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**Original Research Article**

# Drug Polymorph Recrystallization Evaluation and Research using GC-MS and FTIR-Spectroscopy

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**Abstract:** The computer produced a chromatogram, a graph based on the signals, while the instrument was running. With each peak signalling the elution of a substance from the gas chromatography column into the detector, the chromatogram revealed the process. The signal strength was used to quantify the component in the injected sample and the RT was plotted on the X-axis. After passing through the Gas chromatographic column and then the electron ionisation (mass spectroscopy) detector the compounds were broken up during elution. It was discovered that the pieces found were ions, ions are charged and each ion has a particular mass. The mass spec graph, which is like a fingerprint for molecules, was used to tweak the mass-charge ratio, M/Z. Initial oven temperature, gas flow rate, and electron gun programming was necessary for gas chromatography and mass spectrometry studies of the extract. The oven was heated to 100°C and kept at that temperature during the whole process. Polymorphism occurs when there are more than one crystalline form of a drug. All polymorphs have the same molecular formula, but different solubility and other physicochemical properties which make them exert different pharmacological effects on the human body. The aim of this study was to investigate the role of solvent polarity and processing conditions on the crystallisation and the physicochemical properties of Dexamethasone. The crystals were produced under different processing conditions such as deep freezing, law temperature cooling (4C°) as well as room temperature. Microscopy and Fourier transform infrared spectroscopy were used by the researchers to hunt for drug polymorphisms. Results showed that the crystals' physicochemical properties were affected by solvents and processing parameters. Distinct spectra were picked up using FT-IR. The properties of crystals can be modified by changing the processing conditions and polarity of the solvent used.

**Keywords:** Drug, Recrystallization, GC-MS, FTIR-Spectroscopy.

## INTRODUCTION

Crystalline materials are frequently used in the formulation of a dosage form. Some may experience other crystal shapes. Such changes in the crystal lattice could be due to several reasons. A variety of processing parameters can have a significant effect such as the crystallisation process that the drug undergoes, the solvent(s) employed, the temperature, pressure, cooling rate, agitation, co-solvent usage, and the presence of other ions and solutes [1, 2]. Many pharmaceutical solids are polymorphic, i.e. they can exist in two or more crystal structures having different molecular structure and/or conformation in the crystal lattice [3]. As discussed in [4-7], the rate of dissolution may be different when the crystal habit is changed by using different solvents. Some drug preparation practices may affect important physical characteristics of the drug, such as rate of dissolution, powder flow and compressibility [8-10]. The studies conducted by [11–14], and Dang *et al*., (2011) [15], demonstrate that topical treatment with the steroid anti-inflammatory drug dexamethasone was effective in decreasing inflammation. There are several devices that incorporate dexamethasone: Tan *et al*., (1999) [16] studied DM containing devices for treating intraocular inflammation after cataract surgery. Dev *et al*., (1997) [17], have investigated microspheres and tablets of DM for use in treating inflammatory bowel illness. Local DM release was also used for vascular applications. For example, we tried to treat the arterial wall during balloon angioplasty in order to reduce neointimal growth by delivering DM at the arterial wall using microspheres and nanoparticles. To further decrease the risk of restenosis, DM

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was delivered by an intravascular eluting stent [18]. Other drugs used in place of desamethasone are 9α-Fluoro-16α-methylprednisolone. This medicine is sometimes called Aeroseb-Dex, Decaderm, Decalix, Dexacortisyl, Dexasone, Millicorten and Oradexon. One of the ingredients in the medicine Maxitrol is this. The chemical formula of the compound is C22H29FO5 and its CAS number is 50-02-2. Dexamethasone is a synthetic glucocorticoid which is an isomer of betamethasone. A white powder formed in crystals, it is in state of breakdown in temperature of 268-271 °. Solutions of dialloxan are dipole-rotatory. It is very volatile in acetone, very little soluble in methanol, almost insoluble in ether and very soluble in water. It is soluble in ethanol (1:42) and chloroform (1:165). One popular way for drugs to be purified in the later stages of manufacture is by crystallisation from a solution. Crystallisation process can be used to alter crystal size, polymorphism and habit. The extent of such changes is dependent upon several crystallisation parameters such as the concentration of impurities, type of solvent used and the rate of cooling [19]. APIs are used in various aspects of manufacturing, formulation and development in the pharmaceutical industry and the crystallinity and solubility of APIs are important for these processes. In addition, X-ray powder diffraction [20], can be used to provide conclusive proof of polymorphism. The aim of the present attempt was to: [1], learn about the crystallisation of Dexamethasone as a function of solvent polarity, (2) find the optimum experimental design to obtain polymorphs. Gain knowledge of the habits and behaviours of these gems.

**Dexamethasone Acetate**

Very much so. Dexamethasone acetate. Use of trademarks without permission. Injection suspensions are an option such as Decadron-LA, Dexacen-La-8, Dexasone L.A., and Fortecortin. The given equation 2CF=434 is accurate.5. CAS—1177-87-3 (soluable) and 55812-90-3 (single hydrate). A white substance that melts at about 225 degrees, and is dusty. It is not water-soluble, but can be dissolved in ether, chloroform, dehydrated alcohol, ethanol, acetone, and methanol.

**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

**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.

**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.

**Ultraviolet Spectrum**

Methanol—240 nm ($A^1_1$=385a).

**Infra–Red Spectrum**

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

**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.

**Therapeutic Concentration**

A bolus injection of 0.369 mg/kg of dexamethasone sodium phosphate was given intravenously to seven babies with a very low birth weight, an average gestational age of 25.6 weeks, and bronchoplumonary dysplasia. The average concentrations reached a maximum of 250.5 µg/L.

# MATERIALS AND METHODS

**Preparation of Crystals**

Scanning electron microscopy (Jeol JSM T200, Tokyo, Japan) and optical microscopy (Olympus BX60, Japan) were used to analyse the particle size and morphology of the crystals. Specimens were mounted on a metal stub with

double-sided adhesive tape, and then coated with gold in an argon-filled vacuum chamber before they were observed. After taking measurements of 100 crystals in terms of length and width, the distributions of all crystals were reported.

**Deep Freezing Technique**

It is essential that containers be stoppered when using the deep freezing method. Occasionally, higher levels of agitation would be required to ensure that the crystals were in the correct state. The isolated nuclei were used to build new crystals. The crystals were collected from the solution, air dried and placed in a dessicator until required for use.

**Low Temperature Cooling Technique**

The drug solutions in various solvents were kept in the lower part of the freezer at the temperature range of 8-15°C for 8-10 days to facilitate the nucleation and crystallization process following the low temperature cooling approach. The crystals were removed from the solution, air dried for two days at room temperature and then dried in a dessicator.

**The Cooling Method by Room Temperature**

It took 8-10 days for the drug-solvent saturated solutions to conclude nucleation and crystal formation at room temperature, allowing the samples to be prepared under room temperature cooling (no stress situations). After two days at room temperature, the crystals were removed from the solution.

**Characterization of Crystals**

**Microscopical Observation**

Photographs were taken to compare the crystals with the pure substance; the structure of the crystals was investigated under a 40x magnification microscope.

**Fourier Transformed Infra-Red (FT-IR) Spectroscopy**

The sample powder was first ground into a powder and then analyzed using FT-IR. KBr powder was used for dispersion of the powder. FT-IR spectra were obtained by powder distributed reflectance method with Perkin-Elmer FT-IR 1600 spectrophotometer.

**A Method of Chemical Analysis That Uses Gas Chromatography and Mass Spectrum Analysis**

An automated gas chromatography-mass spectrometer (QP 2010 Plus SHIMADZU) set up to operate at 70 eV was used to examine the dexamethasone plant extract. Using about 1μL of the methanol extract via a small syringe, scan the GC-MS for 45 minutes. After separation of the chemicals in the column, an electrical signal was generated when a compound was detected. Computers were able to see a stronger signal as the concentration of the sample was increased. The time elapsed from the point of injection (beginning of the run) to the point of elution (end of the run) is the retention time (RT). Helium gas helped to serve two purposes: eluent and carrier. The flow of helium was fixed at 1 mL/min. About 70 eV of energy was released by the electron cannon of the mass detector. We used a 100% dimethyl poly siloxane column Elite 1 for this separation. Comparisons with RI and fragmentation pattern from the library and published literature by mass spectra allowed us to identify the constituents of the extracts. The chemicals were identified by comparing their spectra with the one in the mass spectral library of NIST/EPA/NHI and Wiley.

## RESULTS AND DISCUSSION

There are several methods for determining the structure, crystalline or amorphous, and the habit of a solid.

**Under the Microscope Examination**

The dexamethasone crystals and samples made using various solvents and processing were analysed using a 40x microscope. Morphological characterisation images taken using CCD camera. The original sample of Dexamethasone medication is presented in figure 3, while the crystals obtained from various processing conditions like room temperature chilling, low temperature cooling and deep freezing are presented in Table 1 and figures 4-8). These findings were confirmed using microscopy.

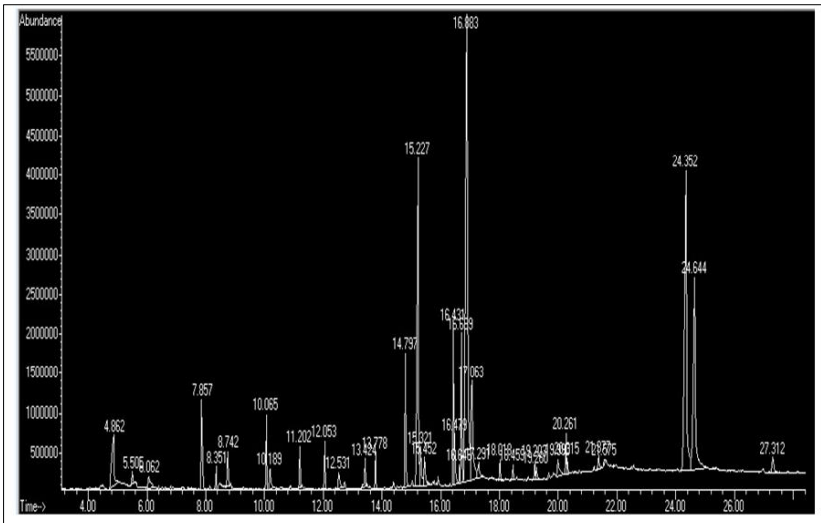



**Figure 1.** GC-MS chromatogram of tablet Dexamethasone.

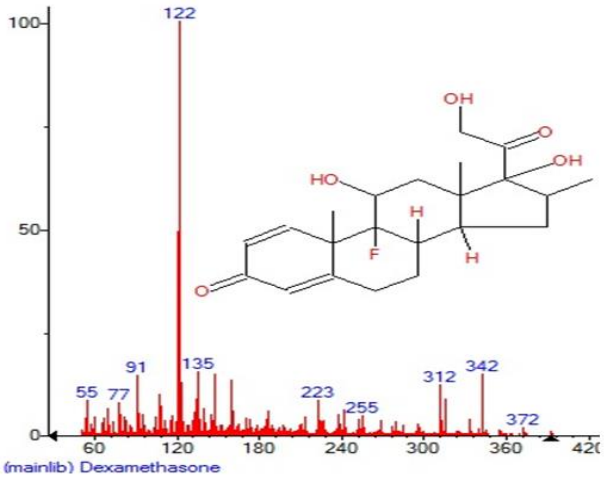



**Figure 2.** Mass spectrum of Dexamethasone with Retention Time (RT)= 24.352, exact mass formula $C_{22}H_{29}FO_5$

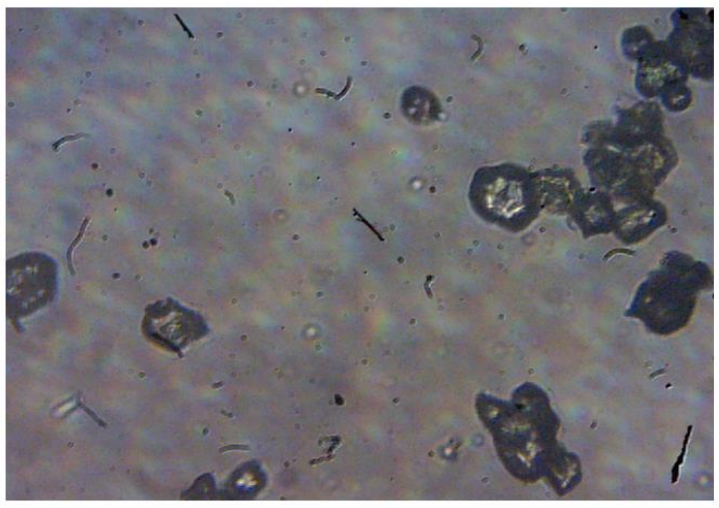


**Figure3: Microscopic test of original Dexamethasone crystal 40x.**

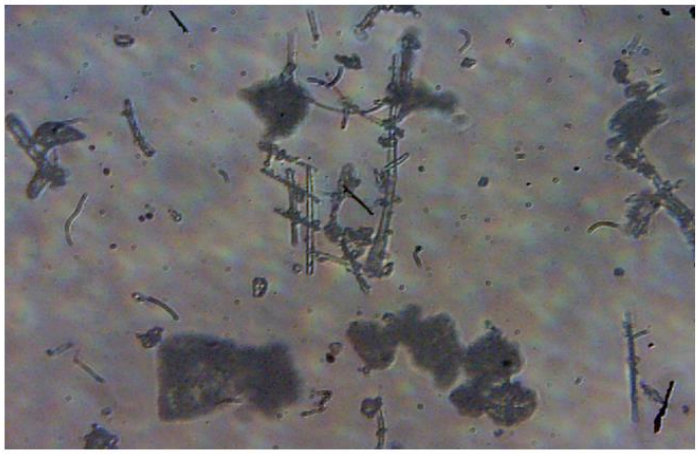


**Figure 4:** Microscopic test of Dexamethasone recrystallization (Methanolic solvent and room temperature) 40x.

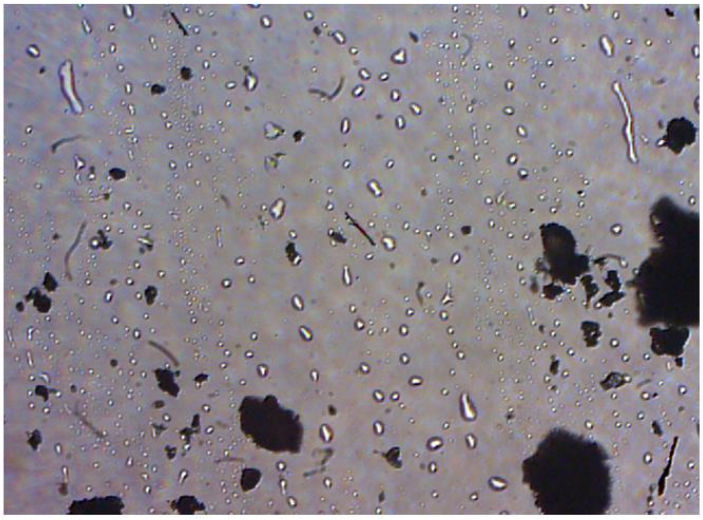


**Figure 5:** Microscopic test of Dexamethasone recrystallization (Methanolic solvent and 4C°) 40x.

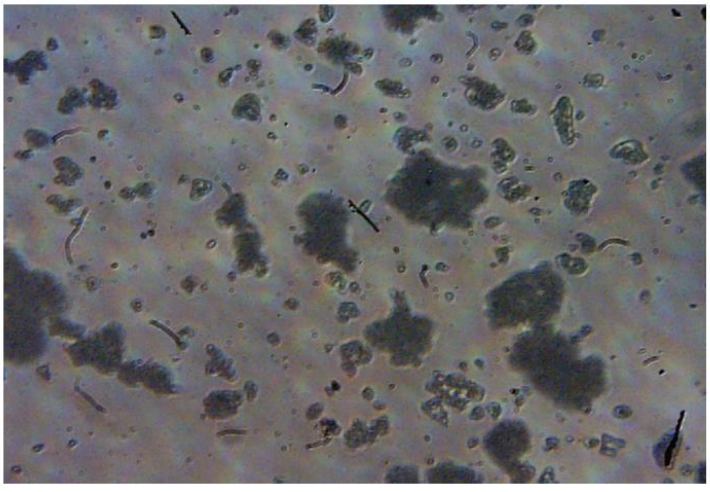


**Figure 6:** Microscopic test of Dexamethasone recrystallization (Methanolic solvent and deep freez) 40x.

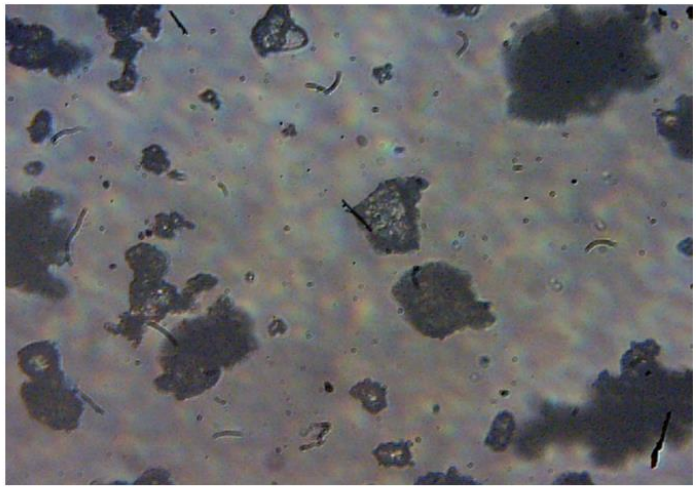


**Figure 7:** Microscopic test of Dexamethasone recrystallization (Aceton solvent and room temperature) 40x.

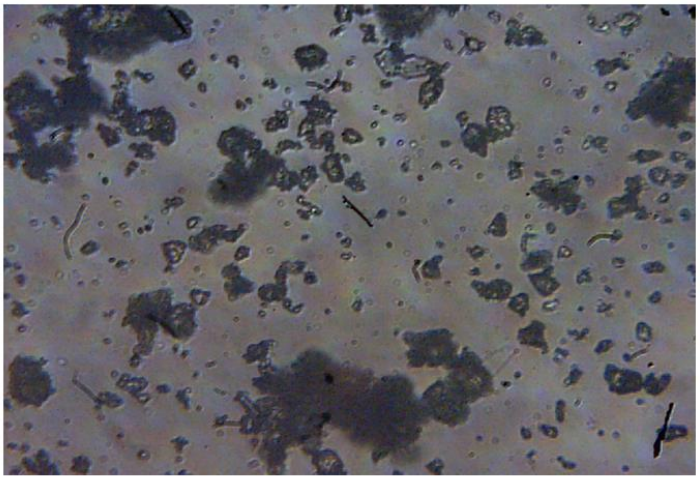


**Figure 8:** Microscopic test of Dexamethasone recrystallization (Aceton solvent and deep freez) 40x.

**Table (1):** Microscopic observations (40x) of dexamethasone crystals.

| 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 |

**FT-IR Spectroscopic Analysis**

The pure drug was used for the comparison. The first stage of spectral analysis was to find the drug by its distinct bands, and the second stage was to discover polymorphisms. All the unique bands are listed in Table 2, which were determined from the Dexamethasone structure. Dexamethasone seemed to be the only drug being investigated. The crystals generated in this investigation had the same distinguishing bands. None of the Dexamethasone crystals showed significant spectrum changes when compared to the pure drug, although they were all synthesised in a variety of experimental conditions using different solvents. Fingerprint bands were not found in the infrared spectra.

**Table (2): FTIR spectra of dexamethasone crystals.**

| 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): The Fourier transform infrared spectra of dexamethasone crystals synthesized in an acetonic solvent**

| 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 | - | - | - | - |

## CONCLUSIONS

The following conclusions could be drawn for the present investigation: Deep freezing the crystals of Dexamethasone in acetone resulted in crystals with the highest solubility (D1), however, the processing conditions and changes in polarity can affect the physicochemical characteristics of the crystals.

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