DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 3(1), 65-72 (1977)

SULFITE INDUCED ANAEROBIC DEGRADATION OF EPINEPHRINE IN LIDOCAINE HYDROCHLORIDE INJECTION

B.R. Hajratwala

Department of Pharmacy

University of Otago

Dunedin, New Zealand

ABSTRACT

The sulfite induced anaerobic degradation of epinephrine in lidocaine hydrochloride injection, U.S.P. was studied, at pH 4.0 and 4.4. The epinephrine concentration was 0.001 per cent. The activation energy parameters were evaluated from arrhenius type plots. $\Delta H^{\ddagger}$ was found to be 23.6 and 23.9 kcal $mole^{-1}$ for pH 4.0 and 4.4 respectively and compared favourably with literature value. Based on these results, shelf life was predicted and changes in U.S.P. monograph are suggested.

The anaerobic degradation of epinephrine in aqueous solution over the 3.63 - 5.00 pH range was reported earlier (1) as a preliminary to stability studies on products containing

epinephrine. The degradation of epinephrine was induced by sodium metabisulfite.

The purpose of this investigation was to study the sulfite induced anaerobic degradation of epinephrine in Lidocaine Hydrochloride Injection, U.S.P.

EXPERIMENTAL

Materials: All materials used were of analytically pure grade. These included epinephrine (the l-form), anhydrous sodium acetate, acetic acid, sodium chloride, sodium metabisulfite and lidocaine hydrochloride.

Kinetic Studies: The standardization of epinephrine was previously reported (1). The kinetic studies were carried out as previously reported (1) at 72°, 81°, 86° and 91° ($\pm$ 0.1°). The epinephrine contents were determined using U.S.P. XVIII spectrofluorometric method (2). The pH of each sample was measured to ensure the constancy of pH during the entire procedure and was found to be so. The degradation followed first order kinetics as represented earlier (1). The apparent first order rate constants were obtained from first order plots of log epinephrine concentration versus time. All straight line results were calculated by linear regression analysis.

Formulation of Lidocaine Hydrochloride Injection with Epinephrine: All formulations were prepared under anaerobic conditions (using nitrogen) in water for injection and

contained sodium metabisulfite 0.05%, Methyl paraben 0.1%, Epinephrine 0.001%, 0.03M acetate buffer enough to adjust pH to either 4.0 and 4.4 and Lidocaine Hydrochloride 1 or 2%. All formulations were made isotonic with sodium chloride.

RESULTS AND DISCUSSION

Table I shows four different formulations which were selected. The formulations for marketed Lidocaine hydrochloride injections with epinephrine vary considerably in their content and concentrations of active ingredients and additives. The lidocaine hydrochloride concentration ranges from 0.5 to 2%. One and two percent were selected being the most common ones. Since the maximum epinephrine content allowed in U.S.P. product is 0.001 percent, this was used in the present study. The previous study (1) reported the effects of sodium metabisulfite, sodium chloride and acetate buffers and pH. The present study was carried out at two pH values, 4.0 and 4.4 as the catalytic effects by these was minimal at these pH values. The methyl paraben, 0.1 percent was selected based on the earlier survey of marketed products (3).

Figure 1 shows the effect of temperature on epinephrine degradation in four different formulations of lidocaine hydrochloride injection. The parallel lines indicate that the mechanism of degradation at two pH values is similar. The various parameters evaluated from Figure 1 are

TABLE I

Different Formulations + of Lidocaine Hydrochloride Injection with Epinephrine.

Formulation	Lidocaine Hydrochloride, %	pH
R1	2	4.4
R2	2	4.0
R3	1	4.4
R4	1	4.0

+ All formulations contain 0.001% epinephrine, 0.05% sodium metabisulfite, 0.1% methyl paraben, 0.03M acetate buffer to adjust pH and enough sodium chloride to adjust isotonicity.

presented in Table II. There does not appear to be any significant difference between one and two percent lidocaine hydrochloride containing formulations for a given pH and hence data for these were combined for evaluating activation energy parameters. The present findings compare favourably with the literature value for $\Delta H^{\ddagger}$ of 23.19 k cal $mole^{-1}$ obtained by Schroeter and Higuchi (4). They used epinephrine in the 0.05 to 0.1 molar range in perchloric and hydrochloric

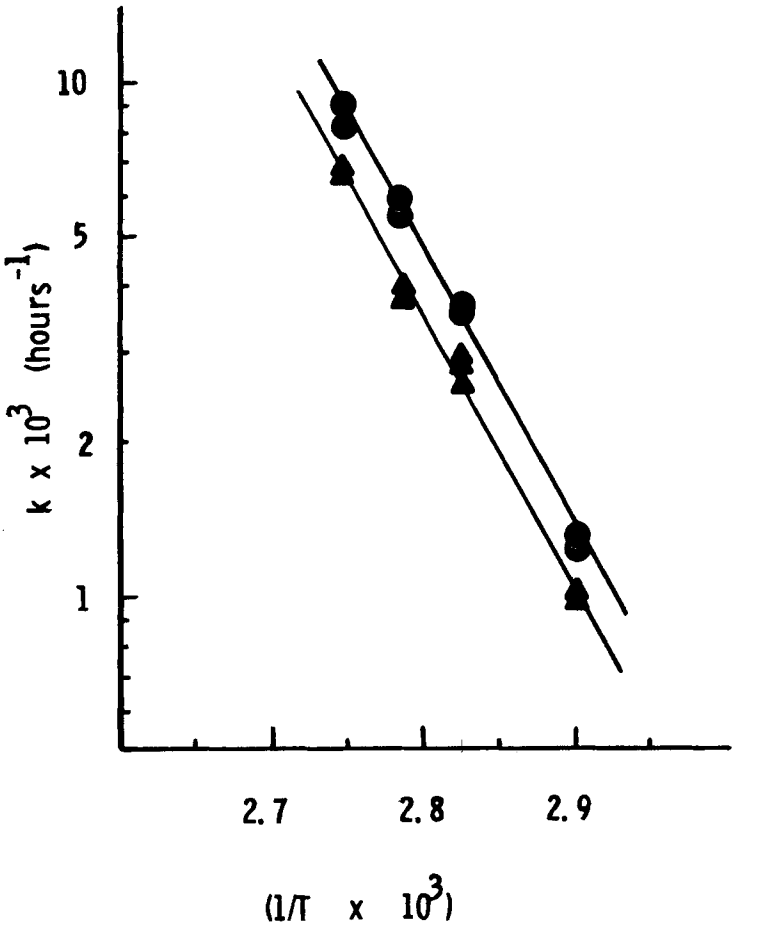

Figure 1: Effect of temperature on sulfite induced anaerobic degradation of epinephrine in Lidocaine Hydrochloride Injection. U.S.P. Key: ●, pH 4.4; ▲, pH 4.0.

acid solution containing 0.1% sodium bisulfite. The pH values ranged from 0.2 to 1.2. The temperature range used by these workers was 43.4° to 73.0°.

TABLE II

Various Parameters Calculated for Epinephrine Degradation in Lidocaine Hydrochloride Injection at 25°.

Parameter	pH 4.0	pH 4.4	From Ref. 4
Ea, kcal $mole^{-1}$	24.2	24.5	
$\Delta H^{\ddagger}$, kcal $mole^{-1}$	23.6	23.9	23.19
$\Delta S^{\ddagger}$, cal $mole^{-1}$ deg^{-1}	-20.2	-19.0	
A, sec^{-1} (arrhenius frequency factor)	6.4×10^{8}	1.2×10^{9}	
S_E, Std error of estimate	0.0326	0.0813	
r, correlation coefficient	-0.995	-0.969	

The U.S.P. XVIII (2) monograph on Lidocaine hydrochloride has a range of 90 to 115 percent epinephrine. An earlier report (3) showed the presence of up to 30 percent excess of label claim in marketed products. Thus assuming that a starting concentration of 115 percent epinephrine is present, U.S.P. monograph allows approximately 22 percent degradation. The results obtained from arrhenius type plots can be used for predicting shelf life at various temperatures. The problems associated with such techniques are well summarized

by Garrett (5). Using lower limit of 95% confidence limit as an expiration date for 15 percent degradation of epinephrine ($t_{0.15}$), the following values are obtained using data of Table II for formulations at pH 4.4. At 30°, $t_{0.15}$ of 15 months, at 15° $t_{0.15}$ of 11 years and at 8° $t_{0.15}$ of 31 years. The U.S.P. monograph has limits of 3.3 to 5.5 for pH and no storage temperature specifications for this dosage form. (The U.S.P. does not have storage temperature specifications for any of epinephrine containing products). Obviously at a pH greater than 4.4, the $t_{0.15}$ is going to be much shorter than 15 months, which supports the data presented earlier (3). The following proposals are made for U.S.P. monograph:

1. The higher limit for pH specification be 4.4;
2. Storage conditions be store in cold place' and
3. If the above proposals are acceptable then the present specifications for epinephrine concentration of 90 to 115 percent is too wide and be limited to 90 to 105 percent epinephrine.

ACKNOWLEDGEMENT

The work was carried out in part at Research and Development Department, Invenex Pharmaceuticals, San Francisco, CA, 94124.

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