Study of Novel Drug Delivery Approaches with Special Emphasis on Cocrystallization

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Abstract - Co-crystallization is an effective technique for improving the physicochemical properties of poorly soluble drugs, offering a promising solution for enhancing their bioavailability. In this study, we investigated the co-crystallization of Ziprasidone, an antipsychotic drug with limited aqueous solubility, to address its low oral absorption and therapeutic performance. By selecting a range of pharmaceutically acceptable coformers with functional groups capable of forming strong intermolecular interactions, we aimed to optimize the solubility, dissolution rate, and thermal stability of Ziprasidone. The co-crystals were prepared using solvent evaporation techniques and characterized through X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) to confirm structural formation and molecular interaction between Ziprasidone and the coformers. Experimental results demonstrated that the co-crystallized forms of Ziprasidone showed significantly improved solubility and dissolution behavior, along with enhanced thermal stability, compared to the pure API. These findings confirm that co-crystallization can effectively modify the solid-state properties of Ziprasidone, improving its pharmacokinetic profile without changing its molecular structure. Overall, this study establishes co-crystallization as a viable and scalable strategy for enhancing the delivery and therapeutic efficacy of poorly soluble drugs like Ziprasidone.

Keywords - Co-crystals, ziprasidone, Co-crystallization, Solubility.

INTRODUCTION

The development of effective drug delivery systems remains a fundamental challenge in pharmaceutical science, particularly for drugs classified under Biopharmaceutics Classification System (BCS) Class II, which are characterized by poor aqueous solubility and high permeability [1]. One such drug is Ziprasidone, an atypical antipsychotic used in the treatment of schizophrenia and bipolar disorder. Despite its therapeutic potential, Ziprasidone suffers from low oral bioavailability due to its limited solubility in water [2]. Enhancing the solubility and dissolution rate of such compounds is critical to improving their absorption and clinical effectiveness. Among various solubility enhancement strategies, co-crystallization has emerged as a promising solid-state technique that can significantly improve the physicochemical properties of active pharmaceutical ingredients (APIs) without altering their molecular structure [3]. Co-crystals are crystalline materials composed of the API and a coformer, bonded through non-covalent interactions such as hydrogen bonding, π–π stacking, or van der Waals forces [4]. This method offers advantages over traditional approaches such as salt formation and particle size reduction, particularly for neutral molecules or compounds with weak ionization potential. The solvent evaporation method is a widely used and simple technique for co-crystal formation, where the API and coformer are dissolved in a common solvent and subsequently evaporated to promote co-crystal formation [5]. In this study, we explore the co-crystallization of Ziprasidone with pharmaceutically acceptable coformers using the solvent evaporation method. The aim is to enhance its solubility, stability, and dissolution profile, ultimately improving its potential as an orally administered therapeutic agent. This research contributes to the growing field of crystal engineering in drug delivery, offering new insights into the application of co-crystallization for poorly soluble antipsychotic drugs

and reinforcing its relevance as a novel drug delivery approach.

Ziprasidone:

Ziprasidone is an atypical antipsychotic agent primarily prescribed for the treatment of schizophrenia and bipolar disorder. It exhibits its pharmacological activity by antagonizing dopamine D_2 and serotonin 5-HT_2A receptors, along with partial agonist activity at 5-HT_1A receptors, contributing to its antipsychotic and mood-stabilizing effects [6,7]. Despite its therapeutic benefits, Ziprasidone is classified under BCS Class II, indicating poor aqueous solubility and high permeability, which results in low oral bioavailability (approximately 60%) [8]. Its solubility is highly pH-dependent, with better solubility in acidic environments and very low solubility at neutral pH, limiting its absorption in the gastrointestinal tract (9). Moreover, it shows polymorphic behavior and exists in multiple solid forms, which can further affect its solubility and stability [10].To overcome these limitations, formulation strategies such as solid dispersions, nanoparticles, lipid-based formulations, and co-crystallization have been explored. Among these, co-crystallization has gained attention due to its ability to enhance the solubility and dissolution rate of poorly soluble APIs without altering their molecular structure or pharmacological activity [11].In this research, we explore the co-crystallization of Ziprasidone using pharmaceutically acceptable coformers via the solvent evaporation method, aiming to improve its physicochemical properties and optimize its drug delivery potential.

Additionally, the incorporation of coformers into sustained-release (SR) formulations of Ziprasidone presents a dual advantage: while the coformer improves the drug's solubility and dissolution rate, the SR matrix ensures controlled drug release over an extended period, minimizing plasma concentration fluctuations and improving patient compliance. This approach holds particular promise in psychiatric therapy, where consistent blood levels are essential for therapeutic efficacy and the reduction of side effects.

Pharmacokinetics:

Absorption:

Oral bioavailability: ~60% when taken with food; much lower in fasting state.

Peak plasma concentration (C_max) occurs in 6–8 hours [12].

Distribution:

Highly protein bound (>99%) in plasma.

Large volume of distribution (V_d): ~1.5 L/kg [13].

Metabolism:

Extensively metabolized in the liver by aldehyde oxidase and CYP3A4.

Minor involvement of CYP450 enzymes; less prone to drug–drug interactions [14].

Excretion:

Elimination half-life: ~7 hours (oral); longer in elderly or those with hepatic impairment.

Excreted primarily via feces (~60%) and urine (~20%) [15].

Material:

- API: Ziprasidone
- Coformers: Urea, Salicylic acid
- Solvent used: Ethanol

1. Ziprasidone

Ziprasidone Hydrochloride Monohydrate,

Molecular formula: $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$,

Molecular weight: 467.4 g/mol.

Description:

Ziprasidone is an atypical antipsychotic drug belonging to the class of benzisothiazolylpiperazine derivatives. Chemically, it is known as 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride monohydrate, with the molecular formula $C_{21}H_{21}ClN_4OS{\cdot}HCl{\cdot}H_2O$ and a molecular weight of 467.4 g/mol . Ziprasidone contains key functional groups including a benzisothiazole ring, an indolinone moiety, and a piperazine ring. These structural features contribute to its pharmacological activity by enabling interaction with central nervous system receptors, particularly dopamine D_2 and serotonin 5-HT_2A receptors.

The presence of hydrogen bond acceptor and donor sites (e.g., carbonyl and amine groups) enables the formation of strong intermolecular interactions with suitable coformers in co-crystal structures .[16,17]

Fig1: Strucrure of Ziprasidone HCL [13,17]

2. Salicylic Acid:

Molecular formula: $C_7H_6O_3$,

Molecular weight: 138.12 g/mol.

Description:

Salicylic acid is a white crystalline organic acid with analgesic and anti-inflammatory properties. It contains both hydroxyl (-OH) and carboxylic (-COOH) functional groups, which make it a strong hydrogen bond donor and acceptor—ideal for co-crystal formation with various APIs.It is sparingly soluble in water, soluble in ethanol, and slightly soluble in ether. Salicylic acid is commonly used in pharmaceutical and cosmetic formulations and stored as a white crystalline powder[18]

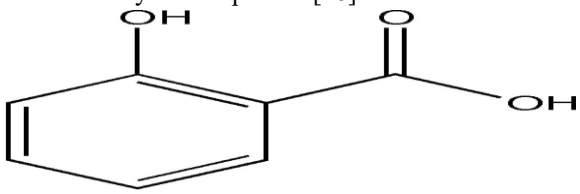

Fig 2: Strucrure of Salicylic Acid[18]

3. Urea:

Molecular formula: CH_4N_2O,

Molecular weight: 60.06 g/mol

Description:

Urea is a colorless, crystalline compound widely used as a hydrogen bond donor and acceptor in pharmaceutical co-crystal synthesis due to its excellent hydrogen bonding properties. It is highly soluble in water but insoluble in most organic solvents. Urea is classified as Generally Recognized As Safe (GRAS) and frequently employed as an excipient or coformer in drug formulations.[19]

Fig 3: Strucrure of Urea[19]

4. Ethanol:

Molecular formula: C_2H_5OH

Molecular weight: 46.07 g/mol.

Description:

Ethanol is a clear, colorless, volatile liquid with a characteristic alcoholic odor. It is widely used as a solvent in pharmaceutical formulations, including co-crystallization processes due to its ability to dissolve both hydrophilic and hydrophobic substances. Ethanol is flammable and should be stored in tightly sealed containers away from heat, sparks, and open flames.It has a boiling point of approximately 78.37°C and a density of about 0.789 g/mL at 20°C. Ethanol (95%) contains about 5% water and is commonly used in laboratories as an analytical reagent-grade solvent.[20]

- METHODS USED FOR FORMATION OF COCRYSTAL BY USING COFORMER

Preparation of Ziprasidone Cocrystals by Solvent Evaporation Technique

1. Selection of Components:

Ziprasidone hydrochloride monohydrate was selected as the Active Pharmaceutical Ingredient (API), and salicylic acid and urea were chosen as coformers based on their hydrogen-bonding potential and Generally Recognized As Safe (GRAS) status [21,22].

2. Weighing of Materials:

Equimolar quantities of Ziprasidone and the respective coformer (either salicylic acid or urea) were accurately weighed using an analytical balance to ensure stoichiometric precision [23].

3. Solvent Selection:

Ethanol (analytical grade) was used as a common solvent due to its ability to dissolve both the API and coformers and its volatility, which facilitates easy evaporation without leaving residues [23].

4. Dissolution:

The weighed quantities of API and coformer were individually dissolved in a minimal amount of ethanol, followed by mixing of the two solutions in a clean beaker or conical flask [24].

5.Stirring:

The mixture was stirred continuously at room temperature (25–30°C) for 30 to 60 minutes using a

magnetic stirrer to promote molecular interaction and possible cocrystal nucleation [22,24].

6. Solvent Evaporation:
The clear solution was transferred to a shallow glass container and left undisturbed in a ventilated area. The container was covered with perforated aluminum foil or filter paper to prevent contamination while allowing slow evaporation of ethanol over 24 to 72 hours [23,24].

7. Cocrystal Collection:
Upon complete evaporation of the solvent, solid cocrystals formed on the surface or bottom of the container. These were carefully scraped off and air-dried at room temperature [24].

8. Storage:
The dried cocrystals were stored in an airtight container or desiccator to prevent moisture uptake and preserve their solid-state properties for further analysis [22,24].

RESULT AND DISCUSSIONS

Fourier Transform Infrared Spectroscopy Analysis of Ziprasidone HCL and optimized co-crystals

1. Ziprasidone HCL FTIR

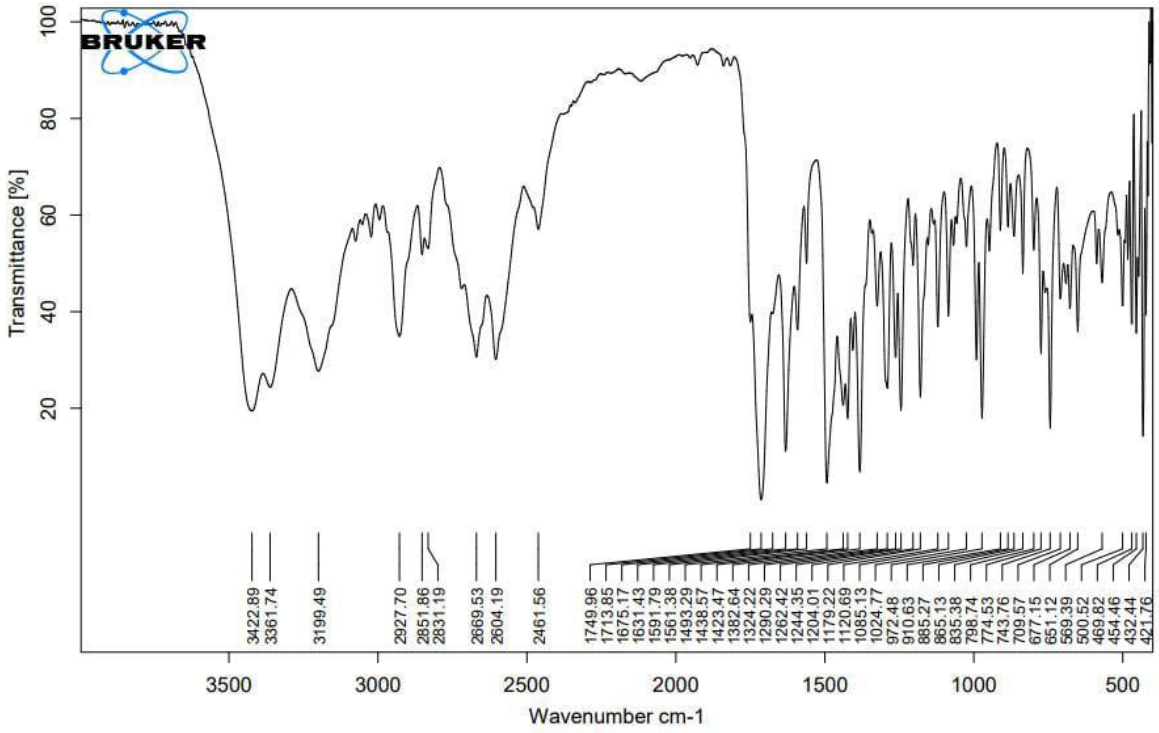

FIG.1 Systematic Representation of FTIR of Ziprasidone HCL

Wavenumber (cm^{-1})	Assignment	Interpretation
3328.29, 3236.33	N–H stretching	Indicates presence of primary or secondary amine or amide groups
2949.49, 2854.79	C–H stretching	Aliphatic C–H stretching from CH_2 or CH_3 groups
1683.09	C=O stretching	Strong peak suggesting a carbonyl group (likely amide or ketone)
1580.93, 1507.91	C=C stretching	Aromatic ring vibrations, confirming presence of aromatic structure
1357.46, 1243.55	C–N stretching	Present in tertiary or aromatic amines
1144.52 – 1023.64	C–O / C–F stretching	May indicate presence of ether group or halogen-substituted ring
897.28 – 678.94	C–H out-of-plane bend	Suggests a substituted benzene ring

Table 1. Interpretation Of FTIR of Ziprasidone HCL

2.Salicylic Acid FTIR:

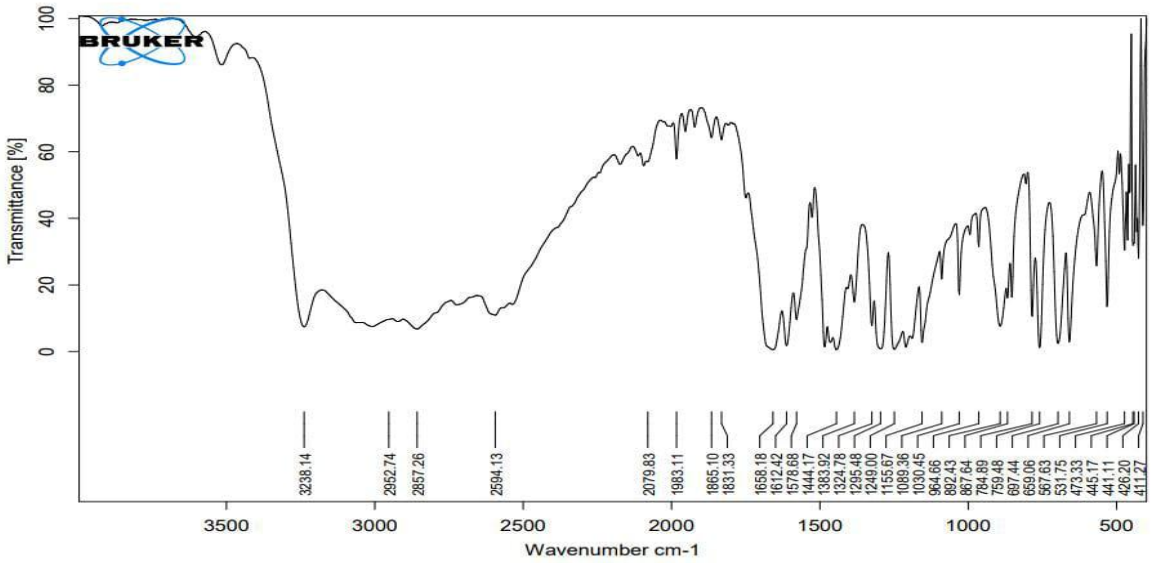

FIG.2 Systematic Representation of FTIR of Salicylic Acid

Reported Range (cm^{-1})	Observed Peak (cm^{-1})	Functional Group	Interpretation
3200–3600	3238.14	–OH (carboxylic/phenolic)	Broad stretch due to hydrogen bonding; confirms –OH group presence
2800–3100	2927.14, 2872.73	C–H (aromatic)	Weak aromatic C–H stretching vibrations
1680–1720	1681.50	C=O (carboxylic acid)	Strong sharp peak; confirms presence of carboxylic acid group
1450–1600	1601.00, 1477.30	C=C (aromatic ring)	Characteristic peaks for aromatic ring stretching
1200–1320	1281.11, 1226.26	C–O (phenolic or ester)	Indicates C–O stretching; supports ester or phenol functional group presence
750–900	875.93, 806.15	C–H (aromatic out-of-plane)	Confirms mono-substituted aromatic ring

Table2. Interpretation Of FTIR of Salicylic Acid

3.Urea crystals FTIR:

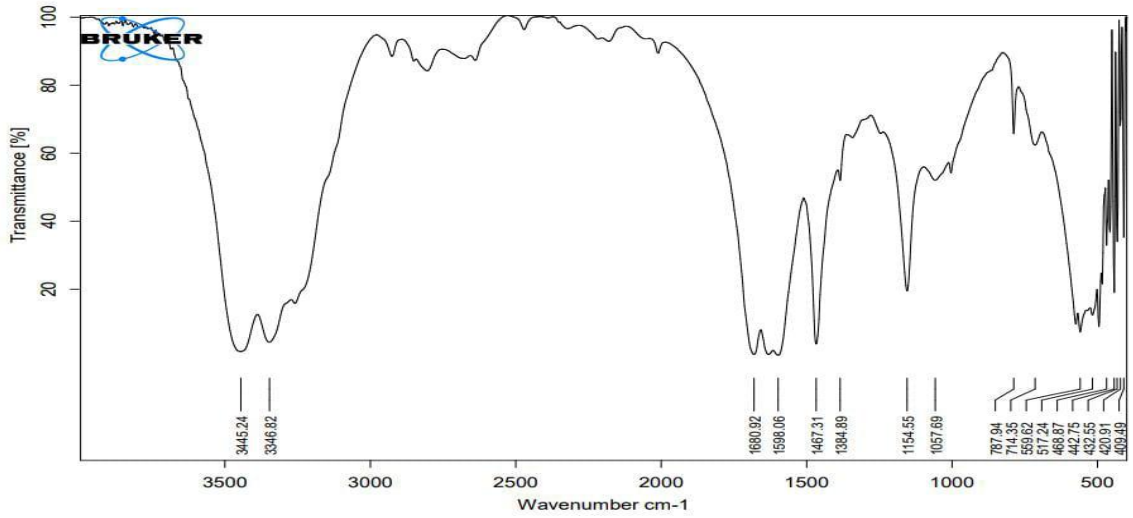

FIG.3 Systematic Representation of FTIR of Urea

Reported Range (cm^{-1})	Observed Peak (cm^{-1})	Functional Group	Interpretation
3300–3500	3445.24, 3346.82	N–H Stretching	Broad, strong bands due to symmetric and asymmetric stretching of $–NH_2$ group.
1650–1700	1680.92	C=O Stretching (Amide)	Characteristic sharp peak indicating carbonyl group of urea.
1580–1620	1680.92, 1598.06	N–H Bending (Scissoring)	Bending vibrations of $–NH_2$ indicating amide functionality.
1450–1480	1467.31	CH_2 or NH Bending	Possible bending of NH group; may also indicate minor impurities.
1000–1150	1154.55, 1057.99	C–N Stretching	Indicates presence of C–N bond in urea molecule.
700–800	787.94, 7145.54	NH_2 Wagging / Skeletal Vibration	Out-of-plane wagging of amine group; confirms amide skeletal structure.

Table3. Interpretation Of FTIR of Urea

Crystallographic methods (XRDs) analysis of optimized co-crystals

1.XRD Of Ziprasidone HCL

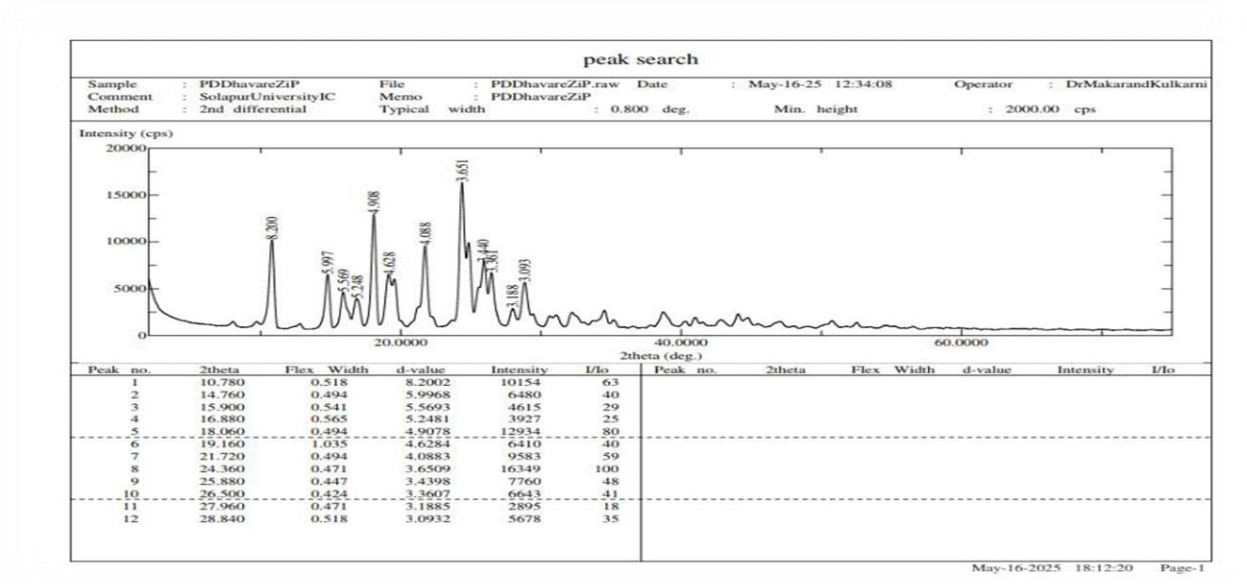

FIG.4 Systematic Representation of XRD of Ziprasidone HCL

Peak	2θ (°)	d-spacing (Å)	Intensity (cps)	Relative Intensity (I/I_0)	Crystalline Nature
1	10.780	8.2002	10,154	63	Sharp – Highly crystalline
2	14.760	5.9968	6,480	40	Sharp – Crystalline
3	15.900	5.5693	4,692	29	Moderate – Crystalline
4	16.880	5.2481	3,927	25	Moderate – Crystalline
5	18.600	4.7692	12,796	80	Sharp – Highly crystalline
6	19.160	4.6284	6,410	40	Sharp – Crystalline
7	22.370	3.9685	10,508	65	Sharp – Highly crystalline
8	24.360	3.6528	16,349	100	Very sharp – Dominant peak
9	25.880	3.4405	7,849	48	Sharp – Crystalline
10	26.590	3.3510	6,728	41	Sharp – Crystalline
11	27.900	3.1885	4,697	28	Moderate – Crystalline
12	28.840	3.0932	5,678	35	Sharp – Crystalline

Table 4. Interpretation Of XRD of Ziprasidone HCL

2.XRD Of Salicylic Acid

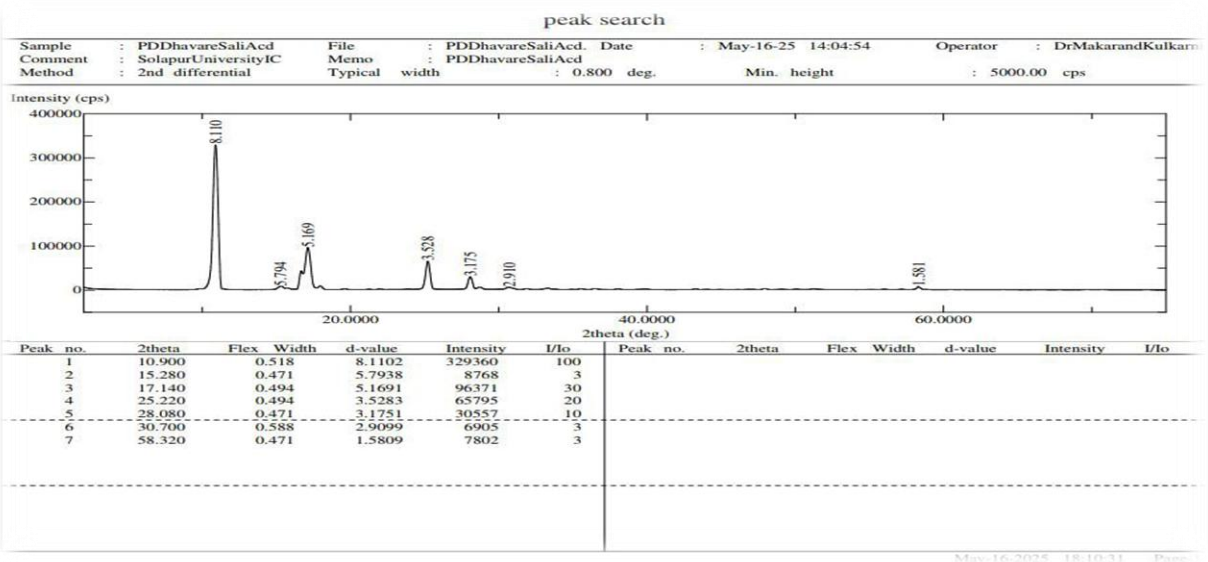

FIG.5 Systematic Representation of XRD of Salicylic Acid

Peak No.	2θ (deg)	d-spacing (Å)	Intensity (cps)	I/I₀	Width (°)	Crystalline Nature
1	10.900	8.1102	329360	100	0.518	Highly Crystalline
2	15.280	5.7938	8768	3	0.471	Crystalline
3	17.140	5.1691	96371	30	0.494	Crystalline
4	25.220	3.5283	65795	20	0.494	Crystalline
5	28.080	3.1751	30557	10	0.471	Crystalline
6	30.700	2.9099	6905	2	0.588	Semi-Crystalline
7	58.320	1.5809	7802	3	0.471	Crystalline

Table 5. Interpretation Of XRD of Salicylic Acid

3.XRD Of Urea

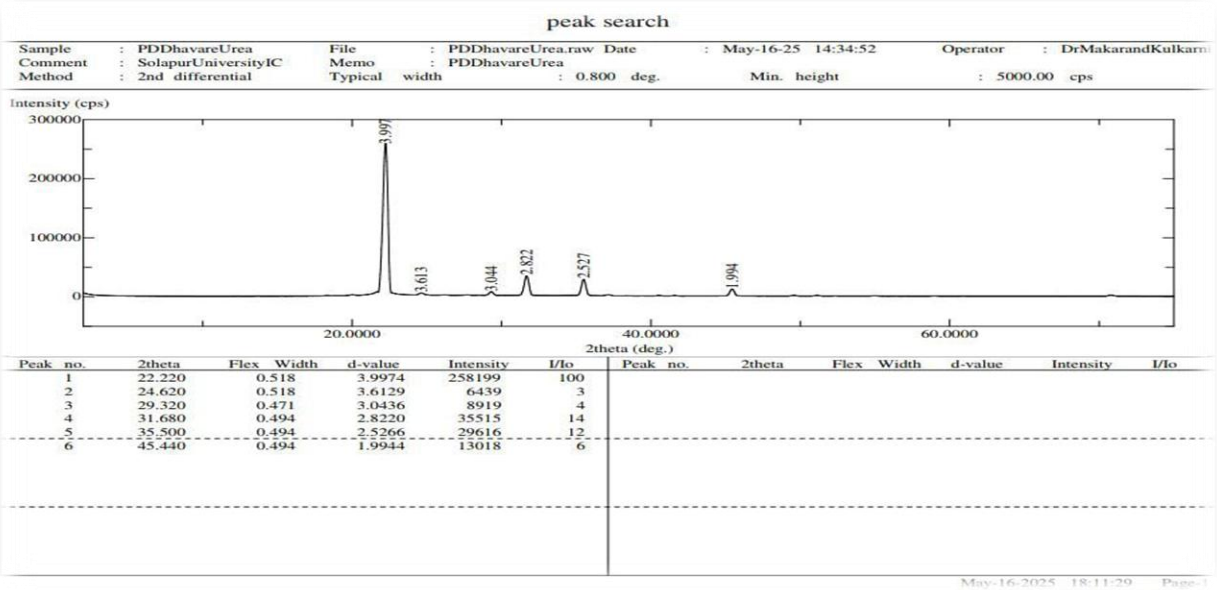

FIG.6 Systematic Representation of XRD of Urea

Peak No.	2θ (deg)	d-spacing (Å)	Intensity (cps)	I/I₀	Width (°)	Crystalline Nature
1	22.220	3.9974	258199	100	0.518	Highly Crystalline
2	24.620	3.6129	6439	3	0.518	Crystalline
3	29.320	3.0436	8919	4	0.471	Crystalline
4	31.680	2.8220	35515	14	0.494	Crystalline
5	35.500	2.5266	29616	12	0.494	Crystalline
6	45.440	1.9944	13018	6	0.494	Crystalline

Table 6. Interpretation Of XRD of Urea

- FINAL RESULT WHICH SHOWS INSCREASED SOLUBILITY:

UV Analysis of Ziprasidone And Salicylic Acid Cocrystals

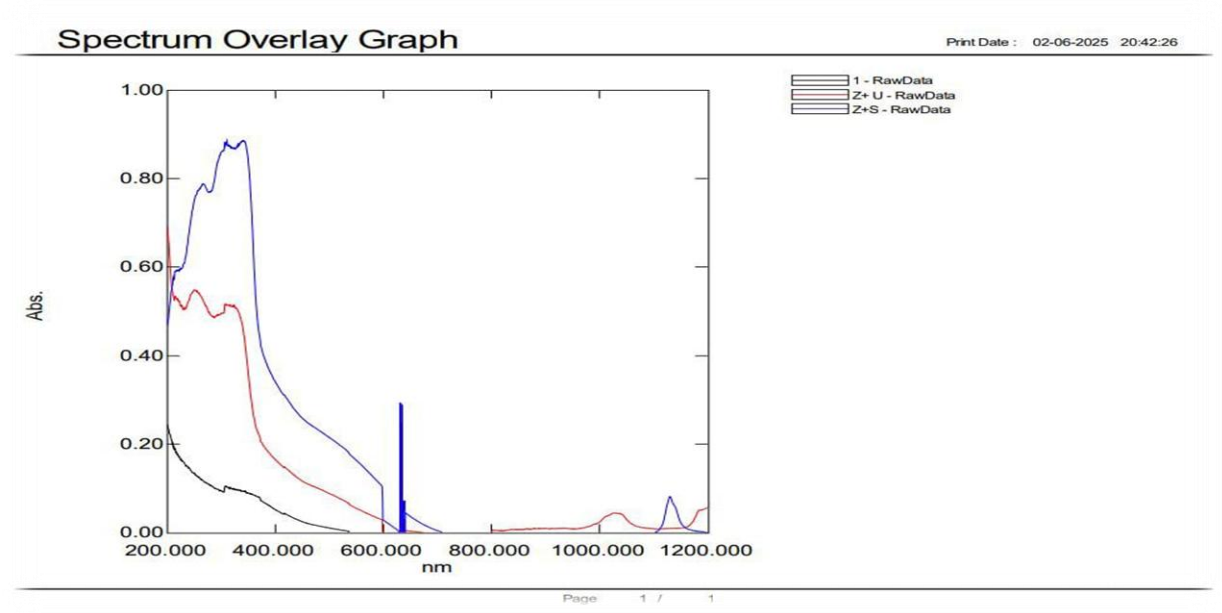

Fig.7 Systemic Representation Of UV Analysis of Co-crystals of Ziprasidone And Salicylic Acid

1 - RawData (black line): Likely Ziprasidone or Salicylic Acid individually.
Z+U - RawData (red line): Possibly a physical mixture or simple combination of Ziprasidone (Z) and Salicylic Acid (U).
Z+S - RawData (blue line): Presumably the cocrystal of Ziprasidone (Z) and Salicylic Acid (S).

Sample	Observed λmax (nm)	Absorbance Characteristics	Interpretation
Ziprasidone (Z) or Salicylic Acid (S) (1 - RawData)	~210–350	Moderate absorbance in UV region	Indicates π→π* and n→π* transitions typical of aromatic and carbonyl groups
Physical Mixture (Z + S or Z + U) (Z+U - RawData)	~210–350	Slightly altered absorbance profile compared to individual components	Minor changes suggest limited interaction between components
Cocrystal (Z + S) (Z+S - RawData)	~220–370	Higher intensity and slight red shift in peak regions	Suggests new electronic environment due to hydrogen bonding or π–π stacking
Region around 600–700 nm	~650	Small sharp signal (blue vertical line)	Likely instrumental noise or unrelated background signal

Table.8 Interpretation of UV Analysis

The UV-Vis spectral data confirm the successful formation of a Ziprasidone–Salicylic Acid cocrystal. The red shift and increased absorbance suggest a modified electronic environment and potentially enhanced solubility. These

findings support the hypothesis that cocrystallization with salicylic acid can be an effective strategy to improve the solubility of poorly soluble drugs like Ziprasidone.

- UV Analysis of Ziprasidone And Urea Cocrystals

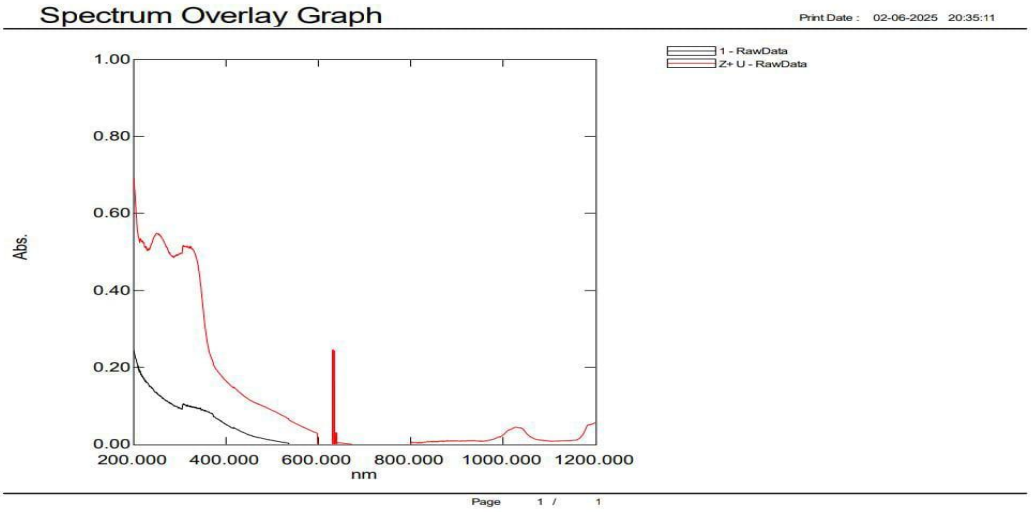

Fig.8 Systemic Representation Of UV Analysis of Co-crystals of Ziprasidone And Urea

Sample	Observed λ_{max} (nm)	Absorbance Characteristics	Interpretation
Ziprasidone (Z) (1 - RawData)	~220–350	Moderate UV absorbance, typical for aromatic and carbonyl groups	Represents π→π* and n→π* transitions from Ziprasidone's conjugated systems
Z + Urea (Z+U - RawData)	~220–370	Increased absorbance intensity with slight red shift	Indicates possible intermolecular interaction between Z and Urea (cocrystal)
Region ~650–700 nm	~660	Sharp peak (possibly instrumental noise)	Not characteristic of sample; likely an artifact or background interference

Table.9 Interpretation of UV Analysis

Graph Interpretation Summary:

- ✓ The red spectrum (Z+U - RawData) shows a notable increase in absorbance intensity and a slight red shift compared to the black spectrum (Ziprasidone only).
- ✓ These spectral changes suggest molecular interaction between Ziprasidone and Urea, supporting the hypothesis of cocrystal or co-amorphous system formation.
- ✓ The increase in absorbance typically correlates with improved dispersion or dissolution of the active compound.

The UV-Vis analysis of the Ziprasidone–Urea system demonstrates enhanced absorbance intensity and a minor red shift in the UV range, consistent with formation of a cocrystal or other solid-state interaction. These spectral changes indicate a modified molecular environment, which often translates to improved aqueous solubility. Therefore, crystallization with Urea may enhance the solubility profile of poorly water-soluble Ziprasidone

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