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Disssolution Characteristics of Phenobarbital and Phenobarbital-PVP Coprecipitate

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Phenobarbital 및 Phenobarbital-PVP 共沈物의 溶出에 관한 硏究

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Phenobarbital의 溶出速度를 증가시키기 위하여 PVP와의 共沈物을 形成한 후 一定한 表面積하에서의 溶出速度를 比較檢討하였다.

37°C, 150r.p.m×에서의 rate constannt of dissolution, k, 는 phenobarbital이 8.75×10^{-6}M/min, 1 : 2 phenobarbital-PVP coprecipiate는 5.35×10^{-5}M/min이었으며, activation energy of dissolution, Ea는 phenobarbital이 약 10,600cal/mole coprecipitate는 약 5,800cal/mol이었다. 그리고 X-ray diffraction study에 依하면 페노바르비탈 單一物質이나, PVP와의 physical mixture에서는 페노바르비탈의 결정피크를 나타내었으나, PVP와의 共沈物의 境遇에는 페노바르비탈의 결정피크를 認知할 수 없었다.

The dissolution rate of a drug might have a marked effect upon the absorption of the drug from a soild dosage form. This has led to an increasing interest to enhance the in vitro dissolution rate.

Several inrestigators[1-8] demonstrated that the formation of coprecipitates of relatively water insoblule druge with various water soluble carriers can increase the dissolution rates and the extent of absorption of hydrophobic drugs.

In the recently published reports from this laboratory, it was shown that many pharmaceuticals [9,10] were increased in dissolution rate by forming coprecipitates with pharmacologically inert, water soluble carriers.

On the basis of these finding, it was decided to investigate the dissolution chracteristics of phenobarbital, a poorly water soluble hypnotics, and its coprecipitates with PVP, under the constant surface area. The dissolution rate of non-disintegrating disks of pure allobarbital and of allobarbital-PVP coprecipitate were measured by rotating disk method in 200ml of 0.005M acetic acid medium(pH 3.05) under the constant surface area at 150r.p.m. and the various temperatures (25, 37, and 50°C).

X-ray diffraction study was carried out for allobarbital test systems in an attempt to elucidate this physicochemical modification.

EXPERIMENTAL

Materials-The phenobarbital, polyvinyvinylpyrrolidone of pharmaceutical grade were empolyed in this study. The polyvinylpyrrolidone (PVP) used had an average molecular weight of about 40,000.

Apparatus-Dissolution rate tester. Hitachi double beam spectrophotometer, RPM meter. X-ray diffractometer.

Test Preparation of the Non-Disintegrating Disks Containing Constant Surface Area-The 1.5cm diameter, flat-faced, non-disintegrating disks of pure allobarbital, and of phenobarbital-PVP coprecipitate containing constant surface area were prepared by the method described in the previous paper.[10]

Particulate Dissolution Rate Studies-The dissolution rates for the powder test prep arations, and the disk preparations were carried out by the method in previous paper[10].

Equilibrium Solubility Determination-The eduilibrium solubility of phenobarbital, 1 : 2 phenobarbital-PVP coprecipitate, and the same ratio physical mixture were also determined by the method described in the previous paper[10].

X-Ray Diffraction Study-X-ray diffraction study was carried out using Shimadzu GX-2B X-ray diffractometer. The target was Cu-tube (Ni-filtered), 35KV, 15mA and the detector was proportional counter, 1.7KV for detector voltage.

RESULTS AND DISCUSSION

Studies on the Powder State-The dissolved amounts of phenobarbital, for the 1 : 2 phenobarbital-PVP coprecipitate and the same ratio physical mixture are shown in Fig. 1 as microgram per milliliter against time while pure phenobarbital is included as reference. The dissolved rate of phenobarbital in the physical mixture was slightly increased comparing with pure phenobarbital and that in the coprecipitate system was

increased as compared with physical mixture (Fig. 1).

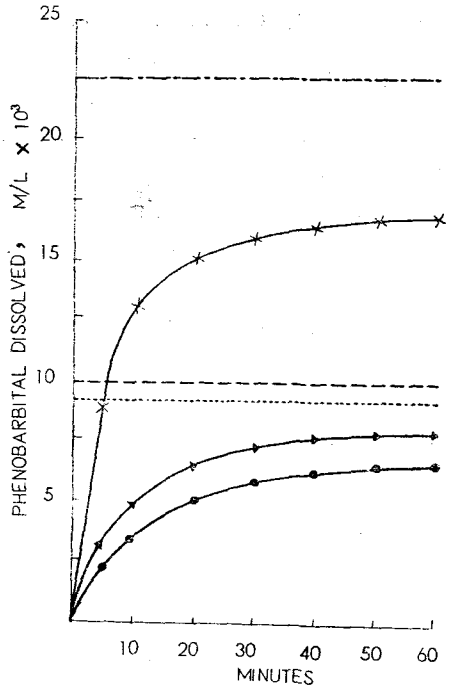

Figure 1 -Dissolution rates of phenobarbital in powder state.
Key: •, pure phenobarbital;
×, 1 : 2 ratio phenobarbital-PVP co-precipitate;
▲, 1 : 2 ratio phenobarbital-PVP physical mixture;
·····, equilibrium solubility of phenobarbital;
– – –, equilibrium solubility of 1 : 2 phenobarbital-PVP physical mixture;
——, equilibrium solubility of 1 : 2 phenobarbital-PVP coprecipitate.

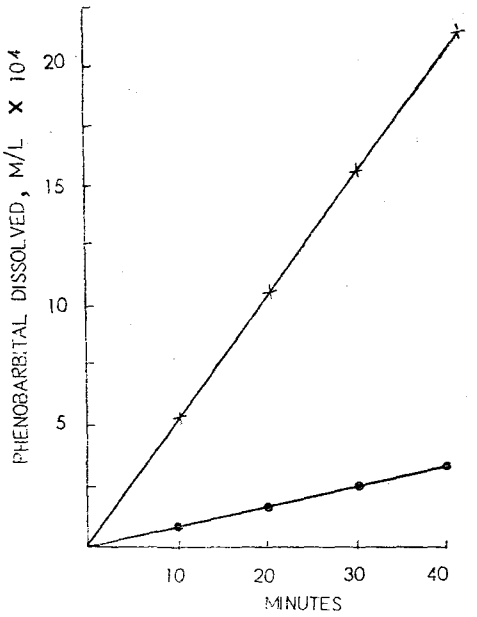

Figure 2- Dissolution rates of phenobarbital in non-disintegrating disk state at 37°C, 150 r. p. m.
Key: •, pure phenobarbital;
×, 1 : 2 ratio phenobarbital-PVP co-precipitate.

This result indicates that the mere presence of PVP in the coprecipitate as compared to the physical mixture is not responsible for the enhanced dissolution rate of phenobarbital. Accordingly, it may be proposed that a high energy form of phenobarbital most proably amorphous in nature is formed as a result of coprecipitate system.

Studies on the Non-Disintegrating Disk State-The dissolving particles could be changed in the powder state and the surface area might be changed as the time passes, and thus the comparison of the dissolution behavior was evaluated from the flat-faced, non-disintegrating disks of drug alone, and of coprecipitate with PVP under the constant surface area. The dissolved amounts of phenobarbital under the constant

surface area only for the first 40 minutes are depicted in Fig. 2 as mole concentration against time. The rate constant of dissolution, k, at 37°, 150r. p. m. are 8.75×10^{-6} M/min in the pure phenobarbital disk and 5.35×10^{-5}M/min in the 1 : 2 phenobarbital-PVP coprecipitate respectively. The rate constant of dissolution of phenobarbital was increased about 6-fold from 1 : 2 phenobarbital-PVP coprecipitate disk by comparing that from pure phenobarbital disk.

However, the physical mixture disk was disintegrated after short time during the experiment and the surface area of the dissolving particles were not held constant, the dissolution rate experiments could not be carried on. The disintegration of the disk was brought about in the physical mixture, in contrast, was not in the coprecipitate. In other to say, the phenobarbital and PVP act respectively in the physical mixture, while, the two components act in a unit in the coprecipitate.

Therefore, it is suggested that there may be binding forces between phenobarbital and PVP.

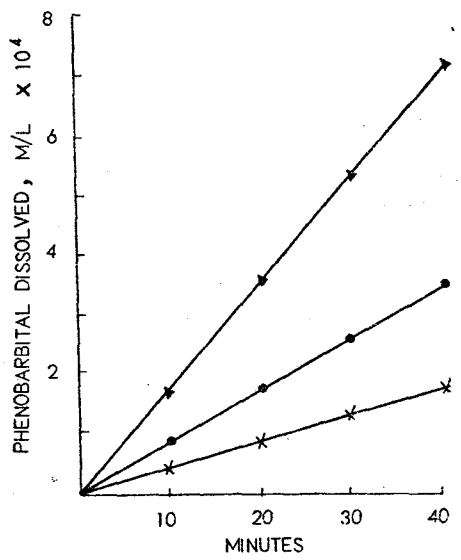

Figure 3 -Dissolution rates of phenobarbital from phenobarbital disks at 150 r. p. m. Key: ×, at 25; at 37°; at 50°.

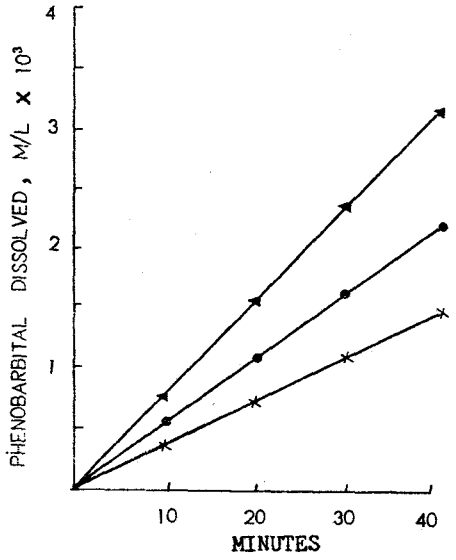

Figure 4 - Dissolution rates of phenobarbital from phenobarbital-PVP coprecipitate disks at 150 r. p. m. Key: ×, at 25° ; ·, at 37°, at 50°.

Effect of Temperature on the Dissolution Rate-The dissolved amount of phenobarbital at various temperatures (15°, 37°, and 50°C) is shown in Fig. 3 and that of 1: 2 phenobarbital-PVP coprecipitate is in Fig. 4. The rate constant of dissolution, k, at 25° was about 4.38×10^{-6}M/min from the phenobarbital, 3.65×10^{-5}/min from the 1 : 2 phenobarbital-PVP coprecipitate, and that at 50° was 1.75×10^{-6}M/min from the phenobarbital, 7.80×10^{-5}M/mn from the 1 : 2 phenobarbital-PVP copreccipitate. The rate constant of dissolution was increased about 1. 9-fold at 25°, about 1. 7-fold at 37°, and

about 1.5-fold at 50°. The rate constant of dissolution was increased about 1.9-fold at 25°, 1.7-fold at 37°, and 1.5-fold at 50°. The rate constant of dissolution, k, was high at low temperature. The dependence of rate constant of dissolution of phenobarbital, k, on the temperature at 150r.p.m. is denoted in Fig. 5. The activation energy calculated from the Arrhenius plot (Fig. 5) was about 10,600 cal/mol for pure phenobarbital and 5,800cal/mol for the 1 : 2 phenobarbital-PVP coprecipitate. The activation energy of dissolution decreased following the formation of the coprecipitates.

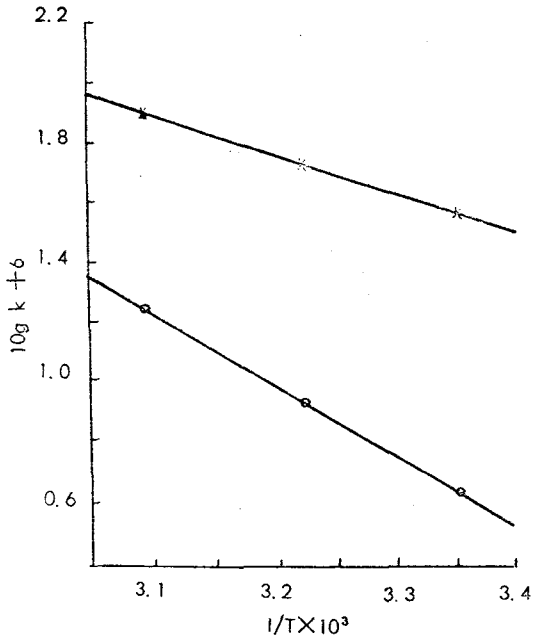

Figure 5 - Dependence of rate constant, k, of phenobarbital on the temperature at 150 r.p.m. Key: ×, pure phenobarbital; 1 : 2 ratio phenobarbital-PVP coprecipitate.

X-Ray Diffraction Studies-Even though the same combination ratio of drug to PVP, the dissolution rates between the coprecipitate and the physical mixture were differentiated. X-ray diffraction studies were undertaken for the phenobarbital test systems in an attempt to elucidate this physicochemical midification. The 1 : 2 phenobarbital-PVP coprecipitate and same ratio physical mixture were quite differentiated. The pure phenobarbital and the physical mixture also showed crystallinity supposedly due to the presence of crystalline phenobarbital (Fig. 6), however, the 1 : 2 phenobarbital-PVP coprecipitate did not show any crystallinity, likewise pure PVP (Fig. 7). The mere presence of PVP should not interfere the characterization of phenobarbital present in the physical mixture by comparing the coprecipitate system.

This result reveals that phenobarbital may be present as the amorphous form in the 1 : 2 phenobarbital-PVP coprecipitate system.

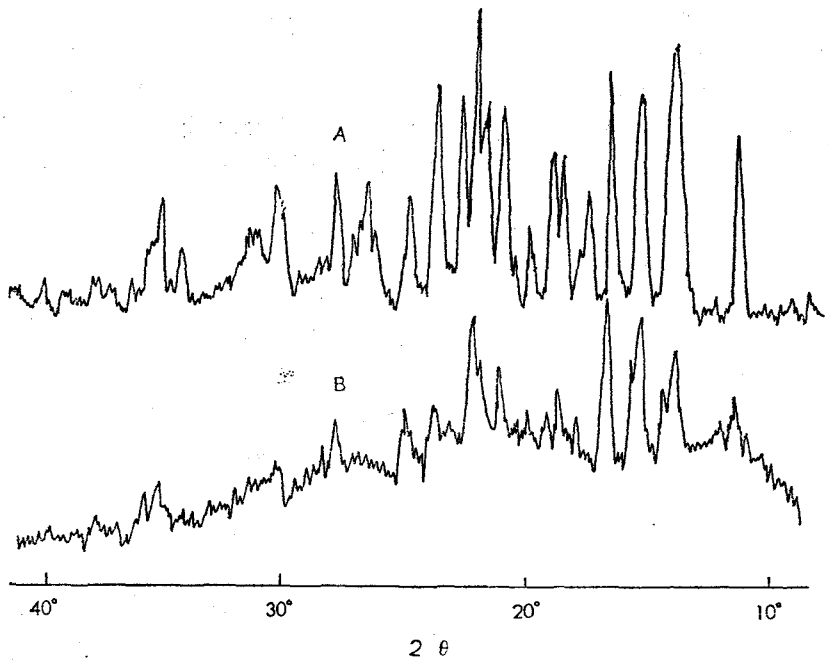

Figure 6 — Comparison of X-ray spectra
Key: A, pure phenobarbital: B, 1 : 2 ratio phenobarbital-PVP physical mixture.

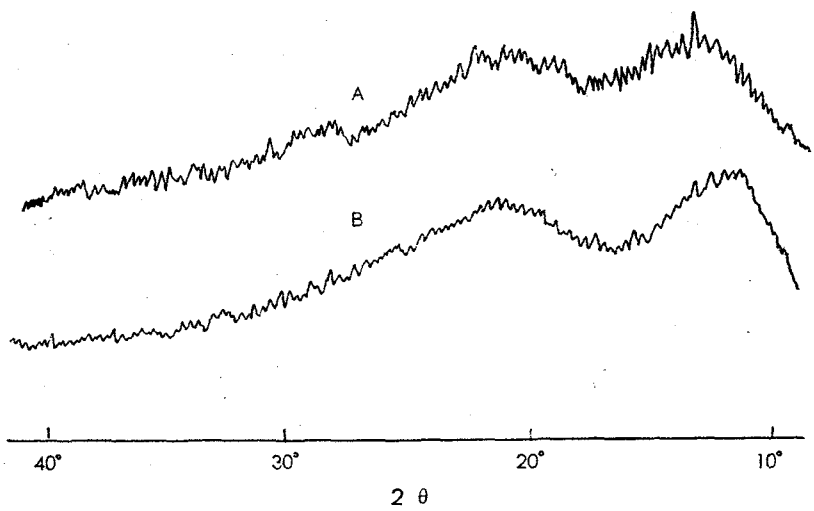

Figure 7 - Comparison of X-ray spectra
Key: A, 1 : 2 ratio phenobarbital-PVP coprecipitate; B, pure PVP.

CONCLUSIONS

The present study showed that the coprecipitate with PVP was increased in dissolution rates and could be summarized as following;

1. The dissolution rates of phenobarbital disk and 1 : 2 phenobarbital-PVP coprecipitate disk are in accordance with the Noyes-Nernst equation.

2. The rate constant of dissolution, k, of pure phenobarbital and 1 : 2 (w/w) phenobarbital-PVP coprecipitate under the above conditions are 8.75×10^{-6}M/min., and 5.35×10^{-5}M/min, respectively.

3. The activation energy of dissolution, Ea, is about 10,600cal/mole, for pure phenobarbital, and about 5,800cal/mole, for 1 : 2 phenobarbital-PVP coprecipitate.

4. X-ray diffraction study revealed that the pure phenobarbital and the phenobarbital in the PVP physical mixture are crystalline, in contrast, there is no crystallinity in the 1 : 2 phenobarbital-PVP coprecipitate.

REFERENCE

1) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9**, 866—72 (1961)
2) A. H. Goldberg, Mille Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **54**, 1145—8 (1965)
3) W.L. Chiou and S, Riegelman, *J. Pharm. Sci.*, **58**, 1505—10 (1969)
4) T.R. Bates; *J. Pharm. Pharmac.*, **21**, 710 (1969)
5) J.G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969)
6) A.P. Simonelli, S.C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **58**, 538—49(1969)
7) E.I. Stupak, H.A. Rosenberg, and T.R. Bates, *J. Pharmacokinetics Biopharmaceuties*, **2** (6), 511—24 (1974)
8) E.I. Stupak, and T.R. Bates, *J. Pharm. Sci.*, **62**, 1806—09 (1973)
9) S. C. Shin, M.H. Lee, and C.H. Woo, *J. Korean Pharm. Sci.*, **6**, 48—57 (1976)
10) S.C. Shin, Y.B. Kim, and M.H. Lee, *Seoul Univ. J. Pharm. Sci.*, **2**, 95 (1977).