ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

SOLID STATE INVESTIGATION OF NABUMETONE

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ABSTRACT:

The present report was aimed at solid state manipulation of nabumetone. Nabumetone is a nonsteroidal anti inflammatory agent with slightly low risk of GI side effects. Different crystal forms of nabumetone were prepared using solvents of different polarity by four techniques, namely solvent evaporation, heating, quench-cooling and seeding. Microscopy, FTIR, X-ray diffractometry (XRD), and differential scanning calorimetry (DSC), were used to characterize crystalline forms of the nabumetone. Acicular and rod shaped crystals were obtained. Metastable polymorphs of nabumetone were identified on the basis of low melting points, and converted into stable form as indicated by the high melting point over a period of 2 months. The polymorph was identified as Form II was reported by earlier works. Evidence indicated that there are two different crystal habit of nabumetone. Physicochemical properties such as melting point, solubility and dissolution were evaluated. Crystals obtained from isopropyl alcohol, and isobutyl alcohol had nearly two fold higher aqueous solubility. Crystals obtained from ethanol has gradual and increased dissolution rate. These crystals may have still low risk of GI side effects.

Key words: Nabumetone, Glipizide, Solubility, Ethanol, Dissolution, Crystals.

INTRODUCTION

Polymorphism may be defined as the ability of a compound to exhibit different crystalline forms.Polymorphs may exhibit significantly different pharmaceutically relevant properties, and hence characterization of polymorphs is essential steps in the preformulation.[2] The polymorphism of an API determines its packing, thermodynamic, spectroscopic, kinetic surface, and mechanical properties in the solid state. The crystal structure can have a direct effect on the solubility of a solid. As different lattice energies characterize different crystal structures, the solubility of different crystal polymorphs must differ as well [1-3].

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The present work reported different crystal forms of nabumetone and their characterization. Nabumetone is a non steroidal anti-inflammatory drug used due to its slightly low risk of gastro intestinal side effects. The literature reports on the nabumetone polymorphs is scanty and only one unstable crystal form was reported so far. There is a need to explore the crystal habit further using different methods of preparation, which were not reported. Further, physicochemical properties of the crystals (solubility and dissolution) were reported in this work. Dissolution is a critical parameter in the evaluation of pharmaceutical dosage forms[4].

Materials & Methods

Nabumetone was a gift sample from Reddy's Laboratory Ltd. Hyderabad, India. The solvents used for crystallization were acetone, chloroform, benzene, ethanol, ethyl acetate, isopropyl alcohol, isobutyl alcohol, DMSO, dimethyl formamide, methanol, tetrahydrofuran and distilled water. The solvents have diverse polarity. These solvents were obtained from S.D. Fine Chemicals Ltd. Mumbai, India.

Crystallization Techniques

The various factors affecting crystal habits are supersaturation, rate of cooling and degree of solution agitation, nature of crystallizing solvent, presence of cosolutes, co solvents and absorbable foreign ions and constancy of conditions. The crystalline forms of nabumetone were prepared by four methods, solvent evaporation, heating, quench cooling and seeding.

a) Solvent evaporation: Saturated solutions were prepared by adding excess quantity of the nabumetone to the solvent at room temperature. The crystals were obtained at room temperature (without any stress conditions). The supernatant was decanted. The crystals were collected and stored in the desiccator until further use.[5,6] The method facilitates the expression of intrinsic behavior of nabumetone.
b) Heating: Saturated solutions were prepared by heating the sample in solvents for 5 minutes. Then crystallization was achieved at room temperature.[7]
c) Quench cooling: Crystals of nabumetone were prepared by sudden cooling of the heated sample. Therefore, the imperfections can be easily induced during solidification. [8,9]
d) Seeding: Nabumetone crystals obtained by method (a) and (b) are separated under microscope. Two shapes of crystals were obtained, rod and acicular. The acicular ones were collected and placed in the boiling tube containing saturated solution of nabumetone in ethyl acetate.[4]

Microscopy:

Photomicrographs of crystals were obtained under microscope (Model Magnus Magnification MLX using Pentax 100 DCIM digital camera.[10]

Melting Point: Melting points were determined using capillary tubes (microprocessor, DBK, Mumbai). Nabumetone have the melting point of about 75.0 – 79.0 ºC (Lit value = 80 ºC).[11]

Infrared Spectroscopy: The crystals were dispersed in KBr powder and analyzed by FT–IR (Shimadzu, Japan).

Differential Scanning Calorimetry (DSC): The themographs of crystals were recorded on DSC of 6300 (Sicko, Japan) apparatus calibrated with indium at a heating rate of 5 ºC/min. The thermal behavior was studied at a scan rate of 5 ºC/min in a covered sample pan under nitrogen gas flow.

Powder X – ray Diffractometry (PXRD): A PXRD diffractometer (Shimadzu, Japan) was used to characterize the crystal habit. The samples were exposed to Cu Kα radiation (45 KV and 40 mA). The divergent slit size was 1 mm, the receiving slit 1 mm, and the detector slit 0.1 mm.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

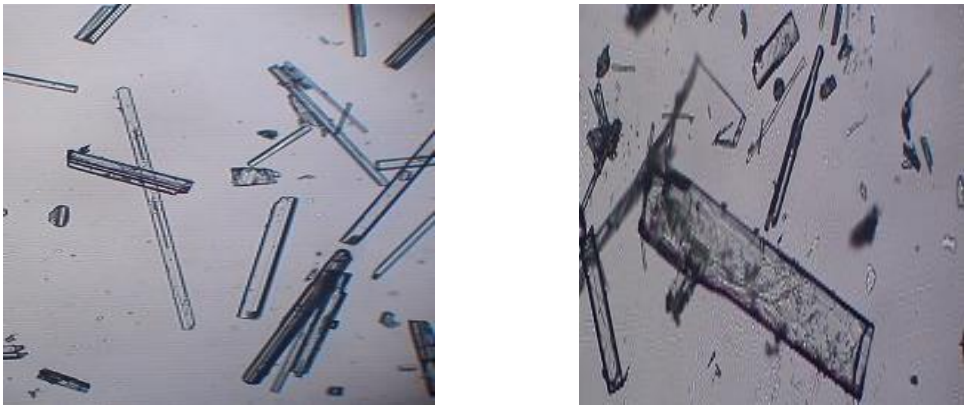
Solubility: Solubility determination is of vital importance for pharmaceutical compounds, especially BCS class II drugs. Nabumetone is a BCS class II drug. Standard plot of nabumetone was obtained in 0.1 N hydrochloric acid at 331 nm. Beer-Lambert obeyed in the concentration range of 20 to 100 µg/ml. The solubility of nabumetone crystals was studied in distilled water by adding excess drug. The flasks were agitated in orbital shaker (Kemi, Kerela) at room temperature (25 ºC) for 24 hours to obtain equilibrium at 100 rpm. Aliquots were withdrawn, filtered, diluted with 0.1 N hydrochloric acid solution (50 % methanol) and analyzed at 331 nm using spectrophotometer (Shimadzu – 1700, Japan).[11]

Dissolution Profile: Samples of crystal forms (250 mg) were taken and kept in contact with 2% SLS dissolution medium at 37 ± 0.5 ºC with agitation at 50 rpm (paddle).[12] Samples were withdrawn at 5, 10, 20, 30, 40 and 50 minutes. The samples were filtered through 0.45 µm filter, diluted and analyzed spectrophotometrically at 270 nm using 2 % w/w solution of SLS as a reagent blank. All investigations were carried out in triplicate. A standard plot of nabumetone was obtained in 2% sodium lauryl sulphate solution at 270 nm (λ_{max}). Beer Lambert's law obeyed in the concentration range of 10 to 50 µg/ml. Sodium lauryl sulphate did not interfere with the analytical wavelength (270 nm) of nabumetone ($r^2 = 0.9961$). The method was as reported earlier.[12-14]

Results and Discussion

Crystals of nabumetone were successfully obtained from 11 solvents using solvent evaporation method. Crystals of nabumetone were studied by microscopy, melting points, IR, DSC, XRPD, solubility and dissolution studies.

Microscopy: The microscopic photographs of a few characteristic crystals were given in Figure 1. There is a clear differentiation of crystal habit. Crystallization of nabumetone provided consistently two types of crystals on replicate experiments.



Acicular, crystals from ethanol Rods, crystals from chloroform

Figure 1. Microphotographs of crystals of nabumetone (10 X magnification).

Melting Point:

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The melting points of nabumetone crystals together with the solvents were given in Table 1. The melting points of nabumetone crystals obtained from chloroform, acetone and ethanol were lower than that of the commercial sample. The differences in melting points were large indicating three different crystal habit or polymorphs. From the Table 1 it can be inferred that metastable crystals were formed. These forms remained stable for 2 months and converted in to stable form, as indicated by the changes in the melting points. In the literature, nabumetone crystals were obtained and designated as Form I (82 ºC) and Form I (68 ºC).In this work, metastable form must be different from the earlier report, melting point 34 to 50 ºC (Table 1). The time for the conversion from metastable to stable form was not reported earlier, due the method of study, hot stage microscopy.[8]

Table 1. Characterization of Nabumetone Crystals obtained from Solvents

Solvent of crystallization	**Polarity [13]**	**Mean melting point, ºC up to 45 days**	**Shape of crystals under microscope**
Commercial sample	-	77.00	Acicular and rod
Chloroform	3.1	52.26	Rod
Acetone	10.4	40.33	Acicular
Ethanol	8.8	34.01	Acicular
Benzene	0	72.09	Acicular
Ethyl acetate	5.3	72.68	Rod
Isopropyl alcohol	6.1	77.37	Acicular
Isobutyl alcohol	3.9	78.88	Acicular
Dichloromethane	7.3	71.87	Rod
Dimethyl sulphoxide	16.4	71.5	Acicular
Tetrahydrofuran	5.7	75.21	Rod
Methanol	12.3	74.94	Rod

FTIR Spectroscopy

FTIR was used for exploring differences in molecular confirmations, crystal packing and hydrogen bonding arrangements for different solid – state forms of an organic compound. FTIR spectra of commercial sample showed characteristic bands: 2955 cm^{-1} (CH_3 stretching – asymmetric), 2889.01 cm^{-1} (CH_3 stretching – symmetric), 1631 cm^{-}

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

[1], 1705 cm^{-1} (C = O stretching), 1226, 1257, 1265 cm^{-1} (Ar – OR asymmetric peak), 1026 cm^{-1} (Ar – OR symmetric peak) and 844 cm^{-1} (aromatic hydrocarbon – bending). Crystals obtained by all the four methods indicated that there is no significant changes in IR. IR failed to indicate the changes in the crystal habit or polymorphs. So, further studies by DSC and XRPD were required for the confirmation of polymorphic changes (if any).

Differential Scanning Calorimetry

DSC indicated that the fusion peaks of nabumetone and the enthalpy of crystals remained same. No significant changes were observed. The differences in the peak onset temperature were marginal (82.3 to 84 ºC) and ΔH_f values (151 to155 J/g) observed between the pure drug and crystals. The molar heat of fusions were matching with the literature (ΔH_f = 31.2 KJ/mol as against the present work, 35.11 KJ/mol).[14] The heat flow differences were significant for nabumetone crystals indicating substantial difference in the packing of the crystals. The DSC spectra failed to provide conclusive evidence of crystal habit changes were observed.

X-ray Diffraction

X – ray powder diffractometry (PXRD) technique was used for characterizing polymorphs. The important peaks were recorded in Table 2 along with observations. A comparison of PXRD with the literature indicated that crystals of nabumetone obtained from ethyl acetate matches with the form II.[4] The commercial sample was Form I. New crystal habits were obtained from solvents acetone and ethyl acetate of nabumetone.

Table 2. Powder XRD Pattern Comparison for Characteristic Changes of Nabumetone Crystals

Sl. No.	Solvent of crystallization	2θ value, º	Intensity, %	Observations	Inference
1	Commercial sample Form I	21.4 24.40 24.83	100 92.70 90.86	Many peaks in pattern indicated crystallinity	Micro crystals under microscope
2	Crystals obtained from acetone	20.90 17.38 21.51	100 47.70 45.67	At two different 2θ values, changes were observed	May be polymorph
3	Crystals obtained from dichloromethane Form II	5.42 24.81 20.62	100 46.86 40.74	At two different 2θ values, changes were observed	May be polymorph
4	Crystals obtained from ethyl acetate	23.16 30.97 7.83	100 38.14 23.00	At two different 2θ values, changes were observed	May be polymorph

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Solubility:

The solubility of nabumetone crystals in water was attempted and the data were recorded in Table 3. The solubility of nabumetone was higher in case of crystals obtained from isopropyl alcohol and isobutyl alcohol than commercial sample. Higher aqueous solubility was obtained, when the polarity of solvents was between 3.1 and 6.1. Solubility data of nabumetone crystals obtained from other solvents was not recorded in this write up because of low aqueous solubility. Among the two forms (acicular and rod shaped), acicular shaped crystals are expected to exhibit higher aqueous solubility than rod shaped, on account of surface area. Thus morphology and polarity of solvents influenced the solubility of nabumetone

Table 3. Physicochemical Data of Nabumetone Crystals from Various Solvents

Solvents used for crystallization	**Polarity index**	**Crystal habit**	**Solubility, mg/ml**	**Cumulative, % dissolved at 30 min**	**Correlation coefficient of regressed equation (R^2 value)**
Ethanol	8.8	Acicular	0.0010	70.8	0.9691
Ethyl acetate	5.3	Rod	0.0003	56.8	0.9491
Isopropyl alcohol	6.1	Acicular	0.0022	60.8	0.9887
Isobutyl alcohol	3.9	Acicular	0.0018	43.0	0.9862
Commercial sample	-	Acicular and rod	0.0012	60.0	0.8467

Dissolution studies

Dissolution rate profiles of all the different crystal forms of nabumetone were evaluated. The order of dissolution of the crystals after 50 minutes is ethanol > isobutyl alcohol > isopropyl alcohol > ethyl acetate > commercial sample > methanol > acetone > chloroform > tetrahydrofuran > benzene > DMSO > dichloromethane. The dissolution profiles of the nabumetone crystals of higher dissolution were recorded in Figure 2. The data of R^2 values in only four crystals of higher dissolution was reported. The profiles indicated that the dissolution trends were gradual and constant as time progressed. However drug dissolution from commercial sample was rapid in 10 minutes. Though 2% sodium lauryl sulfate solution was used as dissolution medium, the relationship between solubility and dissolution was appreciable. Acicular crystals exhibited higher dissolution.[10]

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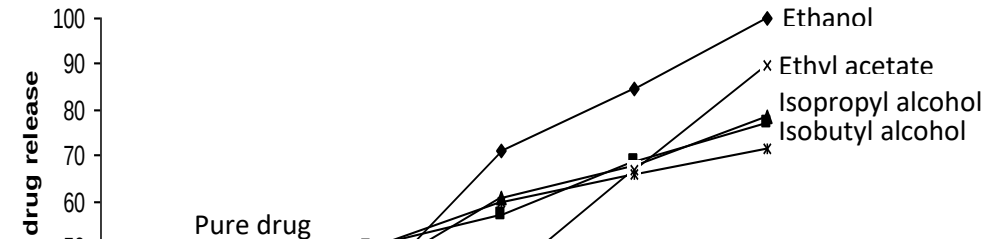

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Figure 2. Dissolution - time profile of nabumetone crystals.

Crystals were also obtained by heating the saturated solution and ambient cooling. Only three solvents namely isopropyl alcohol, tetrahydrofuran and methanol were used. The crystal habit was identical to that of crystals obtained from solvent evaporation method, acicular and rod shaped. The melting points of all crystals remained same indicating the absence of polymorphs. IR spectra did not exhibit significant changes for characterizing polymorphs.

Quench cooling method was expected to exhibit solid state imperfections leading to the formation of metastable crystals. The melting point and IR spectra were similar to the commercial sample. The DSC and XRPD spectra data was recorded in Table IV. DSC pattern remained same except the differences in heat flow (Table 4). PXRD demonstrated the differences in the crystal habit, but it is difficult to conclude the formation of polymorph.

Table 4. Nabumetone Crystal Characterization – Quench Cooling

Sample/ Method	**DSC data**		**PXRD data**	
	ΔH_f , J/g	**Heat flow, J/g.T**	**2θ, °**	**Intensity, %**
Commercial sample (mixture of acicular and rod shaped)	154	14.28	21.84 24.40 24.83	100 92.70 90.86
Quench cooling crystals, Acicular	153	25.52	22.0 24.5 20.5	100 50 42.34

Seeding method of the nabumetone crystal obtained from ethyl acetate indicated that there is no difference in the photomicrographs. The optical microscopy of nabumetone crystal obtained from ethyl acetate showed no difference in their melting point.

Conclusions

Nabumetone crystals were obtained successfully using solvent evaporation, heating, quench cooling and seeding methods. Microscopic observations confirm the changes in crystal morphology. The melting points of nabumetone crystals obtained from various solvents were found to have marginal changes. Based on the microscopy, the crystals of nabumetone were categorized in to two (acicular and rod). The

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

stable form, Form I, is agreeing with the commercial sample. One metastable form was obtained based on melting point and microscopy and was identified as Form II. IR did not show significant changes in their bands**.** The DSC exhibited the characteristic of fusion endotherms of the nabumetone, but no significant changes were observed. As per XRPD, one metastable form was obtained. Two other crystal habit calls for identification XRPD indicated different crystal habit by quench cooling method. The solubility of nabumetone crystals obtained from isopropyl alcohol and isobutyl alcohol showed higher aqueous solubility in water than commercial nabumetone. Dissolution of nabumetone crystals obtained from ethanol, ethyl acetate, isopropyl alcohol and isobutyl alcohol showed higher dissolution than commercial sample, but the dissolution is gradual. Nabumetone crystal obtained from acetone, ethanol and chloroform were polymorphs (melting point) while crystals obtained from solvents, ethanol, isobutyl alcohol and isopropyl alcohol were useful crystal habits because of solubility and dissolution.

Acknowledgments

The authors thank Reddy's Laboratories, Hyderabad, India, for providing the nabumetone sample. Central University, Hyderabad for performing PXRD studies and Kelvin Labs, Hyderabad, for performing DSC studies. The authors thank Dr R.V. Raghavendra, Dept of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Hyderabad for sharing his thoughts.

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ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021