Journal of Clinical Trials and Case Studies

Open access

Crystalline Solid forms of Metaxalone, a Muscle Relaxant-A Crystal Engineering Perspective

Vasanthi Palanisamy, Palash Sanphui*

* *Department of Chemistry, SRM Institute of Science and Technology, Kattankulathur, Tamilnadu-603203, India*

REVIEW ARTICLE

ABSTRACT

Metaxalone (hereafter MET) is a muscle relaxant used to alleviate pain and discomfort associated with musculoskeletal conditions, including muscle spasms and back pain. The BCS Class-II drug, MET exhibits poor aqueous solubility and high permeability (log P 2.42), necessitating high dose (800 mg) formulation. Despite extensive research on MET's Chemistry and biological perspective, its poor solubility and bioavailability limit its therapeutic applications. Recent studies have explored solubility enhancement via nano-suspensions, nano-emulsions, and excipient/additive incorporation in addition to single and multicomponent solid forms. The crystalline solid forms, such as polymorphs, cocrystals, salts offer additional opportunities for property modulation. Notably, MET's solid phases, including two polymorphs and various cocrystals with carboxylic acids including cocrystal polymorphs with salicylic acid and carboxamides, have been reported recently. Presence of oxazolidinone moiety without any ionic functionalities don't offer any salts formation. Understanding these solid phases is crucial for tailoring physicochemical properties, as they serve as alternative pre-formulations with significant pharmaceutical applications. This review covers MET's crystalline solid forms, including polymorphs, cocrystals, preparation methods, and crystal structures, highlighting their impact on solubility, as reported in the literature and patents.

KEYWORDS

Metaxalone, Polymorphs, Cocrystals, Amorphous phases, Solubility

Correspondence to: Dr. Palash Sanphui, Department of Chemistry, SRM Institute of Science and Technology, Kattankulathur, Tamilnadu-603203, India, Email: palashi@srmist.edu.in

Received: November 14, 2024, **Accepted**: November 19, 2024, **Published**: November 25, 2024

DOI: 10.1042/JCTCS.7.1.0015

Citation: Palash Sanphui, 2024, Crystalline Solid forms of Metaxalone-A Muscle Relaxant-A Crystal Engineering Perspective. JCTCS. Vol 7.

INTRODUCTION

Solid form screening is a crucial step during new drug development because solid forms (crystalline or amorphous) of a drug substance significantly affect stability, dissolution, pharmaceutics, and manufacturing processes. This perspective introduces solid-state Chemistry practically, aiming to reduce knowledge gaps and promote communications among scientists with diverse backgrounds [1]. In fact, nowadays, both innovator and generic pharma industries are very careful during solid form screening before finalizing the most suitable solid form. The academic-industry partnership helps to sort out the problems faced by them and benefitted equally. This perspective starts with a concise overview followed by a discussion on the timeline and goals of solid form screening [2-5]. Crystalline solid forms offer different physicochemical properties like solubility, dissolution rate, bioavailability, permeability, tabletability, etc. depending upon the structural aspects within their crystal lattices and several other factors. Crystalline forms may exist as polymorphs, cocrystals, salts, amorphous phases, eutectics, and solid solutions; which are generally obtained during high throughput solid form screening. Structural aspects and other characterizations of the MET solid phases e.g. two polymorphs (A and B) and several cocrystals with aliphatic and aromatic mono/di-carboxylic acids are then discussed. Subsequently, the perspective presents commonly used methods in MET solid form screening and introduces criteria and strategies to select a favourable solid form based on their suitable physicochemical properties. The last section summarizes current practices in pharmaceutical solid forms and suggests potential in drug dissolution, and future research /development.

Metaxalone

MET [Chemical name: 5-[(3,5-dimethylphenoxy)methyl]-1,3-oxazolidin-2-one)] is a muscle relaxant that relieves pain caused by strains and sprains. The drug was approved for therapeutic use in 1962 and has been synthesized by Elan Pharmaceuticals under the brand name Skelaxin and distributed by King Pharmaceuticals [6]. The drug is poorly aqueous soluble (91 mg L^{-1}). MET also features in the top 200 U.S. oral drug products list [7]. Poor solubility and high intestinal permeability (log *P* 2.3) of the drug fall in the Bio pharmaceutics Classification System (BCS) class II category [8]. The poor bioavailable drug, MET is orally administered as high doses as 400 and 800 mg tablets. The high doses of the drug provoke serious side effects on the potential central nervous system, particularly among elder patients [9]. Due to the low aqueous solubility of MET, the drug product (finished dosage

form) or the drug substance Bulk Active Pharmaceutical Ingredient (API) made from different manufacturing batches or from different manufacturing locations are not uniform or consistent in their bioavailability. To increase the bioavailability of MET, the administration of an oral dosage form with food may be applicable between 30 min prior to or 2 h after consuming food [10, 11].

MET is a poorly aqueous soluble drug due to the presence of a hydrophobic aromatic skeleton and cyclic carboxamate ring in its structure. Improving the solubility of MET is an utmost important in order to enhance its bioavailability and also decrease the toxic side effects by lowering the dosage strength. To improve the MET delivery in the biological medium, several methods have been applied, for example, Nano suspension, Nano emulsion additive/excipient additions and surfactants, etc [12-14]. Last two decades, extensive research on MET is going on to explore the Chemistry behind its diverse pharmaceutical applications. Synthetic experts are involved in the extraction and preparation of MET, degradation products, and its derivatives [15]. Several groups reported quantification of the drug using liquid chromatography associated with mass spectroscopy [16]. Further, reverse-phase HPLC methods are developed to estimate MET concentration. Additionally, structural chemists are busy in exploring novel solid forms using crystal engineering principles like polymorphs, cocrystals, eutectics, amorphous and coamorphous phases, etc. of the drug. Furthermore, their structural aspects at the supra-molecular level with improved drug properties like solubility, and bioavailability are addressed.

Solid Forms

Pharmaceutical industry relies heavily on solid forms (e.g. polymorphs, hydrates, salts, cocrystals, amorphous phases) to control the physical properties of active pharmaceutical ingredients (APIs). Polymorphism, a common phenomenon in organic crystals including pharmaceuticals, has a significant impact on the physicochemical properties of solid materials. The ability of a substance to form multiple crystal structures affects various research area, including food, dyes, pigments, high-energy materials, and pharmaceuticals. By using diverse polymorph discovery methods, the likelihood of finding polymorphs with desired properties increases that leads to an optimal performance of the final product [17]. On the other hand, cocrystals are defined as crystalline materials composed of two or more molecular and/or ionic compounds in a specific stoichiometric ratio. Cocrystals offer numerous benefits including enhanced solubility and bioavailability of APIs and thereafter improved drug efficacy. Additionally, cocrystals can stabilize physically or chemically unstable APIs, facilitating production and ensuring the therapeutic benefits of the API maintained throughout the various proceses [18, 19]. By introducing a potential cocrystallizing agent, manufacturers can create a more stable and effective drug product. The burgeoning field of cocrystal research has yielded significant breakthroughs, leading to the commercial approval of various pharmaceutical cocrystals, including ertugliflozin- L-pyroglutamic acid, sacubitril/valsartan, Ipragliozin-L-proline, escitalopram-oxalate and chloral-betaine in last one decade. In addition, numerous cocrystals are currently in clinical trials, underscoring the growing potential of this innovative approach [20]. To date, several cocrystal solid-state strategies have been applied to tune the properties of active pharmaceutical ingredients (APIs), including binary cocrystal (Two different components in the crystal lattice), cocrystal hydrates (Two different components along with a water molecule in the crystal lattice), cocrystal solvates (Two different components along with solvent molecule in the crystal lattice) etc, see Figure 1. Major advantage of cocrystals over salts is former alliance with both the neutral and ionic drugs, while latter is limited to ionized drugs only. The development of MET cocrystals exemplifies this approach, with the successful creation of binary cocrystals and hydrate/solvate cocrystals [17, 20-22].

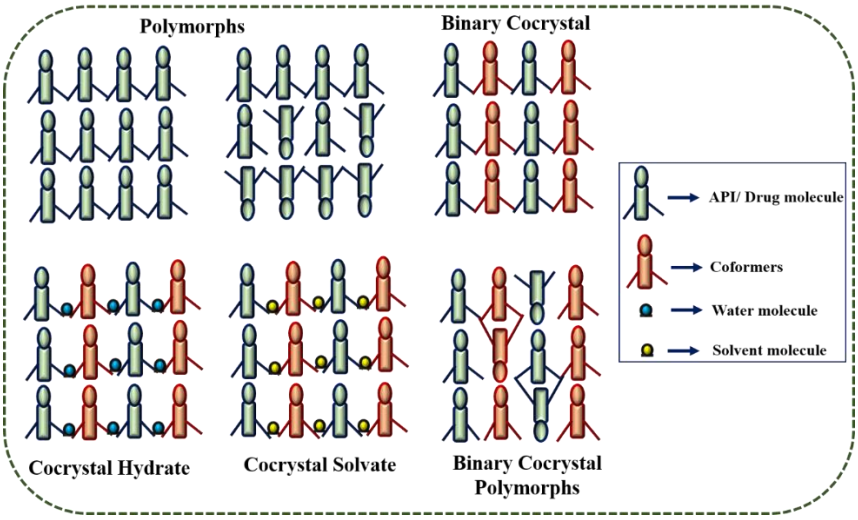
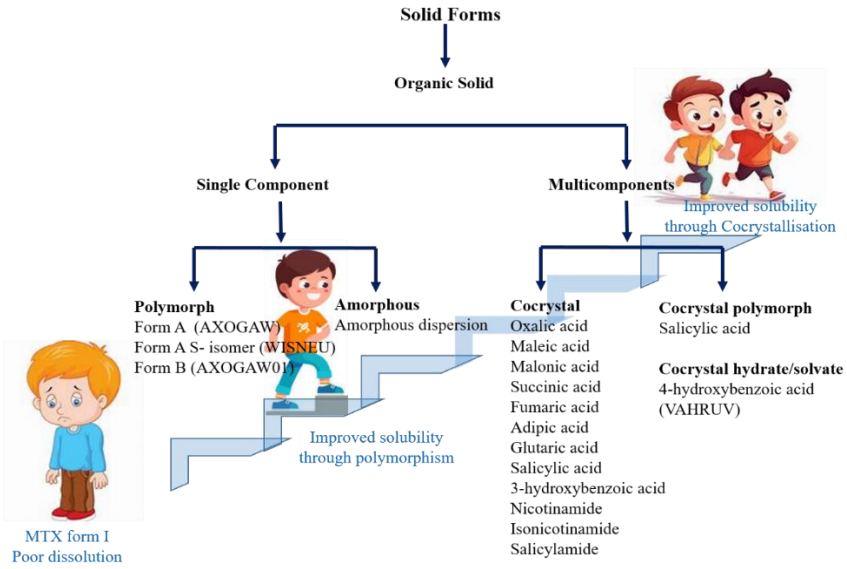


Figure 1: Single component to multicomponent crystalline solid forms.

During the last decade, several research groups worldwide revisited MET solid forms and carried out high throughput solid form screening. As an outcome, novel polymorphs, cocrystals, and amorphous phases of MET are reported with the motif of improving solubility, stability, and bioavailability via the crystal engineering principle. A summary of the reported different solid forms of MET is displayed in Scheme 1. There are two polymorphs of MET (Forms A and B), which are designated as synthon and conformational polymorphs in a US patent 7750165B2 [7] with their crystal structures confirmed by Aitipamula et al [23]. In addition, several cocrystals of MET with dicarboxylic acids (succinic, fumaric, maleic, and adipic acid) and monocarboxylic acid (salicylic acid) are reported in another US patent 8871793B2, [24] with subsequent publication by Lin et al [12]. Notably, the binary crystal structures of MET with fumaric, maleic acid, succinic, adipic acid, maleic, and salicylic acid (polymorphs) are published. Our group also reported a few MET cocrystals with aromatic carboxamides e.g. nicotinamide, isonicotinamide, salicylamide and carboxylic acid with 3-hydroxybenzoic acid, 4-hydroxybenzoic acid. We will discuss their structural aspects after a brief summary of other formulations except crystal engineering approach.



Scheme 1: Several reported solid Forms of MET (from Literature/Patents) to date.

MET Nanosuspension and Nanoemulsion

Nano emulsion and Nano suspension dosage forms have been instrumental in achieving desired drug concentrations, enhancing solubility properties, and prolonging residence time, thereby improving bioavailability. These formulations leverage the benefits of nanotechnology, with Nano emulsions being transparent or translucent systems comprising a dispersed phase and a continuous phase, stabilized by surfactants and co-surfactants, typically with particle size ranging from 10-500 nm. On the other hand, nano-suspension involves the dispersion of nanosized particles in a suitable vehicle, facilitated by surfactants or solubilizes to ensure optimal particle size distribution. Notably, Nano suspensions are particularly well-suited for developing dosage forms of poorly soluble drugs, offering a promising solution for enhanced drug delivery. Vasanani et al. improved the MET solubility up to 2805 µg/ml using poloxamer nanosuspension [25]. Gupta et al. reported the Nano emulsion formulation of MET with sesame oil, Tween 80, and PEG 400, and achieved remarkable encapsulation efficiency of up to 93% [26].

MET Polymorph

MET has been commercialized under the brand name of Skelaxin since 1962 as 800 mg tablet dosage form containing a stable crystalline (racemic) Form A along with several excipients such as alginic acid, ammonium calcium alginate, corn starch, and magnesium stearate [27, 28]. Polymorphs of MET were first reported in a US patent 7750165B2 patent published in 2007, [7] and characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and Fourier transform infrared (FT-IR) spectroscopy [7]. However, no structural reports of MET were available in the public domain until 2010. Tan et al., first reported the polymorphic structures (Form A/B) of MET in 2011 as a concomitant polymorph crystallized via slow evaporation using ethyl acetate as solvent [23]. The concomitant crystallization of MET polymorphs indicates their similar lattice energy and stability. In addition, rapid crystallization of the R/S-MET from a hexane/EtOAc mixture yielded Form A, whereas the slurry experiment of Form A for 24h resulted Form B. The Form A crystal structure was solved in the triclinic space group *P*-1 with two symmetry independent MET molecules in the asymmetric unit (Z' = 2). The Form B structure was solved in a monoclinic $P2_1/c$ space group with one molecule of MET in the asymmetric unit (Z' = 1). Note that it took approximately 50 years since its inception in the market to prove the structural aspects of MET polymorphs, along with their stability, phase transformations, and their dissolution properties. Crystal structure analysis revealed that the MET molecule adopts different conformations in the polymorphs. The imide group of the MET molecule forms an imide-imide catemer synthon in Form A and an imide-imide dimer synthon in Form B, refer Figure 1. Synthon differences in Forms A/B further confirm that they are examples of synthon polymorphs, which are not so common in the literature [23]. A few examples of synthon polymorphs are observed in acemetacine, isonicotinamide, tetrolic acid, and furosemide [29-32]. Thermal analysis and solubility measurements indicate that Form A is the kinetically stable form at ambient conditions, while Form B is a thermodynamically stable phase. Both the crystalline forms melted in the range of 121-123 ºC and are enantiotropically related based on the heat of fusion rule. Notably, the dissolution of MET polymorphs is slower at a lower pH than the neutral buffer medium and the metastable Form A dissolves faster than Form B. The difference in the IDR values in different dissolution media clearly indicates that the dissolution of MET polymorphs is pH-dependent. Experiments involving slurry, solid-state grinding, and dissolution experiments show that Form B is a thermodynamically more stable form.

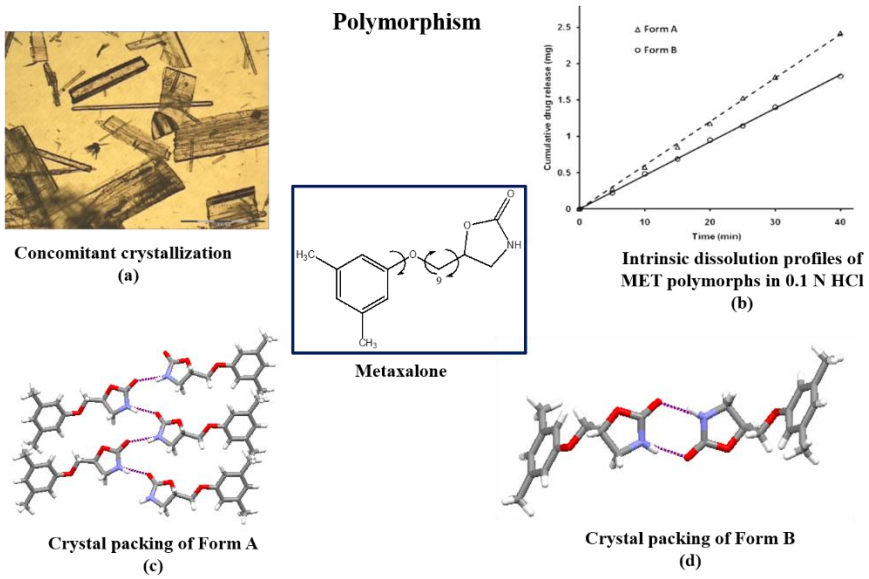


Figure 2: Concomitant polymorphic structure variation and dissolution profile of R/S MET [23].

Bredikhin et al. successfully established an enantiopure (S)-form of MET, along with an unknown metastable form C of R/S MET [33]. S-MET was synthesized by the reaction of 3,5-dimethyl phenol with S-1-chloro, 2,3-dihydroxypropane, followed by treatment with urea at 200 ºC. Note, that S-MET melts at 144.5 ºC, which is higher than its racemic counterpart. The metastable form C was crystallized from the melting crystallization of supercooled R/S-MET. The crystal structure of S-MET was solved in the orthorhombic $P2_12_12_1$ (Z'=1) space group with one molecule in the asymmetric unit. S-MET maintains imide catemer N−H···O hydrogen bonded chain, similar to R/S-Form A, refer Figure 2. MET is a highly flexible molecule and molecular flexibility is observed due to rotation of the oxazolidinone ring along the adjacent C-C and C-O bonds attached to phenyl ring, refer Figure 3.

A detailed thermal analysis (cooling/heating) of individual R/S MET polymorphs and S-MET demonstrated that crystallization of the pure MET sample from their melts is accompanied by the formation of a previously undisclosed metastable phase, which in the case of racemic samples is transformed into a more stable Form A phase, and in the case of enantiomeric (S)-1 samples, see Figure 4.

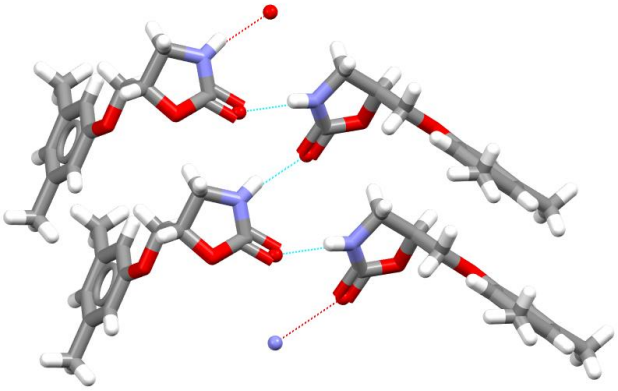


Figure 3: Imide catemer chain in S-MET, similar to R/S-MET Form A [28].

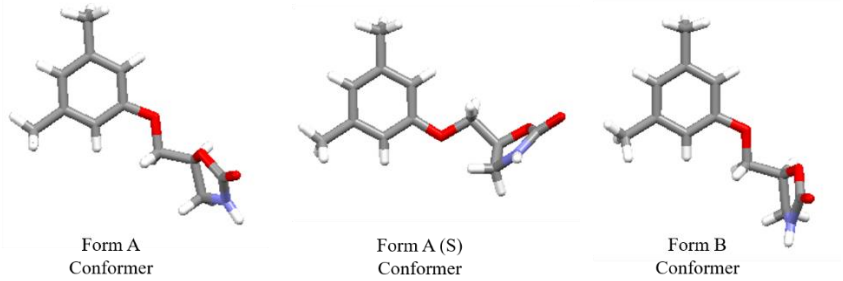


Figure 4: Isomeric configuration and flexibility representation of racemic and S-MET polymorphs.

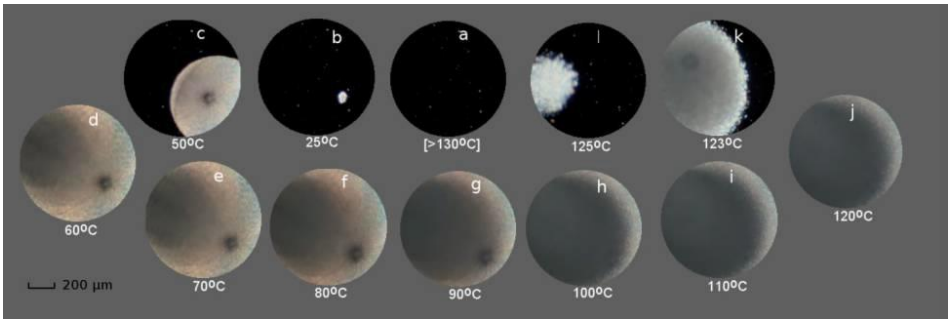


Figure 5: Hot-stage photo micrographic images of R/S-MET phase transformations [33].

Cocrystals of MET with carboxylic acids

MET lacks ionizable functional groups, rather having carboxamate functionality that makes salt formation unfavourable. Therefore, cocrystallization is a viable crystal engineering approach to enhance the drug's solubility and pharmacokinetics. The presence of oxazolidinone (cyclic *syn* imide) moiety in the drug helps to prepare binary complexes with diverse coformers like carboxylic acid, carboxamide, pyridine, sulfonamide functionalities. MET cocrystals with several carboxylic acids and carboxamides are synthesized successfully and reported in the literature [35]. Figure 5 summarizes all the successful acidic and amide coformers that cocrystallize MET. The US8871793B2 patent reports on MET cocrystals with several mono and dicarboxylic acids e.g. succinic acid, fumaric acid, maleic acid, glutaric acid, adipic acid, and salicylic acid targeting hydrogen bonding interactions between imide (drug) and coformers (carboxylic acids) [34]. Researchers employed various techniques, such as grinding, solvent evaporation, or solution crystallization to prepare these cocrystals. The cocrystals were characterized using techniques like powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and ^{1}H NMR to confirm their uniqueness and chemical compositions. The unit cell parameters of these cocrystals are reported in the same patent. The cocrystal structures include MET-fumaric acid (triclinic/*P*-1), MET-salicylic acid (monoclinic/$P2_1/n$), MET-succinic acid (monoclinic/*C*2/c), MET-maleic acid (monoclinic/*C*2/c) and MET-adipic acid (triclinic/*P*-1). In the reported maleic/fumaric/succinic acid cocrystals (1:0.5), the dicarboxylic acids form hydrogen bonds via acid-carbonyl heterosynthons, while the imide-imide homosynthon of the API remains robust in all the cocrystals, refer Figure 6. MET-salicylic acid cocrystal was crystallized as cocrystal polymorphs, while Form I was obtained from EtOH and both forms I and II concomitantly appeared using EtOAc. Surprisingly, both the salicylic acid cocrystal Form I ($P2_1/n$, 1:1) and Form II ($P2_1$, 2:2) form a tetramer hydrogen-bonded synthon, comprising two APIs and two carboxylic acids, while retaining the imide-imide homodimer of MET, although they are different in conformations and crystal packing, refer Figure 7. The dihedral angle between plane containing aryl ring and oxazolidinone ring is 69.5º in Form I, whereas that is 80.4 and 83.6º that indicates more perpendicular arrangement between two aromatic rings in Form II than Form I. Hence, MET-salicylic acid cocrystal polymorphs can be defined as conformational as well as packing polymorphs. The single crystal XRD data and structure refinement parameters of MET-fumaric acid and MET-maleic acid cocrystals are reported by Holland and co-workers [34]. The crystal structures were solved in the triclinic (*P*-1) and monoclinic (C2/c) space groups respectively. The corresponding ORTEP diagrams of the cocrystals are presented in Figure S1, the supporting information (SI).

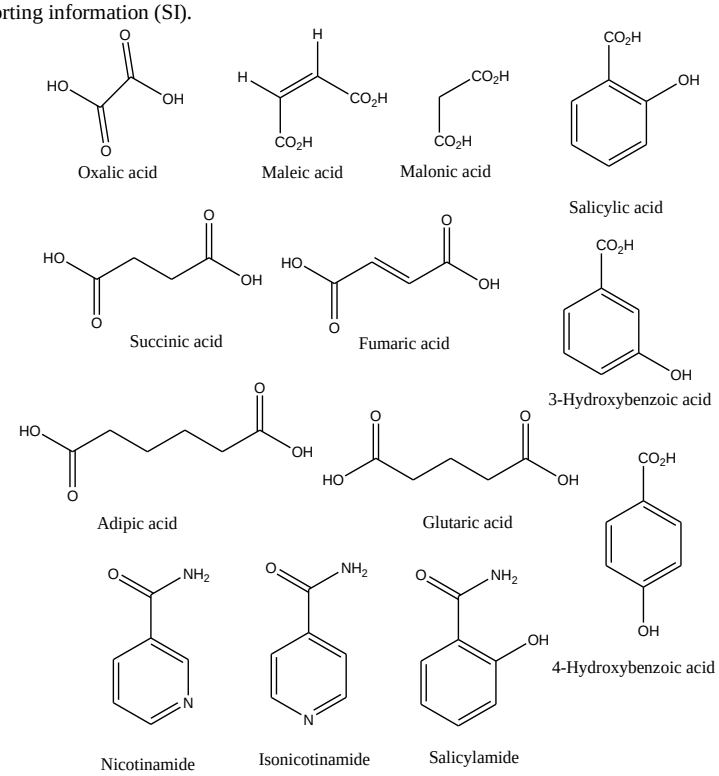


Figure 6: Chemical Structures of MET cocrystal coformers.

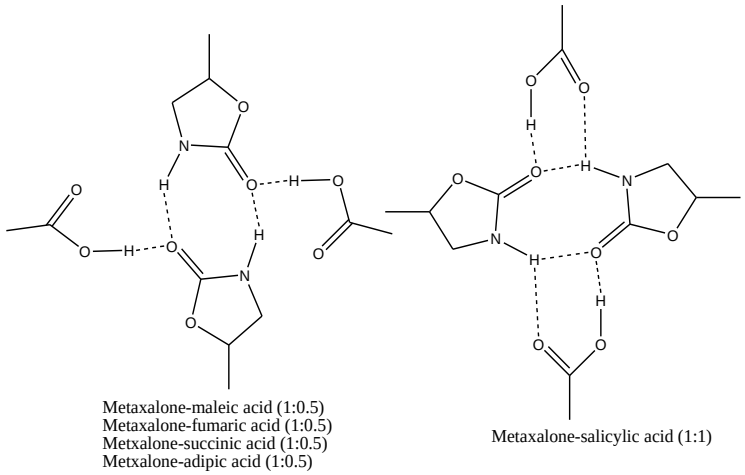


Figure 7: Supramolecular synthons in Metaxalone cocrystals with carboxylic acids.

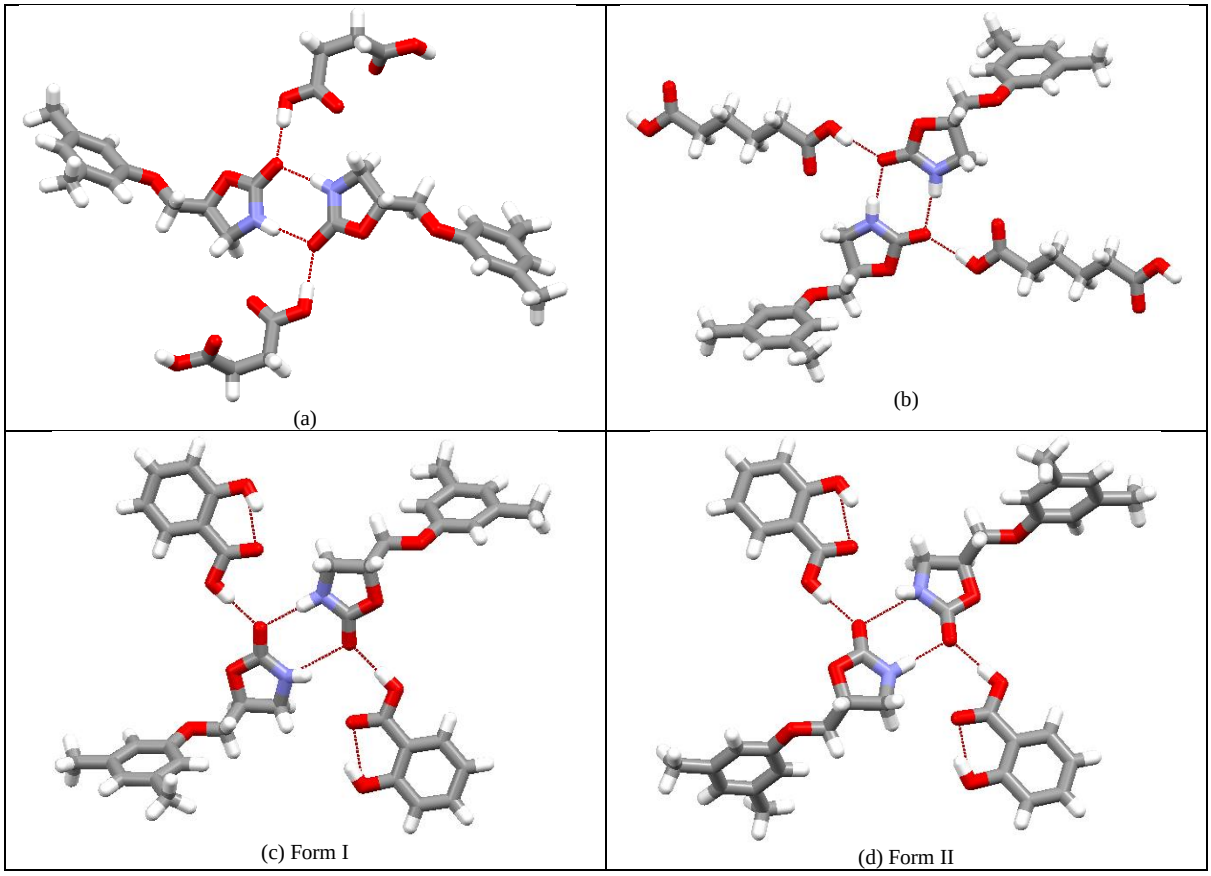


Figure 8: Basic hydrogen bonding in a) MET-succinic acid, b) MET-adipic acid and c,d) MET-salicylic acid cocrystal polymorphs.

Characterizations of MET-dicarboxylic acid cocrystals

In addition to single crystal XRD data, the MET cocrystals with short-chain aliphatic dicarboxylic acids such as oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid and glutaric acid were prepared at 1:0.5 stoichiometric ratio by liquid assistant grinding using ethanol [35]. The binary systems were characterized by their unique melting points (using DSC), FT-IR spectroscopy and PXRD. The MET-maleic acid (1:0.5) cocrystal formation was also quickly estimated by using a one-step simultaneous DSC-FTIR microspectroscopy, refer Figure 8. The cocrystal melted peak at 125 ºC, which is in between the melting point of the native drug (m.p. 124 ºC) and maleic acid (m.p. 144 ºC). The close melting point of the cocrystal similar to native MET is not surprising as it is observed in case of several other cocrystals e.g. RS Naproxin-DL Proline, Niclosamide-Isonicotinamide, Diclofenac-2-amino-4,6-dimethylpyrimidine etc. [36-38].

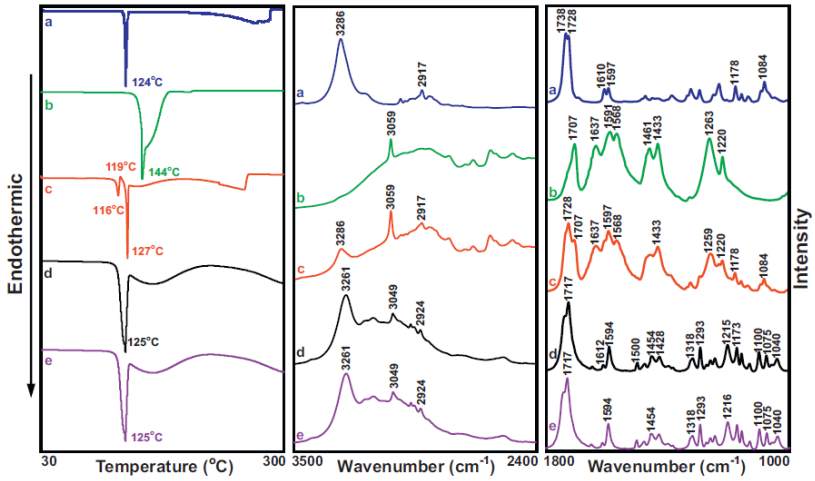


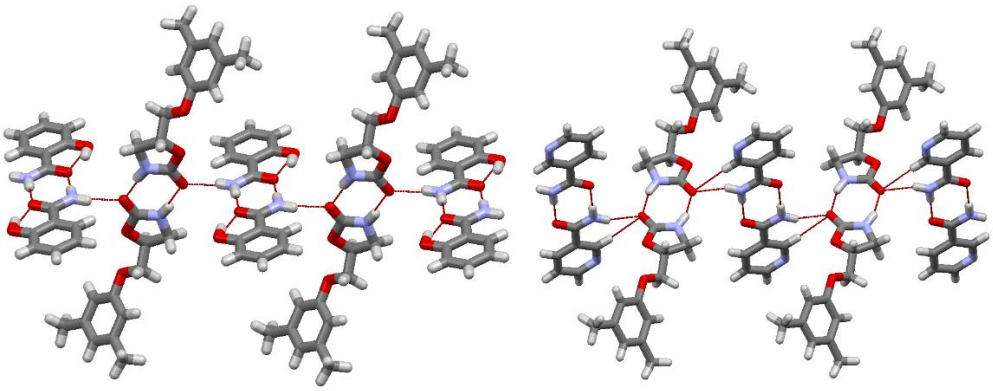
Figure 9: DSC curves and FTIR spectra of MET (a), maleic acid (b), their physical mixture (c), crystallized sample (d), and solvent-assisted ground mixture (e) of MET-maleic acid [35].

MET cocrystals with aromatic carboxylic acids and carboxamides

In addition to the reported MET-salicylic acid cocrystal polymorphs, binary systems are extended with other aromatic carboxylic acids (3-hydroxybenzoic acid, 4-hydroxybenzoic acid) and carboxamides (nicotinamide, isonicotinamide, salicylamide) and synthesized successfully from our group [39]. Characterization techniques like PXRD, FT/IR, ss-NMR, DSC, and single crystal X-ray diffraction confirmed their novelty. Notably, all the MET cocrystals exhibited lower melting endotherms than the drug and coformers, a phenomenon observed in only 29% of literature cases [40]. Vibrational spectroscopy hinted at the stoichiometry of the drug cocrystals based on carbonyl stretching frequencies and hydrate formation. In addition, ^{13}C-ssNMR spectroscopy of the MET-salicylamide cocrystal suggested a reduction in symmetry-independent drug molecules (Z'=2 to Z'=1) and revealed changes in molecular conformation of the native drug.

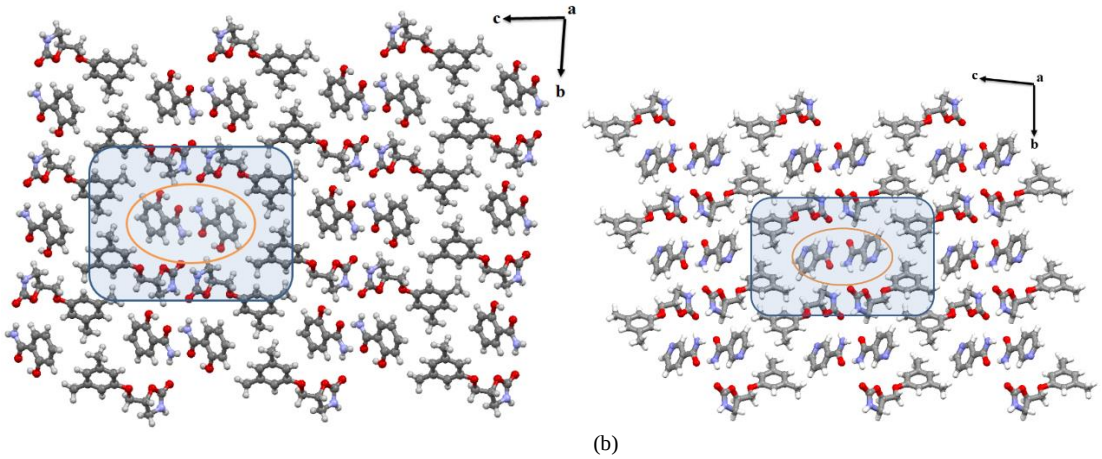
Crystal structure of MET-carboxamide cocrystals

MET-salicylamide cocrystal (*P*-1, Z=2) consists of centrosymmetric homodimers of both MET and salicylamide (SAM) via N-H···**O** hydrogen bonds, refer Figure 9a. These homodimers are perpendicularly interlinked (79°) through bifurcated carbonyl oxygen, forming a 1D chain along the b-axis. The crystal structure of MET-nicotinamide (P-1, Z=2) was solved from PXRD data as corresponding single crystals were challenging to harvest. Both MET and NAM form centrosymmetric hydrogen-bonded homodimers, characterized by N-H···O hydrogen bonds. Specifically, an imide-imide dimer (N-H···O) and an amide-amide dimer (N-H···O) are formed, both exhibiting $R_2^2(8)$ ring motifs Figure 9b. Notably, the hydrogen bonding parameters suggest that the NAM dimer is more strongly hydrogen-bonded than the MET imide dimer. MET forms 2D isostructural cocrystals with SAM and NAM coformers. In crystal structure hydrogen-bonded motifs featuring imide-imide (drug) and amide-amide (coformer) homosynthons exhibit similar arrangements in both MET-NAM and MET–SAM cocrystals, refer Figure 10. Note, NAM and SAM share a high degree of structural similarity, with the exception of an additional ortho hydroxyl group in SAM. This hydroxyl group engages in an intra-molecular hydrogen bond with the amide carbonyl, distinguishing SAM from NAM [39].



(a) (b)

Figure 10: Hydrogen bonding in a) MET-SAM and b) MET–NAM cocrystals [39].



(a) (b)

Figure 11: 2D isostructural close packing of a) MET-SAM and b) MET-NAM cocrystals [39].

MET-4-hydroxybenzoic acid cocrystal solvate

Efforts to obtain high-quality single crystals of the MET–4-hydroxybenzoic acid (HBA) cocrystal from methanol or acetone yielded a nonstoichiometric hydrate of the binary system, for which suitable single crystals were challenging. However, slow evaporation from anisole (solvent) resulted in the formation of cocrystal solvate. The corresponding crystal structure (P-1, Z=2) reveals the asymmetric unit comprising one molecule each of MET and HBA, accompanied by half an equivalent of anisole solvent in a highly disordered state, even at a temperature of 100 K. The cocrystal structure consists of MET and HBA homosynthons of R_2^2 (8) ring via hydrogen bonded imide-imide (N–H···O) and acid-acid (O–H···O) centrosymmetric dimers, Figure 11. These two homodimers are interlinked by the hydroxyl group of HBA, which constitutes intermolecular O–H···O hydrogen bond (O5–H21···O1) with the bifurcated carbonyl group of the MET.

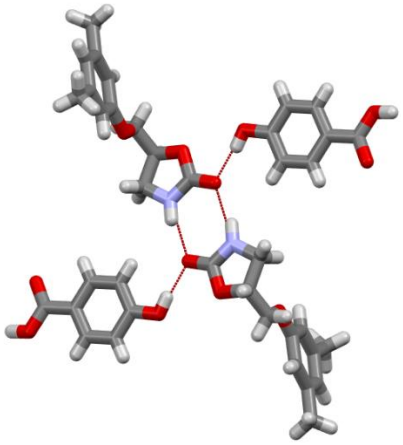


Figure 12: Hydrogen bonding in MET–HBA (1:1) cocrystal solvate [39].

Different conformations of MET

MET exhibits two polymorphic forms as Form A (Z'=2) and Form B (Z'= 1), in which oxazolidinone ring is highly flexible compared to the planar 3,5-dimethylphenoxymethyl fragment. Note, one of the conformation (out of two) of Form A is very similar to that of Form B. The orientation of the five-membered cyclic ring relative to the aryl moiety reveals slight torsional changes along the C-C bond connecting the terminal aromatic rings. Multiple conformations of MET, observed in its polymorphs and cocrystals, refer Figure 12. As expected, the molecular conformations of MET in MET–NAM and MET–SAM cocrystals are identical because of their isostructurility. Quantitative analysis using dihedral angles between aryl and oxazolidinone ring planes confirms similar MET conformation in MET–NAM and MET-SAM cocrystals. There are several distinct MET conformations, with one featuring a close to perpendicular arrangement between aryl and oxazolidinone ring planes in the MET–HBA (anisole) Cocrystal.

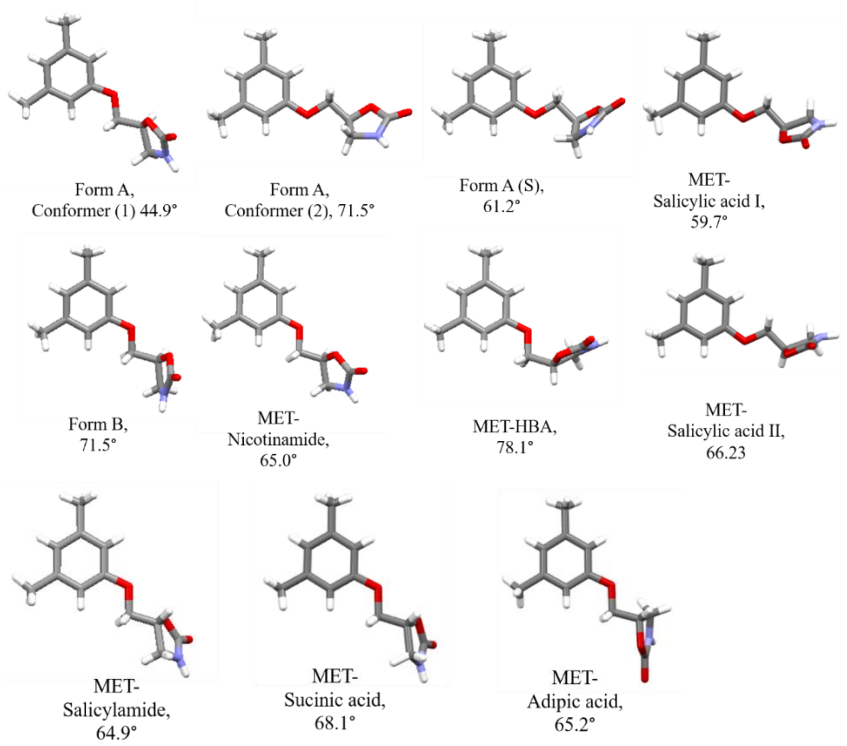


Figure 13: Different confirmations of MET in their crystal Structure (reported Polymorphs/Cocrystals).

Lower melting MET cocrystals

The lower melting points of cocrystals often indicates their eutectic nature, where two components with size/shape mismatch interact through non-covalent interactions. A comprehensive survey of 727 pharmaceutical cocrystals of variable stoichiometry by Perlovich et al. revealed that 29% (211 cocrystals) exhibited melting points lower than those of their individual components, while 55% (400 cocrystals) melted within the range of the API and coformers [40-44].. Notably, cocrystals with lower melting points may offer advantages for thermo-labile drugs, such as insulin and diazepam. The commercial MET Form A displayed a single melting endotherm at 126.2°C. Notably, most cocrystals exhibited lower melting points than both the API and coformers, except those with fumaric acid and succinic acid, refer Table 1. Note, MET-NAM and MET-SAM melted at 107.4°C and 119.5°C, respectively. Isostructural cocrystals MET-NAM and MET-SAM showed similar thermodynamic properties, like enthalpy of fusion 125.7 J/g and 126.4 J/g respectively, supporting their similar packing arrangements. MET-HBA (hydrate) exhibited a melting endotherm at 116.5°C [45].

S.No	Components	Melting point (API/cocrystals)	Melting point of the coformer	Sources
1.	MET (Form A)	126.2°C	--	Aitipamula et al. 2011
2.	MET–Oxalic acid (1:0.5)	128°C	183°C	S.-Y. Lin et al. 2014
3.	MET–Malonic acid (1:0.5)	87°C	137°C	S.-Y. Lin et al. 2014
4.	MET–Succinic acid (1:0.5)	148.5°C	184°C	S.-Y. Lin et al. 2014
5	MET–Fumaric acid (1:0.5)	154.3°C	287°C	S.-Y. Lin et al. 2014
6	MET–Maleic acid (1:0.5)	125°C	135°C	S.-Y. Lin et al. 2014
7	MET–Glutaric acid (1:0.5)	80°C	99°C	S.-Y. Lin et al. 2014
8.	MET–Adipic acid (1:1)	115.1°C	152.1°C	Holland et al. 2010
9.	MET–Maleic acid (1:1)	128.1°C	135°C	Holland et al. 2010
10	MET–Salicylic acid (1:1)	102.9°C	158.6°C	Holland et al. 2010

11	MET–nicotinamide (1:1)	105.3°C	130.9°C	Sanphui et al. 2019, 2021
12	MET–isonicotinamide (1:1)	105.2°C	158.1°C	Sanphui et al. 2019
13.	MET–salicylamide (1:1)	119.4°C	144°C	Sanphui et al. 2019, 2021
14.	MET–3-hydroxybenzoic acid (1:1)	99.5°C	205.3°C	Sanphui et al. 2019
15.	MET–4-hydroxybenzoic acid (hyd)	104.4°C and 116.5°C	215.5°C	Sanphui et al. 2019
16.	MET–4-hydroxybenzoic acid (1:1) hemi anisole solvate	100.0°C and 113.4°C	215.5°C	Sanphui et al. 2021

Table 1: Summary of melting points of MET cocrystals.

Solid State NMR Spectra analysis

Our group investigated the ^{13}C solid-state NMR spectra of MET to glean structural insights, including molecular conformation and hydrogen bonding, in its cocrystal with salicylamide. Ss-NMR analysis of MET (Form I) reveals the presence of two symmetry-independent molecules (Z'=2) in the starting material, evidenced by double resonances for C1, C10, C11, and C12 atoms due to conformational flexibility in the oxazolidinone ring [39]. However, in the cocrystals, most carbon resonances merge into a single signal, indicating a single drug molecule in the asymmetric unit. Notably, the MET carbonyl (C12) resonance shifts from 161.3 ppm in the pure drug to 163.6 ppm in the cocrystal, suggesting intermolecular hydrogen bonding between the MET and salicylamide. Conversely, the coformer carbonyl resonance remains unchanged (174.5/174.2 ppm), implying retention of the imide-imide homosynthon in the cocrystal, See Figure 13. To summarize, SSNMR can be exploited to define molecular conformations, and hydrogen bonding aspects in multicomponent solids. In the last two decades, ^{15}N SSNMR is exploited to differentiate between cocrystal, salt or salt-cocrystal continuum based on the position of ionized N-atom resonance.

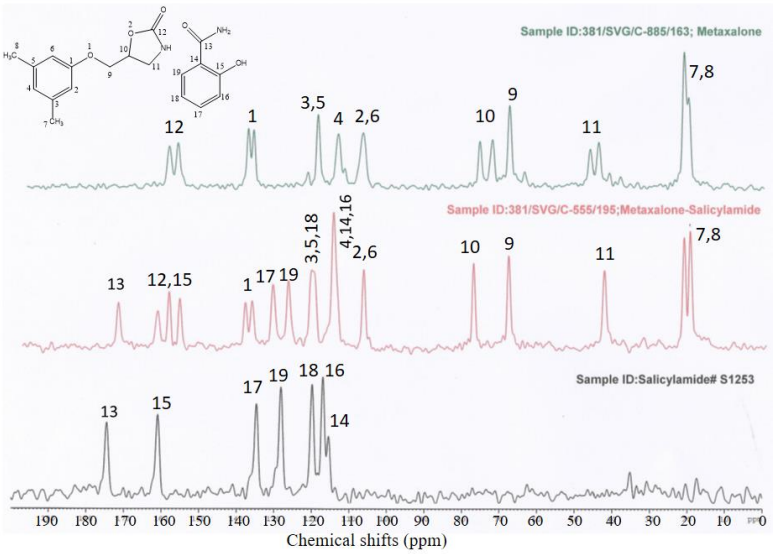


Figure 14: ^{13}C-ss-NMR spectra comparison between MET and its cocrystal with salicylamide [39].

Solubility and dissolution studies

MET is a poorly aqueous soluble drug due to its hydrophobic aromatic skeleton and cyclic carboxamate ring. Enhancing MET's solubility is crucial to improve its bioavailability and mitigate toxic side effects. The solubility of MET polymorphs was carried out in several aqueous medium. The solubility ratio between the polymorphs of MET is 1.1 (in water), 1.3 (in 0.1 N HCl), and 1.1 (in pH 7.4 buffer), which is consistent with the general solubility trend of polymorphs which suggest that the ratio of polymorph solubility is typically less than 2 [23]. The intrinsic dissolution experiments were conducted at 37 ºC in the 0.1 N HCl (pH 1.2) and pH 7.4 buffer solutions. Figure 14a shows the corresponding dissolution profiles of MET polymorphs that indicates that the metastable Form A dissolves faster than the stable Form B. Our group carried out the powder dissolution profiles of MET cocrystals using a paddle method in 500 mL pH 6.8 phosphate buffer medium at 37°C [39]. The MET–NAM cocrystal significantly enhanced the aqueous solubility of MET by 8.6-fold within 4 h, compared to the native drug and the dissolution order was followed as MET-NAM > MET-SAM > MET-HBA (hydrate)> MET, refer Figure 14b.

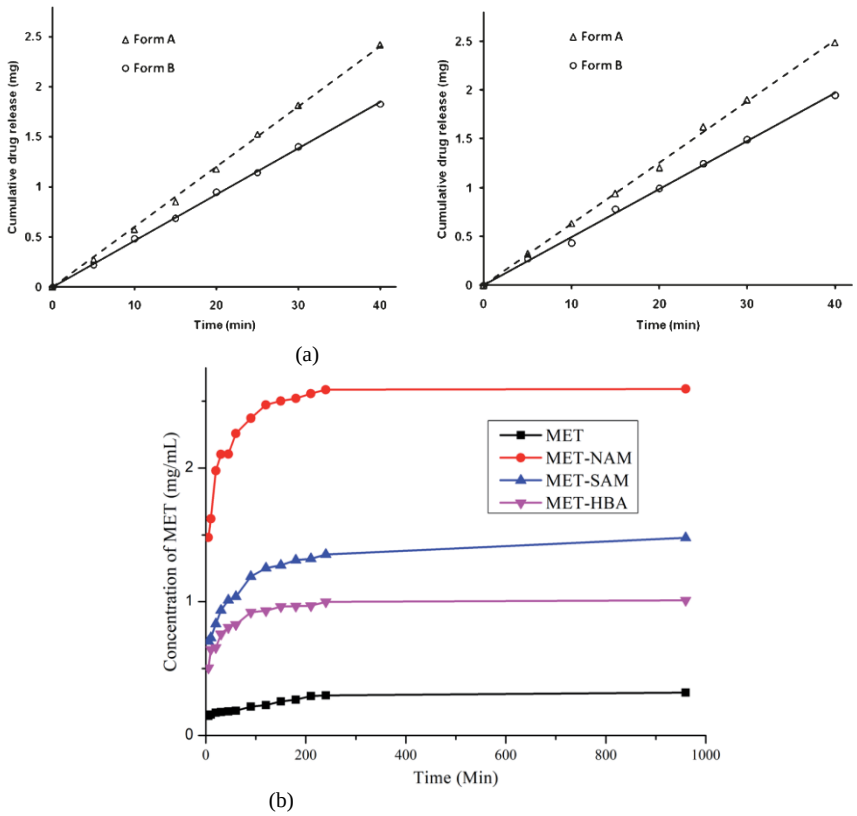


Figure 15: Dissolution profile of a) MET polymorphs in pH 1.2 (left) and pH 7.4 buffer (right), (b) its cocrystals with aromatic carboxamides and carboxylic acid [23, 39].

Pharmacokinetics studies

MET is known as poor soluble drug which affects its bioavailability. In order to achieve sufficient drug concentration in the biological system, high dose is prescribed. Hence increasing bioavailability is utmost important and selection of suitable MET cocrystal is utmost important. Holland et al. conducted to compare the pharmacokinetics study of MET-fumaric acid and MET-succinic acid cocrystals, and compared with the native drug MET in beagle dogs, after receiving a single dose of 21 mg/kg via oral administration in a fasted state [24]. Fumaric acid cocrystals exhibited two fold plasma concentration (Cmax) as well as area under the curve (AUC) compared to the API, refer Figure 15 and Table S1, SI for pharmacokinetics parameters such as maximum plasma concentration (Cmax), area under the curve (AUC) and maximum time (Tmax) required to achieve Cmax. The promising high soluble MET-NAM cocrystal may be taken forward for its pharmacokinetics study and further drug development along with MET-fumaric acid system.

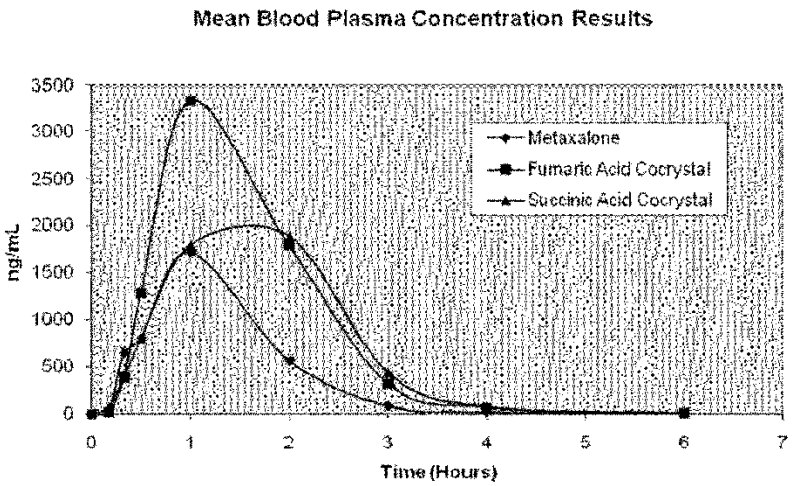


Figure 16: Pharmacokinetics profile of MET and its cocrystals [24].

CONCLUSIONS

Metaxalone exhibits synthon polymorphism, with Form A featuring imide-imide catemer synthon, while Form B as imide-imide dimer synthon. Several research groups carried out solid-form screening that resulted a total of 14 cocrystals with carboxalic acid/carboxamides including cocrystal polymorph

with salicylic acid in variable stoichiometric ratio. In cocrystals with maleic, fumaric, and succinic acids (1:0.5), dicarboxylic acids engage in O-H/O hydrogen bonding via acid-carbonyl heterosynthons. Notably, the imide-imide homosynthon of the API remains consistent across these cocrystals. In contrast, the salicylic acid cocrystal polymorphs (1:1/2:2) form a tetramer hydrogen-bonded synthon, comprising two API molecules and two carboxylic acid molecules, while maintaining the imide-imide homodimer of metaxalone. The salicylamide cocrystal exhibits a distinct arrangement, featuring imide-imide dimers of the API and amide-amide dimers of salicylamide, in an almost perpendicular orientation. Interestingly, among the cocrystals, only the metaxalone-4-hydroxybenzoic acid combination exists as a hydrate/anisole solvate, whereas the others form anhydrous binary adducts. Interestingly, most of the MET cocrystals melted below the m.p. of the native drug and coformer, which is common among one-third of the cocrystals. Fumaric acid cocrystal is the promising candidate that exhibited almost double plasma concentration compared to the API alone in beagle dogs and are currently under advanced clinical trials. In addition, high soluble nicotinamide cocrystals need to carry out pharmacokinetics study to examine its potential as drug candidate. Despite the various cocrystals investigated, none successfully disrupted the API-API homodimer in their crystal structures. Since breaking this dimer is expected to substantially improve MET solubility, future research should prioritize reconstructing solid forms in that direction, which may enhance bioavailability. Additionally, in cocrystal research, there is a significant gap in the literature regarding ternary cocrystals of metaxalone, which presents a substantial challenge in crystal engineering and drug-drug combinations with similar biologically effective drugs e.g. carisoprodol and methocarbamol. To fully harness the potential of metaxalone, further comprehensive research is necessary to develop and optimize cocrystal screening methodologies, encompassing eutectic, amorphous, and coamorphous systems. This will enable the enhancement of their physicochemical properties. This review provides a comprehensive overview of existing structural data on metaxalone solid forms, highlighting avenues for improving its notoriously poor bioavailability. In summary, systematic investigations are crucial in the near term to unlock metaxalone's therapeutic potential and develop optimized dosage forms.

SUPPORTING INFORMATION

The Supporting Information includes ORTEP diagram of MET cocrystals and summary of pharmacokinetics parameters.

FUNDING SOURCES

VP and PS acknowledge the Department of Science and Technology (DST) for the improvement of S & T Infrastructure (FIST) with grant no. SR/FST/CST-266/2015(c) for the funding support.

CONFLICTS OF INTEREST

There are no conflicts to declare.

REFERENCES

1. Taylor LS, Braun DE, Tajber L, Steed JW. Crystallizing the role of solid-state form in drug delivery. Cryst Growth Des. 2022, 22:4663-4665.
2. Zheng Q, Unruh DK, Hutchins KM. Cocrystallization of Trimethoprim and solubility enhancement via salt formation. Cryst Growth Des. 2021, 21:1507-1511.
3. Wathoni N, Sari WA, Elamin KM, Mohammed AFA, Suharyani I. A review of Coformer utilization in multicomponent crystal formation. Molec. 2022, 27:8693.
4. Berry DJ, Steed JW. Pharmaceutical cocrystals, salts and multicomponent systems: Intermolecular interactions and property based design. Adv. Drug Del Rev. 2017, 117:3-24.
5. Nasrallah S, Alhadid A, Minceva M. Revealing the Solubility enhancement of active pharmaceutical ingredients through eutectic mixtures formation: A parameter study. Cryst. Growth Des. 2024, 24:6364-6372.
6. Bruce RB, Turnbull L, Newman J, Pitts JJ. Metabolism of Metaxalone. Med Chem. 1966, 9:286-288.
7. Chattopadhyay J, Sarkar S, Mahanty JS, Hazra S, Mitra M, et al. Metaxalone polymorphs. Patent US7750165B2 (2007).
8. Metaxalonebelongs to BCS Class II drug; Center for Drug Evaluation and Research, 2015.
9. Waldman SD. Skeletal muscle relaxants. Pain Rev. 2009, 28:651-656.
10. Dailymed label of SKELAXIN® tablet.
11. Colaco S, Ramesh N, Shabaraya R. Demonstration of relative bioavailability of newly developed and innovator drug metaxalone 800 mg in healthy subjects under fed condition. J Adv Pharm Technol Res. 2022, 13:123-127.
12. Lee CA, Tang M, Ho SL, Chen YP. Solubilities of chlormezanone, metaxalone, and methocarbamol in supercritical carbon dioxide. J Super Fluids. 2014, 85:11-16.
13. Anuar N, Bustami AHS, Effendi TJ. Hamid AK. Development and characterisation of ibuprofen-loaded nanoemulsion with enhanced oral bioavailability. Heliyon. 2020, 1:6-7.
14. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020, 15:24.
15. Marothun VK, Dash RN, Vemula S, Donkena S, Devi R, et al, Kinetics study of metaxalone degradation under hydrolytic, oxidative and thermal stress conditions using stability- indicating HPLC method. J Pharm Anal. 2012, 2:431-436.
16. Rao RN, Farah H, Sahu PK, Janarthan M, Naidu Ch. G. Development and validation of a stability indicating assay including the isolation and characterization of degradation products of metaxalone by LC-MS. Biomed Chromatogr. 2013, 12:733-740.
17. Bolla G, Sarma B, Nangia AK. Crystal engineering of pharmaceutical cocrystals in the discovery and development of improved drugs. Chem Rev. 2022, 122:11514-11603.
18. Shi Q, Chen H, Wang Y, Xu J, Liu Z, et al. Recent advances in drug polymorphs: Aspects of pharmaceutical properties and selective crystallization. Int J Pharm. 2022, 611:121320.
19. Bhatiaa M, Devi S. Co-crystallization: a green approach for the solubility enhancement of poorly soluble drugs. Cryst Eng Comm. 2024, 26:293-311.

20. Kavanagh ON, Croker DM, Walker GM, Zaworotko MJ. Pharmaceutical cocrystals: from serendipity to design to application. Drug Dis Today. 2019, 24:796-804.
21. Wang X, Du S, Zhang R, Jia X, Yang T, et al. Drug-drug cocrystals: Opportunities and challenges. Asian J Pharm Scie. 2021, 16:307-317.
22. Karki S, Friscic T, Jones W, Motherwell WDS. Screening for pharmaceutical cocrystal hydrates via neat and liquid-assisted grinding. Mol Pharm. 2007, 4: 347-354.
23. Aitipamulas A, Chow PS, Tan RBH. Conformational polymorphs of a muscle relaxant, metaxalone. Cryst Growth Des. 2011, 11:4101-4109.
24. Holland J, Frampton C, Chorlton A, Gooding D, Metaxalone Cocrystals, Patent US 8871793B2 (2010).
25. Vasanani PR, Patel LD, Detroja CM. Formulation and development of stable Metaxalone nanosuspension using 32 factorial design. Int J Phar Sci Drug Res. 2016; 8:223-228.
26. Pawar SS, Rane BR, Jain AS. Development and evaluation of nanoemulsion loaded Metaxalone for the treatment of pain and injury. Eng. Proc. 2023, 56:100.
27. Rxlist 2002. Metaxalone monograph.
28. Chattopadhyay J, Sarkar S, Mahanty JS, Hazra S, Mitra M, et al. Metaxalone polymorphs. Patent US2007/0185177 A1.
29. Sanphui P, Bolla G, Das U, Mukherjee AK, Nangia A. Acemetacin polymorphs: a rare case of carboxylic acid catemer and dimer synthons. Cryst Eng Comm, 2013, 15:34-38.
30. Fellah N, Zhang CJ, Chen C, Hu CT, Kahr B, et al. Shtukenberg highly polymorphous Nicotinamide and Isonicotinamide: solution versus Melt Crystallization. Cryst Growth Des. 2021, 21: 4713-4724.
31. Gavezzotti A, Filippini G, Kroon J, van Eijck BP, Klewinghaus P. The crystal polymorphism of Tetrolic Acid (CH,C&COOH): A molecular dynamics study of precursors in solution, and a crystal structure generation. Chem Eur J. 1997, 3:6.
32. Babu NJ, Cherukuvada S, Thakuria R, Nangia A. Conformational and Synthon polymorphism in furosemide (Lasix). Cryst Growth Des. 2010, 10:1979-1989.
33. Bredikhin AA, Zakharychev DV, Gubaidullin AT, Bredikhina ZA. Solid phase behavior, polymorphism and crystallographic features of chiral drug Metaxalone. Cryst Growth Des. 2018, 18:6627-6639.
34. Holland J, Frampton C, Chorlton A, Gooding D. Metaxalone Cocrystals, Patent US 8871793B2 (2010).
35. Lin HL, Wu TK, Lin SY. Screening and characterization of cocrystal formation of metaxalone with short-chain dicarboxylic acids induced by solvent assisted grinding approach. Thermochim Acta. 2014, 575:313-321.
36. Tumanova N, Tumanov N, Fischer F, Morelle F, Ban VK et al. Exploring polymorphism and stoichiometric diversity in naproxen/proline cocrystals. Cryst Eng Comm. 2018, 20:7308-7321.
37. Sanphui P, Kumar SS, Nangia A. Pharmaceutical Cocrystals of Niclosamide. Cryst Growth Des. 2012, 12:4588-4599.
38. Aakeröy CB, Grommet AB, Desper J. Co-crystal screening of diclofenac. Pharmaceutic. 2011, 3:601-614.
39. Gohel SV, Sanphui P, Singh GP, Bhat K, Prakash M. Lower melting pharmaceutical cocrystals of metaxalone with carboxamide functionalities. J Molec Struct. 2019, 1178:479-490.
40. Perlovich GL. Thermodynamic characteristics of cocrystal formation and melting points for rational design of pharmaceutical two-component systems. Cryst Eng Comm. 2015, 17:7019-7028.
41. Gohel SK, Palanisamy V, Sanphui P, Prakash M, Singha GP et al. Isostructural cocrystals of metaxalone with improved dissolution characteristics. RSC Adv. 2021, 11:30689.
42. Chettri A, Subba A, Singh GP, Bag PP. Pharmaceutical co-crystals: A green way to enhance drug stability and solubility for improved therapeutic efficacy. J Pharm Pharmacol. 2024, 76:1-12.
43. Nanubolu JB, Ravikumar K. Correlating the melting point alteration with the supramolecular structure in Aripiprazole drug cocrystals. Cryst Eng Comm. 2016, 18:1024-1038.
44. Qiao S, Wang J, Yu Y, Liu Y, Yang Z, et al. Two novel TNB energetic cocrystals with low melting point: a potential strategy to construct melt cast explosive carriers. Cryst Eng Comm. 2022, 24:2948-2953.
45. Gohel SV, Sanphui P, Singh GP, Bhat K, Prakash M. Lower melting pharmaceutical cocrystals of metaxalone with carboxamide functionalities. J Molec Struct. 2019, 1178:479-490.