8–16, and 16–64 μg/ml, respectively, variations normal to the twofold serial dilution technique. These results confirm the work of Houang *et al.* (8), who were unable to detect resistance to this drug.

These studies show that the development of drug resistance can be an important factor in the choice of a skin antiseptic. Pharmaceutical scientists should share equal awareness of this limitation with microbiologists and physicians. There is no evidence from either the literature (8) or the present work that resistance to povidone-iodine is a potential problem in medical practice. However, previous observations of resistance to chlorhexidine and benzalkonium chloride (5) were confirmed and extended. Development of resistance to chlorhexidine in the genus *Serratia* is newly reported here (MIC = 2000 μg/ml). This concentration can be obtained easily in the hospital with only a 20-fold dilution of full-strength surgical scrub.

The practical significance of these findings with respect to nosocomial infections should not be underestimated, especially with increased use of chlorhexidine as a preservative, antiseptic, and oral drug.

REFERENCES

(1) G. E. Davies, J. Francis, A. R. Martin, F. L. Rose, and G. Swain, *Br. J. Pharmacol.*, **9**, 192 (1954).

(2) W. A. Gillespie, G. G. Lennon, K. B. Linton, and G. A. Phippen, *Br. Med. J.*, **3**, 90 (1967).

(3) J. D. O'Flynn and D. J. Stickler, *Lancet*, **1**, 489 (1972).

(4) D. J. Sticker, C. B. Wilmont, and J. D. O'Flynn, *Paraplegia*, **8**, 243 (1971).

(5) D. J. Stickler, *J. Clin. Pathol.*, **27**, 284 (1974).

(6) E. Grunberg and H. N. Prince, "IIId International Congress of Chemotherapy," Georg Thieme Verlag, Stuttgart, West Germany, 1964, pp. 51–58.

(7) E. Grunberg, J. Berger, G. Beskid, R. Cleeland, H. N. Prince, and E. Titsworth, *Chemotherapia*, **12**, 272 (1967).

(8) E. T. Houang, O. J. A. Gilmore, C. Reid, and E. J. Shaw, *J. Clin. Pathol.*, **29**, 752 (1976).

Aspirin Stability in Solid Dispersion Binary Systems

H. M. EL-BANNA ˣ, N. A. DAABIS, and S. ABD EL-FATTAH

Received December 7, 1977, from the *Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.* Accepted for publication February 27, 1978.

Abstract □ The stability of aspirin in its solid dispersion with urea or povidone was investigated at two accelerated storage conditions. The observed aspirin degradation in both systems followed the first-order rate equation. The water sorption ability of the two carriers as well as the alkalinity imparted by urea could possibly be the most important factors responsible for the observed acceleration of aspirin decomposition. The results also showed that the temperature effect was more pronounced than the humidity effect. Generally, coprecipitated samples exhibited slightly higher degradation rates than physically mixed ones.

Keyphrases □ Aspirin—stability in solid dispersion binary systems with urea or povidone, effect of temperature and humidity □ Solid dispersions—aspirin in binary systems with urea or povidone, effect of temperature and humidity □ Stability—aspirin in solid dispersion binary systems with urea or povidone, effect of temperature and humidity □ Dosage forms—solid dispersion binary systems, aspirin with urea or povidone, effect of temperature and humidity on stability □ Analgesics—aspirin, stability in solid dispersion binary systems with urea or povidone, effect of temperature and humidity

Aspirin decomposition in the solid form is considered to be due to a hydrolytic reaction in the presence of water. The first reported humidity- and temperature-controlled experiments with aspirin tablets was conducted by Canback (1). Stability studies on aspirin incorporated with antacids or lubricants in solid dosage forms were reviewed (2), and aspirin stability in various liquid and semisolid bases was investigated (3, 4). Blocking free hydroxyl groups on polyethylene glycols retarded aspirin decomposition resulting from transesterification (5, 6).

BACKGROUND

In 1961, a unique approach was demonstrated (7) to reduce the particle size and increase the dissolution rates and absorption of poorly soluble drugs *via* the formation of solid dispersions with inert, highly soluble carriers. Since then, this concept has been applied successfully to the formulation of fast-release dosage forms containing sparingly water-soluble drugs (8–12). An investigation of possible enhancement of the dissolution rate of aspirin *via* coprecipitation with polyethylene glycol 6000 was reported (8). Urea and povidone were used commonly as inert carriers in solid dispersion binary systems (9–12).

A literature review revealed that the effect of aging or storage under various conditions on the fast-release characteristics and chemical stability of drugs in solid dispersion systems had not been reported extensively. Aging effects were manifested only as coarsening of eutectic mixtures (13), precipitation from solid solutions (14) or glass solutions (15), and polymorphic transformations or changes in dissolution rates (16).

The present study was undertaken to evaluate the chemical stability of aspirin in its solid dispersion with a water-soluble carrier such as urea or povidone and to determine the influence of solid dispersion systems on drug stability.

EXPERIMENTAL

Materials—Aspirin[1], urea[2], povidone[3], and calcium chloride hexahydrate[4] were used as obtained. Absolute ethanol[5] and chloroform[5] were analytical grade.

Sample Preparation—Solid dispersion samples of aspirin with urea or povidone were prepared by the solvent method to avoid any possible aspirin decomposition if samples were prepared by the melt method (17). Coprecipitates of aspirin with both carriers in a ratio of 3:1 were obtained by dissolving the components in the minimum volume of absolute ethanol and subsequently evaporating the solvent *in vacuo* at room temperature using a rotary evaporator. The residue was finely ground, sieved to a particle-size range of 80–125 μm, and stored in a desiccator over anhydrous calcium sulfate.

Physical mixtures of the same compositions as the coprecipitates were prepared by simple mixing of ingredients possessing the same particle-size range. Pure crystalline aspirin (80–125 μm) served as a control sample.

Accelerated Storage Conditions—Samples, equivalent to 50 mg of aspirin, were placed in separate small beakers and kept in a desiccator under controlled relative humidity (R.H.) and temperature conditions of 100% R.H.–40° and 42% R.H.–65°. The latter condition was attained by using a saturated solution of calcium chloride hexahydrate. No ap-

[1] Bayer, Leverkusen, West Germany.
[2] E. Merck, Darmstadt, West Germany.
[3] BASF, Ludwigshafen/Rhein, West Germany.
[4] Riedel-De Haen AG, Seelze-Hannover, West Germany.
[5] BDH Chemicals Ltd., Poole, England.

0022-3549/78/1100-1631$01.00/0

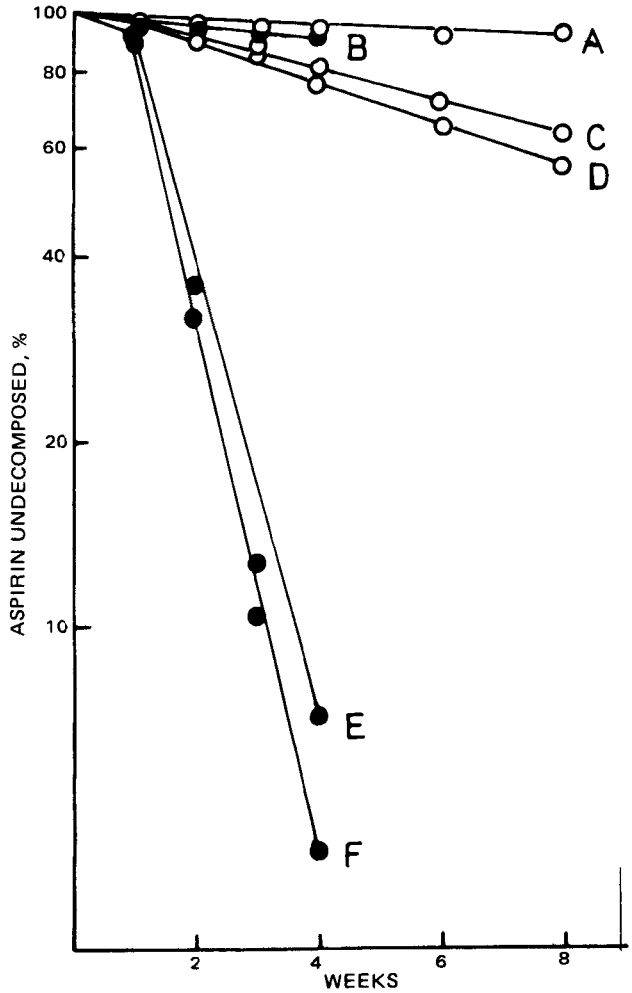

Figure 1 —*Semilogarithmic plots of percentage of aspirin undecomposed in aspirin–urea system (3:1 ratio) against time at 100% R.H.–40° (○) and at 42% R.H.–65° (●). Key: A and B, crystalline aspirin; C and E, physical mixture; and D and F, coprecipitate.*

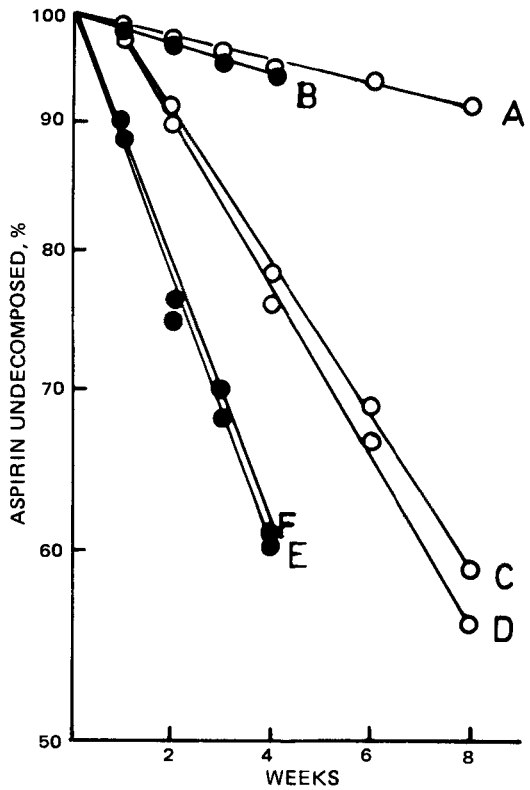

Figure 2—*Semilogarithmic plots of percentage of aspirin undecomposed in aspirin–povidone system (3:1 ratio) against time at 100% R.H. –40° (○) and at 42% R.H.–65° (●). Key: A and B, crystalline aspirin; C and E, physical mixture; and D and F, coprecipitate.*

preciable change in humidity was observed during the experiment. At frequent intervals, samples were withdrawn and assayed.

Assay—UV spectrophotometric analysis, as reported by Tinker and McBay (18), was employed to measure aspirin and salicylic acid. The content of each beaker, equivalent to 50 mg of aspirin, was dissolved in 20 ml of chloroform containing 1% acetic acid. After filtration and further appropriate dilution, the absorbance was read[6] at 282 nm for aspirin and 310 nm for salicylic acid. The calculation of the quantities of aspirin and salicylic acid was based on the standard method of simultaneous spectrophotometric determinations.

RESULTS AND DISCUSSION

Accelerated storage conditions were applied to evaluate aspirin stability in solid dispersion systems. Only samples having the same mesh size were investigated to avoid any discrepancies due to particle-size effect (19). Figures 1 and 2 show the semilogarithmic plots of the percentage of aspirin undecomposed in the control sample and physically mixed and coprecipitated samples with urea and povidone, respectively, against time after storage at 100% R.H.–40° and 42% R.H.–65°.

Under the accelerated storage conditions, an initial induction period, which could be attributed to water absorption, was generally observed (Figs. 1 and 2). After this lag period, aspirin degradation appeared to follow the first-order rate equation.

Crystalline Aspirin System—As may be seen from Figs. 1 and 2, crystalline aspirin (curve A) was the most stable. In this sample, no decomposition was noted during the 1st week of storage at either studied condition. Less than 10% degradation was detected after either 8 weeks of storage at 100% R.H.–40° (curve A) or 4 weeks at 42% R.H.–65° (curve B); the degradation rate constants were 0.008 and 0.015 week^{-1}, respectively. This relatively slight amount of aspirin decomposition could have been caused by small moisture sorption by the hydrophobic aspirin (20).

Aspirin–Urea System—Contrary to the reported stability of aspirin mixed with urea as a powder or tablet after 1 year of storage (21), urea showed an adversely affected aspirin degradation in the present study. The physically mixed aspirin–urea sample exhibited a high degradation rate constant of 0.061 week^{-1} after 8 weeks of storage at 100% R.H.–40° (Fig. 1, curve C). Furthermore, a comparison of curves C and E of Fig. 1 shows a drastic difference in the aspirin decomposition rate in the physically mixed sample stored at 100% R.H.–40° compared to that stored at 42% R.H.–65°. At the former condition, the decomposition reached approximately 35% after 8 weeks; at the latter storage condition, the decomposition was greater than 90% after only 4 weeks, the samples being melted and changed in color.

The acceleration of aspirin hydrolysis in the presence of urea could possibly be due to the hydrophilicity of this carrier and its ability to absorb water. One could describe this system as a suspension of aspirin in a minimum quantity of water in which urea is dissolved or as particles with each surrounded by a thin film of solubilized aspirin in a saturated urea solution. Moreover, urea itself imparts a slight alkalinity to this humid microatmospheric film, which further increases the degradation rate. This film is likely to be present at the two humidities studied.

Therefore, it was not surprising that, at the low humidity and high temperature condition (42% R.H.–65°), aspirin in this system exhibited a much higher degradation rate of 0.891 week^{-1} compared to that at the other storage condition. The marked instability of aspirin at this high temperature could be due to the effect of increased pH on the medium by ammonia caused by the partial decomposition of urea during heating (17). In addition, an increase in temperature could enhance the passage of aspirin to the surrounding film of urea solution, resulting in further degradation.

As may be seen from Fig. 1, the degradation rate constants of aspirin from the coprecipitated samples were 0.077 and 1.05 week^{-1} (curves D and F, respectively), which were higher than those from the physically mixed samples of identical composition (curves C and E). Aspirin par-

[6] Unicam SP 1800 UV spectrophotometer.

ticles in the coprecipitated samples are in a fine state of subdivision and in intimate contact with urea. In such a solid dispersion system, the reduced particle size of aspirin, the concomitant increase in its surface area exposed to the suggested film layer of urea solution, and the resultant increase in its solubility appear to be the major factors responsible for the observed acceleration of aspirin degradation. Traces of alcohol in the coprecipitated sample also may play a part (22).

Aspirin–Povidone System—In the aspirin–povidone system, the effects of humidity, temperature, and aspirin solubilization by this water-soluble carrier seem to be operating in the microenvironment surrounding aspirin particles at the two storage conditions studied. The physically mixed and coprecipitated aspirin–povidone samples (curves C and D) exhibited decomposition rate constants of 0.069 and 0.077 $week^{-1}$, respectively (Fig. 2), which were comparable to those found with the aspirin–urea system. Possibly, the degradation-enhancing effect due to the high moisture sorption inherent to povidone (23), compared to that with urea, would be outweighed by the slight alkalinity imparted by urea.

However, for comparable times, the percent decomposition of both physically mixed and coprecipitated aspirin–povidone samples stored at 42% R.H.–65° was approximately one-seventh that observed with the same samples in the aspirin–urea system. This difference in aspirin stability could be attributed to the partial decomposition of urea at this high temperature. The apparent similarity between the stability of both physically mixed and coprecipitated aspirin–povidone samples stored at 42% R.H.–65° may be due to a complex reaction (24) that seems to be temperature dependent. This complex formation was reported for aspirin with other similar, structurally related compounds (25).

From these results, it can be concluded that the polar and perhaps the hygroscopic nature of urea and povidone tend to allow aspirin to degrade when incorporated into this type of carrier as physical mixtures or coprecipitates. Although the aspirin–povidone system exhibited lower degradation rates than those for the aspirin–urea system, the percent of decomposition in the former system was still prohibitively high. Consequently, the application of solid dispersion should be handled with care for drugs showing stability problems.

REFERENCES

(1) T. Canback, *Sv. Farm. Tidskr.*, **47**, 621 (1943); through *Chem. Abstr.*, **38**, 5644[6] (1944).

(2) C. A. Kelly, *J. Pharm. Sci.*, **59**, 1053 (1970).

(3) C. W. Whitworth, L. A. Luzzi, B. B. Thompson, and H. W. Jun, *ibid.*, **62**, 1372 (1973).

(4) C. W. Whitworth and A. Asker, *ibid.*, **64**, 2018 (1975).

(5) C. W. Whitworth, H. W. Jun, and L. A. Luzzi, *ibid.*, **62**, 1184 (1973).

(6) H. W. Jun, C. W. Whitworth, and L. A. Luzzi, *ibid.*, **61**, 1160 (1972).

(7) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9**, 866 (1961).

(8) A. F. Asker and C. W. Whitworth, *Pharmazie*, **30**, 530 (1975).

(9) H. M. El-Banna, S. Abd El-Fattah, and N. A. Daabis, *ibid.*, **29**, 396 (1974).

(10) N. A. Daabis, S. Abd El-Fattah, and H. M. El-Banna, *ibid.*, **29**, 400 (1974).

(11) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, **58**, 538 (1969).

(12) T. R. Bates, *J. Pharm. Pharmacol.*, **21**, 710 (1969).

(13) R. P. Rastogi and P. S. Bassi, *J. Phys. Chem.*, **98**, 2398 (1964).

(14) R. Smoluchoweski, "Phase Transformation in Solids," Wiley, New York, N.Y., 1951.

(15) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1281 (1971).

(16) W. L. Chiou and S. Niazi, *ibid.*, **60**, 1333 (1971).

(17) C. C. Edison and M. G. Ines, *Ann. R. Acad. Farm.*, **40**, 487 (1974).

(18) R. B. Tinker and A. J. McBay, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 315 (1954).

(19) R. Yamamoto and T. Takahashi, *Ann. Rep. Shionogi Res. Lab.*, **3**, 112 (1953).

(20) L. J. Leeson and A. M. Mattocks, *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 329 (1958).

(21) I. Grabowska, *Gdansk. Tow. Nauk., Rozpr. Wydz.*, **3**, 193 (1964); through *Chem. Abstr.*, **64**, 14029a (1966).

(22) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 3401 (1957).

(23) "Martindale, The Extra Pharmacopoeia," N. W. Blacow, Ed., 26th ed., Pharmaceutical Press, London, England, 1972, p. 1085.

(24) S. M. Blaug and J. W. Weslowski, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 691 (1959).

(25) A. N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea & Febiger, Philadelphia, Pa., 1973, p. 334.

Odoratin and Paucin: Cytotoxic Sesquiterpene Lactones from *Baileya pauciradiata* (Compositae)

JOSEPH J. HOFFMANN, SHIVANAND D. JOLAD, STERLING J. TORRANCE, DORI J. LUZBETAK, RICHARD M. WIEDHOPF, and JACK R. COLE ˣ

Received December 23, 1977, from the *Division of Pharmaceutical Chemistry, College of Pharmacy, University of Arizona, Tucson, AZ 85721.* Accepted for publication March 2, 1978.

Abstract □ An ethanol extract of *Baileya pauciradiata* exhibited cytotoxic activity against the human epidermoid carcinoma of the nasopharynx and the lymphocytic leukemia test systems. Two constituents responsible for this activity were isolated and identified as odoratin and paucin. Their identities were proven by IR, PMR, and mass spectral data; elemental analysis; preparation of their acetates; and melting-point determinations. Odoratin was confirmed by comparison with an authentic sample.

Keyphrases □ *Baileya pauciradiata*—whole plant ethanol extract, odoratin and paucin isolated and identified □ Paucin—isolated and identified from whole plant ethanol extract of *Baileya pauciradiata* □ Odoratin—isolated and identified from whole plant ethanol extract of *Baileya pauciradiata* □ Cytotoxic sesquiterpene lactones—odoratin and paucin, isolated from whole plant ethanol extract of *Baileya pauciradiata*

In the continuing search for plants having antitumor properties, an ethanol extract of the whole plant of *Baileya pauciradiata* Harv. and Gray (Compositae)[1] exhibited cytotoxic activity against the human epidermoid carcinoma of the nasopharynx (KB) and lymphocytic leukemia (P-388) test systems[2].

[1] The plant was collected in California in March 1972. Identification was confirmed by Dr. Robert E. Perdue, Medicinal Plant Resources Laboratory, U.S. Department of Agriculture, Beltsville, Md., where a reference specimen (PR25375) is maintained.

[2] Data on the cytotoxic and *in vivo* activity were provided through the courtesy of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Md.

0022-3549/78/1100-1633$01.00/0