



Original Article

# Synthesis and Characterization of Polymorphs in Caffeine

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Polymorphism is the ability for a single chemical entity to form two or more crystalline phases. Many APIs exhibit several polymorphic forms and in many cases, there is only one desired polymorph, which is decided upon by numerous factors. In this research work, preliminary studies on the polymorphism of Caffeine were performed. The recrystallization of Caffeine was carried out by using different organic solvents such as ethanol, methanol, chloroform, dichloromethane, acetone, isopropyl alcohol, and carbon tetrachloride. After recrystallization, the crystals were collected and dried at room temperature and then subjected for the characterization to identify the presence of polymorphs. Different techniques, such as Differential Scanning Calorimetry, UV-Spectrophotometry, and FTIR Spectrophotometry, were used to determine the polymorphic changes in the obtained crystals of Caffeine crystals. The data obtained from analytical techniques concludes that Caffeine crystals obtained by using carbon tetrachloride showed a significant difference in the melting behavior, but no change in the chemical structure and hence can be found to have different polymorphic Caffeine.

**Keywords:** Caffeine, Polymorphs, Differential Scanning Calorimetry, Spectrophotometry.

## 1. INTRODUCTION

Polymorphism is the ability for a single chemical entity to form two or more crystalline phases. Many APIs exhibit several polymorphic forms and in many cases, there is only one desired polymorph, which is decided upon by numerous factors. According to statistics, at least 80% of organic substances form two or more polymorphs<sup>1</sup>. In materials science, polymorphism is the ability of a solid material to exist in more than one form or crystal structure.

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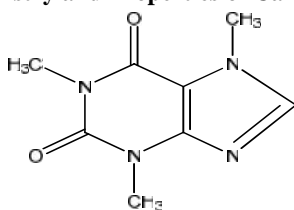
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Polymorphism can potentially be found in any crystalline material, including polymers, minerals, and metals, and is related to allotropy, which refers to chemical elements<sup>2</sup>. Polymorphism is relevant to the fields of pharmaceuticals, agrochemicals, pigments, dyestuffs, foods, and explosives. Polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature<sup>3</sup>. They also exhibit different melting points, solubility which affect the dissolution rate of drug and consequently, its bioavailability in the body<sup>4</sup>.

#### **Caffeine:**

Caffeine is a central nervous system stimulant, chemically purine, a methylxanthine alkaloid, and is related to the adenine and guanine bases of deoxyribonucleic acid and ribonucleic acid. It is the world's most consumed psychoactive drug and also used to stimulate certain portions of the autonomic nervous system. It is a bitter, white crystalline powder<sup>5</sup>.

#### **Chemistry and Properties of Caffeine<sup>6</sup>:**



**1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione**

Chemically Caffeine is 1,3,7-Trimethylpurine-2,6-dione. Pure anhydrous caffeine is a bitter-tasting, white, odorless powder with a melting point of 235–238 °C. Caffeine is moderately soluble in water at room temperature but very soluble in boiling water. It is also moderately soluble in ethanol. The xanthine core of caffeine contains two fused rings, a pyrimidinedione, and imidazole. The pyrimidinedione, in turn, contains two amide functional groups that exist predominantly in a zwitter ionic resonance the location from which the nitrogen atoms are double bonded to their adjacent amide carbons atoms.

Literature survey has been done on polymorphism studies on caffeine. Few research works related to the water content behavior of crystalline caffeine hydrate<sup>7</sup> and polymorphic transformation of anhydrous caffeine under compression and grinding re-evaluation has been reported<sup>8</sup>.

In the present research work, an attempt has been made to synthesize different forms of Caffeine crystals using various solvents system and to identify the presence of any polymorphs by characterizing with different analytical techniques.

## **2. MATERIALS AND METHODS**

### **2.1 Instruments:**

DSC-60 Shimadzu was used to record the melting point of Caffeine crystals. To measure the maximum absorbance wavelength of pure Caffeine and its crystals UV-1800 Shimadzu with UV probe software were used, Fourier

Transform Infrared Spectroscopy (FTIR) Shimadzu (Affinity-1) 800 were used to identify the functional groups in pure Caffeine and their synthesized crystals.

**2.2 Chemicals and solvents used:** All the solvents used for the crystallization were pure and analytical grade. Caffeine was obtained from Loba Chemie Pvt. Ltd.

### **2.3 Methodology:**

#### **2.3.1 Selection of solvents:**

Based on the solubilities of Caffeine, various solvents were selected for the re-crystallization of Caffeine. Ethanol, Methanol, Ethyl acetate, Chloroform, Dichloromethane (DCM), Acetone, Isopropyl alcohol (IPA) and Carbon tetrachloride (CCl<sub>4</sub>) were used as solvents.

#### **2.3.2 Recrystallization of Caffeine:**

A small amount of Caffeine was taken and dissolved in 10 mL of above mentioned organic solvents, and then saturated solutions were prepared by heating. After achieving the saturation, the resulted solutions were kept for the evaporation to obtained dried crystals at room temperature.

#### **2.3.3 Characterization of Caffeine and Synthesized Crystals by Analytical Techniques:**

The crystals of Caffeine obtained which were prepared in different solvents were subjected to different analytical techniques to identify the polymorphs. The crystals were subjected to DSC analysis to find the change in melting behavior. The UV-Spectrophotometric analysis was carried out to observe the spectrum and maximum absorbance wavelength and was also subjected to IR studies to observe the structural and functional changes in the molecule.

#### **2.3.4 Preliminary Determination of polymorphs by DSC:**

To identify the polymorphs in synthesized crystals, the crystals were subjected for DSC analysis by crimping the sample in aluminum pans, at the heating rate of 10°C/min and analyzed.

#### **2.3.5 UV-Spectrophotometric analysis of Caffeine crystals:**

The crystals of Caffeine were dissolved in distilled water and spectrum was obtained by scanning the solutions between the range of 400-200 nm. The maximum absorbance wavelength was measured.

#### **2.3.6 FTIR-Spectrophotometric analysis for Caffeine crystals:**

The FTIR spectrum was obtained by mixing crystals of caffeine with potassium bromide (99:1), and spectrum were obtained and analyzed.

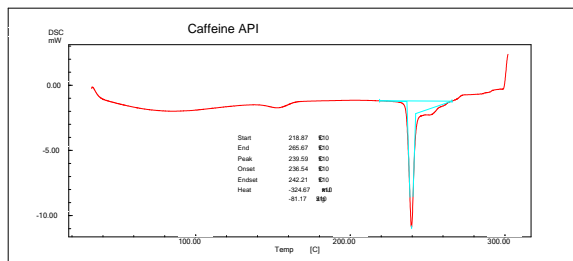
## **3. RESULTS AND DISCUSSION**

Pure Caffeine was taken and re-crystallized by using different organic solvents, and thermogram of each was determined. The thermogram of pure Caffeine was found to be 235°C. The melting point of each crystal obtained in different solvents are shown in Table No:1 and their thermogram were showed in Fig 1-9. The UV-Spectrum of different crystals of Caffeine was presented in Fig 10-18,

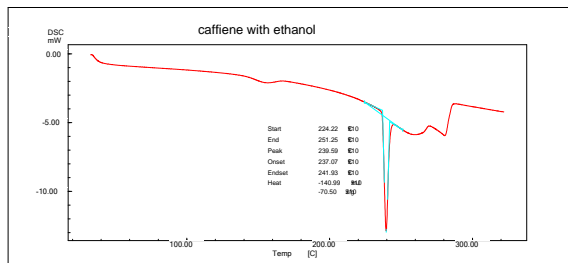
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 and maximum absorbance values were presented in Table No:1.

**Table 1: Melting point and maximum absorbance of Caffeine Crystals**

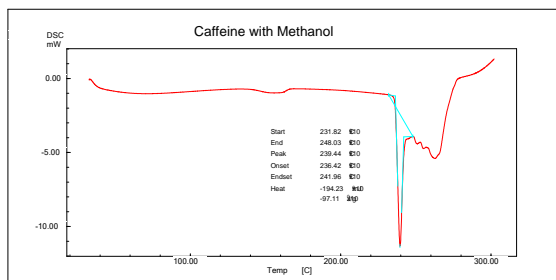
Sr. No.	Caffeine and its crystals in Organic Solvents	Melting point	Maximum absorbance
1	Pure Caffeine	235.00°C	273nm
2	Caffeine re-crystallized in ethanol	239.59 <sup>0</sup> C	273 nm
3	Caffeine re-crystallized in methanol	239.44 <sup>0</sup> C	273 nm
4	Caffeine re-crystallized in isopropyl alcohol	239.24 <sup>0</sup> C	273 nm
5	Caffeine re-crystallized in ethyl acetate	240.29 <sup>0</sup> C	273 nm
6	Caffeine re-crystallized in chloroform	241.45 <sup>0</sup> C	273 nm
7	Caffeine re-crystallized in dichloromethane	241.23 <sup>0</sup> C	273 nm
8	Caffeine re-crystallized in carbon tetrachloride	242.61 <sup>0</sup> C	273 nm
9	Caffeine re-crystallized in acetone	241.47 <sup>0</sup> C	273 nm



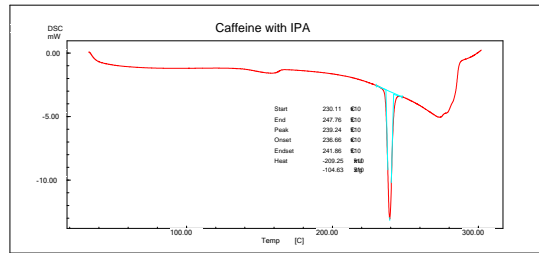
**Fig 1: DSC Thermogram of pure Caffeine**



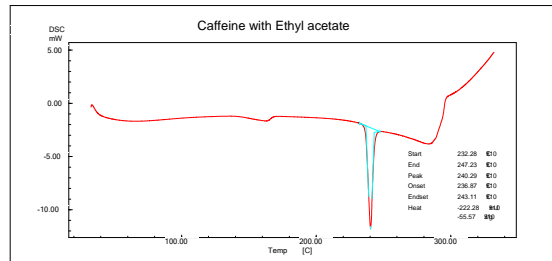
**Fig 2: DSC Thermogram of Caffeine crystals in Ethanol**



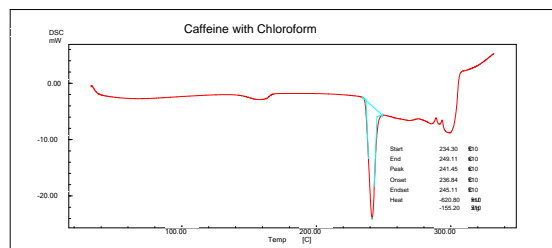
**Fig 3: DSC Thermogram of Caffeine crystals in Methanol**



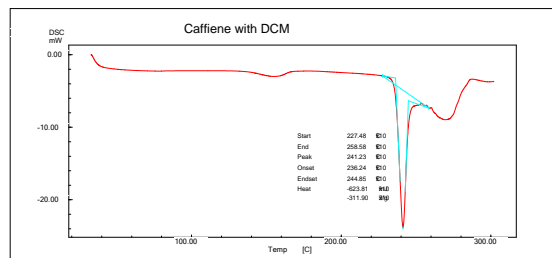
**Fig 4: DSC Thermogram of Caffeine crystals in Isopropyl alcohol**



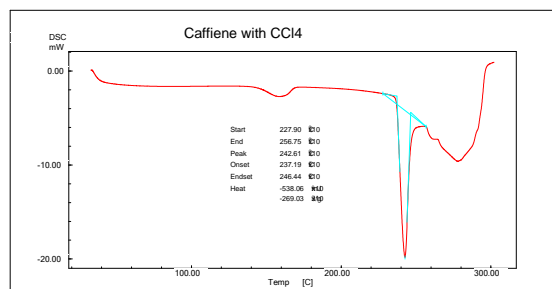
**Fig 5: DSC Thermogram of Caffeine crystals in Ethyl acetate**



**Fig 6: DSC Thermogram of Caffeine crystals in Chloroform**



**Fig 7: DSC Thermogram of Caffeine crystals in DCM**



**Fig 8: DSC Thermogram of Caffeine crystals in CCl<sub>4</sub>**

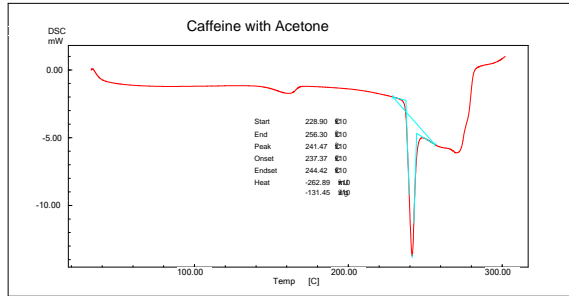


Fig 9: DSC Thermogram of Caffeine crystals in Acetone

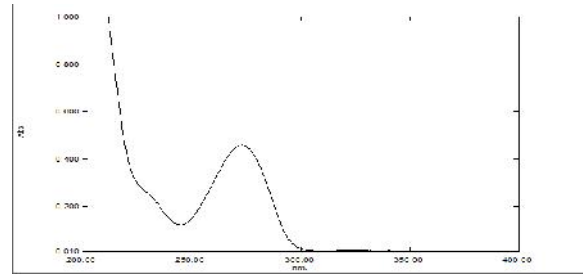


Fig 14: UV-Spectra of Caffeine crystals in Ethyl Acetate

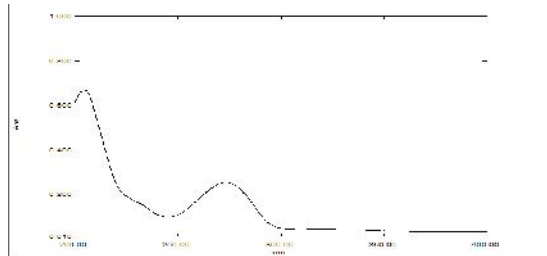


Fig 10: UV-Spectra of Pure Caffeine

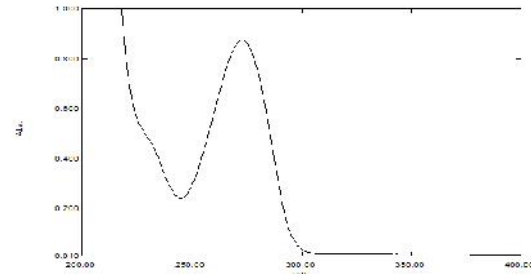


Fig 15: UV-Spectra of Caffeine crystals in Chloroform

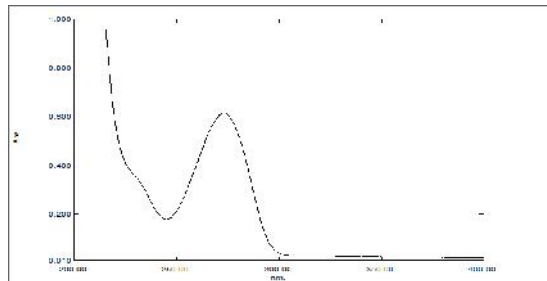


Fig 11: UV-Spectra of Caffeine crystals in Ethanol

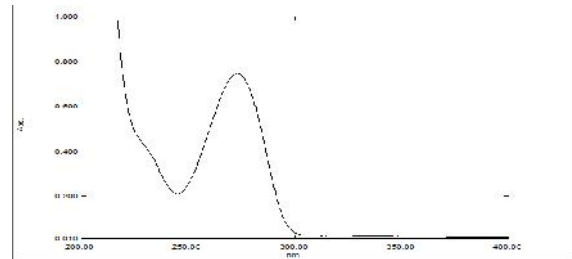


Fig 16: UV Spectra of Caffeine crystals in DCM

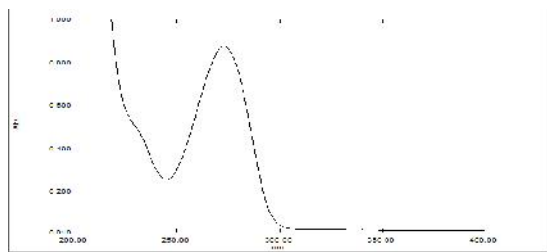


Fig 12: UV-Spectra of Caffeine crystals in Methanol

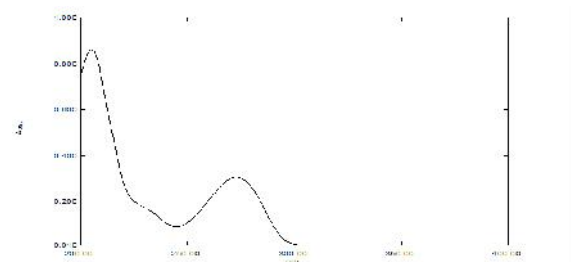


Fig 17: UV Spectra of Caffeine crystals in Acetone

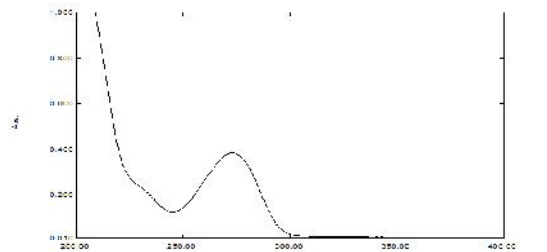


Fig 13: UV-Spectra of Caffeine crystals in IPA

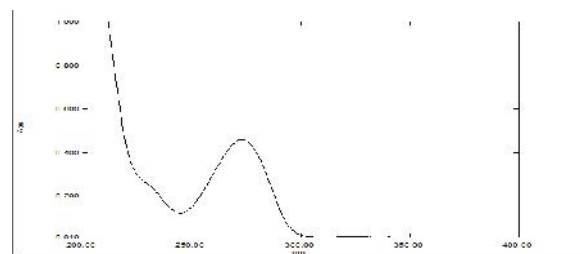


Fig 18: UV Spectra of Caffeine crystals in CCl<sub>4</sub>

**Characterization of Caffeine Crystals by FTIR Spectrophotometer:**

The spectrum observed in FTIR for each crystal were recorded and compared with standard caffeine and shown in Figure No:-19-27.

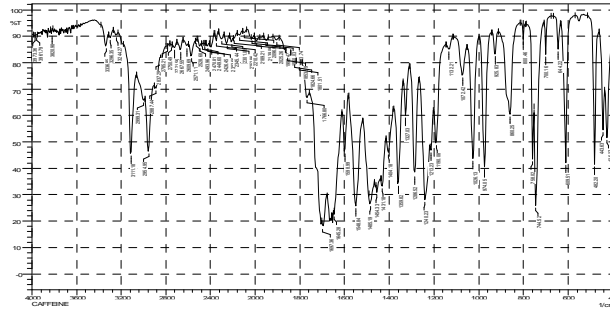


Fig 19: FTIR (KBr,Cm<sup>-1</sup>) spectrum of pure Caffeine

Table 2: Interpreted FTIR data of pure Caffeine

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640Cm <sup>-1</sup>	1645.28Cm <sup>-1</sup>
02	C=N	1250-1020Cm <sup>-1</sup>	1240.23Cm <sup>-1</sup>
03	C=O	1760-1690Cm <sup>-1</sup>	1697.36Cm <sup>-1</sup>
04	N-CH <sub>3</sub>	700-610Cm <sup>-1</sup>	609.51Cm <sup>-1</sup>
05	C-H	3100-300Cm <sup>-1</sup>	2954.95Cm <sup>-1</sup>

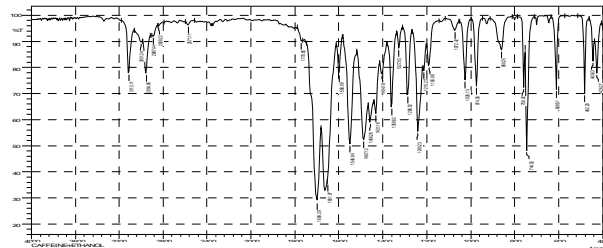


Fig 20: FTIR (KBr, Cm<sup>-1</sup>) Spectrum of Caffeine crystals in Ethanol

Table 3: Interpreted FTIR data of Caffeine crystals in Ethanol

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640Cm <sup>-1</sup>	1651.07Cm <sup>-1</sup>
02	C=N	1250-1020Cm <sup>-1</sup>	1240.23Cm <sup>-1</sup>
03	C=O	1760-1690Cm <sup>-1</sup>	1699.29Cm <sup>-1</sup>
04	N-CH <sub>3</sub>	700-610Cm <sup>-1</sup>	609.51Cm <sup>-1</sup>
05	C-H	3100-300Cm <sup>-1</sup>	2954.95Cm <sup>-1</sup>

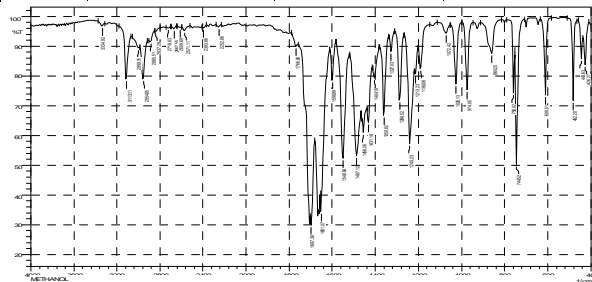


Fig 21: FTIR (KBr, Cm<sup>-1</sup>) Spectrum of Caffeine crystals in Methanol

Table 4: Interpreted FTIR data of Caffeine crystals in Methanol

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640Cm <sup>-1</sup>	1651.07Cm <sup>-1</sup>
02	C=N	1250-1020Cm <sup>-1</sup>	1240.23Cm <sup>-1</sup>
03	C=O	1760-1690Cm <sup>-1</sup>	1697.36Cm <sup>-1</sup>
04	N-CH <sub>3</sub>	700-610Cm <sup>-1</sup>	609.51Cm <sup>-1</sup>
05	C-H	3100-300Cm <sup>-1</sup>	2954.95Cm <sup>-1</sup>

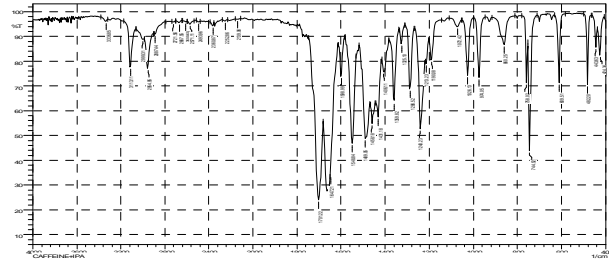


Fig 22: FTIR (KBr, Cm<sup>-1</sup>) Spectrum of Caffeine crystals in IPA

Table 5: Interpreted FTIR data of Caffeine crystals in IPA

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640Cm <sup>-1</sup>	1647.21Cm <sup>-1</sup>
02	C=N	1250-1020Cm <sup>-1</sup>	1240.23Cm <sup>-1</sup>
03	C=O	1760-1690Cm <sup>-1</sup>	1701.22Cm <sup>-1</sup>
04	N-CH <sub>3</sub>	700-610Cm <sup>-1</sup>	609.51Cm <sup>-1</sup>
05	C-H	3100-300Cm <sup>-1</sup>	2954.95Cm <sup>-1</sup>

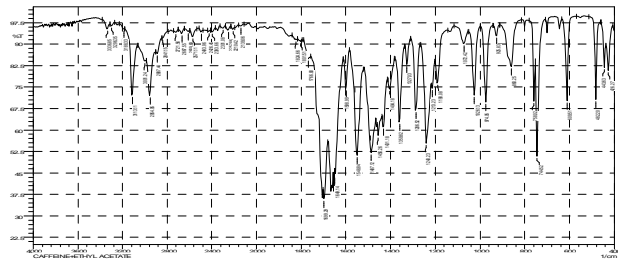


Fig 23: FTIR (KBr, Cm<sup>-1</sup>) Spectrum and data of Caffeine crystals in Ethyl acetate

Table 6: Interpreted FTIR data of Caffeine crystals in Ethyl acetate

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640Cm <sup>-1</sup>	1649.14Cm <sup>-1</sup>
02	C=N	1250-1020Cm <sup>-1</sup>	1240.23Cm <sup>-1</sup>
03	C=O	1760-1690Cm <sup>-1</sup>	1699.29Cm <sup>-1</sup>
04	N-CH <sub>3</sub>	700-610Cm <sup>-1</sup>	609.51Cm <sup>-1</sup>
05	C-H	3100-300Cm <sup>-1</sup>	2954.95Cm <sup>-1</sup>

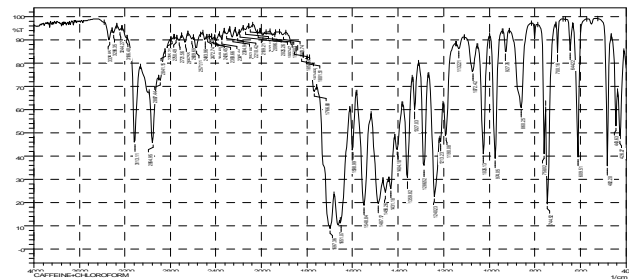


Fig 24: FTIR (KBr, Cm<sup>-1</sup>) Spectrum of Caffeine crystals in chloroform

Table 7: Interpreted FTIR data of Caffeine crystals in chloroform

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640Cm <sup>-1</sup>	1651.07Cm <sup>-1</sup>
02	C=N	1250-1020Cm <sup>-1</sup>	1240.23Cm <sup>-1</sup>
03	C=O	1760-1690Cm <sup>-1</sup>	1697.36Cm <sup>-1</sup>
04	N-CH <sub>3</sub>	700-610Cm <sup>-1</sup>	609.51Cm <sup>-1</sup>
05	C-H	3100-300Cm <sup>-1</sup>	2954.95Cm <sup>-1</sup>

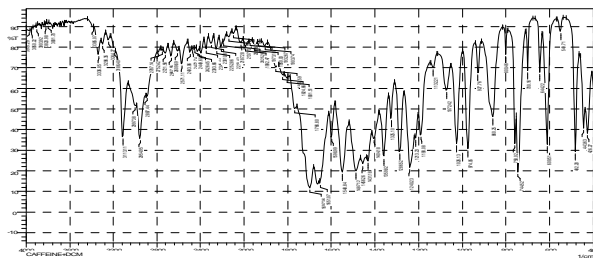


Fig 25: FTIR (KBr,  $\text{Cm}^{-1}$ ) Spectrum and data of Caffeine crystals in DCM

Table 8: Interpreted FTIR data of Caffeine crystals in DCM

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640 $\text{Cm}^{-1}$	1651.07 $\text{Cm}^{-1}$
02	C=N	1250-1020 $\text{Cm}^{-1}$	1240.23 $\text{Cm}^{-1}$
03	C=O	1760-1690 $\text{Cm}^{-1}$	1697.36 $\text{Cm}^{-1}$
04	N-CH <sub>3</sub>	700-610 $\text{Cm}^{-1}$	609.51 $\text{Cm}^{-1}$
05	C-H	3100-300 $\text{Cm}^{-1}$	2954.95 $\text{Cm}^{-1}$

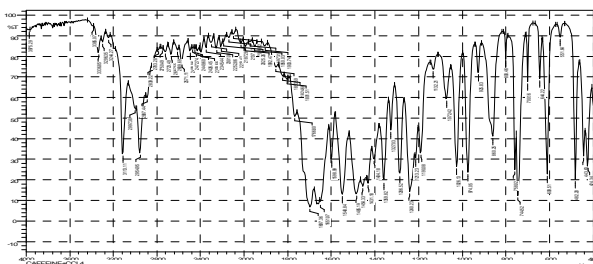


Fig 26: FTIR (KBr,  $\text{Cm}^{-1}$ ) Spectrum of Caffeine crystals in  $\text{CCl}_4$

Table 9: Interpreted FTIR data of Caffeine crystals in  $\text{CCl}_4$

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640 $\text{Cm}^{-1}$	1651.07 $\text{Cm}^{-1}$
02	C=N	1250-1020 $\text{Cm}^{-1}$	1240.23 $\text{Cm}^{-1}$
03	C=O	1760-1690 $\text{Cm}^{-1}$	1697.36 $\text{Cm}^{-1}$
04	N-CH <sub>3</sub>	700-610 $\text{Cm}^{-1}$	609.51 $\text{Cm}^{-1}$
05	C-H	3100-300 $\text{Cm}^{-1}$	2954.95 $\text{Cm}^{-1}$

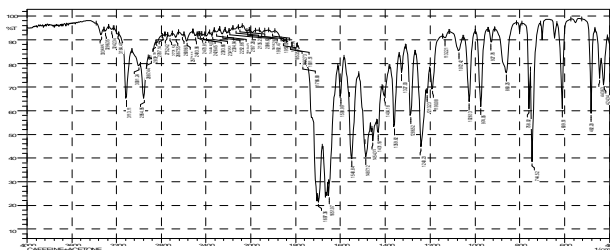


Fig 27: FTIR (KBr,  $\text{Cm}^{-1}$ ) Spectrum of Caffeine crystals in Acetone

Table 10: Interpreted FTIR data of Caffeine crystals in Acetone

Sr.no	Functional group	Standard value	Obtained value
01	C=C	1680-1640 $\text{Cm}^{-1}$	1651.07 $\text{Cm}^{-1}$
02	C=N	1250-1020 $\text{Cm}^{-1}$	1240.23 $\text{Cm}^{-1}$
03	C=O	1760-1690 $\text{Cm}^{-1}$	1697.36 $\text{Cm}^{-1}$
04	N-CH <sub>3</sub>	700-610 $\text{Cm}^{-1}$	609.51 $\text{Cm}^{-1}$
05	C-H	3100-300 $\text{Cm}^{-1}$	2954.95 $\text{Cm}^{-1}$

In the present research, caffeine crystals were prepared in different solvents, dried and subjected for the characterization by using different analytical techniques. The melting behavior of crystals was identified by using the DSC, and data obtained showed that Caffeine crystals

showed different melting behavior than that of the pure Caffeine. The caffeine crystals in carbon tetrachloride showed the maximum change in melting behavior, which indicates the change in the physical property. The UV-Spectrum crystals showed that the maximum absorbance wavelength of all the crystals was 273 nm. Interpreted FTIR data showed that no change in the observed IR values of each group in the structure of caffeine as the observed IR values falls within the acceptance limit of standard values. The UV and IR data indicates that there are no structural changes when compared with standard.

#### 4. CONCLUSION

Recrystallization of Caffeine was carried out by using various organic solvents. The crystals obtained were showed different melting points, which were different from the melting point of pure caffeine. This indicates that recrystallized crystals of Caffeine have some change in the geometry of the structure and can be regarded as polymorphs. Caffeine crystals re-crystallized with  $\text{CCl}_4$  showed a maximum change in their melting point. Hence DSC data indicates the change in the physical properties of caffeine crystals, whereas UV and IR data indicate, no change in the chemical structure. Hence study may conclude that there are possibilities to have a new polymorph in the synthesized crystals. Further, there is a need for characterizing the crystals using NMR, Mass Spectrometry, SEM and XRD techniques.

#### 5. ACKNOWLEDGMENT

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**Conflict of Interest: None**

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