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Original Research

Assessment and Research on Recrystallization on Dexamethasone Polymorph by the Use of Gas Chromatography-Mass Spectrometry and Fourier Transform Infrared Spectroscopy

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Abstract

The presence of more than one crystalline form of a medication is known as polymorphism. Polymorphs have the same molecular formula but varied physicochemical features, such as solubility, which impact the pharmacological effects in the body. This paper set out to investigate how processing conditions and solvent polarity affected the crystallization and physicochemical properties of Dexamethasone. Deep freezing, law temperature cooling (4C°), and room temperature were among the processing conditions used to prepare the crystals, which can have varying degrees of solvent polarity. Researchers looked for drug polymorphisms using microscopy and Fourier transform infrared spectroscopy. The results show that the physicochemical properties of crystals were affected by the solvents and processing conditions used to create them. FT-IR detected spectra that differed from one another. Varying the polarity of the solvent and the processing conditions can lead to crystals with varying characteristics.

Keywords: Polymorphism; crystallization; Dexamethasone; FT-IR; GC-MS

Introduction

Dosage form design frequently makes use of crystalline materials. Various crystalline forms may occur for some. Such shifts in the crystal lattice can occur for a number of different causes. In addition to the drug's method of crystallization and the solvent(s) utilized, processing factors including temperature, pressure, cooling pace, agitation, co-solvent usage, and the presence of additional ions and solutes play a significant role (Haleblium, 1975; Wells, 1988). The ability of a material to exist as two or more crystalline phases

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with distinct layouts and/or conformations of the molecules in the crystal lattice is commonly referred to as polymorphism, and many medicinal solids display this property (Grant, 1999). According to Khan et al. (1998), Hammouda et al. (1998a), Tiwary (2001), and Rasenack and Müller (2002), crystal habit can be changed by using different solvents, which in turn can affect the rate of dissolution. Pharmaceutically relevant properties, such as dissolving rate, powder flow, and compressibility, might vary among different drug habits (York, 1983; Marshall and York, 1983; Garekani et al., 1999). Research conducted by Hickey et al. (2002), Patil et al. (2004), Bhardwaj et al. (2007), Anderson et al. (2008), and Dang et al. (2011) indicates that dexamethasone, a steroid anti-inflammatory medicine, can alleviate inflammation when administered topically. For multiple applications, dexamethasone has been integrated into bioresorbable systems: Research on DM-containing systems for intraocular inflammation treatment after cataract surgery has been conducted by Chang and Wong (1999), Tan et al. (1999), Kagaya et al. (2002), and Kodama et al. (2003). Nakase et al. (2000), Leopold CS, Eikeler (2000), Okazaki et al. (2002), and Nakase et al. (2003) investigated DM-containing microspheres and tablets for the treatment of inflammatory bowel disease. Vascular applications also made use of local DM release. As an illustration, Guzman et al. (1996) and Dev et al. (1997) utilized microspheres and nanoparticles to localize DM administration to the artery wall, with the goal of reducing neointimal development during balloon angioplasty. An intravascular eluting stent was also used to release DM in an effort to prevent restenosis (Lincoff et al., 1997). Desamethasone and 9α-Fluoro-16α-methylprednisolone are alternatives. Common brand names for this medication include Aeroseb-Dex, Decaderm, Decadron (elixir and pills), Decalix, Decaspray, Dexacortisyl, Dexalocal, Dexasone, Dezone, Fortecortin, Hexadrol, Maxidex, Millicorten, Miral, and Oradexon. This is a component of the drug Maxitrol. Chlorofluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, with molecular formula C22H29FO5=392.5 and CAS number 50-02-2. An isomer of betamethasone, dexamethasone is a synthetic glucocorticoid. The powder is white and crystalline. decomposition, m.p. 268–271 degrees. Dialoxan solutions are dextrorotatory. Solvent in acetone, sparsely soluble in methanol, hardly soluble in ether, practically insoluble in water, and soluble in ethanol and chloroform at a ratio of 1:42 and 1:165, respectively. In the last phases of drug production, crystallization from a solution is a common method for drug purification. Crystal size, polymorphism, and habit are all modifiable by the crystallization process. Impurity concentration, solvent type, and cooling rate are some of the crystallization parameters that determine the magnitude of these changes (Mullin, 1983). An API's crystallinity, solubility, and other qualities are crucial to the pharmaceutical industry's production, formulation, and development processes (Lee et al., 2006). Another method that can be employed to offer clear evidence of polymorphism is X-ray powder diffraction (Antonio et al., 2011). For the purpose of characterizing polymorphic forms, additional methods such as thermal analysis (e.g., thermal gravimetric analysis, hot-stage microscopy, and differential scanning calorimetry; spectroscopy, infrared (IR), Raman, and solid-state nuclear magnetic resonance; Brittain, 1999; Evans, 2004; FDA, 2007; Shinbyoung et al., 2007) are useful.

The goals of the current project were to:

1. Investigate how Dexamethasone crystallizes in response to varying processing conditions and solvent polarities,
2. Find the best way to conduct experiments in order to get polymorphs.
3. Learn how these crystals behave and describe their habit.

1.2. Dexamethasone Acetate

The same thing. Acetate of dexamethasone. Brand names without authorization. The injection suspensions Decadron-LA, Dexacen-La-8,

Dexasone L.A., and Fortecortin are available. The formula 2CF=434 is correct.5. CAS—1177-87-3 (in anhydrous form) and 55812-90-3 (in monohydrate form). A decomposing white powder having a melting point of around 225°. Very little soluble in water; ethanol, dehydrated alcohol, chloroform, and ether are all solvents; acetone and methanol are free-flowing solvents.

1.3. Dexamethasone Isonicotinate

Synonym. Dexamethasone 21–isonicotinate. Proprietary names. Auxison(e). It is an ingredient of Dexa-Rhinaspray. $C_{28}H_{32}FNO_6$=497.6**.** CAS—2265–64–7**.** Crystals. M.p. 250° to 252°.

1.4. Dexamethasone Sodium Phosphate

Synonym. Sodium 9α-fluoro–16α-methylprednisolone 21–phosphate. Proprietary names. Dalaron; Decadron (injection); Decasone; Dexacen–4; Dexasone (injection); Dezone (injection); Fortecortin (injection); Hexadrol (injection); Novadex; Oradexon (injection); Savacort-D; Turbinaire Decadron.

$C_{22}H_{28}FNa_2O_8P$=516.4

CAS—2392–39–4

A white or slightly yellow, very hygroscopic, crystalline powder. M.p. 233° to 235°.

Soluble 1 in 2 of water; sparingly soluble in dehydrated alcohol; practically insoluble in chloroform and ether.

1.5. Dexamethasone Tebutate

Synonyms. Dexamethasone butylacetate; Dexamethasone TBA; Dexamethasone tertiary butylacetate.

Proprietary name. Decadron-TBA

$C_{28}H_{39}FO_6$=490.6

CAS—24668–75–5

Practically insoluble in water; soluble in ethanol and acetone.

1.6. Thin–layer Chromatography.

System TP—Rf 32; system TQ—Rf 08; system TR—Rf 00; system TS—Rf 00; system TAJ—Rf 38; system TAK—Rf 07; system TAL—Rf 75; system TAM—Rf 66. (DPST solution.)

1.7. High Performance Liquid Chromatography

System HT—k 4.8; system HY—RI 381; system HZ—retention time 3.4 min; system HAA—retention time 13.1 min.

1.8. Ultraviolet Spectrum Methanol—240 nm (A^1_1=385a).

1.9. Infra–red Spectrum

Principal peaks at wavenumbers 1663, 896, 1622, 1695, 1052, 1603 cm^{-1}.

1.10. Disposition in the Body

Rapidly absorbed after oral administration. Up to 65% of a dose is excreted in the urine in 24 h, mainly as metabolites.

1.11. Therapeutic concentration

Seven extremely low birth weight infants, mean gestational age 25.6 weeks, suffering from bronchoplumonary dysplasia, were administered an IV bolus dose of 0.369 mg/kg dexamethasone sodium phosphate. A mean peak concentration of 250.5 μg/L was reached (Charles, 1993)

2. Materials and Methods:

2.1.1. Preparation of Crystals:

Optical and scanning electron microscopy were used to examine the crystals' particle sizes and shapes (Olympus BX60, Japan, and Jeol JSM T200, Tokyo, Japan, respectively). The specimens were prepared for observation by mounting them on a metal stub using double-sided adhesive tape and coating them with gold under vacuum in an argon atmosphere. The distributions of all crystals were reported after measuring the length and width of at least 100 crystals.

2.1.2. Deep freezing technique:

Always use stoppers to seal containers when using the deep freezing procedure. To ensure the crystals were correct, occasional agitation was employed. The nuclei were isolated and used as building blocks for new crystals. The solution's crystals were collected, allowed to dry at room

temperature, and then placed in a dessicator for future use.

2.1.3. Low temperature cooling technique:

Saturated drug solutions in various solvents were kept in the lower freezer compartment at temperatures ranging from 8 to 15°C for 8 to 10 days to finish nucleation and crystal formation using the low temperature cooling approach. After removing the crystals from the solution, they were allowed to dry for two days at ambient temperature before being placed in a dessicator.

2.1.4. Room temperature cooling technique:

To prepare the samples under room temperature cooling (no stress circumstances), the drug-solvent saturated solutions were left at room temperature for 8-10 days to allow nucleation and crystal growth to finish. After two days of drying at room temperature, the solution's crystals were extracted.

2.2. Characterization of Crystals:

2.2.1. Microscopical Observation:

Under a 40x magnification microscope, the crystals' structure was studied, and pictures were taken to compare them to the pure substance.

2.2.2. Fourier Transformed Infra-Red (FT-IR) Spectroscopy

Pellets were made from the sample powder and examined using FT-IR. The powder was disseminated in KBr powder. Powder diffused reflectance on an FT-IR spectrophotometer (FT-IR 1600 Perkin-Elmer) was used to acquire FT-IR spectra. (Laurance et al., 2006; Press et al., 1999; Brittain, 1999)

2.2.3. Gas chromatography – mass spectrum analysis

The plant extract of dexamethasone was analyzed by gas chromatography–mass spectrometry using a computer-controlled apparatus (QP 2010 Plus SHIMADZU) operating at 70 eV. Using a tiny syringe, about 1µL of the methanol extract was introduced into the GC-MS, and scanning was continued for a duration of 45 minutes. Eluting from the column, the separated chemicals went into a detector that could generate an electrical signal anytime it detected a substance. Computers were able to discern a stronger signal in relation to the sample concentration. The retention time (RT) is the amount of time that elapsed between the injection (the initial time) and the time when the compound was eluted.The computer created a chromatogram, a graph based on the signal, while the instrument was running. As compounds were eluted from the gas chromatography column and into the detector, the chromatogram showed signals at each peak. To quantify the component in the injected sample, the RT was shown on the X-axis and the signal strength was evaluated on the Y-axis. After passing down the Gas chromatographic column, the chemicals were subjected to a stream of electrons in the electron ionization (mass spectroscopy) detector, which caused them to fragment as they were eluted. The discovered fragments were, in fact, ions with charges and a certain mass.The mass-charge ratio, M/Z, was adjusted using the mass spectrum graph, which serves as a molecule's unique fingerprint. Gas chromatography and mass spectrometry analyses of the extract required initial programming of oven temperature, gas flow rate, and electron gun. The oven was kept at a constant temperature of 100°C. Helium gas served dual purposes as both a carrier and an eluent. The helium flow rate was adjusted to 1 milliliter per minute. About 70 eV of energy was released by the electron gun of the mass detector.Here, a column made of 100% dimethyl poly siloxane, known as Elite 1, was used for component separation. We were able to determine the components' identities in the extracts by comparing their retention indices and mass spectra fragmentation patterns with those in the library's collection and in published works. Spectra were compared to those in the Wiley and NIST/EPA/NIH mass spectral libraries to determine the compounds' identities.

3. Results and Discussion

There are a variety of methods that can be used to determine the solid's crystalline or amorphous structure and determine its habit.

3.1. Detection of Dexamethasone by GC-MS (Figures 1 and 2).

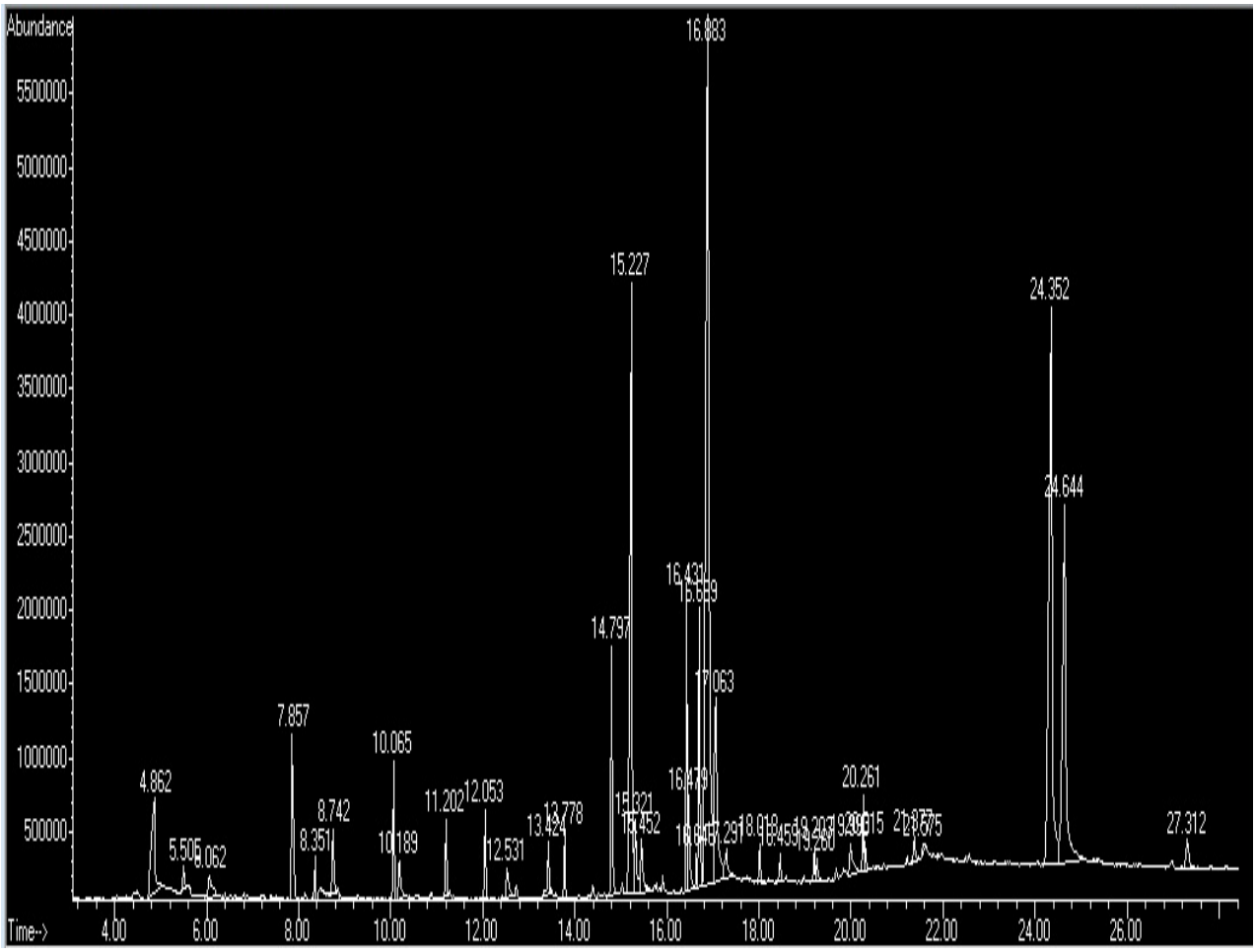

Figure (3-1). GC-MS chromatogram of tablet Dexamethasone.

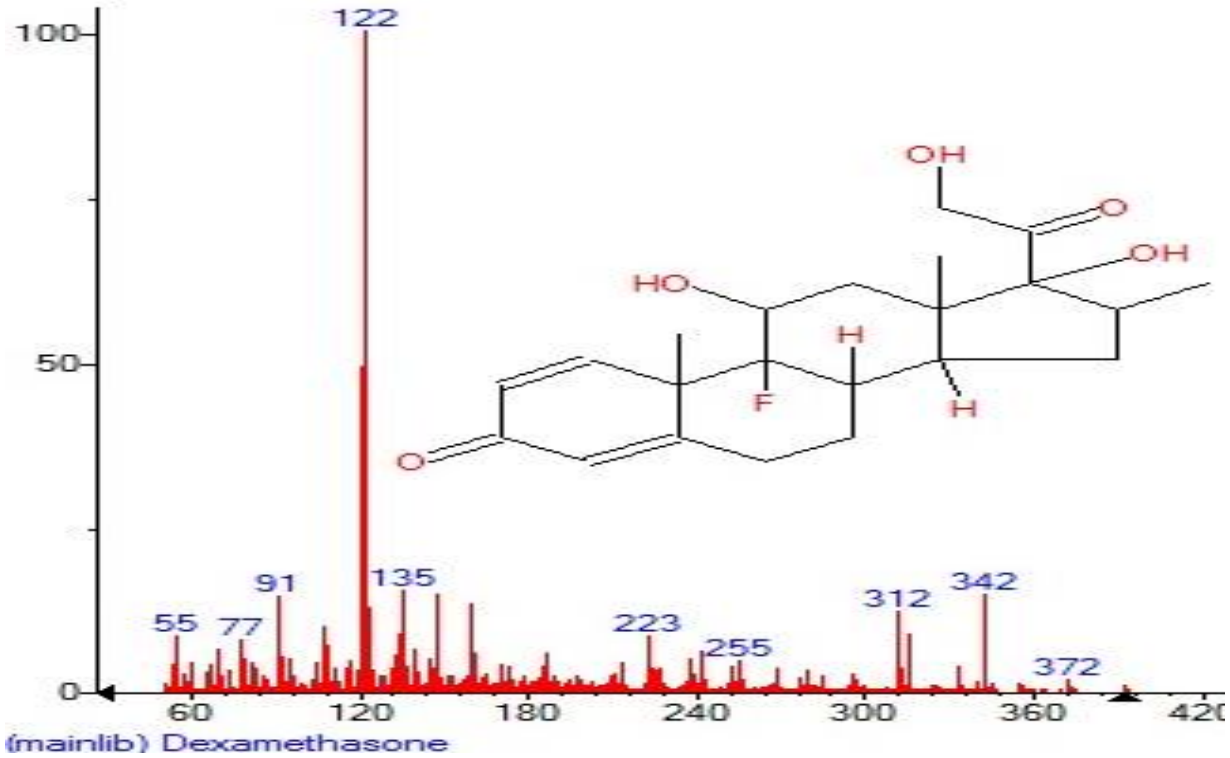

Figure 2. Mass spectrum of Dexamethasone with Retention Time (RT)= 24.352, exact mass formula $C_{22}H_{29}FO_5$

3.2. Microscopical Observation:

The crystals of the medication dexamethasone and samples made using various solvents and processing conditions were examined under a 40x microscope. For the purpose of morphological characterization, photographs were captured using a CCD camera. Figure 3 shows the original Dexamethasone medication sample; Table 1 and Figures 4-8) show crystals generated by various processing settings, such as room temperature chilling, low temperature cooling, and deep freezing procedures. Microscopic analysis confirmed these findings.

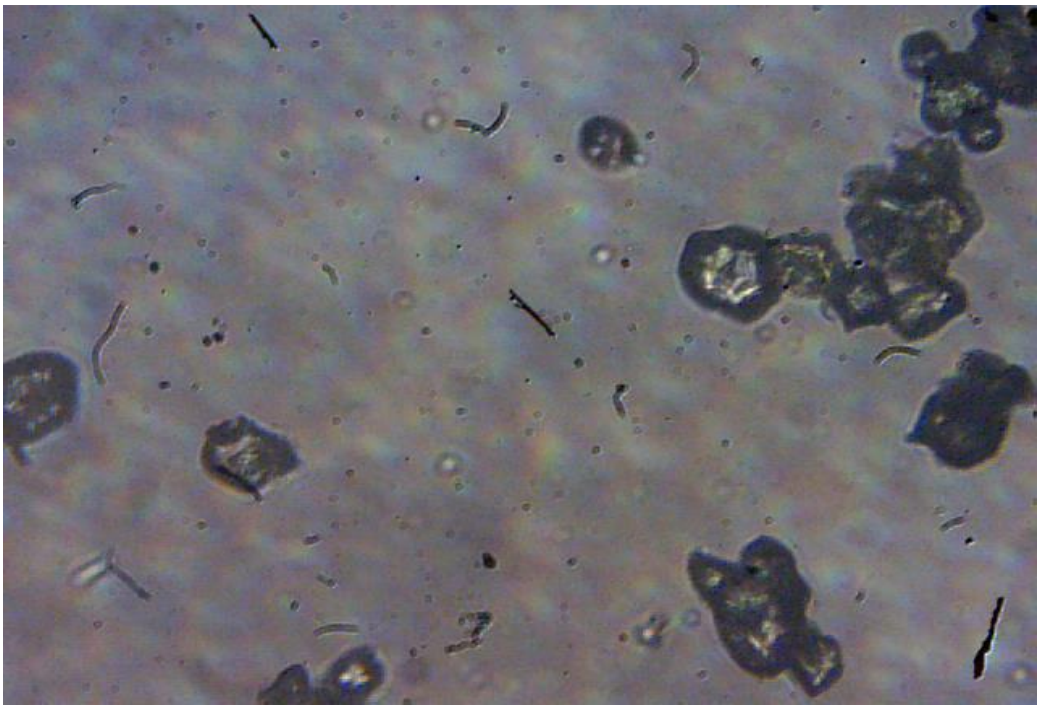

Figure3: Microscopic test of original Dexamethasone crystal 40x.

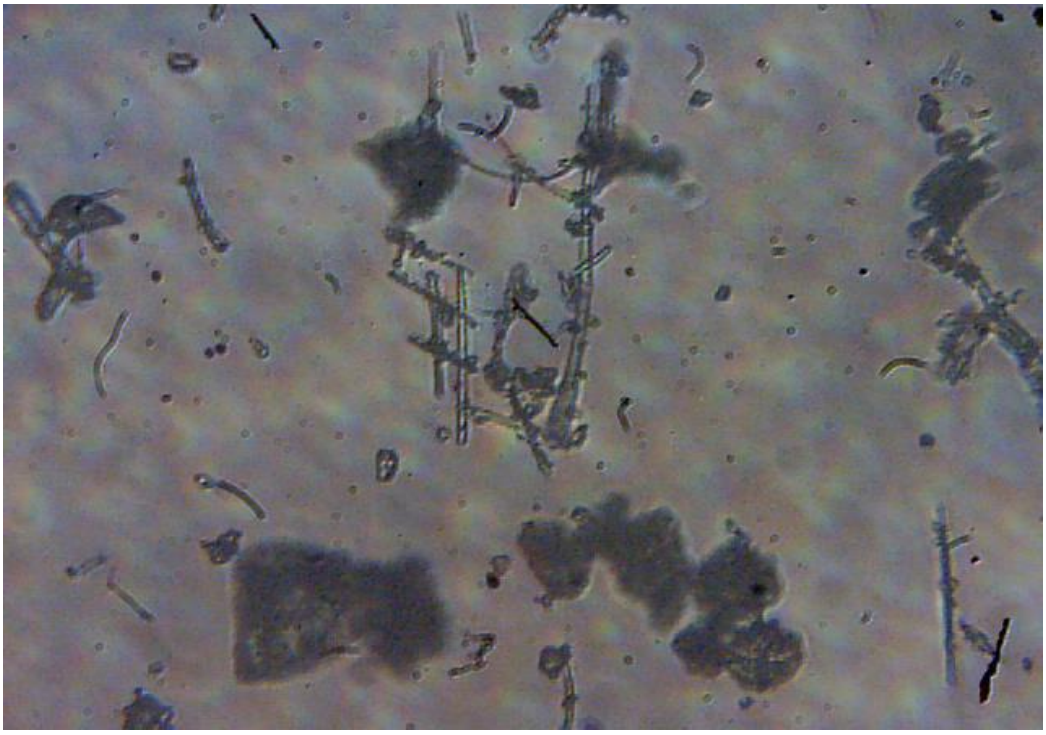

Figure 4: Microscopic test of Dexamethasone recrystallization (Methanolic solvent and room temperature) 40x.

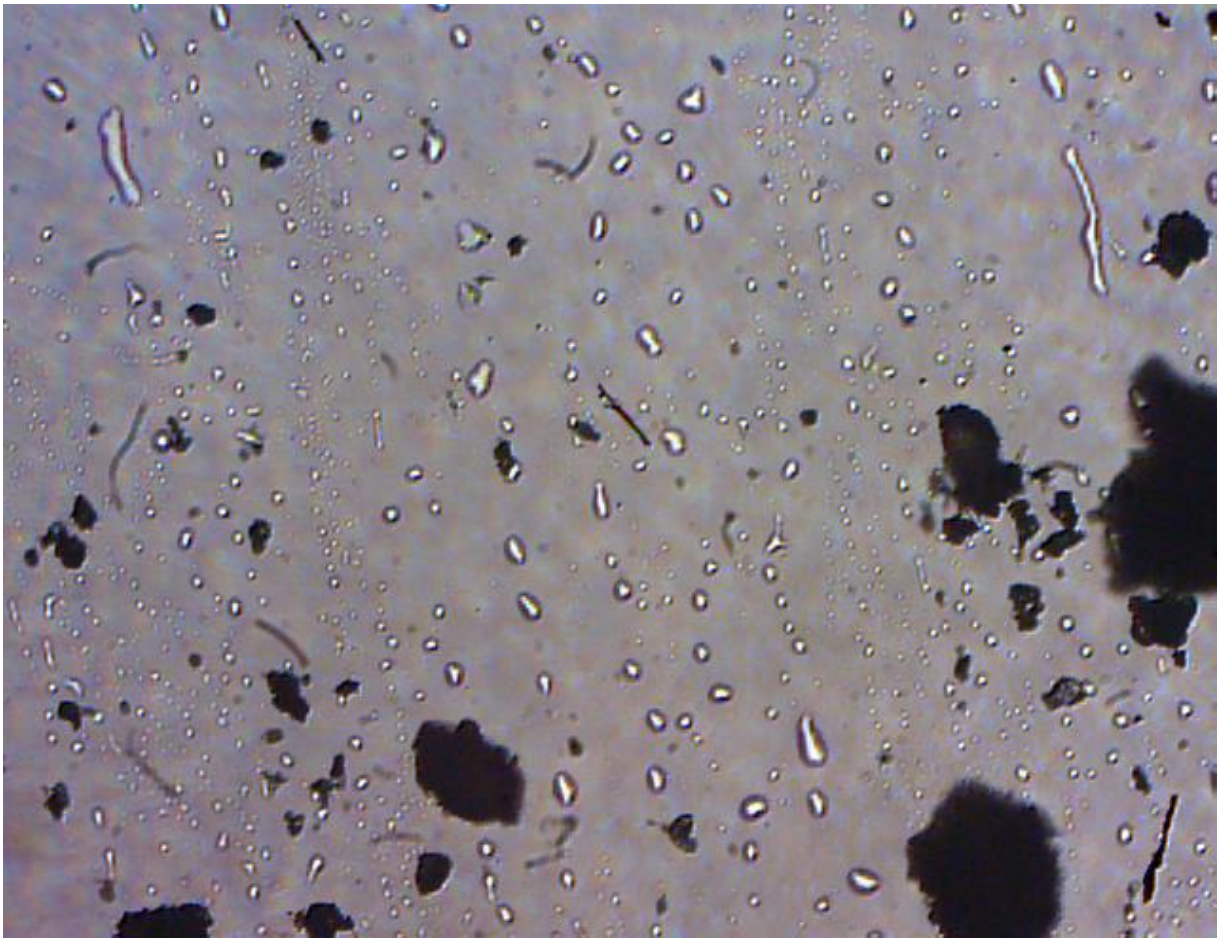

Figure 5: Microscopic test of Dexamethasone recrystallization (Methanolic solvent and 4C°) 40x.

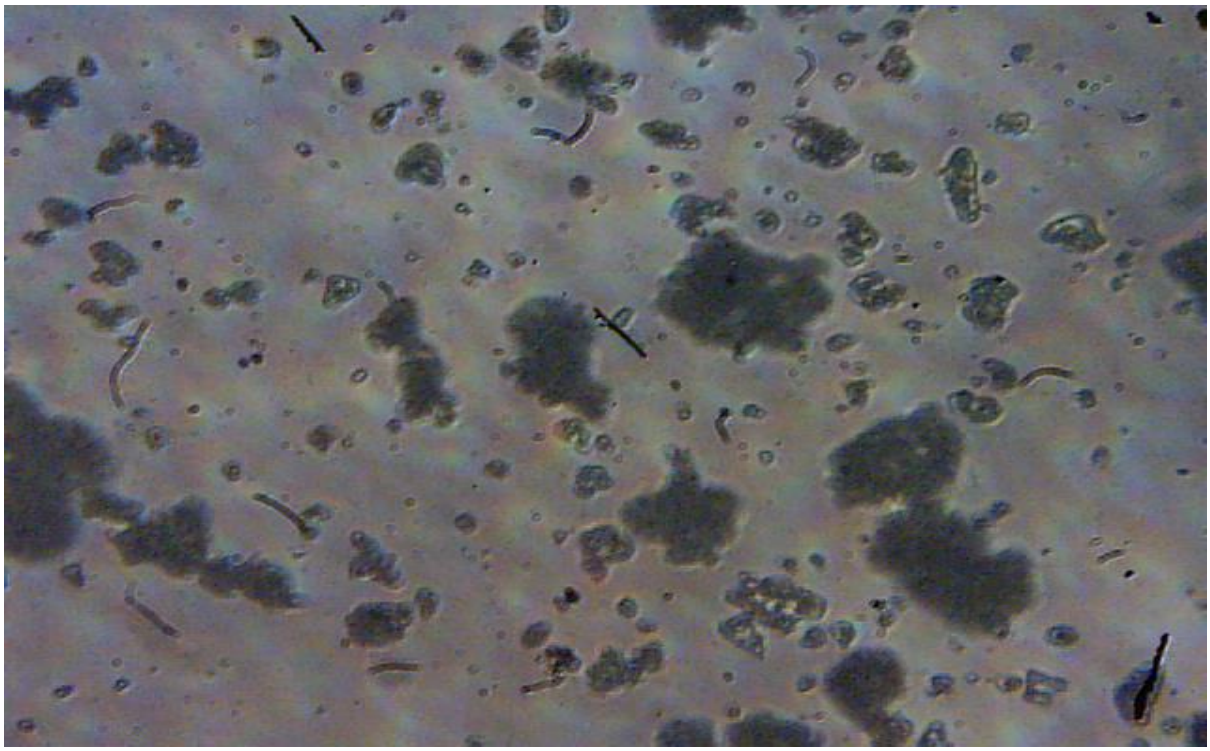

Figure 6: Microscopic test of Dexamethasone recrystallization (Methanolic solvent and deep freez) 40x.

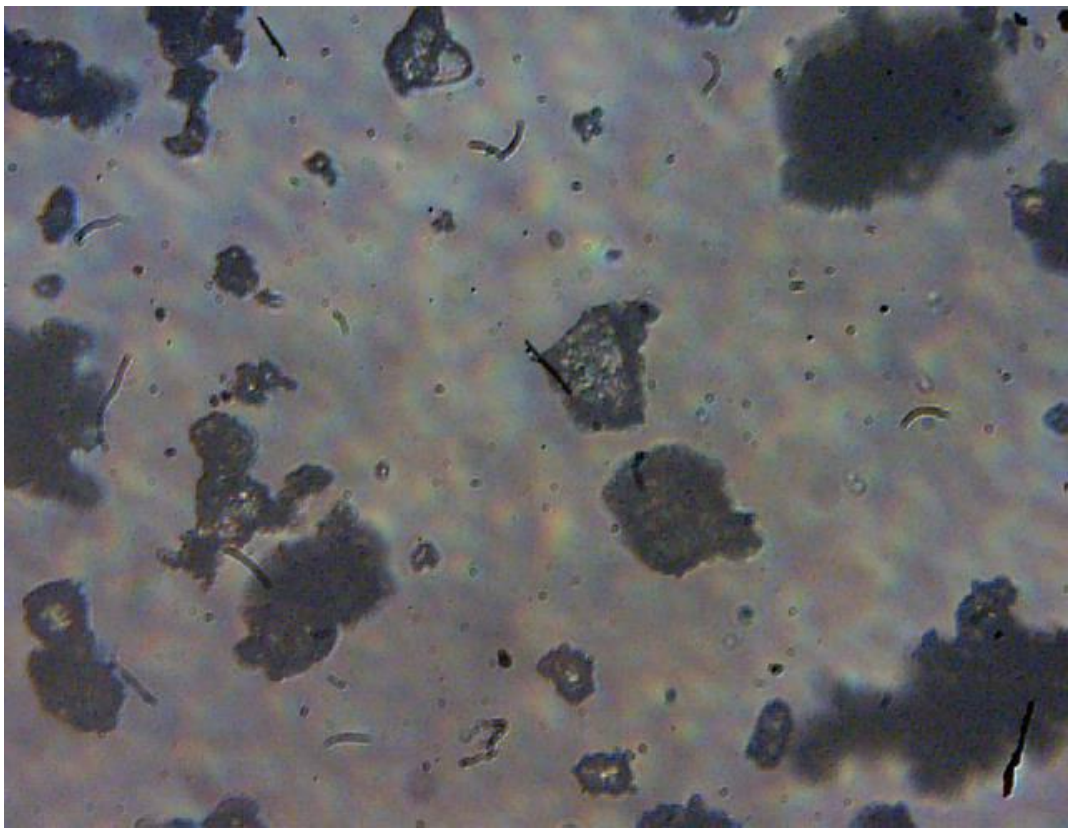

Figure 7: Microscopic test of Dexamethasone recrystallization (Aceton solvent and room temperature) 40x.

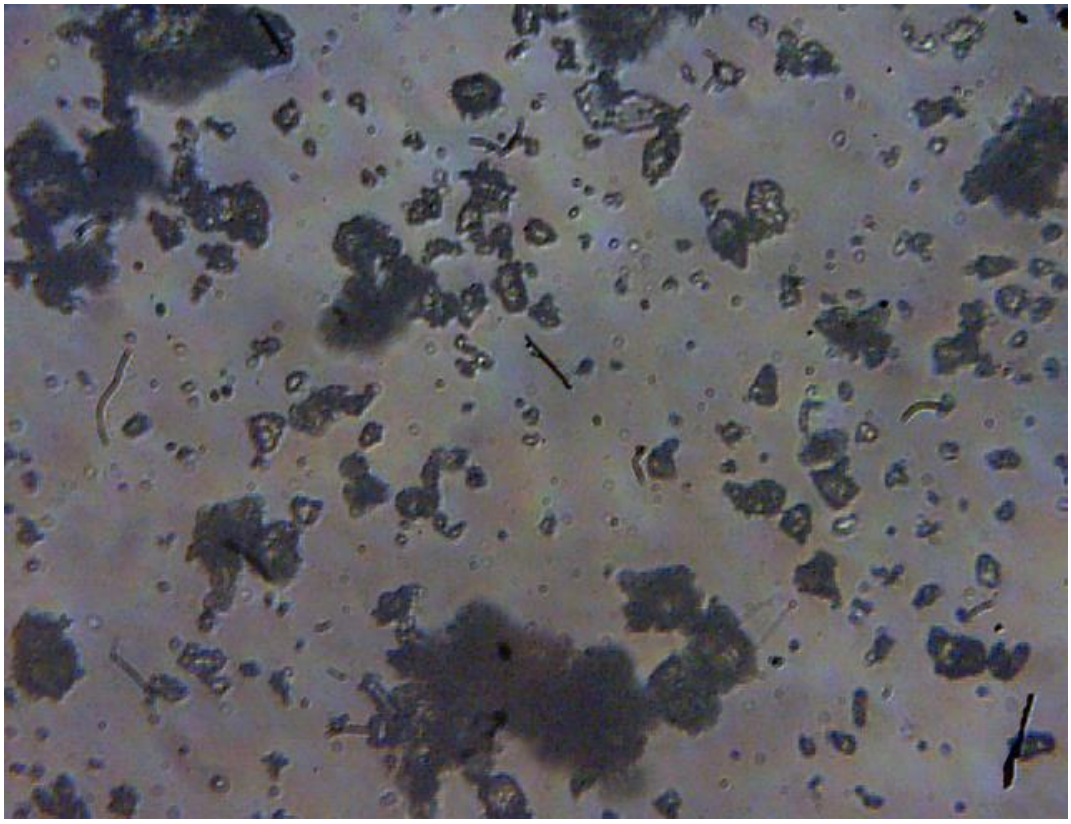

Figure 8: Microscopic test of Dexamethasone recrystallization (Aceton solvent and deep freez) 40x.

Table (3-1): Microscopic observations (40x) of dexamethasone crystals obtained by room temperature low temperature cooling and deep freezing method.

No.	Solvent of crystallization	Processing conditions on the crystallization of dexamethasone		
		Room temperature	**Low temperature**	**Deep freezing**
1.	Methanol	Platy square shape and blunt at both the ends. Transparent crystals	Thick needles, pointed at one end, transparent with little bit broad shape crystals	Small size, hexagonal shaped, transparent and thin as compared to crystals obtained from acetone
2.	Ethanol	Small size, irregular shape, transparent crystals	Irregular shape with small size crystals, Thin needles, shorter in length, opaque crystals	Larger in size, square shaped and thick crystals
3.	Ethyl-acetate	Small size, irregular shaped crystals, Large size, irregular shape, pitted and transparent crystals	Pitted square shaped crystals with little thickness	Small size, almost triangular shaped, thin crystals
4.	Acetone	Large size, irregular shape, platy crystals	Transparent, small size, transparent crystals	Small size, square shaped and thick crystals

3.3. FT-IR Spectroscopic Analysis:

Figure 9–14 displays the FT-IR spectra acquired for many Dexamethasone crystals using various solvents and processing settings. To make a comparison, we utilized the pure drug. The initial step of the spectral analysis was to identify the medicine by its characteristic bands, and the second step was to identify any polymorphisms. The distinctive bands were determined from the structure of Dexamethasone and are listed in Table 2. It seems that the sole substance that was studied was Dexamethasone. According to Mutalik et al. (2007a,b), the crystals grown in this study exhibited the same identifying bands. Figure 8 shows that, despite being synthesized under multiple experimental circumstances with different solvents, none of the Dexamethasone crystals showed significant alterations in the spectra when compared to the pure drug. No fingerprint-specific band has been detected in the infrared spectra.

Table (3-2): FTIR spectra of dexamethasone crystals synthesized in a methanolic solvent subjected to three distinct processing conditions: room temperature, low temperature cooling, and deep freezing.

FTIR wave numbers of recrystallized samples of dexamethasone					
Room temperature		Low temperature 4C°		Deep freezing	
Peak	Intensity	Peak	Intensity	Peak	Intensity
669.30	60.553	667.37	55.829	667.37	53.644
761.88	68.765	704.02	61.170	704.02	59.576
858.68	72.355	759.95	64.109	761.88	62.770
927.76	65.141	860.25	67.573	860.25	66.686
995.27	34.310	927.76	60.287	929.69	59.331
1976.28	60.726	995.27	27.792	995.27	24.211
1147.65	70.034	1076.28	55.330	1076.28	53.939
1242.16	85.739	1147.65	65.407	1149.57	64.364
1292.31	83.358	1242.16	84.188	1242.31	83.855
1334.74	81.617	1296.16	81.930	1292.16	80.402
2341.58	89.684	1334.74	78.932	1334.74	78.529
2841.15	89.500	2341.58	89.560	2341.58	89.463
2902.87	86.804	2671.41	91.923	2671.41	92.304
2929.87	86.431	2727.35	91.169	2839.22	88.421
3277.06	76.733	2839.22	88.544	2929.87	83.941
3331.07	76.655	2904.80	85.159	3300.20	70.421
-	-	2929.87	84.396	3309.85	70.400
-	-	3284.77	71.741	-	-
-	-	3300.20	71.604	-	-
-	-	3309.85	71.625	-	-

Table (3-3): The Fourier transform infrared spectra of dexamethasone crystals synthesized in an acetonic solvent under three different processing conditions: room temperature, low temperature cooling, and deep freezing.

FTIR wave numbers of recrystallized samples of dexamethasone					
Room temperature		Low temperature 4C°		Deep freezing	
Peak	Intensity	Peak	Intensity	Peak	Intensity
657.73	63.217	667.37	61.063	667.37	60.536
669.30	59.062	759.95	70.893	761.88	71.573
761.88	96.632	850.61	73.204	850.61	73.556
850.61	72.304	931.62	66.283	933.55	66.412
860.25	72.369	997.20	37.456	997.20	36.563
931.62	65.168	1076.28	63.877	1076.28	64.914
997.20	34.989	1147.65	72.592	1147.65	73.746
1076.28	62.941	1234.44	85.058	1234.44	85.691
1149.58	71.887	1288.45	81.181	1288.45	82.218
1234.44	84.871	1334.74	83.184	1334.74	83.619
1288.45	80.609	1423.47	82.419	1423.47	83.529
1334.74	82.589	2341.58	89.420	2341.58	88.573
1423.47	81.972	2841.15	91.733	2839.22	91.645

1658.78	**78.660**	**2889.37**	**89.008**	**2889.37**	**89.349**
2341.58	**88.884**	**2924.09**	**88.996**	**2924.09**	**89.477**
2839.22	**91.030**	**3277.06**	**81.196**	**3286.70**	**82.275**
2924.09	**88.215**	-	-	-	-
3261.63	**80.455**	-	-	-	-
3311.78	**79.950**	-	-	-	-

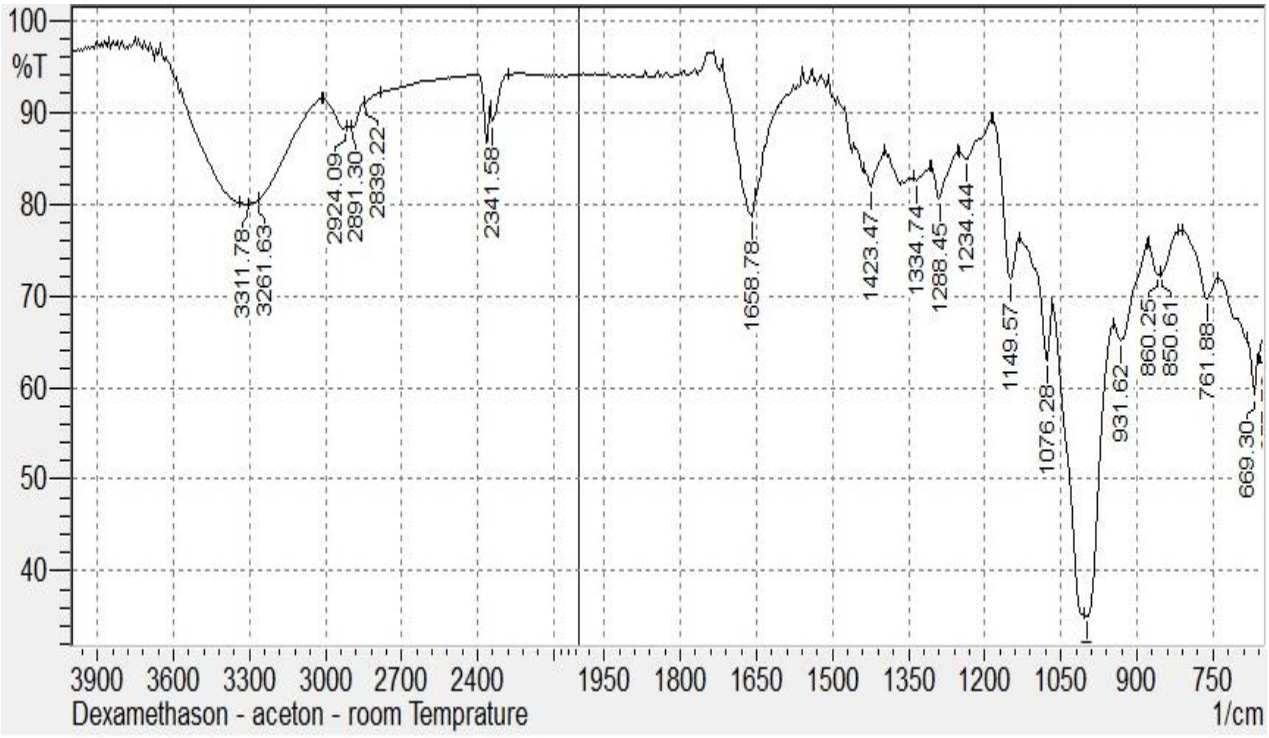

Figure 9. FTIR spectra of the crystals of dexamethasone obtained from acetonic solvent at room temperature.

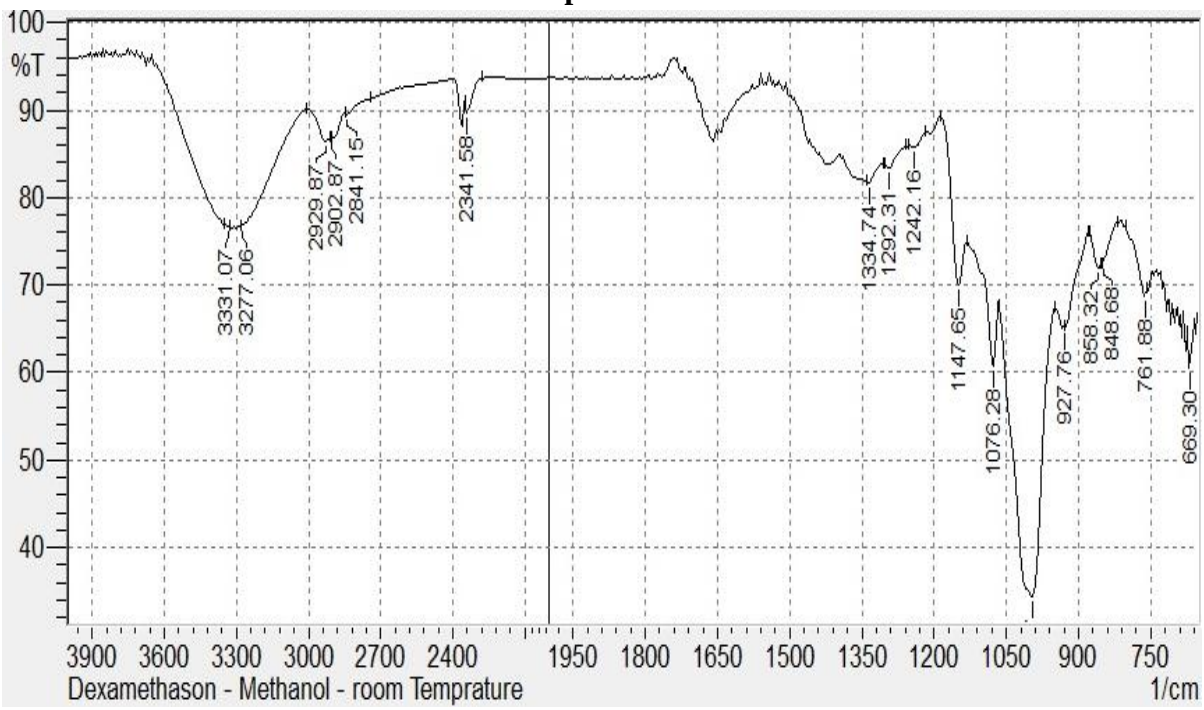

Figure 10. FTIR spectra of the crystals of dexamethasone obtained from methanolic solvent at room temperature.

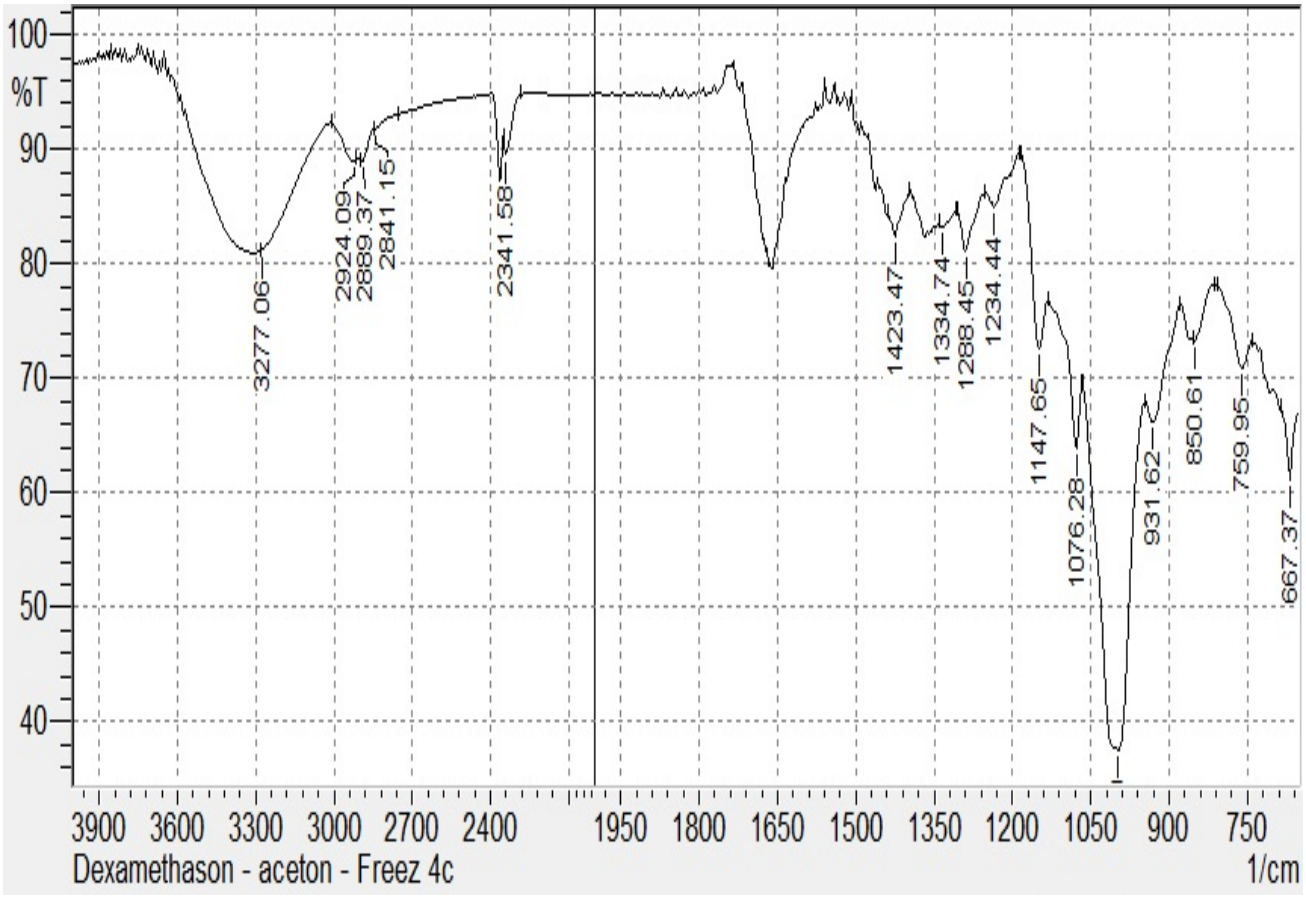

Figure 11. FTIR spectra of the crystals of dexamethasone obtained from acetonic solvent at low temperature.

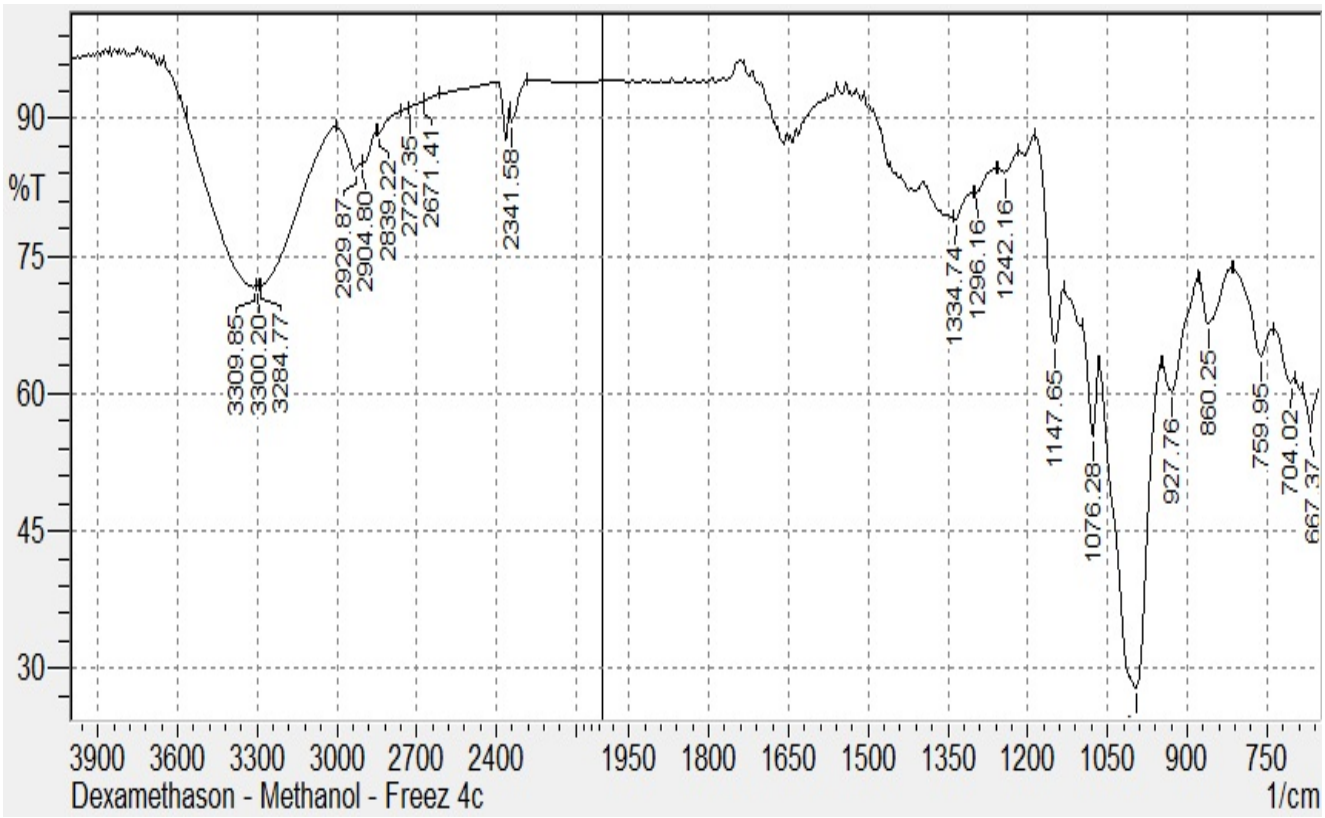

Figure 12. FTIR spectra of the crystals of dexamethasone obtained from methanolic solvent at low temperature.

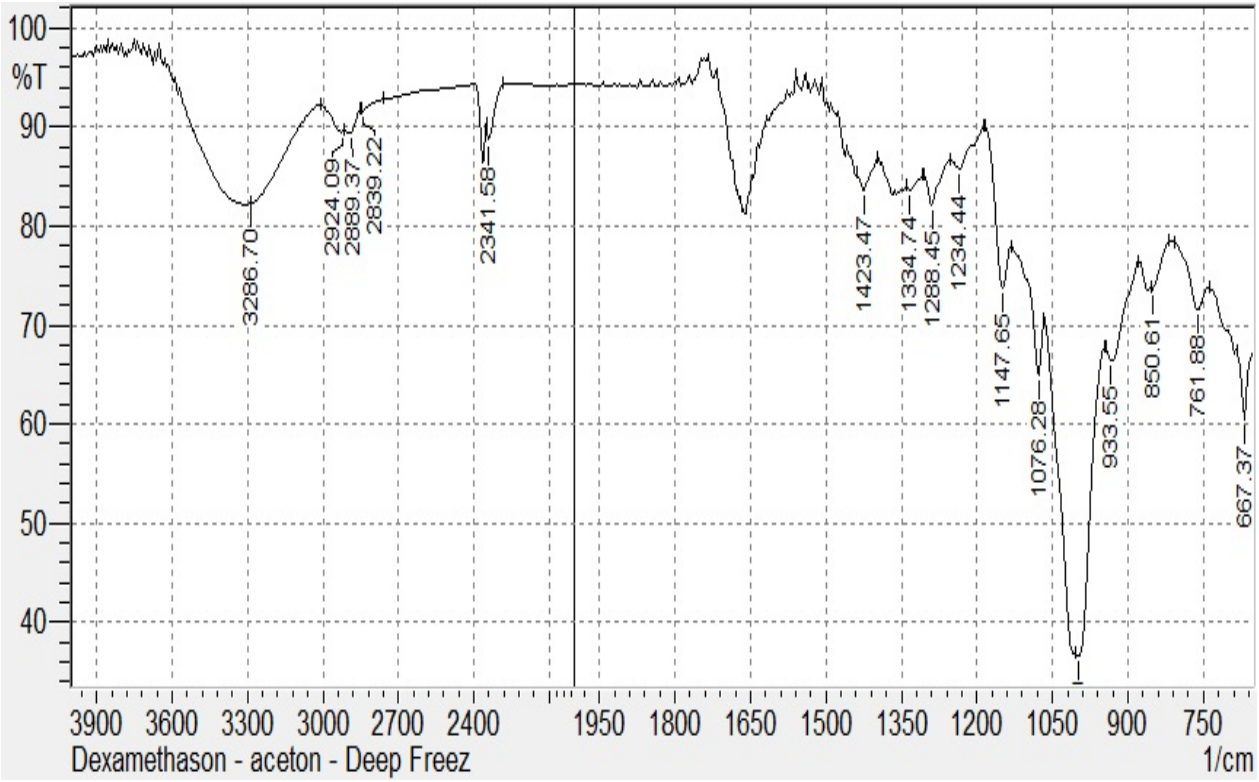

Figure 13. FTIR spectra of the crystals of dexamethasone obtained from acetonic solvent at deep freezing.

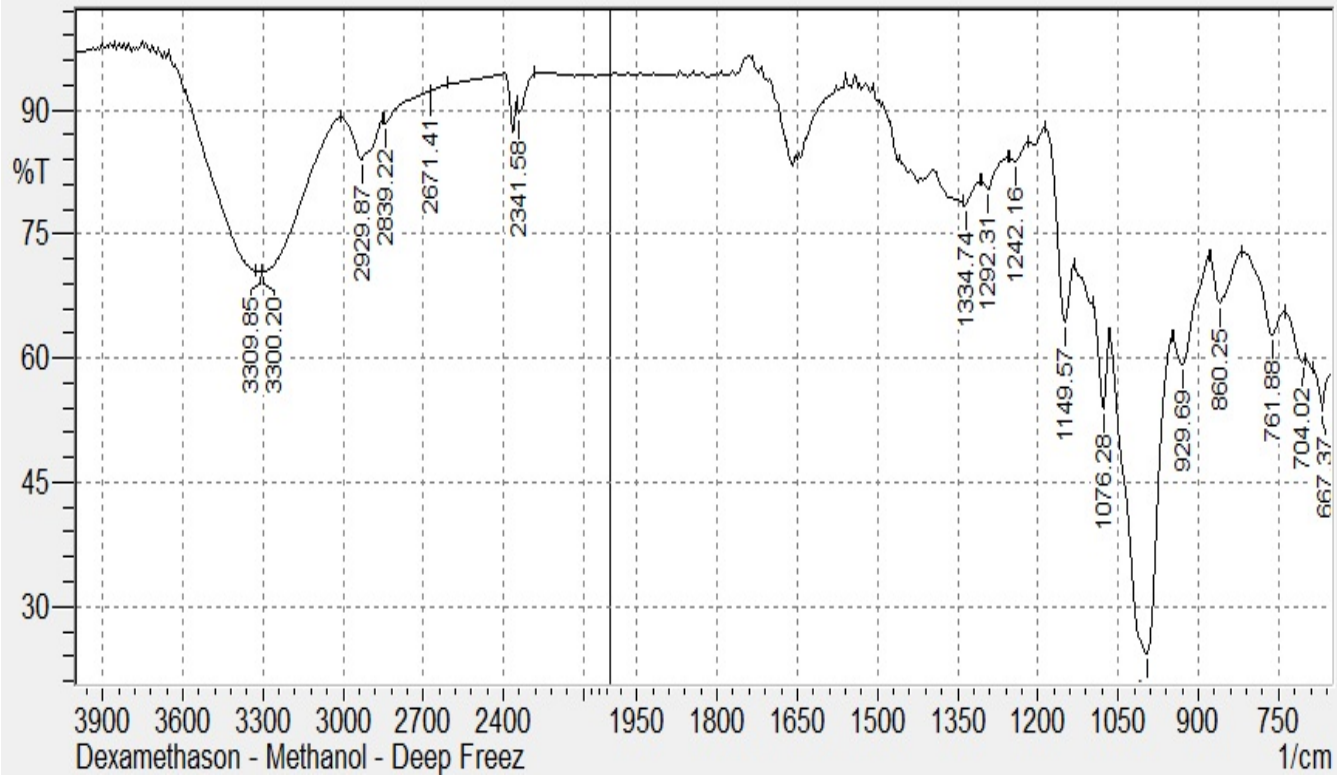

Figure 14. FTIR spectra of the crystals of dexamethasone obtained from methanolic solvent at deep freezing.

Conclusions

The conclusions that have been drawn from the present study include: The crystals obtained from acetone by deep freezing techniques (D1) showed highest solubility as well as change in the polarity and processing conditions can affect the physicochemical properties of Dexamethasone crystals.

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