GLOBAL JOURNAL OF PURE AND APPLIED SCIENCES VOL. 10, NO. 2, MARCH 2004: 297 - 300
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THE KINETICS OF HYDROLYSIS OF ACETYLSALICYLIC ACID (ASPIRIN) IN DIFFERENT POLAR MEDIA

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(Received 18 November 2002; Revision accepted 31 July 2003)

ABSTRACT

The kinetics of hydrolysis of Acetylsalicylic acid (Aspirin) to salicylic acid was followed by the direct spectrophotometric measurement of the amount of salicylic acid produced with time. Salicylic acid was complexed with ferric ion giving a characteristic purple colour (λm 523nm). The kinetics of hydrolysis was found to follow pseudo first-order reaction. Of the polar solvents studied aspirin was most stable in phosphate buffer (0.1 M, pH7.4) with half-life of 537.21 ± 8.42 hours and least stable in glycerol/water system (half-life, 155.31 ± 2.33 hours). Boric acid buffer (pH 10.4) and 10% dextrose solution hydrolyzed aspirin to the same magnitude (half-life 256.67 ± 2.35 and 261.61 ± 2.306) respectively.

KEY WORDS: Aspirin, Hydrolysis, Kinetic studies.

INTRODUCTION

Acetylsalicylic acid or aspirin is one of the first generation non-narcotic analgesic drugs. The pharmacological properties has been well documented (Parma et al., 1998; Angi et al., 1998; Petty et al., 1999). Aspirin continues to be of interest to Scientists because it is a model hydrolabile ester drug with so many pharmacological and physiological properties (Lynch, 1999; Song et al., 1999). In aqueous suspension, aspirin has been reported to hydrolyze spontaneously to salicylic acid and acetic acid but can be stabilized by a variety of compounds (Mazzeo et al. 1982; Jun et al. 1974). The hydrolysis rate constant of aspirin in water has been shown to follow pseudo first-order kinetics (Lasso et al. 1981; Ujhelyi and Racz, 1985; Choudhury and Mitra, 1993; Alibrandi et al. 1996). In most of the studies reported the mechanism of hydrolysis of aspirin was by trans-esterification.

The stability of aspirin powders and in pharmaceutical formulations has been studied using various compounds. Unsubstituted polyhydric alcohols have been shown to stabilize aspirin in aqueous solutions more than substituted polyhydric alcohols (Jun et al., 1974). Similarly, poloxamine 1508 was reported to stabilize aspirin 2-3 fold at pH 1.0 to pH 10.0 (Spancake et al., 1991). In another report, the influence of moisture present in diluents on the stability of aspirin and in the presence of mixed sugars did not significantly affect the stability of aspirin because the moiture molecules were shown to be unavailable to react with aspirin molecules (Snavely et al., 1993). In the presence of basic amino acids like lysine and arginine, the stability of aspirin was greatly enhanced at sub-zero temperatures as compared to room temperature (Gonullu and Guven, 1997). As would be expected the rate of decomposition of aspirin was temperature- and time-dependent (Snavely et al., 1993; Gonullu and Guven, 1997). In a recent report (Ujhelyi and Racz, 1985; Alibrandi et al., 1996; Kishore and Nagwekar, 1990) it was observed that estimates of the shelf-life of aspirin could be misleading and even wrong when decomposition rate constant and activation energies are used for the calculation of the shelf-life.

Ultraviolet (Mazzeo et al., 1982), infra-red and Raman spectrometry (Wang et al. 1997) and reverse-phase HPLC (Gupta, 1980; El Shanawany et al., 1991) has been utilized in stability studies of aspirin under different conditions. The use of ferric salts for both quantitative and qualitative determinations of aspirin stability (Higuchi and Brochmann-Hanssen, 1961) is still attractive because of its simplicity and accuracy of determination. In less developed laboratories, the need for simple, accurate and reproducible techniques for the quality assurance of aspirin is desirable.

The objective of the present study is to adapt the basic principles of the reaction between ferric salts and salicylic acid to the determination of the stability of aspirin in different polar solvent media. This information will be helpful in the kind of excipients and additives employed during the formulation of aspirin.

MATERIALS AND METHODS

Materials

Dr I.S. Okafor of the Department of Pharmaceutics and Pharmaceutical technology, University of Jos, kindly donated salicylic acid and

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Table 1.0: Hydrolysis constant and half-life of aspirin in different polar solvents.

Solvent system	Rate Constant ± S.E.M. Hr^{-1}	Half-life ± S.E.M. Hr	Shelf-life ± S.E.M. Hr^{-1}
Distilled water	$2.13 \times 10^{-3} \pm 1.15 \times 10^{-4}$	325.35 ± 17.596	44.755 ± 2.421
Phosphate buffer (0.1M, pH 7.0	$1.651 \times 10^{-3} \pm 1.529 \times 10^{-4}$	419.75 ± 38.87	57.739 ± 5.347
Phosphate buffer (0.1 M, pH 7.4	$1.29 \times 10^{-3} \pm 1.643 \times 10^{-4}$	537.209 ± 8.421	73.897 ± 3.412
Hydrochloric acid buffer (0.1 M pH 1.0)	$2.340 \times 10^{-3} \pm 1.643 \times 10^{-4}$	296.154 ± 2.074	45.034 ± 2.162
Boric acid buffer (0.1M, pH 8.4)	$3.86 \times 10^{-3} \pm 2.381 \times 10^{-4}$	179.534 ± 1.107	27.301 ±1.684
Boric acid buffer (0.1M,pH 10.4)	$2.700 \times 10^{-3} \pm 2.471 \times 10^{-4}$	256.667 ± 2.349	39.029 ± 3.572
Glycerol	$3.380 \times 10^{-3} \pm 1.561 \times 10^{-4}$	205. 030 ± 9.408	36.175 ± 1.660
Glycerol-water (4 : 1)	$4.462 \times 10^{-3} \pm 1.819 \times 10^{-4}$	155.312 ± 2.332	57.348 ± 2.338
Propylene glycol 400	$2.021 \times 10^{-3} \pm 2.11 \times 10^{-4}$	342.894 ± 5.799	52.164 ± 2.446
5 % dextrose soln. pH 7.0	$2.667 \times 10^{-3} \pm 2.233 \times 10^{-4}$	259.843 ± 8.756	39.512 ± 3.308
10 % dextrose soln. pH 7.0	$2.812 \times 10^{-3} \pm 2.479 \times 10^{-4}$	261.608 ± 2.306	26.272 ± 1.435

acetylsalicylic acid powders (BDH Chemicals Ltd, England: 99.9 % each). Identification tests were carried out according to the British Pharmacopoeia (British Pharmacopoeia, vol. 1) methods to authenticate the samples. They were used without further purification.

The following solvents and reagent grade, BDH Chemicals Ltd, poole, England, were used: Ethanol, 96 %, Glycerol, Ferric chloride, disodium hydrogen orthophosphate, concentrated hydrochloric acid, sodium hydroxide pellets, sodium chloride, boric acid and dextrose. A pye-Unicam UV/vis spectrophotometer was used for the analysis of absorbance. Melting point apparatus was Griffin Gallenkemp (UK)

2.2 Determination of absorption maximum for salicylic acid-ferric ion complex.

Equal volumes of 1 % solutions of ferric chloride and salicylic acid were mixed thoroughly in a test-tube. A dilution of 1.0 mL in 100 mL was prepared and absorption maximum determined by scanning in the visible region of the spectrum (400-600 nm) using Pye-Unicam spectrophotometer. The limit of detection of the complex was established by several dilutions of the stock solution.

Determination of absorbance with concentration.

A stock solution of salicylic acid (0.07246M) was prepared. Serial dilutions of the stock solution were prepared and 1.0 mL of ferric chloride (0.05518 M) solution was added to each flask, and the volume made up to mark. The final concentration of salicylic acid ranged from 1.0×10^{-3} M to 8.0×10^{-3} M. The absorbance of each concentration was read and a graph of absorbance against concentration was plotted (i.e. Beer/Lambert plot).

3.4 Preparation of Buffer Solutions:

Hydrochloric acid buffer (0.1 M, pH 1.0); phosphate buffer (0.1 M, pH 7.0 and pH 7.4; Boric acid buffer (0.1 M, pH 8.4 and 10.4) were prepared according to the methods of British Pharmacopoeia (British Pharmacopoeia vol. 2 p A131).

Preparation of 5 % and 10 % Dextrose Solutions

Analytical grade dextrose solutions were prepared by respectively dissolving 5.0 g and 10.0 g per 100mL distilled water.

Hydrolysis of Aspirin in different solvent media:

The solvent systems used for the study of the hydrolysis of Aspirin were: distilled water, hydrochloric acid buffer (0.1 M, pH 1.0); Phosphate buffer (0.1 M, pH 7.0 and 7.4); boric acid buffer (0.1 M, pH 8.4 and 10.4); glycerol, glycerol/water (4:1); propylene glycol 400; dextrose solutions buffered to pH 7.0. Aspirin stock solution (0.02778 M) was prepared by dissolving 0.5 g of aspirin in 20 mL of ethanol (96 %), then diluted with distilled water to 100 mL in a volumetric flask. For glycerol and propylene glycol 400, separate stock solutions of the same molarity were similarly prepared. From each stock

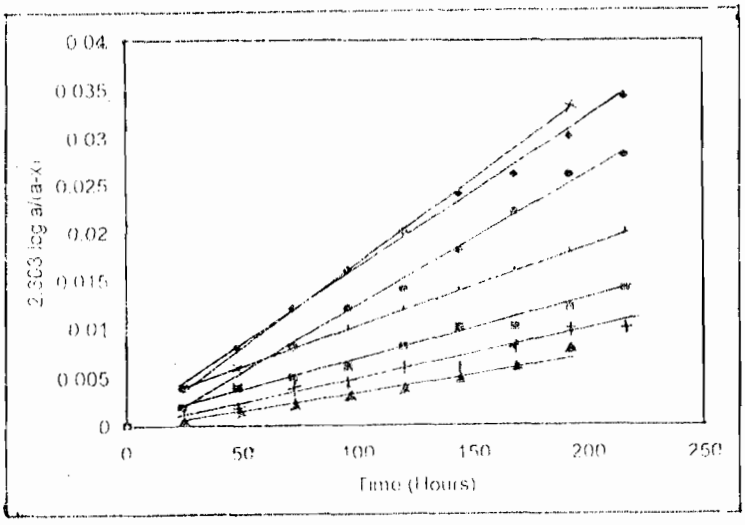

Fig.1: Plots of rates of hydrolysis of acetylsalicylic acid (aspirin) in differet polar media: water = (◆); hydrochloric acid buffer (■); Phosphate buffer pH 7.4 (▲); Boric acid buffer (×): Glycerol/water (●); propylene glycol (-✱); 5 % Dextrose solution (+).

solution 10 mL was diluted to 100 mL in an appropriate solvent using the calibration flask. These flasks were left to stand under the laboratory conditions (26 ° ± 1°C). Samples were withdrawn at intervals of 24 hrs for up to 336 hrs and analyzed spectrophotometrically after mixing with ferric chloride solution. The hydrolysis constant was determined graphically by monitoring the rate of formation of salicylic acid.

RESULTS AND DISCUSSION

The rate of hydrolysis of acetylsalicylic acid (Aspirin) to salicylic acid was followed by the direct measurement of the amount of salicylic acid produced with time. The intensity of the colour formation between ferric ion and salicylic acid is one of the oldest quantitative methods used in the determination of salts or esters of salicylic acids in medicine.

The absorption maximum for the salicylic acid-ferric ion complex was found to be 523 nm (Literature value: 525 nm, (Higuchi and Brochmann-Hanssen, 1961). This observed difference could be due to variations that are usually encountered with different spectrophotometer models. The lower limit of detectability was between 5.0ppm and 7.0ppm. A linear relationship was obtained in the concentration range studied satisfied the following model equation:

$$A_{523} = 0.000386 + 54.3x$$

and the regression coefficient by the method of least squares was 0.996.

The kinetic rate constant for the hydrolysis of aspirin in each solvent system was determined by graphical method. The plot fitted the equation of pseudo first-order kinetics (Fig. 1). Amongst the hydroxylic solvents studied, aspirin was found to be most stable in the phosphate buffers, followed by water, hydrochloric acid and dextrose solutions (Table 1.0). This investigation also reveals that aspirin was less stable in glycerol-water system than glycerol alone, while boric acid buffers and dextrose produced about the same magnitude of hydrolysis (Table 1.0). The relative stability of aspirin in polyethylene glycol-water system found in this study is consistent with earlier reported value (Baker and Niazi, 1983).

The established mechanism of hydrolysis of aspirin in the presence of polyhydric alcohols is by trans-esterification (Jun et al. 1974; Baker and Niazi, 1983; Chang and Whitworth, 1984). The observed stability of aspirin in polyethylene glycol- water system in this study suggests that trans-esterification pathway may have been disrupted. The probable mechanism of hydrolysis in the aqueous buffers and dextrose solutions is by electrophilic type of reaction since trans-esterification is not likely in these circumstances.

Although these polar substances are not usual compounds in the formulation of aspirin, if good manufacturing practices are not maintained, these substances can find their way into excipients and binders as contaminants. In tropical regions of the World, relative humidity is extremely high so the effect of any of these contaminants in combination with moisture will greatly affect the stability of the formulation.

CONCLUSION

The reaction between Ferric ion and salicylic acid produces an intense colour that

facilitates the quantitative determination of the salt. Any protic solvent has the potential to hydrolze acetylsalicylic acid as a result of the presence of a sensitive hydrolabile ester bond. The hydrolysis constant of acetylsalicylic acid in the various buffer systems directly relates to their buffer capacity. In this investigation the kinetics of hydrolysis follows a pseudo-first-order reaction. Both the pure and the formulated forms of salicylic acid need to be handled with caution.

ACKNOWLEDGMENT

The author is grateful to the Department of Pharmaceutical Chemistry, University of Jos, for material assistance.

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