[Chem. Pharm. Bull. 32(3)1091—1095(1984)]

Enhanced Absorption of Phenobarbital from Suppositories Containing Phenobarbital Povidone Coprecipitate[1)]

REIKO IWAOKU,* YUHKO OKAMATSU, SHIGEMI KINO, KAZUHIKO ARIMORI, and MASAHIRO NAKANO

Department of Pharmaceutical Services, Kumamoto University, Hospital, 1-1-1 Honjo, Kumamoto 860, Japan

(Received June 27, 1983)

Phenobarbital was released fastest from Witepsol H15 suppository among four Witepsol bases tested. A coprecipitate of phenobarbital and povidone (ratio, 1 : 3) gave an X-ray diffraction pattern which indicates that the drug is in an amorphous form in the coprecipitate, and the dissolution and permeation patterns of the drug from the coprecipitate indicated that drug dissolution from the coprecipitate was rapid. Release of the drug from a Witepsol H15 suppository containing the coprecipitate was faster than that from Witepsol H15 containing the drug alone or containing a physical mixture of the two components. Administration of the suppository containing the coprecipitate also gave the highest blood levels of the drug.

Keywords——phenobarbital; povidone coprecipitate; Witepsol; macrogol; suppository; dissolution rate; release rate; blood level; rabbit rectal absorption

Phenobarbital is often used in the form of suppositories in the treatment of febrile convulsion in infants. Bioavailability of the drug by rectal administration has been studied in pediatric patients.[2)] Since rapid absorption of the drug is desirable in such an emergency situation as febrile convulsion, we have been examining possible ways to facilitate release of the drug from suppositories. The use of β-cyclodextrin inclusion complex has been reported.[3)] In the present work, the use of povidone coprecipitate was examined since increased dissolution of drugs from povidone coprecipitates has been reported.[4)]

Experimental

Materials——Phenobarbital (pharmacopoeial grade) and Witepsol suppository bases (Vosco H15, E75, and S55) were purchased from Maruishi Seiyaku Co., macrogol 1000 & 4000 from Wako Junyaku Kogyo Co., and povidone (polyvinylpyrrolidone) K-15 (labeled average molecular weight of 10000) from Tokyo Kasei Kogyo Co. Witepsol W35 was generously supplied by Maruishi Seiyaku Co. Sodium phenobarbital for injection was a product of Daiichi Seiyaku Co. Other chemicals were of reagent grade.

Preparation of Suppositories——The macrogol suppository base employed was a mixture of macrogol 1000 and according to the following procedure. Phenobarbital and povidone in a suitable weight ratio were dissolved in 99.5% ethanol. The solvent was then removed by using a rotary evaporator at about 40 °C. The residue was dried at about 70 °C for 3 h. A physical mixture was prepared by simply blending phenobarbital and povidone in a mortar with a spatula.

Preparation of Suppositories——The macrogol suppository base employed was a mixture of macrogol 1000 and 4000 in a weight ratio of 3 : 1. The drug or the coprecipitate was suspended in the suppository bases after the bases had been melted. The molten mass was then poured into a suppository mold (Erweka). In each batch, sufficient drug was suspended to give 50 mg of the drug in each suppository.

Measurement of Drug Content——Phenobarbital in a suppository was dissolved in 1 ml of saline, 2 ml of ethanol and 7 ml of 0.05 M borax solution, then a 1 ml aliquot was diluted with the same solution. The absorbance at 241 nm was measured, and the drug content was calculated.

Measurement of X-Ray Diffraction Patterns——X-Ray powder diffraction patterns of phenobarbital, the physical mixture and the coprecipitate were obtained with a Toshiba ADX-103 X-ray diffractometer employing Ni-

filtered Cu$K\alpha$ radiation with a scanning speed at 1 °/min.

Measurement of Dissolution Patterns——Powder containing 50 mg of the drug was added to 300 ml of saline in a flask kept at 37.0±0.2 °C by means of a thermostated water bath. The suspension was stirred with a magnetic bar at a rate of 100 rpm. One ml of sample solution was pipeted through a cotton plug and its absorbance at 241 nm was measured after dilution with 2 ml of ethanol and 7 ml of 0.05 M borax solution.

Measurement of Permeation Patterns——An apparatus for the measurement of drug release from suppositories, model TMS-103, Toyama Sangyo Co., was employed for the measurement of permeation patterns. A 300 ml portion of saline was warmed to 37.0±0.1 °C in the flask and 3 ml of saline was put into the cylindrical cell. A Millipore filter disk, SSWP 04700, was employed as a membrane. Powder containing 50 mg of the drug was put into the cell. The rotation rate of the steel rod was 25 rpm, whereas the solution in the flask was stirred with a magnetic bar at 100 rpm. One ml of sample solution was pipeted through a cotton plug and its absorbance at 241 nm was measured after dilution with ethanol and 0.05 M borax solution.

Measurement of Release Patterns——An apparatus for the measurement of drug release from suppositories, model TMS-103, Toyama Sangyo Co., was employed according to the procedures reported by Muranishi *et al.*[5] Saline was employed as a release medium. A Millipore filter disk, SSWP 04700, was employed as a membrane. The rotation rate of the steel rod was 25 rpm. At predetermined intervals one ml of sample solution was pipeted through a cotton plug and its absorbance at 241 nm was measured after dilution with ethanol and 0.05 M borax solution.

Measurement of Blood Levels——Male albino rabbits weighing 2.7—3.3 kg were fasted for 24 h prior to rectal drug administration. The animal was secured in a supine position, and a test suppository was inserted into the rectum, then the anus was closed with a clip to prevent possible leakage. At predetermined intervals, a 0.5 ml blood sample was withdrawn from the ear vein. An interval of more than 10 d was allowed prior to the next experiment.

Assay of phenobarbital in blood was performed by a gas chromatographic procedure.[6] A gas chromatograph (Hitachi 063) equipped with a flame ionization detector and a glass column packed with 3% OV-17 on Chromosorb WAW 60—80 mesh was used.

Results and Discussion

Choice of an Appropriate Suppository Base

Release patterns of phenobarbital from four Witepsol bases and the macrogol base are shown in Fig. 1. Release was faster from Witepsol H15 and slowest from Witepsol S55. Since fast release was desired, Witepsol H15 was used for further studies. A few studies have examined the relative release properties of Witepsol bases. In a comparison of release of brilliant blue from Witepsol H15, W35, and S55, the rates of release were H15 > W35 > S55. This order is the reverse of the order of viscosity of the bases at 37 °C, which was S55 > W35 > H15.[7]

X-Ray Diffraction Patterns

X-Ray diffraction patterns of the coprecipitate at a drug to povidone ratio of 1 : 3, the physical mixture, and the drug alone are shown in Fig. 2. Upon coprecipitation of phenobarbital with povidone K-15, sharp diffraction peaks observed in both phenobarbital

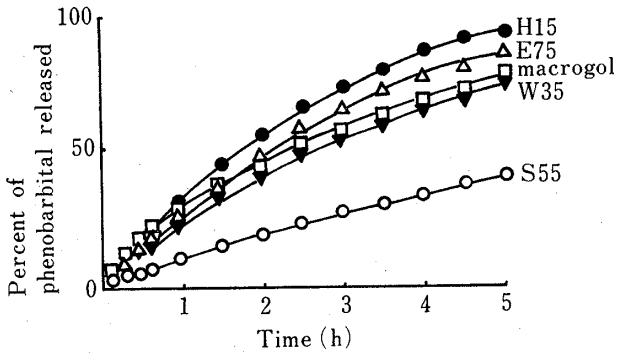

Fig. 1. Effect of Witepsol and Macrogol Bases on Release Patterns of Phenobarbital from Suppositories to Saline

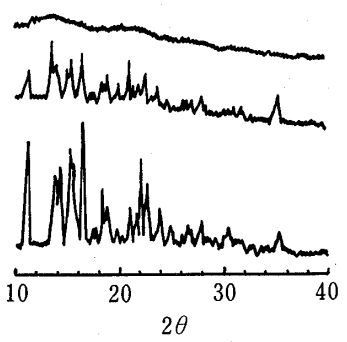

Fig. 2. X-Ray Diffraction Spectra

Top, phenobarbital : povidone K15 1 : 3 coprecipitate; center, phenobarbital : povidone K15 1 : 3 physical mixture; bottom, phenobarbital alone.

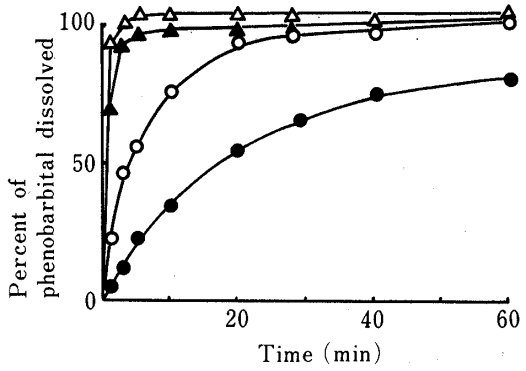

Fig. 3. Dissolution Patterns of Phenobarbital from Povidone Coprecipitates and a Physical Mixture in Saline

Points are the averages of five experiments.
△, phenobarbital : povidone K15 1:3 coprecipitate; ▲, 1:1 coprecipitate; ○, 1:3 physical mixture; ●, phenobarbital alone.

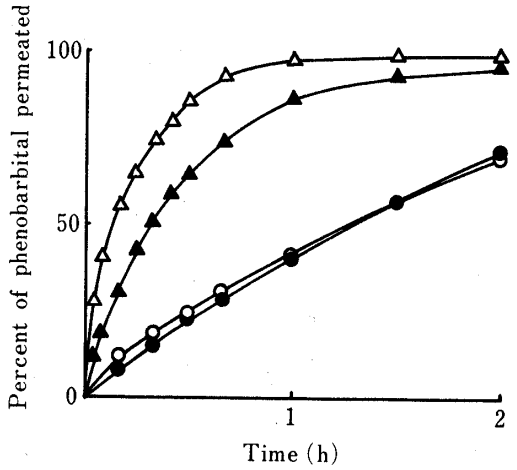

Fig. 4. Permeation Patterns of Phenobarbital to Saline after Dissolution from Povidone Coprecipitates and a Physical Mixture in Saline

Points are averages of five experiments.
△, phenobarbital : povidone K15 1:3 coprecipitate; ▲, 1:1 coprecipitate; ○, 1:3 physical mixture; ●, phenobarbital alone.

alone and the physical mixture disappeared and only the halo was observed in an X-ray diffraction pattern of the coprecipitate. Thus, phenobarbital is considered to exist as an amorphous solid in the coprecipitate when enough povidone is present.

Dissolution Patterns

Dissolution patterns of the drug from the coprecipitates, the physical mixture and the drug alone are shown in Fig. 3. The drug dissolved faster from the physical mixture than from the drug alone, possibly because of a wetting effect of povidone on the hydrophobic drug particle surfaces. Dissolution of the drug from the coprecipitates was faster than that from the physical mixture and increased as the ratio of the drug to povidone was decreased, possibly because of a greater dispersive effect of the macromolecules as the povidone content is increased. Since the small absorbance exhibited by povidone at the wavelength of phenobarbital determination (241 nm) was neglected in the present experiment, the apparent amount of phenobarbital dissolved tended to be greater than the actual amount in the presence of povidone.

Permeation Patterns

Permeation profiles of the drug through a membrane from a small amount of the aqueous solution following dissolution are shown in Fig. 4. As expected from the dissolution patterns shown in Fig. 3, the drug permeated faster from the coprecipitate than from the drug alone. As the ratio of the drug to povidone was decreased, the permeation rate increased, reflecting faster dissolution from well dispersed coprecipitates. Permeation from the physical mixture was not much faster than from the drug alone. Although the presence of povidone tended to aid dissolution of phenobarbital, possibly due to a wetting effect of the polymer on drug particle surfaces, povidone at as high a level as 5% (150 mg in 3 ml of saline) may have retarded permeation and dissolution of the drug because of the decreased diffusion rate of the drug through a viscous solution. These two opposing effects may have cancelled out, so that little increase in permeation rate as observed.

Weight Variation and Content Uniformity of Suppositories

Weight variation and content uniformity of the suppositories employed in the release

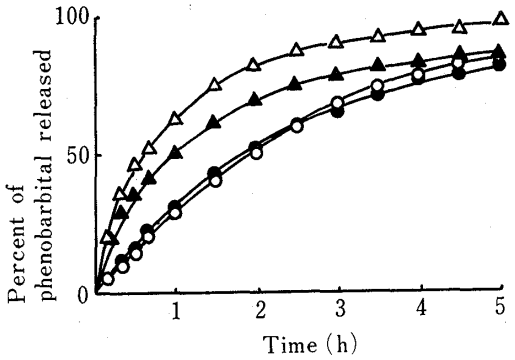

Fig. 5. Release Patterns of Phenobarbital from Witepsol H15 Suppositories in Saline

Points are averages of five experiments.
△, phenobarbital : povidone K15 1:3 coprecipitate; ▲, 1:1 coprecipitate; ○, 1:3 physical mixture; ●, phenobarbital alone.

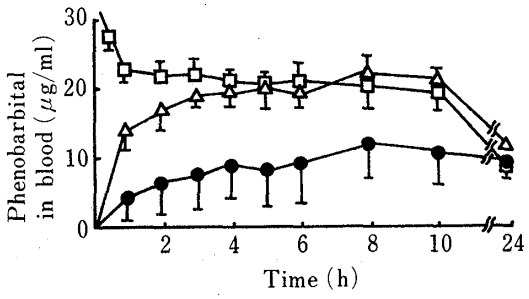

Fig. 6. Blood Levels Following Rectal Administration of Phenobarbital in Witepsol H15 Suppositories

Points are averages and SEM of five rabbits.
△, phenobarbital : povidone K15 1:3 coprecipitate; ●, phenobarbital alone; □, intravenous administration.

TABLE I. Weight Variation and Content Uniformity of Witepsol H15 Suppository

Phenobarbital–povidone ratio		Weight, g average	$n=24$ SEM	Drug content, mg average	$n=5$ SEM
Drug alone	1:0	1.131	0.019	52.12	0.40
Coprecipitate	1:3	1.169	0.019	51.43	0.33
	1:2	1.153	0.004	51.95	0.70
	1:1	1.142	0.006	51.03	0.51
Physical mixture	1:3	1.173	0.027	49.35	0.71

studies and rectal administration are shown in Table I.

Release Patterns

Release patterns of the drug from Witepsol H15 suppositories are shown in Fig. 5. Release rates from suppositories containing the coprecipitates were greater than those from suppositories containing the physical mixture or the drug alone, reflecting the permeation patterns shown in Fig. 4.

Blood Level Patterns

Blood levels of phenobarbital following administration of suppositories to rabbits are compared with that after intravenous administration of sodium phenobarbital for injection. Although blood levels following administration of the suppository containing the coprecipitate were lower than those after intravenous administration for the first few hours, they were significantly ($p<0.01$) greater than those following administration of the suppository containing the drug alone from 1 to 10 h. Average blood levels were 3 times greater at 1 h and twice as great (22 μg/ml *vs.* 12 μg/ml) at 8 h (t_{max}).

AUC_{0-10} was 186 μg h/ml for the coprecipitate and 86 μg h/ml for the drug alone. Thus, both the rate of bioavailability and the extent of bioavailability were improved by rectal administration of the povidone coprecipitate.

Acknowledgement The authors are grateful to Mr. Ogawa for obtaining the X-ray diffraction spectra.

References and Notes

1) This work was presented at the 102nd Meeting of the Pharmaceutical Society of Japan, Osaka, April 1982; Abstracts of Papers, 102nd Meeting, 1982, p. 687.
2) M. Matsukura, A. Higashi, T. Ikeda, and I. Matsuda, *Pediat. Pharmacol.*, **1**, 259 (1981).
3) R. Iwaoku, K. Arimori, M. Nakano, and K. Uekama, *Chem. Pharm. Bull.*, **30**, 1416 (1982).
4) *a*) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **58**, 538 (1969); *b*) O. I. Corrigan and R. F. Timoney, *J. Pharm. Pharmacol.*, **27**, 759 (1975); *c*) H. Sekikawa, J. Fujiwara, T. Naganuma, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 3033 (1978).
5) S. Muranishi, Y. Okubo, and H. Sezaki, *Yakuzaigaku*, **39**, 1 (1979).
6) H. Sato, *Igaku no Ayumi*, **107**, 330 (1978).
7) H. Yoshino, M. Kobayashi, and M. Samejima, *Yakuzaigaku*, **41**, 102 (1981).