Infrared Attenuated Total Reflectance (ATR) Method for Observing the Water-Mediated Surface Phase Reversion of Methylprednisolone II to I During Dissolution

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Abstract □ The IR attenuated total reflectance spectrophotometric technique has been employed to demonstrate the surface reversion of methylprednisolone Polymorph II to Polymorph I in the presence of water. The process occurs rapidly enough (minutes) to account for the slower than expected dissolution rates of nondisintegrating pellets of Form II in water. The unusual effects of agitation upon the dissolution rate of Form II pellets are also thus explained.

Keyphrases □ Methylprednisolone Polymorph II—surface reversion, Polymorph I □ Polymorphic reversion—methylprednisolone in water □ Solubility—methylprednisolone polymorphs □ Attenuated total reflectance spectrophotometry—polymorph identity

Recently, studies (1–4) were reported describing the dissolution rate behavior of the thermodynamically unstable polymorphs of methylprednisolone and sulfathiazole in various solvents. It was deduced from the amount dissolved *versus* time plots that in certain solvents the higher energy forms of both sulfathiazole and methylprednisolone undergo simultaneous dissolution and reversion to the more stable crystalline modifications. This is consistent with the crystal growth kinetics data (5) and with the idea that simultaneous dissolution and reversion may take place when the crystal growth of the more stable phase occurs relatively rapidly near or below the solution concentration corresponding to the solubility of the higher energy form.

One of the systems of particular interest was methylprednisolone–water. Here (see Fig. 7 of *Reference 3*) the reversion of the unstable modification (II) to the stable one (I) appeared to begin immediately but took place relatively slowly. It was believed (3) that the unusual effects of the rate of medium agitation upon the relative dissolution rates of the two polymorphs were related to this. The data were attributed to a mixture phenomenon and a theory based on such a model was proposed.

It occurred to one of the authors (W.E.H.) that a direct way of following the II → I surface transformation might be provided by the IR spectrophotometric attenuated total reflectance (ATR) technique. It was hoped that the method would firmly establish the postulated mechanism.

This report describes the results of the ATR experiments for the methylprednisolone–water system. The data, consistent with earlier deductions, show that in the same time periods as in the dissolution rate experiments the II → I reversion occurs at the surface when II is in contact with water. These studies also show that the ATR technique may be a powerful, unique tool in investigating similar situations in other systems.

GENERAL CONSIDERATIONS

According to the theory (3), the formation of a relatively thin surface layer of Form I on the surface of a Form II pellet should markedly affect the dissolution rate of the pellet. This is shown by an analysis of the following equation (3):

$$R = \frac{D}{(\tau L/\epsilon) + h} C_s^{II} \qquad \text{(Eq. 1)}$$

Here R is the dissolution rate per unit area of the tablet, D is the diffusion coefficient, h is the effective liquid diffusion layer, L is the thickness of the Form I layer, ϵ and τ are, respectively, the porosity and tortuosity of this layer, and C_s^{II} is the solubility of the Form II phase. From Eq. 1 it can be seen that in the limit when

$$\frac{C_s^{II}}{(\tau L/\epsilon) + h} = \frac{C_s^{II}}{h} \qquad \text{(Eq. 2)}$$

the pellet should dissolve at the same rate as that for a pure Form I pellet. Here the solubility of the Form I phase, C_s^{I}, $\simeq C_s^{II}/1.7$ for methylprednisolone in water. Therefore when $L = (0.7\ \epsilon h)/\tau$ the dissolution rate of an initially pure Form II pellet becomes indistinguishable from a pure Form I pellet.

From the experiments of Higuchi *et al.* (3) $h \simeq 25\ \mu$ for agitation speeds around 150 r.p.m. Reasonable values for ϵ and τ are 0.2–0.8 and 1.5–3, respectively. Therefore L in the neighborhood of 1–10 μ should make a Form II pellet indistinguishable from a Form I pellet.

The existence of such thin layers would be extremely difficult to reproducibly demonstrate by conventional methods (X-ray, IR). Thus after consideration of these other techniques the ATR method was selected, since penetration of the surface by the IR energy to the extent of 5–10 μ was expected.

EXPERIMENTAL

Sample Treatment—Pellets of methylprednisolone Form I and Form II were prepared as before (3) by compressing the pure substances in a Carver press. The die mounted pellets were exposed to water at 37° in the same apparatus as that employed in the dissolution rate studies. A stirrer speed of 50 r.p.m was used in all cases.

At predetermined times the die with the pellet was removed, the pellet surface was lightly contacted with lens tissue to remove the bulk of the liquid on the surface, and then the die was placed immediately in a vacuum desiccator. In all instances it appeared that removal of water from the pellet surfaces by the vacuum was complete in less than 1 min. The pellets were permitted to remain in the desiccator under vacuum overnight then removed from the die, and stored in a desiccator until the ATR experiments were performed.

The ATR spectra were obtained with a double beam multiple internal reflection attachment (Wilks model 12) (7) and a 2-mm. thick internal reflector plate (KRS-5) at a 45° angle of incidence. The exposed surface of the pellet was brought into contact with the reflector plate in the solid sample holder. A drop of mineral oil at the interface of the reflector plate and the pellet surface facilitated good contact. The spectra were recorded with a grating IR spectrophotometer (Perkin-Elmer model 621). Duplicate spectra were obtained.

Powder spectra were also obtained for both polymorphs employing the KBr disk method.

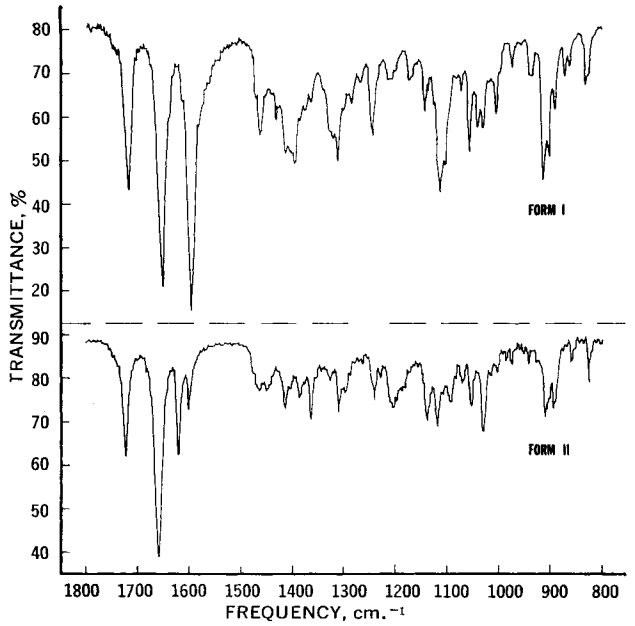

Figure 1—*Powder IR spectra for the two polymorphs of methylprednisolone obtained using the KBr disk method.*

RESULTS AND DISCUSSION

Powder Spectra (KBr Disk)—Figure 1 shows the powder spectra for the two polymorphs obtained by the KBr disk method. These agree with those reported by Bernardo (6). Four frequency regions showing distinct differences between the two polymorphs have been designated A (1580–1750 cm.$^{-1}$), B (1075–1150 cm.$^{-1}$), C (990–1075 cm.$^{-1}$), and D (880–920 cm.$^{-1}$) in Fig. 1.

In Region A Form I shows three strong absorption peaks while Form II shows four distinct peaks with the two small peaks around 1600 cm.$^{-1}$ appearing to be a splitting of the single strong absorption peak at 1600 cm.$^{-1}$ in Form I. In Region B Form II exhibits three peaks of about the same intensity while in Form I a relatively strong absorption at around 1100 cm.$^{-1}$, absent in Form II, overshadows the one at about 1190 cm.$^{-1}$. The differences in Region C between the two polymorphs are obvious but more difficult to describe. The presence of a relatively strong peak at around 1000 cm.$^{-1}$ in Form I that is absent in Form II is the most prominent difference. In Region D Form II shows two peaks of comparable intensity at 890 and 910 cm.$^{-1}$ while Form I shows three peaks at 810, 900, and 910 cm.$^{-1}$ with intensities increasing with increasing frequency.

There are other differences in the powder spectra for the two modifications of methylprednisolone. However, these four regions were selected because, as will be seen, the most systematic changes occur in these regions of the ATR spectra of the Form II pellet surface.

ATR Spectra—Figures 2 and 3 give the ATR spectra obtained from the pellets. Spectra I–IV give the typical results for the Form

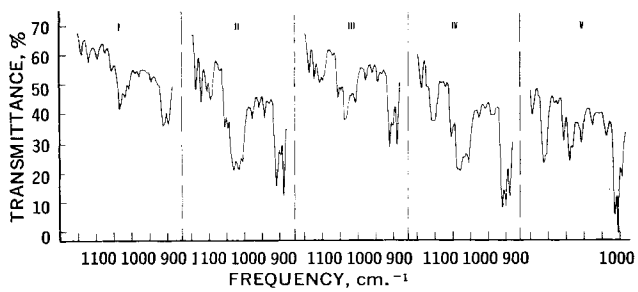

Figure 2—*ATR spectra for the water-exposed surfaces of Form II pellets of methylprednisolone. Spectra I to IV correspond to exposure times of 0, 2, 30, and 120 min., respectively. Spectrum V is that for a Form I pellet surface.*

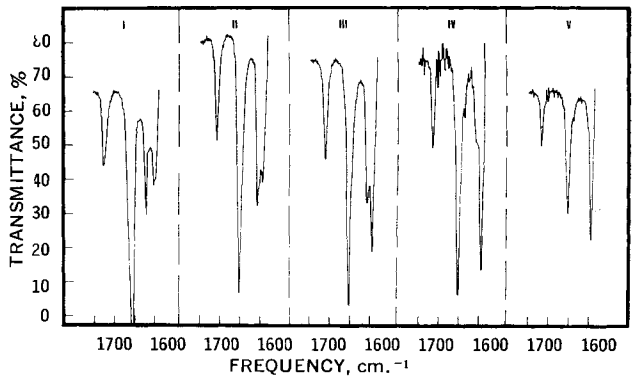

Figure 3—*ATR spectra for the water-exposed surfaces of Form II pellets of methylprednisolone. Spectra I to IV correspond to exposure times of 0, 2, 30, and 120 min., respectively. Spectrum V is that for a Form I pellet surface.*

II pellets exposed 0, 2, 30, and 120 min. to water, respectively. Spectrum V gives that for the Form I pellet surface. Most of the results obtained for the Form II pellets exposed up to 30 min. in water were reproducible. Variations in results obtained for longer ($\gtrsim$ 120 min.) exposure time were greater.

First note that a comparison of Spectra I and V of Figs. 2 and 3 and those for the powder (Fig. 1) shows the good agreement of the major absorption characteristics in the four regions A, B, C, and D. Except for some expected distortion in the ATR spectra, I in Figs. 2 and 3 agrees well with the powder spectra for Form II, particularly in Regions A, B, and D. Also V of Figs. 2 and 3 agrees well with the Form I powder spectra in all regions. The intermediate spectra, II, III, and IV—corresponding to increasing water exposure times, show increasing Form I character in all frequency regions. Even for the 2-min. exposure (Spectrum II), there appears to be significant Form I character. This shows that appreciable conversion of Form II to Form I occurred even in this short time period. In 30 min. (Spectrum III) the amount of the Form II → Form I conversion appears to be quite extensive.

In order to eliminate the possibility that appreciable crystallization of Form I occurred during the vacuum drying of the pellet surface, ATR experiments were carried with pellets that were not dried. While the spectra in these instances were not always as well defined, the Form I characteristics were found in all experiments in good agreement with the above findings.

While these results can be interpreted only semiquantitatively, there is little question that the transformation has occurred in the period of minutes. These results, therefore, support the conclusions based on the dissolution rate data (Fig. 7 of *Reference 3*) and the theory postulated for the unusual behavior of this system.

REFERENCES

(1) W. E. Hamlin, E. Nelson, B. E. Ballard, and J. G. Wagner, *J. Pharm. Sci.*, **51**, 432(1962).

(2) G. Levy and J. A. Procknal, *ibid.*, **53**, 656(1964).

(3) W. I. Higuchi, P. D. Bernardo, and S. C. Mehta, *ibid.*, **56**, 200(1967).

(4) G. Milosovich, *ibid.*, **53**, 484(1964).

(5) P. D. Bernardo, W. I. Higuchi, and S. C. Mehta, to be published.

(6) P. D. Bernardo, Ph.D. thesis, University of Michigan, 1966.

(7) M. R. Iszard and P. A. Wilks, Wilks Scientific Corp., South Norwalk, Conn.; paper presented at the 148th National ACS Meetings Symposium on New Instruments and Techniques for Studying Surfaces, Chicago, September 3, 1964.

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