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Research Paper

Additive-Induced Metastable Single Crystal of Mefenamic Acid

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Purpose. To utilize additives to develop a strategy and a method to grow single crystals that allow structure determination of a metastable form of a drug.
Materials and Methods. The metastable form of mefenamic acid (MFA) was grown in the presence of various amounts of the structurally similar additive flufenamic acid (FFA) in ethanol. Single crystal X-ray analysis was performed on the single crystals of MFA II that were formed. The solubility of MFA in the presence of FFA was measured to elucidate the mechanism of MFA II formation.
Results. A supersaturated solution of MFA in ethanol produced the metastable form using FFA as an additive. Ethanol–water mixtures and toluene were also used to investigate the relationships between form produced and solvent since these two solvent systems do not produce MFA II.
Conclusions. Additives can be used to obtain the metastable form of pharmaceutical compounds, and the relationships between molecules and solvent as well as between host and guest molecules are critical to obtaining the desired form.

KEY WORDS: flufenamic acid; mefenamic acid; polymorph selection; single crystal; XRPD.

INTRODUCTION

Polymorphs exist when the same compounds adopt different crystal packing and/or conformations in the crystalline state (1). The differences in internal crystal structure of the same compound result in different physical and chemical properties. Therefore, it is important to identify polymorphs and maintain the desired form throughout the manufacturing process and storage. The most stable form is usually preferred and used because there is a chance for a metastable form to convert into the stable form during processing. The stability of one polymorph *vs*. the other polymorphs can be displayed using an energy/temperature diagram based on solubility studies, slurry conversion studies, calorimetric measurements, and/or density measurements. It is well known that the differences in energy of the different forms of a drug are related to conformational forces, hydrogen bonding forces, and/or crystal packing forces of each polymorph. For the characterization of polymorphs, single crystal X-ray diffraction is considered the definitive tool, and visual analysis of X-ray powder diffraction, thermal analysis, microscopy techniques, and/or spectroscopy are considered supplemental tools (2). Single crystal X-ray diffraction data is also used to predict the most stable polymorph or possible polymorphic forms using the computational calculations of the molecular structure in the crystal (3). However, single crystals suitable for single crystal X-ray analysis are often not easily obtained using conventional crystallization methods such as cooling of supersaturated solution, evaporation, or anti-solvent method, *etc*. This is especially true for metastable forms.

There are literature reports dealing with the tailor-made additive effect on the crystals of racemic and polymorphic compounds. These studies have also described ways to resolve conglomerates of enantiomorphic crystals and assign absolute configurations (4,5). The idea of resolving conglomerates of enantiomorphic crystals is based on the concept that additives structurally similar to one enantiomer or polymorphic form of host molecules inhibit the growth of this enantiomer, by blocking the addition of subsequent molecules to the growing crystal. Some researchers have been very successful in assigning the absolute configuration of chiral polar crystals or chiral molecules or in designing the stereoselective etchants for organic crystals by utilizing "tailor-made" additives (4–7). However, there has been little work performed utilizing structurally similar compounds to crystallize the desired polymorph of pharmaceutical compounds. In this study, flufenamic acid, a structurally related compound and one of fenamates, was used to grow the metastable form of mefenamic acid.

Mefenamic acid is one of the well known fenamates showing a potent analgesic effect (8). This effect may be explained by the receptor binding mechanisms since potent fenamates such as mefenamic acid, flufenamic acid, and meclofenamic acid have conformational similarities based on Nuclear Magnetic Resonance (NMR) Spectroscopy (9), crystallographic and theoretical study (10). Fenamates have conformational similarities in that carboxyl group, the imino group between two six-membered rings and the six-membered ring containing the carboxyl group are coplanar. Resonance interaction and an intra hydrogen bonding

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between the bridging imino and carboxyl groups stabilize the coplanar structure (11). In addition, a number of other materials properties of fenamates have been studied including solubility and dissolution rate, (12,13), manufacturability and tableting properties (14,15) and polymorphic transformation (16,17), respectively. This makes this an ideal system for analysis of the effect of structurally similar impurities on crystallization.

According to the literature above, mefenamic acid is known to have two polymorphic forms, Form I and Form II (12). Two forms are enantiotropically related. The crystal structure of mefenamic acid Form I was reported in 1976 (18). The crystal structure of Form II has not been determined. There are two known methods to obtain the metastable MFA II (12,13): one is to heat MFA I crystals above the transition temperature, and the other is to use rapid cooling of supersaturated solution in *N*,*N*-Dimethylformamide. However, neither method produces MFA II suitable for single crystal X-ray analysis. The thermal method results in the formation of a polycrystalline mass, and rapid cooling usually produces very small poor quality crystals. In addition, rapid cooling can also produce the solvate of MFA when *N*,*N*-Dimethylformamide is used.

This system is typical of other polymorphic pharmaceuticals. The stable form can be obtained with relative ease, and its crystal structure is known. However, the metastable form can only be obtained using kinetic crystallizations. Such crystallizations typically produce small poorly formed crystals which are not amenable to single crystal structure determination. Since, from both a science and a regulatory point of view, it is highly desirable to have the crystal structure of as many forms as possible, new methods of obtaining a metastable form in relatively large well-formed crystals are needed. This paper reports a strategy based on the use of structurally related additives to block the crystal growth of the stable form thereby allowing growth of the metastable form.

MATERIALS AND METHODS

Materials

Mefenamic acid and flufenamic acid (Fig. 1) were purchased from Sigma–Aldrich (St. Louis, MO, USA).

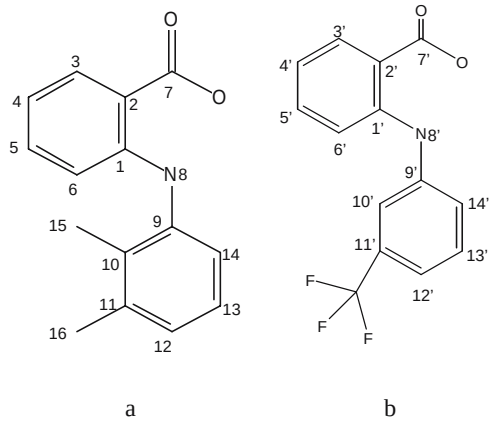

Fig. 1. Molecular structures of (a) mefenamic acid and (b) flufenamic acid.

Table I. Experimental Design for MFA II Crystal Growth Using Different Ratios of FFA and MFA (a) Change in the Amounts of FFA when the Amounts of MFA is Fixed and (b) Change in the Amounts of MFA when the Amounts of FFA is Fixed

(a)	FFA (g)		
MFA (0.2 g)	1.2 MFA II	1.4 MFA II	1.6 MFA II
(b)	MFA (g)		
FFA (2.02 g)	0.2 MFA II	0.3 MFA II	0.4 MFA II

Ethanol was obtained from Pharmco (Brookfield, CT, USA). Water with trifluoroacetic acid 0.1% (v/v) was purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI, USA), and HPLC-grade acetonitrile was obtained from Mallinckrodt Baker, Inc (Phillipsburg, NJ, USA). Water was double-distilled and filtered with Milli-Q® ultrapure water purification system (Billerica, MA, USA).

Crystallization of MFA form II using FFA as an additive

Form II crystals of mefenamic acid were crystallized by cooling the supersaturation solution of MFA with FFA as additives. Supersaturated solutions were prepared in scintillation vials by dissolving the required amounts of MFA and FFA powder in 10 ml ethanol at 60°C (Table I). After dissolution of the powder, the solution was kept still in a hood at room temperature or in a water bath at 15°C. After 20 days, crystals were harvested, washed and dried.

Single crystal X-ray diffraction

Preliminary data were collected on a Nonius Kappa CCD using graphite monochromated Mo K_α radiation (λ = 0.71073 Å) for a colorless plate of MFA with dimensions of 0.48 × 0.43 × 0.30 mm at 150 K. Crystal had moderate

Table II. Crystal Data and Details of Refinements

Parameter	MFA Form II	MFA Form I[a]
Chemical formula	$C_{15}H_{15}NO_2$	$C_{15}H_{15}NO_2$
Formula weight	241.29	241.29
Crystal system	$P\bar{1}$	$P\bar{1}]] >$
Space group	Triclinic	Triclinic
a (Å)	7.6969	14.556
b (Å)	9.1234	6.811
c(Å)	9.4535	7.657
α (°)	107.113	119.57
β (°)	91.791	103.93
γ (°)	101.481	91.30
V (Å^3)	618.89	631.766
Z	2	2
2**θ** range (degree)	4.53–55.75	**θ** < 70°
Unique reflections	2,823	2,387
R(F_o)	0.052	0.045
$R_w(F_O^2)$	0.134	
Goodness-of-fit, S	1.045	
Program used	SHELXTL	MULTAN

[a] J. F. McConnell and F. Z. Company, Cryst. Struct. Comm. **1976. 5, 81**.

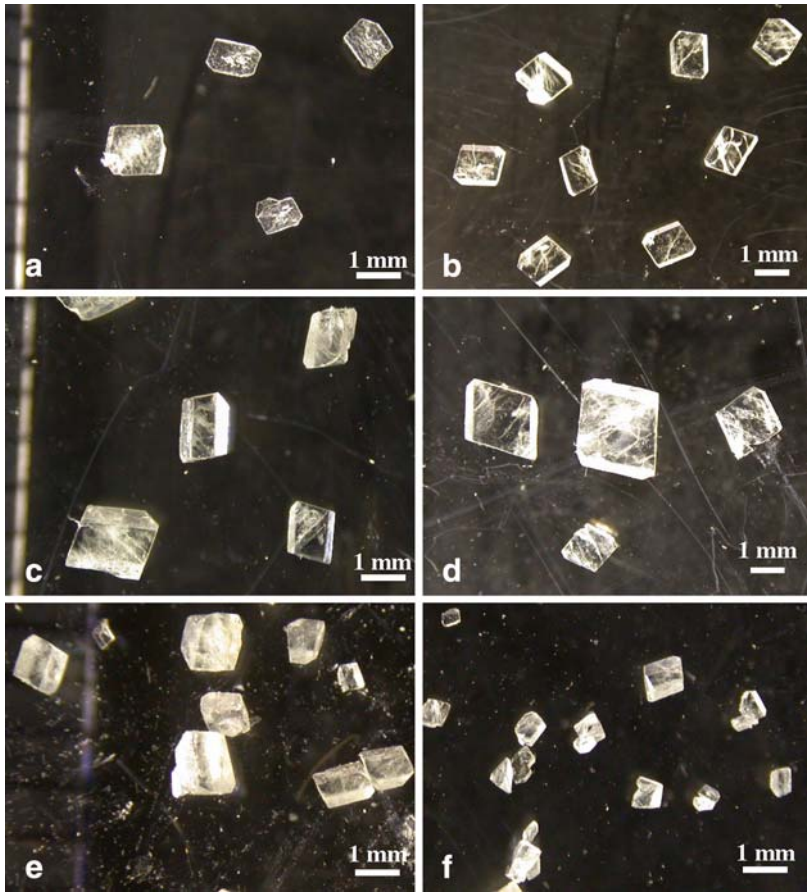

Fig. 2. Pictures of MFA Form II grown in ethanol with help of FFA. Ratio of (a) FFA:MFA = 6:1, (b) FFA:MFA = 7:1, (c) FFA:MFA = 8:1, (d) FFA:MFA=10.1:1, (e) FFA:MFA = 6.7:1, and (f) FFA:MFA = 5.1:1. Same order as shown in (Table I).

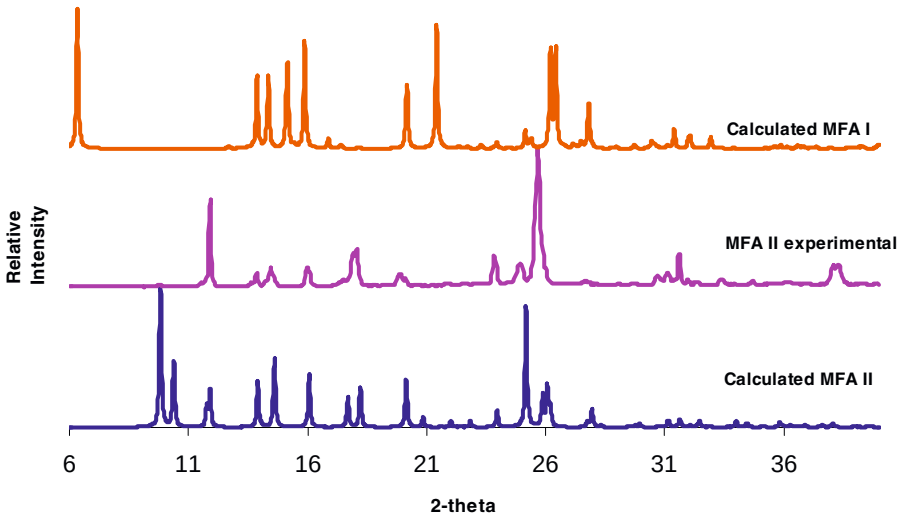

Fig. 3. X-ray powder diffraction pattern of calculated MFA Form I from single crystal X-ray diffraction data (*upper*), X-ray powder diffraction pattern of MFA Form II grown with FFA in ethanol (*upper middle*), X-ray powder diffraction pattern of MFA Form II obtained by heating the MFA Form I at 160°C (peaks at 38° is for Cu) (*lower middle*), and X-ray powder diffraction pattern of calculated MFA Form II from single crystal X-ray diffraction data (lower).

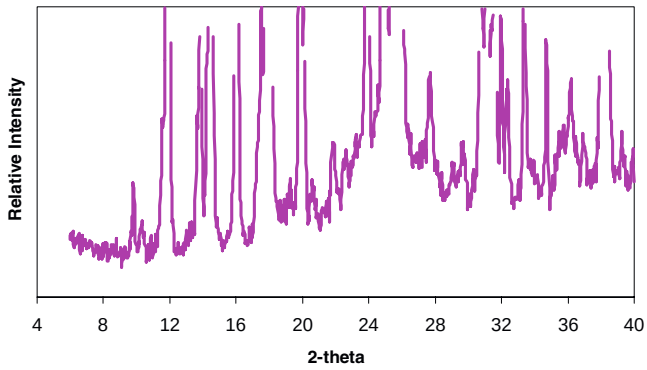

Fig. 4. Enlarged X-ray powder diffraction pattern of MFA Form II grown with FFA in ethanol to show two small peaks around 9 to 10° 2θ (peaks at 38° is for Cu).

quality based on the refined mosaicity (0.96°) from DENZO/SCALEPACK (19). The space group was determined as P-1 (#2) using the program XPREP (20); there were no systematic absences. DENZO–SMN (19) was used to integrate frames. Lorentz and polarization corrections and an empirical absorption correction using SCALEPACK (19) were applied to the data. Direct method in SIR2004 (21) was used to obtain the crystal structure. Refinement was conducted on a LINUX PC using SHELX-97 (22).

High-performance liquid chromatography (HPLC) of FFA and MFA

The amounts of MFA and FFA were determined by HPLC, Agilent 1100 series (Agilent Technologies, Inc., CA, US) with a diode array detector. HP Chemstation was used for data analysis. A zorbax reversephase-C_8, 4.6 × 250 mm analytical column (Agilent, USA) was used at 30°C. The mobile phase consisted of A (water with trifluoroacetic acid 0.1% v/v) and B (Acetonitrile) (60:40, v/v). The flow-rate was 2 ml/min. Samples were analyzed at UV λ = 280 nm.

X-ray powder diffraction

X-ray powder diffraction analysis was performed on MFA powders obtained by crushing MFA crystals and by heating MFA Form I powder over 180°C for 30 min. using a Siemens' X-ray diffractometer equipped with Cu K_α radiation. Samples were analyzed over 6–40° at the rate of 4°/min. Calculated powder patterns of the single crystal were obtained utilizing Mercury 1.4 (The Cambridge Crystallographic Data Centre, Cambridge, UK).

Solubility measurements

Known amounts of FFA (FFA 3.2 g in EtOH, FFA 2.02 g in ethanol–water mixtures (EtOH:H_2O = 8:2) and toluene and MFA 0.5 g in EtOH and 0.2 g in ethanol–water mixture and toluene were placed in scintillation vials. 10 ml of each solvent was added, and the solutions were stirred with magnetic stirrer in a jacketed beaker at 15°C controlled by Circulator, Fisher Isotemp Refrigerating, programmable Model 3016 P. The solution was filtered and the concentration of supernatant was determined by HPLC.

RESULTS AND DISCUSSION

Characterization of MFA II

Single crystal X-ray data obtained for MFA II crystallized using the additive method and MFA I (CSD refcode: XYANAC) (18) are summarized in s(Table II). Both Form I and Form II have the same crystal system P-1. However, cell parameters show large differences. Form I has more elongated unit cell dimensions. In ethanol solvent system, MFA Form I grows as very small needle shape crystals, and MFA Form II with FFA as additives grows into tabular shape crystals (Fig. 2). The X-ray pattern of the tabular crystals matches X-ray patterns of MFA II (Figs. 3 and 4) (12). MFA II has three distinct peaks around 9–12° at low 2θ, and MFA I has a very strong peak around 7° at low 2θ. The overall peak patterns from MFA I and MFA II are distinguishable. HPLC data shows that there is less than 10% w/w of FFA in MFA. Scanning Electron Microscopy suggests that FFA is deposited on the surface of MFA crystals when MFA crystals are harvested. This is supported by the observation that the amounts of FFA detected in MFA increase as the amounts of FFA in the initial solution increase. There is no evidence that FFA molecules are actually incorporated into the single crystals of MFA II although the presence of small amounts cannot be conclusively ruled out.

Effect of FFA on the Crystallization of MFA

In a related study, it was recently reported that aspirin Form II was obtained in the process of co-crystallization of aspirin and levetiracetam (23). In the aspirin work as with

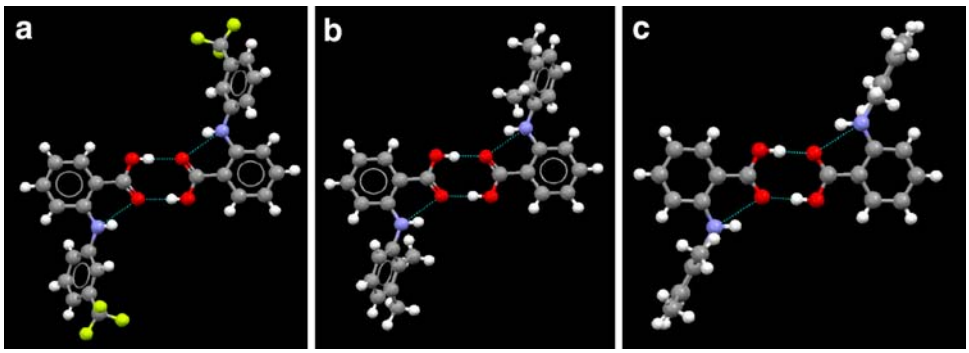

Fig. 5. Crystal packing structures of (a) FFA Form I, (b) MFA Form I, and (c) MFA Form II. FFA Form I and MFA Form I show similar crystal packing structures.

Table III. Comparison of Torsion Angles Between MFA Form I and Form II and FFA Form I

Torsion angle	MFA Form I[a]	MFA Form II[a]	MFA Form II[b]	FFA Form I[a]
τ_1	−179.34	−177.75	176.05	179.21
τ_2	−119.99	−71.66	76.09	−130.06
τ_3	−1.71	−0.43	−0.43	−3.69

MFA I[a] J. F. McConnell and F. Z. Company, Cryst. Struct. Comm. **1976**. 5, 81.
MFA II[a] Occupancy factor of 0.65 for MFA II.
MFA II[b] Occupancy factor of 0.35 for MFA II.
FFA I[a] H. M. Krishna Murthy, T. N. Bhat and M. Vijayan, Acta Cryst. **1982**. B38, 315.

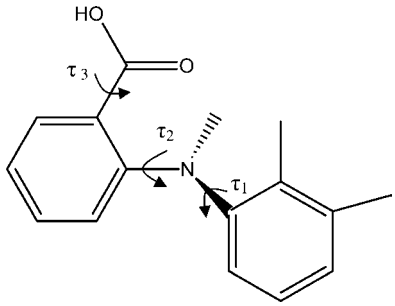

Fig. 6. Definition of MFA torsion angle: τ_1 is the angle between C2–C1 and N–C9 bonds, τ_2 the angle between C1–N and C9–C10 bonds, τ_3 the angle between C1–C2 and C–O7.

our study, it appears that the additive allowed crystallization of single crystals of a metastable form. In contrast to the aspirin study, our investigation involves the study of the ability of structurally similar FFA molecules (Fig. 1) to induce the crystallization of the metastable form of MFA. Crystallization of MFA from ethanol in the absence of additives always produces Form I. However, a supersaturated solution of MFA produces single crystals suitable for single crystal X-ray analysis when a structurally similar additive, FFA, is used.

Structurally similar additives are known to affect nucleation and/or growth process of host crystals and thus, can be used to select the desired form of some compounds. Structurally similar guest molecules can be attached to the host crystal surface as host molecules do during nucleation and crystal growth process. However, these guest molecules prevent the attachment of new host molecules on the growing crystal surface. As a result, growth of host crystals is inhibited. Interestingly, outcomes of this process are different depending upon the stage of nucleation and crystal growth. If this inhibition occurs during nucleation process, further growth of pre-nuclear aggregates into critical size nuclei will be inhibited. In this case, the other polymorphic form, which is structurally different from the additive guest molecules, will grow. In the other case, the effect of guest molecules is predominantly on the crystal growth process; in this case, the affected crystal face becomes larger by the same mechanism. In our work, FFA which has similar structure to MFA I seems to block the nucleation process of MFA Form I. Therefore, MFA II is formed. This is consistent with the observation that FFA delays the initiation of growth of MFA I. This suggests that FFA allows MFA II to grow by the same mechanism as observed for other additives.

FFA Form I crystal packing patterns are very similar to MFA Form I packing patterns (Fig. 5) (24). Intramolecular hydrogen bonding between the carboxylic group and imino N atom connecting two six-membered rings and a six-membered ring containing carboxyl group and intermolecular hydrogen bonding which lead to hydrogen bonding dimers in crystal packing are the major bonding force for both MFA I, MFA II, and FFA. The difference in crystal packing between MFA I and MFA II comes from torsion angle τ_2. Torsion angle τ_2 of FFA I (−130.06°) is not similar to that of MFA II (−71.66°, 76.09°) but similar to that of MFA I (−119.99°) (Table III, Fig. 6). These torsion angle differences between MFA I and MFA II are hypothesized to induce the difference in crystal packing structures shown in Fig. 5. In solution state, torsional angles may not be the same as torsional angles in crystalline state. However, torsional angles in crystalline state can have some analogy to those in the solution state, and this similarity is supported by NMR study especially at high concentration of solute (9). If the torsional angle resemblance between solution state and crystalline state is assumed, FFA having similar torsional angle to MFA I will interact with MFA I prenuclei. This attachment possibly by intermolecular hydrogen bonding between carboxyl groups of FFA and MFA I may interfere with the further growth of MFA I since subsequent attachment of MFA molecules to FFA on prenulei can be interrupted. This inhibition can result in delay of stable form formation and thus result in metastable form formation by kinetic control. In addition, this kinetic control can be supported by induction time delay. Usually induction time for MFA I grown in ethanol in our crystallization conditions is less than 1 day. However, induction time for MFA II grown with FFA is from 1 week to several months. This induction time delay is also evidence that FFA inhibits the nucleation process of MFA I and thus helps MFA II grow.

Another important consideration in crystallization is the solvent. Although most published work emphasized the structural relationships between host and guest molecules (25,26), our studies show the solvent system can influence additive effects. In some cases additive effects can be different due to differences in solubility in different solvents. In ethanol the high solubility of FFA (0.224 g/ml) allows it to act as an additive allowing crystallization of MFA II since the amounts of FFA in the solution were below the solubility limit (Table IV). Therefore, crystallization of FFA did not occur. However, in ethanol–water mixtures and toluene, FFA is much less soluble (0.065 g/ml for ethanol–water mixtures and 0.056 g/ml for toluene). Therefore, FFA in ethanol–water

Table IV. Solubility of FFA and MFA in Different Solvent System at 15°C

Solvent	Solubility (mg/ml)	
	FFA	MFA I
EtOH	224	5.44
Ethanol–water mixture	65.1	1.46
Toluene	56.3	0.50

mixtures and toluene were supersaturated in our experimental conditions, and these solutions resulted in FFA crystals containing MFA or mixtures of FFA and MFA. These FFA crystals contain some amounts of MFA incorporated into the crystal lattice and surface. In fact, the amount of MFA incorporated depends on the concentration of MFA in solution. From these results and based on structure analysis (Fig. 5, Table III), it can be deduced that molecules with the conformation of MFA I may interact with FFA molecules in different ways in the different solvent systems. However, molecules with the conformation of MFA II may not interact with FFA. Therefore, molecules with the MFA I conformation are incorporated into FFA crystals when FFA crystallizes in ethanol–water mixtures and toluene.

CONCLUSION

These studies suggest that structurally related additives can be used to induce the growth of metastable forms for single crystal analysis. Thus, deliberately chosen additives are good candidates for metastable form generators. However, the relationships between conformations of the host and guest and the crystallization solvent are equally important.

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