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THE STABILITY OF ASPIRIN IN A MOISTURE CONTAINING DIRECT COMPRESSION TABLET FORMULATION

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ABSTRACT

Studies were conducted on the stability of a direct compression tablet formulation containing aspirin as a model hydrolabile drug. Emdex^{R} (a mixed-sugar diluent containing approximately 8 percent moisture) and stearic acid (a lubricant) made up the remainder of the formulation. Both tablets and uncompressed powder blend were manufactured, packaged in storage containers and placed on stability at different storage temperatures. Stability samples were assayed for aspirin and salicylic acid using a

stability indicating analytical method. Analysis of the stability data showed that the rate of aspirin decomposition accelerated with time. Also, the aspirin decompostion rate increased with temperature. The data were fit to the empirical equation $y = 100 - kt^n$, where y is the percent aspirin remaining, t is time, and k and n are constants. The formulation showed good stability, with less than one percent decomposition occuring after 1.75 years of storage at room temperature. This result indicates that although the aspirin formulation contained approximately 8 percent moisture, at room temperature the majority of the moisture present in the formulation is not available to react with the aspirin. The apparent activation energy of the solid-state aspirin decomposition was 46 kcal/mole, which is higher than expected. This result may be due to a temperature dependent release of moisture from the Emdex^R. Further studies are needed to verify this explanation.

INTRODUCTION

Where feasible, the manufacture of tablets by direct compression provides some important advantages over other methods of tablet manufacture. These advantages include lower costs, elimination of heat and moisture from the manufacturing process and potentially better product stability (1). Direct compression tableting involves the use of special diluents which

have suitable flow and compression characterisitics. Most directly compressible diluents contain moisture, and the moisture content of these diluents affect their flow and compression properties. The influence of the moisture present in such diluents on the stability of a model hydrolabile drug, such as aspirin, is of both practical and theoretical importance. This study is concerned with the stability of aspirin in the presence of Emdex^{R}, a mixed-sugar direct compression tablet diluent.

EXPERIMENTAL

Materials

The following ingredients were used in this study: aspirin powder, USP (Ruger), salicylic acid (Sigma), acetonitrile (Baker), stearic acid (Baker) and Emdex^{R} (Mendell).

Tablet Manufacture

Tablets were manufactured using a Stokes single punch tablet press. The formulation ingredients were: aspirin powder (5%), stearic acid (2%) and Emdex (93%). A low level of aspirin (5%) was used in order to maximize the exposure of aspirin to the diluent. The batch size was 800 gm, and the target tablet weight was 300 mg. Prior to blending, the Emdex was passed through a 30 mesh sieve, and the stearic acid was passed through a 60 mesh sieve. The ingredients were mixed in a suitable twin shell blender as follows: the

aspirin and the Emdex were mixed for 20 minutes, then the stearic acid was added and blended for 3 minutes. A portion of the powder blend was compressed into tablets; the tablets and the uncompressed powder blend were packaged into storage containers as described under stability studies.

Stability Studies

Accelerated stability studies were carried out on both tablets and uncompressed powder blend. The storage containers were 5 dram glass bottles with screw caps fitted with Teflon cap liners (Wheaton). For the tablet studies, ten tablets were stored per bottle. For the powder blend studies, 3 grams of powder blend were stored per bottle. The samples were stored at room temperature, 35, 40, 45 and 50°C for appropriate periods of time depending on the decomposition rate.

Aspirin Assay

A stability indicating, simultaneous UV assay similar to that used by Tinker and McBay (2) was utilized. The assay measures both aspirin and salicylic acid levels. The contents of each bottle were placed in a glass mortar, and the bottle then rinsed with a suitable portion of acetonitrile. The rinse was added to the mortar, and the contents of the mortar were ground and extracted with acetonitrile. The acetonitrile extract was filtered through glass wool, and assayed for aspirin and salicylic acid.

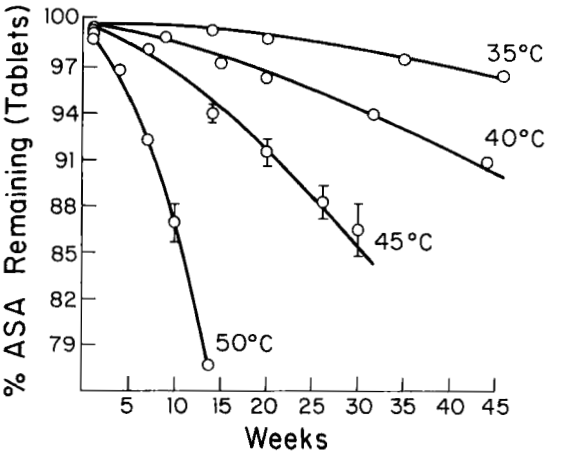

FIGURE 1

Aspirin tablet stability profiles (mean ± SD) at indicated temperatures.

Assays were done in triplicate, and mean ± standard deviation values were calculated for each interval. The percent recovery of the assay was 99 percent, and the relative standard deviation was 0.2 percent.

Moisture Analysis

Sample moisture contents were determined by Karl Fisher titration. The standard was sodium tartrate dihydrate, and formamide was used as the solvent.

RESULTS AND DISCUSSION

Figure 1 plots the percent aspirin remaining versus time for tablet samples stored at 35, 40, 45 and 50°C. The plot is concave downward, indicating that the reaction is accelerating with time. Similar acceleration plots, or sigmoid decomposition plots with

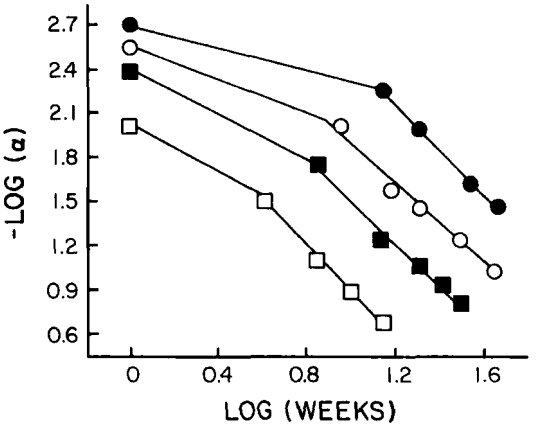

FIGURE 2

Aspirin tablet stability data plotted according to Eq. 2. (●) 35°C, (○) 40°C, (■) 45°C, (□) 50°C.

initial acceleration phases, have been reported previously for aspirin and other compounds (3-8). Yoshioka and Carstensen (9) reported that the acceleration phase of sigmoid decomposition curves may be approximated by the equation:

$$x = kt^n \qquad (1)$$

where x is the percent decomposed, t is time and k and n are constants. They also reported that the initial data of Carstensen and Attarchi (10) fit a logarithmic form of equation 1 similar to:

$$\log \alpha = n \log t + \log k \qquad (2)$$

where α is the fraction of aspirin decomposed. Figure 2 is a plot of the aspirin tablet data from this study fit to Eq. (2). The curves are biphasic, and the

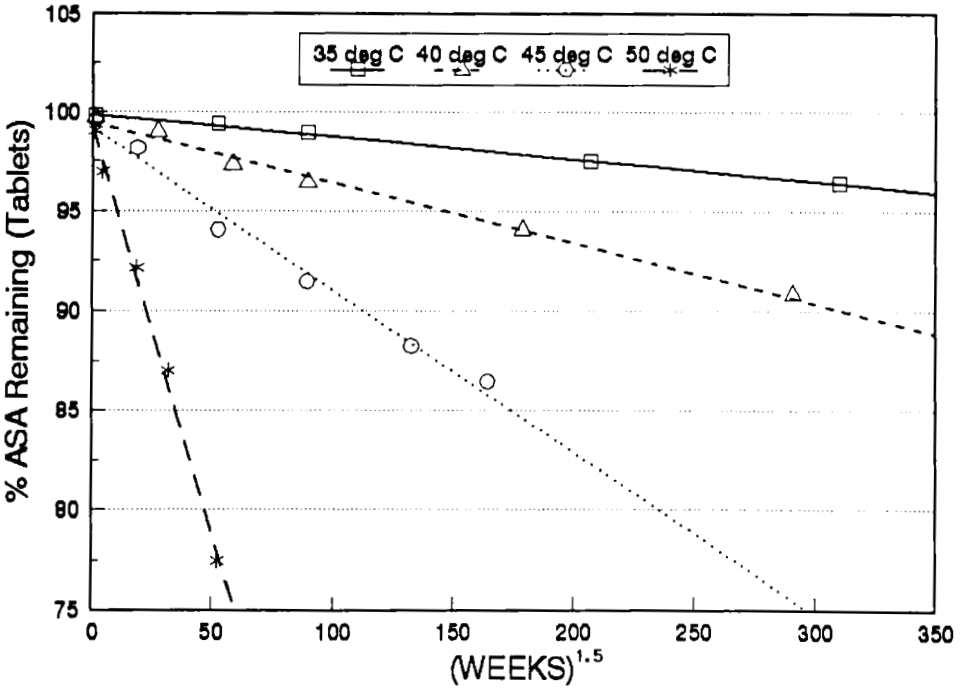

FIGURE 3

Aspirin tablet stability data plotted according to Eq. 4.

terminal linear portions have an average slope of 1.5. Therefore, after an initial lag phase, the data in this study may be fit by the equation:

$$x = kt^{1.5} \quad (3)$$

or

$$y = 100 - kt^{1.5} \quad (4)$$

where y is the percent aspirin remaining. Figure 3 is the aspirin tablet data plotted according to Eq. (4), and the figure shows that the data fit Eq. (4) well.

Figure 4 contains Arrhenius plots of the tablet and powder blend rate constants. The plots show good

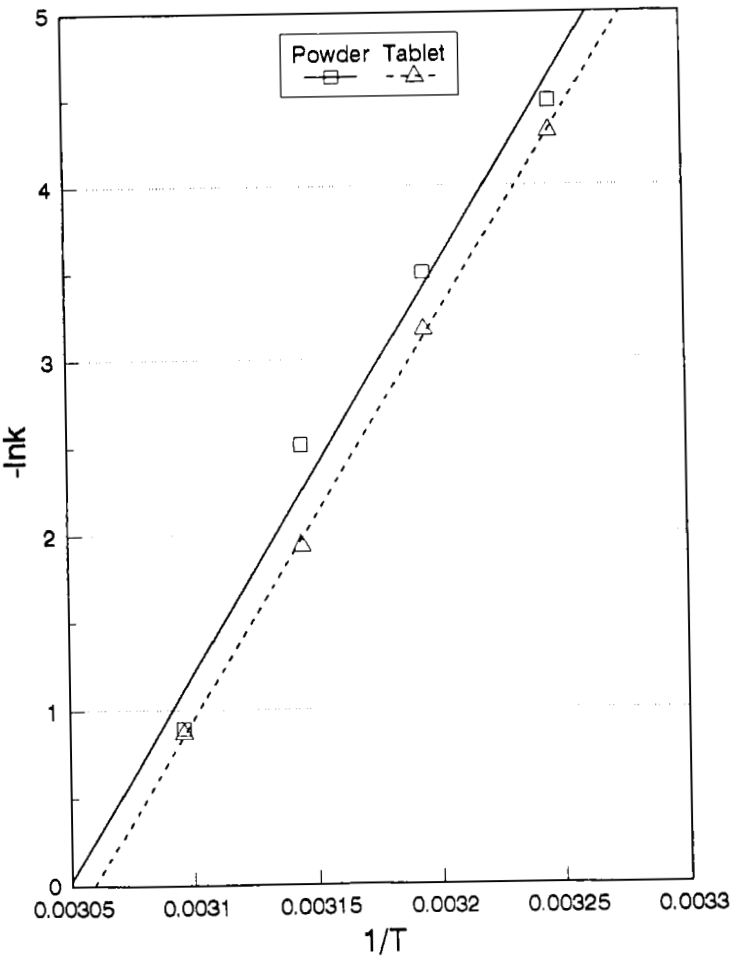

FIGURE 4

Arrhenius plot of Aspirin tablet and powder rate constants.

linearity and are parallel. The apparent activation energy of the solid-state aspirin decomposition, calculated from the slopes of the Arrhenius plots, is approximately 46 kcal/mole. Storage of the product for 1.75 years at ambient temperature resulted in less than 1 percent aspirin decomposition. The Arrhenius plots

are in good agreement with this observation, as they predict less than 1 percent decomposition after 1.75 years of storage at room temperature.

The moisture content of the aspirin formulation was approximately 8 to 8.5 percent both initially and after completion of the stability studies. Thus, although the formulation contained 8 percent moisture, it showed good stability at room temperature. This indicates that, at room temperature, most of the moisture in the formulation is not available to react with the aspirin. However, the apparent activation energy of the solid-state aspirin decomposition is 46 kcal/mole, compared to 15.6 kcal/mole for aspirin solution at pH 0-1 (11). The high apparent activation energy of the solid-state decomposition may be due to a temperature dependent release of moisture from the Emdex^{R}. Further studies are needed to verify this explanation.

REFERENCES

1. B.B. Sheth, F.J. Bandelin and R.F. Shangraw, in " Pharmaceutical Dosage Forms: Tablets, Vol. 1", H.A. Lieberman and L. Lachman, eds., Marcel Dekker, Inc., New York, 1980, pp. 147 - 173.
2. R.B. Tinker and A.J. McBay, J. Am. Pharm. Assoc., Sci. Ed., 43, 315 (1954).
3. L.J. Leeson and A.M. Mattocks, J. Am. Pharm. Assoc. Sci. Ed., 47(5), 329 (1958).

4. J. Hasegawa, M. Hanano and S. Awazu, Chem. Pharm. Bull., 23, 86 (1975).
5. W.H. Yang and D. Brooke, Int. J. Pharm., 11, 271 (1982).
6. S. Yoshioka and M. Uchiyama, J. Pharm. Sci., 75, 92 (1986).
7. J.T. Carstensen, F. Attarchi and X. Hou, J Pharm Sci., 74(7), 741 (1985).
8. W.L. Ng, Austr. J. Chem., 28, 1169 (1975).
9. S. Yoshioka and J.T. Carstensen, J. Pharm. Sci., 79, 799 (1990).
10. J.T. Carstensen and F. Attarchi, J. Pharm. Sci., 77(4), 314 (1988).
11. L.J. Edwards, Tran. Faraday Soc., 46, 696 (1952).