SURFACE INHIBITED NUCLEATION – A NEW METHOD FOR THE SELECTIVE GROWTH OF STABLE DRUG POLYMORPHS

A Major Qualifying Project Report:

submitted to the Faculty

of the

WORCESTER POLYTECHNIC INSTITUTE

in partial fulfillment of the requirements for the

Degree of Bachelor of Science

by

Lori A. Ferris

Date: April 26, 2007

Approved:

Professor Venkat R. Thalladi, Major Advisor
Department of Chemistry and Biochemistry

ABSTRACT

We report a new technique, surface inhibited nucleation, to achieve control over the selective growth of pharmaceutical polymorphs. It is widely known that fluorous substrates such as Teflon exhibit favorable intermolecular interactions with other fluorous entities but disfavorable interactions with hydrophilic as well as oleophilic entities. In this work we show that the supramolecular xenophobia exhibited by fluorous surfaces can be used as a tool to inhibit crystal nucleation and growth. We describe the unique ability of perfluoroalkyl terminated silane monolayers in promoting the exclusive growth of the stable polymorph (g-form) of indomethacin, a non-steroidal anti-inflammatory drug (NSAID). This selective growth is promoted not by the enhanced nucleation of the g-form, but by the suppressed nucleation of the metastable polymorph (a-form). This suppression is due to the disfavored interactions between the non-fluorous faces of the crystal nuclei and fluorous walls of the vial. This selectivity can be reversed by using a drug for which the crystal faces are bounded by fluorous surfaces. Thus, crystallization of flufenamic acid (an NSAID) in fluorous vials yields the growth of metastable polymorph, but crystals of stable polymorph are grown in vials exposing hydroxy groups. Unlike the surface enabled crystal growth methodologies developed before, the current technique does not require the knowledge of specific interfacial interactions. Thus, this new method can be applied to any solid drug even if it's structural, morphological and other physical properties are unknown. We expect that the use of this method will significantly increase the probability of finding the thermodynamically stable drug polymorphs at the early stages of pharmaceutical development.

TABLE OF CONTENTS

TABLE OF FIGURES

INTRODUCTION

Polymorphism, the ability of a chemical entity (organic molecule, ion pair, polypeptide) to exist in multiple crystal structures, is a fundamental solid state property that affects a variety of industries especially the pharmaceutical industry.[1] Different polymorphs of the same compound often exhibit very different properties that can affect a drug's potency in the body.[2] Dissolution rate, solubility, chemical stability, and tabletability can vary widely between different polymorphic forms.[3] In addition to differences in their properties, different polymorphs can be patented separately, so the discovery of a new polymorph has important implications for protection of intellectual property. The importance of polymorphism in the pharmaceutical industry and public health is illustrated by ritonavir, a protease inhibitor drug manufactured by Abbott[4]. Two years after the launch of this drug, a new polymorph that is more stable began to crystallize, rendering this life-saving drug six times less soluble[56]. Ritonavir had to be pulled from the market, which cost millions of dollars and human suffering. It was reformulated later, and re-released in a liquid formulation. Instances like this show the need for intense screening for different polymorphs of a drug before it is released into the market.

In this report, we will detail our methods for selective polymorph growth through glass slides and vials with their surface properties altered to promote or inhibit nucleation of certain polymorphs. We will explain the benefits of our new method of forming self assembled monolayers on the inside of glass vials. Using these monolayer surfaces, we show the selective nucleation and crystal growth of indomethacin, flufenamic acid, and

nitrofurantoin. We will also detail why fluorous surfaces are important in promoting thermodynamically stable polymorphs.

BACKGROUND

The first distinction of different polymorphic forms occurs at nucleation. Theoretically, if one can control the nucleation of crystals, it is possible to grow exclusively one polymorph from solution.

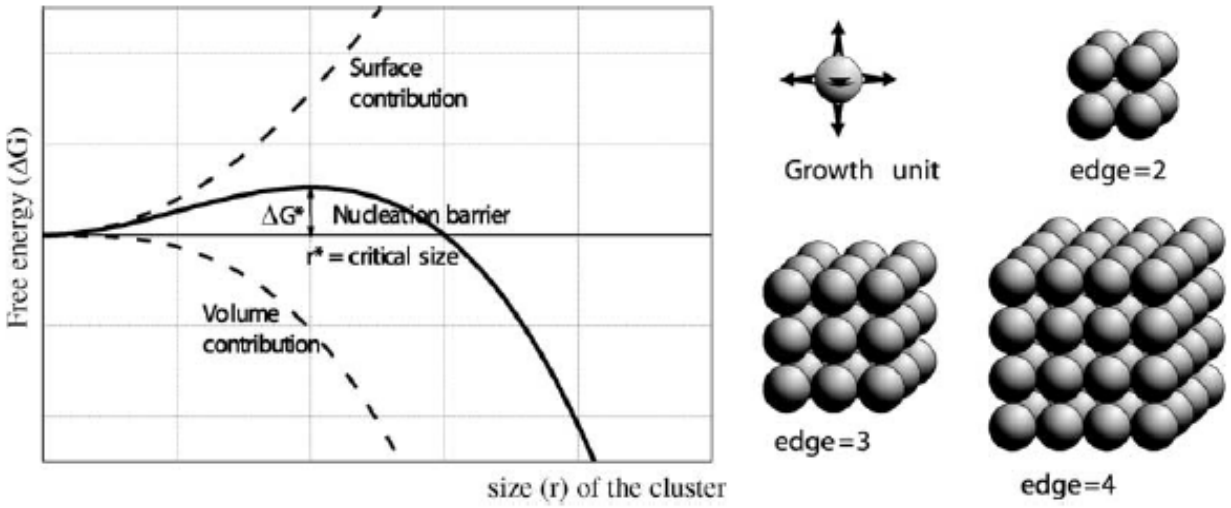

Figure 1. Surface and volume contribution to the potential energy of a growing crystal nuclei. Initially the surface forces exceed volume forces; as the cluster grows the contributions from volume forces increases. When the clusters reach a critical size the two forces are balanced; those clusters are termed crystal nuclei. The growth of these critical clusters into larger clusters and crystals is referred to as nucleation.[7]

For a crystal to nucleate, it must overcome the nucleation energy barrier (Figure 1). For any cluster of molecules in solution, there are forces between the molecules holding them together (volume forces), as well as forces from the solvent pulling them apart (surface forces). Nucleating crystals become stable and keep growing when the volume contributions outweigh the surface contributions. The polymorphic form that a crystal takes at the point where it is large enough not to break apart from solvent interactions will

be a template for more molecules to add onto, and can seed the rest of the solution. To lower the interaction between growing nuclei and the surroundings (e.g. solvent), and thus decrease the nucleation barrier, crystals usually nucleate on a surface, removing an entire face from solvent interaction. Metastable or kinetically stable polymorphs will typically form first in solution because their nucleation barrier is lower than the thermodynamically stable form. As metastable forms have weaker interactions within the crystals than thermodynamically stable forms, they are more easily broken apart by solvent interactions.[8] Providing a nucleation surface to limit solvent interaction can promote the exclusive growth of a metastable form. Similarly, providing a surface with favorable interactions such as hydrogen bonding with a metastable form can promote its exclusive growth. Thermodynamically stable polymorphs can be favored by providing surfaces with favorable interactions. As shown later in this paper, thermodynamically stable forms can also be favored by inhibiting nucleation on surfaces through disfavorable surface interactions with the metastable form. This inhibition not only increases the nucleation barrier of the metastable form, but also allows for crystal nucleation below the solvent level, allowing Ostwald ripening to promote the growth of thermodynamically stable crystals at the expense of their metastable competitors.

FORMATION OF FUNCTIONALIZED SURFACES

Our early work on functionalized surfaces used glass slides coated with various self assembled silane monolayers. Described below are the methods of preparing the monolayers on slides and in vials.

Slide preparation

Silane Monolayers on Glass Slides[9]

Preparation of the slides involved first cutting the glass into small rectangles (approximately 1x2 cm) to fit inside vials containing the solution of the pharmaceutical. These cut slides were cleaned with piranha solution (70% sulfuric acid, 30% hydrogen peroxide) for at least 30 minutes, and then rinsed with DI water. The clean slides were placed in a KOH solution to hydroxylate the surface for at least one hour. The slides were again rinsed and dried with nitrogen gas. A solution of fresh dilute trichlorosilane in dichloromethane (approx 1 drop trichlorosilane per 100 mL) was prepared. The hydroxylated slides were immersed into the silane solutions for a minimum of two hours. Careful preparation and handling of this solution was necessary, as the trichlorosilanes readily reacted with water. The slides were taken out of solution and rinsed with both dichloromethane and ethyl acetate. If slides appeared cloudy, they were cleaned again with ethyl acetate until clear surfaces were obtained. Figure 2 lists the trichlorosilanes used in this work.

Silane Monolayers on Glass vials

Glass vials of various sizes were filled with piranha solution and left for at least 30 minutes. The vials were rinsed with DI water several times before being filled with a KOH solution. This solution was left in the vial for at least one hour, after which the slides were rinsed again. The vials were dried with nitrogen gas to remove any moisture and then filled with a dilute dichloromethane solution of the desired trichlorosilane. The vials were capped and allowed to sit for at least two hours. The vials were then rinsed

with dichloromethane and ethyl acetate. If they remained cloudy, vials were sonicated while filled with ethyl acetate until they were clear.

For a more efficient and less hazardous preparation of functionalized glass vials, we substituted plasma oxidation for oxidation with piranha. The glass vials were placed in the chamber of an SPI Plasma Prep II apparatus. The vials were oxidized by oxygen plasma under vacuum for at least one minute. They were then immediately removed and filled with a dilute dichloromethane solution of the desired trichlorosilane. The vials were capped to prevent moisture from the atmosphere from contaminating the solution, and left for at least two hours. The vials were rinsed with dichloromethane and ethyl acetate, and sonicated while filled with ethyl acetate to remove any cloudiness.

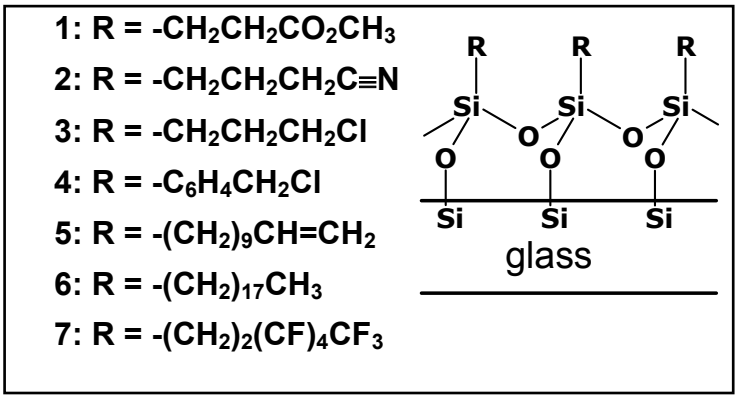

Figure 2. Structures of trichlorosilanes used in this work. The image on the right shows the schematic structure of a silane monolayer. The monolayer "7" leads to "perfluorinated" or "fluorous" surfaces.[10,11,12]

METHODS OF CRYSTALLIZATION

Crystallization on slides

Solutions of desired pharmaceuticals were placed in vials containing glass slides in two configurations. One method was to have the glass slide laying flat on the bottom of the vial as seen in Figure 3a. The functionalized surface was facing upwards to allow interaction with the solvent. Vials were filled with solution of the desired pharmaceutical to about 1/3 of the height of the vial. Another method was to have the glass slide at an angle in the vial, with the functionalized surface facing upwards, as shown in Figure 3b. Formation of crystals on this surface should show some affinity of the solid to the surface to allow them to stick. Vials were filled with solutions of pharmaceuticals to a point just above the top of the slide.

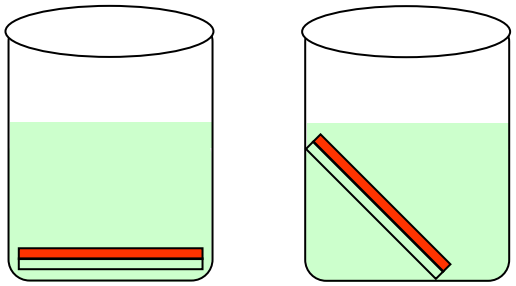

Figure 3. Crystal growth on functionalized glass slides that are laid flat (a) in inclined (b) from solutions placed in plain (unmodified) glass vials.

Both of these methods were used for crystallizations of pharmaceutical compounds. One issue we had to deal with was possible growth of crystals from solution and vial surfaces that did not expose the desired monolayer. We observed crystal growth mainly at edges between the slide and the vial as opposed to desired crystal growth on the functionalized surface of the slide.

Crystallization in functionalized vials

To eliminate undesired nucleation sites, the entire interior of a glass vial was functionalized with a particular monolayer. This method forces nucleation to occur either on the desired surface or in solution. We used vials with three different sizes in this work: ½ dram, 3 dram, and 20 mL. Most work was done in ½ dram vials shown in Figure 4. Vials were filled with the solution of a desired pharmaceutical compound to about 1/3rd of the height of the vial used.

Figure 4. Optical photograph of a ½ dram vial.

Preparation of solutions

All the solutions of pharmaceuticals that we prepared were either saturated or nearly saturated to enforce surface induced crystal growth. The pharmaceutical compound was weighed out and placed in a flask containing the desired solvent. The solution was sonicated until the drug was completely dissolved; it was then heated and stirred for at least 30 minutes to break apart any clusters present in solution. In a given set of experiments, the same crystallization solution was used in vials with different functionalized surfaces to ensure consistency. Vials were then capped with aluminum foil to prevent dust and other contaminants from getting into the vial and 4-5 holes were made in the foil to allow evaporation. Vials were placed in various locations, but were

mainly contained to a hood to prevent atmospheric changes or accidental contact from affecting crystal growth.

INDOMETHACIN

Indomethacin is a drug used for the treatment of arthritis and gout; it falls into the category of NSAIDs (non-steroidal anti-inflammatory drugs). This is an interesting drug because its two widely known polymorphs (α and γ) crystallize concomitantly from solution at room temperature.[13]

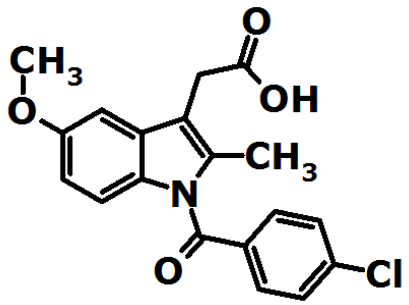

Figure 5. The structure of indomethacin. Notice the carboxy, imido, chloro and methoxy functional groups.

The α form of indomethacin is kinetically stable (metastable), and the γ form is thermodynamically stable (stable). Under normal conditions both forms grow concomitantly from ethanol solutions in glass vials and on glass slides. Several glass slides were prepared with each of the monolayers listed in Figure 2. Indomethacin was allowed to crystallize from ethanol at room temperature in a clean vial with these slides laying flat at the bottom of the vial. It was observed that on every slide except for the perfluorinated slides, both forms were present. On the perfluorinated slides only the γ

form was observed, even though the α form was growing at other points in the vial (predominantly on the walls).

These experiments were repeated with glass vials functionalized with the same monolayers. Again, it was observed in every vial except for those with the perfluoro surfaces both α and γ forms were present, with the α form being predominant. The vials coated with the perfluoro surface grew exclusively the γ form. Another interesting observation was that in all vials except for perfluorinated vials crystals were present on the walls. Figures 7-11 show the optical images of the crystals, experimental powder X-ray diffraction patterns and packing structures drawn from reported crystal structures.[14,15,16]

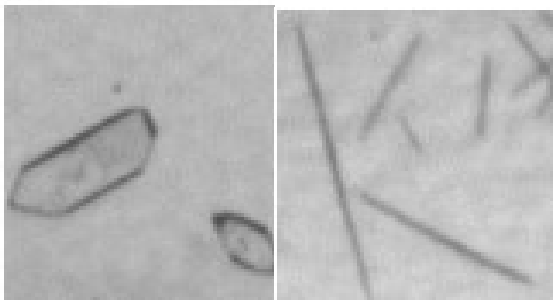

Figure 6. Microscope images of the stable (γ) form of indomethacin on the left, and metastable (α) form on the right.

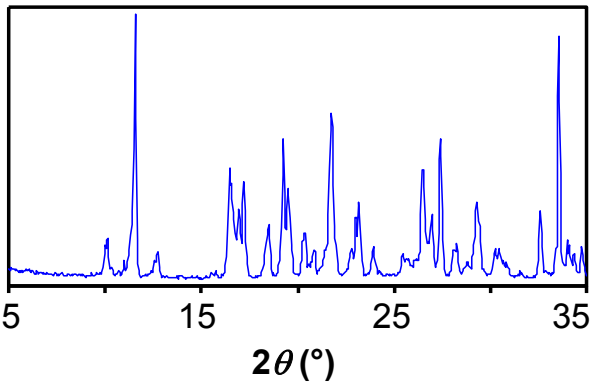

Figure 7. Powder X-ray diffraction pattern of the γ (stable) form.

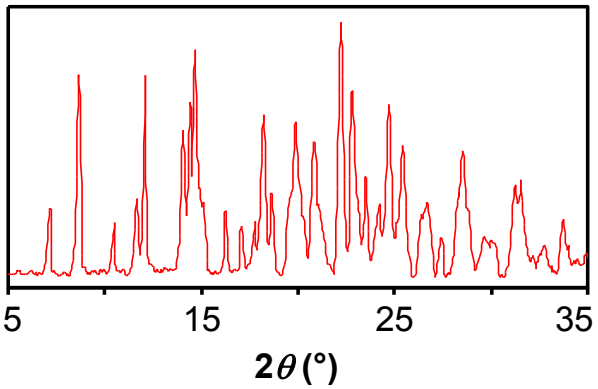

Figure 8. Powder X-ray diffraction pattern of the α (metastable) form.

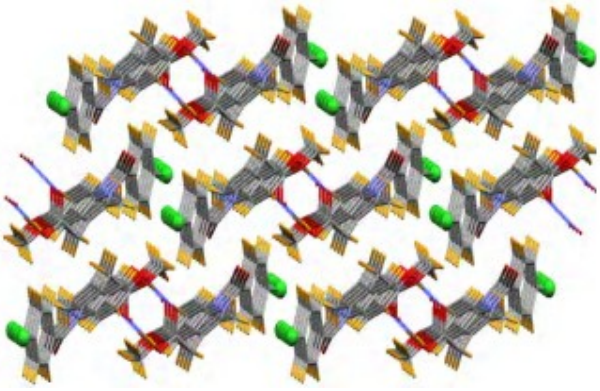

Figure 6. Crystal structure of the γ (stable) form of indomethacin.

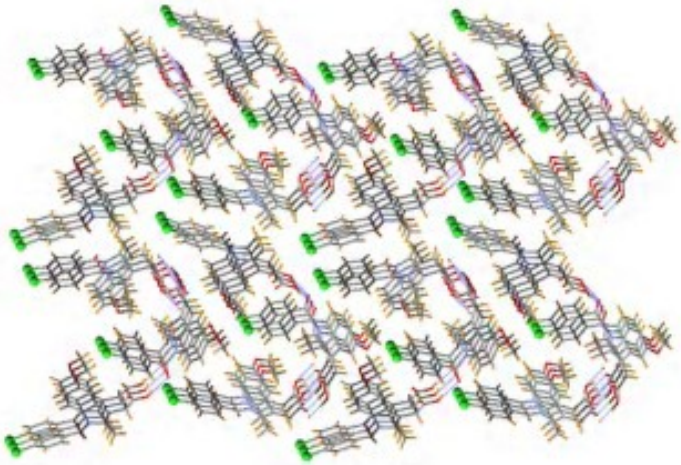

Figure 7. Crystal structure of the α (metastable) form of indomethacin.

The exclusive growth of the γ form of indomethacin on perfluorinated surfaces, and the concomitant growth of both α and γ forms on every other surface led us to conclude that the fluorous surfaces play a critical role in the nucleation process. Additionally, the α – form crystallized predominantly on the walls of vials coated with non-fluorous silane monolayers (1-6). The walls of the vials coated with fluorous monolayers are "clean", showing no affinity for crystal growth. These observations led us to postulate that the perfluorinated surfaces suppress the growth of the α form by preventing the adhesion of nucleating crystals to the surface. The suppression of surface induced nucleation allows more time for the thermodynamically stable γ form to nucleate in the solution. With time, the stable form continues to grow while the solvent is still present, at the expense of any metastable α crystals that may be present. This phenomenon of the growth of a stable species at the expense of a metastable species is widely known as Ostwald ripening.[17],[18] This effect is not seen in vials containing other monolayers because these surfaces enable the attachment of crystal nuclei of α form and their further growth into macroscopic crystals.

FLUFENAMIC ACID

Flufenamic acid is an NSAID that is used in the treatment of musculoskeletal and joint disorders.[19] This drug was of particular interest to us because of its many polymorphic forms (two forms being stable at room temperature), its CF_3 group, and the layered crystal structures of the two polymorphs.

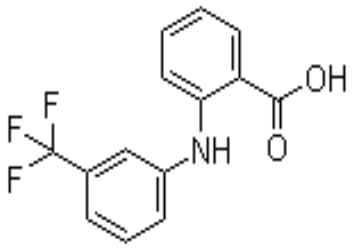

Figure 8. Structure of flufenamic acid. Note the carboxy, secondary amino, and especially the trifluoro-methyl functional groups.

One curious trait of flufenamic acid is the temperature dependence of polymorph stability. Below 42 ºC, form III is the thermodynamically stable polymorph, and form I is the metastable polymorph.[20,21] Above 42 ºC form I is the most thermodynamically stable, and form III becomes the metastable polymorph. Above 104 ºC form II becomes more stable than form III. The relationships between polymorph stability can be seen in Figure 12 below.[22] Forms I and III are readily obtained through solvent evaporation; they are both stable at room temperature and enantiotropic to each other.[23] Form II can be obtained from sublimation. Single crystal X-ray diffraction data is available for forms I and III, while powder X-ray diffraction data is available for form II.

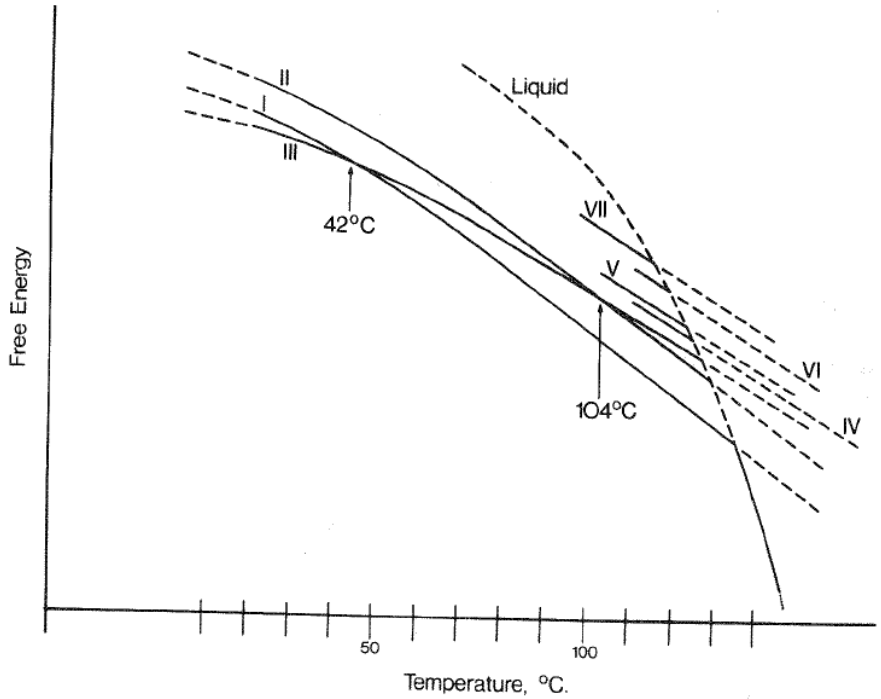

Figure 9. Relative free energies of various polymorphs of flufenamic acid plotted as a function of temperature. Taken from reference 22.

Flufenamic acid was studied by conducting crystallizations exclusively in glass vials. Our first attempts at detecting surface specific polymorphism used saturated solutions of flufenamic acid in ethanol. Vials with several functionalized surfaces were filled with the same saturated solution. Two of each clean glass, hydroxyl (plasma treated glass), carbomethoxy (2), undecenyl (5), and perfluoro (7) vials were filled about 1/3 of the way with the solution. Vials were left in the hood until all solvent had evaporated. All vials produced yellow crystals appearing as thin needles under microscope except for the perfluoro vials. Crystals formed at the bottom of the perfluorinated vial were white and appeared more powdery than the yellow crystals seen in other vials. A clump of yellow crystals was formed on top of this white powder, but was not in contact with the walls or the bottom of the vial. The white powder was shown to be form I by powder X-ray

diffraction, and the yellow needles were shown to be form III also by powder diffraction. These results were very encouraging, and another experiment was set up. This time, five vials with perfluorinated surfaces, and five with hydroxyl surfaces were filled with a fresh saturated solution of flufenamic acid. These two surfaces were selected because they showed the greatest difference in solvent affinity (contact angles). The vials were capped with aluminum foil and left in the same hood as the previous experiment until all solvent was evaporated. The results of this were clear block shaped crystals in all of the perfluorinated vials, and yellow needles in all of the hydroxy vials that can be seen in Figures 13 and 14. Crystals formed in the perfluorinated vials were confirmed to be form I by powder X-ray diffraction (Figure 15), and crystals from hydroxy vials were confirmed to be form III also by powder X-ray diffraction (Figure 16). Contrary to every other drug crystallized in hydroxyl vials, the flufenamic acid did not stick to the sides but crystallized at the bottom, typically in a ring shape as shown in Figure 13.

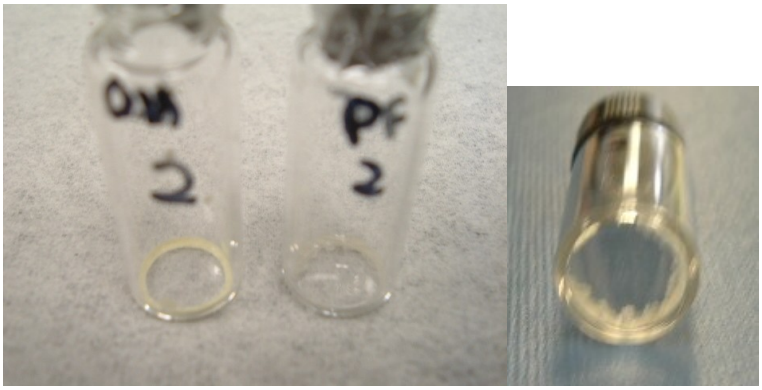

Figure 10. Crystal growth of flufenamic acid from the same bulk solutionin hydroxy and perfluoro vials. Form III is the yellow form seen in the hydroxy vial (OH), form I can be seen in the perfluorinated vial (PF). A view from the bottom of the perfluorinated vial shows the block shaped crystals of form I.

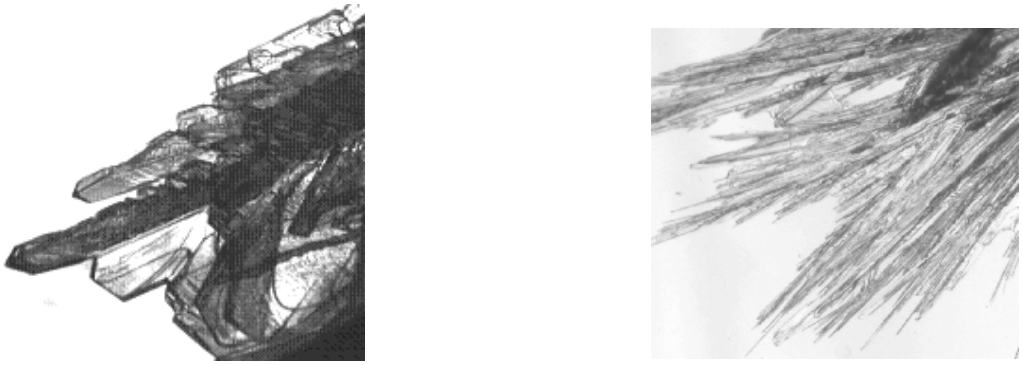

Figure 11. Microscopic images of form I grown in a perfluorinated vial (left), and form III grown in a hydroxy vial (right).

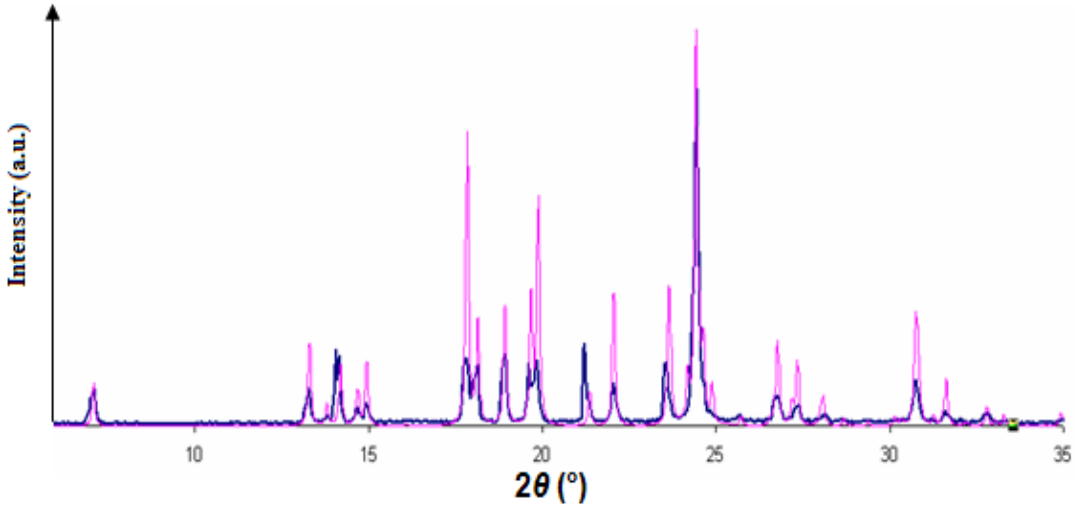

Figure 12. Powder X-ray diffraction pattern of form I. The blue line is the experimental result from a perfluorinated vial; the magenta line is the diffraction pattern calculated from single crystal X-ray data.

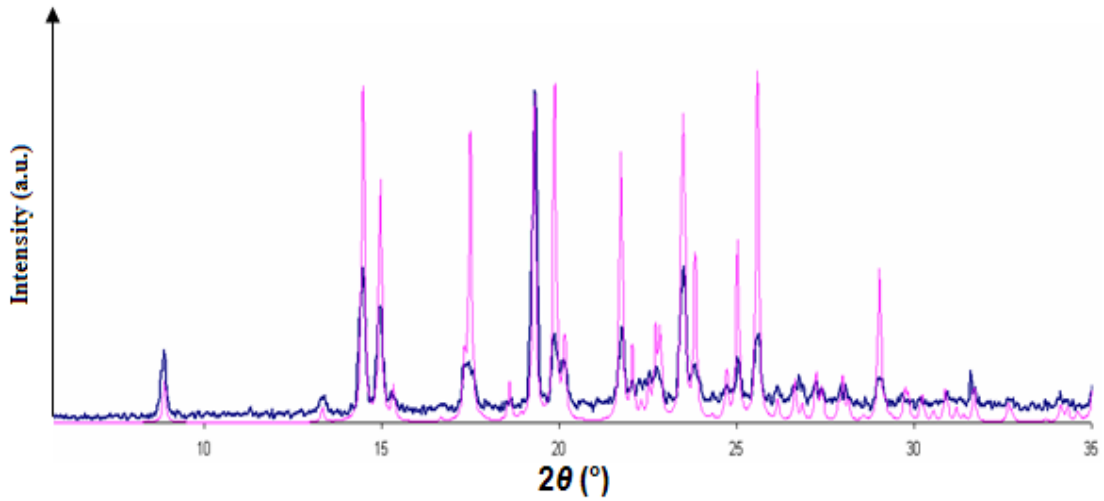

Figure 13. Powder X-ray diffraction pattern of form III. The blue line is the experimental result from a hydroxy vial, and the magenta line is the diffraction pattern calculated from single crystal X-ray data.

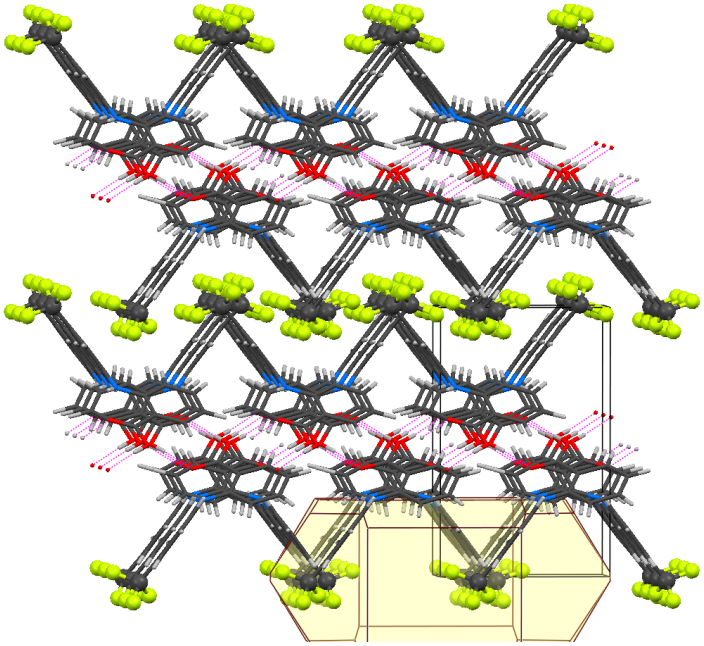

Figure 14. Crystal structure of form I. Notice the layered arrangement of molecules and exposure of CF_3 groups at layers parallel to largest crystal faces. Notice also the wave-like (trough and crest) pattern at the surface and the inter-digitation of CF_3 groups.

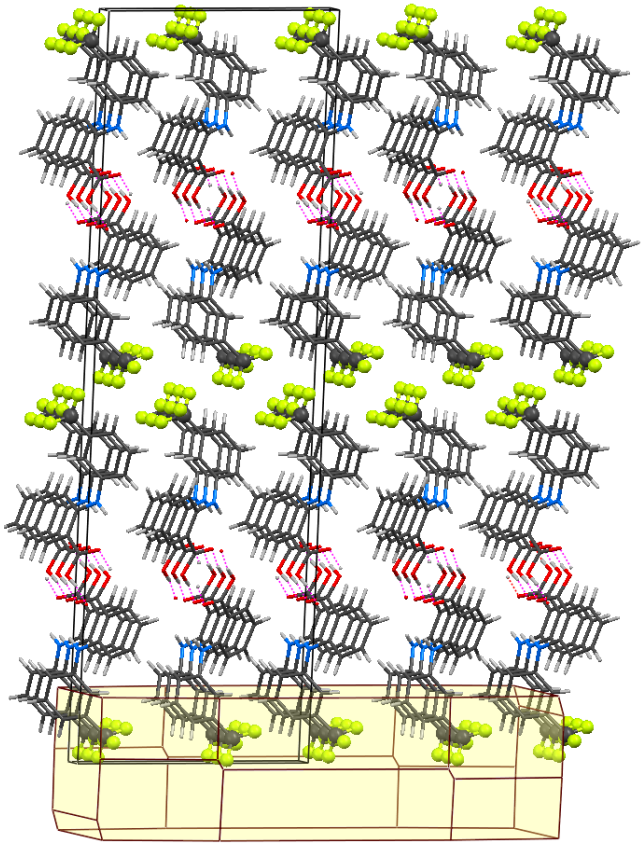

Figure 15. Crystal structure of form III. Notice the layered structure with CF_3 groups at the layer surface. Contrast figures 17 and 18 to notice the absence of wave-like structure and inter-digitation of CF_3 groups.

Crystallizations of flufenamic acid in hydroxy and perfluorinated vials at room temperature were repeated several times, and the results were found to be consistently reproducible.

The enantiotropic relationship between forms I and III was tested with differential scanning calorimetry (DSC), as seen in Figures 19 and 20. Form I did not show a peak corresponding to a transition (Figure 20), confirming that it is the most stable polymorph at temperatures close to the melting point. Form III shows a dip just below the melting point (Figure 19) that is not seen in form I indicating that it is transforming to some more

stable polymorph. These results were found to be consistent for every sample tested with DSC.

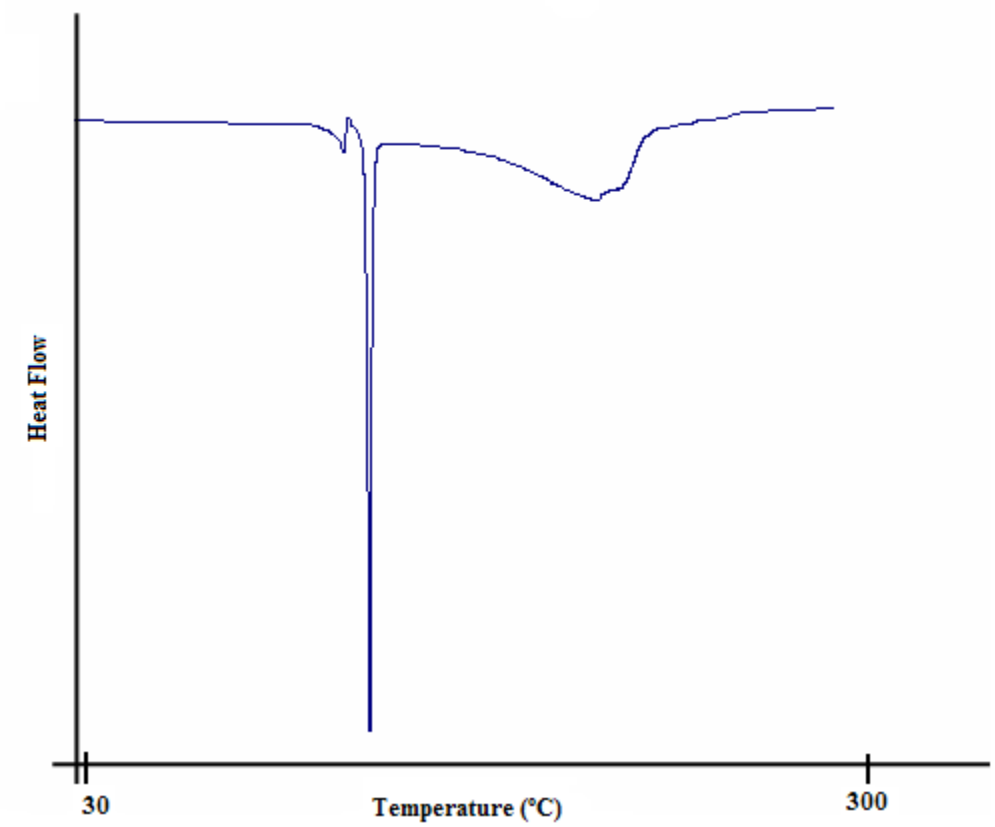

Figure 16. DSC trace of form III grown in a hydroxy vial.

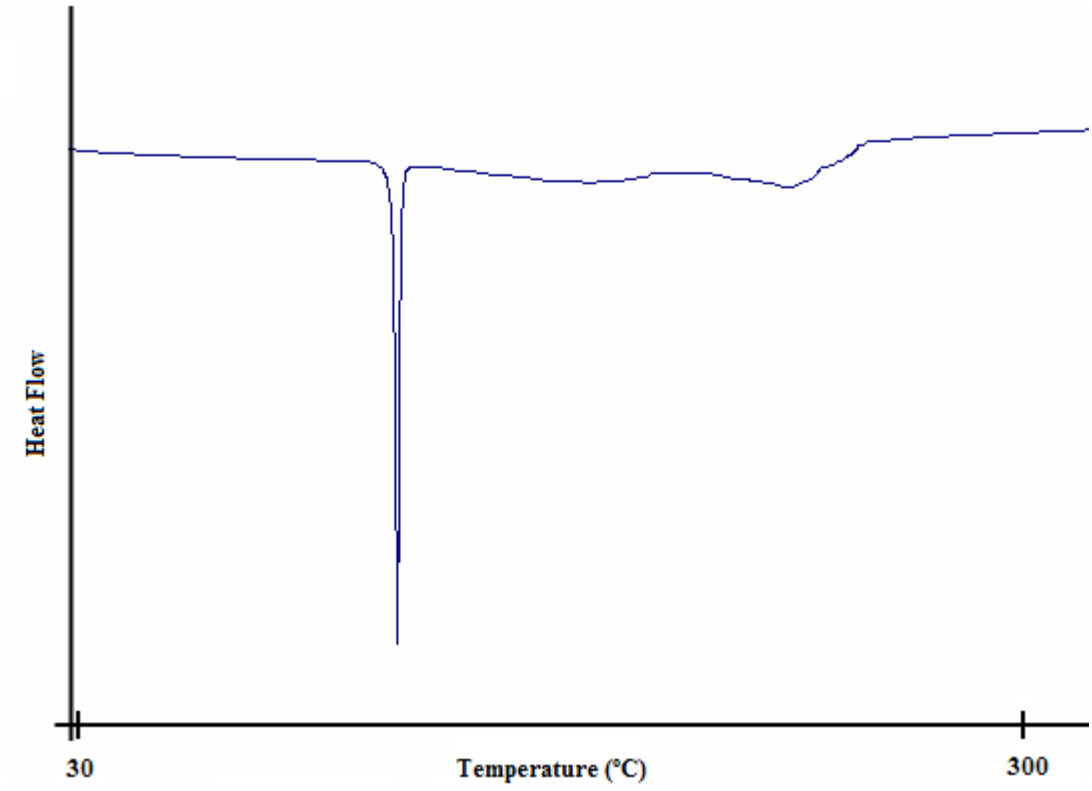

Figure 17. DSC trace of form I grown in from a perfluorinated vial.

To expand on our research with flufenamic acid, several sets of hydroxy and perfluorinated vials were filled with a solution of flufenamic acid in ethanol and allowed to crystallize at several different temperatures. All vials were filled with the same stock solution. Vials left in the hood at room temperature grew form I in perfluorinated vials, and form III in the hydroxy vials. Vials left in an oven set to approximately 42 ºC grew exclusively form III regardless of the SAM. Vials left in an oven above 80 ºC grew exclusively form III. To solve the problem of the solvent evaporating too quickly to allow the surface to have a significant effect, the experiments were repeated with solutions of flufenamic acid in toluene. Vials left at room temperature grew exclusively form I regardless of SAM. Vials left at approximately 42 ºC were also exclusively form I regardless of SAM. Vials left above 80 ºC grew form I from hydroxy surfaces, and an

off-white crystal from perfluorinated surfaces. When the off-white crystals were ground a day later it became a white powder and the diffraction pattern proved the powder to be form I. Being wary of a possible transition to form I from another form, the high temperature experiments were repeated again, with the oven reading 90 ºC at the time the vials were left to crystallize. As soon as all solvent had evaporated (approx 24 hours later), the off-white crystals which had again formed in the perfluorinated vial were ground and remained an off-white color. The diffraction pattern did not match forms I or III, but had some key peaks reported from a literature powder diffraction pattern of form II. The sample was left on the diffraction slide overnight, and approximately one day later appeared lighter in color. Another diffraction pattern was taken of the same sample that had not been altered in any way, and matched the calculated pattern of form I.

Ethanol solutions of flufenamic acid at room temperature (approx 20-25 ºC) grow exclusively form I (metastable) in vials with perfluorinated surfaces. The same solution at the same temperature grows exclusively form III (stable) in vials with hydroxy surfaces. These results are contrary to the previous results with indomethacin. This may be tied into the fact that flufenamic acid is the only pharmaceutical we screened that did not stick to the sides of vials with hydroxy surfaces. Fluorous surfaces and compounds are very xenophobic, which may explain why flufenamic acid does not stick to the sides of vials during crystallization. The CF_3 group may have more favorable interactions with the fluorous surface than the hydroxy surface, which would explain why we see the stable form in the hydroxy vials, and the metastable form in perfluorinated vials. As seen from

the crystal structure in Fgure 17 form I has exposed CF_3 groups along a major face which may be able to interact favorably with a similar surface.[24]

The crystallization results from toluene were equally interesting. It is known that form I is typically obtained by evaporation from non-polar solvents, so this may explain why only form I was seen at room temperature regardless of the vial used. The appearance of what seemed to be form II at high temperatures in perfluorinated vials fits with the theory that interactions between CF_3 groups of the compound and surface promote formation of the metastable form. Above 104 ºC form II becomes the metastable form, and it is highly likely that the temperature in the region of the oven where crystallization occurred was above this temperature. This was evidenced by apparent decomposition of flufenamic acid left at the bottom of the oven where the temperature was highest. The vials that produced form II were on the first rack up from the bottom of the oven, while the thermometer was at the very top. The oven is heated from the bottom, and it is fair to assume that the lower in the oven the vial is placed, the higher the temperature. The oven temperature reading when the vials were added was 90 ºC, right after the door had been opened. This also suggests that the average temperature of the oven was somewhat above this number. As form II and form I are monotropic to each other, it makes sense that form II transformed to form I when left at room temperature for any significant amount of time. This relationship was also shown by the fact that form II was not seen when forms I and III were simply left in the oven at high temperature after crystallizing out of solution. We suspect the formation of exclusively form III from ethanol solutions at high temperatures was due to fast solvent evaporation. Form III was metastable at

these temperatures, and probably crashed out of solution before having a chance to rearrange to the more stable form I. Ethanol boils below the transition temperature when form II overtakes form III as the metastable form, so it is highly unlikely that form II would be stable enough to exist, and thus would not be seen in ethanol solution.

NITROFURANTOIN

Nitrofurantoin (Figure 21) is an antibiotic used to eliminate bacteria from the body in the treatment of some kinds of infections.[25] Nitrofurantoin is an excellent pharmaceutical for these types of studies because it is known to exist in two anhydrous polymorphs (β and α) as well as two monohydrates.

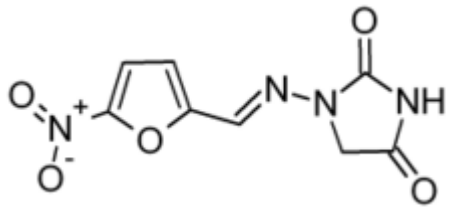

Figure 18. Structure of nitrofurantoin.

We set up crystallizations of nitrofurantoin from acetone in vials with many different monolayers. All vials were filled with the same nitrofurantoin stock solution, and kept under the same conditions. This first set of crystallizations took place on a lab benchtop. The first results obtained appeared to be all of the same morphology. Every vial contained thin yellow needles. Upon closer inspection, it could be seen that in the perfluorinated vials underneath the yellow needles were very small red blocks. Powder X-ray diffraction confirmed that the yellow needles were a monohydrate (we only

encountered one monohydrate through all experiments), and the red blocks produced a pattern similar to the β form. There was not a large amount of sample, so the pattern was difficult to confirm. The experiment was repeated, this time using only perfluorinated vials and hydroxy vials. These vials were left in the hood to crystallize to prevent any outside stimuli from affecting nucleation. These crystallizations produced all red blocks in every vial regardless of SAM. These red blocks were confirmed to be β by powder X-ray diffraction as seen in figure 22. Assuming the level of moisture was a contribution the experiments were repeated with a carefully prepared anhydrous solutions, as well as a solution containing approximately 5% water. These crystallizations produced all red blocks from the anhydrous solution, and all yellow needles from the 5% water solution. Yellow needles were confirmed to be the monohydrate by both X-ray diffraction and DSC.

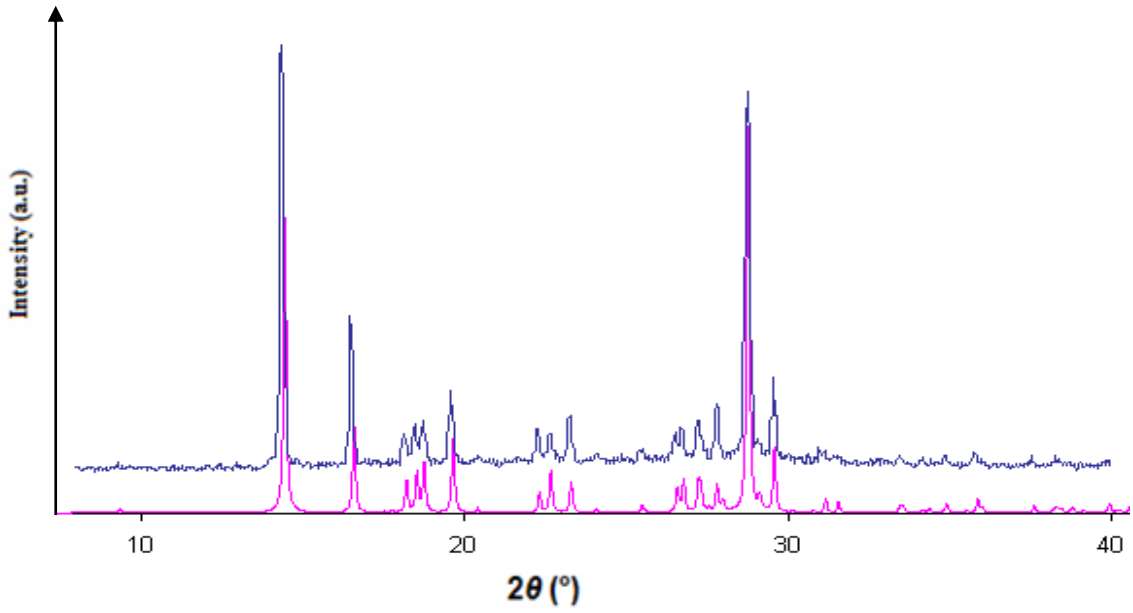

Figure 19. Diffraction pattern of β grown in perfluorinated vials (blue) vs. the calculated pattern (magenta).

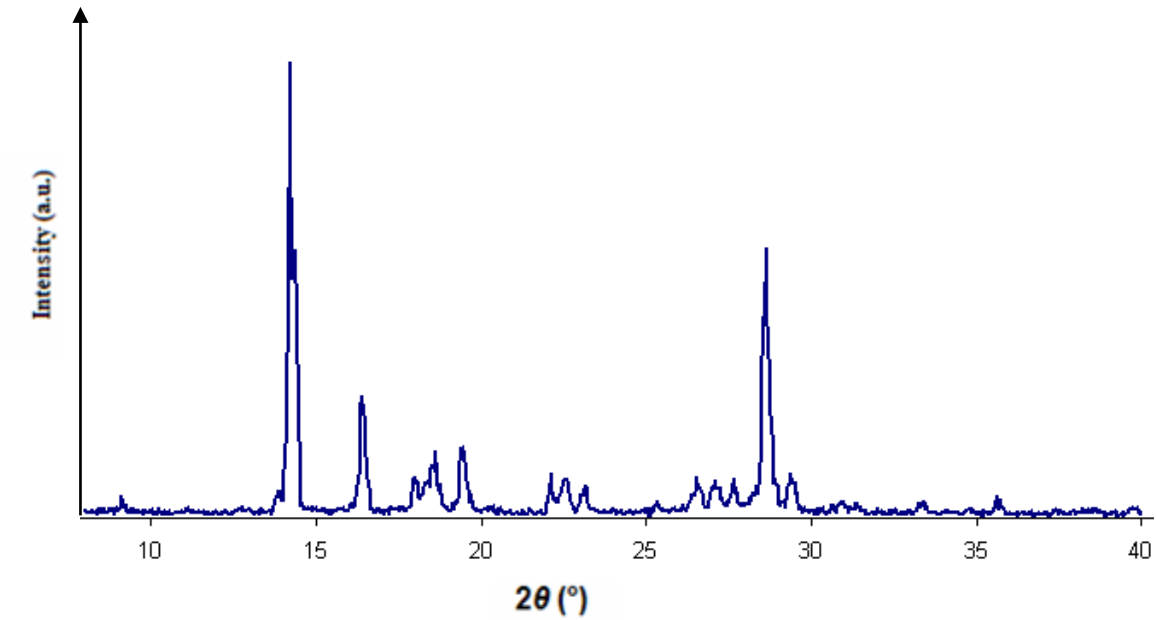

Figure 20. Diffraction pattern of orange crystals grown in hydroxy vials.

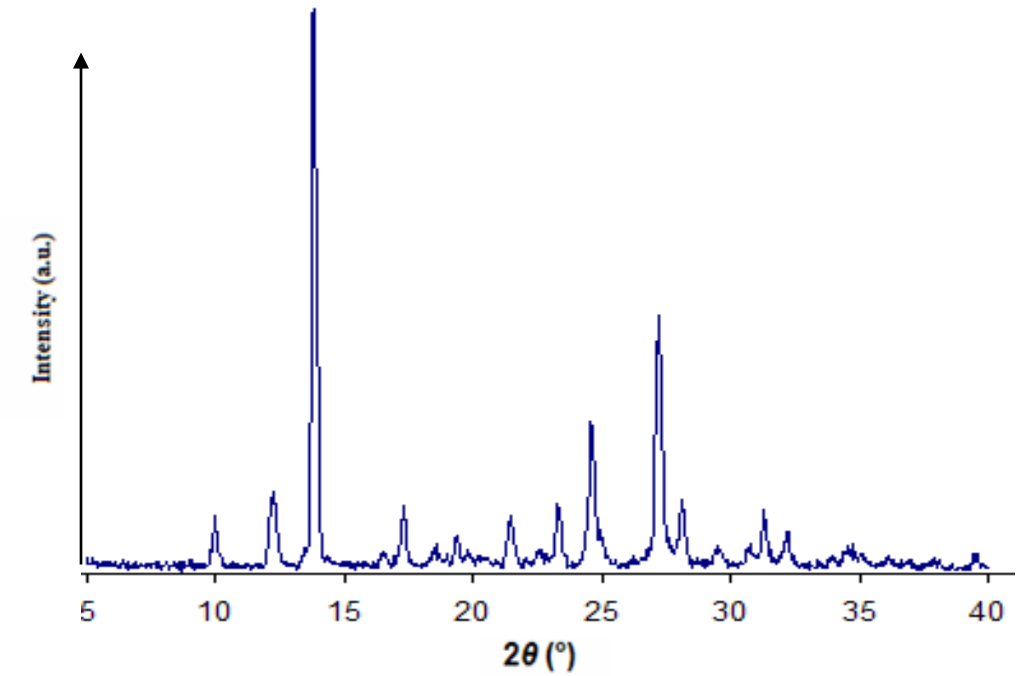

Figure 21. Diffraction pattern of thin yellow needles grown in hydroxy vials with 5% water solution

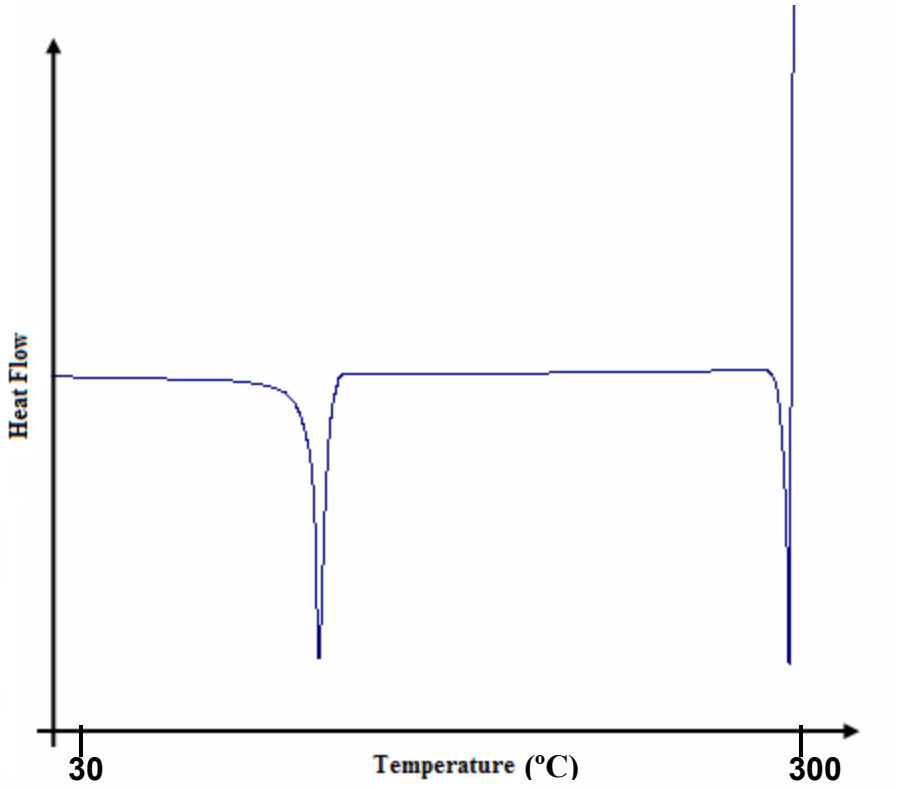

Figure 22. DSC data of yellow needles grown in hydroxy vials with 5% water solution showing loss of water well before decomposition.

The anhydrous experiments were repeated again, and this time upon closer inspection a slight color change was seen between the perfluorinated vials and hydroxy vials. Crystals growing on the sides of the hydroxy vials were a lighter orange in color, originally thought to be a different color because of smaller crystal size; it was observed under a microscope that the crystals themselves looked physically different from the ones formed in perfluorinated vials. Many small vials were set up with perfluorinated and hydroxy surfaces and left at various locations. All of the hydroxy vials shared the orange crystals, and perfluorinated vials showed mainly red crystals. However, diffraction patterns still all matched β. The orange crystals showed a few discrepancies with the calculated literature pattern, but did not show characteristic peaks of α.

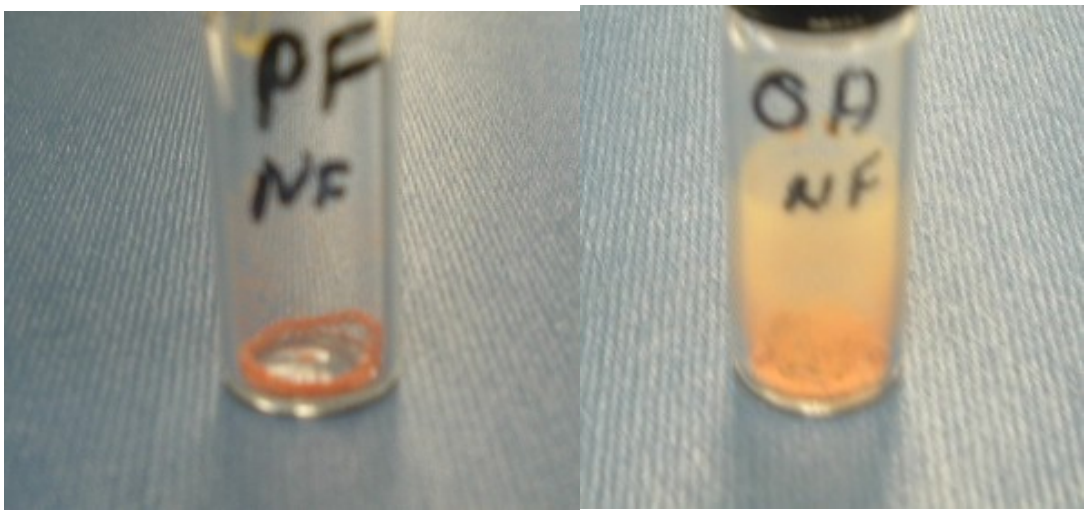

Figure 23. Red crystals of nitrofurantoin grown in PF vial and orange crystals grown in the hydroxy vial.

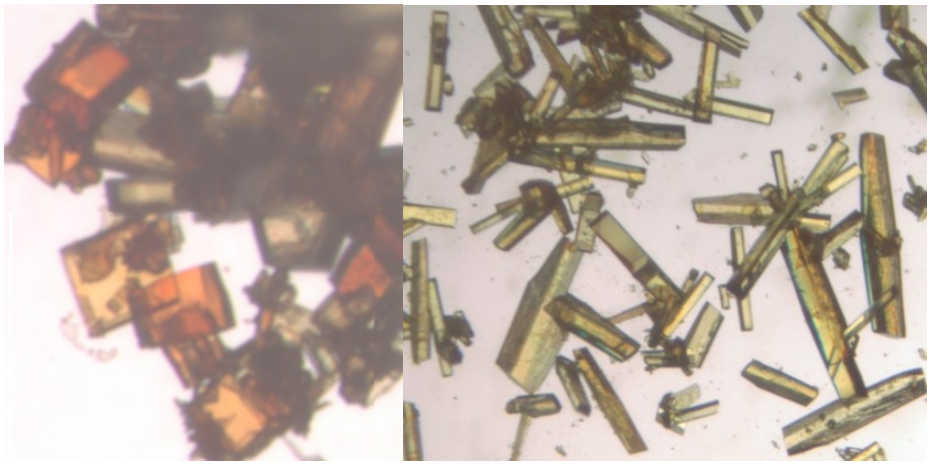

Figure 24. Images taken with a microscope camera. Red crystals from PF vials can be seen on the left, yellow/orange crystals from hydroxy vials can be seen on the right.

The appearance of the yellow needles indicates that the original solution used for crystallization may have been contaminated with water, or perhaps moisture in the atmosphere was high at that particular time. We have no reason to believe that the original red blocks seen were another monohydrate, as their diffraction pattern was very similar to the calculated patter for the β form. It is very interesting that the anhydrous form grew only in the perfluorinated vial, and was not seen on any other surface. It is possible that the perfluorinated surface promotes formation of the anhydrous form, but as

the results were not reproducible it is impossible to conclude this certainly. What is more interesting was the presence of the red form in all of the perfluorinated vials thereafter, excluding the vials containing 5% water solution. These crystals had a diffraction pattern matching that of the β form perfectly. In the hydroxy vials, the orange crystals which appeared different under a microscope also produced a pattern similar to the calculated pattern. There were small differences, but no hard evidence through X-ray diffraction to suggest that they were a different form. The main reason another form is suspected is the shape and color differ from the crystals seen in perfluorinated vials. We suspect that the red blocks are the more stable form, and that the orange crystals are transforming during grinding for powder diffraction. This observation along with the fact that there were no crystals seen growing on the sides of the perfluorinated vials indicated that perfluorinated surfaces promote the more stable form. We suspect that the metastable form grows on the sides of the hydroxyl vials at the solvent line, seeding the rest of the solution and promoting growth of the metastable form. The perfluorinated vials allow for the stable form to grow over a longer period of time, and raise the nucleation barrier for the metastable form by inhibiting surface nucleation. These findings match well with the previous results with indomethacin.

CONCLUSIONS

All of our results indicate that there is something special about fluorous surfaces. They have unique non-stick properties not exhibited by any other surface we used in these studies. By inhibiting the growth of crystals at the solvent line, they often promote the growth of the more stable form. The exception is flufenamic acid, which displays similar properties to the surface itself. The drug would not stick to the walls of any vial regardless of surface, and the reverse results were observed: perfluorinated surfaces promoted the metastable form. In the case of all drugs tested, fluorous surfaces provided fewer and larger crystals than hydroxy vials containing the exact same solution of pharmaceutical. This new approach to selectively growing stable polymorphs by removing nucleation sites could be of immense use to the industry. Fluorous surfaces could be used to grow high quality crystals for analysis as well as providing seed crystals for pharmaceutical manufacture. Fluorous surfaces may also be used in the pharmaceutical industry to screen for thermodynamically stable polymorphs.

REFERENCES

[1] J. Bernstein, *Polymorphism in Molecular Crystals*, Oxford University Press, New York, 1999.
[2] H. G. Brittain, *Polymorphism in Pharmaceutical Solids*, Marcel Dekker, New York, 1999.
[3] R. Milfiker, *Polymorphism in the Pharmaceutical Industry,* Wiley-VCH, Weinheim, 2006.
[4] Danner SA, Carr A, Leonard JM, Lehman LM, Gudiol F, Gonzales J, Raventos A, Rubio R, Bouza E, Pintado V, et al., *N. Eng.J. Med.* 1995 Dec 7;333(23):1528-33.
[5] S.R. Chemburkar, J. Bauer, K. Deming, H. Spiwek, K. Patel, J. Morris, R. Henry, S. Spanton, W. Porter, J. Quick, P. Bauer, J. Donaubauer, B. A. Narayanan, M. Soldani, D. Riley, K. McFarland, *Org. Process Res. Dev.* 2000, 4: 413-417.
[6] J. M. Miller, B. M. Collman, L. R. Greene, D. J. W. Grant, A. C. Blackburn, *Pharm. Dev. Technol.* 2005, 10: 291-297.
[7] Garcia-Ruiz, J.M., *J. Struct. Biol*. 2003, 142: 22-31.
[8] S. R. Byrn, R. R. Pfeiffer, J. G. Stowell, *Solid-State Chemistry of Drugs*, SSCI, West Lafayette, 1999.
[9] P. W. Carter, M. D. Ward, *Langmuir*, 1994, 116: 769-770.
[10] J. Sagiv, *J. Am. Chem. Soc*, 1980, 102: 92-98.
[11] S. R. Wasserman, Y. T. Tao, G. M. Whitesides, *Langmuir*, 1989, 5: 1074-87.
[12] A. Ulman, *Chem. Rev.* 1996, 96: 1533-1554
[13] B. Legendre, Y. Feutelais, *J. Therm. Anal. Chem.*, 2004, 76: 255-264.
[14] L. Borka, *Acta Pharm. Suec.* 1974, 11: 295-303.
[15] S. Y. Lin, *J. Pharm. Sci,.* 1992, 81: 572-576.
[16] T. Wu, L. Yu, *J. Phys. Chem. B,* 2006, 110: 15694-15699.
[17] W. Ostwald, *Z. Phys. Chem.* 1897, 22: 289-330.
[18] T. Threlfall, *Org. Process Res. Dev.,* 2003, 7: 1017-1027.
[19] J. D. Pruitt, T. A. Ryde, W. H. Bosch, *PCT Int. Appl.,* 2005.
[20] S. Romero, P. Bustamante, B. Escalera, M. Cirri, *Journal of Thermal Analysis and Calorimetry,*. 2004, 77: 541–554.
[21] E. Abignente, P. De Caprariis, *Analytical Profiles of Drug Substances,* 1982, 11: 313-346.
[22] Krc, J., *The Microscope* 25(1977): 31-46.
[23] Z. Galdecki, M. L. Glowka, Z. Gorkiewics, *Acta. Pol. Pharm.,* 1978, 35: 77.
[24] J. Starbuck, R. Docherty, M, H. Charlton, D. Buttar, *J. Chem. Soc*., 1999, 2: 677–691.
[25] C. C. McOsker, P. M. Fitzpatrick, *J. Antimicrob. Chemother*, 1994, 33 Suppl. A: 23-30.