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Far-Infrared Spectroscopy as A Probe for Polymorph Discrimination

Kuthuru Suresh^a, Jeffrey S. Ashe^a, and Adam J. Matzger^{*,a,b}

^aDepartment of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, USA.

^bDepartment of Macromolecular Science and Engineering, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, USA.

Abstract

Pharmaceutical crystalline polymorph and amorphous form detection and quantification is a standard requirement in the pharmaceutical industry. Infrared (IR) spectroscopy provides an important probe for the characterization of polymorphs. Nonetheless, characterization and discrimination among polymorphs using mid-IR spectroscopy is not always possible in part because the technique mainly probes vibrational modes arising from functional groups in the sample. In the present work, far-infrared (far-IR) spectroscopy is demonstrated for the discrimination of polymorphs. This region is influenced by delocalized lattice vibrational modes derived from intermolecular forces and packing arrangements in the crystal structure. A total of ten polymorphic pharmaceuticals were prepared to conduct a critical evaluation of the question does this far-IR region add value for polymorph differentiation? It is demonstrated that the far-IR region offers high discriminating power for polymorphs compared to the mid-infrared spectral region. In addition, structural similarity and dissimilarity in polymorphic packing arrangements can be derived from this analysis.

Graphical Abstract

*Correspondence: matzger@umich.edu.

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Associated content: Experimental details, PXRD data of all pharmaceutical polymorphs, Table of Far-IR frequency vibrational modes for the polymorphs of studied pharmaceuticals. mid-IR data of acetaminophen, carbamazepine and caffeine. Crystal diagrams of carbamazepine and caffeine.

Keywords

Pharmaceuticals; polymorph; amorphous; crystal packing; far-IR spectroscopy

Introduction:

Crystal polymorphism is a prevalent phenomenon that is observed in more than half of active pharmaceutical ingredients (APIs).^{1–3} It is defined as the ability of a substance to exist in two or more crystalline forms in which the molecules have different arrangements.^{1,2} Polymorphism has received tremendous attention in pharmaceuticals because the discovery of a novel polymorphic form of an existing marketed API, ideally with improved physicochemical properties, can gain early access into the marketplace for generic manufacturers.^{3–5} At the same time, due to intellectual property considerations, pharmaceutical innovators are motivated to find all possible polymorphs of the API and may leverage patents to extend the exclusivity of their products. Different polymorphs can exhibit significantly altered physicochemical and mechanical properties such as solubility, dissolution rate, physical/chemical stability, bioavailability and tabletability.^{3–5} Polymorphs are usually generated by crystallization methods such as crystallization from solution, water/solvent medium slurry, sublimation, vapor diffusion, polymer-induced heteronucleation, and high throughput crystallization approaches that typically leverage one or more of these approaches in parallel.^{3–7} Similarly, various techniques such as X-ray diffraction (single crystal and powder), thermal analysis (DSC and TGA), spectroscopy (vibrational including infrared and Raman, nuclear magnetic resonance), and microscopy (optical, SEM and TEM) techniques have been utilized to characterize polymorphs. The vibrational spectroscopy techniques are non-destructive, rapid, and suitable tools for process analytical technology (PAT) application thus offering a pathway to meeting increasingly stringent regulatory compliance related to crystalline form control in manufacture.^{8,9}

The vibrational spectroscopy techniques, mid-infrared (mid-IR) and Raman, discriminate among crystalline forms by probing vibrations associated with a change of dipole moment (IR-active bands) and vibrations accompanied by the change of polarizability (Raman-active bands). For organic molecules, these spectroscopic techniques are dominated by numerous intramolecular vibrational modes of the molecules that arise from functional groups present in the sample and from which structural features can be resolved qualitatively and

quantitatively. Identification and analysis of crystalline phases/polymorphs by these techniques is often complicated by the relatively local nature of the vibrational modes. The low wavenumber spectral region, by contrast, is influenced by delocalized lattice vibrations derived from intermolecular forces and packing arrangements in the crystal structure.^{10–12} Thus, the observed bands in this region more directly relate to the crystal structure of a molecule. Hence, this region might act as fingerprint for discrimination among polymorphs even if the mid-IR region does not show significant differences. Based on this notion, low wavenumber Raman spectroscopy and terahertz (THz) spectroscopy has been used for polymorphs discrimination.^{13–15} Much less work has been conducted in pharmaceuticals with infrared spectroscopy in this low wavenumber region, in spite of the fact that FT-IR is the most common of all vibrational spectroscopies. This apparent paradox can be traced to the typical configuration of mid-IR spectrophotometers which are equipped with window materials that absorb far-IR radiation. The question explored here is, does this far-IR (400–100 cm⁻¹) region add value for polymorph differentiation. A total of ten polymorphic pharmaceuticals were prepared to conduct a critical evaluation. Among these a few pharmaceuticals and their different solid forms (polymorph, amorphous, and hydrate) have been characterized using THz spectroscopy.^{15–21}

Results and Discussion:

A Nicolet™ iS50 FT-IR equipped with ATR module was employed in this study. This spectrophotometer combines a diamond ATR crystal and both mid-IR (KBr beam splitter and KBr DTGS detector) and far-IR (solid substrate beam splitter and DTGS detector) optics such that it is possible to record both the mid-IR and far-IR spectroscopy sequentially on the same sample. High-quality spectra were acquired in a couple of minutes and spectra analyzed using the OMNIC software. A total of ten pharmaceuticals were selected for the study, and the structures are represented in Figure 1. Polymorphs of these pharmaceuticals were prepared either from methods reported in the literature or through polymer-induced heteronucleation methods^{6,7} as described in Supporting Information. Initially, polymorphic phases were analyzed by PXRD (Figure S1a–j) to confirm phase homogeneity, then the polymorphic phases were subjected to far-IR spectroscopy. All far-IR vibrational frequencies for the polymorphs of the pharmaceuticals are listed in Table S1, Supporting Information accompanied by additional data processing procedures including advanced ATR correction that accounts for shifting infrared absorption peaks and the effects of variation in depth of penetration.

Acetaminophen:

Acetaminophen^{22–24} exhibits two stable polymorphic forms, a monoclinic form I and orthorhombic form II, under ambient conditions. It is a familiar example of polymorphs that exhibit different compaction behavior.²⁵ Form II can be directly tableted whereas form I cannot, and this difference in mechanical properties can be directly correlated with differences in packing arrangements. Form I crystallizes in a herringbone structure (Figure 2a) whereas form II has a layered structure (Figure 2b). These polymorphs were obtained from slow solvent evaporation and polymer-induced heteronucleation at isothermal conditions and were further analyzed by both mid-IR and far-IR spectra. However, the mid-

IR spectra are very similar for both polymorphic forms due to their similar conformations in the crystal lattice (Figure S2, Supporting Information). The polymorphic forms I and II can be easily discriminated from the far-IR spectra (Figure 2c). Form I exhibits the characteristic strong peak at 217.6 cm^{-1} whereas form II exhibits a peak at 188.4 cm^{-1} . Additionally, acetaminophen polymorphs (I, II, III) and amorphous form have been characterized in the region below 100 cm^{-1} ($<3\text{ THz}$) using THz spectroscopy.¹⁵

Mefenamic acid:

Mefenamic acid²⁶ is a nonsteroidal anti-inflammatory drug (NSAID) that exists in two polymorphic forms. Form I was obtained from slow solvent evaporation from ethanol, and form II was obtained by heating form I at $160\text{ }^{\circ}\text{C}$ to allow for solid-state transformation. Structural analysis shows that form I and II crystallize in same crystal system and differ by packing arrangements in the crystal structure. These two forms can be distinguished in the far-IR region. Form I has some characteristic peaks at 232.5 and 251.0 cm^{-1} and form II shows a distinctive peak at 236.0 cm^{-1} (Figure 3a). Additionally, mefenamic acid polymorphic forms I and II forms have been characterized in the region below 200 cm^{-1} ($<6\text{ THz}$) using THz spectroscopy.¹⁶

Tolfenamic acid:

Tolfenamic acid²⁷ is a highly polymorphic NSAID. Among all polymorphic forms, crystallization from organic solvent readily yields form I and form II. Both contain a carboxylic acid dimer synthon which is frequently observed for carboxylic acids and exhibit conformational differences in the crystal structure. In Form I the methyl group is in an *anti*-position relative to the NH (amine) group whereas in form II the same methyl group is in a *syn*-position. Both forms are stable at room temperature and show distinguishable peaks in the far-IR region. Form I has characteristic peaks at 187.9 , 289.0 , 340.7 , 355.4 cm^{-1} and form II shows intense peaks at 222.7 , 247.2 , 262.2 , 283.0 , 347.7 , 386.4 cm^{-1} (Figure 3b).

Furosemide:

Furosemide²⁸ is a loop diuretic drug used to treat heart failure. It exists in three polymorphs (Form I, II and III) which are produced by slow solvent evaporation. These forms exhibit conformational and synthon differences in the crystal structure. This is an example of differences in sulfonamide group synthons (dimer and catemer) in polymorphic structures and such modifications are distinguished by far-IR spectra. Form I exhibits peaks at 123.3 , 154.0 , 247.1 cm^{-1} whereas form II shows peaks at 132.7 , 169.3 , 224.4 , 261.7 cm^{-1} and form III shows peaks at 147.0 , 172.2 , 252.0 cm^{-1} (Figure 3c). Additionally, furosemide three polymorphic forms (I, II, and III) and two solvates (N,N-dimethylformamide and 1,4-dioxane) have been characterized in the region below 66 cm^{-1} ($<2\text{ THz}$) using THz spectroscopy.¹⁷

Pyrazinamide:

Pyrazinamide^{29,30} is a first-line anti-tuberculosis drug and is administered with isoniazid, ethambutol dihydrochloride, and rifampicin in a fixed dose combination. It is an example of a conformationally rigid molecule with four polymorphs (α , β , γ and δ). Crystallization in

different organic solvents and sublimation experiments produce all four forms. These forms exhibit synthon differences and dissimilar molecular packing arrangements in the crystal structure which are easily discriminated using the far-IR spectra. Form α is characterized by peaks at 108.9, 263.0, 394.0 cm^{-1} while form β shows peak at 124.2, 177.5, 251.2, 388.7 cm^{-1} . The spectrum for form γ shows peaks at 120.3, 233.9, 381.8 cm^{-1} and form δ has peaks at 147.7, 265.5, 385.7 cm^{-1} (Figure 3d).

Nabumetone:

Nabumetone^{31,32} is an anti-inflammatory drug. It exists in two polymorphic forms (form I and II). Form II differs in weak C–H...O supramolecular interactions from form I. Crystallization from solution yields form I and II which are discriminated using far-IR spectra. Form I shows characteristic peaks at 152.1, 207.2, 273.6 cm^{-1} and form II shows broad peaks at 135.9, 258.7 cm^{-1} (shown in Figure 3e). Additionally, nabumetone form I has been characterized in the region below 100 cm^{-1} (<3 THz) using THz spectroscopy.¹⁸

Sulindac:

Two polymorphs (monoclinic form I and orthorhombic form II) of the anti-inflammatory drug sulindac³³ were characterized with far-IR spectroscopy. Crystallization from solution afforded crystals form I and form II which are discriminated in the far-IR region. Form I shows characteristic peaks at 220.4, 287.5, 308.1, 334.4, 384.1, and 396.6 cm^{-1} and form II exhibits distinctive peaks at 143.1, 152.6, 161.3, 183.6, 361.1, and 393.5 cm^{-1} (Figure 3f).

Sulfamethazine:

Sulfamethazine³⁴ is an antibacterial drug that exists in one stable crystalline form and an amorphous form. The crystalline phase shows strong absorption in the far-IR region while the amorphous phase exhibits broad/weak absorption. The crystalline phase exhibits ten strong peaks and the amorphous phase has broad peaks at 237.8, 281.2, 379.7 cm^{-1} (Figure 3g). The change of peak intensities demonstrates that far-IR spectroscopy can distinguish the amorphous and crystalline phases of the same compound. Similarly, *in situ* amorphization from crystalline sample³⁵ can be detected using far-IR spectroscopy and should serve useful to quantify the crystalline content present in an amorphous pharmaceutical. Additionally, sulfamethazine crystalline form has been characterized in the region below 66 cm^{-1} (<2 THz) using THz spectroscopy.¹⁹

The above analysis demonstrates that facile discrimination among different polymorphs is possible through far-IR spectroscopy. The above polymorphic phases of each system exhibit unique packing arrangements and delocalized vibrations from the crystal lattice are unique. Furthermore, far-IR spectroscopy shows promise in differentiating between polymorphic forms that exhibit similar packing arrangements and are not easily differentiated by mid-IR and PXRD. Below the far-IR spectra of pharmaceuticals carbamazepine and caffeine, drugs that show similar packing arrangements for their polymorphs, are discussed.

Carbamazepine:

Carbamazepine^{36–39} is highly polymorphic. Among all polymorphic forms, forms I, II and III are most commonly observed at room temperature. Here we obtained these three forms

by solvent crystallization and controlled heating experiments. Structural analysis of polymorphs show that form I and II contain similar packing arrangements although they crystallize in different crystal systems (form I triclinic *P*-1 and form II hexagonal *R*-3) and exhibit robust amide-amide dimer hydrogen bonding interactions (Figure S3 a and b). Form III has dissimilar packing in its crystal structure and is the most stable form at room temperature (Figure S3c). The far-IR spectra of form I and II are very similar whereas form III has a completely distinct far-IR spectrum with well-resolved peaks at 244.2 and 267.0 cm⁻¹, and it is easily discriminated from both forms I and II. Comparably, the similarity of the far-IR spectra of form I and II reflects the similarity of the packing in the crystal lattice. However, the two forms can be distinguished through peak shifting in the far-IR region (shown in Figure 4a), and mid-IR spectra (Figure S4). Additionally, carbamazepine form I, III and hydrates have been characterized in the region below 130 cm⁻¹ (<4 THz) using THz spectroscopy.²⁰

Caffeine:

Caffeine⁴⁰ is a blood-brain barrier crossing drug and acts on the central nervous system. It is the world's most widely consumed psychoactive drug. It exists in two polymorphs which are solved in different crystal systems (form 1, *C*2/*c* and form 2, *R*-3*c*). Both forms exhibit similar packing arrangements (Figure S5). The forms are not clearly distinguishable via mid-IR spectroscopy (Figure S6), but these forms are resolved in the far-IR region although they contain similar packing arrangements. Form 1 shows characteristic peaks at 168.8, 372.4 cm⁻¹ and form 2 exhibits peaks at 172.6, 371.1 cm⁻¹ (Figure 4b). Additionally, caffeine form I has been characterized in the region below 100 cm⁻¹ (<3 THz) using THz spectroscopy.²¹

Conclusions:

In summary, ten pharmaceutical polymorphic systems were probed using far-IR spectroscopy. The spectra of all polymorphic systems show well defined and resolved peaks in this region for crystalline forms. Thus far-IR spectroscopy is a fast and highly capable analytical tool for polymorphic phase characterization and discrimination. Among polymorphs, the significant features of far-IR are a result of delocalized vibrations derived from combination of intermolecular interactions, internal and external vibrations in the crystal lattice. Hence, this reflects dissimilarities in structural packing. In addition, the similarities in the far-IR region, were correlated with structural similarity in the crystal structures which supports the idea that it is also possible to assess the gross packing similarities in the crystal lattice. In addition, for colored pharmaceuticals, and their polymorphs, characterization through far-IR spectroscopy is preferred over Raman spectroscopy, because these compounds can decompose and/or show fluorescence when irradiated by the laser beam. In this light, we believe that these findings motivated use of far-IR spectroscopy as a PAT tool for polymorphic discrimination during manufacturing processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Bernstein J Polymorphism in Molecular Crystals, Oxford University Press Inc., New York, 2002.
2. Nangia A Conformational Polymorphism in Organic Crystals. *Acc Chem Res* 2008;41:595–604. [PubMed: 18348538]
3. Brittain HG Polymorphism in Pharmaceutical Solids; Marcel Dekker: New York, 1999.
4. Byrn SR, Pfeiffer RR, Stowell JG. Solid-State Chemistry of Drugs. SSCI: West Lafayette, IN, 1999.
5. Hilfiker R, Blatter F, van Raumer M. Relevance of Solid-state Properties for Pharmaceutical Products Polymorphism in the Pharmaceutical Industry; Hilfiker R, Ed.; Wiley-VCH: Weinheim, 2006:1–19.
6. Lang M, Grzesiak AL, Matzger AJ. The Use of Polymer Heteronuclei for Crystalline Polymorph Selection. *J Am Chem Soc.* 2002;124:14834–14835. [PubMed: 12475310]
7. Price CP, Grzesiak AL, Matzger AJ. Crystalline Polymorph Selection and Discovery with Polymer Heteronuclei. *J Am Chem Soc.* 2005; 127:5512–5517. [PubMed: 15826189]
8. Scott B, Wilcock A. Process analytical technology in the pharmaceutical industry: a toolkit for continuous improvement. *PDA J Pharm Sci Technol.* 2006;60(1):17–53. [PubMed: 17089677]
9. Watts C In PAT - A framework for Innovative Pharmaceutical Development Manufacturing and Quality Assurance, FDA/RPSGB Guidance Workshop, 2004.
10. Chantry GW. Submillimetre spectroscopy: A guide to the theoretical and experimental physics of the far infrared, 1st ed. London: Academic Press Inc. Ltd., 1971:385.
11. Korter TM, Plusquellic DF. Continuous-wave terahertz spectroscopy of biotin. Vibrational anharmonicity in the far-infrared. *Chem Phys Lett.* 2004;385:45–51.
12. Zeitler JA, Newnham DA, Taday PF, Threlfall TL, Lancaster RW, Berg RW, Strachan CJ, Pepper M, Gordon KC, Rades T. Characterization of temperature-induced phase transitions in five polymorphic forms of sulfathiazole by terahertz pulsed spectroscopy and differential scanning calorimetry. *J Pharm Sci* 2006;95:2486–2498. [PubMed: 16892211]
13. Roy S, Chamberlin B, Matzger AJ. Polymorph Discrimination Using Low Wavenumber Raman Spectroscopy. *Org Process Res Dev.* 2013;17:976–980. [PubMed: 27642248]
14. Strachan CJ, Taday PF, Newnham DA, Gordon KC, Zeitler JA, Pepper M, Rades T. Using Terahertz Pulsed Spectroscopy to Quantify Pharmaceutical Polymorphism and Crystallinity. *J Pharm Sci* 2005;94:837–846. [PubMed: 15736195]
15. Sibik J, Löbmann K, Rades T, Zeitler JA. Predicting Crystallization of Amorphous Drugs with Terahertz Spectroscopy. *Mol Pharm* 2015;12:3062–3068. [PubMed: 26090554]
16. Otsuka M, Nishizawa J, Shibata J, Ito M. Quantitative evaluation of mefenamic acid polymorphs by terahertz-chemometrics. *J Pharm Sci* 2010;99(9):4048–53. [PubMed: 20665848]
17. Ge M, Liu G, Ma S, Wang W. Polymorphic Forms of Furosemide Characterized by THz Time Domain Spectroscopy. *Bull. Korean Chem Soc* 2009;30(10):2265–2268.
18. Agrawal M, Deval V, Gupta A, Sangala BR, Prabhu SS. Evaluation of structure-reactivity descriptors and biological activity spectra of 4-(6-methoxy-2-naphthyl)-2-butanone using spectroscopic techniques. *Spectrochim Acta A Mol Biomol Spectrosc.* 2016;167:142–156. [PubMed: 27284764]
19. Redo-Sanchez A, Salvatella G, Galceran R, Roldós E, García-Reguero JA, Castellari M, Tejada J. Assessment of terahertz spectroscopy to detect antibiotic residues in food and feed matrices. *Analyst.* 2011;136(8):1733–1738. [PubMed: 21336350]
20. Zeitler JA, Kogermann K, Rantanen J, Rades T, Taday PF, Pepper M, Aaltonen J, Strachan CJ. Drug hydrate systems and dehydration processes studied by terahertz pulsed spectroscopy. *Int J Pharm.* 2007;334(1–2):78–84. [PubMed: 17129691]

21. Shena J, Wanga G, Jianga D, Liangb L, Xu X. Terahertz spectroscopic investigations of caffeine and 3-acetylmorphine. *Optik* 2010;121:1712–1716.
22. Haisa M, Kashino S, Maeda H. The orthorhombic form of p-hydroxyacetanilide. *Acta Crystallogr., Sect. B* 1974;30:2510–2512.
23. Haisa M, Kashino S, Kawai R, Maeda H. The Monoclinic Form of p-hydroxyacetanilide. *Acta Crystallogr., Sect. B* 1976;32:1283–1285.
24. Sacchetti MJ. Thermodynamic Analysis of DSC Data for Acetaminophen Polymorphs. *Therm Anal Calorim* 2000;63:345–350.
25. Di Martino P, Guyot-Hermann AM, Conflant P, Drache M, Guyot JC. A new pure paracetamol for direct compression: The orthorhombic form. *Int. J. Pharm* 1996;128:1–8.
26. Gilpin RK, Zhou W. Infrared studies of the polymorphic states of the fenamates. *J Pharm Biomed Anal* 2005;37:509–515. [PubMed: 15740911]
27. Lopez-Mejías V, Kampf JW, Matzger AJ. Polymer-Induced Heteronucleation of Tolfenamic Acid: Structural Investigation of a Pentamorph. *J Am Chem Soc* 2009;131:4554–4555. [PubMed: 19334766]
28. Babu NJ, Cherukuvada S, Thakuria R, Nangia A. Conformational and Synthron Polymorphism in Furosemide (Lasix). *Cryst Growth Des* 2010;10:1979–1989.
29. Castro RAE, Maria TMR, Évora AOL, Feiteira JC, Silva MR, Beja AM, Canotilho J and Eusébio MES. A New Insight into Pyrazinamide Polymorphic Forms and their Thermodynamic Relationships. *Cryst Growth Des* 2010;10(1):274–282.
30. Cherukuvada S, Thakuria R, Nangia A. Pyrazinamide Polymorphs: Relative Stability and Vibrational Spectroscopy. *Cryst Growth Des*. 2010;10:3931–3941.
31. Price CP, Grzesiak AL, Lang M, Matzger AJ. Polymorphism of Nabumetone. *Cryst Growth Des* 2002; 2:501–503.
32. Chyall LJ, Tower JM, Coates DA, Houston TL, Childs SL. Polymorph Generation in Capillary Spaces: The Preparation and Structural Analysis of a Metastable Polymorph of Nabumetone. *Cryst Growth Des* 2002; 2:505–510.
33. Grzesiak AL M, Matzger AJ. New Form Discovery for the Analgesics Flurbiprofen and Sulindac Facilitated by Polymer-Induced Heteronucleation. *J Pharm Sci* 2007; 96(11): 2978–2986. [PubMed: 17567888]
34. Yang SS, Guillory JK. Polymorphism in Sulfonamides. *J Pharm Sci* 1972; 61:26–40. [PubMed: 5066733]
35. Zhang C, Kersten KM, Kampf JW, Matzger AJ. Solid-State Insight into the Action of a Pharmaceutical Solvate: Structural, Thermal, and Dissolution Analysis of Indinavir Sulfate Ethanolate. *J Pharm Sci* 2018.
36. Grzesiak AL, Lang M, Kim K, Matzger AJ. Comparison of the Four Anhydrous Polymorphs of Carbamazepine and the Crystal Structure of Form I. *J Pharm Sci* 2003; 92:2260–2271. [PubMed: 14603511]
37. Arlin J-B, Price LS, Price SL, Florence AJ. A strategy for producing predicted polymorphs: catemeric carbamazepine form V. *Chem Commun* 2011; 47:7074–7076.
38. Lang M, Kampf JW, Matzger AJ. Form IV of Carbamazepine. *J Pharm Sci*. 2002; 91:1186–1190. [PubMed: 11948557]
39. Lowes MM, Caira MR, Lötter AP, Van der Watt JG. Physicochemical properties and X-ray structural studies of the trigonal polymorph of carbamazepine. *J Pharm Sci*.1987;76:744–752. [PubMed: 11002813]
40. Enright GD, Terskikh VV, Brouwer DH, Ripmeester JA. The Structure of Two Anhydrous Polymorphs of Caffeine from Single-Crystal Diffraction and Ultrahigh-Field Solid-State ¹³C NMR Spectroscopy. *Cryst Growth Des*. 2007;7:1406–1410.

Figure 1:
Molecular structures of the pharmaceuticals studied.

Figure 2:

Crystal packing diagrams of ACM form I and II. (a) Zigzag chain of ACM molecules connected via O-H...O and O-H...N hydrogen bonding interactions in form I. (b) Layered structure of form II sustained through C-H... π interactions. (c) Far-IR spectra of polymorphs form I and form II (Spectra have been offset along the y-axis for clarity).

Figure 3: Far-IR spectra of (a) mefenamic acid (b) tolfenamic acid (c) furosemide (d) pyrazinamide (e) nabumetone (f) sulindac and (g) sulfamethazine. Spectra have been offset along the y-axis for clarity.

Figure 4:
Far-IR spectra of carbamazepine (a) and caffeine (b). Spectra have been offset along the y-axis for clarity.