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**Research Article**

# Design Synthesis and Characterization of Chloramphenicol Cocrystals

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## ABSTRACT

Chloramphenicol, a broad-spectrum antibiotic, suffers from poor aqueous solubility and bioavailability, limiting its therapeutic efficacy. To address this challenge, we designed and synthesized chloramphenicol cocrystals with co-former, including caeffine. The cocrystals were characterized using UV Spectroscopy, and Fourier transform infrared spectroscopy, Differential Scanning Colorimetry, HPLC. The solubility and dissolution rate of the cocrystals were significantly improved compared to the pure drug.These results demonstrate the potential of cocrystal formation as a strategy to improve the solubility, and therapeutic efficacy of chloramphenicol. The co-crystals were synthesized using the solvent evaporation method, where Chloramphenicol and caffeine were dissolved in a solvent mixture and allowed to crystallize as the solvent evaporated. The synthesis was confirmed using advanced techniques, which revealed a new crystalline structure distinct from the pure drug and coformer.

## INTRODUCTION

### Introduction to Co-crystals

Pharmaceutical cocrystals are defined as crystals that comprise two or more discrete neutral molecules at a stoichiometric ratio and bond together via noncovalent bond interactions (e.g., hydrogen bonding, van der Waals and π···π stacking interactions), in which at least one of the components is API and the others are pharmaceutically acceptable ingredients. Co-crystallization has emerged as a revolutionary approach in pharmaceutical formulation to tackle the solubility and bioavailability challenges of poorly soluble drugs, especially Biopharmaceutical Classification System (BCS) Class II drugs.

**Mechanism:** Co-crystals are formed when an API interacts with a coformer through non- covalent bonds. This interaction results in a unique

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crystalline structure that optimizes the physicochemical properties of the drug.

**Examples:** Common APIs like carbamazepine, paracetamol, and now Chloramphenicol have successfully utilized co-crystallization to enhance their therapeutic profiles.

**Role of BCS (Biopharmaceutics Classification System) in cocrystal formation:**


**Fig no.1: Biopharmaceutics Classification System (BCS**

1. **Class I: High solubility, high permeability**
2. **Class II: Low solubility, high permeability**
3. **Class III: High solubility, low permeability**
4. **Class IV: Low solubility, low permeability**

**Chloramphenicol belongs to Biopharmaceutics Classification System (BCS) Class IV. BCS Class IV Characteristics:**

1. Low Solubility: Chloramphenicol has poor aqueous solubility (<0.1 mg/mL).
2. Low Permeability: Chloramphenicol has limited permeability across biological membranes.
3. Variable Bioavailability: Chloramphenicol's bioavailability can vary significantly depending on the formulation and administration route.

**Applications of Co-crystals**

1. **Improved Drug Delivery:** Co-crystals ensure consistent and efficient delivery of poorly soluble drugs like Brexpiprazole.
2. **Patient-Friendly Formulations:** Enhanced solubility allows for lower dosages, reducing the risk of side effects.
3. **Extended-Release Profiles:** Co-crystals can be used to design formulations with controlled or sustained drug release.
4. **Combination Therapies:** APIs and coformers with synergistic therapeutic effects can be co-crystallized to enhance clinical outcomes.

**Introduction to conformer :**

**What is a Coformer?**

A coformer is a molecule that is co-crystallized with an active pharmaceutical ingredient (API) to form a new crystalline solid, known as a cocrystal.

**Benefits of Using Coformers :**

The use of coformers can offer several benefits, including:

1. Improved solubility and bioavailability
2. Enhanced stability and shelf-life
3. Reduced toxicity and side effects

## DRUG PROFILE

### History and Development of Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic that has played a significant role in medical practice since its discovery. It was first isolated from the bacterium Streptomyces venezuelae in 1947 by American microbiologist Dr. Albert Schatz and his colleagues. This breakthrough marked a turning point in the treatment of various bacterial infections. Chloramphenicol quickly gained popularity due to its effectiveness against a wide range of bacteria, including both Gram-positive and Gram-negative organisms

**SOLUBILITY:** Chloramphenicol is soluble in the following solvent

1. Water: slightly soluble
2. Ethanol: freely soluble
3. Methanol: very soluble
4. Acetone: soluble
5. Chloroform: soluble
6. Ethyl acetate

### STRUCTURE

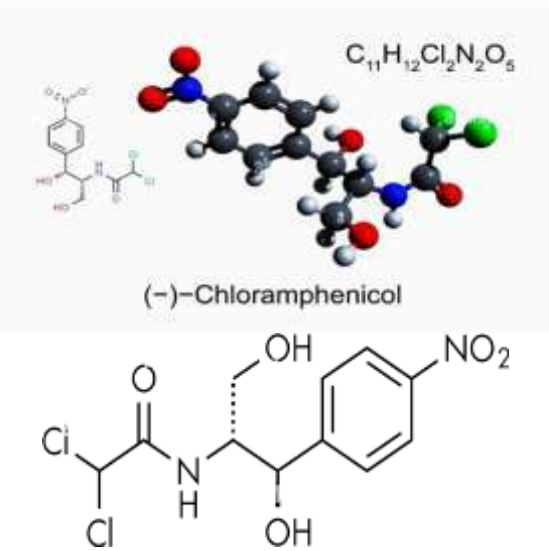



**Fig no.2 : Structure of Chloramphenicol**

### COFORMER : CAEFFINE

Caffeine is a natural stimulant most commonly found in coffee, tea, cacao plants, and certain medications or supplements. It's known for stimulating the central nervous system (CNS), helping you stay alert and prevent tiredness.

### Chemical Information

- Chemical Formula: $C_8H_{10}N_4O_2$
- Type: Alkaloid (specifically a xanthine)
- Natural Sources: Coffee beans, tea leaves, kola nuts, cacao pods, yerba mate

### Chemical Structure of Caffeine

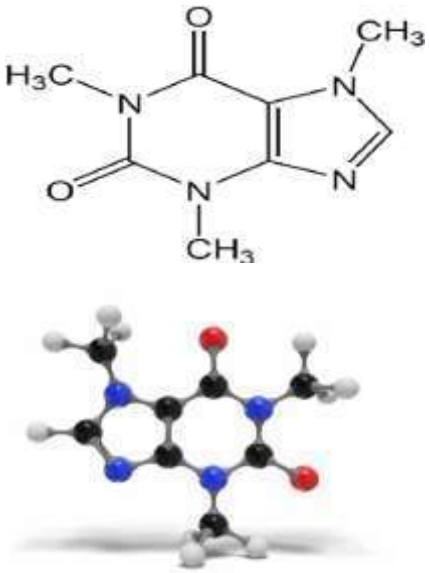



**Fig no.3 : Chemical Structure of Caffeine**

**Role of caffeine as a coformer :** Caffeine's unique properties make it an effective conformer

1. Hydrogen bonding: Caffeine's molecular structure allows for hydrogen bonding with other molecules.
2. Solubility enhancement: Caffeine can improve the solubility of poorly soluble drugs.
3. Stabilization: Caffeine can stabilize the crystal structure and improve physical properties.

### Advantages of caffeine-based cocrystals:

1. Improved bioavailability
2. Enhanced solubility
3. Increased stability
4. Modified release profiles
5. Potential for new intellectual property

## MATERIALS AND METHODS

### SYNTHESIS OF CHLORAMPHENICOL CO-CRYSTALS:

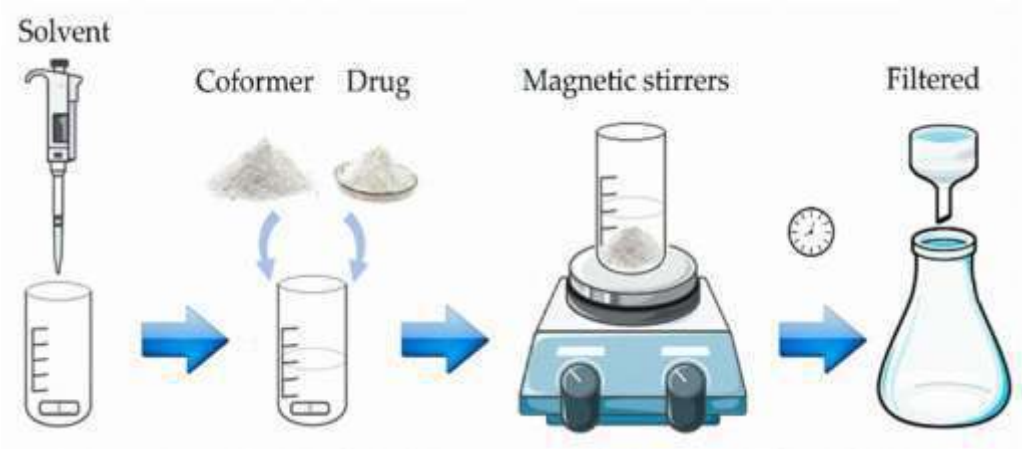



**Fig no. 4: Solvent Evaporation Method**

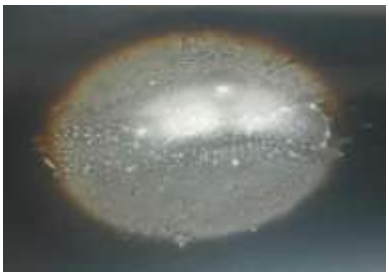


**Fig no.5: Chloramphenicol Cocrystals**

**Observed crystals :**

**Procedure :**

Chloramphenicol (100 mg) and caffeine (100 mg) were dissolved in acetone and stirred for 15 minutes. The solution was filtered and evaporated to form crystals. The cocrystal was found to be soluble in water.

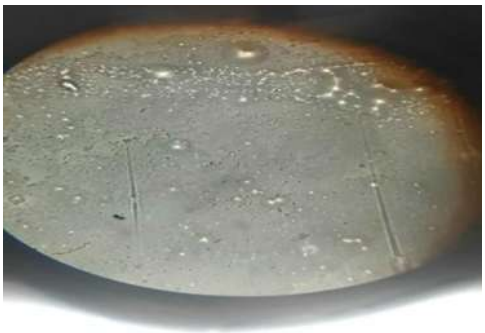


**Fig no. 6: Chloramphenicol cocrystals under microscope**

## RESULT AND DISCUSSION

**UV Analysis of Chloramphenicol and Caffeine Cocrystals:**

UV Spectroscopy is a valuable technique for analyzing chloramphenicol and caffeine cocrystals.

Wavelengths:

1. Chloramphenicol: 278-280
2. Caffeine: 273-275 nm
3. Cocrystal: 272-282 nm (overlap of individual components)

**UV Spectrum: The UV spectrum of the cocrystal shows:**

1. A broad peak at 272-282 nm, indicating overlap of chloramphenicol and caffeine absorption
2. A shoulder peak at 260-265 nm, attributed to chloramphenicol
3. A minor peak at 230-235 nm, due to caffeine


**Fig no. 7: Std Chloramphenicol : 3.796 Abs**


**Fig no.8 : Solution of CAP and CAF: 4.000Abs**

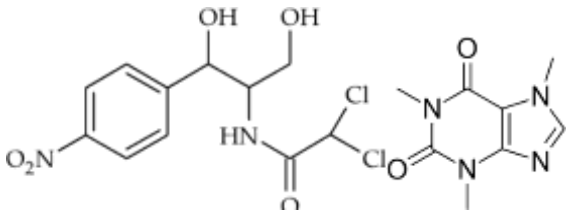
**UV-Visible Analysis:**

1. CAP-CAF cocrystals exhibit bathochromic shift (red shift) compared to individual components.
2. Increased molar absorptivity indicates enhanced molecular interaction.
3. Cocrystal formation affects electronic transitions.

**Applications:**

1. Characterization of CAP-CAF cocrystals.
2. Quantitation of cocrystal formation.
3. Investigation of molecular interactions.

**IR SPECTROSCOPY :**




**Chloramphenicol: Caffeine Cocrystals**

| Sr. No. | Frequency cm-1 | Vibration | Functional Group |
|---|---|---|---|
| 1 | 3887.47 | Stretching | NH |
| 2 | 2981.20 | Stretching | OH |
| 3 | 1547.24 | Stretching | C=O |
| 4 | 640.98 | Stretching | Aromatic |

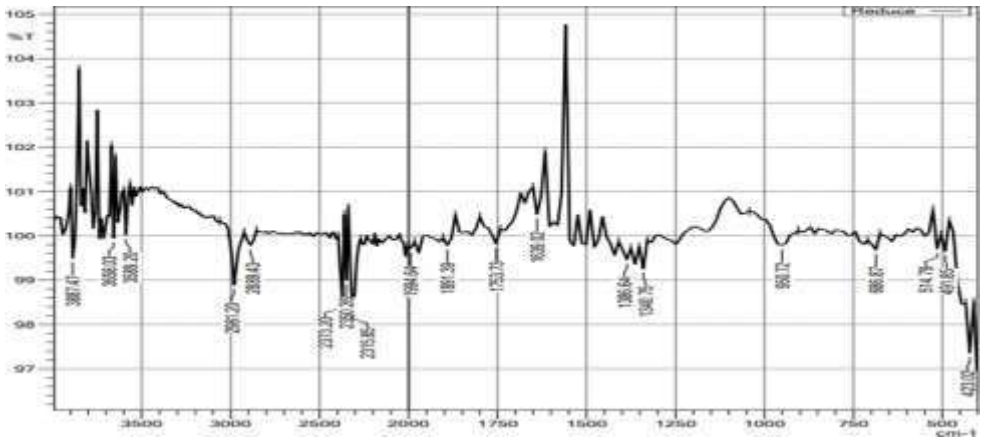


**Fig no.9 IR Spectroscopy**

| | Item | Value |
|---|---|---|
| 2 | Sample name | 18_oct_SCP-CHL-424 |
| 3 | Sample ID | 18_oct_SCP-CHL-424 |
| 4 | Option | |
| 5 | Intensity Mode | %Transmittance |
| 6 | Apodization | Happ-Genzel |
| 9 | No. of Scans | 45 |
| 10 | Resolution | 4 cm-1 |

## IR Spectroscopy Characterization

IR spectroscopy is a widely used technique to characterize the molecular structure and properties of cocrystals. In this study, IR spectroscopy was used to characterize the chloramphenicol and caffeine cocrystals.

## Instrumentation and Methodology

- Instrument: FTIR spectrometer (e.g. Bruker Tensor 27)
- Wavelength range: 4000-400 cm-1
- Sample preparation: KBr pellet method
- Resolution: 4 cm-1
- Scan number: 32

## Conclusion

The IR spectroscopy results demonstrate the formation of chloramphenicol and caffeine cocrystals with distinct molecular interactions. The shifts and changes in intensity of the characteristic peaks indicate the formation of hydrogen bonds between the chloramphenicol and caffeine molecules. These results provide valuable insights into the molecular structure and properties of the cocrystals.

## DIFFERENTIAL SCANNING COLORIMETRY

DSC is used in cocrystal characterization to detect a new, single melting point that differs from the pure components, confirming cocrystal formation. It helps distinguish cocrystals from physical mixtures, assess purity, and evaluate thermal stability.

## Dsc Characterization in Chloramphenicol-Caffeine Cocrystal

- Sample ID: SEP-CHL-424
- Sample Weight: 4.2000 mgOnset
- Temperature: 120.84 °C
- Peak Temperature (Melting Point): 126.42 °C
- Endset Temperature: 134.70 °C
- Enthalpy Change (ΔH): -95.87 J/g (exothermic transition)
- Peak Width: 8.16 °C
- Peak Height: 7.47 mW
- Thermal Event: One sharp endothermic peak

## CONCLUSION :

The DSC curve of the sample SCP-CHL-424 shows a single, sharp endothermic peak at approximately 126.42 °C, indicating a well-defined melting point. The narrow peak width (8.16 °C) and the high enthalpy value (-95.87 J/g) suggest that the material is highly crystalline and pure. The absence of multiple peaks or broad transitions further confirms the thermal stability and uniformity of the sample.

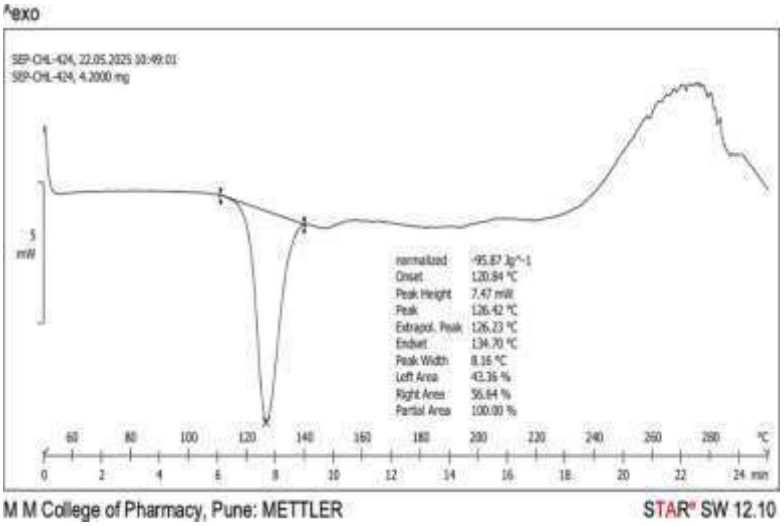



**Fig no.10 Differential Scanning Colorimetry**

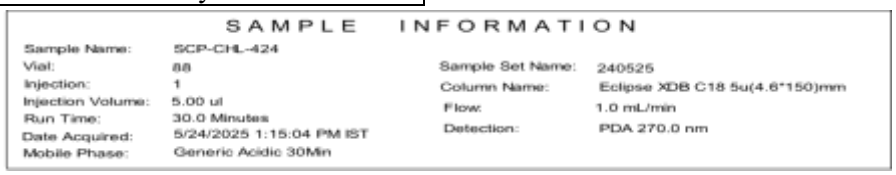
## HPLC

HPLC: High Liquid Performance Chromatography. HPLC is an analytical technique used to separate,identify,and quantify components in a mixture. HPLC is essential in characterizing chloramphenicol–caffeine cocrystals because it ensures:

| Purpose | Role of HPLC |
|---|---|
| Purity | Detects unreacted materials or impurities |
| Quantification | Confirms component ratio in the cocrystal |

### Observation:

The chromatogram of sample SCP-CHL-424 shows two distinct peaks: The major component eluted at 7.902 min, representing 63.22% of the total area. The second component eluted at 11.526 min, contributing 36.78% of the total area. This indicates the sample contains two primary compound with the first one being predominant. The separation appears successful under the given chromatographic conditions.



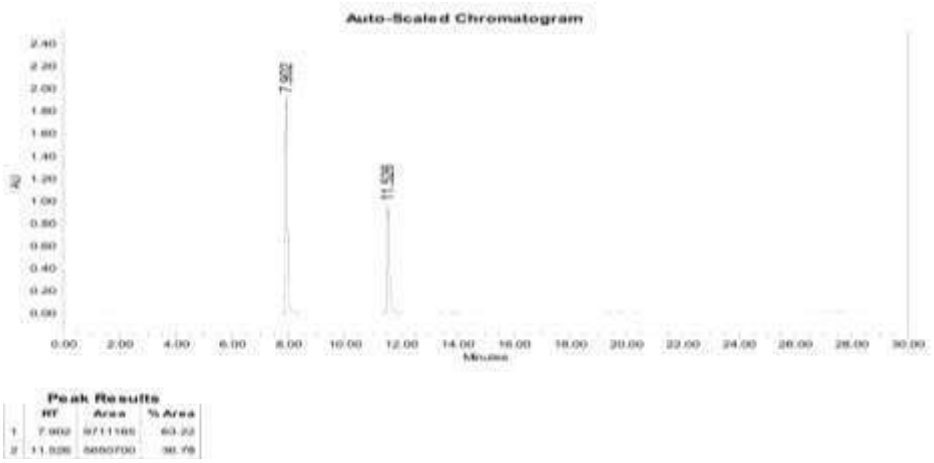



**Fig no.11: High Performance Liquid Chromatography**

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