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Ye.A. Vaksler, D. Benedis, A.A. Dyshin, R.D. Oparin, Natália T. Correia, et al.. Spectroscopic characterization of single co-crystal of mefenamic acid and nicotinamide using supercritical CO<sub>2</sub>. *Journal of Molecular Liquids*, 2021, *Journal of Molecular Liquids*, 334, pp.116117. 10.1016/j.molliq.2021.116117 . hal-04287011

**HAL Id: hal-04287011**

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Submitted on 22 Jul 2024

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## **Spectroscopic characterization of single co-crystal of mefenamic acid and nicotinamide using supercritical CO<sub>2</sub>.**

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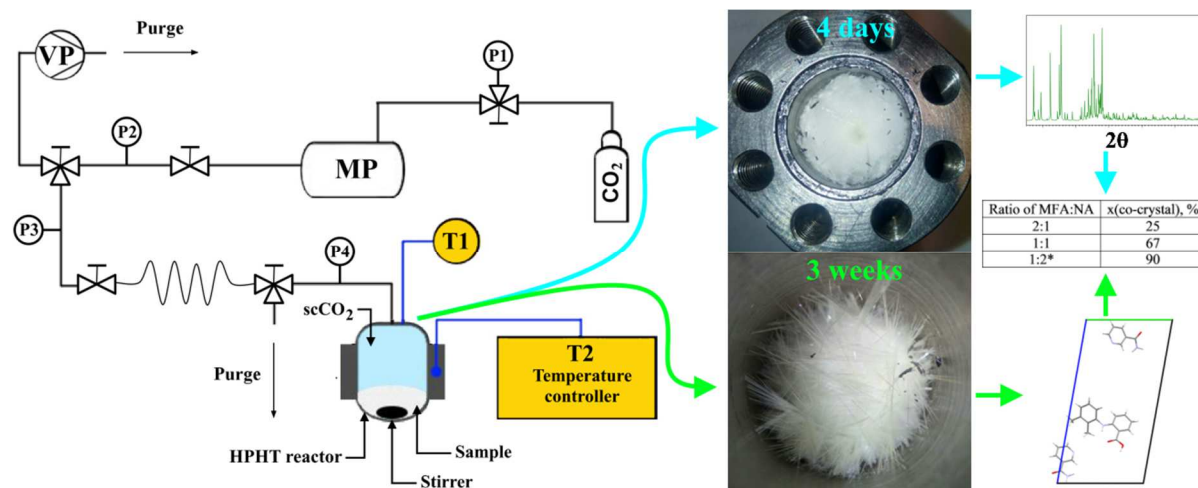
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### **Abstract**

. The present study explores the possibility to synthesize, using supercritical fluid, single crystal of co-crystal formed by mefenamic acid as active pharmaceutical ingredient and nicotinamide as a co-former. The growth of single crystals is important for the determination of co-crystal structure and in particular, for those the unit cells of which contain large number of atoms, it becomes crucial. For this purpose, we analyzed the effect of temperature, solid mixture composition and time duration of the co-crystallization process on the synthesized solid. The structure of the latter was determined using single crystal X-Ray diffraction while the composition of fine powders and the intermolecular interactions involved in their synthesis were analyzed using powder X-Ray diffraction and diffuse reflectance infrared Fourier transform spectroscopy respectively. Our results show that the single crystal of mefenamic acid

and nicotinamide co-crystal is synthesized for the first time in supercritical CO<sub>2</sub> at 90°C, 193 bars and time duration of three weeks.

## Graphical abstract



## Keywords

Co-crystallization, single crystal, supercritical carbon dioxide, X-ray diffraction, infrared spectroscopy.

## Abbreviations

ScCO <sub>2</sub>	supercritical carbon dioxide
SCXRD	single crystal X-ray diffractometry
PXRD	powder X-ray diffractometry
DRIFTS	diffuse reflectance infrared Fourier transform spectroscopy
HPHT	high-pressure high-temperature
RESS	rapid expansion of supercritical solution
API	active pharmaceutical ingredient
MFA	mefenamic acid
NA	nicotinamide

## 1. Introduction

Co-crystallization is a widely used method to improve the chemical properties of the targeted active pharmaceutical ingredient such as its aqueous solubility, bioavailability, dissolution rate, melting point and stability.<sup>1-3</sup> Co-crystallization process may be carried out in eco-friendly supercritical CO<sub>2</sub> that allows to synthesize co-crystals of high purity in a single step process with the possibility to handle thermosensitive APIs.<sup>4-23</sup> Application of scCO<sub>2</sub> can solve most of the drawbacks of synthesizing the co-crystal with commonly used mechanochemical and solution-based methods.<sup>24,25</sup> Specifically, when compared with conventional methods (solid-based or solution mediated ones), utilization of scCO<sub>2</sub> helps to control the thermodynamic parameters (temperature, pressure) and to achieve the repeatability of the proposed process.<sup>26-29</sup> Moreover, when scCO<sub>2</sub> is used as a solvent, the latter is also not retained in the processed solid API<sup>30</sup>, and the final product is stable, as shown in our recent study<sup>31</sup>.

To our best knowledge, using scCO<sub>2</sub>, co-crystals have been synthesized mostly as microcrystalline powders, the structure of which is determined by powder X-Ray diffraction. It is well established that the structure determination using PXRD is a powerful auxiliary implement to single crystal X-ray diffraction. For instance, using the two approaches, the structure determination of the griseofulvin crystal structure gave the same lattice parameters.<sup>32</sup> However, the structure determination using PXRD is more challenging than SCXRD, in particular in the case of organic molecular materials with large number of atoms in an asymmetric unit cell.<sup>33,34</sup> Furthermore, because of the impossibility to obtain single crystals of sufficient size, it was not possible to determine the structure of many synthesized samples.<sup>35,36</sup> We should mention that to our best knowledge the growth of a defect-free single crystal, using scCO<sub>2</sub> was demonstrated only for acetylated carbohydrates.<sup>37</sup>

In the current paper, we propose a new methodology using scCO<sub>2</sub> as a media for the synthesis as single co-crystals with enough size and purity that allow their structure determination using SCXRD. This methodology is based on our recent work, where we succeed to produce a specific polymorphic form of APIs.<sup>31,38</sup> The main idea of our approach is to heat the solid mixture of the API and the co-former, up to a temperature that is close to the melting temperature of one component (co-former in this work) and to hold these conditions for the time enough for the growth of single crystals of the multicomponent system (API:co-former). The supercritical conditions (pressure and temperature) of CO<sub>2</sub> affect the solid mixture-fluid equilibrium interface. From the practical point of view, using scCO<sub>2</sub>

allows to remove water from the initial solid mixture and to avoid its effect on the outcome of the co-crystallization process. As a test multicomponent system, the API mefenamic acid and nicotinamide, vitamin B3, popular co-former, was chosen. MFA:NA co-crystal was synthesized using conventional methods and gas anti-solvent process.<sup>16,39,40</sup> In this paper, we optimized the temperature, mixture composition and time duration of the co-crystallization to synthesize a single crystal of MFA:NA co-crystal in pure scCO<sub>2</sub>. We may mention that the solubility of such a co-crystal in water was declared to be near 1.5 times higher in comparison with that of the pure MFA.<sup>40</sup> Numerous experimental results have shown that, in co-crystallization process in a solvent, the large difference in solubility existing between the API and the co-former in that solvent is an incompatibility factor, which makes the formation of the co-crystal incomplete.<sup>41</sup> For the NA the solubility in water is more than 10<sup>5</sup> times higher than for the MFA under normal conditions.<sup>42,43</sup> However, their solubility in scCO<sub>2</sub> is relatively close.<sup>44,45</sup> This constitutes a favorable condition for the co-crystallization process of the MFA and NA in scCO<sub>2</sub>.

The paper is organized as follow: in the first, details on the experimental methods are given, secondly, the effect of the temperature, the mixture composition as well as the duration of the co-crystallization process is analyzed. The optimal condition for the synthesis of the single crystal of MFA:NA co-crystal is demonstrated. We also showed that even when we obtain only the co-crystal in the powder form, the yield is higher than that obtained by rapid expansion of supercritical solvent method.

## **2. Materials and methods**

### *2.1. High pressure and high temperature reactor*

The MFA and the NA co-former powders were first dried under vacuum equal to 10<sup>-4</sup> bar at 60°C. They were introduced in high pressure and high temperature reactor and were further mixed with a high purity (99.95%) scCO<sub>2</sub> (Fig. 1). The reactor was pumped during 24h to reduce the impact of the moisture at the solid mixture of MFA and NA-fluid interface. Then the reactor was slowly heated (1°C/min) by a cuff-heater to a constant temperature (40 or 90 °C) below the melting temperature of the initial powders or the co-crystal and, in particular, below the melting point of NA. The contents of the HTHP were compressed by a manual press to a pressure corresponding to 1.1 critical density of CO<sub>2</sub> (equal to 11.687 mol·L<sup>-1</sup> according to NIST database<sup>46</sup>). The pressure in the reactor was 91 and 193 bars at 40 and 90°C,

respectively, according to isochoric conditions. The reactor was isolated during the whole duration of the synthesis (4 days or 3 weeks) with constant stirring (300 rpm). MFA:NA mixing ratios of 2:1, 1:1 and 1:2 were tested.

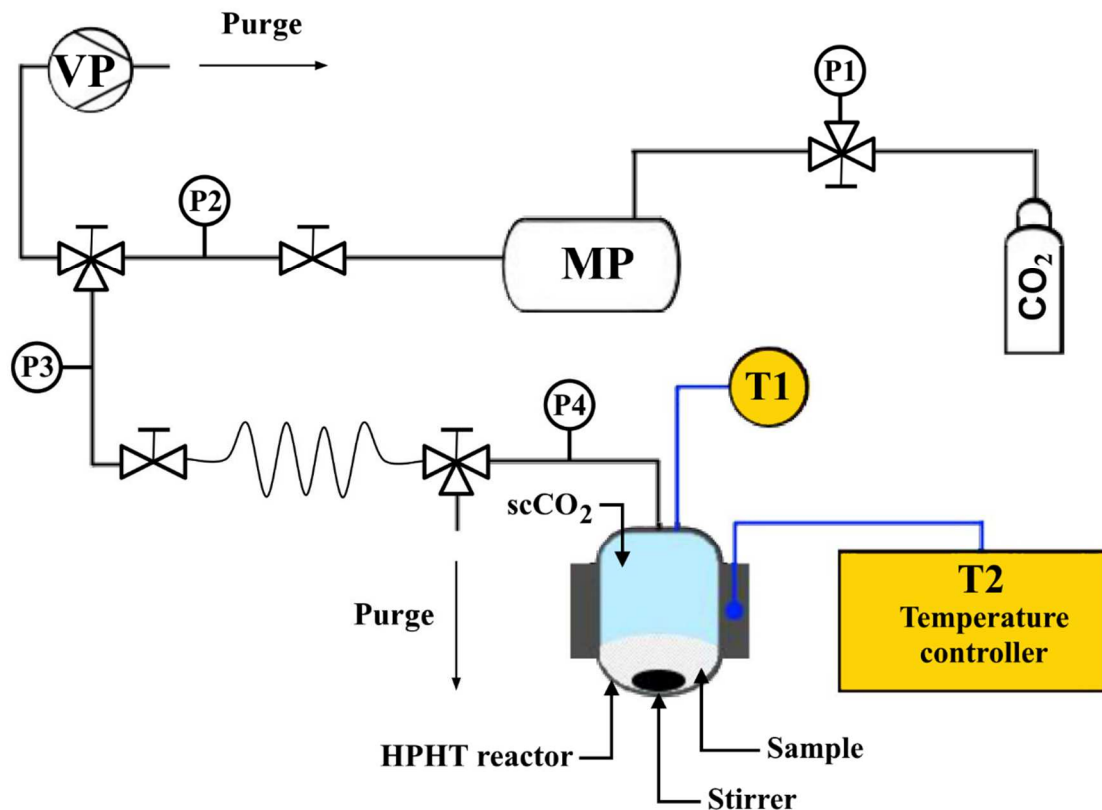


Figure 1. The experimental setup used for the synthesis of the MFA:NA co-crystal: P1-P4 – pressure sensors; T1 – temperature in-cell sensor; T2 – temperature sensor-controller of the cuff-heater; MP – manual press; VP – vacuum pump.

## 2.2. Crystal structure determination

Reflection data and unit cell parameters of the synthesized crystals was measured at the temperature of 100 K using an Apex II CCD 4K Bruker diffractometer ( $\lambda = 0.71073 \text{ \AA}$ ). Correction for Lorentz polarization was performed in SAINT software.<sup>47,48</sup> Empirical absorption corrections introduced in SADABS software.<sup>49</sup> The structure was solved by a direct method using the SHELXTL program package.<sup>50,51</sup> Hydrogen atoms bonded to carbon were placed at geometrically calculated positions. The other H atoms were revealed from the Fourier difference map. The refinement was done in the riding model with  $U_{\text{iso}}$  values scaled to the ones

of the parental heavy atoms. OLEX2 program<sup>52</sup> was used for the visualization and data processing. Previously the structure of the co-crystal with 1:2 MFA:NA ratio was determined from powder X-ray data using not an easily accessible synchrotron source of radiation<sup>53</sup>, so we used it for the comparison with our data.

### *2.3. Powder X-ray diffraction*

PXRD analysis was carried out at room temperature and humidity using a BRUKER AXS D8 ADVANCE diffractometer (Bragg–Brentano geometry) equipped with a 1D PSD detector (Lynx-Eye). Copper ( $K\alpha$ ) radiation was used for the measurements over the  $2\theta$ -range from  $4^\circ$  to  $60^\circ$  with a scan rate of  $0.02^\circ/\text{sec}$  (goniometer continuous mode). The X-ray source operated at the generator voltage of 40 kV and the tube current of 40 mA. Match! Software<sup>54</sup> was used on powder X-ray data to assess semi-quantitatively the phase composition of the synthesized solid.

### *2.4. Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS)*

Vibrational spectra were registered using Bruker Vertex 70V infrared spectrometer equipped with liquid nitrogen cooled MCT detector in the spectral range from  $700$  to  $4000\text{ cm}^{-1}$  with the resolution of  $2\text{ cm}^{-1}$  (256 scans per spectrum). For the DRIFTS a Harrick Scientific Diffuse reflectance attachment “Praying Mantis” combined with cell equipped with  $\text{CaF}_2$  windows was applied. The further data manipulation including Kubelka-Munk transformation were performed in OPUS Bruker software.

## **3. Results and discussion**

### *3.1. Effect of temperature, solid mixture composition and time duration of the co-crystallization process*

In a first stage of our work, we analyzed the effect of the temperature ( $40^\circ\text{C}$  and  $90^\circ\text{C}$ ), the mixture composition (MFA:NA mixing molar ratio of 2:1, 1:1 and 1:2) and the time duration (4 days and three weeks) on the co-crystallization process. We have then systematically analyzed the composition of the synthesized solid form. Our analysis was based on comparing the X-Ray diffraction patterns of the synthesized solids at the different

temperatures, mixture compositions and duration times of the co-crystallization process with that measured for the corresponding physical mixture of the initial components without co-crystallization and the one calculated, using the Mercury program<sup>55</sup>, for the co-crystallized sample (single crystal data).

The results of PXRD analysis showed that the synthesis was not successful at 40°C for all the ratio of initial components and for both duration times. Indeed, as it is illustrated, for the 1:2 mixture in Fig. 2, the obtained powder X-Ray diffraction patterns did not correspond to the 1:2 co-crystal but coincide to a large extent with that of the initial compounds. However, at 90°C, as it is shown in Fig. 3, the emergence of new peaks in the X-ray powder patterns at  $2\theta$  angles of 7.20°, 7.52°, 8.68°, 9.44°, 12.26°, 15.54° evidences the formation of a powder co-crystal phase. More precisely, the semi-quantitative analysis of PXRD data showed that uniquely the co-crystal with stoichiometry 1:2 of MFA to NA was formed.

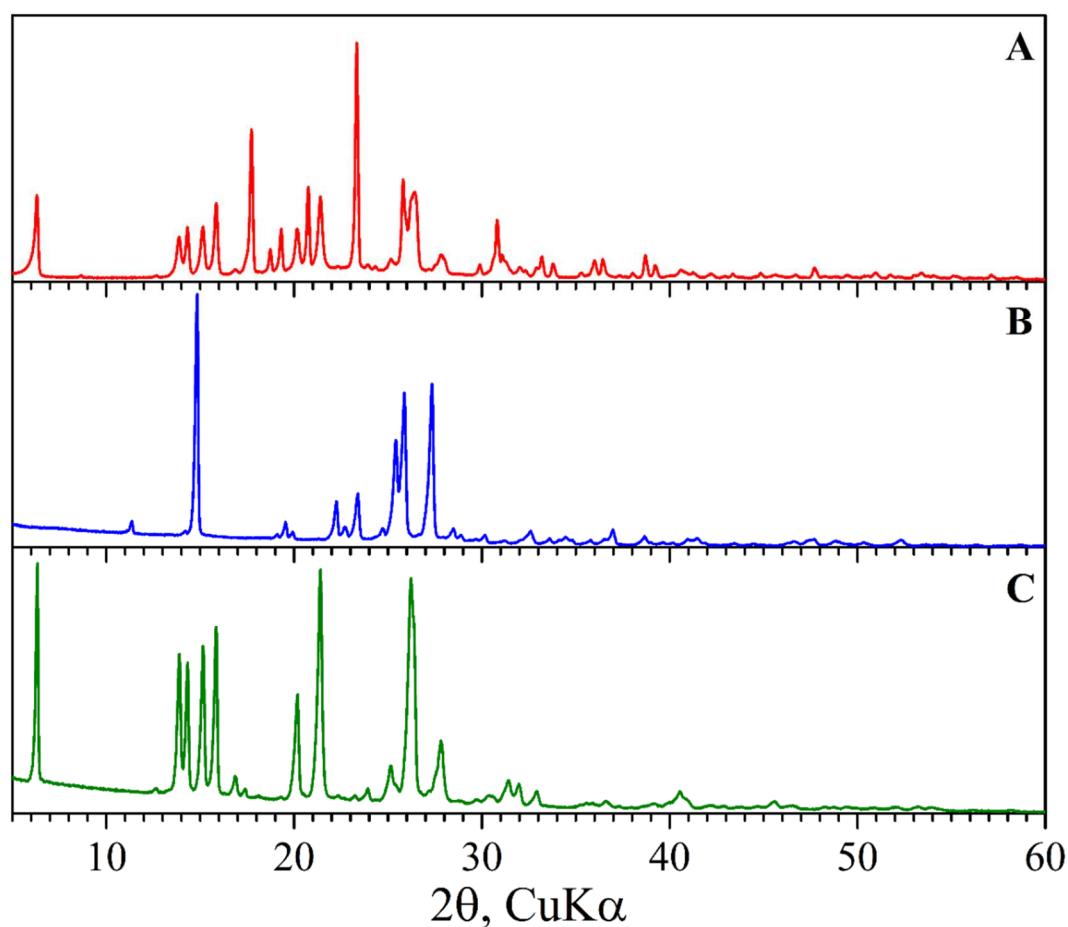


Figure 2. Comparison of the experimental X-Ray diffraction patterns of the synthesized powder obtained at 40°C with acquisition time of 3 weeks (A) and the ones for the initial NA (B) and MFA (C).



The estimation of the co-crystal yield at different temperatures and acquisition times showed no significant difference between the 4 days and 3 weeks (the powder part of the obtained sample) durations. As it shown in Table 1, the co-crystal yield estimation at 90°C is obviously high, of about 90%, when the initial mixing ratio of MFA and NA is 1:2.

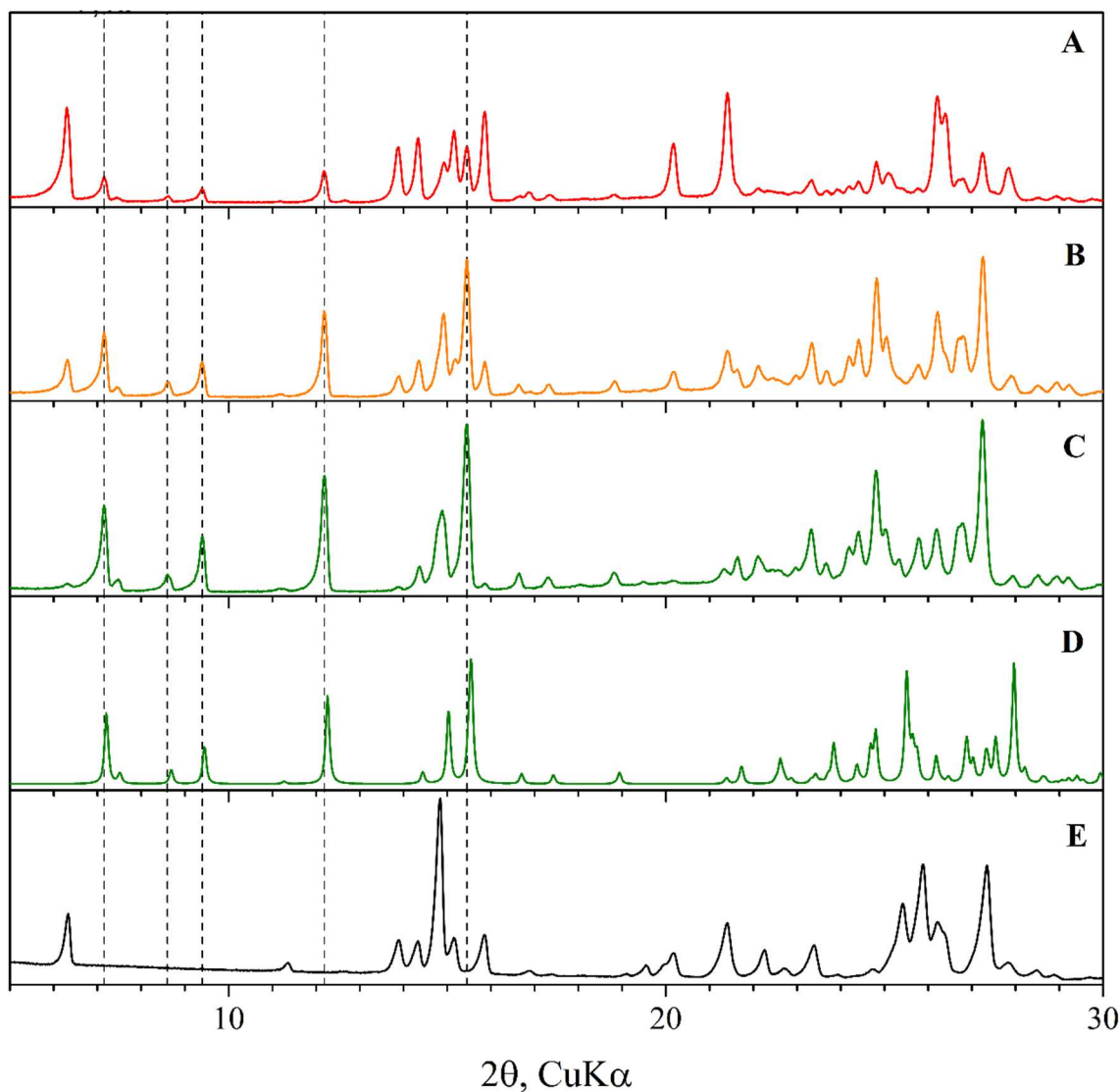


Figure 3. Comparison between the experimental X-ray powder diffraction patterns of the synthesized powder at 90°C with the acquisition time of 4 days in the cases where mefenamic acid and nicotinamide are mixed in the ratio 2:1 (A), 1:1 (B), 1:2 (C) and the sum of the diffractograms of the initial components mixed physically without co-crystallization in the 1:2 ratio (E). The calculated X-Ray powder pattern of the synthesized single co-crystal with the 1:2 ratio of MFA:NA (D). The characteristic peaks appearing on transformation are marked with dashed lines.

Table 1. The initial ratio of MFA and NA and the yield (%) of the co-crystal according to the semi-quantitative analysis of the PXRD data that were obtained at 90°C and the acquisition time of 4 days.

Initial molar ratio of the components (MFA:NA)	x(MFA), %	x(co-crystal), %
2:1	75	25
1:1	33	67
1:2*	>10	90

\*The traces of initial NA were found with pure MFA, but their quantification is impossible due to low values.

The changes in the interactions during the powder co-crystal formation are another point of interest. Thus, we recorded the DRIFT spectra of the synthesized powder co-crystal and we compared them with those of the corresponding initial no processed MFA and NA powders (Fig. 4). Our results show that there are no significant changes in the position of MFA vibration modes (less than 5  $\text{cm}^{-1}$ ). On the contrary, the shifts of the NA vibration modes positions<sup>21,39,40</sup> in the DRIFT spectra is considered a spectral signature of the formation of new intermolecular hydrogen bonds in the obtained co-crystal (Table 2). Thus, the DRIFT spectra can be used for the quick identification of co-crystal formation.

Table 2. Wavenumbers ( $\text{cm}^{-1}$ ) of the peaks in DRIFTS shifted during the powder co-crystal formation (secondary peaks constituents are put in brackets).

Vibration type	Co-crystal	NA	MFA
N-H stretch	3307		3311
	3165	3157	
	3386 (3402)	3361	
N-H bend	1577 (1591)	-	1576
C=O stretch	1649		1647
	1684	1674	

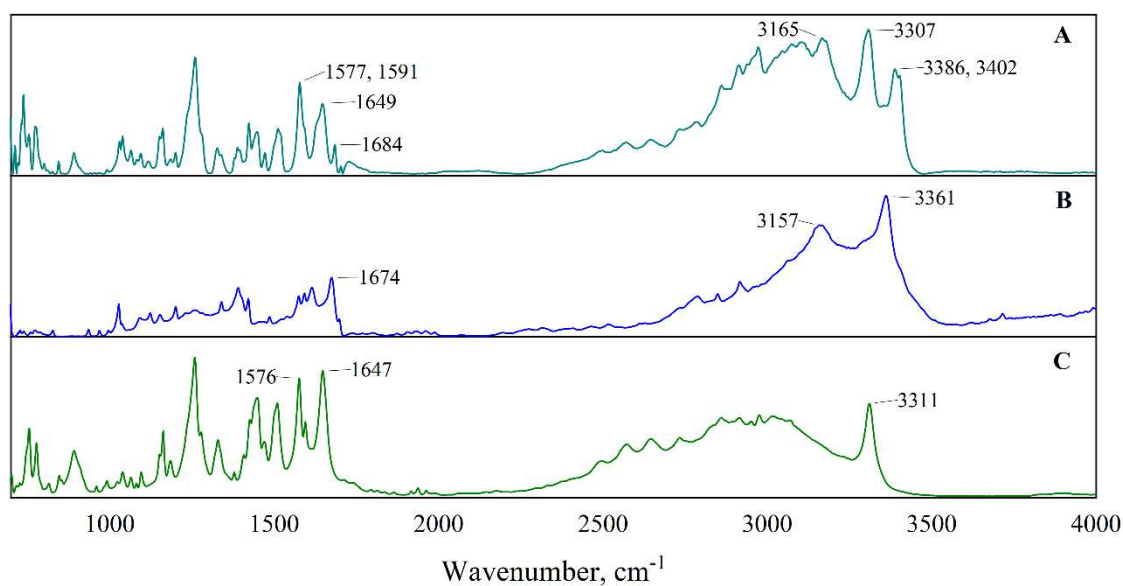


Figure 4. DRIFT spectra of MFA-NA powder co-crystal (A) as well as the initial components: NA (B) and MFA (C). The changes in the positions of the peaks during the co-crystal formation are marked (the main component position is followed by the secondary constituent in case of the complex peaks in co-crystal).

### 3.2. Comparison with the Rapid Expansion of Supercritical Solution (RESS) experiment

In this part of our paper we aimed to compare the obtained powder co-crystal of MFA:NA in the ratio 1:2 at 90°C, the pressure of 193 bars and the duration of 4 days with that obtained using RESS experiment in the same thermodynamic conditions. To this purpose, the extraction unit of the RESS set up was filled with the initial MFA and NA mixture with molar ratio 1:2 and CO<sub>2</sub> was kept under the constant pressure of 193 bars at a temperature of 90°C for 24 hours for the initial conversion of MFA-NA mixture to co-crystal phase. The supercritical solution was expanded through a 100 µm sapphire nozzle into the dry expansion chamber by cycles: 5 pulverizations of 20 seconds each followed by a break for dissolution within 2 hours. The temperature of the nozzle was set to 50°C. The detailed experimental scheme is shown in figure 5.

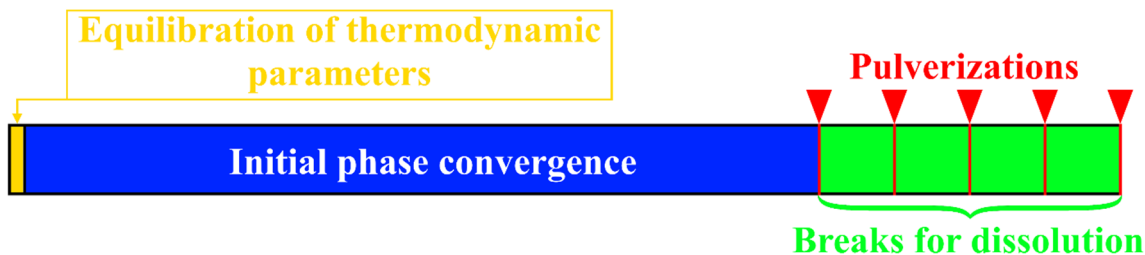


Figure 5. Stages of the RESS experiment for MFA-NA (1:2) mixture.

The X-ray diffraction patterns of the powders obtained by the two methods are compared in figure 6. Their semi-quantitative analysis indicates that near 20% of the initial components mixture was converted into the co-crystal using the RESS technique while with the method using the HPHT reactor about 90% was transformed in the co-crystal even in a relatively short 4 days experiment. This demonstrates the efficiency of our methodology in comparison with the classical fast kinetically controlled method without addition of any non-ecofriendly solvent. This opens a new question on the mechanism of co-crystal formation under constant conditions in HPHT reactor, which will be the subject of our next investigation.

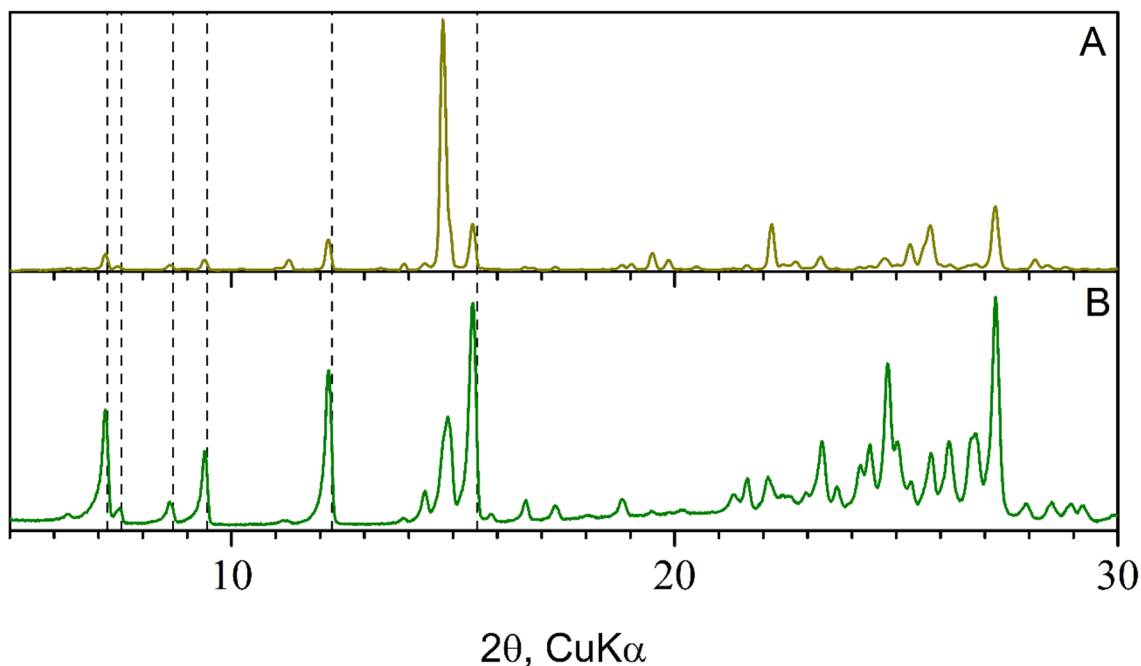


Figure 6. Comparison between the experimental powder X-ray diffraction patterns of the synthesized co-crystal of mefenamic acid and nicotinamide using the RESS experiment (A) and the HPHT reactor (B). The characteristic peaks appearing on transformation are marked with dashed lines.

### 3.3. Synthesis of single crystals of the MFA:NA co-crystal

In this part of the paper we will discuss our main finding, namely the synthesis of the single crystal of MFA:NA co-crystal. As it is shown in Fig. 7, after processing of the MFA and NA raw powders for two test duration times: 4 days and 3 weeks, the single crystals were grown only at 90°C with the acquisition time of 3 weeks. For the shorter duration, as it is seen (Fig. 7a), the product obtained is a powdery mass due to the large excess of initial components, however, in the long-term synthesis (Fig. 7b) thin needle-shaped crystals up to 2 cm length and to 1 mm width were grown. Their structure has been determined by SCXRD (Table 3). The numbering of atoms is displayed in figure 8. It is shown that the benzene fragments are turned relative to each other by 52°. This twist is probably caused by steric repulsion between them (the shortened intramolecular contacts are C6...C10 2.39 Å, H6...C10 2.82 Å, C6...H10 2.58 Å, C1...H10 2.67 Å as compared to van der Waals radii sum<sup>56</sup> C...C 2.42 Å and H...C 2.87 Å). The formation of the N1-H1...O1 intramolecular hydrogen bond (Table. 4) between the carboxyl and amino groups causes the coplanarity of the carboxyl group to the aromatic cycle as well as the stronger conjugation of the nitrogen lone pair with carboxyl substituted benzene ring leading to non-equivalence of the N1-C9 and N1-C1 bonds (1.370(2) Å and 1.409(2) Å respectively). As a result, the molecular conformation change of MFA molecule can occur only due to the rotation around the C1-N1 bond. The carbamide groups of both NA molecules, found in the unit cell asymmetric part, are noticeably turned relative to the pyridine planes (the C<sub>ar</sub>-C<sub>ar</sub>-C<sub>sp2</sub>=O torsion angles are 15° and 24° for molecules A and B, respectively) despite a conjugation between the carbonyl group and aromatic system. It may be presumed that such a non-planarity is caused by the influence of intermolecular hydrogen bonds formation.

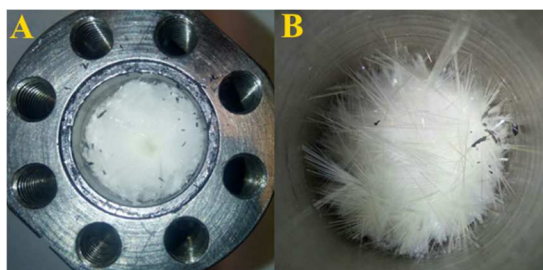


Figure 7. The morphology changes due to different acquisition times: a powdery product from 4-days (A) and crystals from 3-weeks (B) experiments obtained at 90°C with 1:2 initial ratio of MFA to NA.

The analysis of intermolecular interactions (Table 4) in the co-crystal has revealed that two NA molecules differ by their arrangements and role in the crystal structure formation. NA (B) is bound with MFA molecule due to the O2-H2...N4 intermolecular linear hydrogen bond as well as with NA (A) due to the N5-H5A...N2 linear hydrogen bond. In contrary, NA (A) is bound with two NA molecules: with NA (A) through the N3-H3B...O3 intermolecular centrosymmetric hydrogen bond and with NA (B) through the above mentioned N5-H5A...N2 linear hydrogen bond. As a result, hexamer (Fig. 9) containing two MFA and four NA molecules may be separated out as some structural fragment of the co-crystal. The MFA molecules form a sole hydrogen bond, O2-H2...N4, which may explain the previously stated higher availability of MFA in co-crystal in comparison with the pure component.

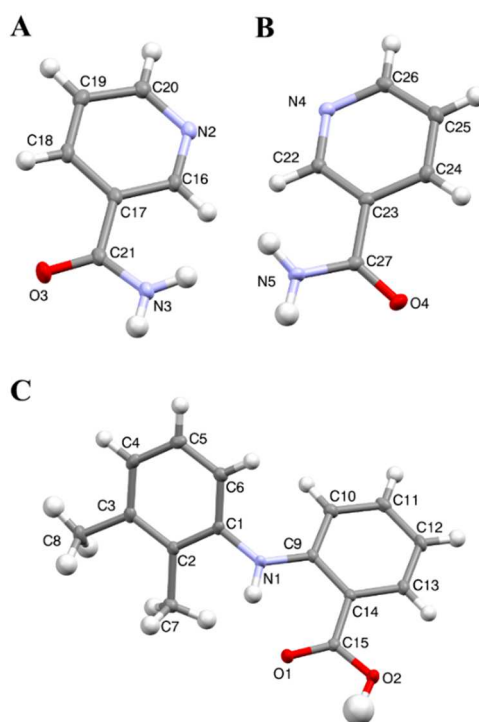


Figure 8. Structure of the molecules involved in the MFA:NA co-crystal: A – NA (A), B – NA (B), C – MFA.

Table 3. Comparison of the crystallographic data received from SCXRD (current paper) and powder synchrotron experiment<sup>53</sup>.

	Current paper	L. Fábíán [et al.]
Formula	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub> , 2(C <sub>6</sub> H <sub>6</sub> N <sub>2</sub> O)	C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>
formula weight	485.54	485.54
crystal system	triclinic	Triclinic
space group	P-1	P-1
a (Å)	3.9660(3)	4.064104(14)
b (Å)	12.4578(9)	12.50989(5)
c (Å)	23.9391(14)	24.08865(10)
α (°)	100.041(3)	99.8930(4)
β (°)	91.621(3)	90.7285(4)
γ (°)	91.820(4)	92.4340(4)
V (Å <sup>3</sup> )	1163.38(14)	1205.154(8)
Z	2	2
D <sub>c</sub> (g*cm <sup>-3</sup> )	1.386	1.338
λ (Å)	0.71073	1.0002
T (K)	100.05	295
2θ range (°)	3.322 – 60.942	2 – 60
data / parameters / restraints	7047 / 351 / 0	15388/240/206
R indices (all data)	R <sub>1</sub> = 0.0648 wR <sub>2</sub> = 0.1259	R <sub>p</sub> = 0.004, R <sub>wp</sub> = 0.006, R <sub>exp</sub> = 0.004
goodness of fit	S = 1.028	χ <sup>2</sup> = 2.574
largest diff. peak and hole (e Å <sup>-3</sup> )	0.401 / -0.233	0.33/0.33

Table 4. Geometric characteristics of hydrogen bonds involved in the 1:2 MFA:NA co-crystal.

Hydrogen bond	Symmetry operation	d(H...A), Å	∠(D-H...A), °
N1-H1...O1	x,y,z	1.91(2)	140(2)
O2-H2...N4	-x,1-y,1-z	1.63(3)	175(2)
N5-H5B...O1	1-x,1-y,1-z	2.18(2)	171(2)
N5-H5A...N2	2-x,1-y,1-z	2.04(2)	175(2)
N3-H3A...O4	1-x,1-y,1-z	2.21(2)	172(2)
N3-H3B...O3	-x,-y,2-z	2.04(2)	172(2)

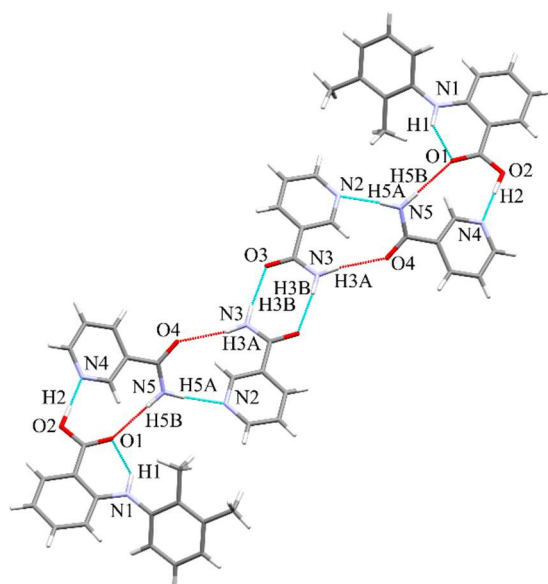


Figure 9. Hexameric building unit formed by intermolecular hydrogen bonds in the structure of the MFA:NA co-crystal. The atoms involved in the hydrogen bonds are marked.

#### 4. Conclusions

In this paper, we analyzed the effect temperature (40°C and 90°C), the solid mixture composition as well as the time duration of the co-crystallization process on the synthesized co-crystals of MFA-NA in supercritical CO<sub>2</sub>. The aim was to synthesize a single crystal of this co-crystal that makes it straightforward to determine its structure using single crystal X-Ray diffraction. Our results show that at 90°C and for all the tested temperatures and pressures, systematically a powder co-crystal is



synthesized. However, in the case of the 3-weeks experiment the significant amount of sample became big enough single crystals, the structure of which was successfully determined using classical SCXRD. The analysis of the X-Ray diffraction, the highest yield is reached, as expected, when the initial mixture is in the ratio 1:2. The intermolecular interactions involved in the formation of MFA:NA co-crystal were analyzed using DRIFTS.

## **Acknowledgements**

Authors deeply acknowledge Florence Danède (MMT-UMET, University of Lille) for performing powder X-ray diffraction experiments.

## **Funding sources**

This work was supported by the following funding sources:

The PHC Kolmogorov N°41129RC.

The fellowship of the French Embassy in Kyiv in Ukraine for Ye.A. Vaksler.

The Erasmus+ fellowship for D. Benedys.

The Interreg 2 Seas program 2014-2020 co-funded by the European Regional Development Fund (FEDER) under subsidy contract 2S01-059\_IMODE.

The project ARCHI-CM, Chevreul Institute (FR 2638), Ministère de l'Enseignement Supérieur et de la Recherche, Région Hauts-de-France.

The European Regional Development Fund (FEDER).

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