DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(3), 515-526 (1984)

ASPIRIN DEGRADATION IN MIXED POLAR SOLVENTS

Rong-Kun Chang and C. W. Whitworth[1]

[1]College of Pharmacy

University of Georgia

Athens, Georgia 30602

ABSTRACT

Degradation studies were conducted on 0.2% w/v aspirin liquid formulation in a wide range of water-propylene glycol mixtures and water-triethylene glycol diacetate mixtures at four temperatures. The effect of a surfactant, polyoxyethylene (20) sorbitan monolaurate, on aspirin stability was also investigated. There was a linear relationship between water content and degradation rate constants. The surfactant increased aspirin degradation in all formulations. Formulations containing the higher concentration of the surfactant showed the greater aspirin decomposition.

INTRODUCTION

Aspirin has now been available for about 80 years, and its usefulness and popularity are undiminished. It possesses superior qualities as an antipyretic, antiinflammatory, and as a general analgesic. Since aspirin is used so widely by the very old and the very young, both of whom may experience difficulty in swallowing solid medication,

0363-9045/84/1003-0515$3.50/0

there is a definite need in the field of pediatrics and geriatrics for a stable liquid formulation of aspirin.

Aqueous or polar solvents are less toxic and preferred to nonpolar solvents for oral products. Research into the degradation rates of aspirin in mixed polar solvents and into methods of slowing the degradation process hoepfully can yield useful information for the eventual development of a stable liquid dosage form of this drug. The objective of the present study was to measure aspirin degradation in a wide range of water-propylene glycol mixtures and water-triethylene glycol diacetate mixtures to determine if it is possible to predict aspirin degradation based on water content of the mixture. Another purpose was to study the effect of a surfactant on aspirin decomposition in these solvent systems.

EXPERIMENTAL

The following chemicals were used as received: aspirin powder[1], salicylic acid[2], propylene glycol[1], triethylene glycol diacetate[3], polyoxyethylene (20) sorbitan monolaurate[1].

Preparation of Formulations - The samples were prepared by dissolving the aspirin in water and water-glycol solvent mixtures with the aid of mechanical agitation[4] at ambient room temperature to give 0.2% w/v of aspirin. The solvents used are shown in Table I.

Formulations for studying the surfactant effect on aspirin stability were prepared to give 0.2% concentration of aspirin with 1% and 5% v/v polyoxyethylene (20) sorbitan monolaurate. A set of blank samples containing no aspirin were prepared for each solvent system to be used in the assay procedure to counter any effect of the solvents on absorbance readings.

Method of Analysis - Aspirin was analyzed spectrophotometrically[5]

in a manner similar to that reported by Tinker, et al (1). The amount of aspirin and salicylic acid in each sample was calculated and percent decomposition determined.

Aspirin Stability Studies - Aspirin formulations were placed in screwcapped 8 fluid ounce prescription bottles and were stored at 4°C, 25°C, 40°C and 60°C.

Analytical samples were taken at zero time and at specific intervals. Since the aspirin degraded very rapidly at higher temperatures, analytical samples were taken more frequently. The assay schedule was as follows: for aspirin formulations stored at 4°C and 25°C, 2 week intervals for 20 weeks; for 40°C and 60°C 24 hour intervals in the first week, then 2 week intervals for 20 weeks. Assays were usually terminated around 50% decomposition of aspirin.

At specific intervals 1 ml samples were pipetted into 50 ml volumetric flasks, diluted with distilled water, and analyzed for salicylic acid and aspirin at 274 and 296 nm. All assays were performed in triplicate.

Aspirin degradation was first order. Semilogarithmic plots of percent aspirin remaining as a function of time and temperature were used to obtain the degradation rate constants for aspirin. Arrehenius plots based on these rate constants were made and showed the temperature dependency of the degradation reaction of aspirin in these solvent systems.

Surfactant Effect on Aspirin Stability - Aspirin formulations with 1% v/v and 5% v/v polyoxyethylene (20) sorbitan monolaurate were stored at 40°C and 60°C. Sampling, diluting and aspirin content analysis were identical to that of aspirin stability studies.

Statistical Methods - The method of least squares was employed to minimize the sum of square of deviations of the points, to find a best fit regression line and to compute the rate constants.

Table 1

Degradation Rate Constants for 0.2% Aspirin Formulations at Four Different Temperatures

No.	Solvent System % Water	% Propylene Glycol	% Triethylene Glycol Diacetate	K x 10^3 Per Day 4°C	25°C	40°C	60°C	t90%[a] at 25°C
1	100			3.48	25.7	121	584	4.10
2	75	25		2.96	20.8	119	435	5.00
3	50	50		2.22	15.5	87.1	371	6.70
4	25	75		1.50[b]	13.9	17.6[b]	154[b]	7.50
5		100		0.643	3.05[b]	18.7[b]	69.8[b]	34.1
6	75		25	1.25	12.0	54.4	359	8.70
7	50		50	0.469	5.59	27.8	162	18.6
8	25		75	0.292	1.53	9.61	59.4	68.0
9			100	0.208	0.929	7.45[b]	29.0[b]	112.0

[a] $t90\% = \frac{0.104}{K}$ = days required for 10% degradation.

[b] First Degradation Rate Constants for Formulations Showing Two Successive First Order Rates.

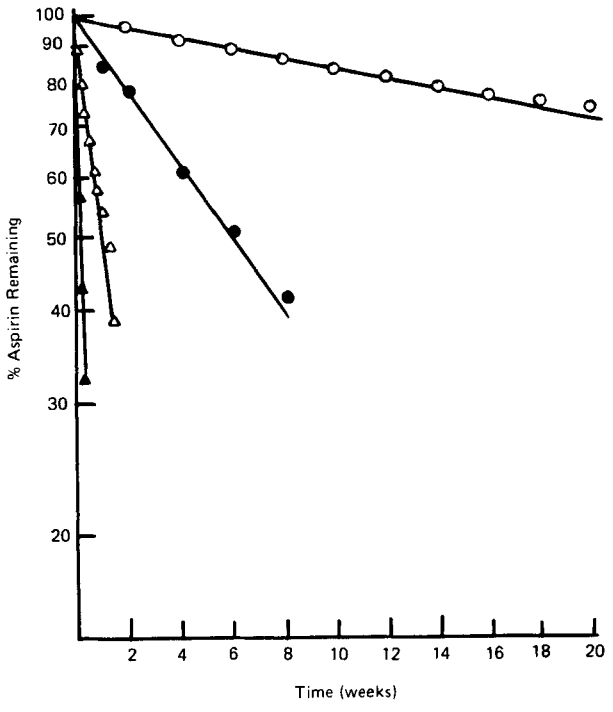

FIGURE 1

Degradation plots for a solution containing 0.2% aspirin in a solvent composed of 50% propylene glycol and 50% water.
Key: ○ 4°C, ● 25°C, △ 40°C and ▲ 60°C

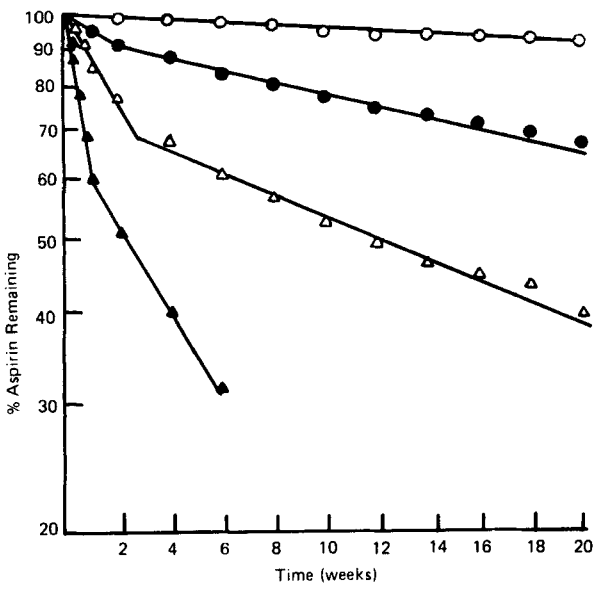

FIGURE 2

Degradation plots for a solution containing 0.2% aspirin in a solvent composed of 100% propylene glycol.
Key: ○ 4°C, ● 25°C, △ 40°C and ▲ 60°C

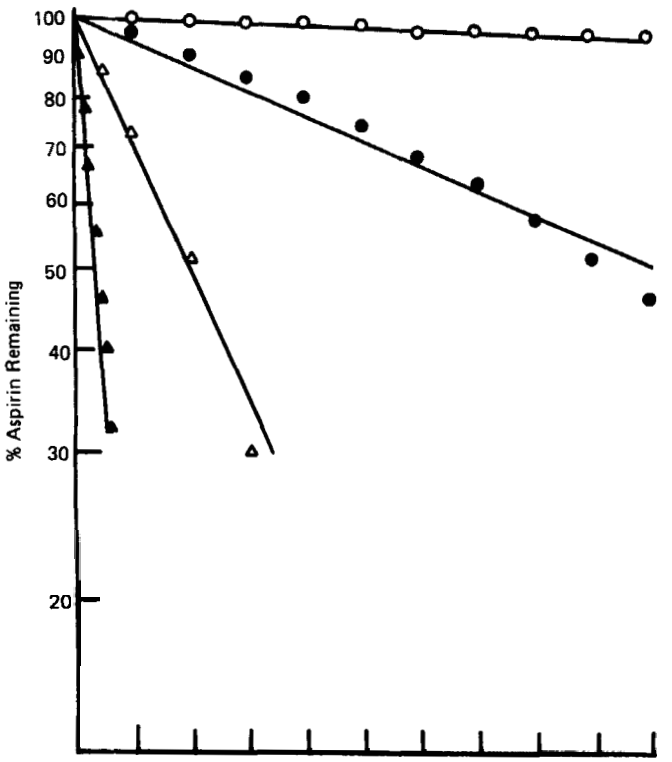

FIGURE 3

Degradation plots for a solution containing 0.2% aspirin in a solvent composed of 50% triethylene glycol diacetate and 50% water.
Key: ○ 4°C, ● 25°C, △ 40°C and ▲ 60°C

RESULTS AND DISCUSSION

Figures 1-4 are typical degradation curves obtained in the study. Figures 2 and 4 show that two successive first order rate constants were obtained with some of the formulations. The initial degradation rate in these instances was fast but then slowed after about two weeks. This change occurred in three of the nine formulations studied, Nos. 4 and 5 containing 75% and 100% propylene glycol respectively and No. 9 containing 100% triethylene glycol diacetate. Transesterification has been found to occur in aspirin-glycol mixtures (2) and acetylation of

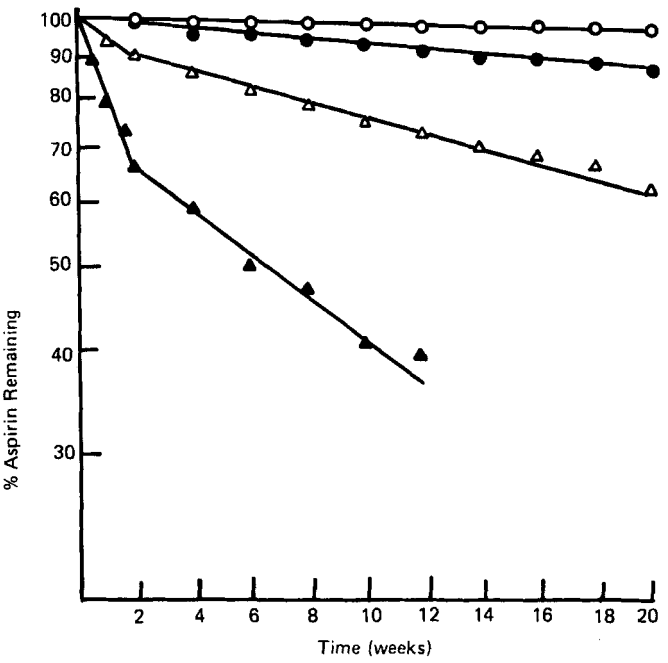

FIGURE 4

Degradation plots for a solution containing 0.2% aspirin in a solvent composed of 100% triethylene glycol diacetate. Key: ○ 4°C, ● 25°C, △ 40°C and ▲ 60°C

the glycols inhibited the aspirin degradation. This may have occurred here to slow the degradation rate.

Table I summarizes the effect of water and temperature on the rate of degradation of aspirin in all the formulations studied. Also shown in Table I is t90% at 25°C which is defined as the number of days required for 10% degradation of aspirin in each solvent system. This shows that aspirin is more stable in the triethylene glycol diacetate mixtures than in those containing propylene glycol. This is consistent with previous findings that aspirin is more stable in glycols whose hydroxyl

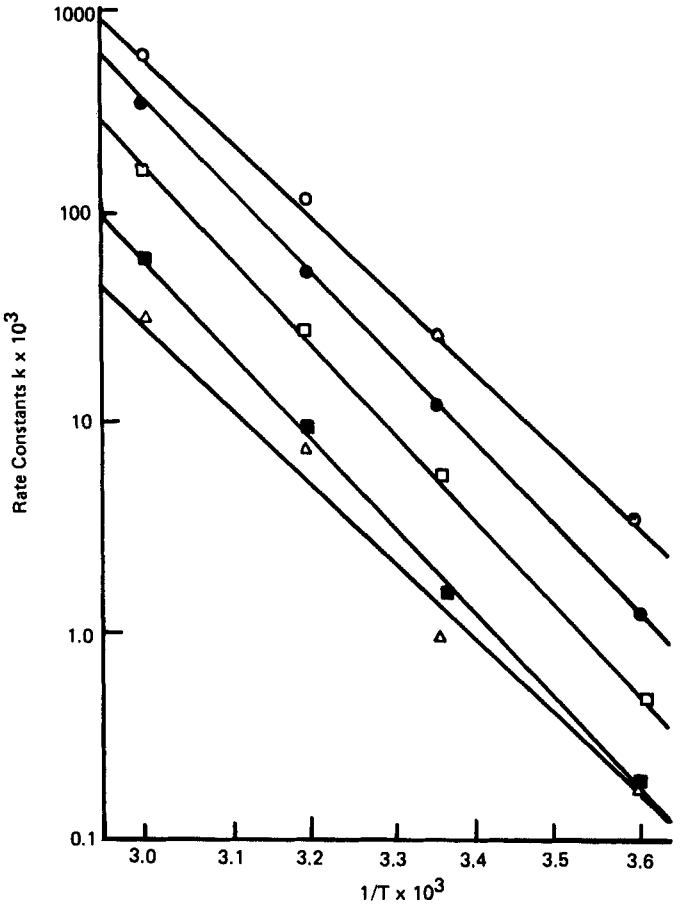

FIGURE 5

Arrhenius plots for several solutions containing 0.2% aspirin. Key: Solvent - ○ water, ● 25% triethylene glycol and 75% water, □ 50% triethylene glycol diacetate and 50% water, ■ 75% triethylene glycol diacetate and 25% water and △ 100% triethylene glycol diacetate.

groups have been partially or completely blocked (3). Figure 5 is an Arrhenius plot showing the temperature dependency of the rate constants for five of the formulations. The four remaining formulations showed similar Arrhenius plots.

There was a linear relationship between water content of the formulations and degradation rate constants which is shown in Figure 6. With these formulations the degradation rates could be predicted based upon known water content.

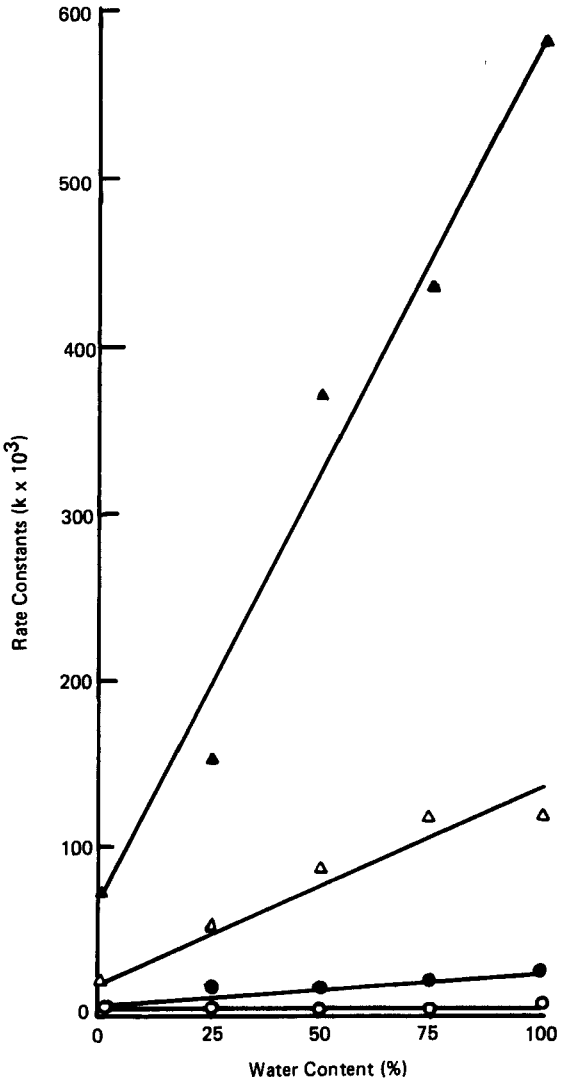

FIGURE 6

Linear relationship between degradation rate constants and water content for formulations 1-5.
Key: ○ 4°C, ● 25°C, △ 40°C and ▲ 60°C

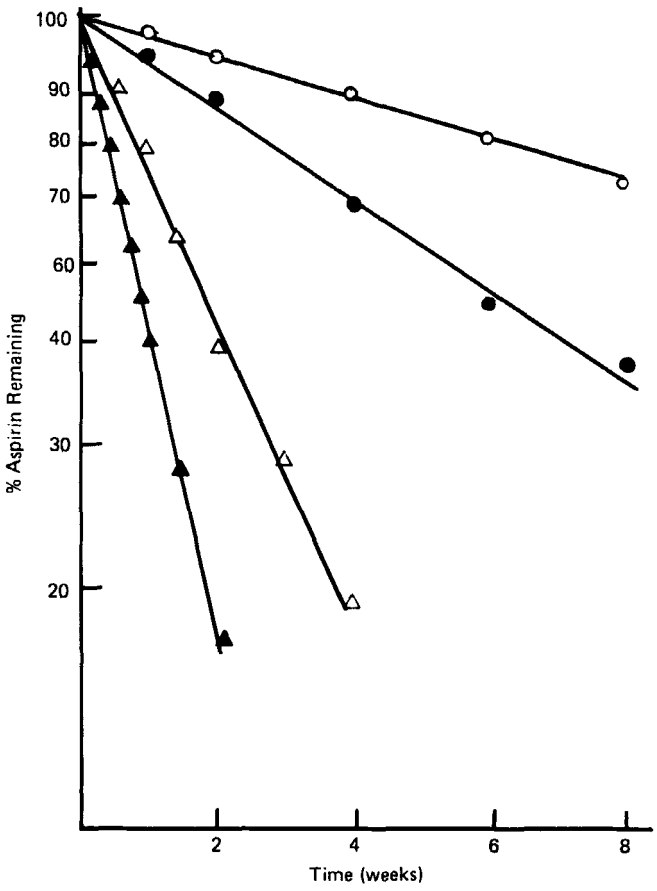

FIGURE 7

Effect of the surfactant polyoxyethylene (20) sorbitan monolaurate on degradation of 0.2% aspirin in a solvent composed of 75% triethylene glycol diacetate and 25% water at two temperatures.
Key: ○ 40°C without surfactant, ● 40°C with 5% surfactant, △ 60° without surfactant, ▲ 60°C with 5% surfactant.

Surface active agents have been reported to accelerate or to decelerate drug degradation (4, 5, 6, 7). Aspirin degradation in an oleaginous suppository base was accelerated by several nonionic surfactants which were polyoxyethylene sorbitan fatty acid esters (8).

Figure 7 shows the effect of inclusion in the formulations of 1% and 5% respectively polyoxyethylene (20) sorbitan monolaurate on aspirin degradation at 40°C. The surfactant increased the aspirin degradation

in all cases and the effect was greater with 5% surfactant. The effect of water content on degradation in the presence of the surfactant was obscured. Similar but more pronounced results were obtained at 60°C.

The mechanism by which the polyoxyethylene sorbitan monolaurate accelerates aspirin degradation may be transesterification as occurs with the glycol solvents. The surfactants contain hydroxyl groups which may be reacting with the acetic acid product to enhance the degradation process. This possibility is strengthened by the fact that aspirin degraded faster in the presence of surfactants which contained more hydroxyl groups, the sorbitan fatty acid esters (8).

When the surfactant was present in the formulations the effect on aspirin decomposition in the mixtures with low water content was considerably more pronounced than in those with high water content. The linear correlation between water content and degradation rate constants was not seen with the formulations containing the surfactant.

As the search continues for a non-toxic solvent in which aspirin is stable it is useful for researchers to study those factors and additives which influence the degradation of this drug.

FOOTNOTES

1. J. T. Baker Chemical Co., Phillipsburg, N.J.
2. Merck and Co. Inc., Rahway, N.J.
3. Union Carbide Corporation, New York, N.Y.
4. Wrist-Action Shaker, Burrell Corp., Pittsburgh, PA.
5. Cary Model 118, Spectrophotometer, Cary Instruments, Mourovia, Californi

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