Solid-State Pharmaceutical Chemistry

S. R. Byrn,*,† R. R. Pfeiffer,† G. Stephenson,† D. J. W. Grant,‡ and W. B. Gleason§

Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Indiana, 47907 and Department of Pharmaceutics and Department of Laboratory Medicine and Pathology, Biomedical Engineering Center, University of Minnesota, Minneapolis, Minnesota 55455

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Solid-state pharmaceutical chemistry encompasses a wide range of studies on pharmaceutical solids including (1) determination of the physical properties of polymorphs and solvates, (2) physical transformations between polymorphs and solvates, (3) chemical reactions in the solid state, and (4) solid–solid reactions which occur in pharmaceutical preparations. Recent advances in this field include improved understanding of crystallization processes, improved understanding of the need for characterization of polymorphs and solvates for both control and regulatory purposes, and a better understanding of the mechanisms of solid-state degradations and solid–solid reactions. This review will briefly describe recent advances in the following areas: (1) crystallization and the properties of crystals of pharmaceutical solids; (2) characterizations of crystal forms of drugs using solid-state NMR spectroscopy.

The study of the solid-state chemistry of drugs not only encompasses many scientific disciplines but also impinges on virtually all phases of the pharmaceutical industry, from discovery to successful marketing. It is clear that an understanding of the molecular structure of the solid state can lead to better design and control of drug performance.

The mission of those working in the field of solid-state pharmaceutical chemistry is to provide each drug in a solid form that has optimum performance in a given application. Pursuit of this mission requires recognition of several general, interrelated points: (1) Drugs can exist in a number of solid forms, each having different properties of pharmaceutical importance, including stability and bioavailability; the number and properties of these forms are largely unpredictable and vary considerably from case to case. (2) The forms of a drug may interconvert under various conditions. (3) Once a solid form is chosen for a product, methods for analysis and control of the form must be devised.

Let us briefly review each of these points with regard to their status in current practice and to some associated scientific challenges that remain.

(1) The most common solid forms that may be found for a given drug substance are as follows: **crystalline polymorphs**, forms having the same chemical composition but different crystal structures and therefore different densities, melting points, solubilities, and many other important properties; **solvates**, forms containing solvent molecules within the crystal structure, giving rise to unique differences in solubility, response to atmospheric moisture, loss of solvent, etc. Sometimes a drug product may be a **desolvated solvate**, formed when solvent is removed from a specific solvate while the crystal structure is essentially retained—again, many important properties are unique to such a form; finally, **amorphous** solid forms that have no long-range molecular order (i.e., no crystallinity) and which tend to be more soluble, more prone to moisture uptake, and less chemically stable than their crystalline counterparts (pharmaceutical processing operations may produce solids of low crystallinity intermediate between that of a crystalline solid and an amorphous solid).

To be sure, differentiating among the various solid forms of a substance is generally a routine matter. A number of analytical methods, used together, make this possible. Various familiar methods reveal the chemical composition of the solid and reveal the presence of solvent. The physical form is further characterized by X-ray powder diffraction, infrared and solid-state NMR spectroscopy, differential scanning calorimetry, and microscopy. The single most valuable piece of information about a crystalline solid, although not always available, is the molecular structure, determined by single-crystal X-ray diffraction.

Perhaps the chief challenge in managing the phenomenon of multiple solid forms of drugs is our inability to predict how many forms can be expected in a given case: too often costly delays are encountered when a less soluble solid form suddenly appears late in a development program. Progress along these lines awaits analysis and quantification of the myriad intermolecular forces within any proposed crystal structure as well as the ability to postulate the likely packing modes for a given molecule in all its configurations. Further research similar to that of Margaret Etter and co-workers, reviewed in section A, will doubtless lead to better success in predicting alternative solid forms of new drugs.

A second challenge relates to the strikingly different reactivity of different solid forms of many substances, whether it be oxidation, dehydration, decarboxylation, or other chemical reactions. Kinetics involving the solid state, in which specific contacts (or noncontacts) between reactive groups are dictated by the structure of a given solid form, are apt to be more complex than kinetics in solution, where the corresponding molecular encounters are much more random. Much the same can be said about the relative difficulty of elucidating mechanisms in these two states. Moreover, reactions in the solid state may be further complicated by other, often unknown factors such

† Purdue University.
‡ Department of Pharmaceutics, University of Minnesota.
§ Department of Laboratory Medicine and Pathology, University of Minnesota.
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as nucleation of a reaction product phase, presence of various amounts of amorphous component, strain or disorder in the crystal structure, and multiplicity of reaction products. As a result, there is very little information available to guide in any general way the prediction of the stability of compounds in the solid state, let alone in their different solid forms or different formulations. Thus, the stability of all but the most rugged products is generally characterized empirically at actual storage temperatures, and the value of studies at elevated temperatures must be assessed case by case. Elucidation of the kinetics and mechanisms of solid-state reactions is pursued in only the most pressing cases.

(2) A dictate of formulation technology is that the physical form of the drug substance, after being defined and verified, should not change once the product has been manufactured. Therefore, in addition to identifying various solid forms of a drug, an understanding of the specific factors that may bring about *transformations* between the forms is also essential.

Rates of solid-to-solid transformations in drugs are affected by one or more of the following variables: temperature, solubility in a given liquid phase, and vapor pressure of solvent. At a minimum, the investigator must therefore first identify and obtain certain physicochemical data on each relevant solid form:

- transition temperature(s) between polymorphs
- solubility of the drug in all solvents and solvent mixtures used in preparation of the final drug substance and throughout the formulation process
- equilibrium water vapor pressure *vs* composition isotherm

This information reveals which solid form is the most physically stable (least soluble) under specific conditions of temperature and composition; thus, if that form is already the one present, no transformation will occur. If, however, a less physically stable (more soluble) form is present, the *direction* of any transformation can now be predicted for given conditions. One might well ask why the most stable form is not always selected and, indeed, that is usually the case. There are however, situations where the peculiar properties of a less stable solid form are required for a product's performance—achieving higher solubility, for example. In such cases, the manufacturer has the added burden of demonstrating the *lack* of transformation to a more stable solid form throughout the life of the product. As discussed in the previous section, this task requires dealing with the problems of solid-state kinetics and must usually be approached empirically.

(3) Two main challenges to the analysis of pharmaceutical solids are dealing quantitatively with mixtures of forms in the drug substance and identifying the solid form of the active ingredient in the formulated product, particularly when the drug is a minor component in the presence of numerous other materials (excipients).

With this background on the current status of solid-state pharmaceutical chemistry, we can now turn to a number of recent advances in this field.

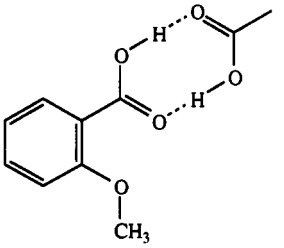
The work of Margaret Etter and co-workers, treated in section A, is an example of how present research addresses some of the issues of structure prediction raised above.

The topics discussed in sections B–D have significant bearing on many of the issues discussed in all three of the introductory subsections.

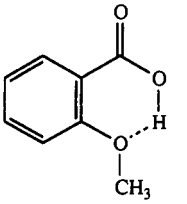
A. Forces Holding Crystals Together

Two main types of forces are responsible for holding drug crystals together: nonbonded interactions and hydrogen bonding. Nonbonded interactions occur in all crystals while hydrogen bonding is important in many compounds, especially pharmaceuticals. Etter has reviewed the extent and types of hydrogen bonding which can exist in organic solids.[1,2]

Carboxylic acids have been a particularly useful class of compounds for investigating alternative hydrogen bonding possibilities. For example, in *o*-alkoxybenzoic acids both dimerization and formation of intramolecular hydrogen bonding are observed.[3] In *o*-anisic acid, dimers are observed in the solid state while intramolecular hydrogen bonds are observed in dilute solution. However,

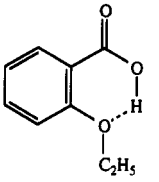


Solid State



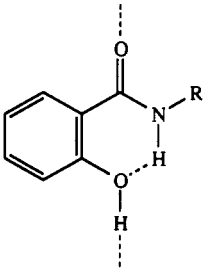
Solution

in *o*-ethoxybenzoic acid, only intramolecular hydrogen bonds are observed in the solid state and in solution.



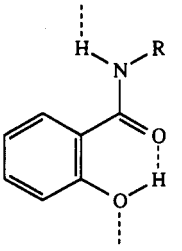
Solution and Solid State

The Etter group studied the hydrogen bonding in salicylamide derivatives and pointed out that two types of hydrogen bonding are possible in these compounds.[4] One type involves an intramolecular NH···O hydrogen bond and an intermolecular C=O···HO— hydrogen bond and the other an intramolecular C=O···HO— hydrogen bond and an intermolecular NH···O hydrogen bond.



Intra: HN··· O

Inter: C=O··· HO



Intra: C=O··· HO

Inter: HN··· O

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(2) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–6.
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Table 1. Reliable and Occasional Hydrogen-Bond Donors and Acceptors

type	functional group involved
reliable donor	–OH,[a] $–NH_2$, –NHR, $–CONH_2$, –CONHR, –COOH
occasional donor	–COH, –XH, –SH, –CH
reliable acceptors	–COOH, –CONHCO–, –NHCONH–, –CON< (1–3°), >P=O, >S=O, –OH
occasional acceptors	>O, $–NO_2$, –CN, –CO, –COOR, –N<, –Cl

[a] Not COH.

Etter, MacDonald, and Bernstein developed a graph-theory-based approach to classifying and symbolically representing the different types of hydrogen bonds that can be formed.[5]

Etter also developed rules governing hydrogen bonding in solids. These rules require a classification of hydrogen bond donors and acceptors into "reliable" hydrogen-bond donors and acceptors and "occasional" donors and acceptors (Table 1). Using these classifications, three rules were devised: (1) All (or as many as possible) good proton donors and acceptors are used in hydrogen bonding. (2) Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds. (3) The best proton donors and acceptors remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds. These rules apply quite well to hydrogen bonding of small molecules. However, in some larger molecules, e.g., erythromycins, steric factors make it impossible to satisfy all of the possible hydrogen bonded interactions, and some donors and acceptors are not involved in any hydrogen bonds.

Cocrystals. An important aspect of research into hydrogen bonding involves the realization that cocrystals can be obtained from certain solutions containing more than one molecular species. Cocrystals can also be formed by mixing or grinding two solids together. Cocrystals are usually formed between a hydrogen-bond donor molecule and a hydrogen-bond acceptor molecule. The nature of hydrogen bonding in cocrystals can also be described using the above rules. The cocrystals observed by Etter's group include numerous ureas with ketones, carboxylic acids with 2-aminopyridine, and also adenine or cytosine combined with many acidic organic compounds[6] such as carboxylic acids and *N*-acylamino acids. Other classes of cocrystals investigated by Etter's group are

pyrimidine, pyridines: carboxylic acids

pyridine-N-oxides: acids, alcohols, amines

phosphine oxides: acids, amides, alcohols, ureas sulfonamides, amines, water

carboxylic acids: other carboxylic acide, amides

m-dinitroureas: acids, ethers, phosphine oxides, sulfoxides, nitroanilines

imides: other imides, amides

The formation of cocrystals may be quite important in explaining solid–solid interactions in many fields including those of pharmaceuticals.

This elegant work of Etter and co-workers has greatly increased our understanding of the hydrogen-bonding interactions of molecules in both the solid state and in solution.

B. How Crystals Form

Crystallization and the factors controlling the formation of crystals is an extremely important area in solid-state pharmaceutical chemistry. Dr. Margaret Etter made an extremely important observation when she pointed out that molecules in solution often tend to form different types of hydrogen-bonded aggregates and hypothesized that these aggregate precursors are related to the crystal structures that form from the supersaturated solution.[2] This concept helps to explain the many different hydrogen-bonding motifs seen in different solids.

A number of factors can affect the crystal formed either by influencing the hydrogen-bonded aggregate precursors in solution or influencing one of the many other factors involved in crystallization. These include (1) solvent composition or polarity, (2) concentration or degree of supersaturation, (3) temperature including cooling rate and the cooling profile, (4) additives, (5) seeds and the presence of seeds, (6) pH (pH is important for crystallization of salts), and (7) agitation.

The composition of the solvent used is known to influence crystallizations either directly or by influencing the temperature at which the crystallization is initiated. For example, in the mannitol system, the α-polymorph is formed by evaporation of 100% ethanol while the β-polymorph is formed by crystallization from aqueous ethanol.[7] In a study of inosine, Suzuki showed that crystallization from water gave the α-form whereas crystallization from 70% DMSO gave the β-form.[8]

A second important factor influencing crystallization is the degree of supersaturation—the ratio of the concentration of the solution to that of a saturated solution. In his study of the polymorphism of cimetidine, Sudo showed[9,10] that in isopropyl alcohol at high supersaturation ratios (greater than 3.6) form A crystallized spontaneously or in the presence of seeds of either form A or form B, whereas in lower supersaturation ratios (less than 2) form A crystallized if there were A seeds and B crystallized if there were B seeds.

Temperature can have a very significant effect on the polymorph produced. Studies by Kitamura[11] on the crystallization of L-glutamic acid showed that at 45° the α-form nucleates slowly resulting in β-form growth, whereas at 25 °C the α-form nucleates rapidly causing α-form growth.

The effect of additives on crystallization has been of interest for many years. Early work by Simonelli indicated that polymeric additives could prevent the crystallization of certain phases.[12] Significantly, studies in recent years by Lahav and co-workers[13] have shown that additives (as

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little as 0.03%) can inhibit nucleation and crystal growth of a stable polymorph, thus favoring the growth of a metastable polymorph. They also showed that it is possible to design crystal nucleation inhibitors to control polymorphism.

In addition, Grant et al. have shown the effects of additives on the properties of adipic acid, acetaminophen (paracetamol), and (*R,S*)-(−)-ephedrinium-2-naphthalenesulfonate, a chiral drug. The effects on each of these crystalline solids will now be considered in turn.

When adipic acid is crystallized from water containing traces of *n*-alkanoic acids[14] or oleic acid,[15] the additive is taken up by the crystals, while the very small water content is not significantly affected. Changes in crystal habit and in the crystal growth kinetics are consistent with a structural model in which the added *n*-alkanoic acid molecules occupy lattice sites at the crystal surfaces.[16] The incorporated additive also changes the thermodynamic properties of the crystal. Notably, the crystal energy and entropy are increased, as measured by reductions in the enthalpies of fusion and solution, while the melting point is little affected.[14,15] In addition, the Gibbs free energy of the crystal increases, as measured by the dissolution rate and the specific surface area, and the density of the crystals is changed. Furthermore, the compaction properties, as measured by Hiestand's indices of tableting performance of the crystals are also modified.[17] Low levels of incorporated *n*-octanoic acid produce an increase in lattice strain, reducing the energy required for plastic deformation leading to improved tableting performance. At higher levels of incorporated *n*-octanoic acid, the tableting performance again approaches that of the pure crystal, indicating a reduction in plasticity. The above results with adipic acid may be explained by the impurity defects and attendant dislocations introduced by incorporated additive, resulting in increased lattice strain at low concentrations of additive and in reversal of the effects at higher concentrations. These proposed changes in lattice strain have recently been confirmed by corresponding increases and decreases in the mosaic spread of the Laue diffraction pattern when single crystals are irradiated by white X-radiation from a synchrotron source.[18]

When acetaminophen is crystallized from water containing the structurally related synthetic impurity, *p*-acetoxyacetanilide (PAA), the additive is incorporated and the crystals become acicular (needle-shaped). Increasing concentrations of PAA lead to increasing uptake of PAA to a maximum constant value (suggesting a saturated solid solution), to a decrease in water content, and to an increase in the length/width ratio.[15] Higher concentrations of PAA cause the length/width ratio and the water content to return to nearly the initial values. The maximum length/width ratio and the minimum in water content correspond approximately to maxima in the enthalpy and entropy of fusion and in the intrinsic dissolution rate of the crystals, the melting point being little affected. The physical properties of the acetaminophen crystals mentioned above were measured under 29 different crystallization conditions, defined by the initial concentration of PAA, the initial supersaturation of acetaminophen, and the rate of stirring of the crystallization solution.[19] Statistical analysis of the properties of these crystals, crystallized and analyzed in triplicate, showed strong correlations between the length/width ratio and the concentration of PAA taken up by the crystal and between the intrinsic dissolution rate and the length/width ratio, the thermodynamic quantities playing a minor role.[20] These results demonstrate the significance of additive-induced changes in crystal habit in influencing the intrinsic dissolution rate of acetaminophen crystals. Thus, whereas the behavior of doped crystals of adipic acid may be attributed to differences in lattice strain, the behavior of doped acetaminophen crystals may be attributed to differences in crystal habit.

In the above examples, adipic acid and acetaminophen exist as achiral molecules and crystallize in achiral space groups. The question arises as to the effect of traces of the opposite enantiomer on the crystal properties of a chiral drug. To help answer this question, the chiral drug (*R,S*)-(−)-ephedrinium 2-naphthalenesulfonate [(−)-EN] was crystallized from aqueous solutions containing traces of the opposite enantiomer (*S,R*)-(+)-ephedrinium 2-naphthalenesulfonate [(+)-EN].[21] Crystals of (−)-EN took up the opposite enantiomer with an appreciable segregation coefficient (0.153), while the water content and melting point of the crystals remained constant. Uptake of the opposite enantiomer led to changes in the thermodynamic properties and intrinsic dissolution rate. These changes are similar to those observed when adipic acid incorporated *n*-alkanoic acid from the crystallization solution. The similar behavior suggests an analogous molecular mechanism in the solid state, implying that doping with the opposite enantiomer produces changes in crystal properties that are analogous to doping of a foreign molecule of different, but related structure. Interestingly, (−)-EN and (+)-EN when heated together give a phase equilibrium diagram with a eutectic (together with limited solid solution formation) between each enantiomer and the racemic compound. This observation suggests that the observed changes in the thermodynamic properties and intrinsic dissolution rate of (−)-EN may be attributed to doping of the crystals with [(+)-EN/(−)-EN] molecular pairs or clusters rather than simply with the added (+)-EN molecules.

Seeding is used extensively to control crystal form and also to control the extent of nucleation (i.e., final particle size). In almost all cases, seeding can be used to control the desired crystal form. For example, Suzuki et al.[8] showed that the α-form of inosine could be obtained by crystallization from water whereas to obtain the β-form, seeds of the β-form must be used. An interesting study of the effect of seeding was reported by Konapudi, and the mechanism of crystallization was elucidated by McBride and Carter.[22] Sodium chlorate crystallizes in both a chiral and a racemic form. Since sodium chlorate is not chiral in solution, crystallization from aqueous solution produces equal numbers of L and D crystals.

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Surprisingly, crystallization of an aqueous solution with stirring gives mostly crystals of one chirality, either L or D. Investigation showed that this effect was due to the fact that once a particular crystal (either L or D) has formed, when that initial crystal collides with the stirrer and is broken into many small seeds which then nucleate further crystallization of that hand crystal (either L or D). This observation supports the idea that one nucleating seed can produce a single crystalline form. It also suggests that in this particular crystallization, if one added a seed of either L or D crystals then one would obtain entirely that crystal form. This is one of the best examples of the concept: one seed, one crystal.

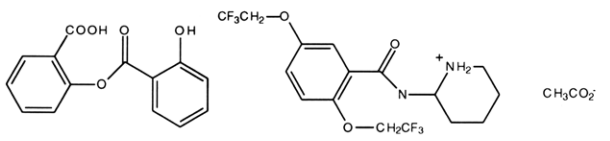
McCrone, in a letter to the editor of the *Journal of Applied Crystallography*, suggested that nucleation by seeding was the best explanation for the situation in which one unexpectedly obtains a new, more stable crystal form and then finds it is difficult or impossible to obtain the older less stable crystal form.[23] In response to this letter Jacewicz et al.[24] suggested that it is not impossible to produce the earlier form. They stated that the original crystal form should be capable of being produced but that the selection of the right conditions may require some time and trouble.

C. Disorder in Crystals of Pharmaceutical Solids

Another solid-state phenomenon which has important implications for pharmaceutical solids is disorder. Just as crystals of chiral and racemic drugs may have different physical properties, the presence of disorder in a crystal may also affect the physical properties of a crystal. One method of classifying disorder is to distinguish between cases involving static and dynamic disorder. Because single-crystal X-ray techniques give results which are averages over a long time period relative to molecular motion, X-ray crystallography at one temperature is usually unable to distinguish between static and dynamic disorder. Static and dynamic disorder can often be distinguished by comparing X-ray thermal parameters (ADPs) for two different temperatures. If the disorder results in observable resonance peaks in solid-state NMR spectra, then clearly this technique can be used to study this disorder.

In the crystallographic literature there are numerous examples of disorder which are caused by a molecule crystallizing in a single conformation but in a different orientation relative to other molecules in the crystal. There are also examples where the disorder is due to molecules crystallizing in different conformations.

Two such examples of conformational disorder are the crystal structures of nonsteroidal antiinflammatory (NSAID) drug salicylsalicylic acid (SALSALATE)[25,26] and the antiarrhythmic compound flecainide (TAMBOCOR).[27]



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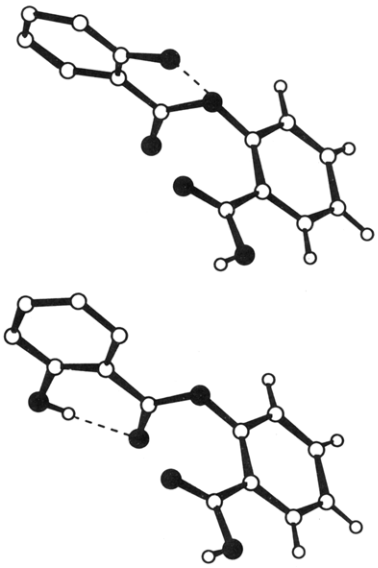

Figure 1. The two geometries of the SALSALATE molecule which are incorporated into the disordered crystal.

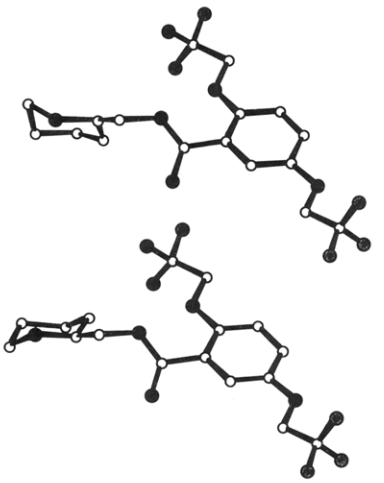

Figure 2. The two geometries of the TAMBOCOR which are incorporated into the disordered crystal.

The salsalate molecule can crystallize in two different conformations, each of which is intramolecularly hydrogen-bonded. Presumably, these two different intramolecular modes of hydrogen bonding are roughly equivalent energetically and the gross shape of the molecule in both conformations is similar so that both conformations can be incorporated into a single crystal as shown in Figure 1.

The other interesting example is the antiarrhythmic compound flecainide which is disordered in the solid state. The form of the compound which exhibits this disorder is actually the acetate salt, which was originally used for therapeutic purposes. Here the piperidinium ring takes on two alternate chair conformations as shown in Figure 2.

What are the consequences of such disorder? At the level of processing, the difficulty in reproducing material with the same properties may be responsible for different

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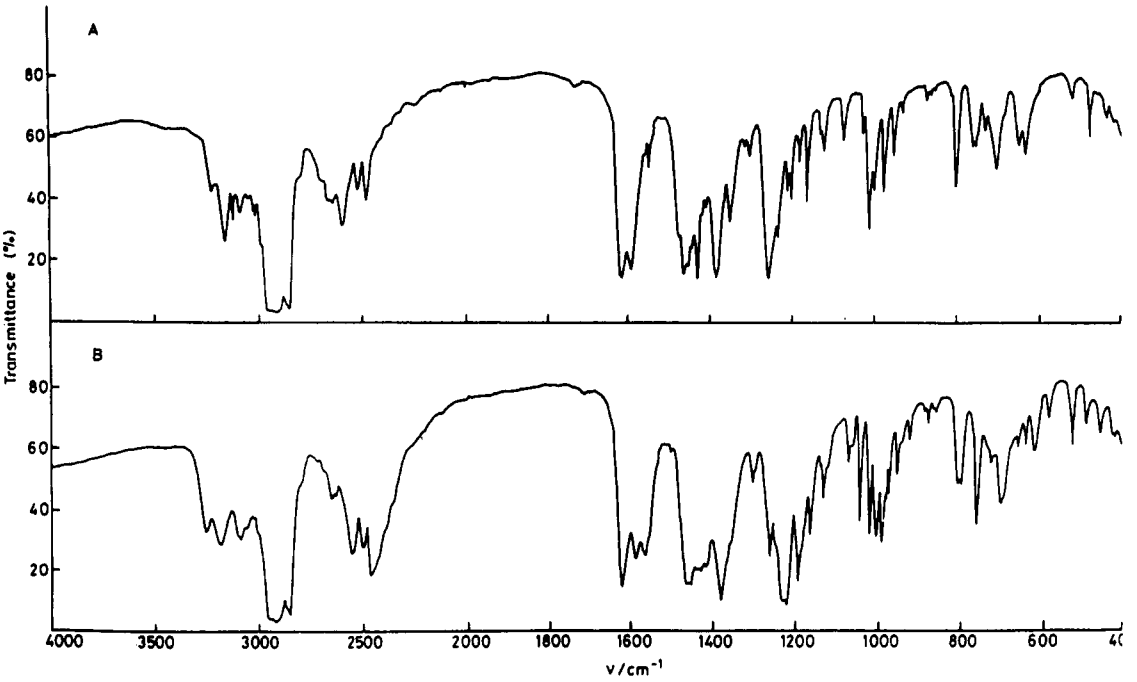


Figure 3. IR spectra of Nujol mulls of the two polymorphs of ranitidine hydrochloride: A, form 1; B, form 2.[29]

batches having dissimilar behavior. Batch-to-batch variability may be caused by differences in the ratio of the different conformations of molecule in the bulk sample.

Although disorder is a well-known phenomenon in the crystallography of small organics, the consequences of disorder in drug molecules appears not to have been widely considered. Just as crystals of chiral and racemic drugs may have different physical properties, the presence of disorder in a crystal may also affect the physical properties of the crystal. The amount of disorder (overall ratio of high occupancy to low occupancy conformations in the batch sample) found in a material may be highly dependent on the exact crystallization conditions. In turn the physical properties of individual batches may range from free-flowing powders to flocculent precipitates suffering badly from the effects of static electricity.

In addition, dynamic disorder reflects enhanced molecular mobility in the solid state. This enhanced molecular mobility may lead to enhanced chemical reactivity as suggested by the four-step mechanism of solid-state reactions first advanced by Paul and Curtin.[28] In this mechanism the first step is molecular loosening. Obviously, crystals possessing dynamic disorder are relatively loosely packed (at least near the site of disorder) and thus may be expected to be more reactive. At Purdue University, we are presently investigating cases in which the disorder of the system may relate to enhanced reactivity.

Are disordered samples with different amounts of disorder distinguishable? One method to distinguish this is discussed later in this review, solid-state NMR spectroscopy. Another approach is powder diffraction. Whether a particular sample will give a powder diffraction line which will change as a function of the disorder is a function of the scattering power of atoms in the alternate conformations and their contribution to scattering for a particular scattering plane. Computer programs are available for the calculation of powder diffraction patterns from single-crystal X-ray diffraction data. In one case we have examined, that of salicylsalicylic acid, our calculations indicate that certain diffraction lines are sensitive to the ratio of high occupancy to low occupancy conformations present in the salicylsalicylate sample. Thus the ratio of the intensities calculated for the two strongest lines in the powder pattern (311/202) varies from 0.80 to 1.75 as the amount of the "major conformer" is varied from 30% to 95%. Even though one must always be concerned with the effect of preferred orientation upon intensities for a powder sample, this calculation is encouraging for the possibility of using powder diffraction as a monitor for disorder in a material intended for pharmaceutical, or other use.

Salicylsalicylic acid crystallizes in Fdd2, an acentric space group, even though the molecule itself is not chiral.[25,26] This compound, as other salicyl esters, also exhibits strong triboluminescence. It is also disordered in the solid. The exact crystallization conditions for this compound can lead to solid material with a broad range of physical behavior. The variability in physical properties of this material may be tied to disorder in the crystalline material and may be a function of the amount of disorder found in the bulk sample.

D. Characterization of Pharmaceutical Solids

In this section the characterization of pharmaceutical solids will be briefly reviewed. This section is intended to provide the reader with a picture of the structure and properties of the various solid forms of pharmaceuticals.

The clearest indication of the existence of polymorphs and solvates comes from X-ray crystallographic examination of single crystals of various samples that are known to have the same composition but which may be suspected of being polymorphic. If single crystals of these materials have different unit-cell parameters then they may be polymorphs. Often, however, X-ray powder diffraction is sufficient to establish the existence of polymorphs. Thus polymorphs can be uniquely identified by their X-ray powder diffraction pattern and their structure completely elucidated by single-crystal X-ray diffraction.

(28) Paul, I. C.; Curtin, D. Y. *Acc. Chem. Res.* **1973**, *7*, 223.

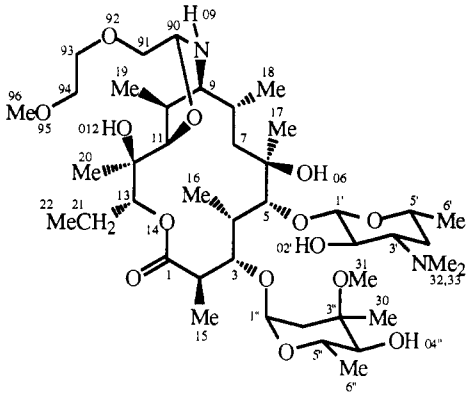
Knowledge of the polymorphs, solvates, and habits in which a drug crystallizes can lead to a dramatic improvement in understanding the stability, bioavailability, and ease of processing of pharmaceutical solids.

1. Infrared Spectroscopy of Solids. Infrared spectroscopy is quite useful for the analysis of solids, because it can be performed on small amounts of the solid substance. The method involves grinding the sample and measuring its infrared spectrum in one of several types of cells available. Infrared spectra of solids can also be obtained after suspending the sample in Nujol or grinding the sample with KBr and compressing this mixture into a disc. FT-IR microscopy can be used to measure the infrared spectrum of a single crystal or group of crystals. If care is taken to study only crystals of the same morphology, this method minimizes the possibility of obtaining infrared spectra of mixtures of crystal forms which is a distinct advantage over approaches that use powdered samples.

The infrared spectrum is extremely sensitive to the structure and conformation of a compound and, thus, can be used to compare the structure and conformation of the compound in different solids or in solid and solution. Infrared spectroscopy is thus a powerful method for the determination of polymorphs.

Cholerton et al.[29] reported the use of infrared spectroscopy to differentiate form 1 and form 2 of ranitidine hydrochloride (Figure 3). This is a classic example of the power of infrared analysis in polymorph studies.

Infrared spectroscopy is also useful for the investigation of solvates, as demonstrated by a study of erythromycin derivative (I).[30] Figure 4 shows the spectra of forms I and



II and the amorphous form of this compound. Clearly these three forms have different spectra especially in the carbonyl region. Note that form I shows two carbonyl absorptions, whereas the amorphous form and form II show only a single carbonyl absorption. Figure 5 shows the infrared spectra of three of the many solvates of this erythromycin derivative. These spectra are fairly similar except for the obvious C≡N stretching absorption in the acetonitrile·$3H_2O$ solvate. There are also slight differences among these three solvates in the fingerprint region. Figure 6 shows the infrared spectra of six solvates which are isomorphous (have the same crystallographic unit cell). These spectra are fairly similar as might be expected since they crystallize in the same unit cell. In cases where the solvents contain keto groups (e and f) the ketone absorption is obvious as a second carbonyl absorption in the spectrum.

(29) Cholerton, T. *J. Chem. Soc., Perkin Trans 2* **1984**, 1761.
(30) Stephenson, G. Unpublished observations, 1993.

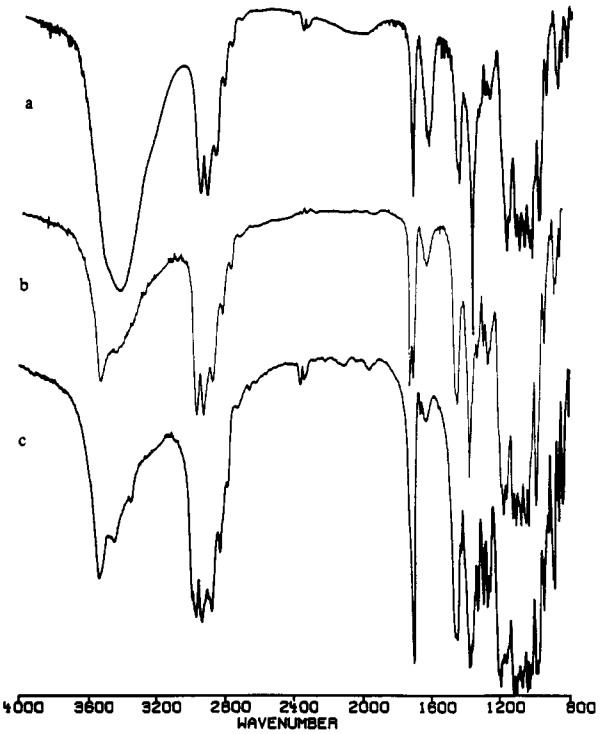


Figure 4. Infrared spectra of the amorphous form (a) and two anhydrous forms, I and II, (b and c) of an erythromycin derivative.[30]

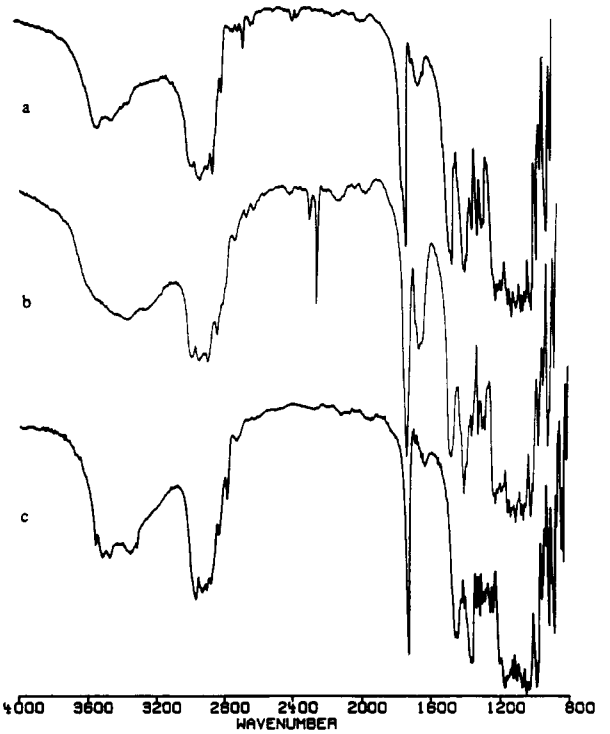


Figure 5. Infrared spectra of three nonisomorphic solvates of an erythromycin derivative: (a) tricyclohexane, (b) acetonitrile·$3H_2O$, and (c) *tert*-butyl alcohol solvate.[30]

Figure 7 shows an enlarged view of the ester carbonyl region of the spectrum in three of the crystal forms of the erythromycin derivative. These spectra suggest that the *n*-propanol solvate contains non-hydrogen-bonded carbonyl groups, that form II contains hydrogen-bonded carbonyl groups, and that form I contains both hydrogen-bonded and non-hydrogen-bonded carbonyl groups. These suggestions have been confirmed by the crystal structures

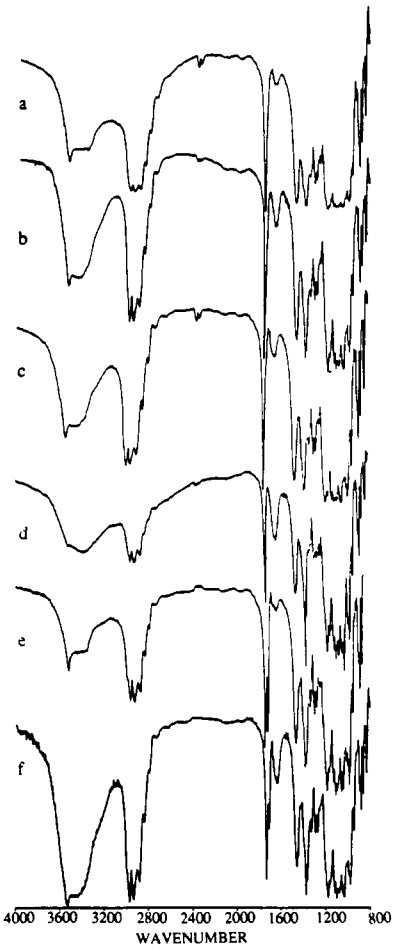


Figure 6. Infrared spectra of the isomorphic solvates of an erythromycin derivative: (a) ethanol, (b) *n*-propanol, (c) isopropyl alcohol, (d) *n*-butanol, (e) acetone, (f) methyl ethyl ketone.[30]

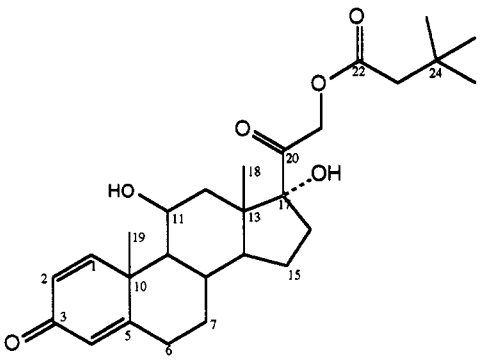
of the *n*-propanol solvate and hydrogen-bonded form II. Unfortunately, the crystal structure of form I could not be determined. Solid-state NMR confirms these suggestions as shown in Figure 8. Again, form I, which shows two carbonyl stretching vibrations in the IR also shows two carbonyl resonances in the solid-state NMR spectrum and the hydrogen bonded form shows a shift to lower field as expected based on model studies (see below).

2. Solid-State NMR Spectroscopy of Pharmaceutical Solids. Solid-state ^{13}C CP/MAS NMR offers significant advantages for the study of solid drugs.[31,32] Figure 9 shows the solid-state ^{13}C NMR spectra of two crystal forms of prednisolone and shows that they can be differentiated on the basis of differences in these spectra. Apparently changing the crystal packing results in significantly different magnetic environments for some of the carbon nuclei. This observation has considerable practical value: Figure 10 shows the ^{13}C CP/MAS NMR spectra of three prednisolone tablets from different vendors. It is clear that one can still observe resonances due to prednisolone, although these tablets contain only 5 mg of prednisolone in 95 mg of excipients. Comparison of Figures 9 and 10 shows that in tablets A and B form I exists, whereas in tablet C form II exists.

(31) Saindon, P. A.; Cauchon, N. S.; Sutton, P. A.; Chang, C. J.; Peck, G.; Byrn, S. R. *Pharm. Res.* **1993**, *10*, 197.
(32) Byrn, S. R.; Sutton, P. A.; Tobias, B. *J. Am. Chem. Soc.* **1988**, *110*, 1609–14.

Other reports show that different polymorphs of cellulose show different ^{13}C CP/MAS NMR spectra.[33] Moreover, solid-state ^{13}C CP/MAS NMR spectroscopy also offers the possibility of the analysis and characterization of amorphous forms. A particularly important question in this area is, What is the mobility of the molecule in amorphous forms? This question can be addressed by comparing the T_1 relaxation times of carbon atoms in the crystalline and amorphous state. In addition, the technique can be used to examine conformational and dynamic changes which occur in solid drugs by determining the coalescence temperature and associated rate constants for the process. In addition, because the time-scale of solid-state NMR spectroscopy is much shorter than X-ray crystallography, it offers the potential for analysis of a range of dynamic processes which cannot be studied by X-ray crystallography. These facts could lead to the widespread use of solid-state NMR spectroscopy in the pharmaceutical industry.

In our laboratory, we have used solid-state NMR to study the different crystal forms of prednisolone *tert*-butylacetate.[32] These studies show that the different crystal forms of prednisolone *tert*-butylacetate have different



Prednisolone 21-*tert*-butylacetate

solid-state NMR spectra. This is no doubt due to different crystal packing. Even forms I and II which have very similar unit cells have slightly different chemical shifts. However, the biggest difference between forms I and II is the position of the solvent peaks. In form I the ethanol solvent shows resonances at 18.1 and 58.2 ppm; in form II the propanol solvent shows resonances at 26.3 and 64.3 ppm. The solid-state NMR spectra of forms III, IV, and V are much different from those of form I and II and from each other. The biggest difference involves carbon 1 which shows chemical shifts which differ by up to 8 ppm from each other in the different crystal forms. Several of the other carbon atoms also show fairly large chemical shift differences. Figure 11 shows a plot of the difference between the solid state and solution chemical shift of carbon 1 vs the hydrogen-bond distance to the O3 carbonyl oxygen which is part of the α,β-unsaturated ketone system which contains carbon 1. It is important to note that this hydrogen bond to O3 is intermolecular and one of the forces responsible for holding the crystals of this steroid together. As can be seen from this plot (Figure 11), there is a more or less gradual shift to larger changes in ppm as the hydrogen-bond distance gets shorter and shorter. This observation is consistent with other studies of hydrogen bonding and also with solution studies

(33) Atalla, R. H.; Gast, J. C.; Sindorf, D. W.; Bartuska, V. J.; Maciel, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 3249.

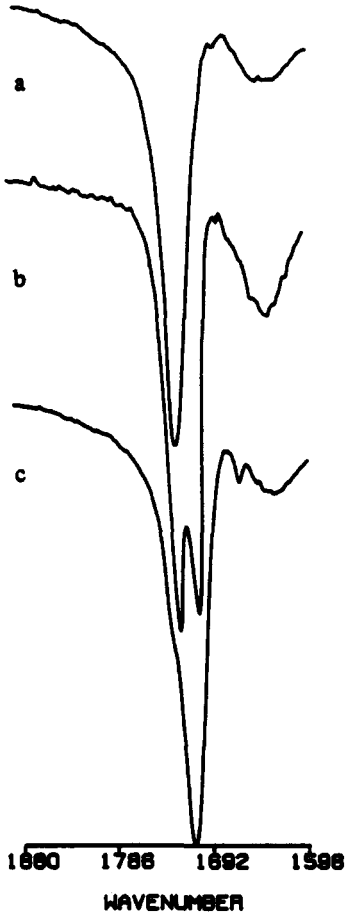
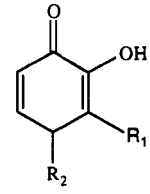


Figure 7. Ester carbonyl region of the *n*-propanol solvate (a), form I (b), and form II (c).[30]

where the stronger the hydrogen bonding the greater the chemical shift changes in ppm.

This type of correlation for different polymorphs and solvates shown in Figure 11 may also apply to members of a series of closely related compounds. Figure 12 shows that the $^{13}C(4)$ chemical shift difference between solid state and solution is a negative linear function of the crystallographic O(4)···O hydrogen bond distance in the crystal structures of a series of 1,2-dialkyl-3-hydroxy-4-pyridones (DAHPs) whose molecular structures are shown below:[34]



EMHP	$R_1 = CH_3$	$R_2 = C_2H_5$
PMHP	$R_1 = CH_3$	$R_2 = C_3H_7$
BMHP	$R_1 = CH_3$	$R_2 = C_4H_9$
MEHP	$R_1 = C_2H_5$	$R_2 = CH_3$
DEHP	$R_1 = C_2H_5$	$R_2 = C_2H_5$
EMHP	$R_1 = C_2H_5$	$R_2 = C_3H_7$

The DHAPs are iron chelators some of which may be promising drugs for oral administration in the treatment of diseases associated with iron overload. Although the crystal structure of the compound BMHP could not be determined, this compound provided an excellent ^{13}C NMR spectrum. The measured $^{13}C(4)$ chemical shift of BMHP might enable the O(4)···O hydrogen bond distance to be predicted using Figure 12, if this correlation is generally applicable.

(34) Ghosh, S. Ph.D. Thesis, University of Minnesota, 1993.

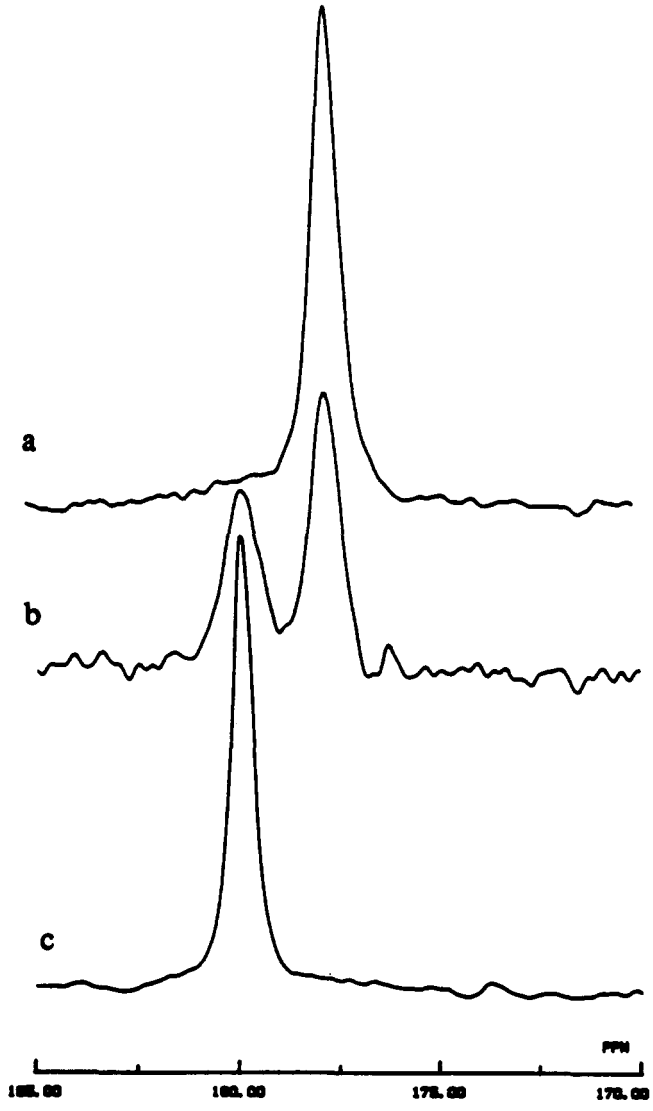


Figure 8. Solid-state NMR spectra of the ester carbonyl carbon: (a) *n*-propanol solvate, (b) form I, and (c) hydrogen-bonded form II.[30]

Solid-state NMR is also useful for the study of mobility in solids. The rate of relaxation of the carbon spins toward equilibrium is characterized by the spin lattice relaxation time, T_1.[35] In this process the excess energy from the spin system is transferred to "the lattice". Interactions of randomly fluctuating magnetic fields at the Larmor frequency of the nucleus stimulate these transitions. Such fields arise from motions of other nuclear magnetic moments such as protons. Spin–lattice relaxation is thus most efficient when these motions are near the Larmor frequency of the nucleus being observed. Studies of relaxation times can give valuable information about fast motions in the megahertz range such as methyl group rotations. Numerous studies of molecular motion using

(35) Fukushima, E.; Roeder, S. B. W. *Experimental Pulse NMR*; AddisonWesley: Reading, MA, 1988.

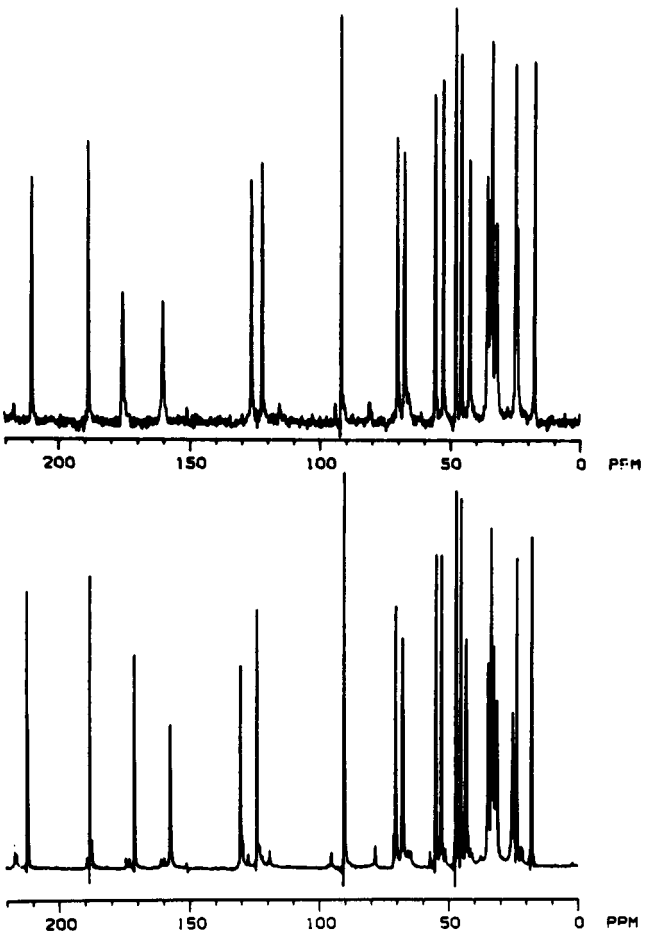


Figure 9. Solid-state ^{13}C CP/MAS NMR spectra of two polymorphs of prednisolone.[31] The top spectrum is form 1 and the bottom spectrum is form 2.

relaxation times have been published.[36] In particular, applications in the field of polymer science have been widespread. For example, solid-state NMR has been used to study both main chain and side group motion in polymers.[37-40] In addition, studies have been made of the relationship between polymer crystallinity and relaxation parameters including T_1, $T_{1\rho}$, and T_2.[41-43]

The mobility of functional groups in solids has been of interest for many years. An understanding of this mobility can lead to insight into the mobility of molecules, the forces responsible for conformational interconversions, and the factors responsible for solid-state reactions. In 1973, Paul and Curtin[28] suggested that molecular loosening or molecular mobility is the first step in a solid-state reaction, and, in our laboratory, we have suggested that solid-state

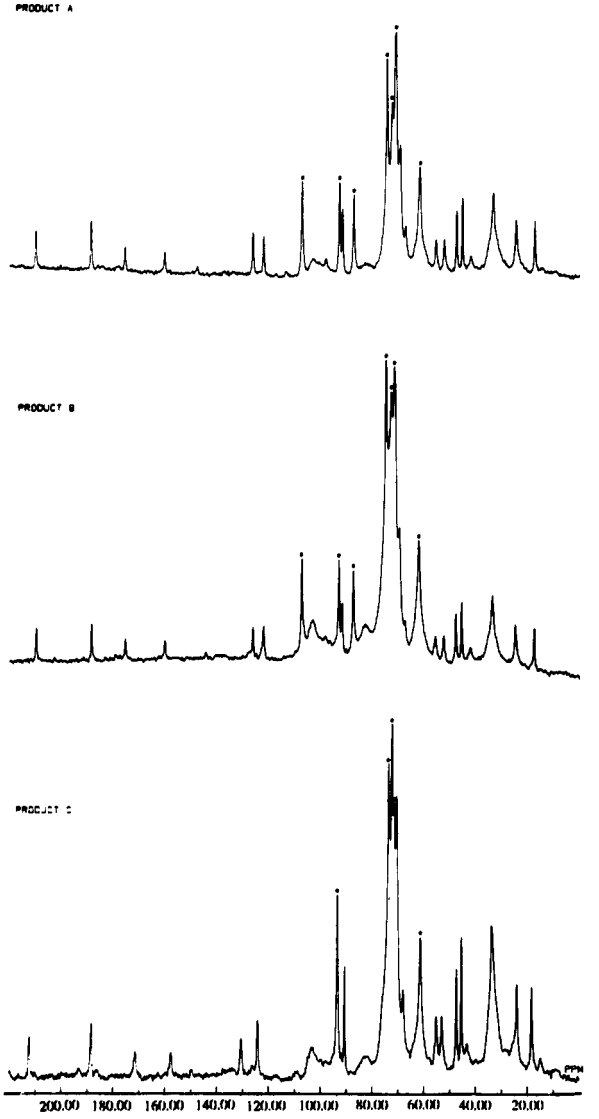


Figure 10. Solid-state ^{13}C CP/MAS NMR spectra of prednisolone tablets from three different vendors.[31]

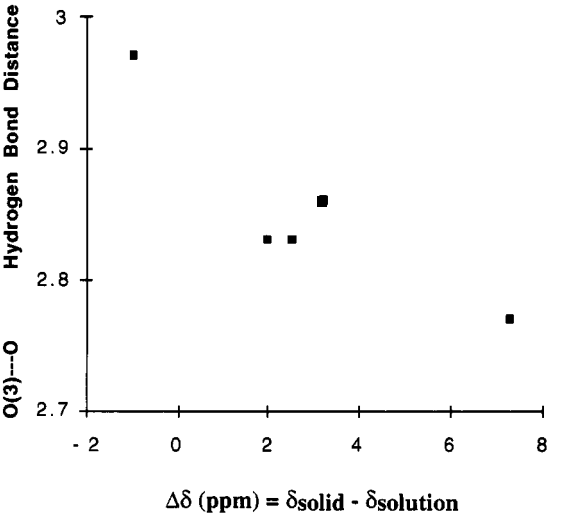


Figure 11. Plot of the difference in chemical shift for carbon 1 between the solid state and solution and the O(3)···O hydrogen bond distance.[32]

degradations of pharmaceuticals are related to molecular mobility.[32,44,45] In addition, Zografi has suggested that water absorption enhances the molecular mobility of amorphous pharmaceutical solids, perhaps explaining the

(36) Fyfe, C. A. *Solid-state NMR for chemists*; CFC Press: Toronto, Ontario, 1983.
(37) Lyerla, J. R. *Contemporary Topics in Polymer Science*; Shen, M., Ed.; Plenum Press: New York, 1979; Vol. 3, pp 143–213.
(38) Garroway, A. N.; Moniz, W. B.; Resing, H. A. In *Carbon-13 NMR in Polymer Science*; Pasika, W. M., Ed.; American Chemical Society: Washington, DC, 1979; pp 67–86.
(39) Tonelli, A. E.; G., M. A.; Tanaka, H.; Schilling, F. C.; Cozine, M. H.; Lovinger, A. J.; Bovey, F. A. *ACS Adv. Chem. Ser.*; Craver, C. D., Provder, T., Eds.; American Chemical Society: Washington, DC, 1990; Vol. 227, pp 409–451.
(40) Axelson, D. E. *Carbon-13 NMR in Polymer Science*; Pasika, W. M., Ed.; American Chemical Society: Washington, DC, 1979; pp 181–214.
(41) Menger, E. M.; Veeman, W. S.; de Boer, E. *Macromolecules* **1982**, *15*, 1406.
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(43) Earl, W. L.; VanderHart, D. L. *Macromolecules* **1979**, *12*, 762.

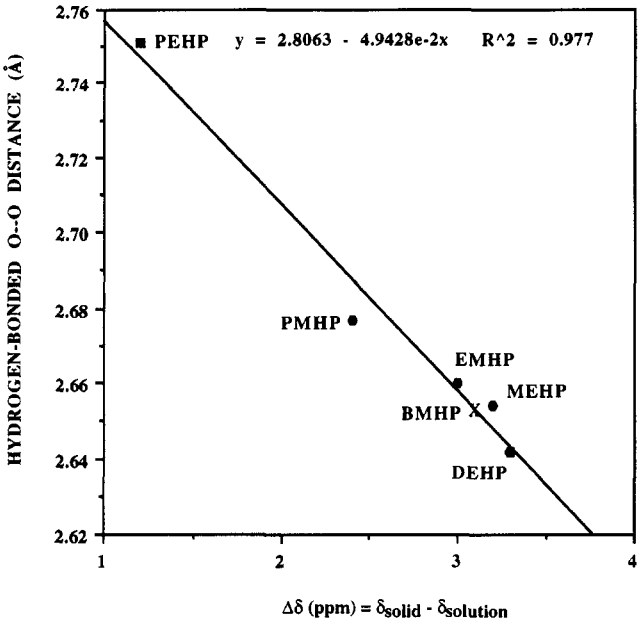


Figure 12. Plot of the hydrogen bonded O···O distances against the differences ($\Delta\delta$) between the ^{13}C chemical shifts of the pyridone carbonyl (O4) and the solid state (δ_{solid}) and the solution state ($\delta_{solution}$) of DAHPs. Although the crystal structure of BMHP is unknown, its hydrogen-bonded O···O distance can be estimated from the plot using the NMR chemical shift data (point X).[34]

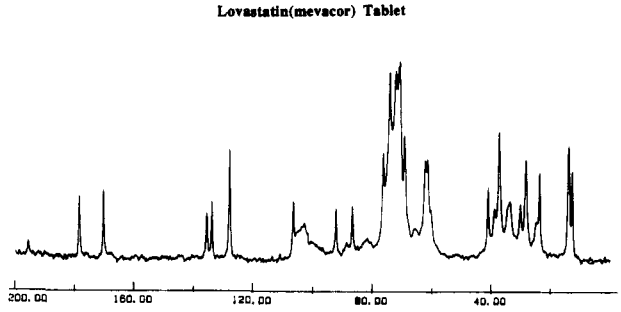
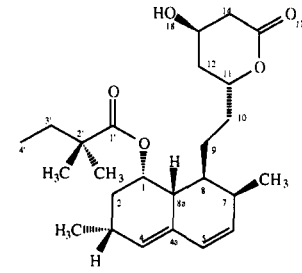


Figure 13. Solid-state CP/MAS NMR spectrum of a lovastatin tablet.

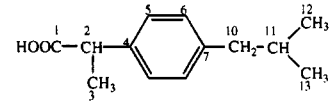
enhanced chemical reactivity of these materials in the presence of water.[46] Further study of the relationship between molecular mobility and solid-state reactivity requires the development of new approaches to determine molecular mobility especially in mixtures such as pharmaceutical dosage forms where single-crystal X-ray methods cannot be used.

Solid-state NMR offers several approaches to studying the molecular mobility of solids. These include (1) determination of the activation energies for T_1 relaxation of individual carbon atoms using variable-temperature solid-state NMR, (2) study of processes which result in peak coalescence of solid-state NMR resonances using variable-temperature solid-state NMR, (3) use of interrupted decoupling to detect methylene and possible methine groups with unusual mobility, and (4) comparison of solid-state MAS spectra measured with and without cross polarization.

Recent research at Purdue University is using all of these approaches but especially the first one to study the relative mobility of methyl groups in a number of drugs which contain multiple methyl groups including simvastatin, lovastatin, ibuprofen, and phenacetin.[47-49] The results of these studies will be published shortly.



Simvastatin



Ibuprofen

In addition, Maverick and Dunitz[50] have suggested that solid-state NMR activation energies and X-ray thermal parameters are related. Therefore, solid-state NMR appears to be a good method for study of the mobility of methyl groups in solids. Because solid-state NMR can be used to study pharmaceutical dosage forms and other mixtures,[31] this powerful method will find increased application in the determination of the molecular mobility of drugs in mixtures and dosage forms.

Surprisingly little research has been done on the solid-state NMR spectra of pharmaceutical dosage forms. To our knowledge, prior to the paper by Saindon et al.,[31] solid-state NMR has been used to study only two tablets both consisting almost entirely of pure drug: aspirin[51,52] and acetaminophen.[53] This paper shows that solid-state NMR is useful for the study of more complex pharmaceutical products.[31]

For example, Figure 13 shows the solid-state NMR spectrum of lovastatin tablets, which contain a rather large excess of excipients. The excipients, which have resonances in the 50–100 ppm range obscure resonances of lovastatin which appear at the same chemical shift but have little effect on resonances at other chemical shifts. Similar results were obtained for tablets of another closely related HMG-CoA reductase inhibitor, simvastatin.

E. Summary

In this review, areas of particular interest to Peggy Etter and her group were discussed including crystallization, hydrogen bonding, solvates and solid-state NMR. It is clear that her pioneering work has tremendously important implications for solid-state pharmaceutical chemistry.

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(45) Byrn, S. R.; Kessler, D. W. *Tetrahedron* **1987**, *43*, 1335–43.
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(47) Cauchon, N. Ph.D. Thesis, Purdue University, 1992.
(48) Saindon, P. Ph.D. Thesis, Purdue University, 1992.
(49) Toma, P. Ph.D. Thesis, Purdue University, 1993.
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(53) Jagannathan, N. R. *Curr. Sci.* **1988**, *56*, 827.