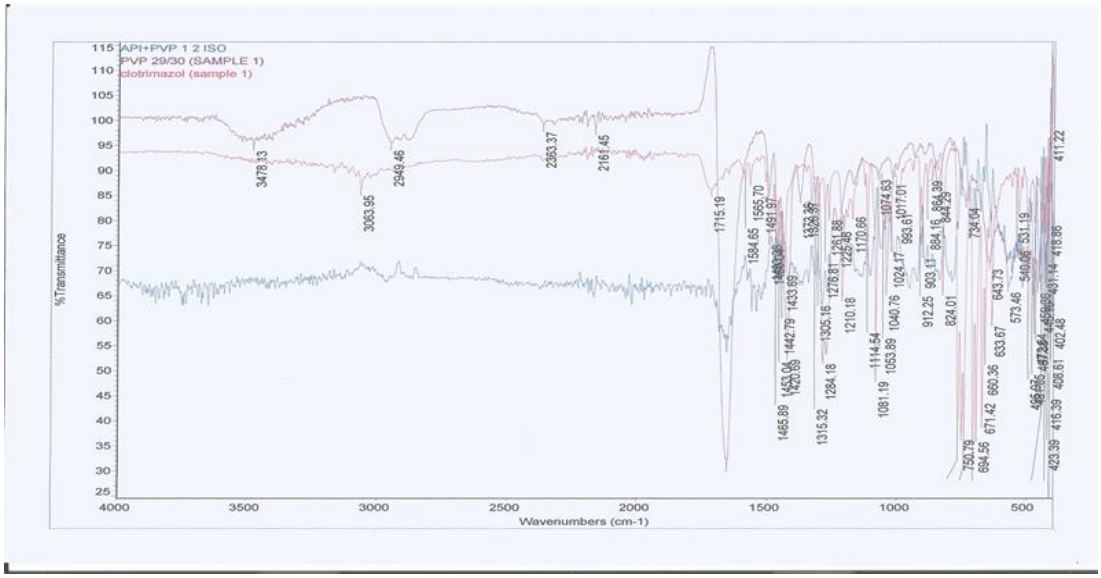


Figure 4.8: FTIR of formula #28

Interaction between PVP C=O and clotrimazole functional groups (often N–H or aromatic donors).

Shifts in these bands C=O stretching C–N and C=C vibrations, Aromatic ring modes indicate chemical interactions, typically hydrogen bonding between clotrimazole triazoles / carbonyl groups and PVP's carbonyl group.

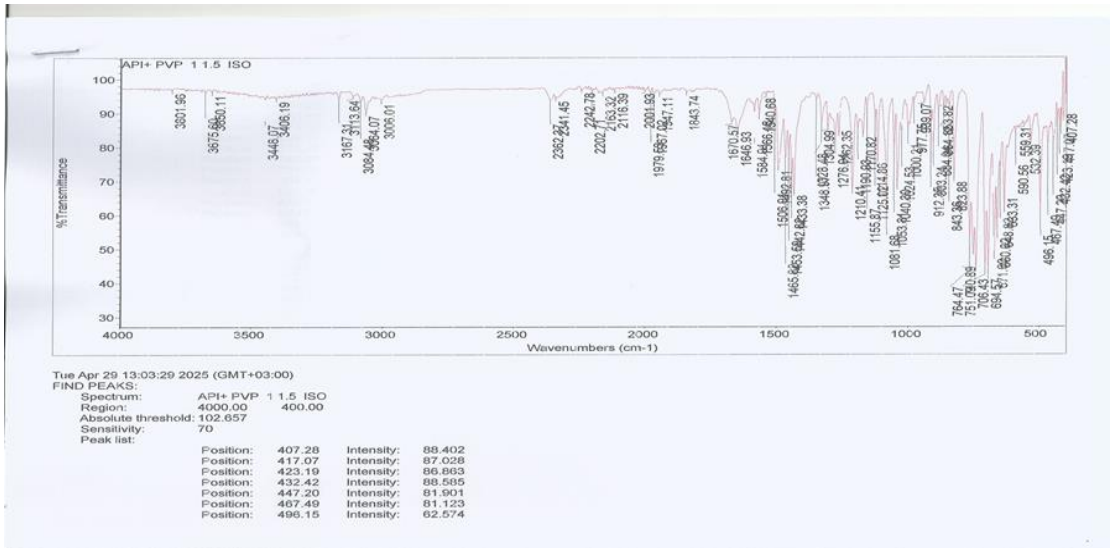


Figure 4.9: FTIR of formula #26

Hydrogen bonding between API and PVP (Shifts in O–H/N–H and C=O stretching regions)**.**
Reduced API crystallinity or full amorphization (Broadening and disappearance of sharp fingerprint peaks).
Formation of a solid dispersion at molecular level (General merging and shifting of multiple peaks).
Strong polymer–drug interactions (Shift of PVP carbonyl band).

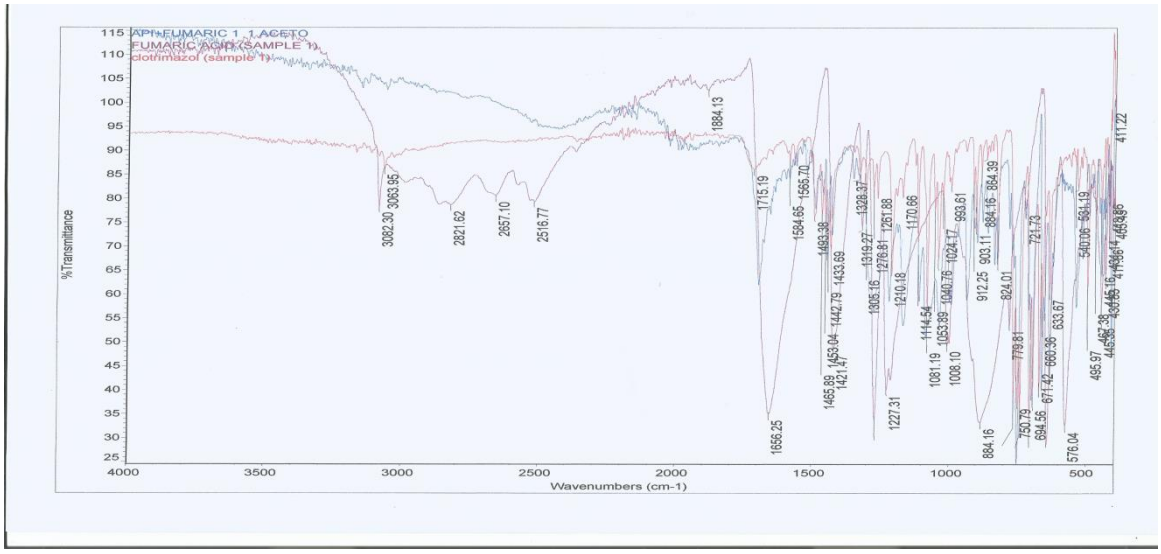


Figure 4.10: FTIR of formula #10

Around 1715–1720 cm^{-1} (C=O stretching) → slight shift and intensity change
Peaks near 1220–1250 cm^{-1} and 1000–1100 cm^{-1} also shift.
These shifts show that the chemical environment of functional groups has changed.

Figure 4.11: FTIR of formula #51

Hydrogen bonding interactions and reduced crystallinity occurred in co-crystals.
This is supported by:
O–H peak broadening and shifting

Changes in mid-IR functional group regions

Altered fingerprint region

The components interact at the molecular level (physically + hydrogen bonding), rather than forming a new chemical compound.

Figure 4.12: FTIR of formula #52

In co-crystals O–H peak of PVA shifted and broadened (3287 cm^{-1}) Clotrimazole interacts physically with PVA forming hydrogen bonding,

Shifting/broadening of PVA's O–H band, Hydrogen bonding between PVA –OH and clotrimazole nitrogen or aromatic rings.

Reduced crystallinity of PVA seen from changes in 1140–1080 cm^{-1} and 850–650 cm^{-1}.

Slight strengthening of aromatic peaks, Clotrimazole is uniformly dispersed in the polymer.

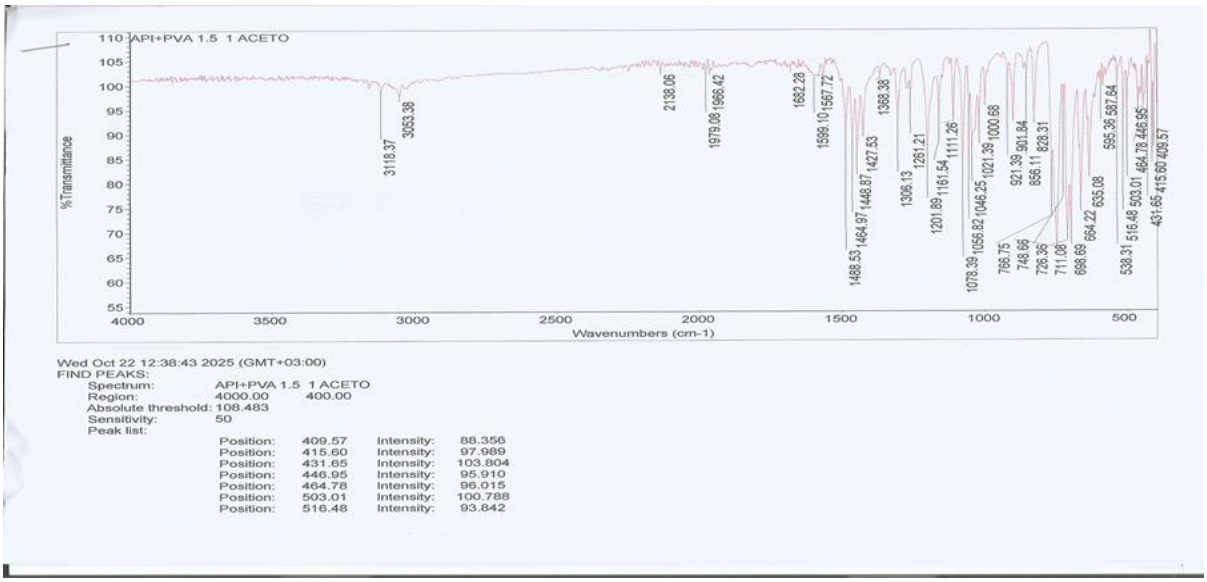


Figure 4.13: FTIR of formula #53

The changes that clotrimazole interacts physically with PVA, mainly through hydrogen bonding.

Peaks for clotrimazole are weakened, slightly shifted, or broadened, but no new peaks appear.

This indicates the API is compatible with PVA and has undergone no chemical changes, only physical mixing and bonding.

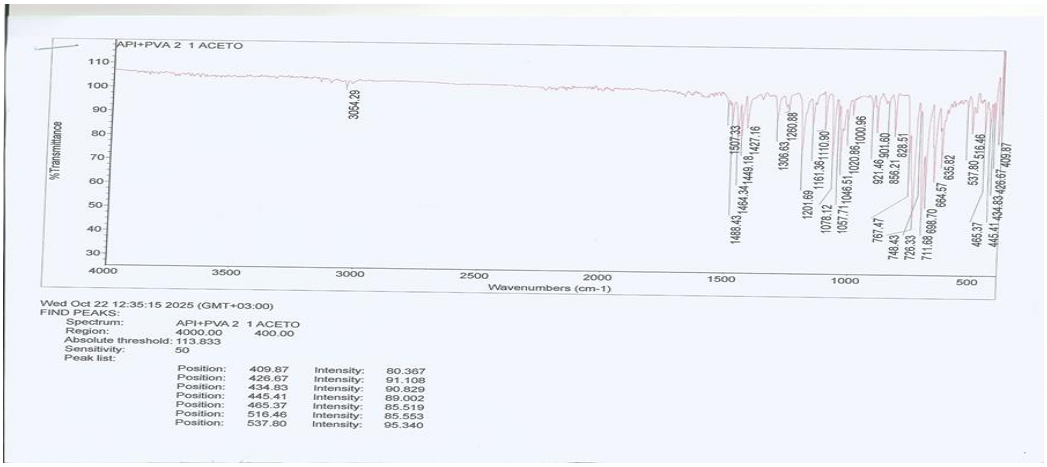


Figure 4.14: FTIR of formula #55

Slight shifts in clotrimazole aromatic peaks, Reduction in API peak intensities Broad enhancement of O–H band due to PVA, Peak merging in 1000–1300 cm^{-1} region, Peak splitting in C–Cl region due to matrix interaction.

The API is physically dispersed within PVA and forms hydrogen-bond–based interactions.

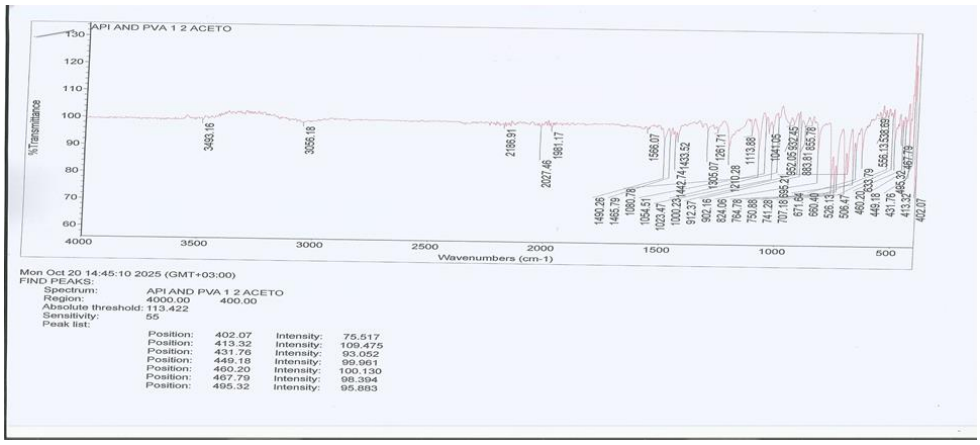


Figure 4.15: FTIR of formula #56

Clotrimazole (API) and PVA form a physically mixed system with hydrogen bonding interactions between the hydroxyl groups of PVA and the heteroatoms (O, N) in Clotrimazole. There is no evidence of chemical reaction, but the FTIR shifts confirm molecular-level interactions useful for improving solubility or film-forming properties.

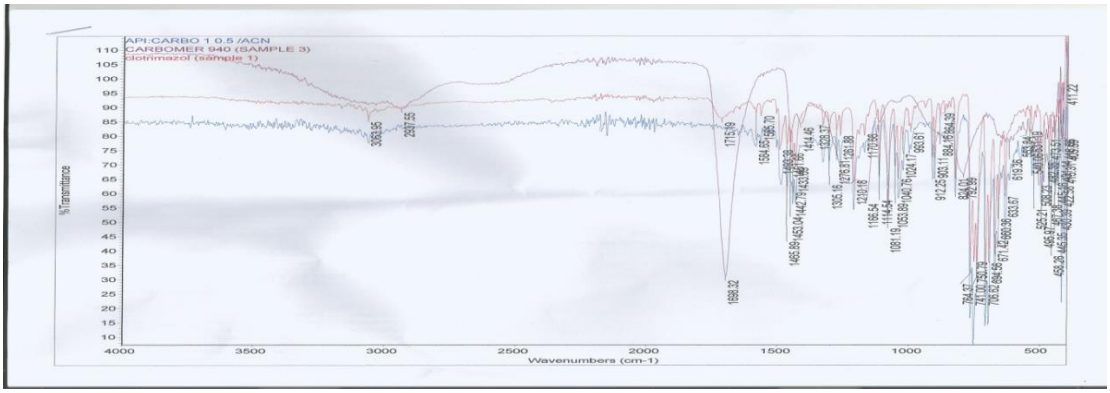


Figure 4.16: FTIR of formula #72

Peak Shifts **,** Particularly in O–H and C=O regions → supports hydrogen bonding.
Peak Intensity Reductions **,** Characteristic Clotrimazole peaks are less intense in the mixture → consistent with polymer dispersion.

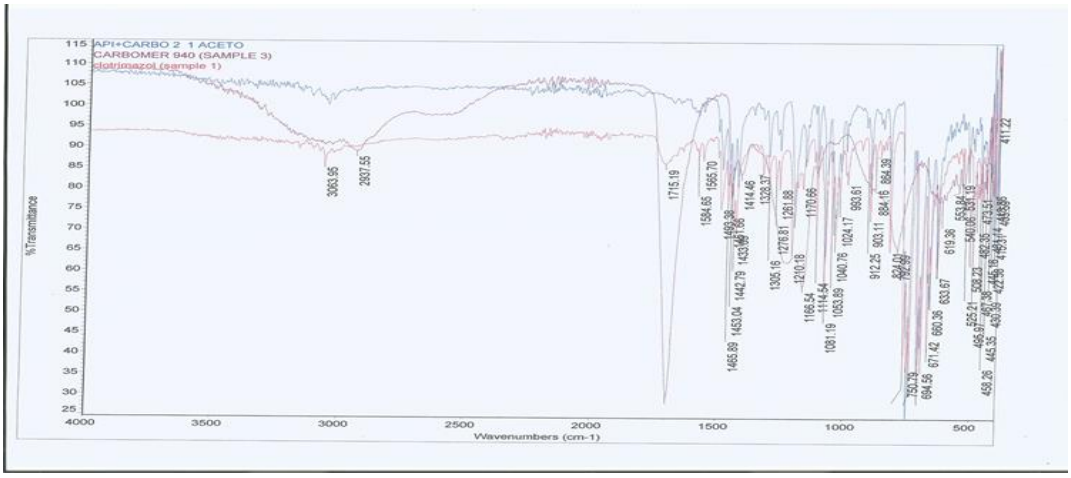


Figure 4.17: FTIR of formula #76

slightly shifts and broadens indicating hydrogen bonding interactions between API and the Carbomer.

C–H stretching (around 2850–2950 cm^{-1}): Minor shifts are seen in these peaks in the physical mixture, suggesting mild van der Waals or hydrophobic interactions.
Peaks around 1240–1000 cm^{-1} (C–O or C–N stretches) also show changes, confirming interacting between the polymer and the API.

The strong C=O stretch at ~1715 cm^{-1} in the Carbomer shifts slightly (to around 1710–1720 cm^{-1}) in the formulation.

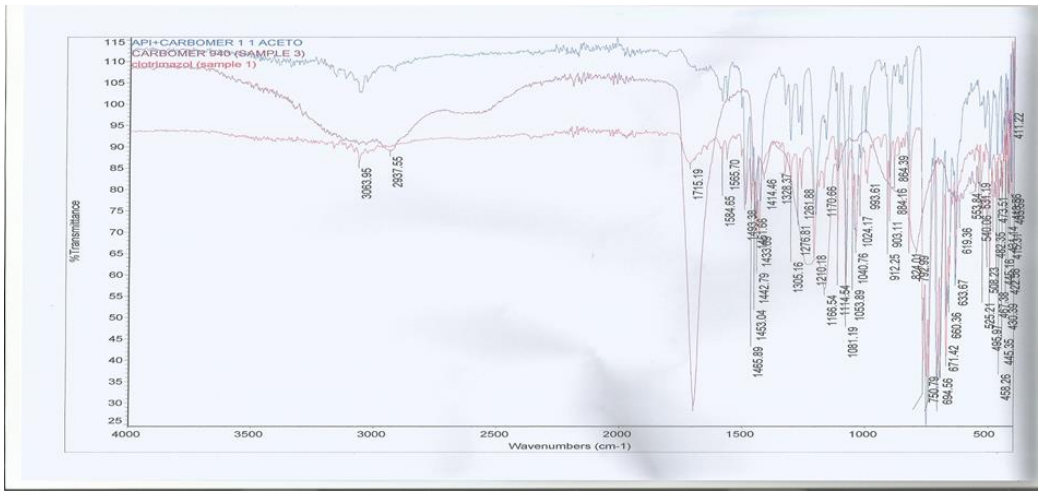


Figure 4.18: FTIR of formula #73

Some peak shifts in the combined sample, hydrogen bonding and physical interaction**,** but no major chemical reaction occurred.

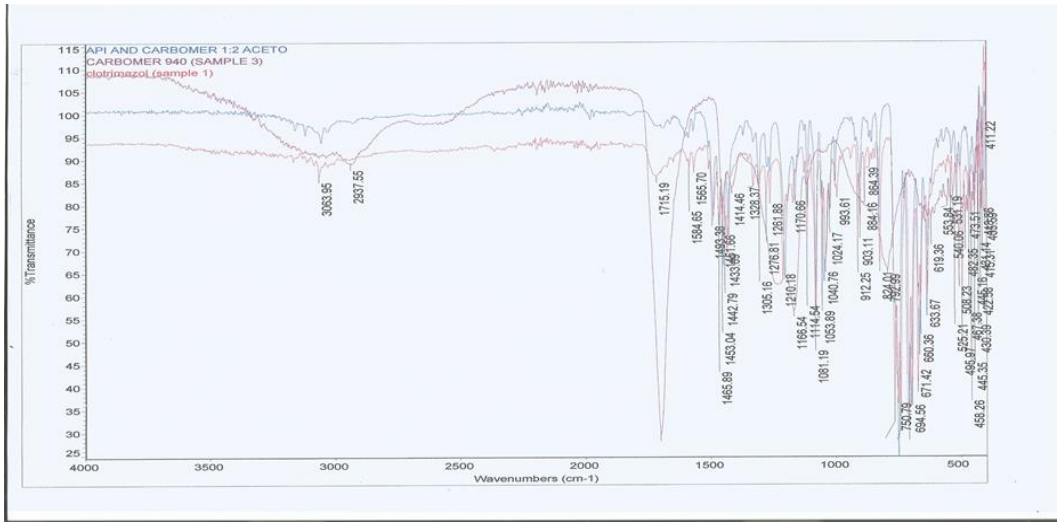


Figure 4.19: FTIR of formula #77

Minor shifts in broad bands (around 3400 and 1700 cm^{-1}) may point to hydrogen bonding or physical mixing effects.

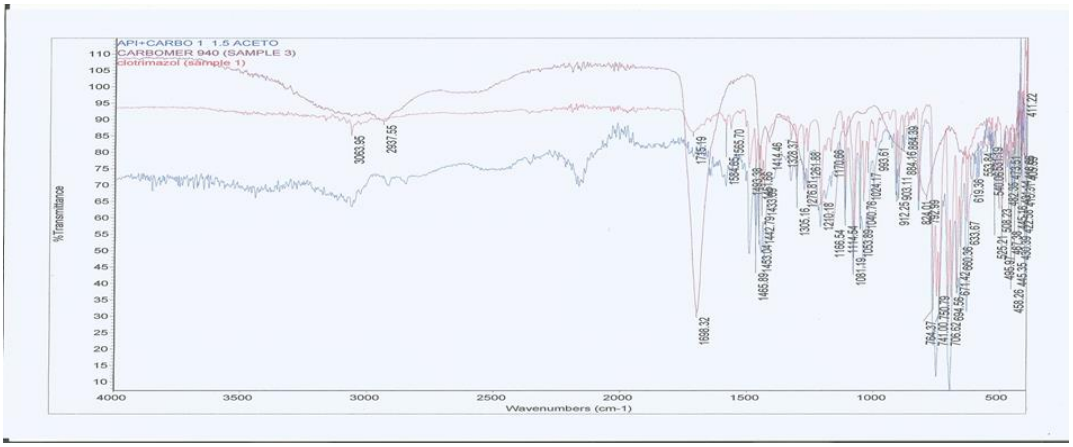


Figure 4.20: FTIR of formula #75

The FTIR spectra confirm that cocrystal formation between Clotrimazole and Carbomer 940 involves hydrogen bonding (between carboxyl groups and imidazole nitrogen) and possibly π–π interactions**.**

These changes result in shifted peak positions and broadened absorption bands**,** indicating successful supramolecular complexation rather than a simple physical mixture.

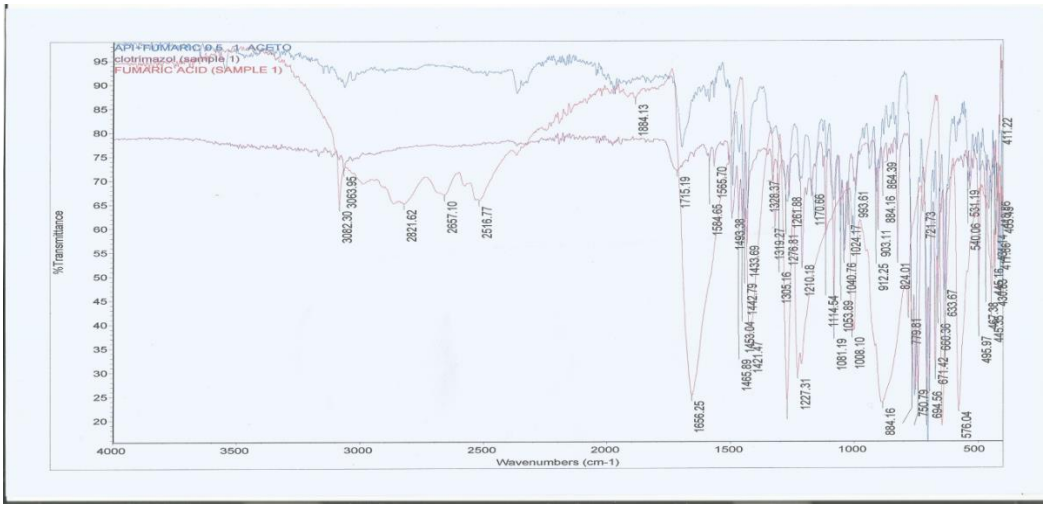


Figure 4.21: FTIR of formula #8

Hydrogen bonding between clotrimazole and Fumaric acid has changed Shifts in C=O, O–H, and fingerprint region confirm molecular interaction The mixture likely forms a physical complex or salt-like association

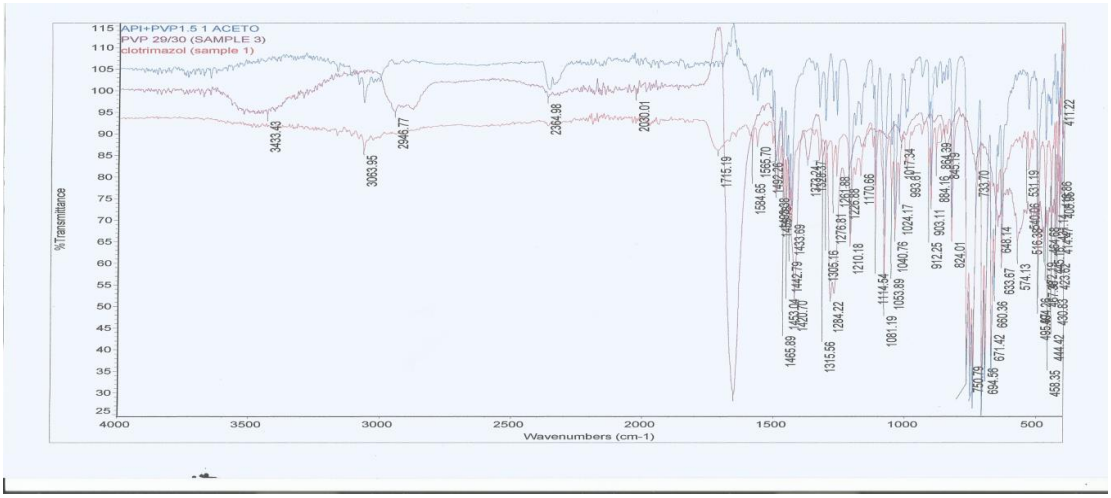


Figure 4.22: FTIR of formula #32

Broadening/Shift of O–H or N–H Stretch (~3200–3500 cm^{-1}),changes around 3349 cm^{-1} / 3365 cm^{-1}, hydrogen bonding between Clotrimazole N–H and PVP's C=O often causes broadening and peak shifts.

The PVP C=O group is engaged in hydrogen bonding with Clotrimazole. This is one of the most important indicators of interaction.

Strong evidence of API – polymer interaction or solid dispersion formation. Hydrogen bonding between Clotrimazole and PVP (major sign: shifts in ~3350 and ~1650 cm^{-1}), Reduced intensity of API crystalline peaks and Shifts in fingerprint-region peaks confirming molecular-level interaction.

FTIR conclusion:
It was shown that FTIR spectra for the co-crystals was different from that of clotrimazole and the interaction between clotrimazole and co-formers. The changes included stretching , shifting and broadening of peaks . These features indicated the formation of H-bonding between clotrimazole and the co-formers which explains the decrease in melting point and increase in solubility.

4.2.3 Co-crystal melting point

The thermal properties of the co-crystals, particularly those demonstrating enhanced drug release profiles, were assessed by determining their melting points. Small amounts of each co-crystal sample were carefully placed into capillary tubes and analysed using a melting point apparatus. This procedure provided valuable information regarding the thermal stability and purity of the co-crystals. Comparing the melting points of the co-crystals with those of the pure components enabled the identification of changes in crystalline structure resulting from co-crystal formation and offered insight into their potential impact on dissolution and bioavailability. (29)

Co-crystal Sample Melting Point Results
Clotrimazole Melting point =143 ^{0}C (141-145)
Ordered in ascending (the instrument enrolls three capillaries and results in one or three)

Table 4.2: Co-crystal melting point results

Formula #	Co-crystals melting point
52-	130,130.2
73-	130,131
77-	130,131
53-	133,130
56-	132.9,131
76-	133,134
75-	133.7,136.7
72-	136,134
8-	134,138.6,137.3
26-	135.1,138.7
55-	136
10-	136,137.2
28-	136,138
48-	134.6,141.6,141.2
25-	135,141
50-	136,140
51-	136,141
43-	140.3,137.9,138.4
40-	138,145
32-	140.9,142,141.6
24-	142.7
81-	142.2,143
63-	143.7/141.2/142.7
31-	143
45-	143
54-	143,147,143.5
30-	144,143
29-	146,143
33-	144
34-	144
35-	144
27-	144.4,144.3
23-	144,145
3-	150,143
13-	151,151.2
4-	155.5,155
5-	155.5,155.2

The variation change between the co-crystal melting point ranges is dependent on the target active pharmaceutical concentration and depending on the molar ratio for each co-crystal tested. The changes depending on the type of co-former and the type of cosolvent used.

4.2.4 DSC analysis Melting points and heat of fusion

Table 4.3: Co-crystal melting point results by DSC

Formula #	Melting point	Heat of fusion ΔH
API	150.98	-65.642-
75-	145.99	-49.013
28-	148.26	-33.031
73-	148.42	-55.470
72-	148.79	-47.170
76-	148.99	-57.941
40-	149.41	-31.731
53-	150.59	-45.721
52-	151.16	-67.068
55-	151.8	-76.900
51-	151.94	-63.957
32-	152.24	-62.342
8-	162.2	-51.787

12 encouraging samples were tested by DSC . It is shown that the results different slightly as compared to melting point testing by capillary method .
This fact is apparent in the literature (30) and explained by the note that these two systems work differently . However , the melting point and ΔH was lower for many co-crystals as compared with API.

4.2.5 Co-crystal solubility in water

The solubility's of selected co-crystals (those that yielded lower melting points than pure material).

Table 4.4: Co-crystal solubility in water results

Formula #	Co-crystals solubility in water (mg/ml)
API	0.22
8-	73.4
40-	49.8
32-	49
77-	37
76-	10.12
56-	8
75-	7
26-	7
10-	6.4
51-	5.1
73-	4.6
28-	4
72-	2.5
25-	2
55-	1.45
53-	1.4
52-	1.12

Results and Discussion

The present study investigated the effect of recrystallization and Cocrystallization techniques on the physicochemical properties of clotrimazole, with particular emphasis on melting point behaviour, intermolecular interactions as revealed by FTIR spectroscopy, and thermal properties assessed by Differential Scanning Calorimetrey (DSC).

Recrystallization of clotrimazole from various organic solvents (methanol, DMSO, ethyl acetate, chloroform, and acetone) did not result in any significant change in melting point when compared to the pure drug. The melting point values of all recrystallized samples remained within the narrow range of 144–145 °C, which is consistent with the reported melting point of clotrimazole. This observation indicates that recrystallization under the applied experimental conditions did not induce polymorphic transformation.

Furthermore, solubility studies demonstrated that recrystallized clotrimazole samples exhibited either comparable or reduced aqueous solubility relative to the untreated API. These findings suggest that simple solvent-mediated recrystallization was insufficient to modify the crystal lattice of clotrimazole in a manner that enhances its solubility. Consequently, recrystallization was deemed an ineffective strategy for improving the physicochemical performance of clotrimazole in this study.

In contrast to recrystallization, Cocrystallization of clotrimazole with various pharmaceutically acceptable co-formers (Fumaric acid, PVP, PVA, and Carbomer 940) produced notable changes in melting behaviour. Several co-crystals exhibited significantly lower melting points compared to the pure drug. The reduction in melting point is indicative of alterations in crystal packing and lattice energy resulting from the formation of new supramolecular assemblies.

The observed variability in melting point among different formulations can be attributed to differences in co-former type, molar ratio, and solvent used during grinding. Lower melting points generally correlate with weaker crystal lattice forces, which can facilitate improved molecular mobility and enhanced dissolution behaviour. These results strongly support successful cocrystal formation in selected formulation.

FTIR spectroscopy provided critical evidence for intermolecular interactions between clotrimazole and the selected co-formers. The FTIR spectra of the co-crystals differed markedly from that of pure clotrimazole, demonstrating peak shifting, broadening, and changes in intensity across key functional group regions.

Notable changes were observed in the O–H and N–H stretching regions (3200–3500 cm^{-1}), suggesting the formation of hydrogen bonds between the imidazole nitrogen atoms of clotrimazole and functional groups such as hydroxyl or carbonyl groups present in the co-formers. Additionally, shifts in the carbonyl stretching region (around 1650–1750 cm^{-1}) further support the involvement of hydrogen bonding interactions.

The absence of new absorption peaks confirms that no covalent chemical reactions occurred during Cocrystallization, indicating that the interactions were purely supramolecular in nature. These findings confirm the formation of stable cocrystals or solid-state complexes rather than chemical derivatives, preserving the pharmacological integrity of clotrimazole.
DSC analysis further corroborated the melting point data obtained by the capillary method. Several co-crystals exhibited endothermic melting events at temperatures lower than that of the pure API, along with reduced enthalpy of fusion (ΔH). A lower ΔH value reflects decreased crystallinity and weaker intermolecular forces within the crystal lattice.

The slight discrepancies between melting points obtained by DSC and those measured using the capillary method are expected due to differences in heating rates, sample environment, and sensitivity of the techniques. Nevertheless, the overall trend remained consistent, with cocrystals showing reduced melting temperatures and altered thermal profiles compared to clotrimazole.

The DSC thermo grams also revealed the absence of additional thermal transitions, indicating the formation of single-phase solid systems rather than physical mixtures. This further confirms the successful formation of new solid-state structures through Cocrystallization.

The combined results from melting point analysis, FTIR spectroscopy, and DSC demonstrate a clear relationship between solid-state modification and enhanced solubility. Co-crystals exhibiting lower melting points and stronger hydrogen bonding interactions showed the greatest improvement in aqueous solubility. This behaviour can be explained by reduced lattice energy, increased wettability, and improved interaction with the aqueous medium.

Overall, Cocrystallization proved to be a superior approach compared to recrystallization for modifying the physicochemical properties of clotrimazole. The successful formation of hydrogen-bonded supramolecular structures led to significant reductions in melting point and crystallinity, ultimately resulting in enhanced solubility and dissolution potential.

Conclusion

In this study we aimed at increasing the solubility of the poorly soluble drug clotrimazole showed that changing the physical form of the drug clotrimazole can change its properties such as melting point and solubility. We did not succeed in manipulating the crystal form of the drug by re-crystallization where we tried to induce polymorphism. We used standard methods where re crystallization from different solvents could form polymorphs that might have less melting point and more solubility's. The results were un encouraging and the method was abandoned. However, co crystallization of clotrimazole with different co formers and using different solvents did result in impressive findings. Many of the co crystals showed less melting points, as shown by capillary melting point measurements and DSC, and the conjugation and interaction with the conformer was shown by FTIR assays. Those

co crystals with less melting points showed a remarkable increase in solubility providing many candidates for future work of formulating an oral dosage form with improved bioavailability.

Future work

Preparation of immediate release of clotrimazole tablet using prepared co-crystals as oral antifungal drug used for the systemic treatment of fungal diseases while it has less side effects on liver than other antifungal drugs.

Other optional dosage form is sublingual or suppositories.
And antimalarial drugs while it shows better activity against chloroquine resistant malarial parasites because of its complex forming ability with free heme.
Future studies should focus on investigating the effect of pH on the solubility behaviour of the selected clotrimazole co-crystals.

Since clotrimazole exhibits pH-dependent solubility, evaluating solubility profiles across different physiological pH conditions (such as gastric and intestinal pH) will provide deeper insight into the dissolution behaviour and potential oral absorption of the developed co-crystal systems.

In addition, determination of the partition coefficient (log P) of clotrimazole co-crystals is recommended to assess changes in lipophilicity resulting from co-crystallization. Evaluating the partition coefficient will help correlate solubility enhancement with membrane permeability and predict the overall impact on bioavailability. Establishing the relationship between solubility, pH, and partition coefficient will contribute to a more comprehensive understanding of the biopharmaceutical performance of clotrimazole co-crystals and support their further development as oral dosage forms.

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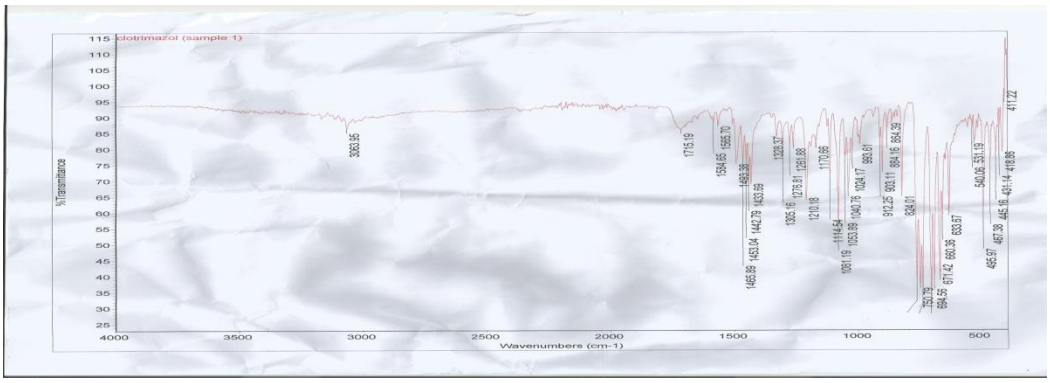
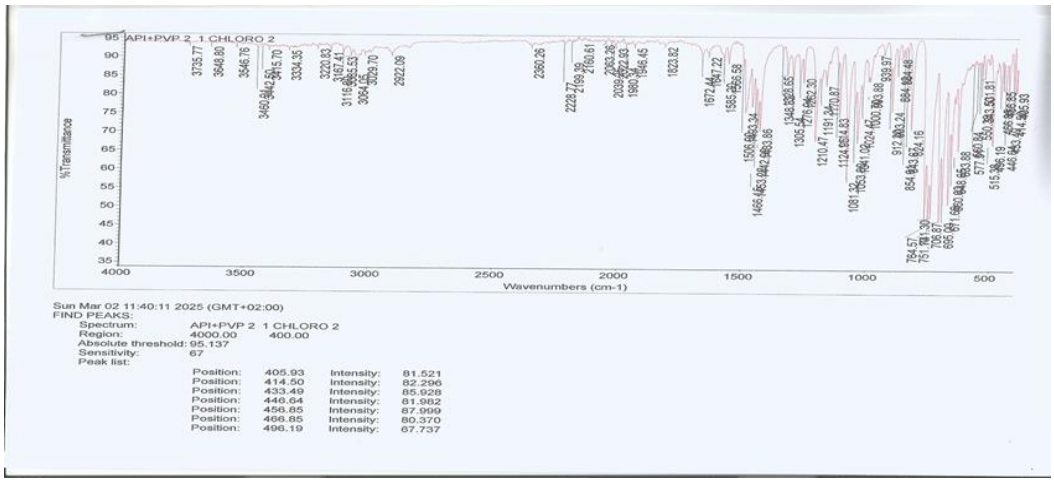
Appendices

Appendix 1 :FTIR of API (clotrimazole) sample



Appendix 2 :FTIR of co-crystals

1- FTIR of Formula # 41



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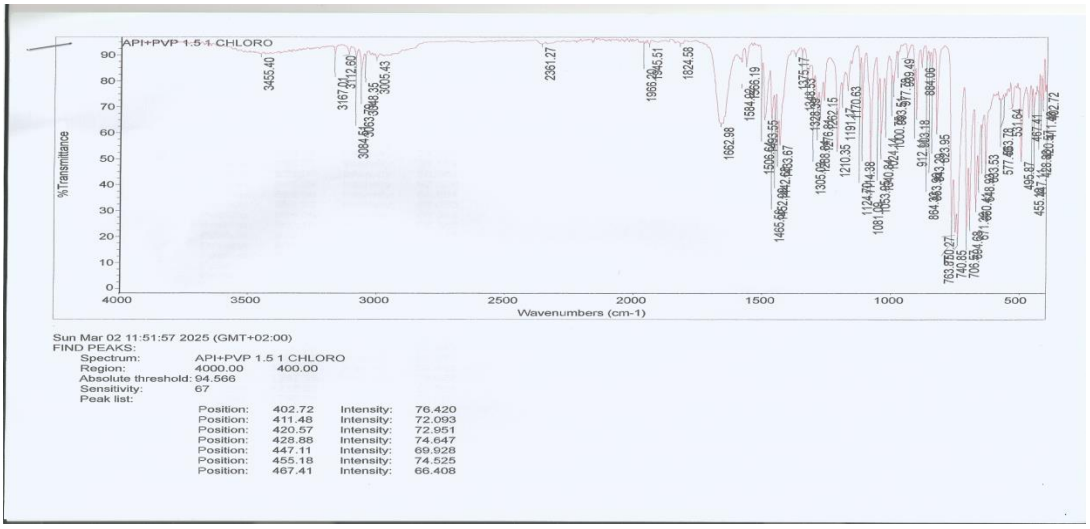

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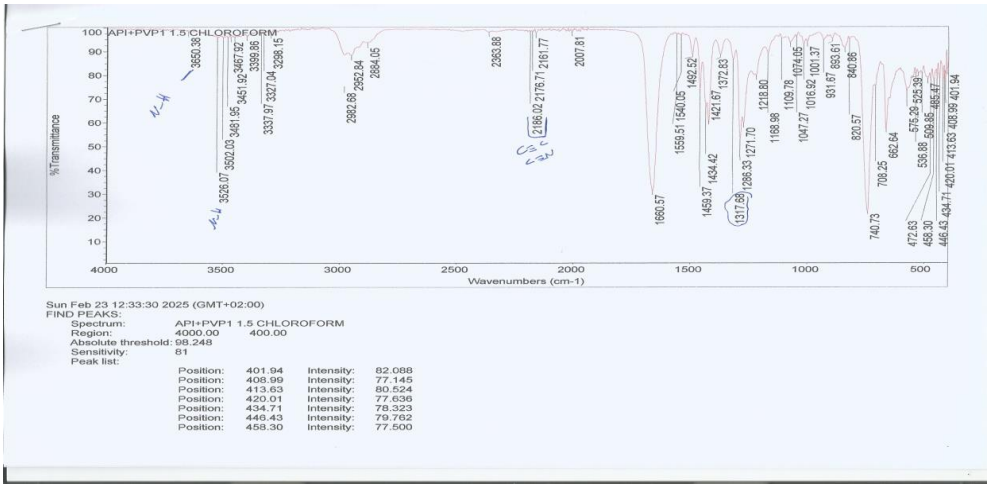

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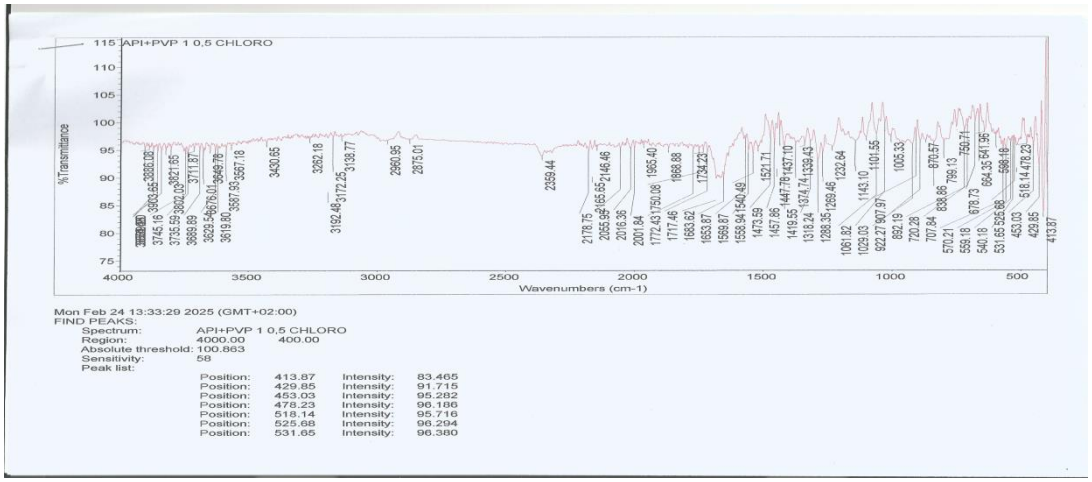

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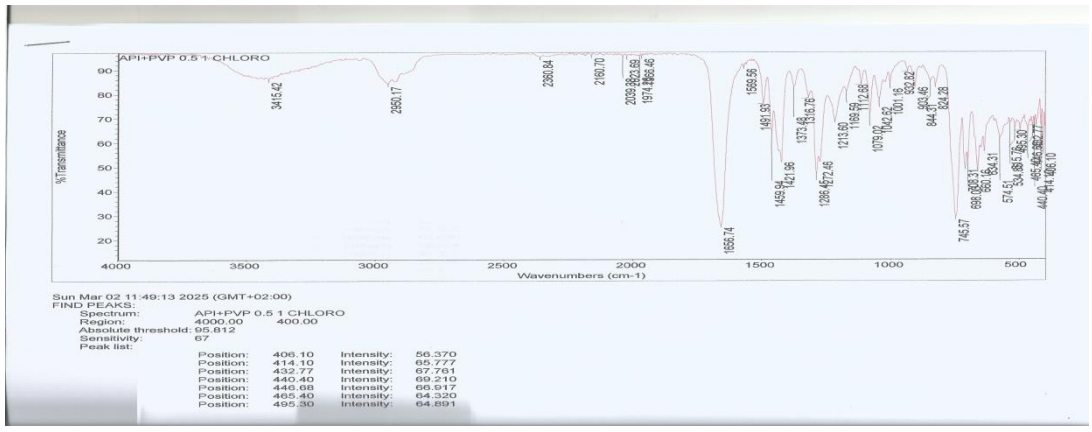
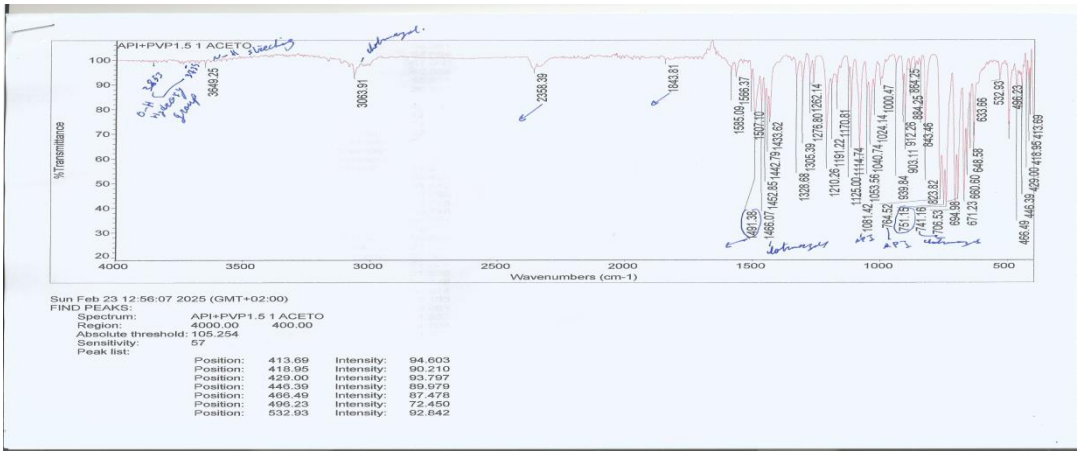


6- FTIR of Formula # 39

7- FTIR of Formula # 32



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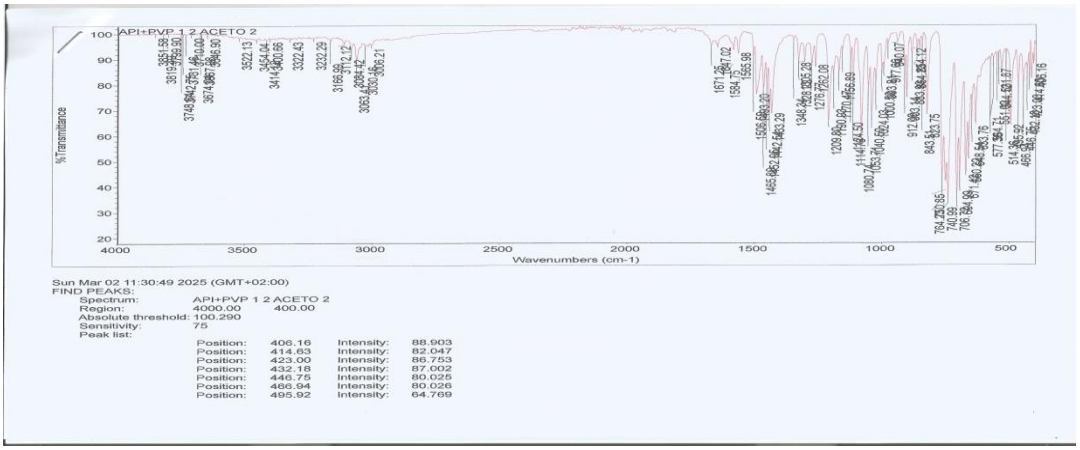

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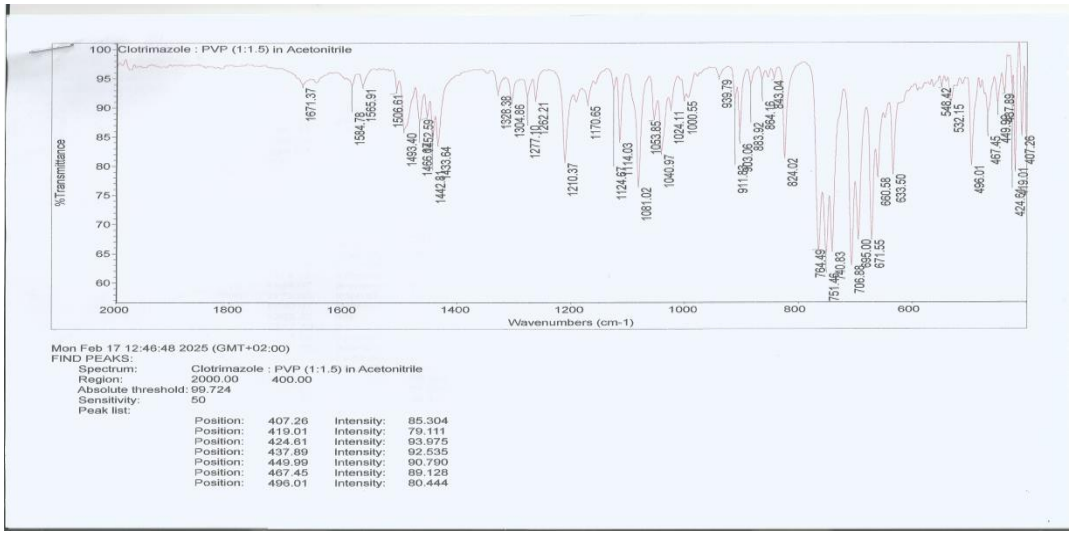

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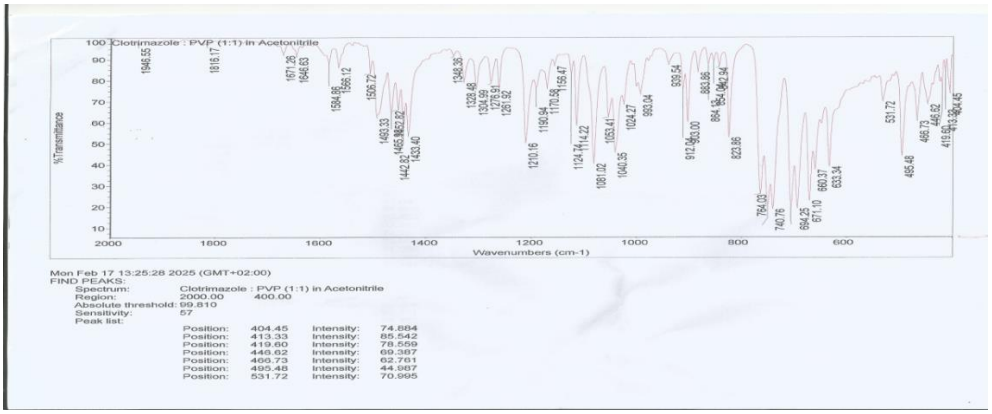

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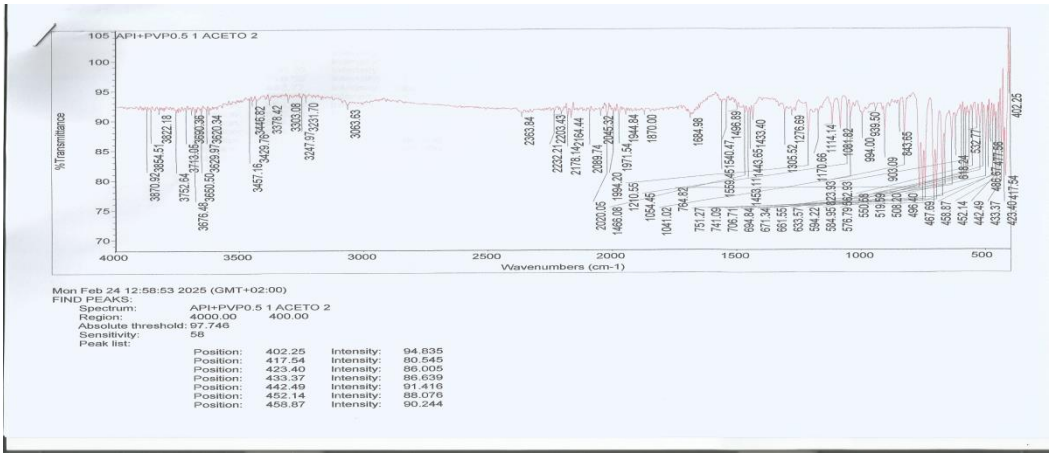

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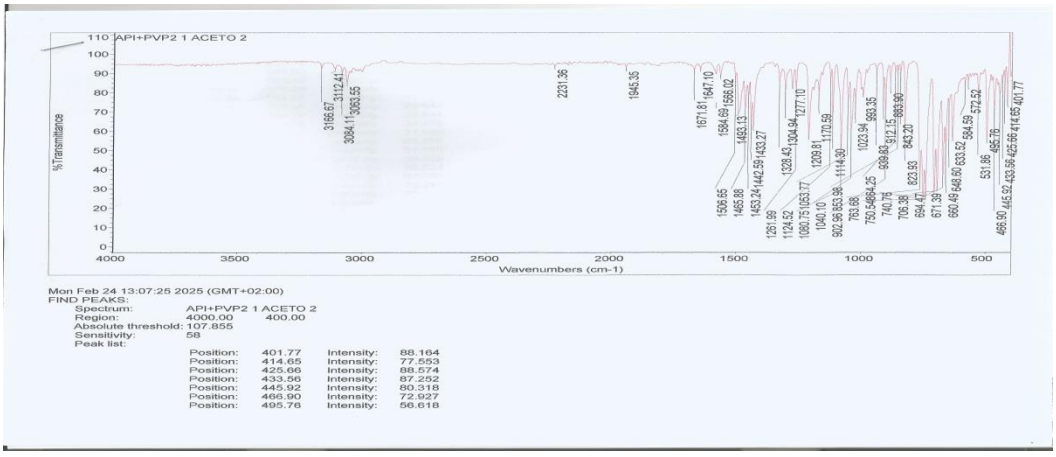

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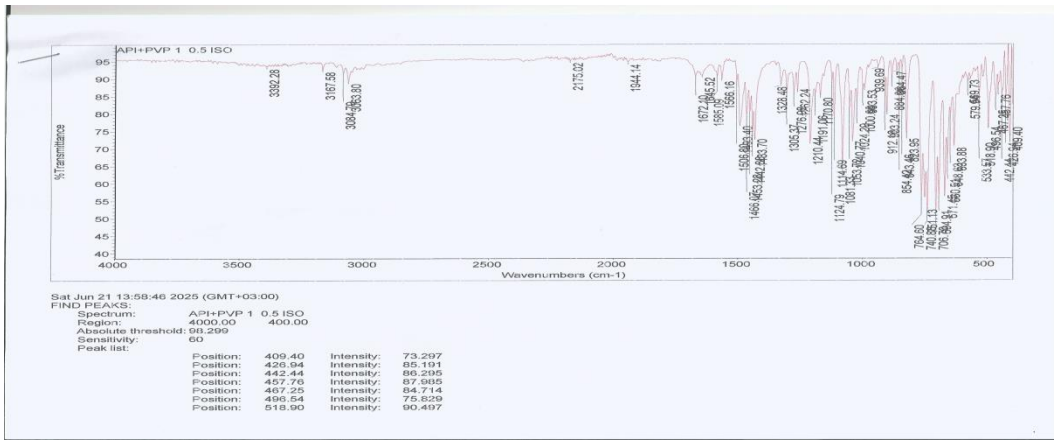

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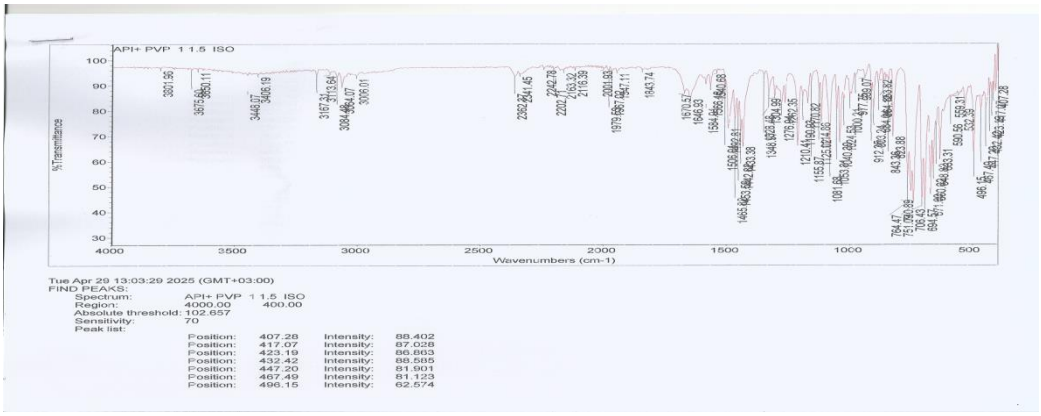

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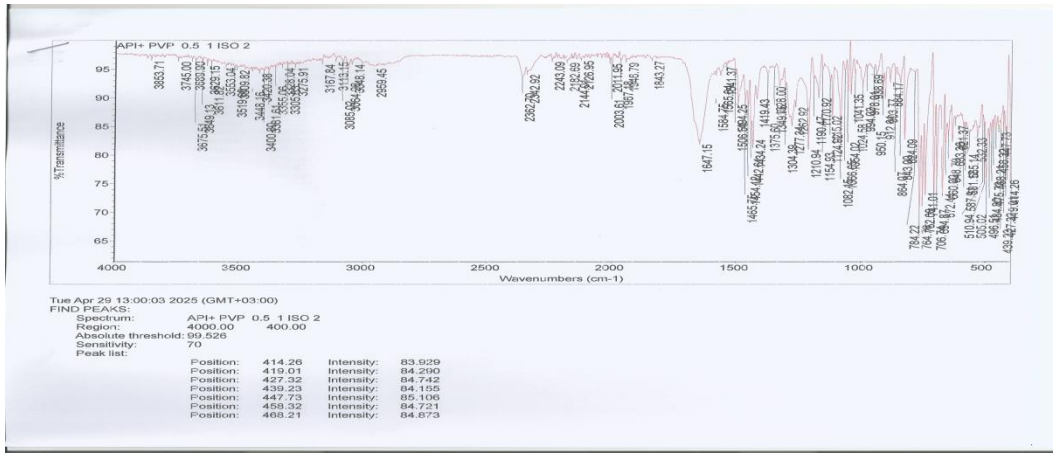
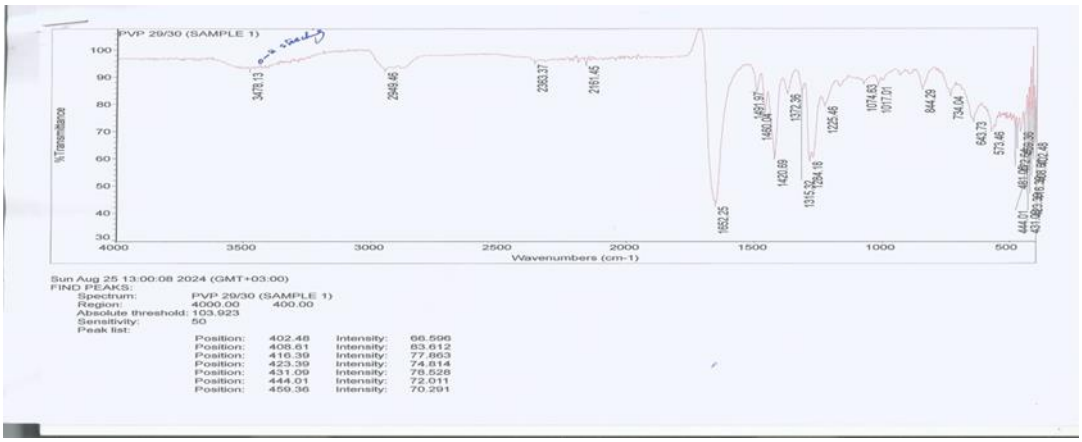


16-FTIR of PVP



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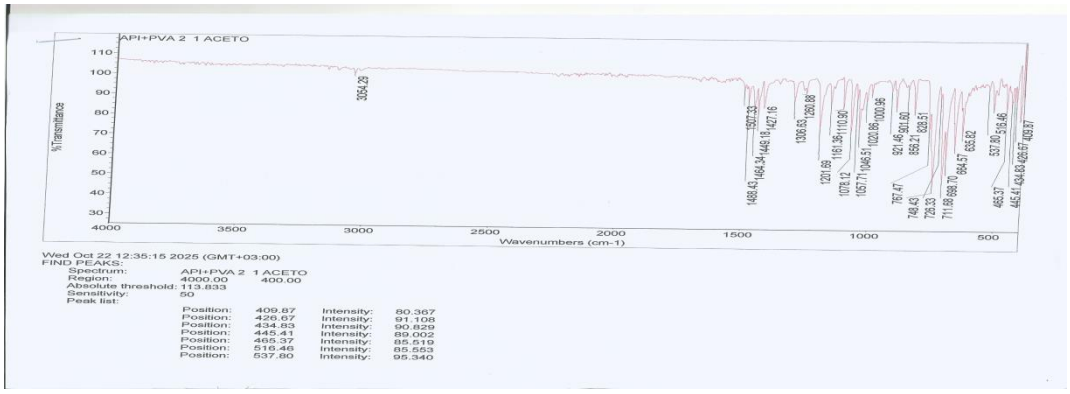

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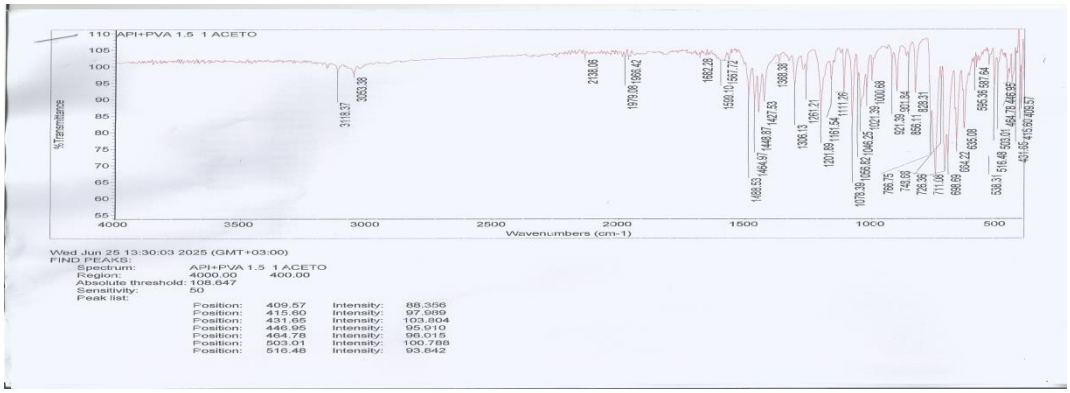

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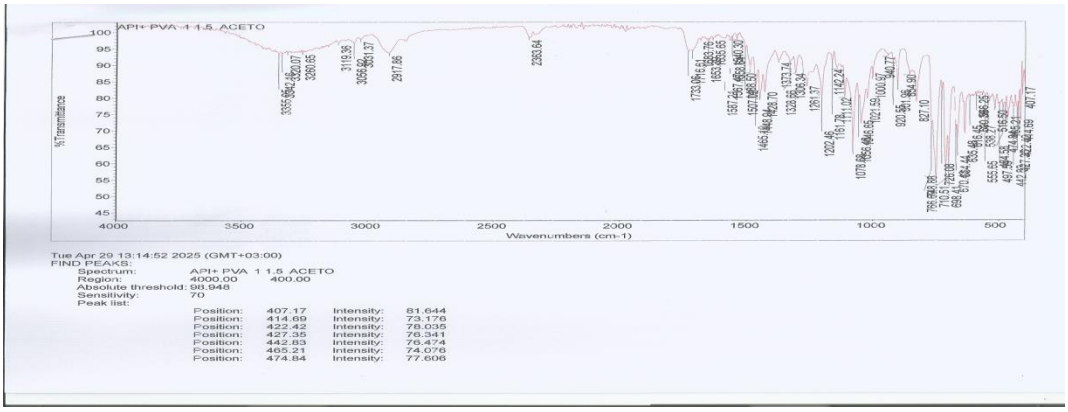

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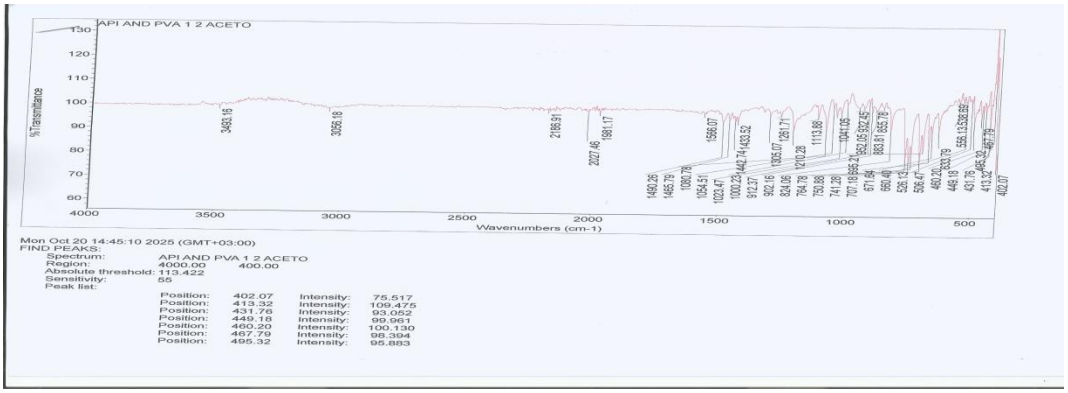

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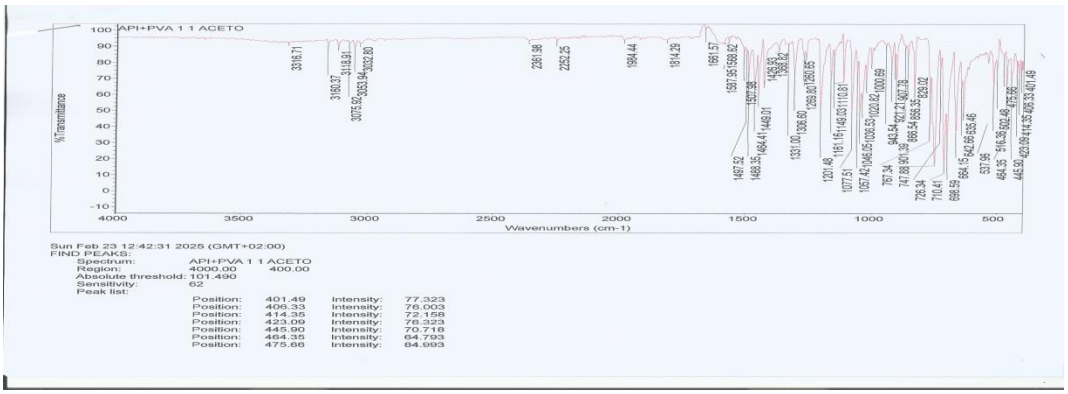

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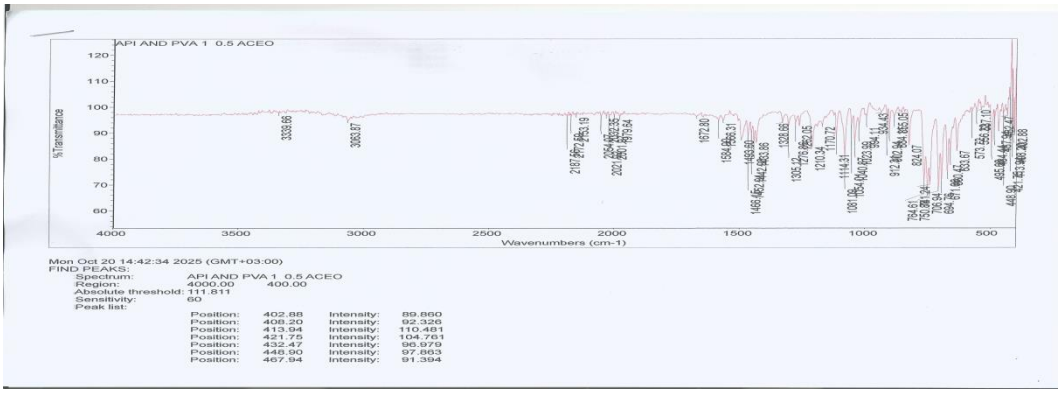

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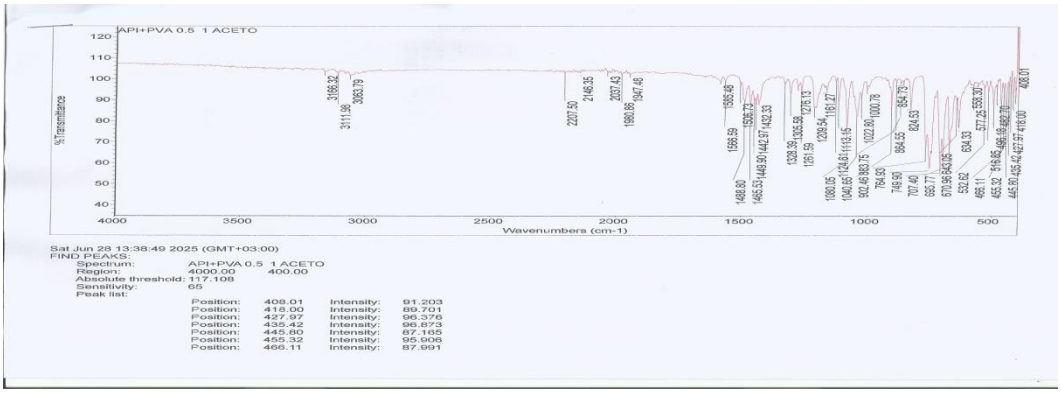

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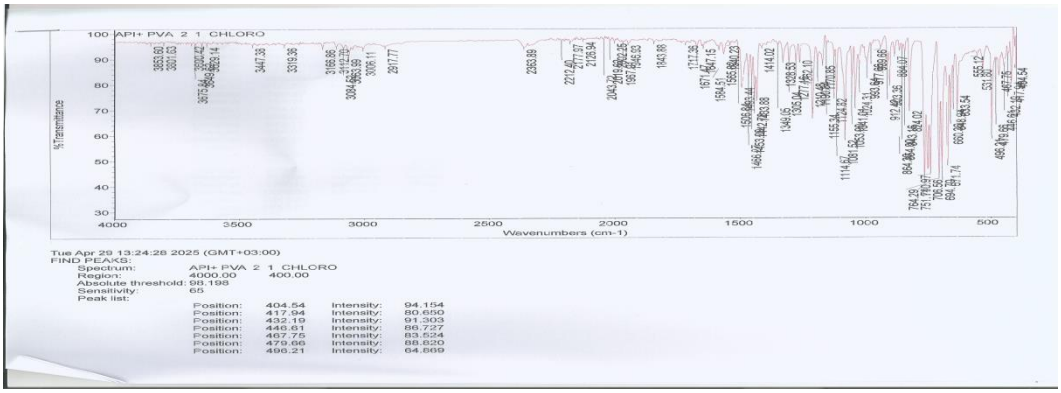

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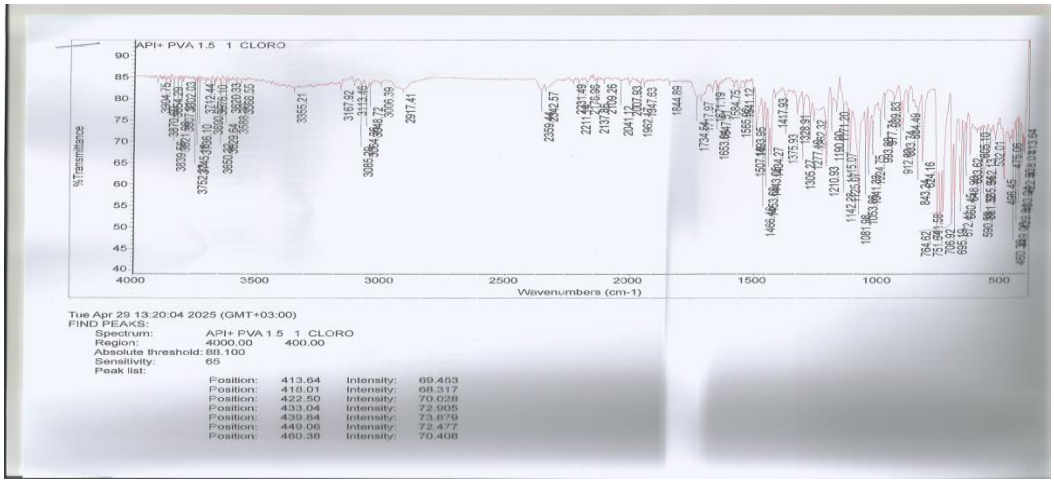

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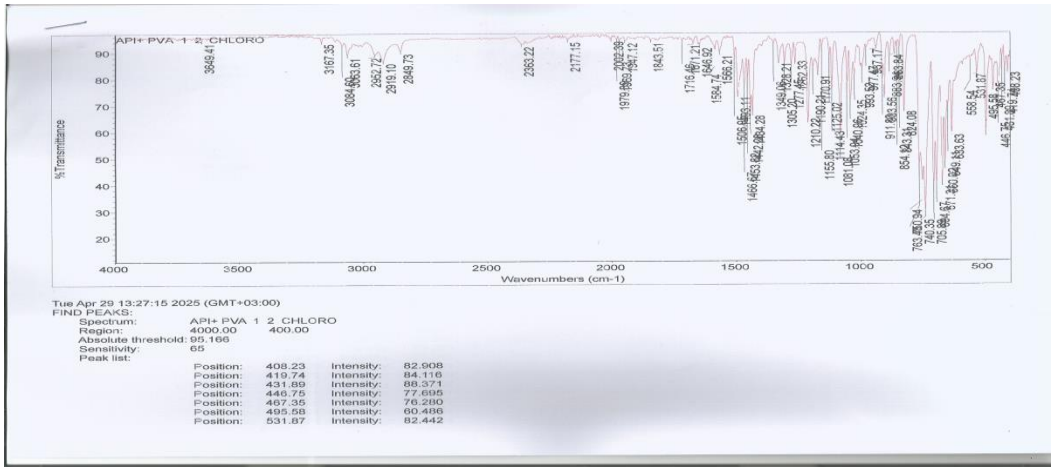

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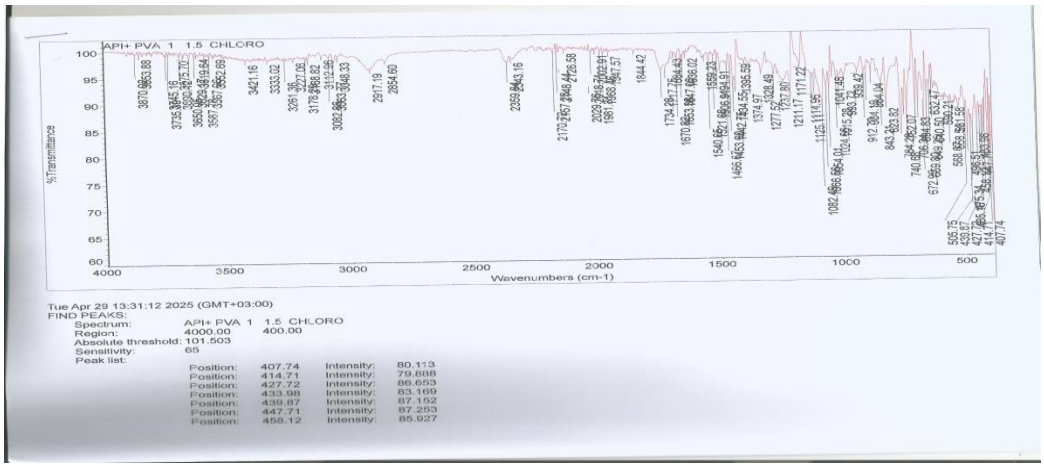

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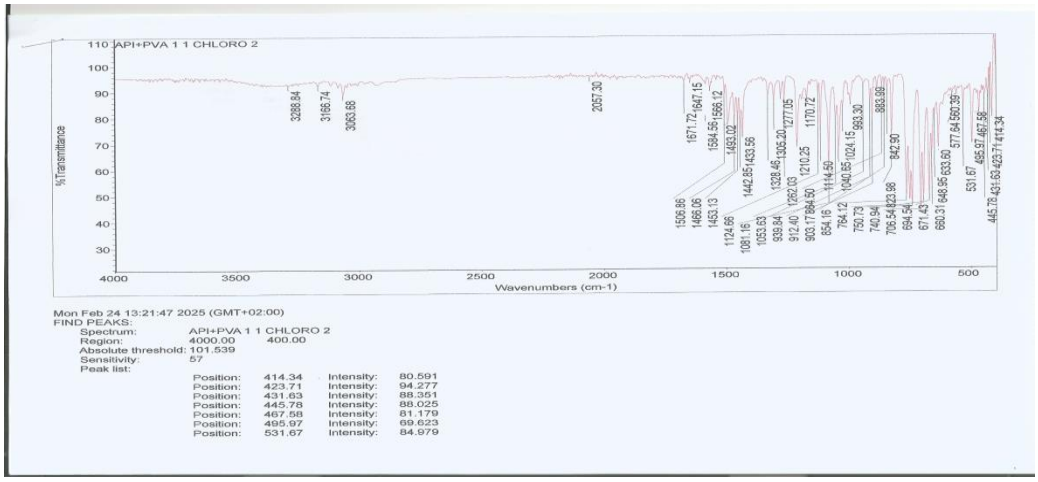

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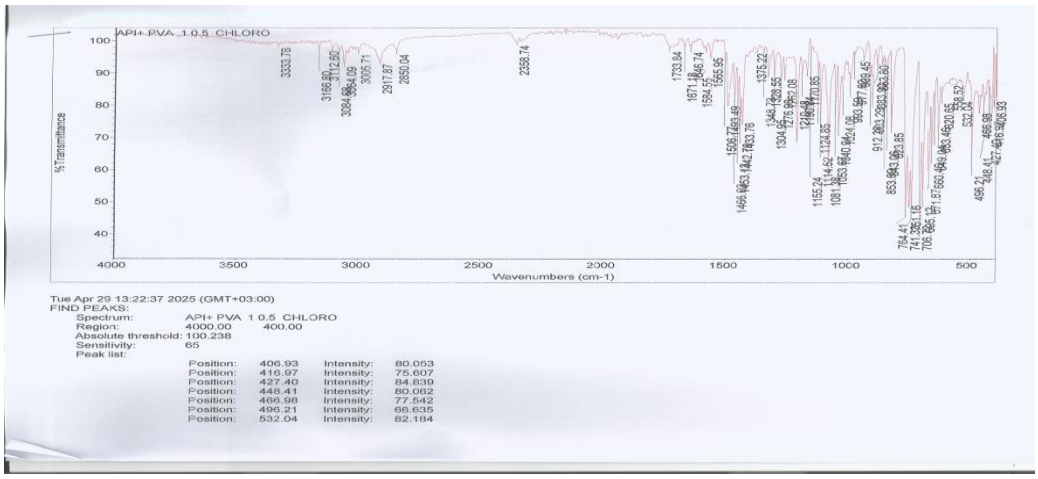

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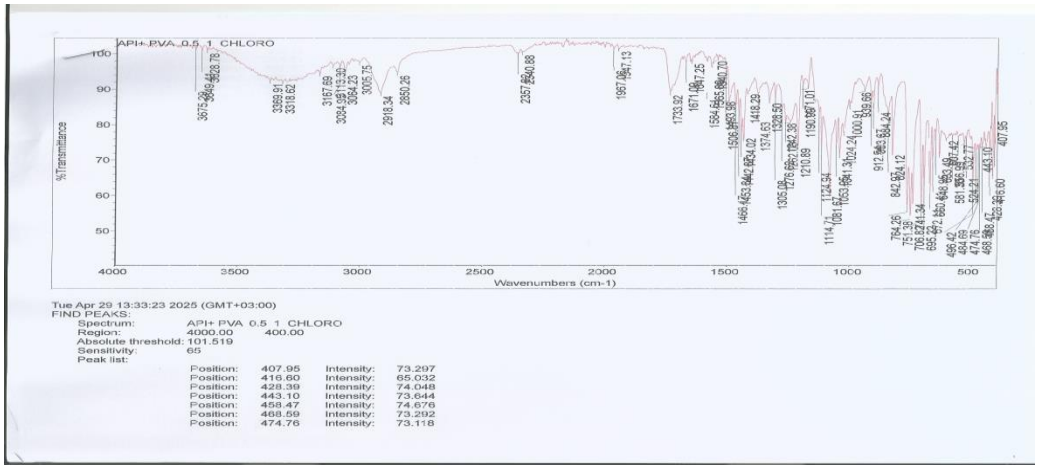
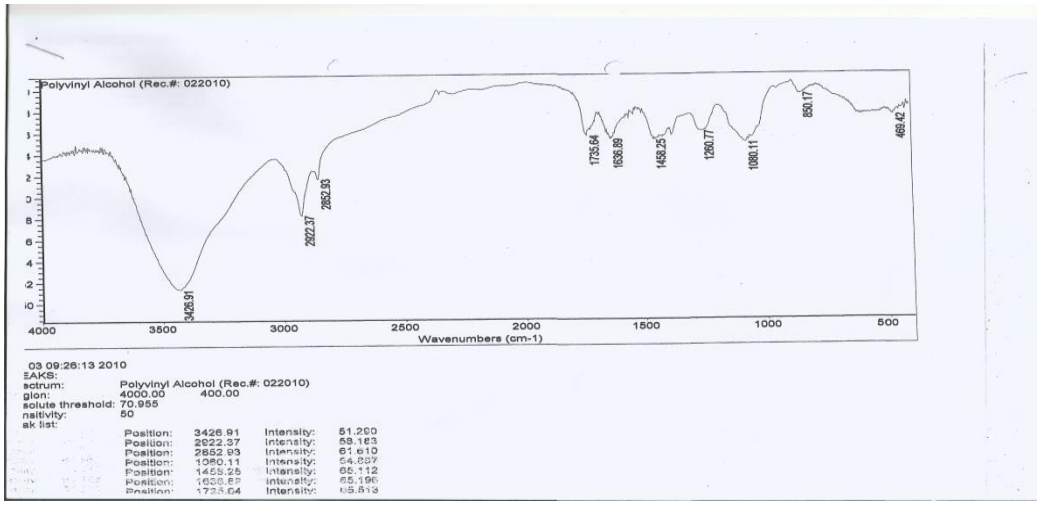


31- FTIR of PVA



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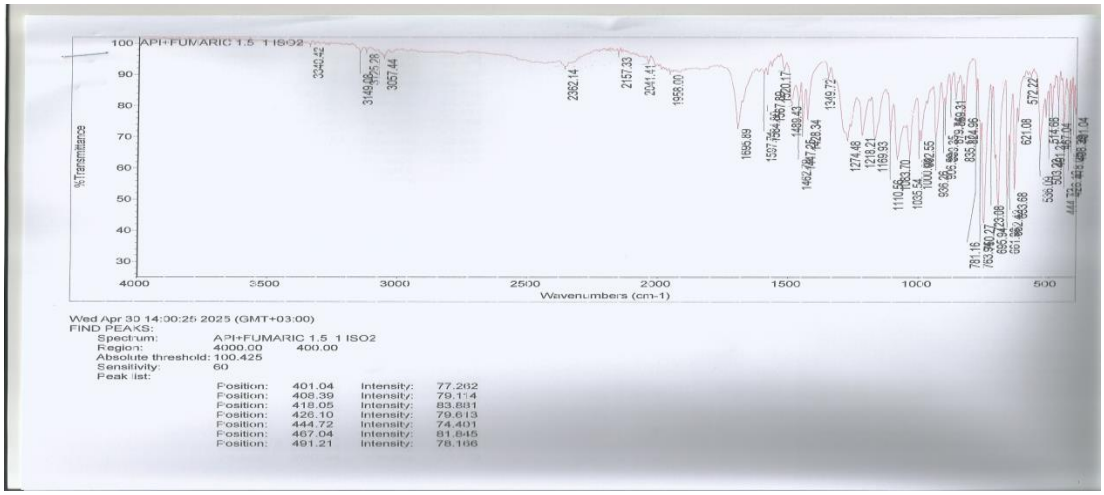

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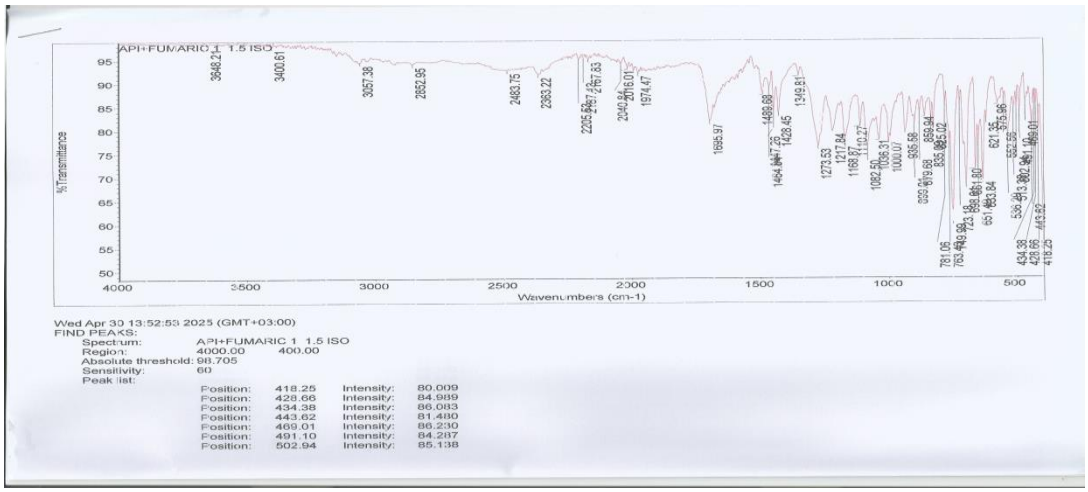

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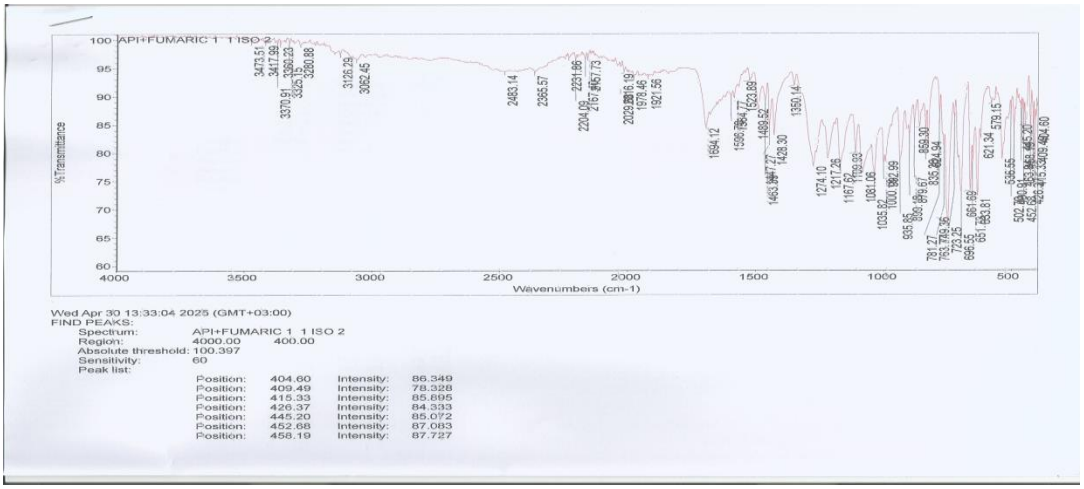

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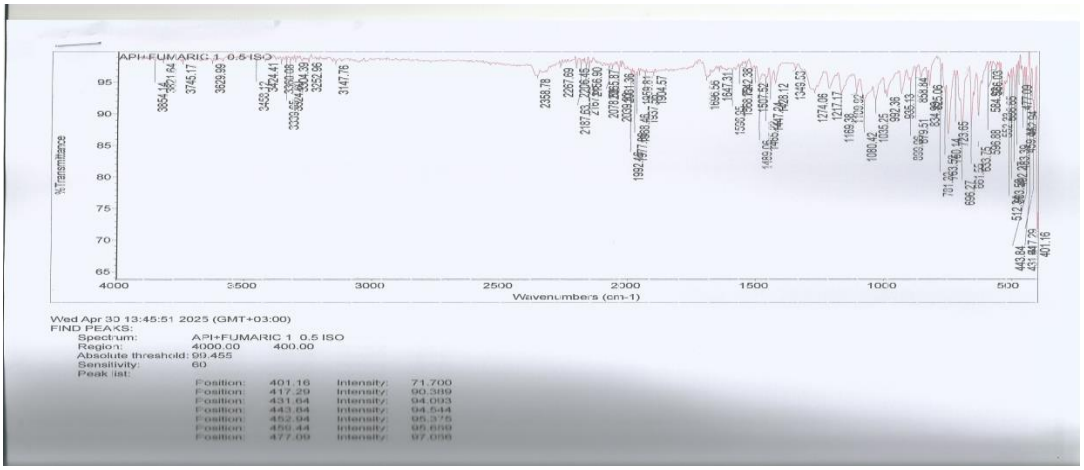

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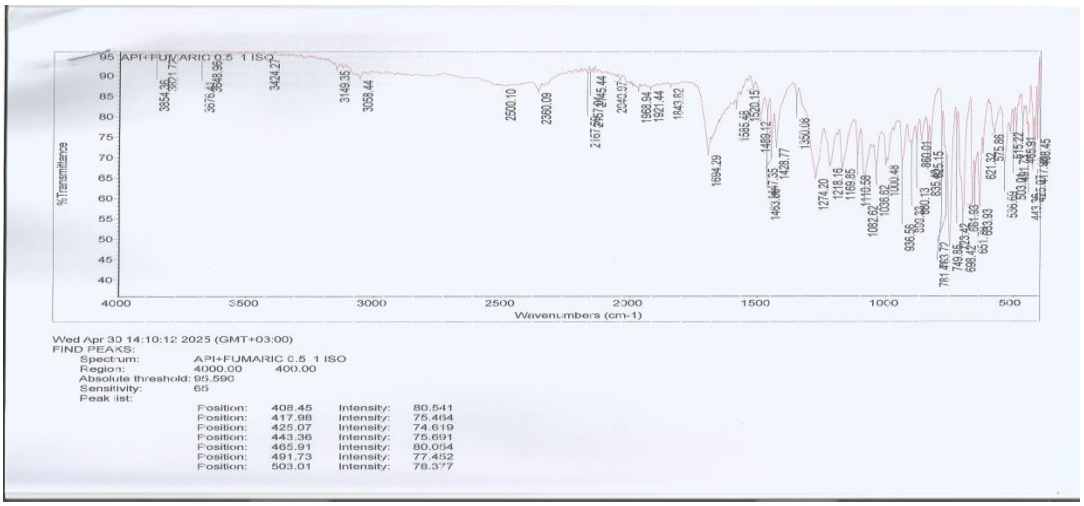

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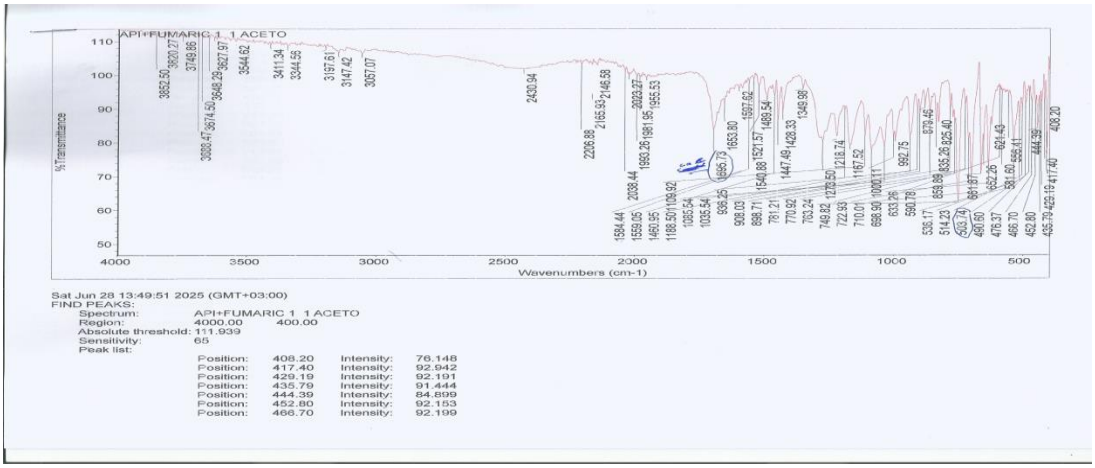
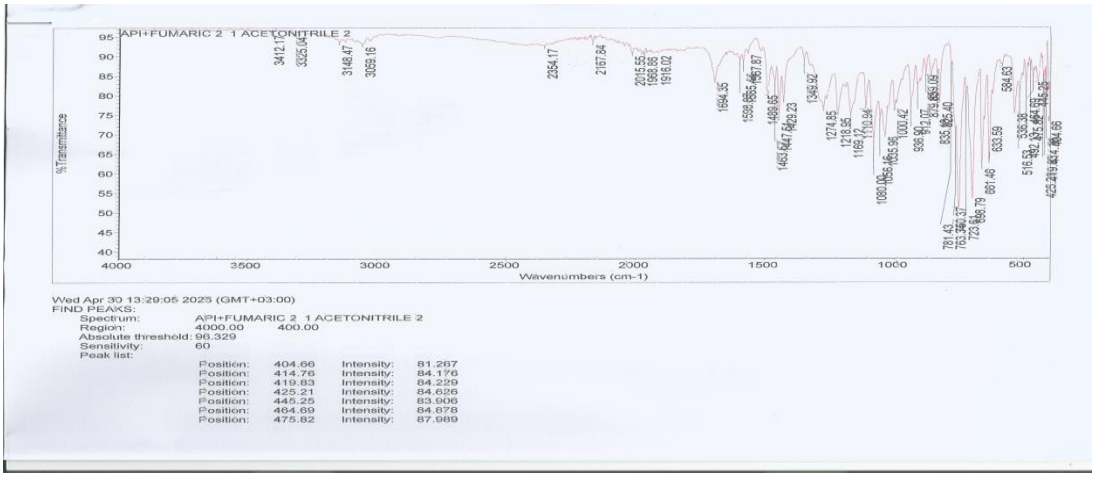
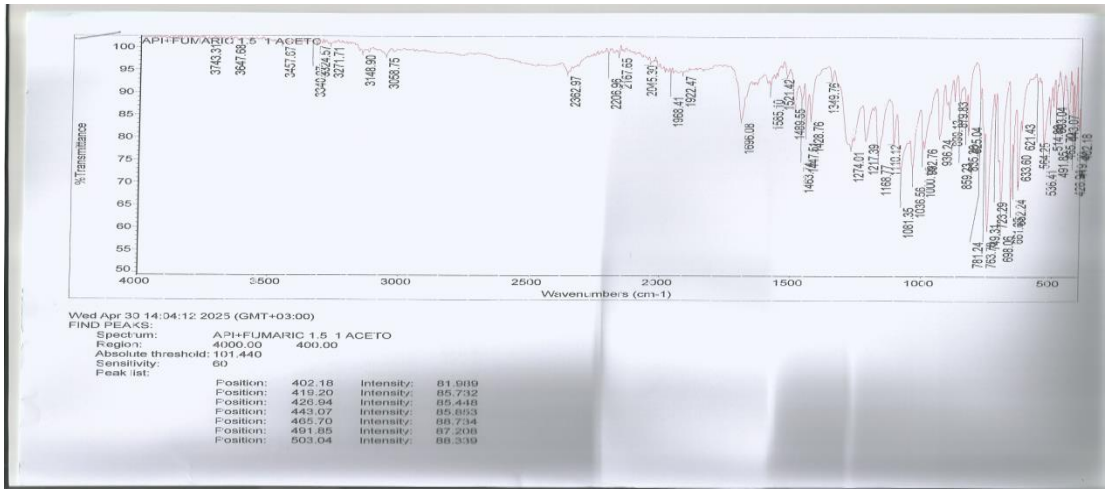


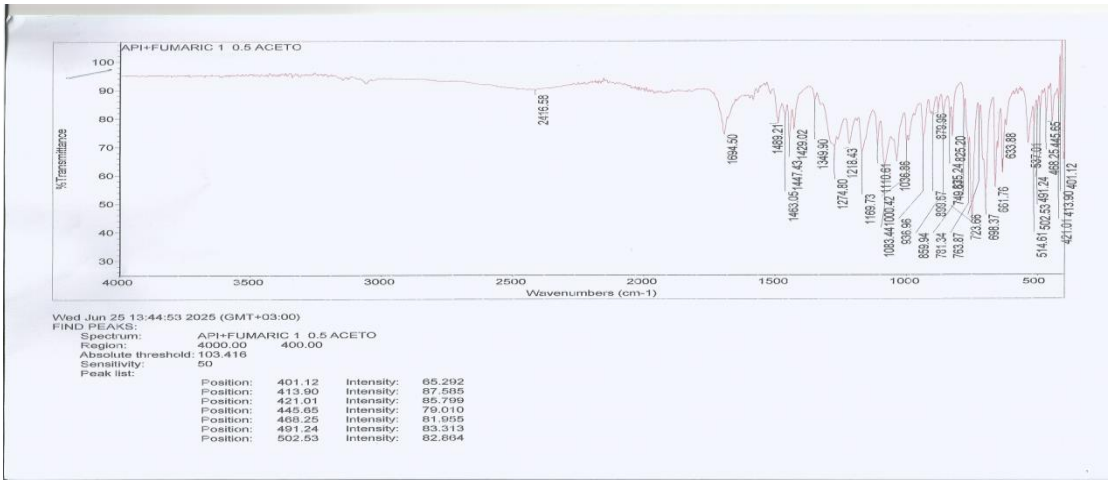
38-FTIR of Formula #13



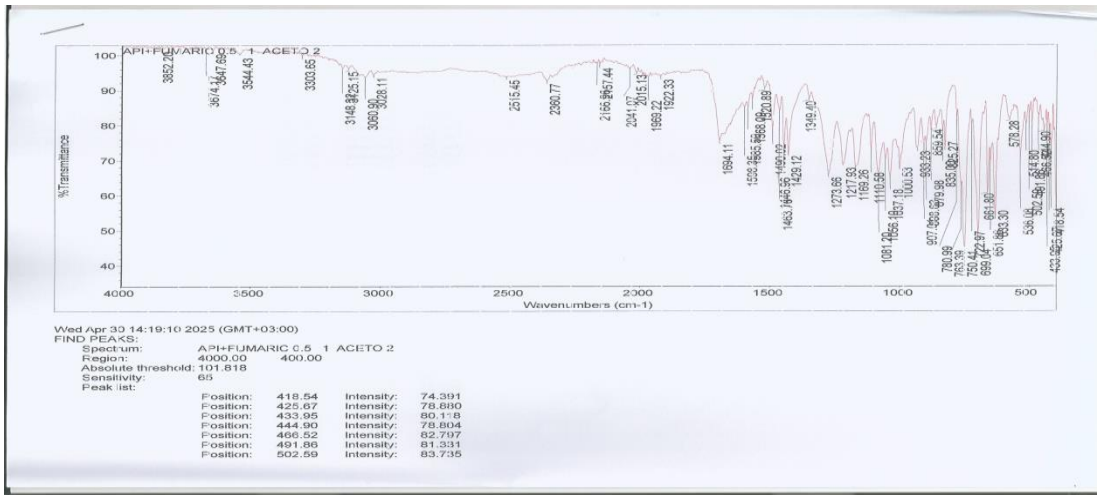
39-FTIR of Formula #11



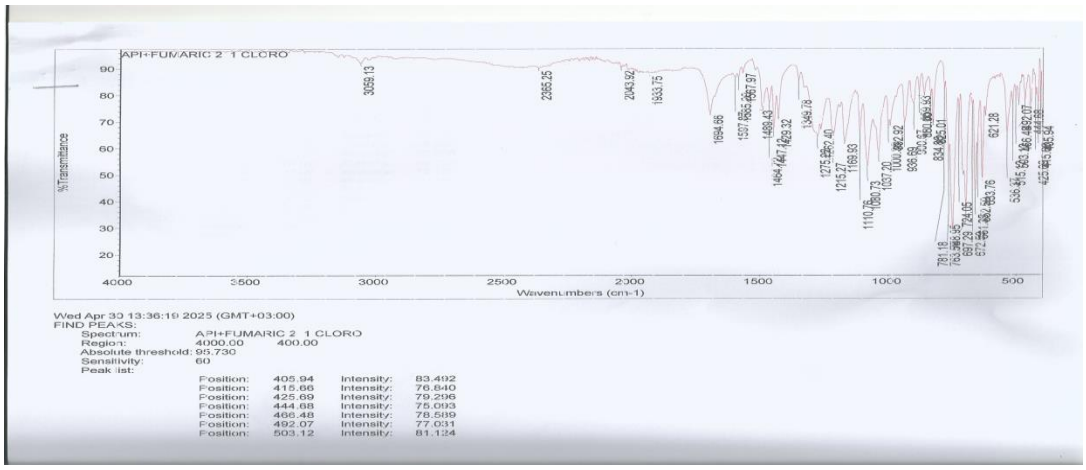
40-FTIR of Formula #9



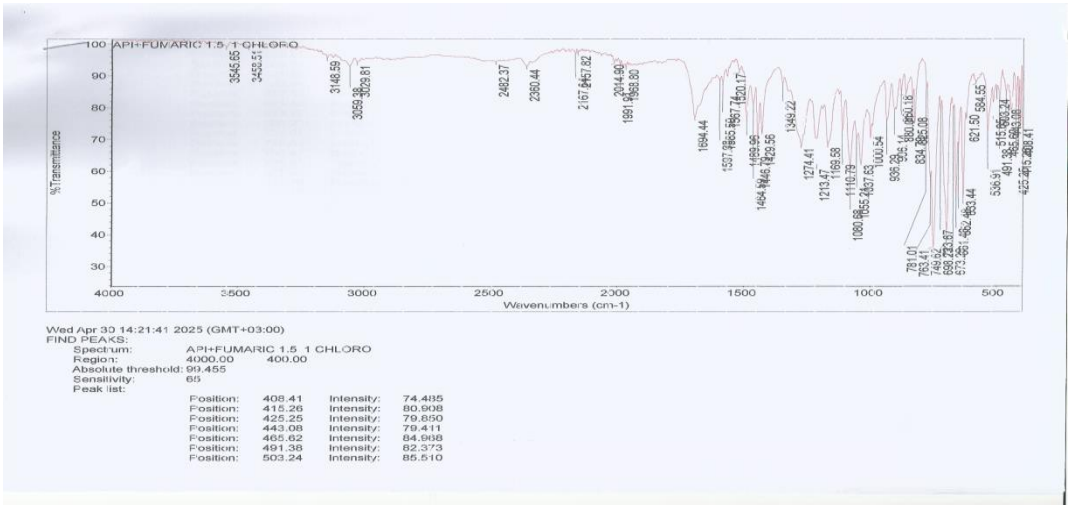
41-FTIR of Formula #8



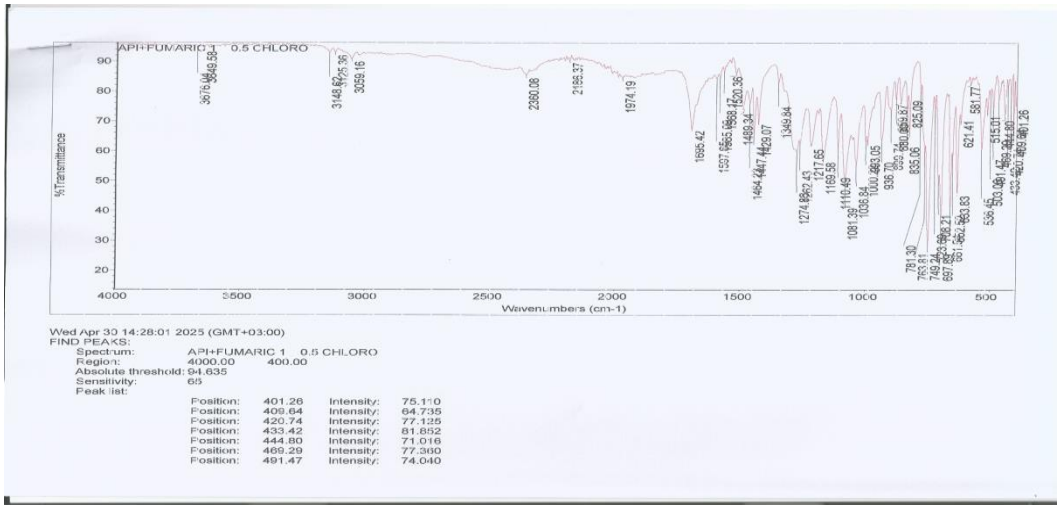
42-FTIR of Formula #20



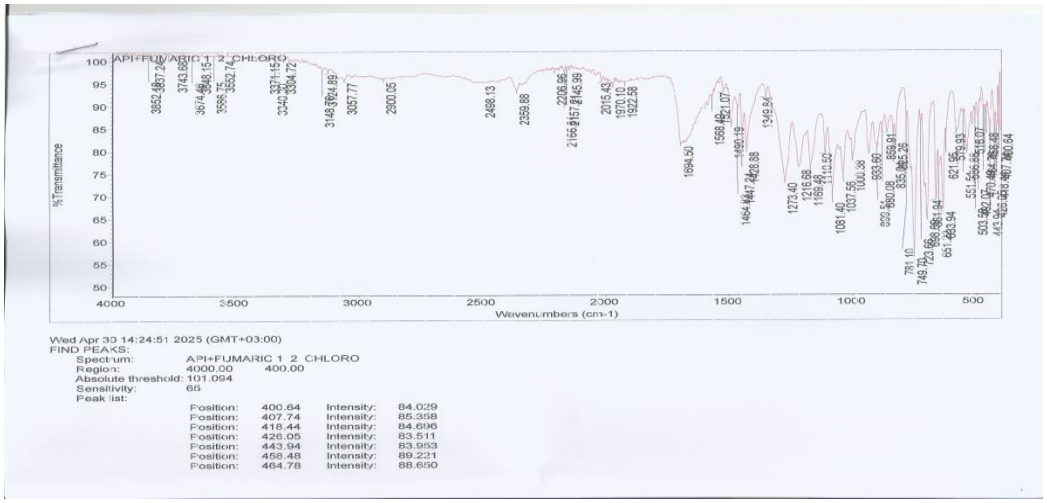
43-FTIR of Formula #18



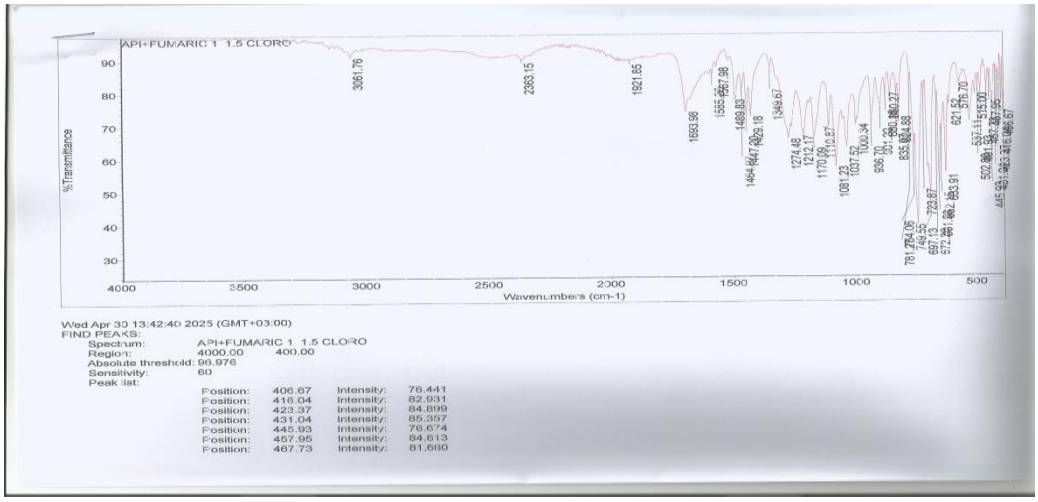
44-FTIR of Formula #16



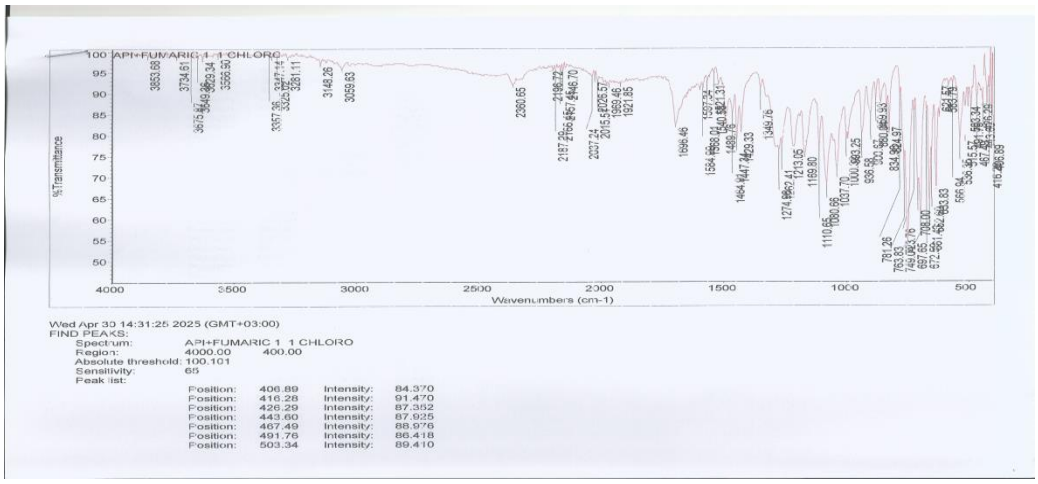
45-FTIR of Formula #21



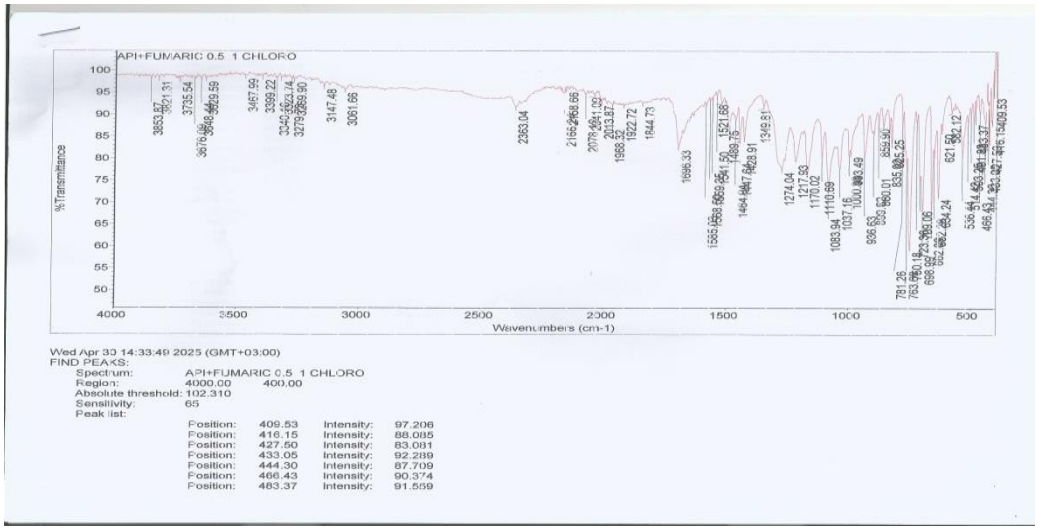
46-FTIR of Formula #19



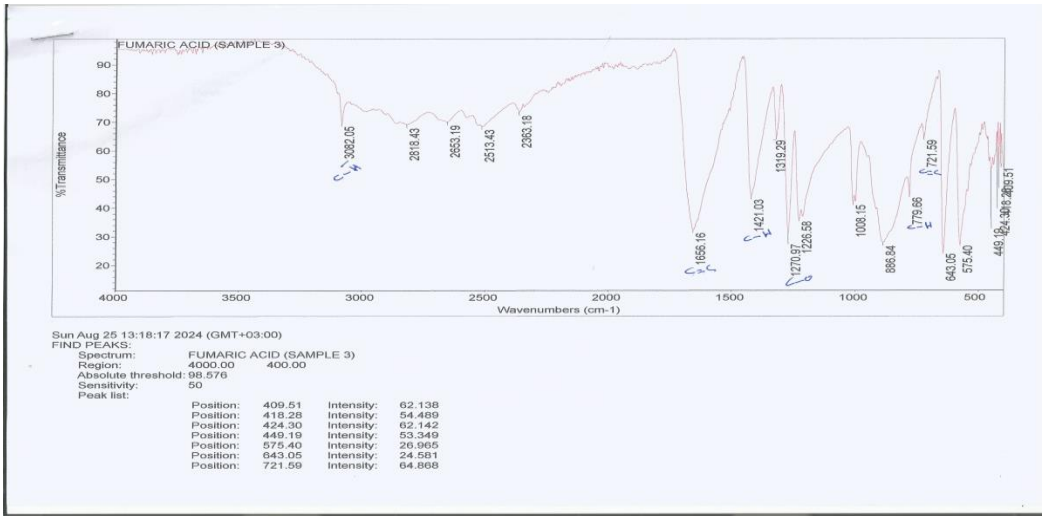
47-FTIR of Formula #17



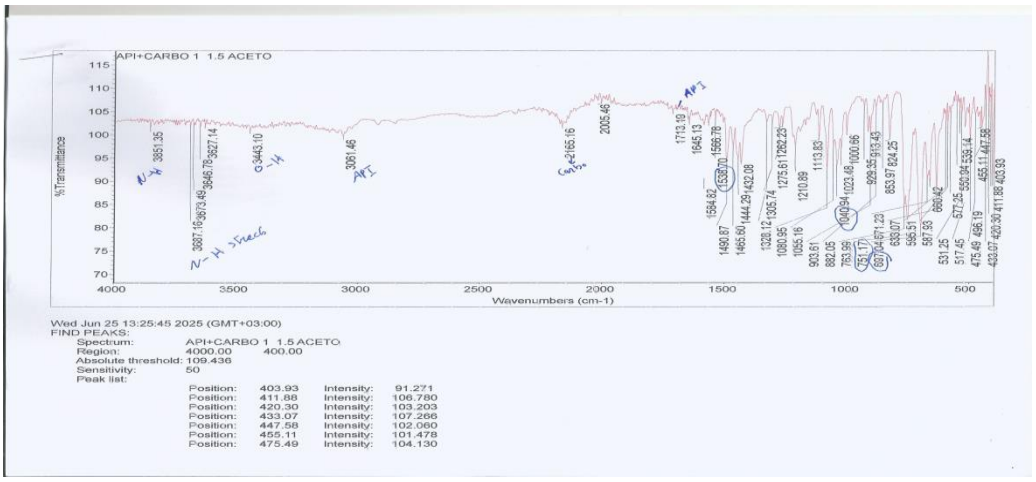
48-FTIR of Formula #15



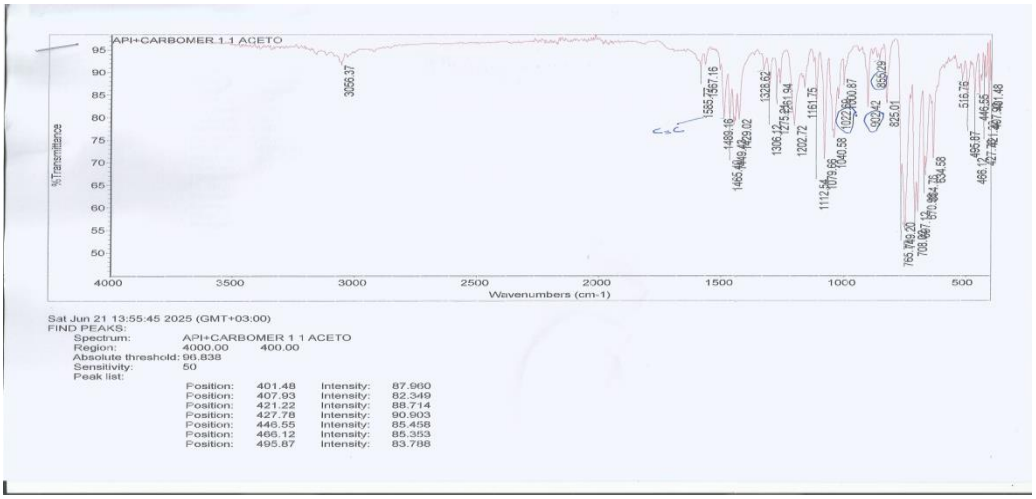
49-FTIR of Fumaric acid



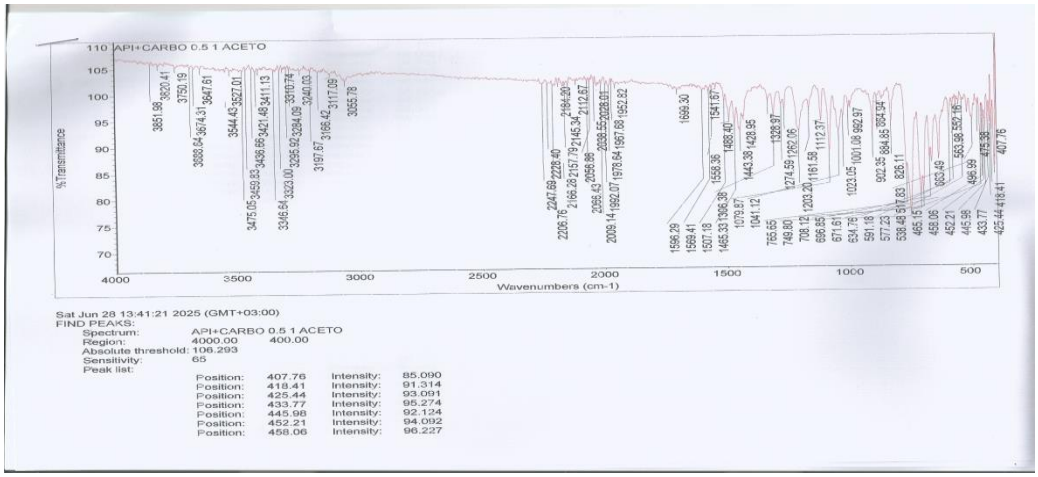
50-FTIR of Formula #75



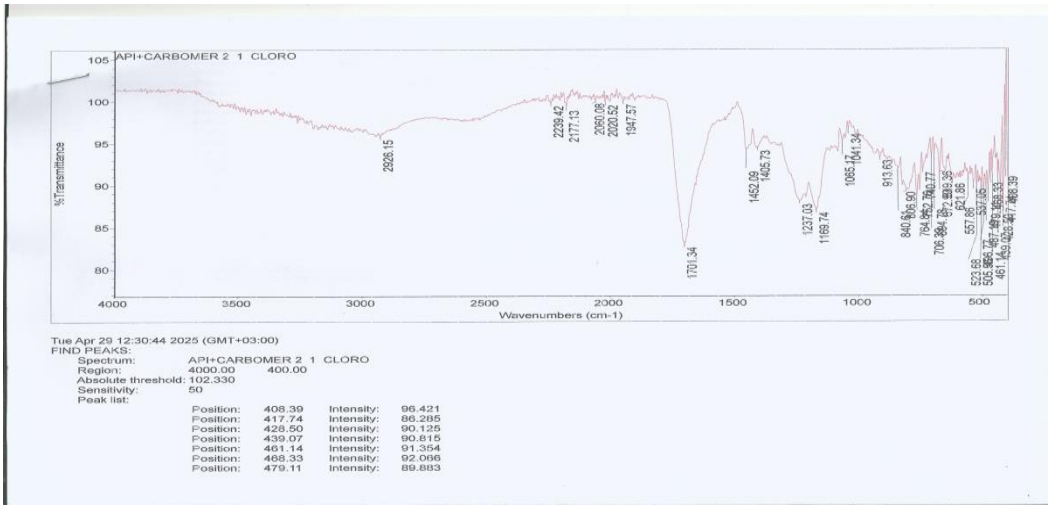
51-FTIR of Formula #73



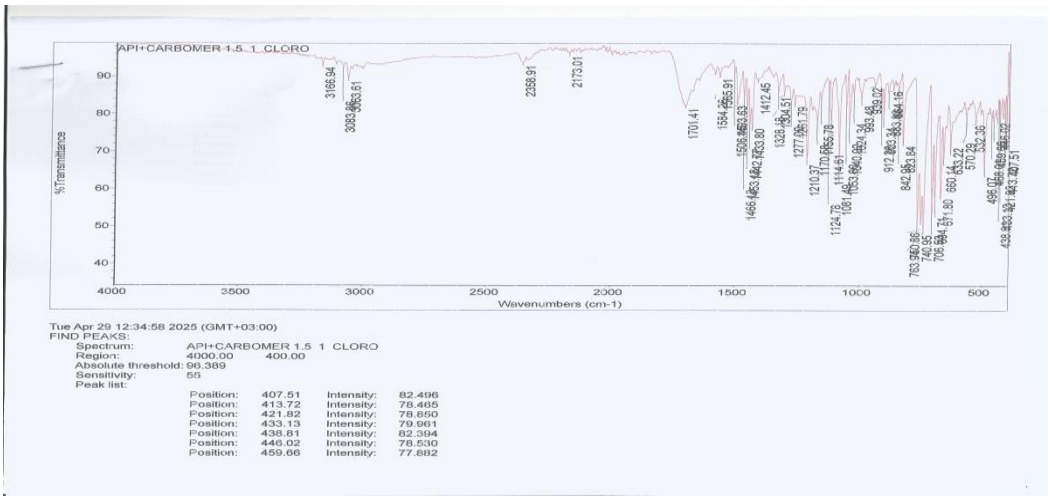
52-FTIR of Formula #71



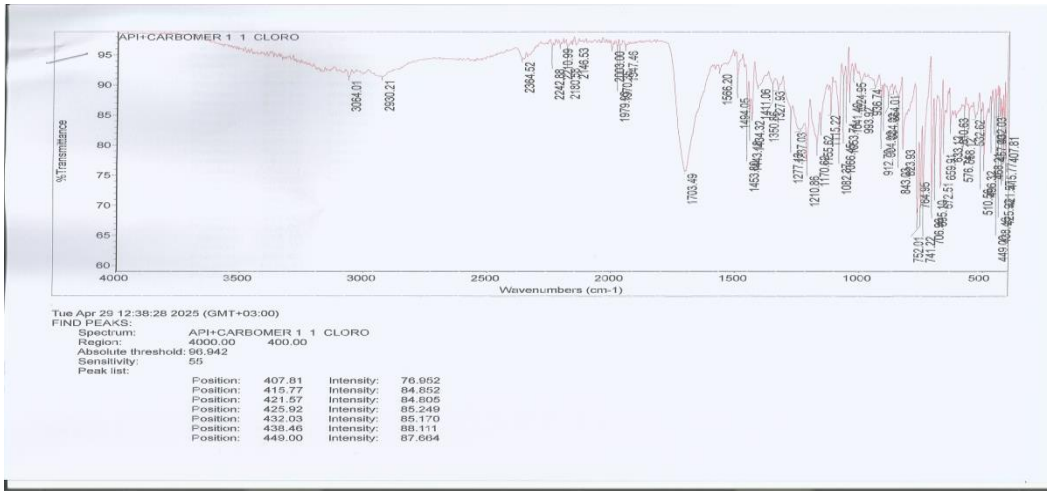
53-FTIR of Formula #83



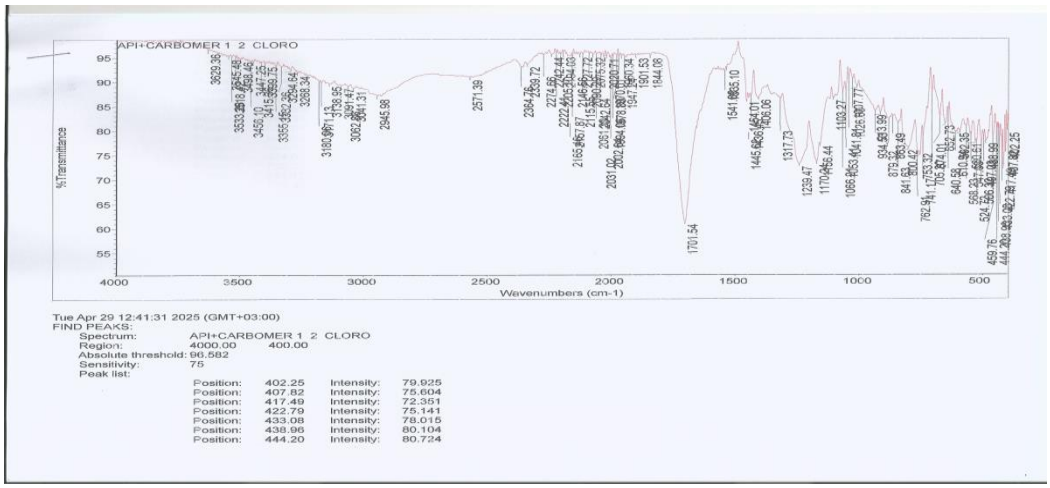
54-FTIR of Formula #81



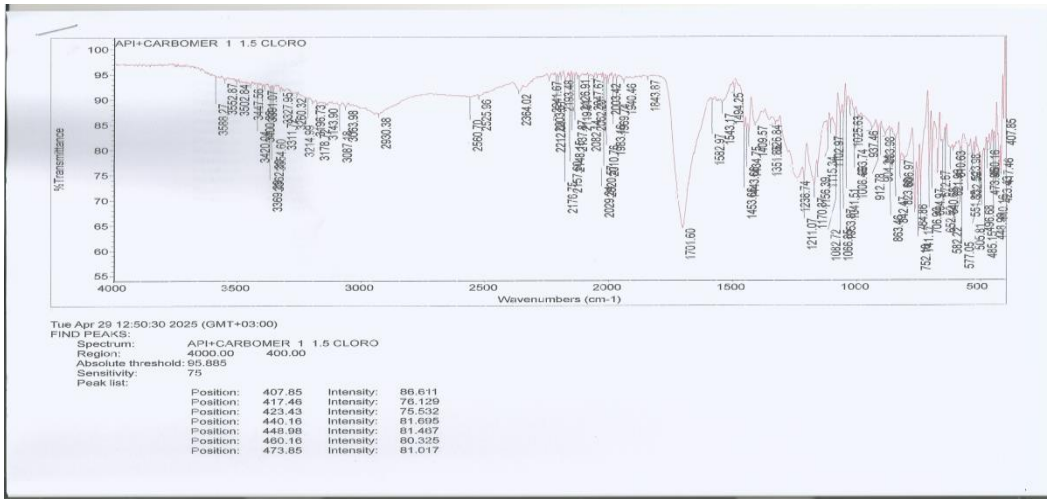
55-FTIR of Formula #80



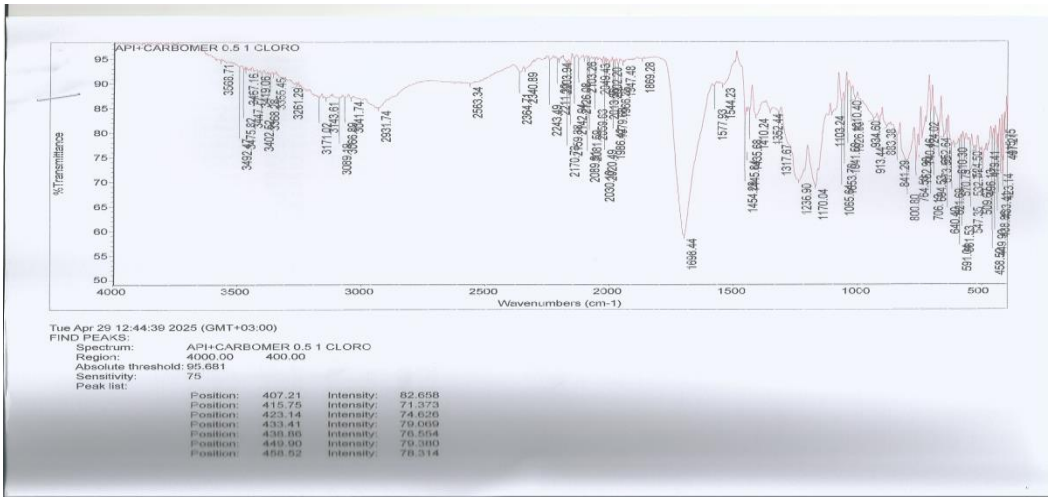
56-FTIR of Formula #84



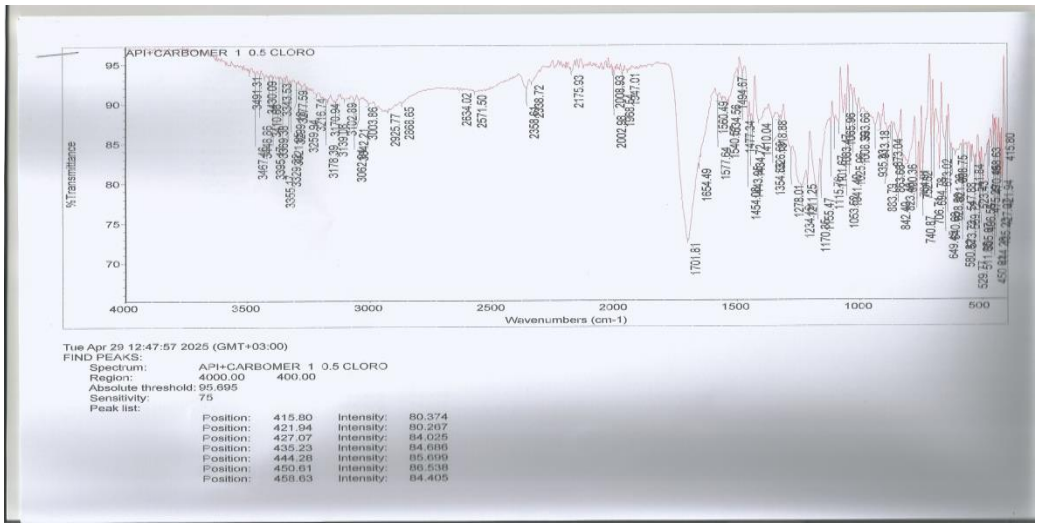
57-FTIR of Formula #82



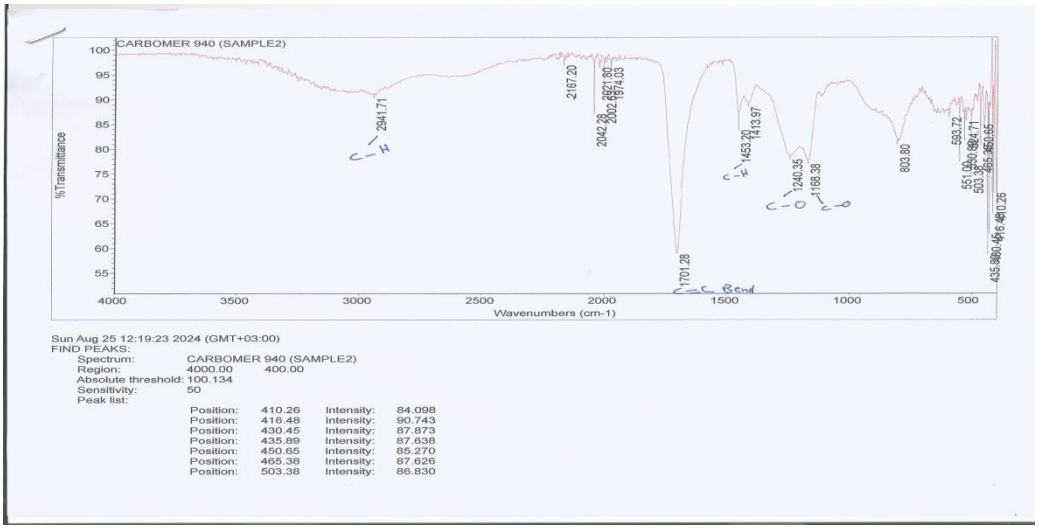
58-FTIR of Formula #78



59-FTIR of Formula #79

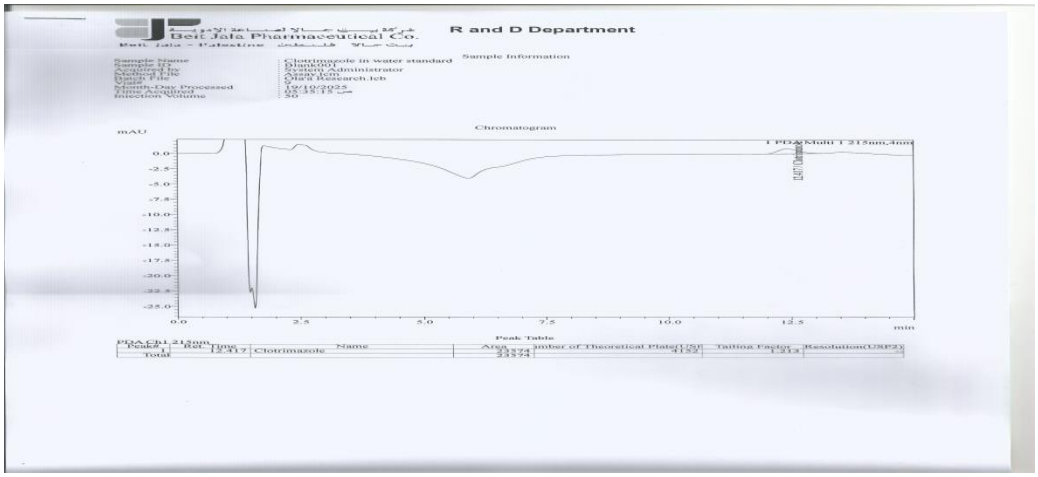


60- FTIR of Carbomer 940

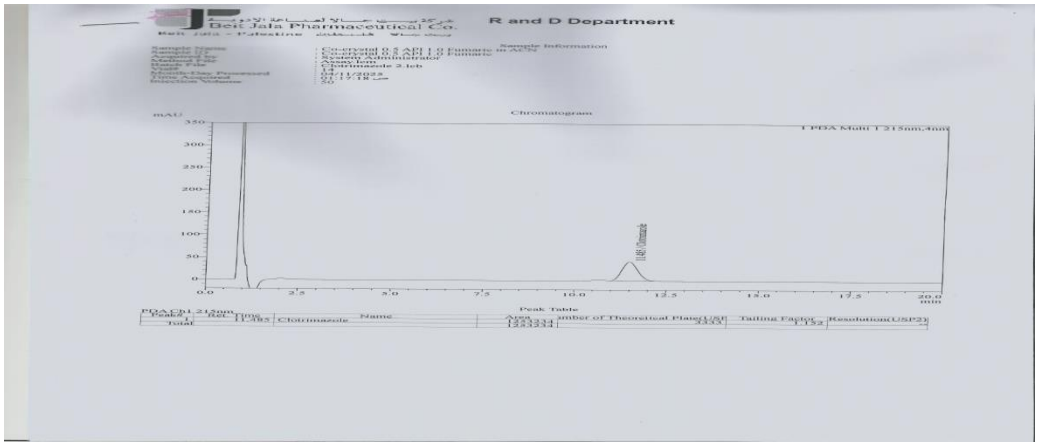


Appendix 3: HPLC results of Co-crystal solubility in water for formulas in table 9

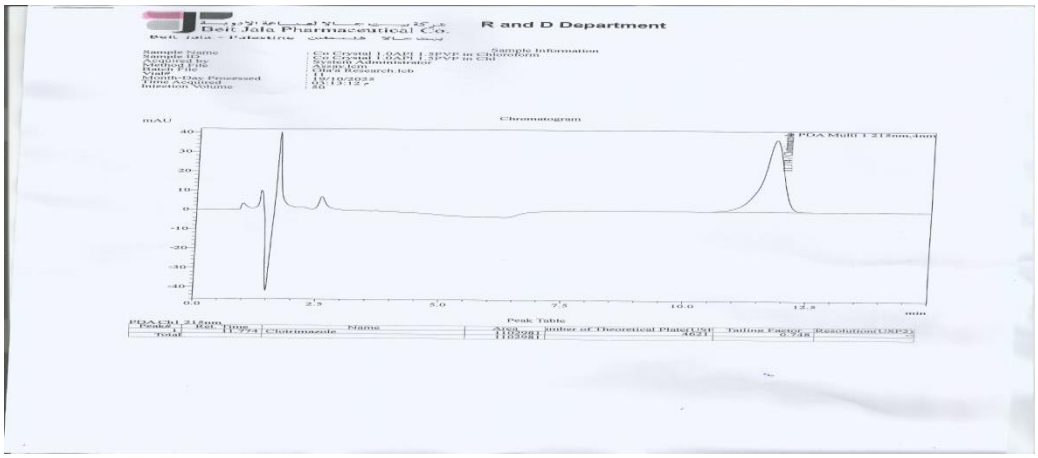
Clotrimazole in water



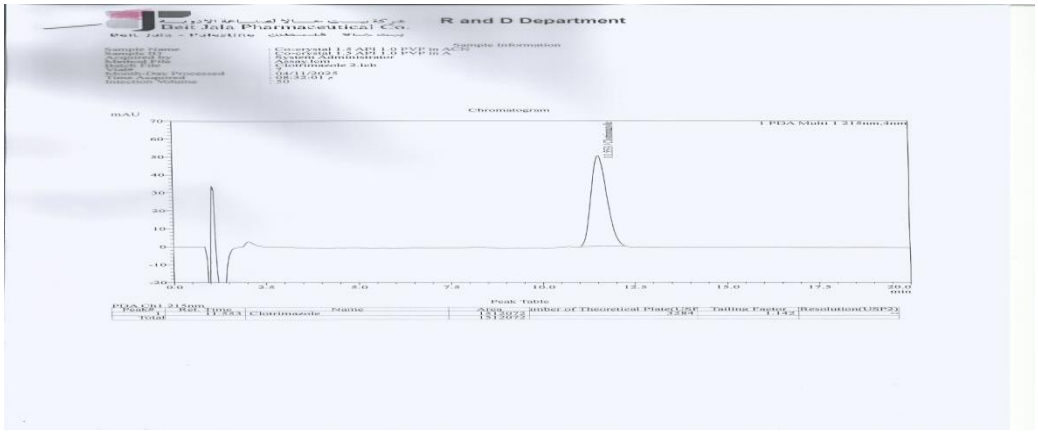
Formula #8



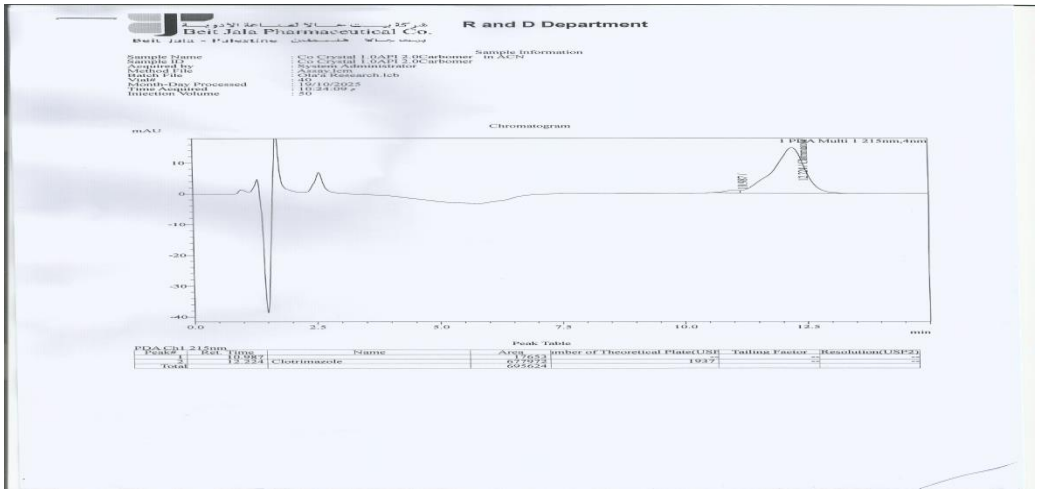
Formula #40



Formula # 32



Formula # 77



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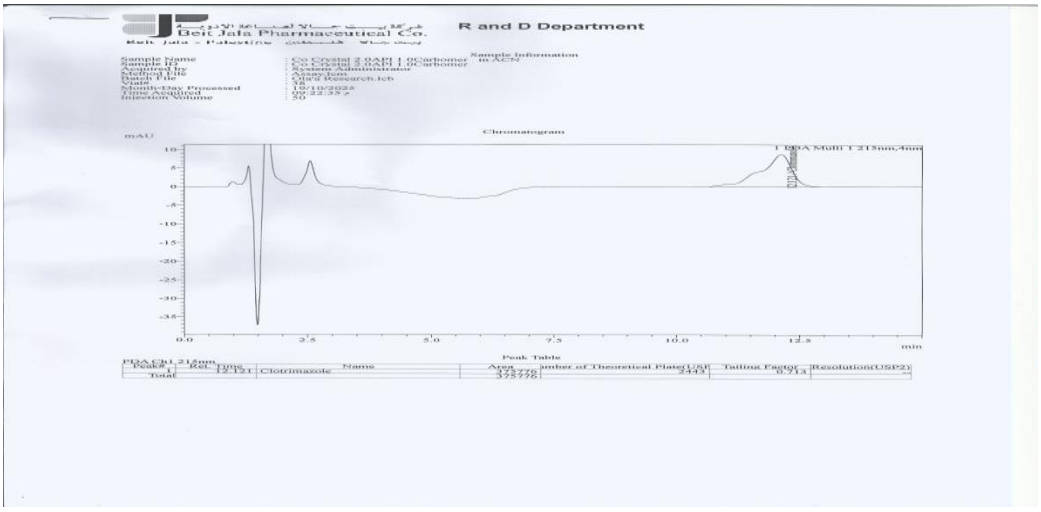
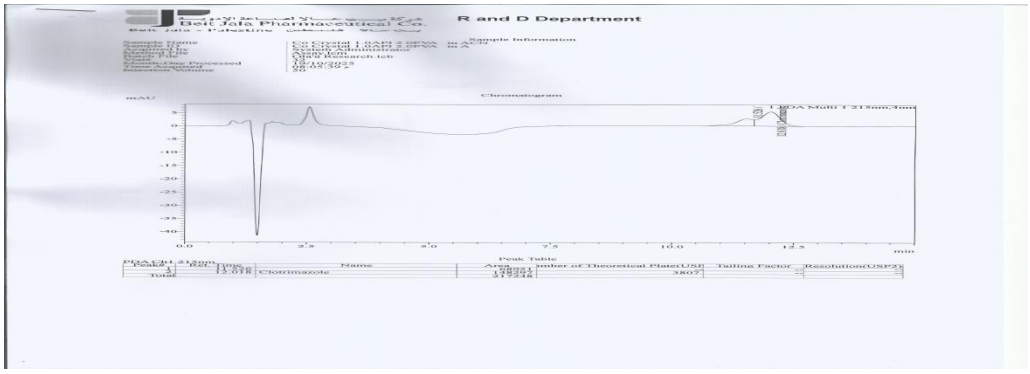
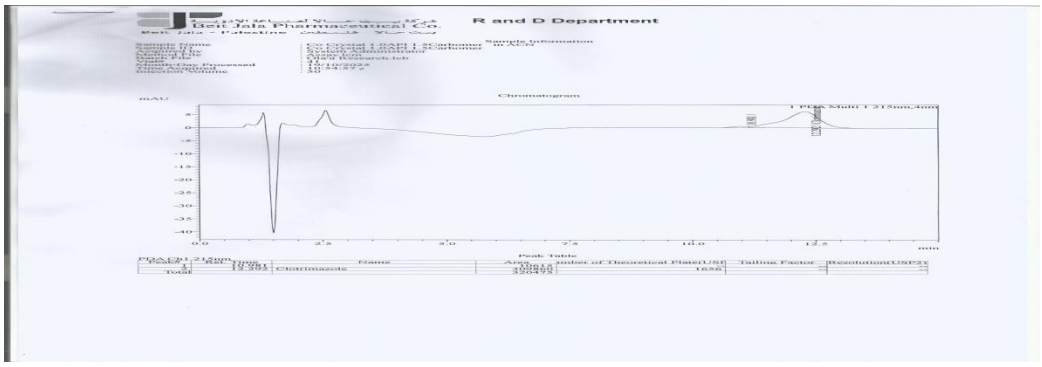


Formula # 56



Formula # 75



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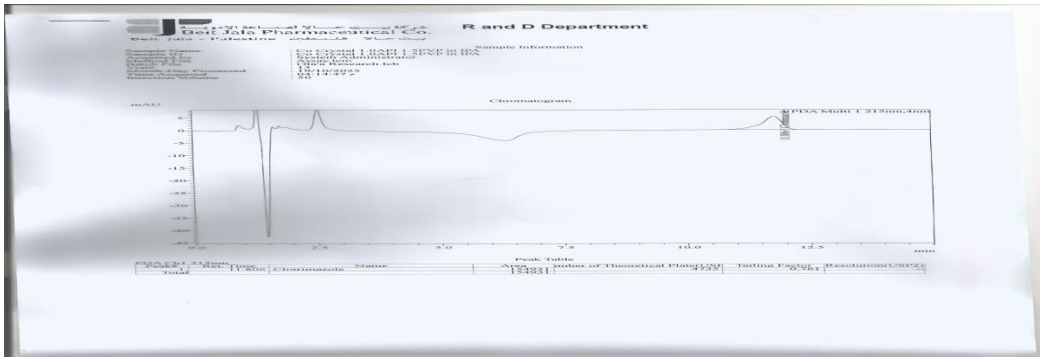
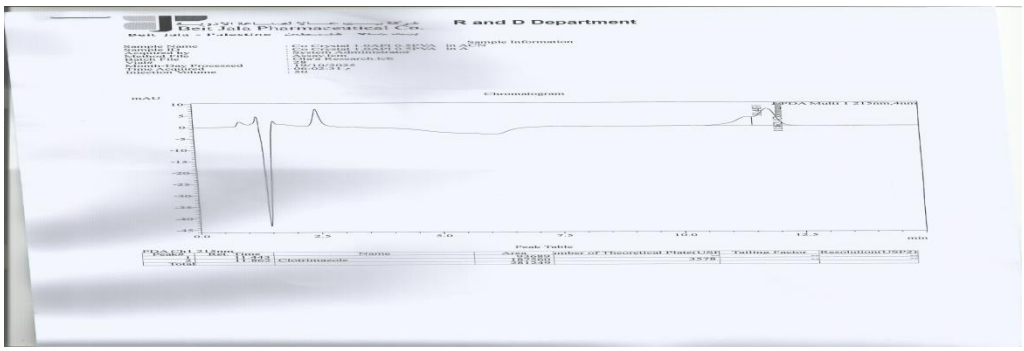
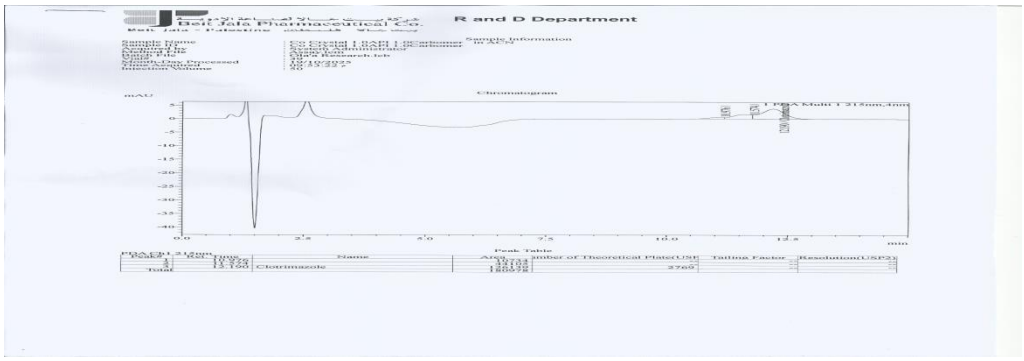


Formula # 10

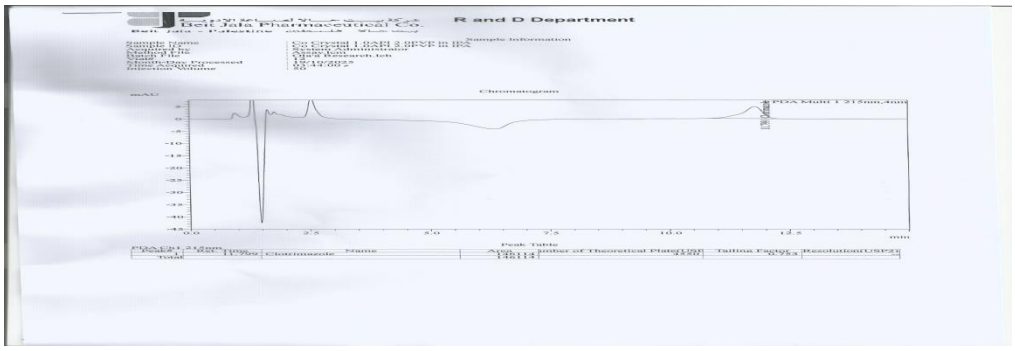
Formula # 51



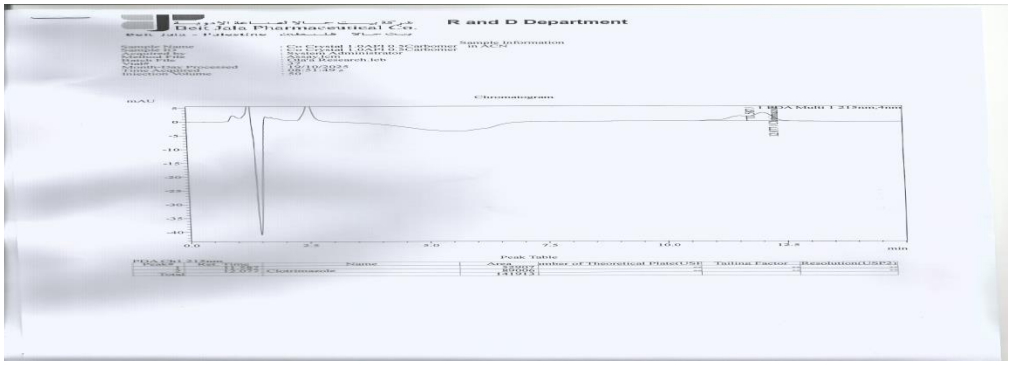
Formula # 73



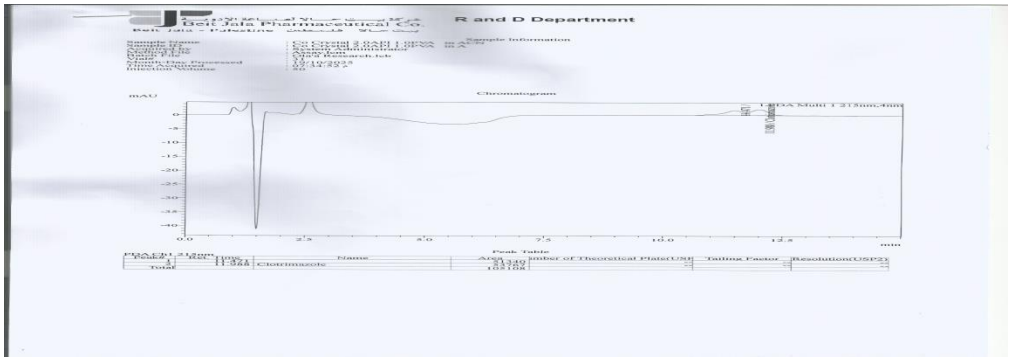
Formula # 28



Formula # 78



Formula # 25



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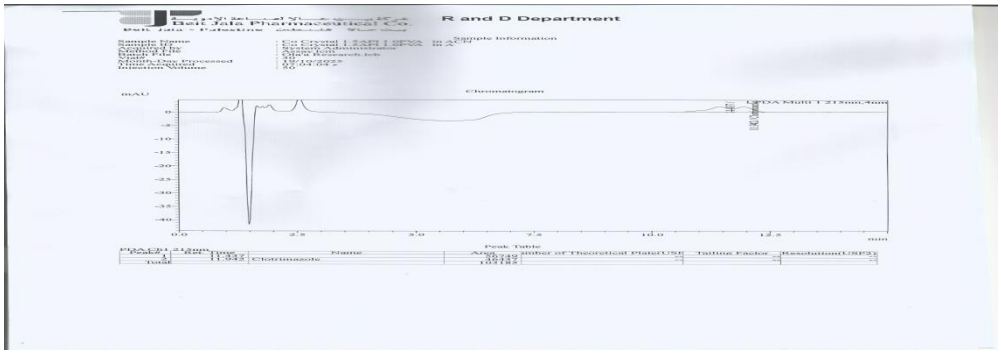
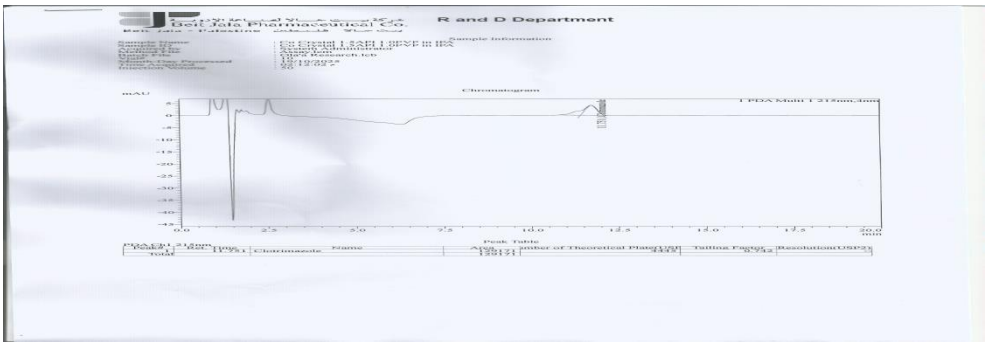
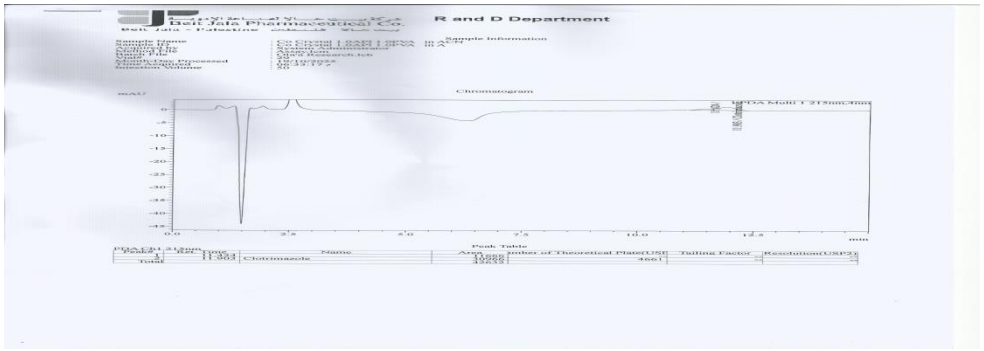


Formula # 53

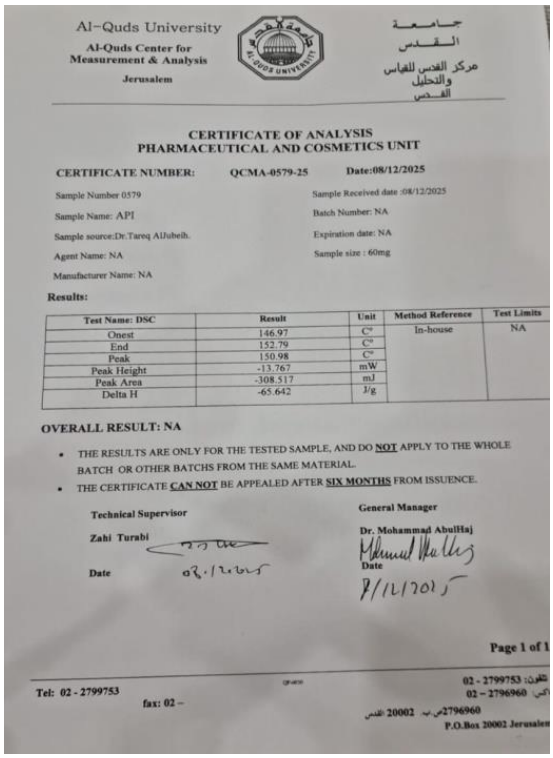


Formula # 52



Appendix 4 :DSC co-crystals melting point results

API



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0579-25 **Date:08/12/2025**

Sample Number 0579
Sample Received date :08/12/2025
Sample Name: API
Batch Number: NA
Sample source:Dr.Tareq AlJubeih.
Expiration date: NA
Agent Name: NA
Sample size : 60mg
Manufacturer Name: NA

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onest	146.97	C°	In-house	NA
End	152.79	C°		
Peak	150.98	C°		
Peak Height	-13.767	mW		
Peak Area	-308.517	mJ		
Delta H	-65.642	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO **NOT** APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE **CAN NOT** BE APPEALED AFTER **SIX MONTHS** FROM ISSUENCE.

Technical Supervisor Zahi Turabi — Date 02.12.2025

General Manager Dr. Mohammad AbuHaj — Date 8/12/2025

Page 1 of 1

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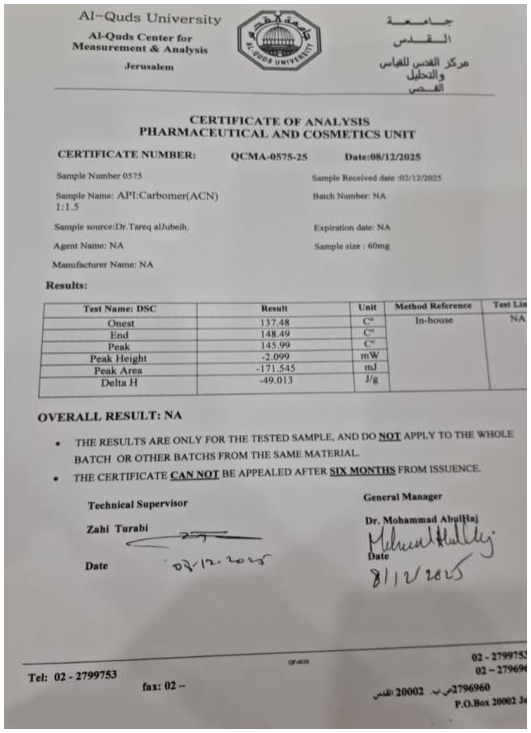
02 – 2796960 فاكس
P.O.Box 20002 Jerusalem ص.ب 20002 القدس

Formula 75



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القدس

CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0575-25 **Date:08/12/2025**

Sample Number 0575
Sample Received date :02/12/2025
Sample Name: API:Carbomer(ACN) 1:1.5
Batch Number: NA
Sample source:Dr.Tareq alJubeih.
Expiration date: NA
Agent Name: NA
Sample size : 60mg
Manufacturer Name: NA

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Lim
Onest	137.48	C°	In-house	NA
End	148.49	C°		
Peak	145.99	C°		
Peak Height	-2.099	mW		
Peak Area	-171.545	mJ		
Delta H	-49.013	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO **NOT** APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE **CAN NOT** BE APPEALED AFTER **SIX MONTHS** FROM ISSUENCE.

Technical Supervisor Zahi Turabi — Date 02.12.2025

General Manager Dr. Mohammad AbuHaj — Date 8/12/2025

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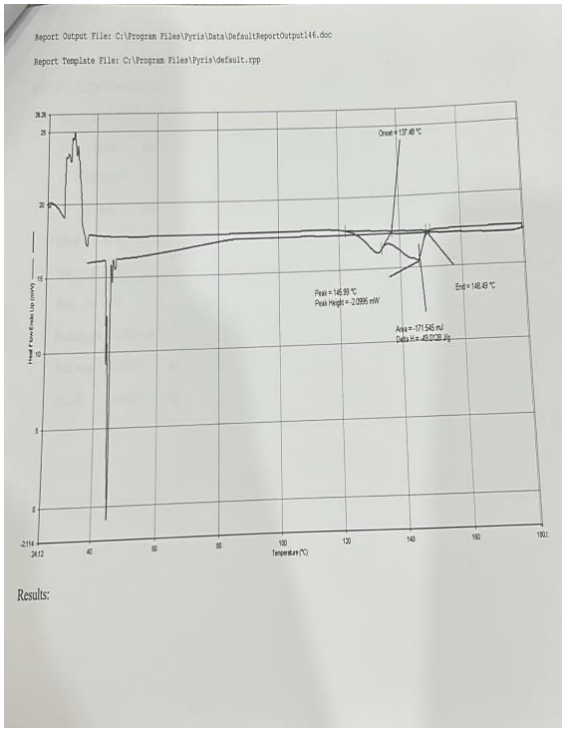
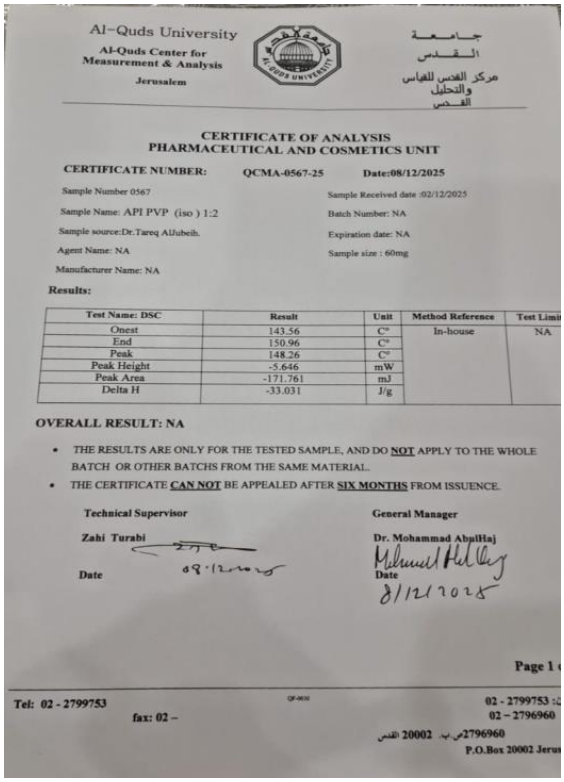


Formula 28



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0567-25 Date:08/12/2025

Sample Number 0567
Sample Name: API PVP (iso) 1:2
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA
Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limi
Onest	143.56	C°	In-house	NA
End	150.96	C°		
Peak	148.26	C°		
Peak Height	-5.646	mW		
Peak Area	-171.761	mJ		
Delta H	-33.031	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

Technical Supervisor: Zahi Turabi — Date: 09/12/2025
General Manager: Dr. Mohammad AbuHaj — Date: 8/12/2025

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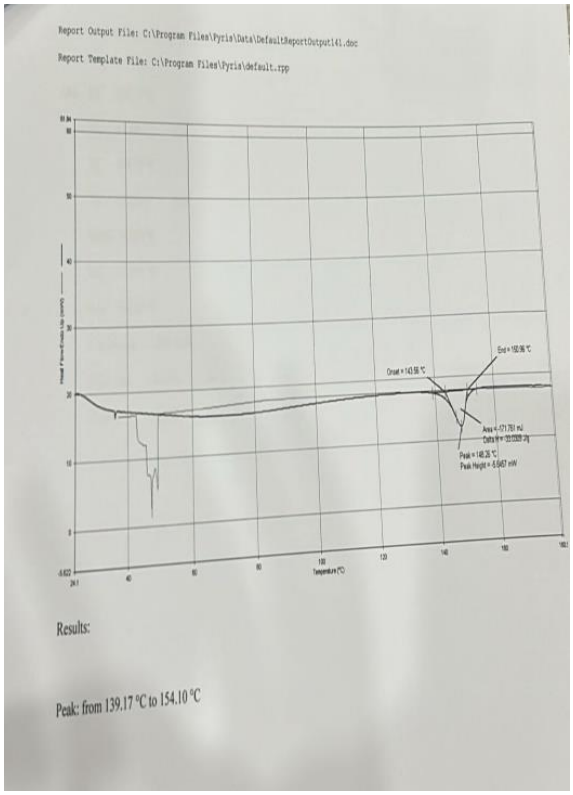


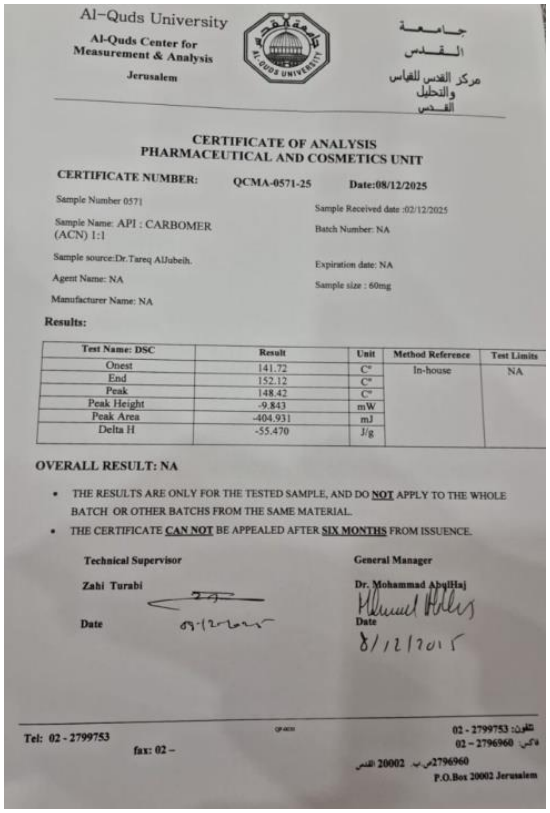
Report Output File: C:\Program Files\Pyris\Data\DefaultReportOutput141.doc
Report Template File: C:\Program Files\Pyris\default.rpp

Onset = 143.56 °C
End = 150.96 °C
Peak = 148.26 °C
Peak Height = -5.647 mW
Area = -171.761 mJ
Delta H = -33.033 J/g
Temperature (°C)

Results:

Peak: from 139.17 °C to 154.10 °C

Formula 73



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CERTIFICATE NUMBER: QCMA-0571-25 Date:08/12/2025

Sample Number 0571
Sample Name: API : CARBOMER (ACN) 1:1
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA
Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onest	141.72	C°	In-house	NA
End	152.12	C°		
Peak	148.42	C°		
Peak Height	-9.843	mW		
Peak Area	-404.931	mJ		
Delta H	-55.470	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

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General Manager: Dr. Mohammad AbuHaj — Date: 8/12/2025

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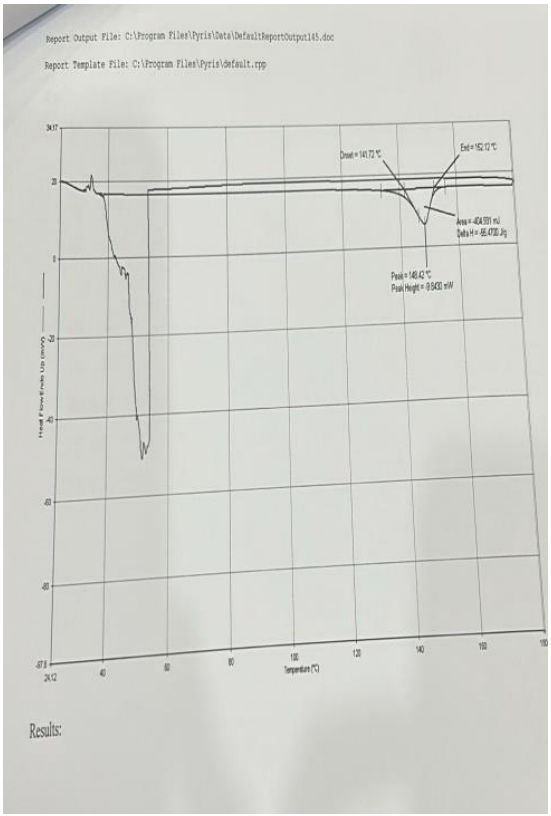
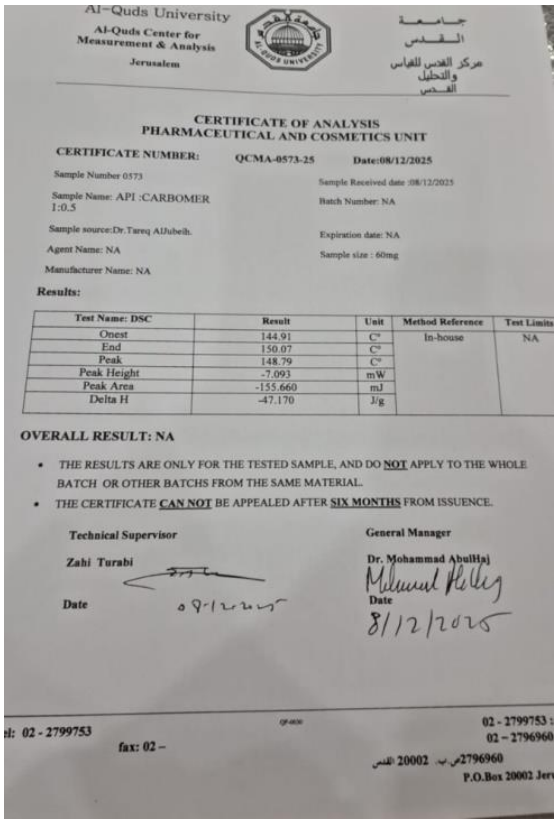


Report Output File: C:\Program Files\Pyris\Data\DefaultReportOutput145.doc
Report Template File: C:\Program Files\Pyris\default.rpp

Onset = 141.72 °C
End = 152.12 °C
Peak = 148.42 °C
Peak Height = -9.8430 mW
Area = -404.931 mJ
Delta H = -55.4700 J/g
Temperature (°C)

Results:

Formula 72



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0573-25 Date:08/12/2025

Sample Number 0573
Sample Name: API :CARBOMER 1:0.5
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA
Sample Received date :08/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onest	144.91	C°	In-house	NA
End	150.07	C°		
Peak	148.79	C°		
Peak Height	-7.093	mW		
Peak Area	-155.660	mJ		
Delta H	-47.170	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

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General Manager: Dr. Mohammad Abulhaj — Date: 8/12/2025

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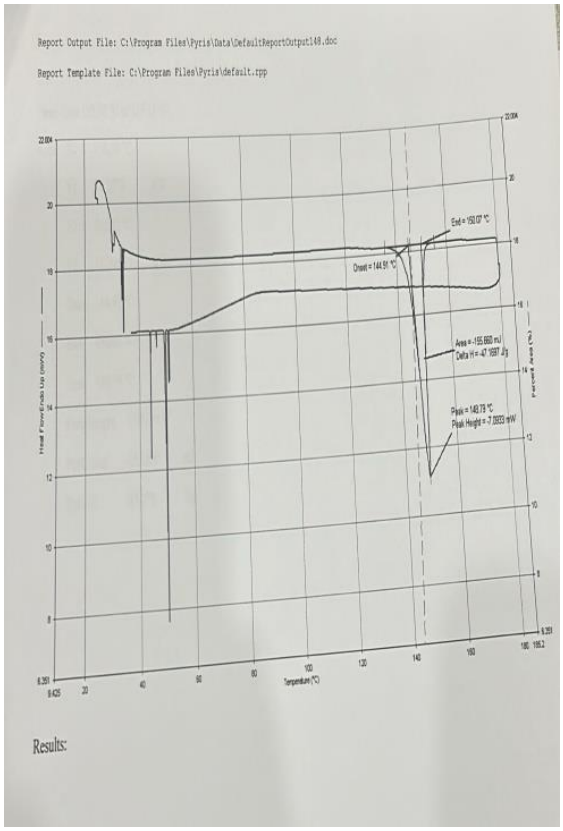
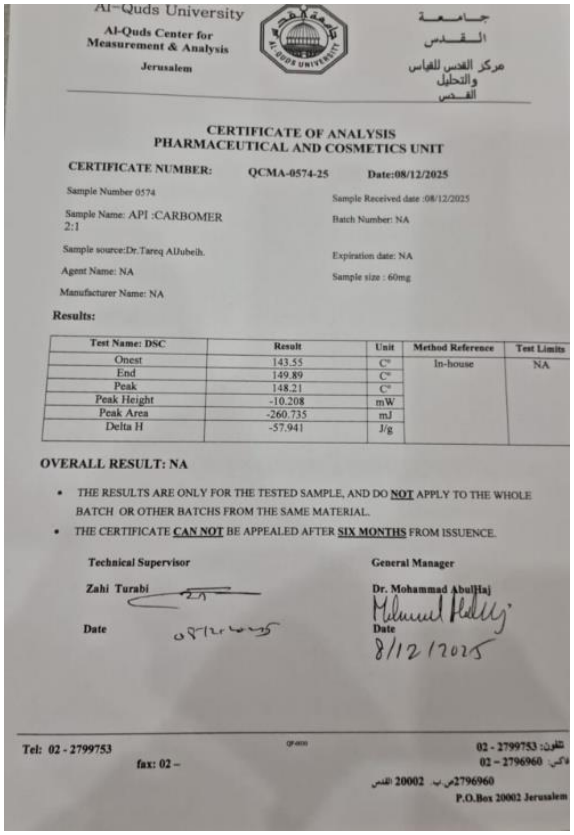


Results:

Formula 76



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0574-25 Date:08/12/2025

Sample Number 0574
Sample Name: API :CARBOMER 2:1
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA
Sample Received date :08/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onest	143.55	C°	In-house	NA
End	149.89	C°		
Peak	148.21	C°		
Peak Height	-10.208	mW		
Peak Area	-260.735	mJ		
Delta H	-57.941	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

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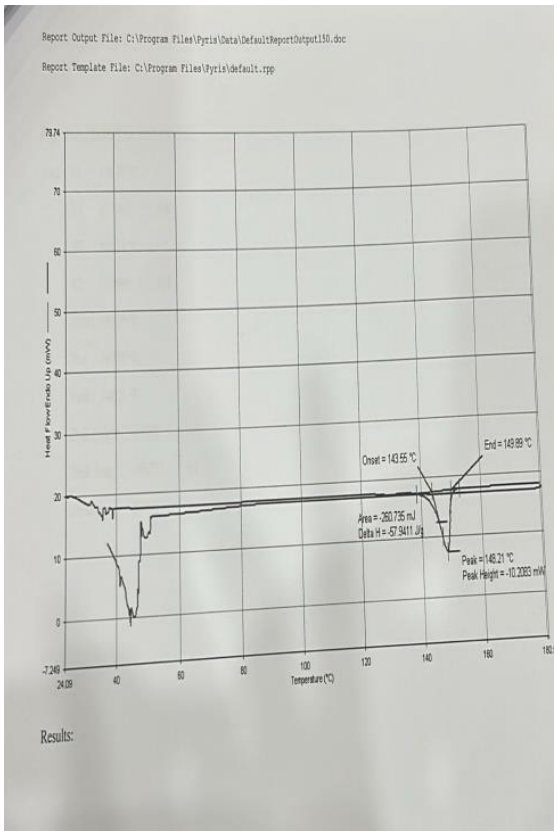
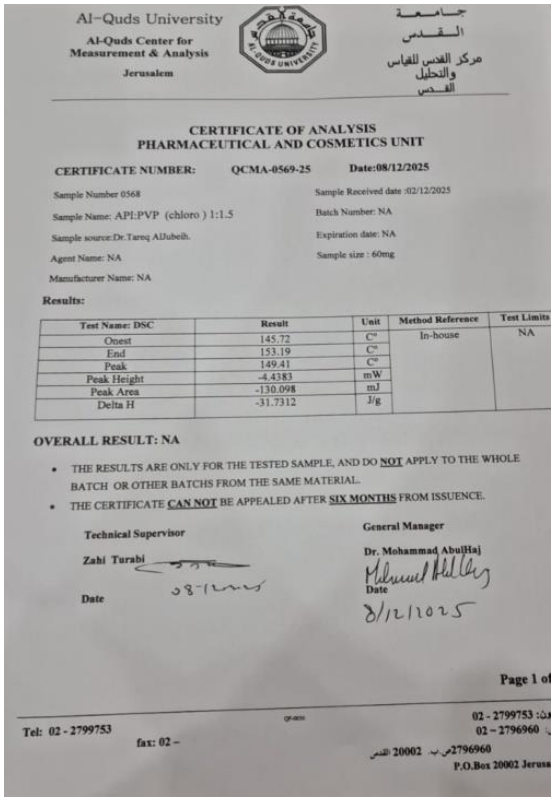


Results:

Formula 40



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0569-25 Date:08/12/2025

Sample Number 0568
Sample Name: API:PVP (chloro) 1:1.5
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA

Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onest	145.72	C°	In-house	NA
End	153.19	C°		
Peak	149.41	C°		
Peak Height	-4.4383	mW		
Peak Area	-130.098	mJ		
Delta H	-31.7312	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

Technical Supervisor
Zahi Turabi
Date 08/12/2025

General Manager
Dr. Mohammad AbulHaj
Date 8/12/2025

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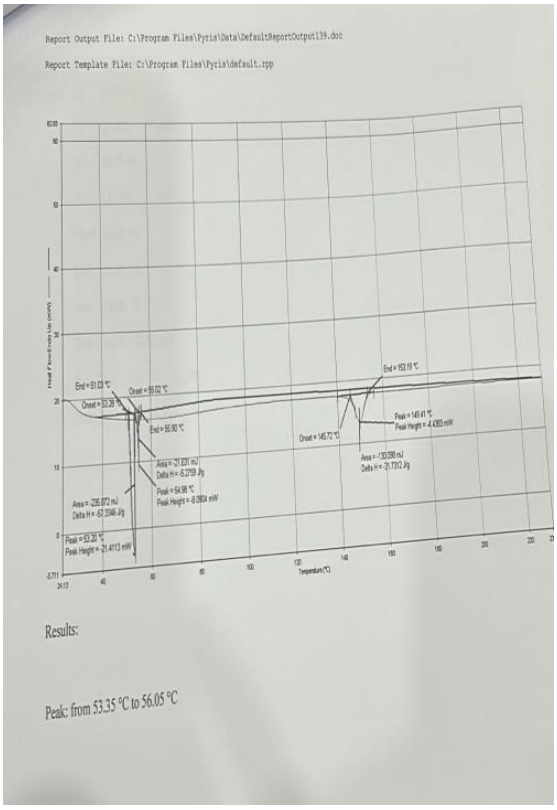
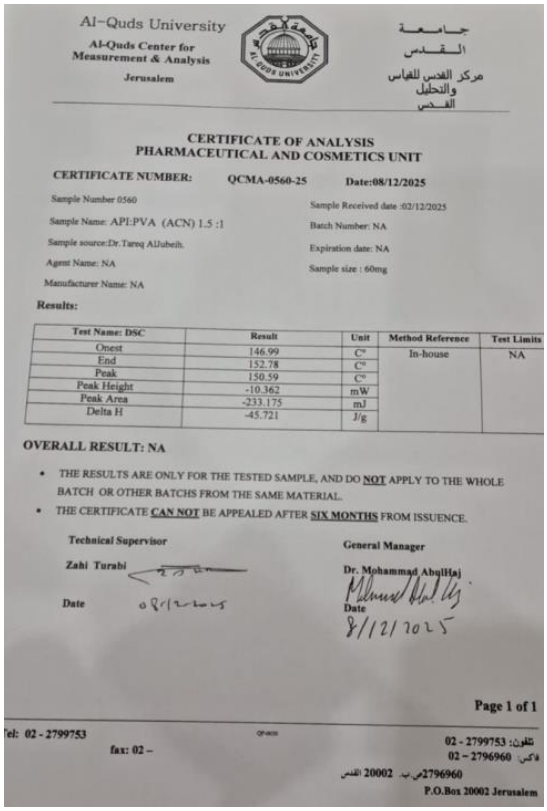


Report Output File: C:\Program Files\Pyris\Data\DefaultReportOutput139.doc
Report Template File: C:\Program Files\Pyris\default.rpp

Results:

Peak: from 53.35 °C to 56.05 °C

Formula 53



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0560-25 Date:08/12/2025

Sample Number 0560
Sample Name: API:PVA (ACN) 1.5 :1
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA

Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onest	146.99	C°	In-house	NA
End	152.78	C°		
Peak	150.59	C°		
Peak Height	-10.362	mW		
Peak Area	-233.175	mJ		
Delta H	-45.721	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

Technical Supervisor
Zahi Turabi
Date 08/12/2025

General Manager
Dr. Mohammad AbulHaj
Date 8/12/2025

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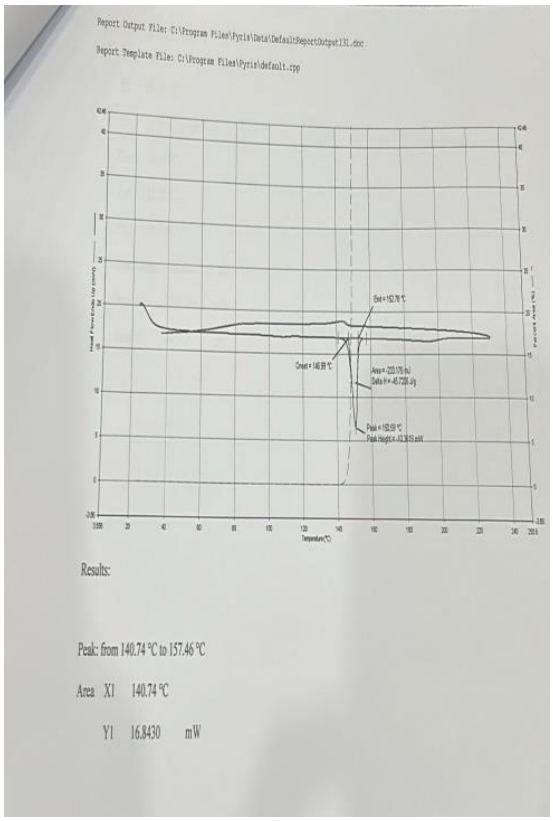


Report Output File: C:\Program Files\Pyris\Data\DefaultReportOutput131.doc
Report Template File: C:\Program Files\Pyris\default.rpp

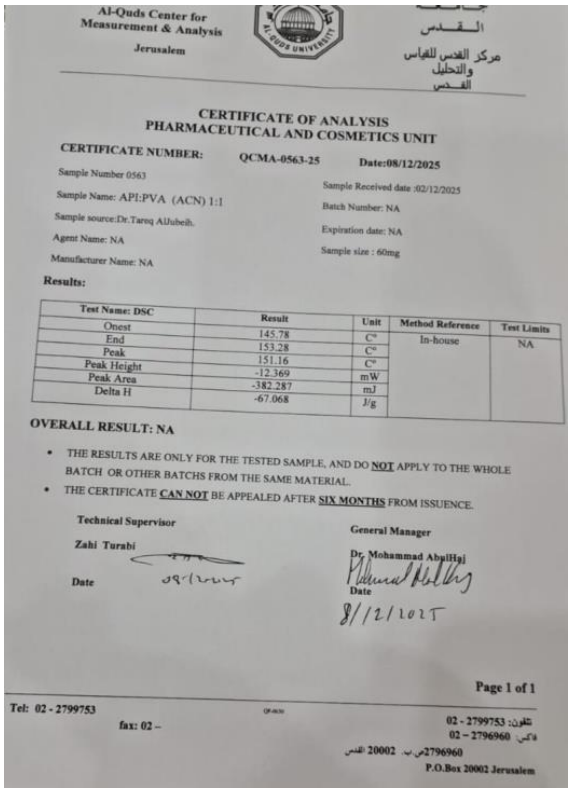
Results:

Peak: from 140.74 °C to 157.46 °C

Area XI 140.74 °C

YI 16.8430 mW

Formula 52



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0563-25 Date:08/12/2025

Sample Number 0563
Sample Name: API:PVA (ACN) 1:1
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA

Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onset	145.78	C°	In-house	NA
End	153.28	C°		
Peak	151.16	C°		
Peak Height	-12.369	mW		
Peak Area	-382.287	mJ		
Delta H	-67.068	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

Technical Supervisor
Zahi Turabi
Date

General Manager
Dr. Mohammad AbuHaj
Date 8/12/2025

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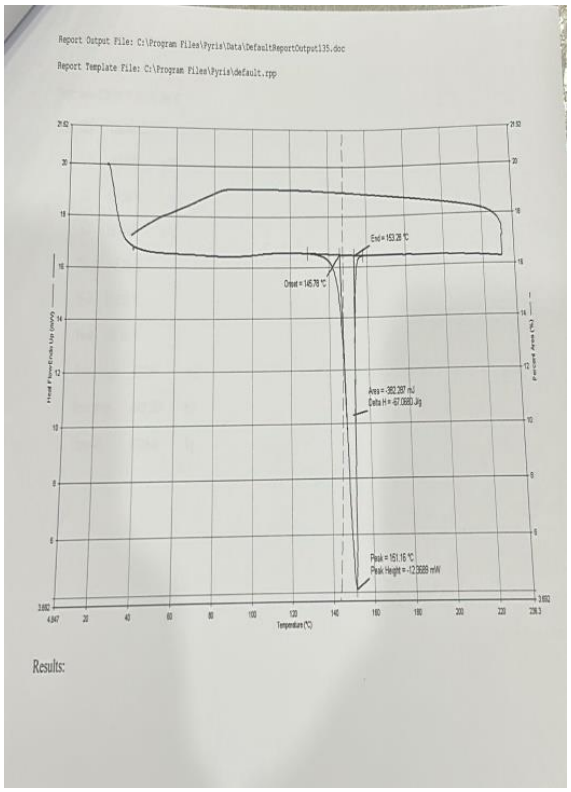
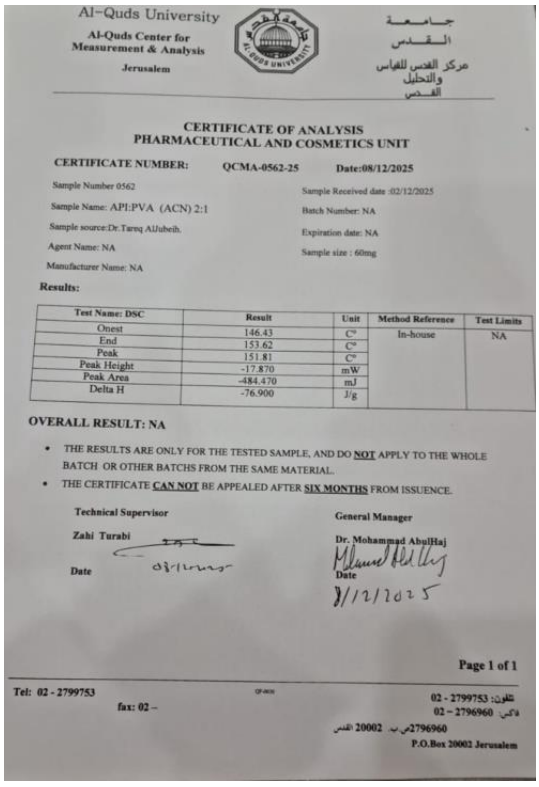


Report Output File: C:\Program Files\Pyris\Data\DefaultReportOutput135.doc
Report Template File: C:\Program Files\Pyris\default.rpp

End = 153.28 °C
Onset = 145.78 °C
Area = -382.287 mJ
Delta H = -67.0680 J/g
Peak = 151.16 °C
Peak Height = -12.3689 mW
Heat Flow Endo Up (mW)
Peak Area (%)
Temperature (°C)

Results:

Formula 55



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0562-25 Date:08/12/2025

Sample Number 0562
Sample Name: API:PVA (ACN) 2:1
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA

Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onset	146.43	C°	In-house	NA
End	153.62	C°		
Peak	151.81	C°		
Peak Height	-17.870	mW		
Peak Area	-484.470	mJ		
Delta H	-76.900	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

Technical Supervisor
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Date

General Manager
Dr. Mohammad AbuHaj
Date 3/12/2025

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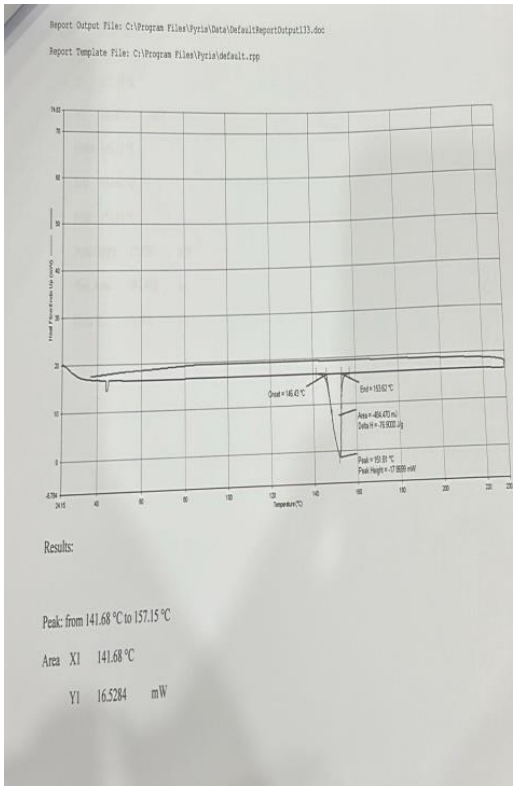


Report Output File: C:\Program Files\Pyris\Data\DefaultReportOutput133.doc
Report Template File: C:\Program Files\Pyris\default.rpp

Onset = 146.43 °C
End = 153.62 °C
Area = -484.470 mJ
Delta H = -76.9000 J/g
Peak = 151.81 °C
Peak Height = -17.8699 mW
Heat Flow Endo Up (mW)
Temperature (°C)

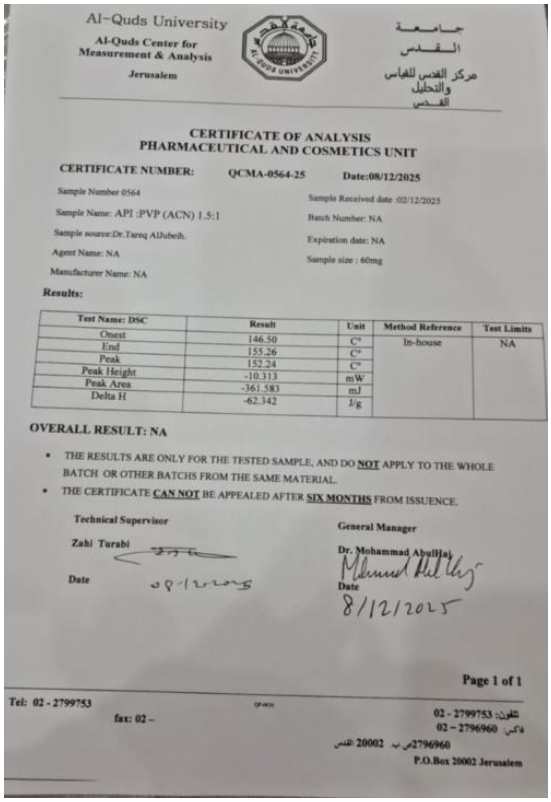
Results:

Peak: from 141.68 °C to 157.15 °C

Area X1 141.68 °C

Y1 16.5284 mW

Formula 32



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CERTIFICATE NUMBER: QCMA-0564-25 Date:08/12/2025

Sample Number 0564
Sample Name: API :PVP (ACN) 1.5:1
Sample source:Dr.Tareq AlJubeih.
Agent Name: NA
Manufacturer Name: NA
Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onset	146.50	C°	In-house	NA
End	155.26	C°		
Peak	152.24	C°		
Peak Height	-10.313	mW		
Peak Area	-361.583	mJ		
Delta H	-62.342	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

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General Manager: Dr. Mohammad AbuHaj — Date: 8/12/2025

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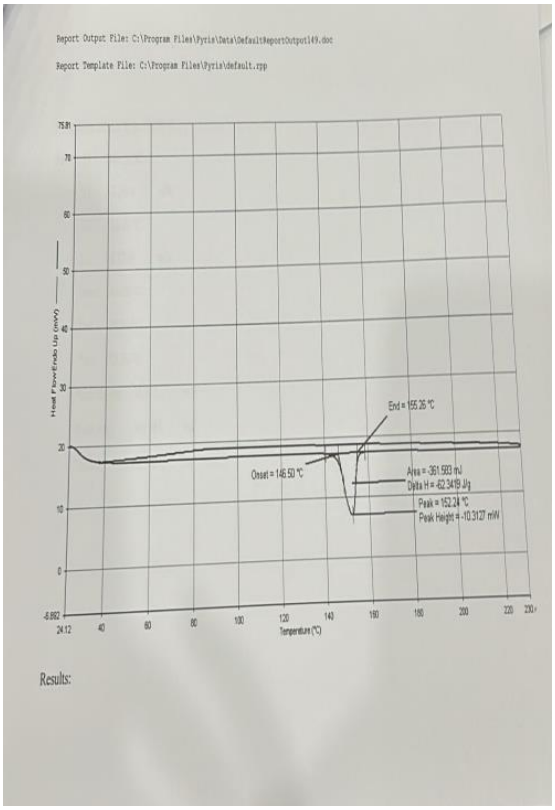
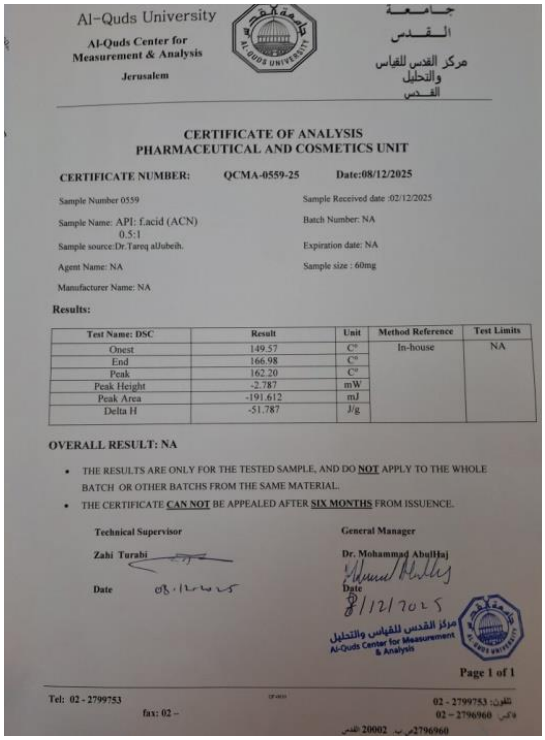


Report Output File: C:\Program Files\Pyris\Data\Default\Report\Output149.doc
Report Template File: C:\Program Files\Pyris\default.rpp

Heat Flow Endo Up (mW)
Temperature (°C)
End = 155.26 °C
Onset = 146.50 °C
Area = -361.583 mJ
Delta H = -62.3478 J/g
Peak = 152.24 °C
Peak Height = -10.3127 mW

Results:

Formula 8



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CERTIFICATE OF ANALYSIS
PHARMACEUTICAL AND COSMETICS UNIT

CERTIFICATE NUMBER: QCMA-0559-25 Date:08/12/2025

Sample Number 0559
Sample Name: API: f.acid (ACN) 0.5:1
Sample source:Dr.Tareq aJubeih.
Agent Name: NA
Manufacturer Name: NA
Sample Received date :02/12/2025
Batch Number: NA
Expiration date: NA
Sample size : 60mg

Results:

Test Name: DSC	Result	Unit	Method Reference	Test Limits
Onset	149.57	C°	In-house	NA
End	166.98	C°		
Peak	162.20	C°		
Peak Height	-2.787	mW		
Peak Area	-191.612	mJ		
Delta H	-51.787	J/g		

OVERALL RESULT: NA

- THE RESULTS ARE ONLY FOR THE TESTED SAMPLE, AND DO NOT APPLY TO THE WHOLE BATCH OR OTHER BATCHS FROM THE SAME MATERIAL.
- THE CERTIFICATE CAN NOT BE APPEALED AFTER SIX MONTHS FROM ISSUENCE.

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General Manager: Dr. Mohammad AbuHaj — Date: 8/12/2025

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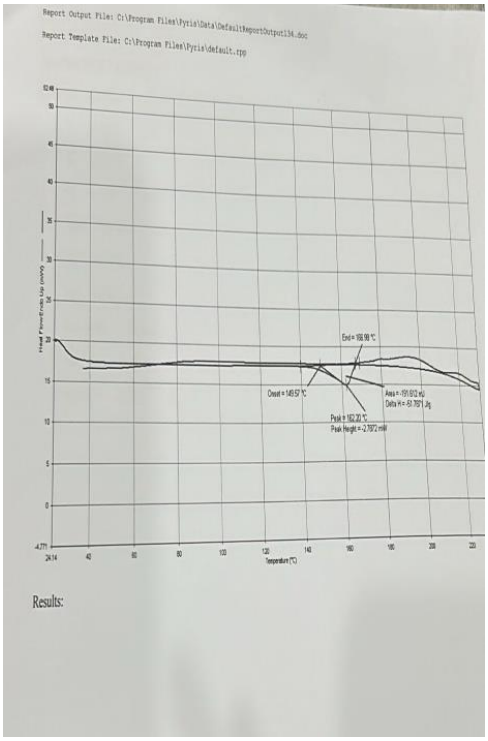

Report Output File: C:\Program Files\Pyris\Data\Default\Report\Output134.doc
Report Template File: C:\Program Files\Pyris\default.rpp

Heat Flow Endo Up (mW)
Temperature (°C)
End = 166.98 °C
Onset = 149.57 °C
Peak = 162.20 °C
Peak Height = -2.787 mW
Area = -191.612 mJ
Delta H = -51.787 J/g

Results:

Abstract in Arabic

تعزيز ذوبانية وسلوك الانحلال للكلوتريمازول ضعيف الذوبان مائياً باستخدام تقنيات إعادة التبلور والتبلور المشترك

إعداد الطالبة: علا عادل مصطفى ابو جمال

الإشراف: د. طارق الجعبة

ملخّص:

المقدمة:

يُعدّ الكلوتريمازول (Clotrimazole) من مضادات الفطريات واسعة الاستخدام، ويُصنَّف ضمن الفئة الثانية من نظام التصنيف الدوائي الحيوي(BCS) ، حيث يتميّز بذائبية مائية منخفضة وتوافر حيوي فموي محدود، مما يقيّد استخدامه الجهازي على الرغم من فعاليته العلاجية الجيدة .هدفت هذه الدراسة إلى تحسين ذائبية الكلوتريمازول وسلوكه الذوباني من خلال تعديل حالته الصلبة باستخدام تقنيتي إعادة التبلور (Recrystallization) والتبلور المشترك (Cocrystallization) .

المنهجية والنتائج:

تمت محاولة تحسين الخصائص الفيزيائية للدواء عبر إعادة التبلور باستخدام عدة مذيبات عضوية بهدف إحداث تغيرات تعددية الشكل(Polymorphism) ، إلا أنّ النتائج لم تُظهر أي تحسّن يُذكر في درجة الانصهار أو الذائبية المائية مقارنة بالمادة الفعالة الأصلية (Clotrimazole) ، مما أدى إلى استبعاد هذه الطريقة .في المقابل تم تحضير بلورات مشتركة للكلوتريمازول (Clotrimazole) باستخدام عدد من المرافِقات المقبولة صيدلانيًا(coformers) مثل حمض (polyvinyl alcohol, Carbomer 940,polyvinyl pyrrolidone. Fumaric acid) وذلك باستخدام تقنية الطحن الميكانيكي وبنسب مولية ومذيبات مختلفة.

جرت دراسة وتوصيف البلورات المشتركة الناتجة باستخدام مطيافية الأشعة تحت الحمراء(FTIR) والمسعر التفاضلي الماسح(DSC) ، وقياسات درجة الانصهار لتأكيد تكوين البلورات المشتركة وتحديد طبيعة التفاعلات الجزيئية .كما أُجريت دراسات الذائبية باستخدام تقنية HPLC أظهرت العديد من البلورات المشتركة انخفاضًا ملحوظًا في درجات الانصهار وزيادة كبيرة في الذائبية المائية مقارنة بالكلوتريمازول النقي.

الخاتمة:

تُظهر نتائج هذه الدراسة أن التبلور المشترك Cocrystallization يُعد استراتيجية فعّالة وواعدة لتحسين ذائبية الكلوتريمازول والتغلب على محدوديةذوبانه، في حين لم تحُقق تقنية إعادة التبلور recrystallization فائدة ملموسة وتشير هذه النتائج إلى إمكانية الاستفادة من البلورات المشتركة المختارة في تطوير أشكال دوائية فموية ذات توافر حيوي أعلى وفعالية علاجية محسّنة.