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Influence of solvents on the crystal habit and properties of paracetamol crystals

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The present study involves the study of the effect of solvents on the crystallization of paracetamol. The crystals were characterized by FT-IR, DSC and powder XRD patterns. The results indicate that the crystals obtained from different solvents exhibited different physicochemical properties. The crystals of desired physicochemical properties may be obtained by selecting solvents of different solubility parameter and dielectric constants.

Many crystalline modifications may have sufficient differences in their physical and thermodynamic properties so that stability and bioavailability may be affected. The importance of polymorphism and pseudopolymorphism in the therapeutic effectiveness of a drug is well recognised and has been previously discussed[2]. There are a variety of reasons for such changes in the crystal morphology. It largely depends on how the crystallization of the drug is conducted, the nature of solvent(s) used, the conditions such as temperature, pressure, cooling rate, agitation, use of cosolvents, presence of other solutes and ions. Though the polymorphs are chemically identical, they exhibit different physicochemical properties such as melting point, solubility and x-ray diffraction pattern. These physicochemical properties further affect the biological properties of drug molecules. Chloramphenicol palmitate exists in various polymorphic states which have been shown to influence its bioavailability significantly[3]. Metastable polymorph and amorphous chloramphenicol palmitate have better bioavailability compared to its stable polymorph. Aspirin though does not qualify to be called as a polymorph, exists in four different crystalline forms[4,5]. These forms have shown differences in dissolution and bioavailability. The crystal habits may influence several pharmaceutical characteristics. For example, tolbutamide has been reported to exist as form A and B and evaluation of tabletting behavior has shown that form B was responsible for both powder bridging in the hopper and extensive capping problems during tabletting. This behavior is due to the platy habit of form B and could be corrected by using nonplaty form A raw material[6].

The aim of the present investigation is to study the effect of various solvents on the crystal forms of paracetamol. Such a study is important because different crystalline forms of the same drug exhibit different thermodynamic and physicochemical properties. Solvents of solubility parameter ranging from 9.8 to 23.4 H were used for crystallizing paracetamol. The crystalline materials were characterized by FT-IR, DSC and P-XRD. Solubility and dissolution studies were also carried out.

EXPERIMENTAL

Preparation of the crystal forms : Paracetamol (Pharmacia India Pvt. Ltd. Hyderabad) was used to prepare the different crystal forms by crystallization from acetone, ethanol, isopropanol, methanol, water and blends of methanol:water (25:75, 50:50, 75:25). The techniques of crystallization from these solvents were essentially the same. An adequate amount of the drug was added to the warm solvent and the saturated solution was allowed to cool. The separated crystals were filtered off and dried under vacuum.

Characterization of crystals : All dynamic differential scanning calorimetry (DSC) studies were carried out

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Table 1 - DSC data of paracetamol crystals

Crystals	Solvent of crystallization	T_o	T_m	T_c	Melt temp range (T_c-T_o)	Heat of* fusion J/gm
a	C.S	168.7	172.7	192.6	23.8	1232.0
b	Isopropanol	167.2	170.5	195.4	28.2	989.4
c	M:W 25:75	166.5	170.5	192.2	25.6	973.2
d	Water	168.8	171.0	191.2	22.3	908.8
e	M:W-75:25	168.8	172.6	199.4	30.6	893.4
f	M:W 50-50	167.3	171.2	195.3	28.0	857.6
g	Acetone	167.3	170.6	173.8	6.5	118.7
h	Ethanol	168.8	172.6	174.8	6.1	88.6
i	1,4 dioxane	167.8	171.4	175.0	7.2	87.8
j	Methanol	166.9	170.8	173.9	7.0	80.0

C.S.-commercial sample, M:W-methanol : water T_o-onset of melt, melting point T_c-completion of the melt. Temperature are reported in degree celsius.
*Mean of three readings.

Table 2 - Cell parameter values of paracetamol crystals

Crystals	Solvent of crystallization	A Å	B Å	C Å	Unit cell Volume $(Å)^3$
a	C.S.	11.78	9.41	7.09	780.2
b	Isopropanol	7.14	9.43	11.53	772.4
c	M:W 25:75	8.09	11.33	9.80	863.8
d	Water	11.73	9.39	7.09	775.6
e	M:W-75:25	11.71	9.42	7.11	778.3
f	M:W-50:50	7.35	9.37	11.48	788.3
g	Acetone	7.26	9.37	11.42	773.9
h	Ethanol	11.67	9.40	7.19	783.6
i	1,4 dioxane	11.66	9.50	7.15	786.9
j	Methanol	7.36	9.37	11.51	791.6

C.S.-Commercial sample, M:W-Methanol:Water

on DuPont 9900 Thermal Analyzer with 910 DSC module. Calorimetric measurements were made with empty cell (high purity alpha alumina discs supplied by DuPont company, USA) as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at a heating rate of 10°/minute in a temperature range of ambient to 250°. About 5-6 mg of sample was subjected to DSC scan. The runs were made in triplicate. X-ray diffraction patterns were recorded using x-ray diffractometer model JOEL JDX-8P, Japan with Cu K_α radiation (γ=1.54056 A). The instrument was operated at a scanning speed of 4000 cps. IR absorption was measured using the KBr pellet method at a compression pressure of 2500 lb/in² on a FT-IR spectrophotometer type FT-IR 1600 Perkin-Elmer Co, Japan.

Dissolution and solubility studies : All dissolution were carried out in distilled water. Electrolab dissolution tester USP XXI a single vessel rotation paddle apparatus Type -II was used. Fifty mg of sieved sample (# 44 sieve) was transferred to the dissolution media (500 ml distilled water) at 37±0.5° and stirred at a rate 50 rpm. The drug concentration in the solution was determined at intervals by measuring the absorbance at 244 nm using a Shimadzu 1601 UV-Vis Spectrophotometer.

Table 3 - Solubility data of paracetamol crystals

Solvent of crystallization	Solubility (mg/ml) Mean ±SD*
C.S	14.6 ± 0.03
1,4 dioxane	14.2 ± 0.00
Isopropanol	13.8 ± 0.06
Acetone	13.8 ± 0.00
Ethanol	13.4 ± 0.00
Methanol	13.2 ± 0.13
M:W-75:25	13.0 ± 0.01
M:W-25:75	12.8 ± 0.01
M:W-50:50	12.6 ± 0.08
Water	12.4 ± 0.03

C.S.-Commercial sample, M:W-Methanol : Water
*Standard Deviation n=3.

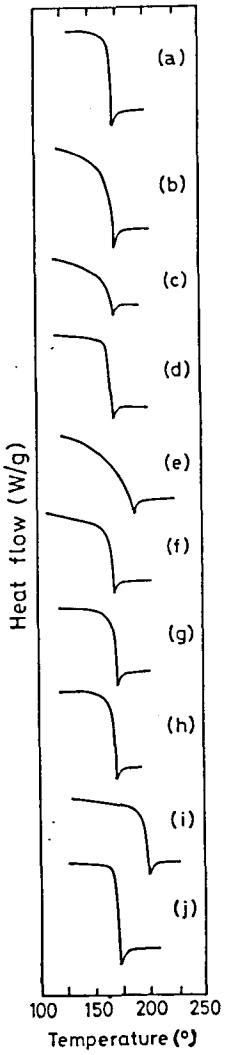

Fig. 1 : DSC thermograms of various crystal forms of Paractamol obtained from different solvents

The solubility of paracetamol crystals in water was studied. The aqueous solubility of paracetamol was found to be 1 in 70. One hundred and fifty milligrams of the sieved crystals (# 44 sieve) were added to 10 ml water in a beaker and stirred for 8 hours at room temperature (32°) with the help of a magnetic stirrer at a speed of 60 rpm. The saturated solution (0.5 ml) was withdrawn with the help of a guarded pipette, appropriately diluted and the absorbance was measured spectrophotometrically at 244 nm.

RESULTS AND DISCUSSION

The infrared absorption spectra of the various crystalline forms showed only slight differences and would

Table 4 - Dissolution time data of paracetamol crystals

Solvent of crystallization	Percent dissolved (Mean ± S.D.*) 10 min	20 min	30 min	40 min	50 min	60 min
C.S	68.0 ± 0.04	78.0 ± 0.00	81.6 ± 0.14	83.4 ± 0.01	90.6 ± 0.00	96.8 ± 0.12
1-4 dioxane	74.0 ± 0.00	76.0 ± 0.11	80.0 ± 0.23	83.4 ± 0.00	89.6 ± 0.06	92.8 ± 0.03
Isopropanol	67.0 ± 0.02	72.0 ± 0.00	80.2 ± 0.01	82.4 ± 0.00	88.6 ± 0.16	90.6 ± 0.00
Acetone	63.0 ± 1.02	73.0 ± 0.00	78.2 ± 0.32	80.4 ± 0.14	82.6 ± 0.07	89.7 ± 0.01
Ethanol	68.0 ± 0.41	72.0 ± 0.26	76.0 ± 0.21	81.4 ± 0.18	84.4 ± 0.60	88.7 ± 0.12
Methanol	67.0 ± 0.03	70.0 ± 0.60	76.0 ± 0.36	80.4 ± 0.00	84.4 ± 0.17	87.6 ± 0.43
M:W 75:25	57.0 ± 0.03	66.0 ± 0.13	70.2 ± 1.20	74.2 ± 0.00	81.4 ± 0.43	86.6 ± 0.23
M:W 25:75	66.0 ± 0.07	69.0 ± 0.01	74.2 ± 0.07	76.4 ± 0.00	80.4 ± 0.72	84.6 ± 1.12
M:W 50:50	58.0 ± 0.00	62.0 ± 0.24	68.0 ± 0.16	74.2 ± 0.13	78.4 ± 0.03	82.6 ± 0.01
Water	64.0 ± 0.10	68.6 ± 0.21	72.2 ± 0.03	74.4 ± 0.01	78.4 ± 0.88	81.6 ± 0.00

C.S.-Commercial sample, M:W-Methanol : Water, *Standard Deviation n=3

not be very useful for differentiating between the crystal forms. DSC thermograms of all the crystals showed sharp single endothermic peaks with characteristic melting points (Figure 1). The data obtained from the DSC scans for the crystals are given in Table 1 in terms of onset of melt (T_o), melting point (T_m) and completion of melt (T_c). The melting points of the crystals are in the range 170-172°. The temperature range of the endothermic peak of all the paracetamol crystals obtained from different solvents lies in the range of 166.5 to 199.4. In DSC the melt temperature of about 25° is normally considered as narrow, indicating a high degree of purity with respect to crystallinity (single crystal structure). The heat of fusion of the crystal forms (calculated from the thermogram peak curves) also differed from each other and are in the order of crystals obtained from isopropanol > methanol: water(25:75)>water>methanol:water (75:25)>methanol:water(50:50)>acetone>ethanol> 1,4 dioxane>methanol. This indicates the crystals obtained from different solvents are different.

Figure 2 shows the x-ray diffraction pattern for all the crystal forms of paracetamol obtained from various solvent. Distinct differences are apparent and are attributed to differences in the arrangement of molecules in the crystal lattices. The observed 2θ data were processed

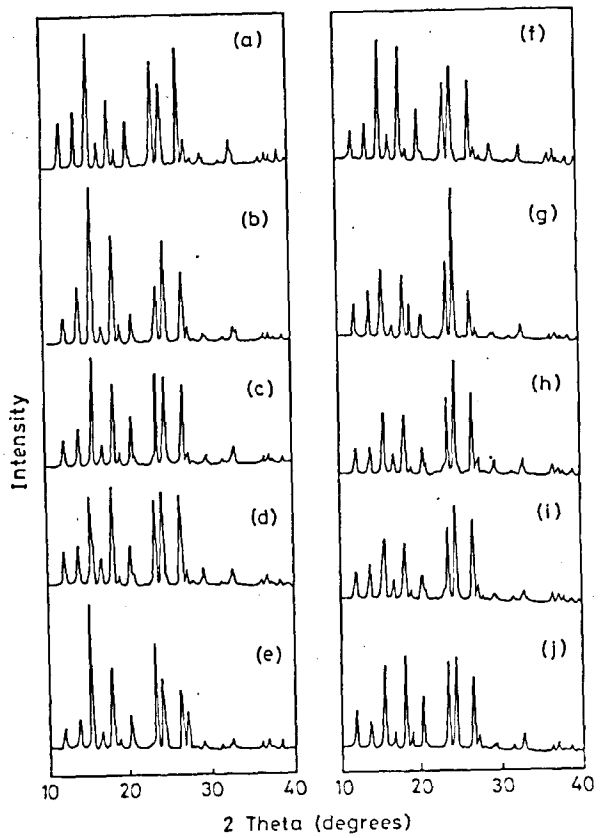

Fig. 2 : X-ray powder diffraction patterns of various crystal forms of paracetamol obtained from different solvents

using multidimension minimization program[7] and cell parameters a,b,c and unit cell volume were obtained (Table 2). A comparison between the solubility of the different crystal forms is shown in Table 3. Crystals obtained from 1,4-dioxane has the maximum solubility (14.2 mg/ml) and crystals obtained from water has the least solubility (12.4 mg/ml). Comparison of the dissolution rates (Table 4) of the different crystal forms indicate that there is a difference in dissolution behaviour.

From these results it is evident that the crystals obtained from different solvents exhibit different physicochemical properties. The physicochemical properties of solvents such as solubility parameters and dielectric constants might have played a role in conferring different characteristics to the crystals of paracetomal. It may be concluded that crystals of desired properties may be obtained by selecting a suitable solvent.

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