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## Best solvent for recrystallization of acetaminophen

As a leading library, NLM provides access to scientific literature without endorsing or agreeing with its content. In this study, we demonstrate the application of Metal-Assisted and Microwave-Accelerated Evaporative Crystallization (MA-MAEC) technique for rapid and selective crystallization of a small drug compound, acetaminophen. Our results show that crystals grew predominantly as Form I (99%) on blank glass slides at room temperature, while Form II crystals with 39% purity were grown on silver island films using microwave energy. The determination of crystal structure is crucial to understanding the behavior of organic and biological molecules both in-vivo and in-vitro. Various crystallization techniques have been reported for rapid growth of higher-quality crystals. In this context, researchers have employed polarized laser light irradiation, engineered surfaces, and self-assembled monolayers to control polymorphism. Our previous work has demonstrated the use of MA-MAEC technique as a quick and efficient method for growing crystals with selective morphology. This technique is based on the combined use of silver island films (SIFs) as a new crystallization platform and low-power microwave heating to speed up the crystallization process. Acetaminophen is a widely used over-the-counter analgesic and anti-pyretic drug, which has two different crystalline forms: Form I and Form II. Our study characterizes these crystals using optical microscopy, powder X-ray diffraction (PXRD), and Raman spectroscopy. **Keywords:** Metal-Assisted and Microwave-Accelerated Evaporative Crystallization, Crystallization, Acetaminophen, Silver Nanoparticles The crystal structure of acetaminophen lacks essential slip planes necessary for plastic deformation, making it difficult to compact during compression. To overcome this limitation, additives are used to enhance compaction properties and shape the molecules into a required form. Form I is obtained through recrystallization from water or alcohol solutions, but adding excipients increases production time and cost. In contrast, Form II crystals have well-defined slip planes, making them suitable for direct compression without the need for additives. However, growing Form II crystals has been challenging due to their metastability at room temperature. Recent studies have successfully grown Form II crystals on a larger scale by melting Form I or amorphous acetaminophen and using it as a seed. Additionally, researchers have explored the selective production of acetaminophen on polymer substrates and developed new methods for controlling polymorphism through heterogeneous nucleation. This study focuses on recrystallizing commercially available acetaminophen from deionized water onto glass or superionic glass fibers (SIFs) at room temperature or using microwave heating at different power levels. The results show a selective growth of different crystal forms under various experimental conditions, including the formation of Form II crystals with 39% purity when grown on SIFs using microwave energy. Previous studies have reported that Form II crystals obtained from water solutions transform into Form I due to residual water in their lattice, highlighting the importance of controlled crystallization conditions. The MA-MAEC technique relies on crystallization of targeted molecules through selective nucleation on Silver Island Films (SIFs) followed by rapid evaporation of the solvent. It's essential to note the evaporative nature of this method, particularly with regards to its tools: SIFs and low-power microwave heating. The experimental setup involves placing a supersaturated aqueous solution of acetaminophen at 80°C on a glass slide or SIFs, allowing it to evaporate at room temperature or through microwave heating. In the case of room temperature evaporation, the complete evaporation of water on a blank glass slide takes approximately 71 seconds, with heat being transferred from warmer water to colder glass and air. The presence of SIFs significantly accelerates this process due to their higher thermal conductivity compared to glass or air. This results in a substantial temperature gradient (~58°C) between the solution and the surface where crystals form. While no direct evidence was obtained, it's believed that the selective nucleation of acetaminophen crystals on SIFs is due to the preferential interaction of its functional groups (e.g., hydroxyl group) with the silver surface, akin to how amino acids interact with silver nanoparticles. The use of microwave heating further enhances this process by increasing the temperature gradient between the solution and surfaces. In contrast, nucleation on glass slides occurs randomly, especially at room temperature. The study's findings indicate that the MA-MAEC technique is capable of efficiently crystallizing targeted molecules through controlled evaporation and selective nucleation on SIFs, with microwave heating serving to enhance this process. Microwave-Assisted Evaporation of Acetaminophen: A Comparative Study When exposed to microwave power levels of 1, 5, and 10, the time it takes for acetaminophen molecules to reach the surface varies significantly. At lower power levels, heating is intermittent, resulting in slower evaporation rates. According to Table 1, the evaporation time on glass slides and SIFs at room temperature was recorded as 71 and 43 seconds, respectively. However, when microwave heating was applied, the evaporation time decreased dramatically. For instance, using microwave power level 5, the evaporation time on SIFs was reduced to just 10 seconds, which is significantly faster than the control experiment without microwave heating. Moreover, silver nanoparticles in the crystallization process at room temperature increased the total evaporation time by ~2-fold. Conversely, microwave heating resulted in a substantial reduction of up to 3- and 4-fold on both glass slides and SIFs. Interestingly, microwave heating was consistently faster on SIFs than glass slides, with the fastest complete evaporation occurring within 10 seconds at power level 5. Overall, these results suggest that microwave-assisted evaporation is a highly efficient method for crystallizing acetaminophen, yielding significantly larger crystal sizes compared to room temperature evaporation. The morphology of acetaminophen crystals formed on glass slides and SIFs is significantly influenced by microwave heating, with varying effects depending on the substrate used. At room temperature, acetaminophen crystals grown on glass contained mostly Form I (98%) with a small percentage of Form II (2%), whereas those formed on SIFs were almost entirely Form I (99%). However, when exposed to microwave heating, the extent of Form I decreased on glass slides while increasing the proportion of Form II. Conversely, acetaminophen crystals grown on SIFs showed an increase in Form II from 4% to 39% purity after microwave heating. These results suggest that SIFs and microwave energy can be used to produce high-purity Form II acetaminophen crystals. Water on Superwetting Interfaces (SIFs) at Room Temperature: Crystal Growth and Formation of Acetaminophen Crystals. Acetaminophen crystals grew rapidly on SIFs within 5 seconds after placement, with the final size achieved in 30-35 seconds. The crystals showed selective growth as Form II, with a significant increase in size compared to those formed on blank glass slides at room temperature. The study found that silver nanoparticles have higher conductivity than glass slides. When acetaminophen solutions are heated with microwaves on both surfaces, the evaporation time is reduced by up to 3 times, and the purity of Form II crystals reaches 39% within 2 hours. This was confirmed through optical microscopy, Raman spectroscopy, and powder XRD analysis. The research team is currently working on applying this technique to other drug compounds and plans to publish their findings soon. The study was supported by a grant from the National Institute of Biomedical Imaging and Bioengineering. The authors would like to thank Dr. Erdogan Ergican for his expertise in interpreting XRD and Raman spectroscopy data. **\*\*Scientific Articles and Research Studies\*\*** This section highlights various scientific articles and research studies related to crystal growth, nucleation, and surface chemistry. **\*** A study published in Langmuir in 2011 investigated the role of surface chemistry and nanoscale pores in heterogeneous nucleation. **\*** Two research papers by Alabanza et al. (2011) and Pinard et al. (2010) explored metal-assisted and microwave-accelerated evaporative crystallization, including its application to L-alanine. **\*** Guggenheimer and Moore (2011) reviewed the therapeutic applications and risks associated with acetaminophen use. **\*** Haisa et al. (1976) studied the monoclinic form of p-hydroxyacetanilide. **\*** Al-Zoubi et al. (2002) used FT-IR and Raman spectroscopy to identify and quantify orthorhombic and monoclinic paracetamol in powder mixes. **\*** Szlachetkiewicz et al. (1999) discussed the potential of Raman techniques for in situ characterization of polymorphic forms. **\*** Kachrimanis et al. (2007) used FT-Raman spectroscopy and PLS regression to analyze paracetamol polymorphs in powder mixtures. **\*** Lang et al. (2002) developed a method using polymer heteronuclei for crystalline polymorph selection. **\*** Chadwick et al. (2011) presented a new method for selecting crystalline substrates through polymorphic control by heterogeneous nucleation. **\*** Klin et al. (2008) studied the shape-controlled synthesis of silver nanoparticles and their preferential surface coordination with citric acid. **\*\*Research Institutions\*\*** This section highlights two research institutions that contributed to the studies mentioned above: **\*** Federal Institute for Materials Research and Testing (BAM), Berlin, Germany **\*** Zuse Institute Berlin (ZIB), Berlin, Germany Submission received: November 19, 2020 / Revised: November 30, 2020 / Accepted: December 2, 2020 / Published: December 4, 2020 (This article belongs to the Special Issue Molecular Modeling in Crystals) The choice of solvents significantly impacts the crystalline solid formed during the crystallization of active pharmaceutical ingredients (APIs). The underlying effects are often not well understood due to the complexity of the systems. Theoretical models are frequently insufficient to describe this phenomenon. This study examined the crystallization behavior of the model drug paracetamol in various solvents using experimental and molecular dynamics data. Time-resolved Raman spectroscopy was employed to follow the crystallization process in situ. Molecular dynamics with simulated annealing algorithm was used to gain an atomistic understanding of the underlying processes. The results indicate that paracetamol molecules adopt a specific geometry in a given solvent, which predefines the crystallization of certain polymorphs. Polymorphs are crystalline modifications exhibiting the same composition but different packing arrangements. This phenomenon is universal and can be found in metals, minerals, and organic molecules. For example, cocoa butter, a key ingredient in chocolate, exhibits at least six different crystal forms with varying properties like appearance, texture, and melting point. Polymorphism is also responsible for the disappearance of certain polymorphs, which can render a desirable form unproducibile in a specific facility. A well-known example is Ritonavir, a drug used to treat HIV infection, which failed dissolution specifications due to the presence of a polymorph with approximately 50% lower intrinsic solubility than the reference form. The crystallization process and the entanglement of physicochemical interactions need to be understood to decipher the fundamental formation processes. The crystallization yields one crystal form out of many polymorphs, depending on various parameters such as cooling rate or choice of solvent. Crystallization is a complex process influenced by various factors such as temperature, solvent nature, concentration, and seed presence. Sophisticated methods are required to gain deeper insights into this phenomenon. Time-resolved Raman spectroscopy enables the monitoring of solution phases and intermediates that eventually form crystals due to its ability to provide quick results. To investigate a specific factor affecting crystallization, such as the solvent, one must minimize other influencing factors like container type, temperature, and humidity. Acoustic levitation with a climate control unit can help minimize side effects like heterogeneous crystallization from container surfaces acting as seeds. Experimental data can be complemented by molecular dynamics (MD) simulations, which provide atomistic information about the process. Successful outcomes supporting both CNT and nonclassical pathways have been achieved using MD simulation studies. The solvent choice is a crucial parameter in obtaining the desired polymorph of an active pharmaceutical ingredient (API). Despite experimental and theoretical efforts, the effects of solvent choice on this process remain one of the mysteries. This study explores the effects of solvents on the crystallization of paracetamol, a model API with changing polymorphic behavior depending on solvent choice. The elusive form III of paracetamol has only been found using thermal cycling in an inert atmosphere, and it was never observed in evaporative crystallization experiments. Forms IV and V can be observed at high pressures of 8 and 11 gigapascals in a diamond-anvil cell. Due to their relatively stable nature, only forms I or II are used in marketed drug formulations. The crystallographic structure of paracetamol shows an extensive hydrogen-bonding network, contributing to the stability of the structure. This polymorphism leads to different processing during formulation of paracetamol tablets, with form I requiring extra binder due to its corrugated packing. Crystal formation in paracetamol solutions was studied using a custom-made acoustic levitator. This device allowed for contact-free crystallization studies and in situ measurements, minimizing external influences such as extrinsic heterogeneous seeding. The setup involved fixing a droplet of solution in a stable position using an ultrasonic field and controlling the environment around the sample regarding surface, temperature, and humidity. The choice of solvent was found to be a driving force towards a particular arrangement of paracetamol molecules, triggering the crystallization of a certain polymorph. Different solvents exhibited varying strengths in driving crystallization towards a specific endpoint in the case of paracetamol. Crystallographic studies from liquid solutions were conducted using a custom-made acoustic levitator and time-resolved Raman spectroscopy. The setup allowed for studying the phenomena of crystallization, minimizing influencing factors such as extrinsic heterogeneous seeding. Researchers studied two forms of paracetamol, denoted as Form I and Form II, which exhibit distinct crystal structures due to unique arrangements of molecules within their crystal structure. By analyzing the hydrogen bonding patterns in these polymorphs, they identified a specific synthon - an explicit structural identifier exclusive to each relative crystal structure. In contrast to Form II, where hydrogen bonds were parallel between molecules, Form I displayed orthogonal molecular arrangements facilitated by a distinct vector passing through nitrogen and oxygen atoms of aromatic rings. To explore the aggregation process of paracetamol molecules via non-covalent interactions, researchers employed simulated annealing as an optimization algorithm to guide their analysis. This approach was adapted from metallurgical principles where controlled heating and cooling processes influence crystal formation. The study diverged from classical simulated annealing methods by not expecting system equilibration; instead, it focused on capturing canonical ensemble statistics during molecular dynamics simulations. By waiting until paracetamol molecules formed specific synthon arrangements within their solvents, researchers could gather necessary statistical weightage regarding the possible angles at which these molecules could interact. The simulations were conducted using GROMACS 4.6 software and the paracetamol-solvent system was parameterized with amber99sb force field. Sixteen paracetamol molecules were added to 1528 ethanol molecules, 1379 methanol molecules, 871 chloroform molecules, and 5337 water molecules in an experimental setup optimized for organic molecules containing C, H, O, and N elements. Although the addition was random, general numbers decreased with increasing molecular size of the solvent. The simulation box was set up as an octahedron with a longest internal diagonal of 6 nanometers under periodic boundary conditions. Energy minimization using the conjugate gradient method ensured a reasonable starting structure, followed by equilibration using the leap-frog integrator at 293 K for 100 ps. The NPT ensemble was used to apply pressure and temperature constant throughout the simulation time of 5 nanoseconds. Simulated annealing cycles were performed from 100 to 600 K over 110 ps to sample as many conformations as possible, allowing more conformational coverage. This procedure helped destabilize intermolecular hydrogen bonds formed during initial cycles, making way for new combinations of interactions in subsequent cycles. The system was simulated with a separate MATLAB parser code named Gro2mat to convert the .xtc file into easy xyz co-ordinates readable in MATLAB. The generated trajectories were analyzed to study the effect of the solvent on the arrangement of paracetamol molecules. The investigation focused on whether these molecules organized according to synthons identified in form I or form II, which requires the formation of a hydrogen bond between two paracetamol molecules. A set of possible arrangements was defined for analysis to quantify the strength of this effect. **###** The study examined hydrogen bonding interactions between paracetamol molecules in various solvents. During the simulation, whenever two molecules approached each other within 2.5 Å, their arrangement was checked for conformity with either Form I or Form II. An orientation vector was defined by a nitrogen atom bound to the C6-ring and an opposite oxygen atom bound to the same ring in each molecule. When a hydrogen bond between two molecules formed, the angle between the two orientation vectors was measured. If this angle fell within 45-135°, indicating a synthon of Form I; otherwise, it was denoted as a synthon of Form II. The simulation results showed that the strength of hydrogen bonds varied depending on the solvent, suggesting its ability to drive paracetamol crystallization towards a specific polymorph. An empirical serial dilution series was created, allowing paracetamol to crystallize from mixed solvents. Experimental findings were consistent with previous studies on paracetamol polymorphs in specific solvents (Table 3). The MD simulations revealed two key effects: the arrangement of paracetamol molecules relative to each other and the number of hydrogen bonds formed in each solvent. The angle between the vectors of participating paracetamol molecules was recorded every time a hydrogen bond was detected, indicating the search for synthons in the simulation trajectory. The number of hydrogen bonds within these synthons varied significantly across solvents (Table 4). Histograms were created to represent the angles between pairs of paracetamol molecules for different solvents (Figure 3, Table 5). In chloroform, 66% of hydrogen bonds fell within the 45-135° range, with a peak at 90° indicating orthogonal orientations. In contrast, water simulations showed only 14.14% hydrogen bonds in this range, with a dip at 90° suggesting parallel orientations typical of Form II. Water as a solvent led to paracetamol crystallization in Form II. Interestingly, closely related solvents ethanol and isopropanol also favored the formation of Form II. The study highlights the significance of solvent strength in driving the crystallization of paracetamol towards specific polymorphs. Paracetamol yielded different polymorphs when used as a solvent. Simulations indicated similar hydrogen bond profiles between ethanol and methanol, but the percentage of bonds within a specific range varied significantly between the two solvents. The chemical nature and miscibility of the solvents, along with their effect on paracetamol's crystallization, made them intriguing cases to explore further. As an aminophenol, paracetamol was doped with another solvent to investigate its effect on crystallization in the wet lab. The results showed distinct effects from each solvent on the self-association of paracetamol molecules. This simplification of larger structures to synthons suggested that the nature of self-association and intermolecular bonding can be crucial for crystal nucleation. The choice of solvent had a significant effect, driving crystallization towards polymorph I or II. When ethanol was slowly introduced into methanol as the solvent, the system became unstable at high concentrations of methanol. This weak solvent behavior was not observed when high concentrations of ethanol were present with low fractions of methanol. Our efforts to understand solvent effects on paracetamol's crystallization revealed that solvent-solute interactions influence preferred hydrogen bonding within the molecules. The total number of hydrogen bonds and their respective positions were affected by the choice of solvent. Recognizing synthons originating from crystallized polymorphs in simulation trajectories can serve as an important tool in understanding solvent effects on drug molecule crystallization, allowing for control over these processes. Experiments with mixed solvents showed a difference in their effects on paracetamol's crystallization, highlighting the significance of solvent choice in controlling crystal formation. Researchers have made significant progress in understanding how to control the crystallization process of certain chemicals, leading to the formation of specific polymorphs (different crystal structures). By analyzing the number of hydrogen bonds in pure solvents, they were able to predict and confirm the results of their experiments. This study paves the way for identifying and ranking solvents that can produce desired outcomes for specific chemical compounds. The research was funded by the German Research Foundation (DFG) and the School of Analytical Sciences at Adlershof, Berlin. The authors would like to thank Yen Nguyen Thi Y.N.T. for her technical support and scientific discussions. This study contributes to a broader understanding of polymorphism, which is crucial in various industries such as pharmaceuticals and food production. The researchers acknowledge the work of previous studies on this topic, including those by Wille, Roth, Bernstein, Bućar, Chemburkar, Hilfiker, and others. The findings have implications for the development of new methods to control nucleation and crystallization processes, which can improve the quality and consistency of final products. Researchers have been studying how crystals form and grow in various solutions, including proteins, salts, and organic compounds. Several studies have shown that crystal nucleation can occur at specific metastable liquid-liquid phase boundaries, where the solution is neither fully dissolved nor completely crystallized. In some cases, crystal growth has been observed to occur within dense liquid clusters or droplets. The use of advanced techniques such as in situ transmission electron microscopy (TEM) and acoustic levitation has allowed researchers to visualize and study the nucleation and growth process at high resolution. These studies have revealed that different pathways can be involved in crystal formation, including direct and indirect mechanisms. Molecular dynamics simulations have also been used to model the crystallization process of various substances, such as ice and organic compounds. These simulations have provided insights into the underlying mechanisms of crystal nucleation and growth. Additionally, researchers have explored the possibility of controlling polymorph formation in organic crystals by manipulating crystallization pathways. The use of acoustic levitation has allowed for the study of crystallization processes in small droplets, providing new opportunities for understanding crystal formation. Research has explored the polymorphism and physical characterization of paracetamol, particularly forms II and III. Studies have employed various techniques such as thermogravimetry, calorimetry, Raman spectroscopy, and X-ray diffraction to analyze the crystal structures and properties of these forms. Specifically, researchers have identified additional forms IV and V of paracetamol at high pressure, and characterized the orthorhombic form of p-hydroxyacetanilide (the chemical name for paracetamol) using X-ray crystallography. Other studies have investigated the compression behavior, bioavailability, and stability of poorly soluble drugs like paracetamol, highlighting the importance of understanding polymorphism in pharmaceuticals. The use of advanced techniques such as acoustic levitators and variable temperature single-crystal X-ray diffraction has enabled researchers to gain insights into the anisotropic crystal structure distortion of paracetamol at high hydrostatic pressures. These findings have implications for the development of efficient methods for reading Gromacs output in MATLAB. The text also references a figure, which is likely a schematic diagram or image illustrating the principles behind acoustic levitators and their application to time-resolved Raman spectroscopy. Note: I've tried to maintain the original meaning and tone of the text while rephrasing it in a more concise and readable format. The crystalline structure of paracetamol's form I features hydrogen bonds that are orthogonal to each other, whereas form II exhibits a parallel arrangement of molecules participating in a hydrogen bond. This is evident from the histograms of paracetamol molecules simulated in different solvents, which indicate the positions of the molecules as they form hydrogen bonds. A summary of paracetamol polymorphs reported so far can be found in Table 1. The table highlights the accessibility and stability of each polymorph, with some being stable at specific pressures or temperatures. Simulated annealing cycles used in GROMACS simulations are detailed in Table 2. Experimental results on polymorphs obtained from different solvents are presented in Table 3, showing that paracetamol form I can be obtained using ethanol, methanol, chloroform, and water as solvents. The number of hydrogen bonds formed during simulation trajectories is analyzed in Table 4, with the results indicating a higher frequency of hydrogen bonding in chloroform compared to other solvents. The percentage distribution of paracetamol simulations within the range of 45-135° is shown in Table 5, revealing differences in the crystallization pathway depending on the solvent used. Additionally, the crystallization pathway can be influenced by using mixed solvents, as seen in Table 6. **Publisher's Note:** The article remains neutral regarding jurisdictional claims and institutional affiliations. The Creative Commons Attribution (CC BY) license is applied to this open-access article. A study conducted by Emmerling and Marcus Weber in 2020 investigated how different solvents affect the crystallization process of paracetamol. The research, published in Crystals, volume 10, issue 12, with article number 1107, provides valuable insights into this phenomenon.