DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(10), 1465-1470 (1988)

COMMUNICATION

COMPATIBILITY STUDY OF PROPOXYPHENE HCL SOLID MIXTURES USING DIFFERENTIAL SCANNING CALORIMETRY

S.L. Law*[1], W.Y. Lo[2], F.M. Lin[1] and C.H. Chiang[3]

[1]Pharmaceutics Research Laboratory, Department of Medical Research, Veterans General Hospital, Taipei, Taiwan, R.O.C.

[2]Copley Pharmaceutical Inc., Boston, Ma 02127, U.S.A.

[3]School of Pharmacy, National Defense Medical Center, Taipei, Taiwan, R.O.C.

*Correspondence

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/25/12
For personal use only.

ABSTRACT

Differential scanning calorimetry was used to investigate the compatibility of propoxyphene HCl-aspirin and propoxyphene HCl-acetaminophen solid mixtures. It was found that the interaction of propoxyphene HCl with aspirin and acetaminophen caused an eutectic mixture. Acetaminophen and propoxyphene HCl showed no degradation in the eutectic mixtures as detected by high performance liquid chromatography.

INTRODUCTION

Propoxyphene HCl is a widely prescribed analgesic[1,2]. It is frequently compounded with aspirin or acetaminophen in a tablet or capsule for oral administration[3]. It has been shown that propoxyphene HCl catalyzed the decomposition of aspirin[4].

Differential scanning calorimetry (DSC) is the fast method in the analysis of solid drug-drug or drug-excipient interaction in preformulation stability studies[5-7].

In this study, an attempt was made to describe the incompatibility of propoxyphene HCl with aspirin and acetaminophen in the

Copyright © 1988 by Marcel Dekker, Inc.

RIGHTSLINK

solid mixtures by DSC. High performance liquid chromatorgraphy (HPLC) method was also used to detect the chemical stability of acetaminophen and propoxyphene HCl in the mixtures.

MATERIALS AND METHODS

Propoxyphene HCl, aspirin and acetaminophen (USP grade) were obtained from Kingdom Pharmaceutical Co. (R.O.C.). P-aminophenol was purchased from Eastman Organic Chemicals (U.S.A.), freshly recrystallized twice.

Samples were made by physical mixing method using either trituration or rolling mixing. The mixtures of drug-drug in various ratios ranging from 1:10 to 1:0.1 were examined. Samples (8-10 mg) were placed in unsealed aluminum pans and analyzed by DSC in an atmosphere of nitrogen. The instrumentation used was a Du Pont 910 DSC cell base equipped with a Du Pont 1090B Thermal Analyzer System. The heating rate was 10°C/min.

HPLC determinations were performed using a Gilson Gradient System (Gilson, France). UV absorption was measured at 214 nm with the sensitivity range of 0.01 aufs. The column employed for analysis was a reversed-phase column (25 cm X 4.6 mm) packed with Vydac 201 HS C18, 10 μm (The Separation Group, U.S.A.). The mobile phase was acetonitril-water (35:65), pH was adjusted to 2.3 with o-phosphoric acid. The flow rate was 1.5 ml/min and the temperature was ambient.

To ensure that the HPLC method was stability-indicating, an attempt was made to degrade propoxyphene HCl by heating (90°C) the intact drug at pH 2.0, pH 11.0 and pH 6.3 aqueous solution for 24 hrs.

Samples of propoxyphene HCl-acetaminophen mixture were capped at 50% humidity and stored at 25°C. Their contents were analyzed with HPLC at one-month intervals during the one-year study period.

RESULTS AND DISCUSSION

The thermogram of propoxyphene HCL (Figure 1a) shows a transition temperature range of 155-177°C and with an endothermic peak at 170°C. The thermogram of aspirin (Figure 1a) shows a transition temperature range of 127-152°C and with an endothermic peak at 143°C. The decomposition of these drugs was found immediately after

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/25/12
For personal use only.

RIGHTSLINK

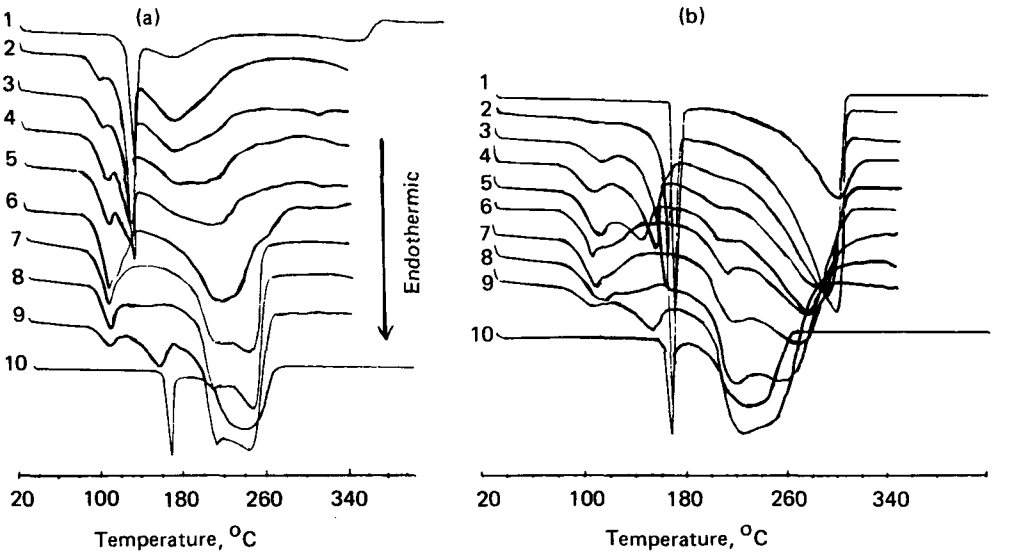

FIGURE 1

DSC thermograms of propoxyphene HCl-aspirin (a) and propoxyphene HCl-acetaminophen (b) solid mixtures at weight ratios of 0:1 (1), 1:10 (2), 1:6 (3), 1:3 (4), 1:2 (5), 1:1 (6), 1:0.5 (7), 1:0.25 (8), 1:0.1 (9) and 1:0 (10).

melting. For aspirin a second decomposition peak was observed at 350°C [8]. The thermograms of propoxyphene HCl-aspirin mixtures (Figure 1a) show broad melting ranges and low melting peaks which demonstrate the occurrence of incompatibility between these two drugs. The mixtures also showed an appearance of stickiness. This indicates the formation of eutectic mixture. A phase diagram of this system constructed from the DSC data is shown in Figure 2a. The eutectic temperature is at 100°C and the eutectic composition is at the weight ratio of 1:0.5 of propoxyphene HCL-aspirin.

The thermogram of acetaminophen (Fgiure 1b) shows a transition temperature range of 166-184°C and with a maximum peak at 172°C. The thermograms of the mixtures of different weight ratios of propoxyphene HCl and acetaminophen (Figure 1b) are similar to those of the propoxyphene HCL-aspirin mixtures. That is to say, incompatibility exists

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/25/12
For personal use only.

RIGHTSLINK

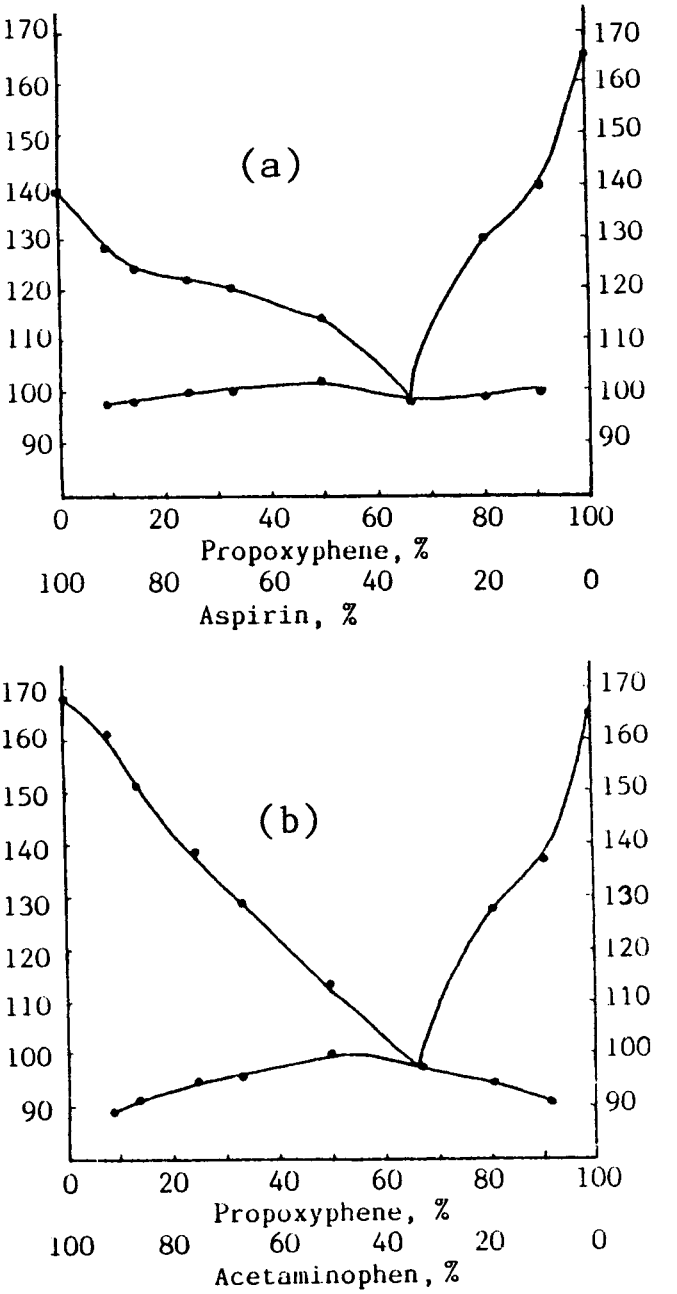

FIGURE 2

Phase diagram for the propoxyphene HCl-aspirin (a) and propoxyphene HCl-acetaminophen (b) solid mixtures.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/25/12
For personal use only.

RIGHTSLINK

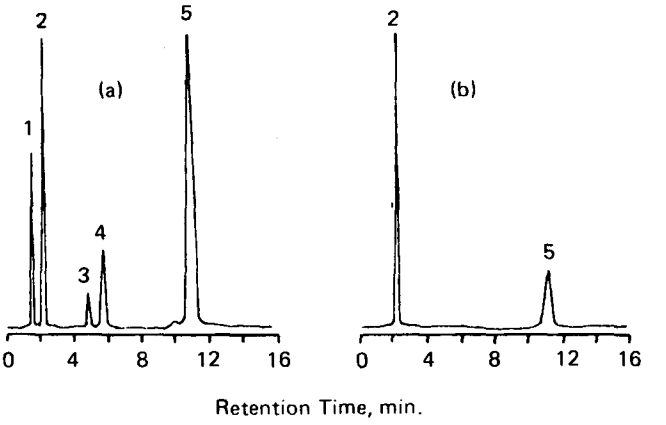

FIGURE 3

(a) HPLC chromatogram for the mixture of p-aminophenol (1), acetaminophen (2), propoxyphene HCl degradation products (3 and 4) and propoxyphene HCl (5).
(b) HPLC chromatogram of 1:0.5 solid mixture of propoxyphene HCl-acetaminophen after one-year storage.

between propoxyphene HCl and acetaminophen. Eutectic interaction occurred in these mixtures resulting in broad melting ranges, low melting peaks and sticky products. The phase diagram (Figure 2b) shows the eutectic composition at 1:0.5 propoxyphene HCl-acetaminophen and with the eutectic temperature of 95°C.

It has been reported that propoxyphene HCl enhanced the decomposition of aspirin[4]. It seems that an eutectic mixture facilitates the hydrolysis of aspirin into acetic acid and salicylic acid.

Koshy and Lach[9] demonstrated that the degradation of acetaminophen yielded p-aminophenol and acetic acid. Chromatogram obtained with the mixture of acetaminophen, propoxyphene HCl and their degradation products is given in Figure 3a. Each of the eluted peak was well separated which indicated that the method was stability-indicating. A sample chromatogram of the propoxyphene HCl-acetaminophen solid mixture after one-year storage is illustrated in Figure 3b; result shows a 1:0.5 weight ratio as representative of the series. No degradation products of acetaminophen or propoxyphe-

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/25/12
For personal use only.

RIGHTSLINK

ne HCl were detected during the one-year study period. The concentrations of acetaminophen and propoxyphene HCl in the mixtures showed no change from the initial concentration after storage. It is possible that acetaminophen and propoxyphene HCl are chemically stable in these mixtures within the time range studied, although an eutectic incompatibility was observed.

ACKNOWLEDGEMENT

The authors wish to thank Drs. M.L. King and Y.P. Hu (Kingdom Pharmaceutical Co.) for their helpful discussions and support.

REFERENCES

1. Fed. Regist. 44, 11837, 1979.
2. W. Modell, H. Schild and A. Wilson, "Applied Pharmacology," Saunders, Philadelpha, Pa., 1976.
3. Martindale, The Extra Pharmacopoeia, 28 ed., The Pharmaceutical Press, 1982, p. 1007.
4. R. Goldberg and C.H. Nightingale, Am. J. Hosp. Pharm., 34, 267, 1977.
5. H.H. El-Shatthwy, D.O. Kildsig and G.E. Peck, Drug Dev. Ind. Pharm., 8,879, 1982.
6. A.A. van Dooren, Drug Dev. Ind. Pharm., 9, 43, 1983.
7. E. Ciranni Signoretti, A. Dell'Utri, A. De Salvo and L. Donini, Drug Dev. Ind. Pharm., 12, 603, 1986.
8. D.J. Ager, K.S. Alexander, A.S. Bhatti, J.S. Blackburn, D. Dollimore, T.S. Koogan, K.A. Mosseman, G.M. Muhvic, B. Sims and V.J. Webb, J. Pharm. Sci., 7, 97, 1986.
9. K.T. Koshy and J. L. Lach, J. Pharm. Sci., 50, 113, 1961.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/25/12
For personal use only.

RIGHTSLINK