Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

Formulation and Evaluation of Active Ingredients and Its Novel Crystalline Forms to Improve Biopharmaceutical Properties of Itraconazole

Meena Singh[1]*, Pankaj Masih[1], Naveen Gupta[1], Ganesh Prasad Patel[1], Brajmohan Kaushal[1]

[1]Department of Pharmacy, Madhyanchal Professional University, Bhopal, M. P.

Address for correspondence

Ms. Meena Singh, Research Scholar, Department of Pharmacy, Madhyanchal Professional University Bhopal M.P.

Received date: 15/09/2025, Revised Date: 16/10/2025 Accepted Date: 06/11/2025

Keywords:

Novel Crystalline forms, Coformers, Crystallization., Itraconazole, Tartaric acid, Resorcinol

ABSTRACT:

Active pharmaceutical industries (APIs) can be present in various individual solid forms, such as solvates, hydrates polymorphs, salts, amorphous solids and cocrystals. Each system can have exclusive physicochemical properties that can affect many attributes of the drug such as drug bioavailability, stability, purification, manufacturability, purification, and performance. Itraconazole is practically insoluble in water and relies on acidic conditions for optimal absorption. Itraconazole, a potent antifungal agent, is classified as a Biopharmaceutics Classification System (BCS) Class II drug, exhibiting high permeability but poor aqueous solubility, which significantly limits its bioavailability and therapeutic efficacy.

Introduction: Drug molecules with limited aqueous solubility are becoming increasingly prevalent in the research and development portfolios of discovery focussed pharmaceutical companies [1]. Molecules of this type can provide a number of challenges in pharmaceutical development and may potentially lead to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent sub-optimal efficacy in patients, particularly when delivered via the oral route of administration [2]. Advances in the pharmaceutical sciences have led to the establishment of a number of approaches for addressing the issues of low aqueous solubility. These strategies for improving and maximizing dissolution rate include micronisation to produce increased surface area for dissolution, the use of salt forms with enhanced dissolution profiles, solubilisation of drugs in co-solvents and micellar solutions, complexation with cyclodextrins and the use of lipidic systems for the delivery of lipophilic drugs [3]. Although these techniques have been shown to be effective at enhancing oral bioavailability, the success of these approaches is dependent at times on the specific physicochemical nature of the molecules being studied [4]. Solubilisation technologies such as micellar systems are reliant on the acceptable solubility and compatibility of therapeutic molecules in a limited range of pharmaceutically acceptable excipients, whilst the increasing number of weakly ionisable and neutral molecules entering development constrains the opportunities for salt formation as a method of improving dissolution rate [5]. Crystal engineering approaches, which can potentially be applied to a wide range of crystalline materials, offer an alternative and potentially fruitful method for improving the solubility, dissolution rate and subsequent bioavailability of poorly soluble drugs [6]. The ability to engineer materials with suitable dissolution characteristics, whilst maintaining suitable physical and chemical stability provides a strong driver for the utilisation of new and existing crystal engineering approaches to drug delivery system design. The challenges of low aqueous solubility provide an ideal situation for the application of crystal engineering techniques for improving bioavailability, whilst also developing stable and robust pharmaceutical products [7]. This article therefore considers the potential utility of crystal engineering as an approach for designing efficacious dosage forms for poorly soluble drugs. Pharmaceutical cocrystals can improve

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

solubility, dissolution, and bioavailability of poorly water soluble drugs [8]. However, true cocrystal solubility is not readily measured for highly soluble cocrystals because they can transform to the most stable drug form in solution. The objectives of this study are to develop a method to estimate the cocrystal solubility in pure solvent and establish the influence of constituent drug and ligand (i.e., coformer) properties. Cocrystal solubility and solubility product were derived from transition concentration measurements where a solution is in equilibrium with solid drug and cocrystal. Transition concentrations and solubilities are reported for carbamazepine cocrystals in water, ethanol, isopropanol, and ethyl acetate [9]. Itraconazole is a white or almost white powder, practically insoluble in water, very slightly soluble in alcohol, freely soluble in dichloromethane, sparingly soluble in tetrahydrofuran. Cocrystals can be defined as molecular crystals that contain more than one of different molecules typically a drug and a cocrystal former "coformers" in the same structure of crystal lattice, which exists as solids at ambient conditions, bonded together by weak intermolecular interactions such as hydrogen bonding, van der waals forces, and π–π stacking Cocrystallization significantly enhances the solubility and bioavailability of Itraconazole. Optimized cocrystals improve dissolution rates, overcoming pH-dependent solubility challenges. Micromeritic properties of the cocrystal formulation facilitate better manufacturability.

Material And Methods

Determination of λ max: The stock solutions (100µg/mL) of the drugs were prepared in 0.1N Hcl (Itraconazole). The stock solutions were appropriately diluted with the respective solvents to obtain a concentration of 20µg /mL. The UV spectrum was recorded in the range of 200-400 nm on Shimadzu 1800 UV spectrophotometer to find the λ max.

Preparation of Calibration Curve: The stock solution (100 µg/mL) was prepared by dissolving 10 mg of the drug in 0.1N Hcl (Itraconazole) in a 100 mL volumetric flask. From the stock solution, solutions containing 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/mL of the drugs were prepared by appropriate dilutions. Absorbance of these solutions was measured at 263 nm for drug against respective blank solvents [8].

Preparation of Cocrystal by Dry Grinding Method: Three formulas were prepared at different stoichiometric ratio (1:1, and 1:2) of itraconazole with tartaric acid and resorcinol as a conformer as shown in table 1. Drug and coformer were mixed in a mortar using pestle and ground for 45 minutes to form cocrystals. These cocrystals have dried overnight at ambient temperature, then stored in tightly closed containers.

Preparation of Cocrystal by Solvent Evaporation Method: Itraconazole with tartaric acid and resorcinol were carefully weighed at different stoichiometric ratio (1:1, and 1:2) as shown in table 1. Each compound was dissolved in ethanol separately. The two solutions were mixed and sonicated for a few minutes, and then the solution of both components was poured into a Petri dish. The prepared solution was allowed to evaporate at room temperature until the solution is completely dry. The obtained cocrystal solids were stored in a tightly closed container for further evaluation [9].

Table 1: Preparation of itraconazole cocrystal with various conformers

F. Code	Itraconazole: Tartaric acid molar ratio	Itraconazole: Resorcinol molar ratio	Cocrystallization methods
ITC1	01:01	-	Co grinding
ITC2	01:02	-	Co grinding
IRC1	-	01:01	Co grinding
IRC2	-	01:02	Co grinding
ITS1	01:01	-	Solvent evaporation
ITS2	01:02	-	Solvent evaporation
IRS1	-	01:01	Solvent evaporation
IRS2	-	01:02	Solvent evaporation

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

Characterization of cocrystals: The prepared cocrystal in the present research work was preliminary confirmed by comparing results.

Saturation Solubility: An excess quantity of drugs and the formulated cocrystals was added to 10 mL vials containing distilled water to determine the saturation solubility. The vials were immersed in shaker water bath, subjected to agitation and allowed to stand for equilibration for 24 hours. Then, the Filtration and dilution of samples were done, and the concentration of drugs was determined from the absorbance measurement at λmax 264 nm for itraconazole by using an ultraviolet-visible light double beam spectrophotometer [10].

Drug Content: An accurate weight of cocrystal powder equivalent to 10 mg of pure drug was taken and dissolved in a 60 mL of 0.1 N HCl and the volume was completed to 100 mL in a volumetric flask. The resulting solution was filtered using Whatman filter paper 41 and the absorbance of the solution was measured at λmax 264 nm for itraconazole by using an ultraviolet light double beam spectrophotometer.

Scanning electron microscopy: The surface morphology of pure tartaric acid, resorcinol and optimized batch were examined using a scanning electron microscope (Nova Nano SEM 450). The powder sample was directly sprinkled over the double-sided adhesive tape that was attached to an aluminium stub that had been coated with platinum (about 5 nm thick) and made electrically conductive by keeping them in a vacuum for 100 s at 30 W. To examine the surface properties, samples were examined using a scanning electron microscope, and micrographs were captured at various magnifications [11].

Preparation of tablet dosage form of drug containing cocrystals: Equivalent to 10 mg content of drugs were prepared by mixing required quantities of Microcrystalline cellulose (Avicel PH - 102), Di-basic calcium phosphate dihydrate, lactose as filler, starch potato (internal binder) and PVP - K30 (10 % solution in iso-propyl alcohol) as a external binder. The wet granulated mass passed through a mesh # 10 and dried at 60 ºC for 1h in a hot air oven. The dried granules were sized by passing through a sieve # 14. The complete batch of dried granules was collected and mixed with talc as glidant and magnesium stearate as lubricating agent. The granules were compacted into tablets using single-punch tablet compression machine (Khera Instruments Pvt. Ltd., New Delhi), fitted with 8.0 mm flat-faced punches. Compression was controlled to produce a 5-kg tablet-crushing strength [12].

Table 2: Preparation of itraconazole cocrystal with various conformers

Ingredients	Amount (mg /tablet)							
	ITC1T	**ITC2T**	**IRC1T**	**IRC2T**	**ITS1T**	**ITS2T**	**IRS1T**	**IRS2T**
Itraconazole tartaric acid cocrystal	ITC1 (200mg)	ITC2 (200mg)	IRC1 (200mg)	IRC2 (200mg)	ITS1 (200mg)	ITS2 (200mg)	IRC1 (200mg)	IRC2 (200mg)
Microcrystalline cellulose (Avicel PH - 102)	140	140	140	140	140	140	140	140
Sodium starsh glycollate	15	15	15	15	15	15	15	15
Di-basic calcium phosphate dihydrate (DBP)	55	55	55	55	55	55	55	55
Lactose	50	50	50	50	50	50	50	50
Starch (Potato)	30	30	30	30	30	30	30	30

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

Talc (Purified)	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Polyvinyl pyrrolidone K-30	10 % w/v in iso-propyl alochol							
Total weight of tablet	500 mg							

Characterization of Tablet:

Flow properties of granules: The flow properties of drug powder were characterized in terms of Carr's index (%), Hausner's ratio and angle of repose (ɵ). The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to previous discuss equations.

Weight variation: Not more than two of the individual weights deviate from the average weight by more than the percent shown below and none deviates by more than twice that percent.

Thickness: The thickness of tablets was performed on 20 tablets from each formulation. The Vernier caliper was used for the study [13].

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils. Force was applied to anvils and crushing strength that causes the tablet to break was recorded. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches. The chamber is allowed to rotate for 100 revolutions. Then the tablets are removed, dusted and again the weight is taken. The difference in the weigh is calculated and the weight loss should not be more than 1% [14].

In- vitro dissolution study: In-vitro study was performed by using USP type II dissolution apparatus with rotation speed of set to 100 rpm. About 900 mL of 0.1N Hcl at 37 ± 0.5 °C was used as a dissolution media. At predetermined time intervals 1 mL samples were withdrawn, filtered through 0.45 µm membrane and 1 mL blank dissolution medium was added for replenishing of the dissolution medium. The amount of dissolved drug was determined at λmax 264 nm for itraconazole using a UV spectrophotometer [15-16].

Results And Discussion

Analytical study of drug itraconazole: The value of λ_{max} was found to be 264 nm in buffer solution of pH ranging from 0.1N Hcl. This is in accordance with the reports published. Various calibration curves of drug in solution of different pH values were constructed. It was observed that drug in concentration of 2-10µg/ml obeys Beer's Lambert law. The calibration curves data were subjected to statistical analysis and parameters like, slope, intercept, equation for straight line, correlation coefficient and standard error was calculated. The linearly regressed calibration curves were plotted and calculated correlation coefficient which was found to be in the range of 0.9996 to 0.9999 showing good linearity between concentration and absorbance within the concentration range 2-10µg/ml. The standard error value indicates good reproducibility of the data as on running experiments in triplicates. The absorption maxima of drug were reduced while scanning a 0.001% w/v drug solution within a range of 200 -400 nm using double beam spectrophotometer.

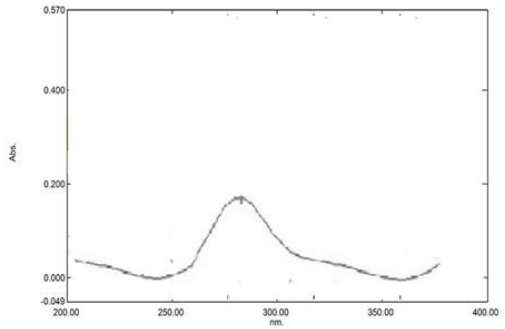

Figure 1: Determination of UV maximum wavelength (λmax 264nm)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

Characterization of Cocrystal for solubility enhancement

The saturation solubility of pure itraconazole in 0.1N HCl (pH 1) at 37°C was found to be 0.8 mg/mL after 24 hours. On the other hand, the cocrystal forms of Itraconazole with tartaric acid and resorcinol at the molar ratio 1:1 and 1:2 prepared by dry grinding method, solvent evaporation method showed an increase in drugs solubility after 24 hours under the same conditions as the pure drug. Cocrystals of itraconazole and tartaric acid prepared by solvent evaporation method at ratio 1:3 showed the highest improvement in dynamic solubility (1.6 mg/mL). The drug content of all formulation was found satisfactory and ranged from 90% ± 0.2 to 98% ± 0.4.

Table 1: Physicochemical properties evaluation of itraconazole cocrystal with conformer

F. Code	Itraconazole: Coformers molar ratio	Cocrystallization methods	Solubility (mg/ml)	Drug content (%)
ITC1	01:01	Co grinding	2.08	95.14
ITC2	01:02	Co grinding	2.74	95.32
IRC1	01:01	Co grinding	10.14	97.45
IRC2	01:02	Co grinding	10.54	98.01
ITS1	01:01	Solvent evaporation	4.78	95.47
ITS2	01:02	Solvent evaporation	5.02	96.01
IRS1	01:01	Solvent evaporation	13.05	98.47
IRS2	01:02	Solvent evaporation	14.11	99.02

Scanning Electron Microscopy (SEM): Morphology and size have a great influence on the physical properties of cocrystal. The SEM micrographs of pure drug itraconazole resorcinol cocrystals are shown in (Figure 2). Crystal habit of itraconazole showed rod-shaped irregular particles with smooth surface morphology and particle size of 500 µm at 100 x magnifications. The coformer resorcinol appeared as block-shaped irregular particles with smooth surface morphology. The prepared cocrystals by a solvent evaporation method, the crystal habit appeared as irregular crystalline shape particles with rough surface in which the particle size was decreased to 20 µm at 2 kx magnification and showed new crystalline materials.

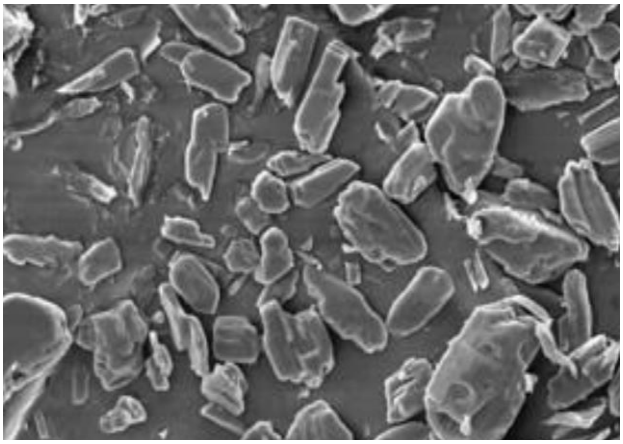

Figure 2: SEM images of IRS2; Itraconazole cocrystal with resorcinol conformer with Solvent evaporation method

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

Characterization of tablet dosage form of drug containing cocrystal: The blend was initially characterized for pre-compression and post-compression parameters. Pre-compression characterization was done for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of pre-compression characterization include angle of repose (21.65-26.77°), bulk density (0299-0.385 g/cm^3), tapped density (0.417 - 0.473 g/cm^3), Carr's index (14-25 - 36.78 %) and Hausners ratio was found to be (1.16 – 1.58) (Table 6.19 – 6.24). Post-compression characterization includes thickness, hardness, friability, weight variation, drug content, buoyancy lag time, floating time and in-vitro drug release. %. The average weights of the entire prepared tablet were 510.15±.05 mg to 491.27±.01 mg which was within the specified limit. The thickness of all the tablets was in the range of 2.59 to 2.51 um. The hardness of all the formulated tablets was found to be in the range of 4-7kg/cm$^{2.}$ Friability was found to be 0.31 to 0.91. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium resulted in immediate tablet floatation with a lag time in between 50 to 180 seconds **(Table 3)**. The drug content of the entire prepared tablet was found to be 95.29±0.98 to 102.32±2.16.

Table 3: Pre-compression characterization of itraconazole cocrystal tablet

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's Ratio	Angle of Repose (Ɵ)	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
ITC1T	0.358	0.433	23.32	1.21	26.77	494.59±0.04	2.54±0.09	8.0±0.02	6.14±0.78	0.91±0.89	97.52±1.26
ITC2T	0.365	0.464	21.33	1.27	22.33	501.07±0.01	2.51±0.04	8.2±0.01	6.24±0.42	0.81±0.46	97.08±1.08
IRC1T	0.311	0.321	24.96	1.14	24.56	494.12±0.03	2.51±0.03	7.9±0.02	6.11±0.91	0.84±0.46	92.41±1.12
IRC2T	0.308	0.331	23.84	1.13	24.34	493.11±0.02	2.49±0.01	8.1±0.02	6.04±0.41	0.78±0.61	97.08±1.08
ITS1T	0.385	0.449	14.25	1.16	26.18	495.28±0.04	2.59±0.01	8.2±0.02	5.92±0.07	0.86±0.43	95.29±1.98
ITS2T	0.343	0.437	21.51	1.27	24.88	493.27±0.01	2.53±0.01	8.1±0.02	6.02±0.03	0.71±0.67	97.15±1.45
IRS1T	0.315	0.321	24.04	1.14	24.31	489.08±0.02	2.50±0.03	8.1±0.02	5.91±0.04	0.79±0.75	95.02±1.28
IRS2T	0.311	0.311	24.14	1.15	24.25	492.07±0.03	2.51±0.02	8.1±0.02	5.94±0.04	0.69±0.45	98.09±1.15

In-vitro drug release study: From permeability study observations and benefits of Itraconazole cocrystal batch prepared using in 1:2 tartaric acid, resorcinol ratio by Co grinding, Solvent evaporation and liquid assisted grinding method was further selected for in vitro drug release study. To conduct in-vitro dissolution study,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

prepared cocrystals were developed into a tablet using direct compression method. These developed tablets showed hardness 5-6 kg/cm2, friability of 0.51 – 0.92%. In-vitro dissolution study was performed to compare release of both drugs from prepared cocrystals and release study is graphically presented and % drug release tablet was found to be 70 % to 95 % for cocrystal tablet at the end 12h **(Figure 3).**

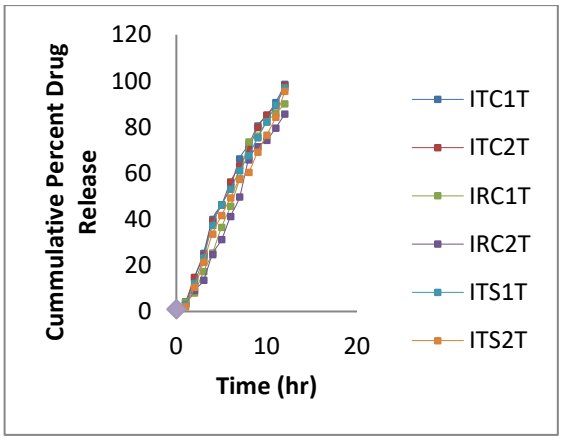

Figure 3: Zero-order release of itraconazole cocrystal tablet

Summary and conclusion: The field of co-crystals, otherwise known as multicompound crystals, is a very interesting and exciting area in the fields of materials research and pharmaceuticals. The future for co-crystals appears bright, but there are problems which still have to be solved. The solubility, stability and bioavailability of drugs could be improved by the use of co-crystals in the field of pharmaceutics. The formation of new classes of pharmaceutical entities can result from the use of co-crystals which have a higher activity and a decreased activity. The use of co-crystals also will increase the Intellectual property protection of the drug molecule which is an elegant way of preserving patentability for an extended period. The necessary interaction between scientists, engineers and regulatory bodies points towards a bright future for co-crystals.

References

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995 Mar;12(3):413-20.
2. S. Agharkar, S. Lindenbaum, T. Higuchi, Enhancement of solubility of drug salts by hydrophilic counter-ions: properties of organic salts of an anti-malarial drug, J. Pharm. Sci. 65 (5) (1976) 747–749.
3. K. Amin, R.-M. Dannenfelser, J. Zielinski, B. Wang, Lyophilization of polyethylene glycol mixtures, J. Pharm. Sci. 93 (9) (2004) 2244–2249.
4. V.P. Torchillin, Micellar nanocarriers: pharmaceutical perspectives, Pharm. Res. 24 (1) (2007) 1–16.
5. R.A. Rajewski, V.J. Stella, Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery, J. Pharm. Sci. 85 (11) (1996) 1142–1169.
6. A.J. Humberstone, W.N. Charman, Lipid-based vehicles for the oral delivery of poorly soluble drugs, Adv. Drug Deliv. Rev. 25 (1) (1997) 103–128.
7. R.H. Müller, C. Jacobs, O. Kayser, Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future, Adv. Drug Deliv. Rev. 47 (1) (2001) 3–19.
8. G.M.J. Schmidt, Topochemistry. Part III. The crystal chemistry of some trans-cinnamic acids, J. Chem. Soc. (1964) 2014.
9. J.W. Steed, J.L. Atwood, Supramolecular Chemistry, John Wiley & Sons, Ltd., 2000.
10. G.R. Desiraju, Supramolecular synthons in crystal engineering — a new organic-synthesis, Angew. Chem., Int. Ed. Engl. 34 (1995) 2311–2327.
11. F.H. Allen, The Cambridge structural database: a quarter of a million crystal structures and rising, Acta Cryst., B 58 (2002) 380–388.
12. I.J. Bruno, J.C. Cole, P.R. Edgington, M.K. Kessler, C.F. Macrae, P. McCabe, J. Pearson, R. Taylor, New software for searching the Cambridge structural database and visualising crystal structures, Acta Cryst., B 58 (2002) 389–397.
13. C.B. Aakeröy, A.M. Beatty, M. Nieuwenhuyzen, M. Zou, Organic assemblies of 2-pyridones with dicarboxylic acids, Tetrahedron 56 (2000) 6693–6699.
14. E. Batchelor, J. Klinowski, W. Jones, Crystal engineering using cocrystallisation of phenazine

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 400-407 | ISSN:2251-6727

with dicarboxylic acids, J. Mater. Chem. 10 (2000) 839–848.

15. M.R. Edwards, W. Jones, W.D.S. Motherwell, Influence of dicarboxylic acid structure on tape networks in co-crystals of 2-pyridone, Cryst. Eng. 5 (2002) 25–36.
16. V.R. Pedireddi, J. PrakashaReddy, Unique homo and hetero carboxylic acid dimer-mediated supramolecular assembly: rational analysis of crystal structure of 3,5-dinitrobenzoic acid and 4-(N-methylamino) benzoic acid, Tetrahedron Lett. 43 (2002) 4927–4930.