DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(8), 1543-1563 (1985)

POLYMORPHISM OF FOSTEDIL: CHRACTERIZATION AND POLYMOPHIC CHANGE BY MECHANICAL TREATMENTS

Yoshiteru Takahashi, Kazuko Nakashima, Toshihiro Ishihara, Hiroshi Nakagawa, and Isao Sugimoto

Pharmaceuticals Research Center, Kanebo, Ltd, 1-5-90 Tomobuchi-cho, Miyakojima-ku, Osaka, 534, Japan

ABSTRACT

Two crystal forms of fostedil were characterized using X-ray diffraction patterns and infrared spectra. The melting points of polymorph I and II were 95.3 °C and 96.4 °C, respectively.

Solubility studies demonstrated that, of the two fostedil polymorphs, form II was slightly more soluble than form I. The free energy difference between two polymorphs was small (71.8 cal/mol at 37 °C). Both crystals melted at about 60 °C in water considerably below the melting points.

0363-9045/85/1108-1543$3.50/0

Compression of form II at a compression force of 500 - 1000 kg/cm^2 induced polymorphic changes in the crystal. Similar changes also were produced through grinding. The effects of some diluents on the polymorphic transformation from form II into form I by grinding were also studied. Microcrystalline cellulose and corn starch showed a polymorphic transfomation-accelerating effects.

Form I is more suitable for the pharmaceutical preparation.

INTRODUCTION

Fostedil (Diethyl 4-(benzothiazol-2-yl) benzyl-phosphonate) is a new calcium antagonist and exerts marked coronary vasodilator and hypotensive actions.[1)] Fig. 1 shows its chemical structure. Many organic compounds can exist in different polymorphic forms and the chois of proper polymorphs will determine whether a pharmaceutical preparation will be chemically or physically stable, or give an appropriate blood level to produce the correct pharmacological response. So, a very important phase of preformulation is determining the crystal forms and polymorph stability of drug substances. In the preformulation study of fostedil, the polymorphic change by grinding was found and two crystal forms (form

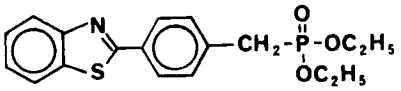

FIGURE 1

Chemical Structure of Fostedil

I and II) were confirmed. It is assumed that crystal transition resulting from milling, granulation, drying, and compressing operations produce changes in the physical and biological characteristics of the dosage forms. So, the present report is concerned with studies carried out to determine the differences in some physico-chemical properties between two crystal forms, and to evaluate the stability against the mechanical treatments of them. And the objective of this study was to characterize fostedil crystals as an aid to trouble-free processing and optimum formulation of dosages.

EXPERIMENTAL

Preparation of Fostedil Crystals —— Form I: Fostedil (10 g) was dissolved in warm ethyl acetate (25 ml) and allowed to recrystallize at 30 °C.

Form II: Fostedil (10 g) was dissolved in warm cyclohexane (100 ml) and allowed to recrystallize at room temperature.

The crystals were filtered off and then dried under vacuum at 60 °C for 3 h.

Polymorph Characterization —— X-ray diffraction: X-ray diffraction patterns were obtained with a Geigerflex 2027 diffractometer (Rigaku Denki Co., LtD.). The measurement conditions were as follows; target Cu, filter Ni, voltage 25 kV, and current 10 mA.

IR spectra: IR spectra were recorded on a Hitachi Perkin-Elmer model 225 grating infrared spectrophotometer (Hitachi Ltd.). Initially, IR spectra were measured by means of KBr disk. However, the spectrum of Form II was partly converted into that of form I, because grinding and compression of form II induced polymorphic change. So, Nujol mull technique and attenuated total reflectance, of which stresses applied to the crystal form were thought to be minimum, were employed. These two spectra fundamentally coincided with each other.

Thermal analysis: The DTA profiles and TG curves were recorded on a Shimadzu thermal analyser DT-20B and TG-20 (Shimadzu Seisakusho Ltd.), respectively, at a heating rate of 10 °C/min. The thermal behavior was studied at a nitrogen gas flow of 30 ml/min.

Solubility Studies —— An excess of 100 - 120 mesh fostedil(1 g) was added to 1 liter of water in a cylindrical vessel with round bottom at 20, 25, 30, 37, 45, and 50 °C. The system was stirred with a

stainless paddle at 150 rpm. At specific intervals, 5 ml of the solution was withdrawn, filtered through a membrane filter (Nuclepore, 1.0 μm), and diluted for spectrophotomic assay at 302 nm.

Grinding and Compression —— Grinding: Fostedil (15 g) was ground in an automated mortar (Type No.16, Ishikawa Kojyo Co., Ltd.). Samples (1 g) were taken out at appropriate intervals (15 min, 30 min, 1 h, 1.5 h, 2 h). Mixtures of fostedil and diluents were ground as same way. Microcrystalline cellulose (JP X) and corn starch (JP X) were used as diluents. Fluid-energy mill (Turbo Counter Jet Mill, model TJ60, Turbo Kogyo Co., Ltd.) and hammer mill (Sample Mill, model KIIW-1, Fuji Powder Co., Ltd) were also used to mill fostedil and mixtures. The operating conditions of fluid-energy mill were as follows: both feed and counter air pressures were 7.5 kg/cm^2. Those of hammer mill were as follows: screen size was 0.5 mm and screen thick was 0.5 mm.

Compression: Fostedil was passed through a 100 mesh screen. One g of the crystal was compressed into a disk in a 16 mm of a diameter stainless steel tablet die at 250, 500, 750, and 1000 kg/cm^2 using an Instron test instrument Model 1115 (Instron Co., Ltd.). The X-ray diffraction patterns of the surface of tablets were measured.

Effects of Temperature and Humidity on the Polymorphic Transformation of Milled Form II of Fostedil——The milled sample (0.4 g) was weighed into a weighing bottle. The weighing bottles were kept in a desiccator adjusted to 0 % relative humidity (R.H.) at various temperatures (20, 40, 50 °C) and 80 % R.H. at 40 °C. Phosphorus pentoxide was used for 0 % R.H.

RESULTS AND DISCUSSION

Characterization of Polymorphs of Fostedil

Fig. 2. shows the X-ray diffraction patterns of the two crystal forms of fostedil. The IR spectra for fostedil forms determined in Nujol mull are illustrated in Fig. 3. The differences observed in the X-ray diffraction patterns and IR spectra are sufficiently distinct to characterize the two crystal forms. In X-ray diffraction pattern of form I, specific diffraction peaks were observed at 2θ = 14.5°, 18.0°, and elsewhere. While, those of form II were observed at 2θ = 8.0°, 16.3°, and elsewhere. In IR spectra, the bands around 1250 cm^{-1} assignable to the P=O stretching vibration were observed at 1260 cm^{-1} and 1240 cm^{-1} in form I and II, respectively. The shift of band was also observed around 770 cm^{-1}. The spectrum patterns of P-O-C stretching around 960 cm^{-1}

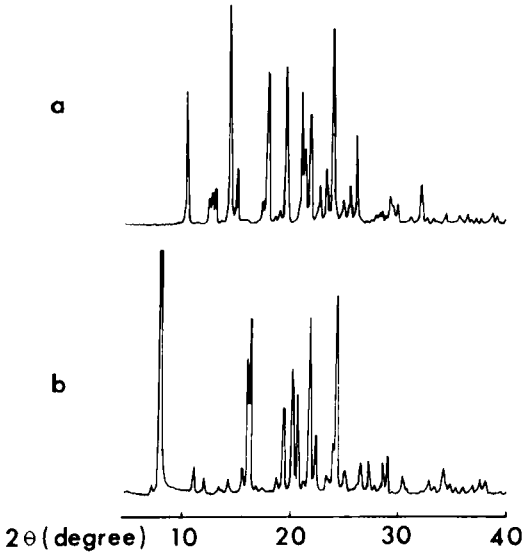

FIGURE 2

X-ray Diffraction Patterns of Fostedil Polymorphs
a, form I; b, form II.

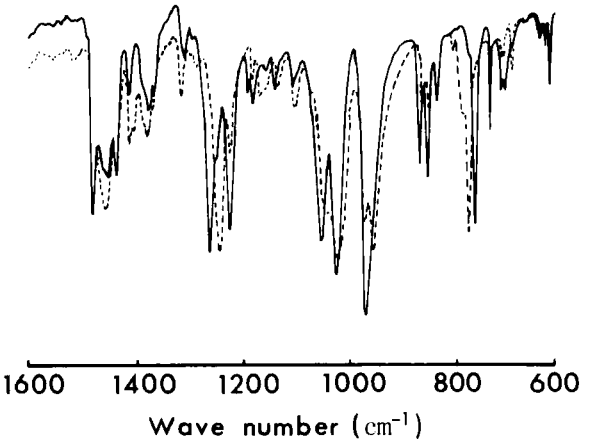

FIGURE 3

Infrared Spectra of Fostedil Polymorphs
——, form I; ----, form II.

were different from each other. These differences may be caused by the difference of P-O-C tortional angle.

The TG and DTA profiles of two crystal forms were depicted in Fig. 4. The thermogravimetric curves show that under the experimental condition of the heating rate of 10 °C/min, the decomposition with weight loss starts at about 200 °C. The endotherms of the DTA profiles represent melting of two crystalline modifications and melting points were 92 °C for form I and 93 °C for form II, respectively. At a heating rate of 1 °C/min, melting points of 95.3 and 96.4 °C were obtained for form I and II, respectively by the capillary tube method. The difference of melting points between two polymorphs was very small.

Solubility Behavior

The solubilities and dissolution behaviors of form I and II at 20, 25, 30, 37, 45, and 50 °C are shown in Fig. 5. The solubility of form II was slightly higher than that of form I. Although the crystal transition from form II to form I in solubility experiment was observed from X-ray diffraction patterns of the samples after the experiment, the degree of transition was small. As shown in Fig. 5, the rate of transition was slow and metastable form II did not undergo a rapid reversion to stable form I in water.

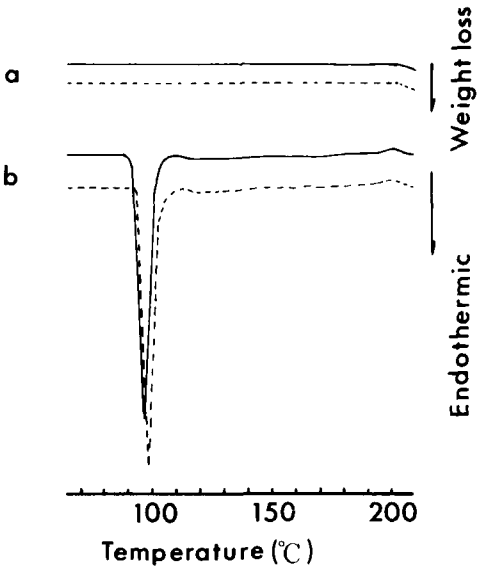

FIGURE 4

TG and DTA Curves of Fostedil Polymorphs Recorded at a Heating Rate of 10 °C/min
——, form I; ----, form II:
a, TG; b, DTA.

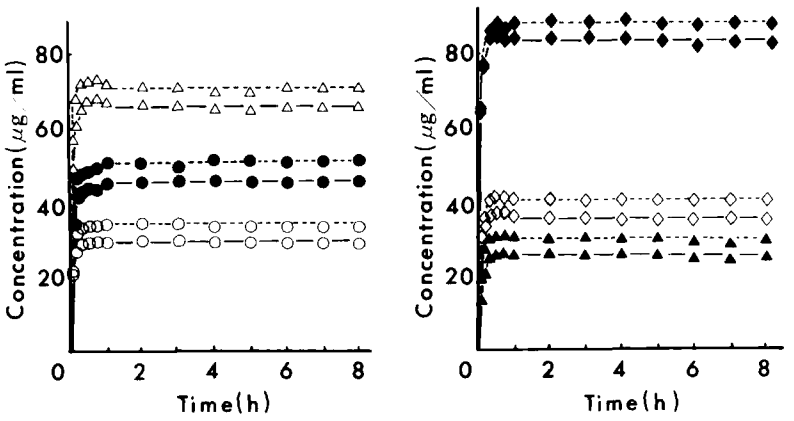

FIGURE 5

Solubility Curves of Fostedil Polymorphs In Water at Various Temperatures
——, form I; ----, form II
◆, 50 °C; △, 45 °C; ●, 37 °C; ◇, 30 °C; ○, 25 °C; ▲, 20 °C.

The apparent solubilities of form I and II determined at various temperatures were plotted according to the van't Hoff plot. As shown in Fig. 6, the value of the solubility cannot be allied to one straight line. When heatig further, both crystal forms melted in water at 58 - 61 °C, which was considerably below the melting points and coincided with the intersection point (60.9 °C) in van't Hoff plots. This phenomenon suggests that there would be an appreciable interaction between fostedil and water molecules. After cooling, those melted samples were filtered off and X-ray diffraction patterns were measured. A mixture of form I and II crystal was obtained and no other polymorphs or hydrate crystals could not be found. It is clear that the difference in thermodynamic properties between form I and II is small. The free energy differences determined from solubility between two polymorphs were only 71.8 cal/mol at 37 °C and 83.6 cal/mol at 30 °C. Aguiar et al.[2] suggested that large difference in free energy content of chloramphenicol palmitate polymorphs (ΔG_{303} = -774 cal/mol) might affect significantly the absorption, and that a small difference as was seen with mefenamic acid (ΔG_{303} = - 251 cal/mol) did not appear to affect the absorbability of the drug. Therefore, almost no difference in absorption would be expected between two polymorphs.

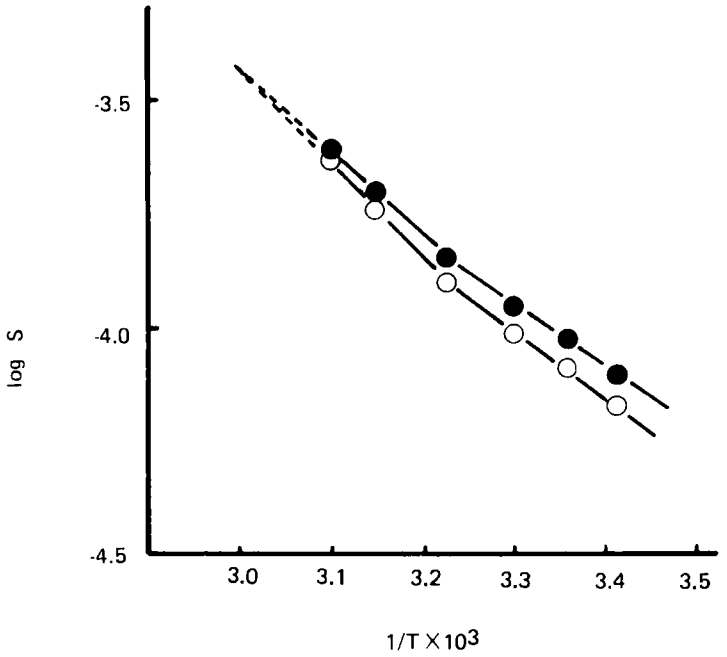

FIGURE 6

Van't Hoff Plots for Forms I and II of Fostedil S, solubility; ○, form I; ●, form II.

Polymorphic Transformation by Mechanical Treatments

Polymorphic transformation by mechanical treatments, such as grinding and compression, occur in some medicinal compounds.[3] Their pharmaceutical importance depends on the rapidity of transition to thermodynamically stable form, and the nature of their altered physical properties. So, the polymorphic stability of fostedil against mechanical treatments was studied.

In the X-ray diffraction patterns of the ground and compressed samples of form II, the diffraction

intensities for form II at 8.0° and 16.3° of 2θ decreased, while the intensities at 14.5°, and 18.0° of 2θ increased. It was shown that form II was transformed into form I by grinding and compression. There are some reports[4] that the degree of polymorphic transformation was determined from the ratio of the intensity of the diffraction lines. However, in this case, the effect of orientation of the crystals on the X-ray diffraction intensities measured by means of the powder method was large, because the form II crystal was a thin plate crystal, and micronization of form II crystal induced polymorphic transformation. So, the calibration curve to determine the degree of polymorphic transformation could not be obtained. Then, the percentage of form II in the crystal part was determined by the modified method of Hermans,[5] which was applied to determine the degree of crystallinity without the calibration curve. The relationship between the mass and the diffraction intensities of characteristic diffraction peaks of form I and II are assumed to be given by the following equations respectively,

$$\text{form I} \qquad M_I = k_I I_I \qquad (1)$$

$$\text{form II} \qquad M_{II} = k_{II} I_{II} \qquad (2)$$

where M is mass of the crystalline; k is constant; and diffraction intensity is denoted I. Sum of M_I and M_{II}

is equal to total crystalline mass M,

$$M_I + M_{II} = M \qquad (3)$$

From above, the following relationship can be given,

$$I_{II} = - (k_I/k_{II})\ I_I + M/k_{II} \qquad (4)$$

And the percent form II is also given by,

$$\% \text{ form II} = (M_{II}/M) \times 100$$

$$= [I_{II}/\{I_{II} + (k_I/k_{II})\ I_I\}] \times 100 \qquad (5)$$

Eqation (4) shows the linear relationship between I_I and I_{II}. Fig. 7 shows the plots of equation (4) in case of the ground sample. Good linearity was obtained and the value of k_I/k_{II} was given by gradient. I_I was determined by the diffraction peaks at $2\theta = 14.5°$ and 18.0°, and I_{II} was done by those at $2\theta = 8.0°$ and 16.3°. Fig. 8 shows the effect of grinding on the polymorphic transformation of form II. Crystalline form II was easily transformed into form I by grinding. Nakai et.al.[6] reported the ground mixture of drug and microcrystalline cellulose and stated that the crystalline form was transformed into the amorphous form. Then, the effect of adding diluents were also studied. Fig. 9 and 10 show the effects of adding microcrystalline cellulose or corn starch on the polymorphic transformation of form II by grinding. Diluents showed an accelerate effect on polymorphic transfomation from form II into form I, especially at the initial phase of grinding. The accelerating effect became larger as the

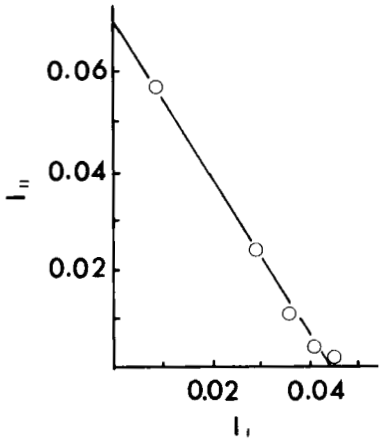

FIGURE 7

Relationship between I_I and I_{II}

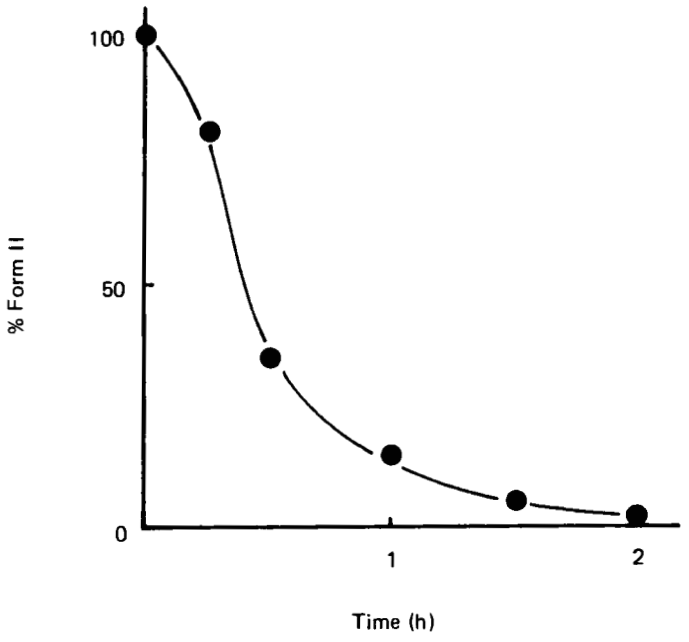

FIGURE 8

Effect of Grinding on the Polymorphic Transformation of Form II of Fostedil

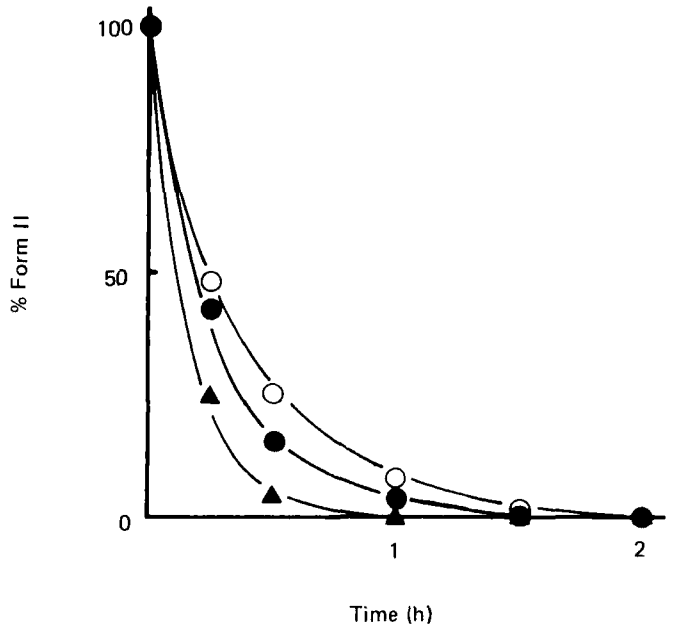

FIGURE 9

Effect of Microcrystalline Cellulose (MCC) on the Polymorphic Transformation of Form II of Fostedil by Grinding
▲, fostedil-MCC (1:3); ●, fostedil-MCC (1:1); ○, fostedil-MCC (3:1).

amount of diluent increased, and the effect of microcrystalline cellulose was larger than corn starch. Table I also shows the effects of them on the transition in the case of milling using fluid-energy mill and hammer mill. The effect of the milling of hammer mill on the crystal transition was little.

Fig, 11 and 12 show the time course of polymorphic transformation of fluid-energy milled and hammer milled sample against temperature and humidity. Fluid-energy

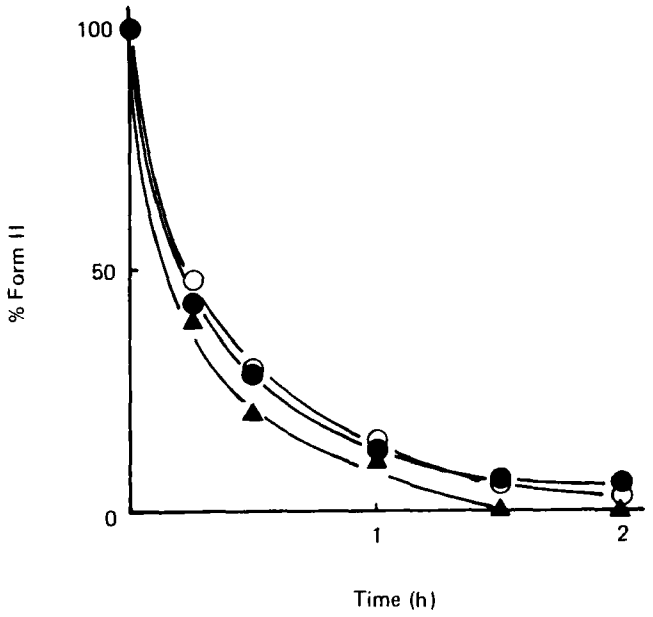

FIGURE 10

Effect of Corn Starch on the Polymorphic Transformation of Form II of Fostedil by Grinding
▲, fostedil-corn starch (1:3);
●, fostedil-corn starch (1:1);
○, fostedil-corn starch (3:1).

milled sample which contained form I larger at initial time, was transformed faster than hammer milled sample. The hammer milled sample showed the crystal transition only at a humid condition. It is probably due to a increse of nuclei of form I crystal in the crystal lattice. While, intact crystalline form II did not be transformed into form I in 1 month at 40 °C and 80 %R.H. The effect of humidity on the polymorphic transformation was large. This phenomenon and the results of solubility study mentioned above suggest

TABLE 1

Changes in Form II Content (%) by Milling Fostedil and Its Mixtures with Microcrystalline Cellulose (MCC) or Corn Starch

Samples	Fluid-energy Mill	Hammer Mill
Fostedil (Form II)	87.8	96.3
Fostedil-MCC (1:3)	68.0	95.2
Fostedil-MCC (1:1)	61.8	96.3
Fostedil-MCC (3:1)	51.0	96.0
Fostedil-Corn Starch (1:3)	78.3	95.6
Fostedil-Corn Starch (1:1)	76.1	96.5
Fostedil-Corn Starch (3:1)	79.5	95.2

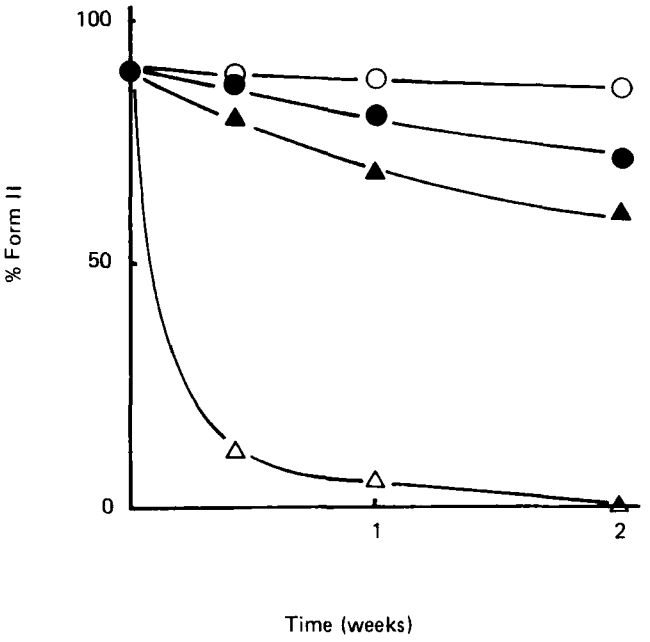

FIGURE 11

Effects of Temperature and Humidity on the Polymorphic Transformation of Fluid-energy milled Form II of Fostedil
storage condition: ○, 20 °C; ●, 40 °C; ▲, 50 °C; △, 40 °C and 80 % R.H.

that an appreciable interaction between fostedil and water molecules occur in solid state and in water. Both the addition of diluents and storage conditions influenced largely on the solid-state polymorphic change of fostedil. So, it is important to study these effects in the preformulation study.

Fig. 13 shows the polymorphic transformation of form II by compression. Crystalline form II was also easily transformed into form I by compression. While,

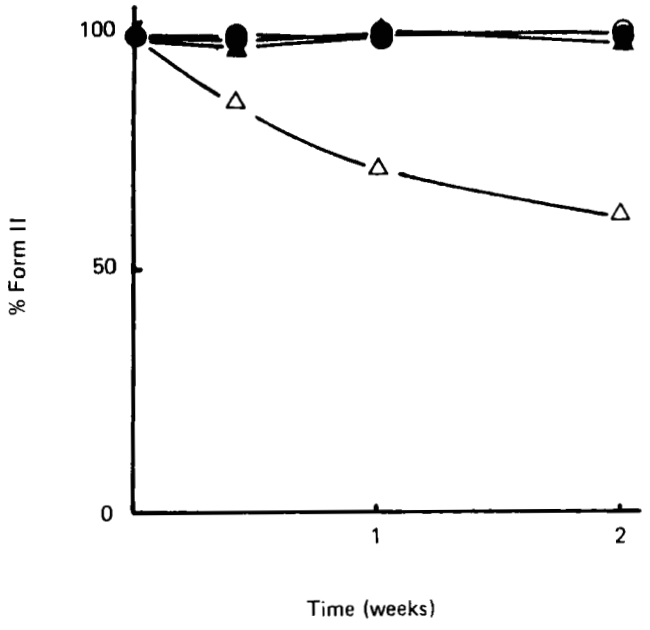

FIGURE 12

Effects of Temperature and Humidity on the Polymorphic Transformation of Hammer Milled Form II of Fostedil storage condition: ○, 20 °C; ●, 40 °C; ▲, 50 °C; △, 40 °C and 80 % R.H.

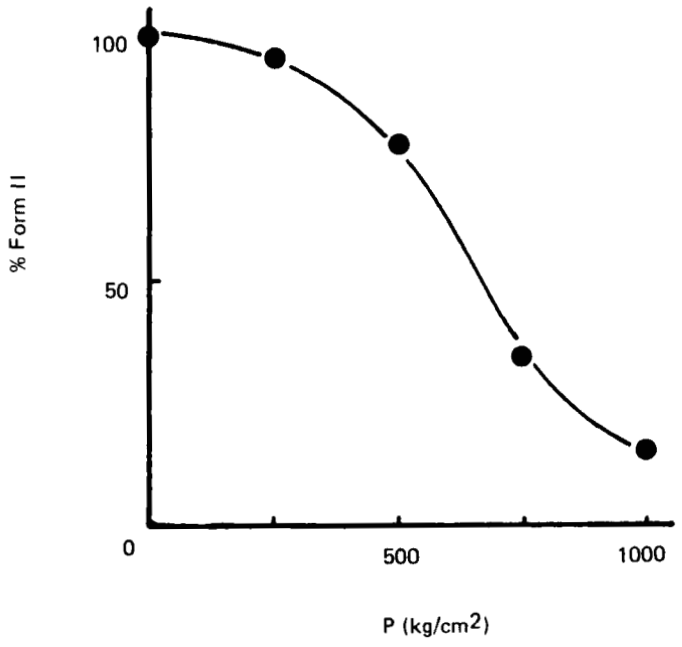

FIGURE 13

Effect of Compression on the Polymorphic Transformation of Form II of Fostedil

form I was stable to these treatments and no change of crystal structure observed.

Since the solubility of fostedil is very low, it is need to be micronized and compressed in pharmacuetical formulation procedure to obtain a tablet which shows a good bioabailability. Form II has a slightly higher solubility than form I. However, the difference in thermodynamic properties between two polymorphs was small, and form II was unstable to mechanical treatments. From these results, it is concluded that form I is more suitable for the pharmacuetical preparation.

REFERENCES

1) T. Morita, K. Yoshino, T. Kanazawa, K. Ito, and T. Nose, Arzneim.- Forsch., 32(II), 1037 (1982); T. Morita, T. Kanazawa, K. Ito, and T. Nose, Ibid., 32(II), 1043 (1982); Idem, Ibid., 32(II), 1047 (1982); T. Morita, K. Ito, and T. Nose, Ibid., 32(II), 1053 (1982); M. Yoshidomi, T. Sukamoto, T. Morita, K. Ito, and T. Nose, Ibid., 32(II), 1056 (1982); T. Morita, T. Fukuda, T. Sukamoto, S. Tajima, I. Sato, Y. Ikeda, T. Kanazawa, Y. Hamada, Y. Morimoto, H. Kitamura, K. Kawakami, K. Ito, and T. Nose, Ibid., 32(II), 1060 (1982).

2) A. J. Aguiar and J. E. Zelmer, J. Pharm. Sci., 58, 983 (1969).

3) M. A. Moustafa, A. R. Ebian, S. A. Khalil, and M. M. Motawi, J. Pharm. Pharmacol., 23, 868 (1971); A. R. Ebian, S. A. Khalil, M. A. Moustafa, and M. W. Gouda, Pharm. Acta Helv., 54, 111 (1979); H. G. Ibrahim, F. Pisano, and A. Bruno, J. Pharm. Sci., 66, 669 (1977); J. Matsunaga, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 24, 1169 (1976); V. H. Junginger, Pharm. Ind., 38, 724 (1976).

4) A. Ikekawa and S. Hayakawa, Bull. Chem. Soc. Jpn., 54, 2587 (1981); H. Yoshino, M. Kobayashi, and M. Samejima, Chem. Pharm. Bull., 29, 2661 (1981); H. Yoshino, Y. Hagiwara, M. Kobayashi, and M. Samejima, ibid., 32, 1523 (1984).

5) P. H. Hermans and A. Weidinger, J. Applied Physics, 19, 491 (1948); Y. Nakai, E. Fukuoka, S. Nakajima, and J. Hasegawa, Chem. Pharm. Bull., 25, 96 (1977).

6) Y. Nakai, J. Soc. Powder Technol., Jpn., 16, 473 (1979); K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, J. Pharm. Sci., 65, 1484 (1976); Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, Chem. Pharm. Bull., 25, 3340 (1977); Y. Nakai, E. Fukuoka, S. Nakajima, and Y. Iida, ibid., 26, 2983 (1978); Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada, and T. Konno, ibid., 26, 3419 (1978).