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A STABILITY STUDY OF CLINDAMYCIN HYDROCHLORIDE AND PHOSPHATE SALTS IN TOPICAL FORMULATIONS

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ABSTRACT

The stability of clindamycin hydrochloride and clindamycin phosphate was studied in topical liquid formulations prepared with the following solvents: solvent A (70% isopropanol, 10% propylene plycol and 20% water), solvent B (48% isopropanol, polyoxyethelene ethers, acetone, salicylic acid and allantoin), solvent C (40% alcohol, acetone, polysorbate 20, fragrance and water) and "standard" (50% isopropyl alcohol, propylene glycol and water) in glass and plastic containers at 25°, 40°, and 50°C.

It was found that, in general, better stability was obtained in glass containers than in plastic containers. At 25°C both the clindamycin hydrochloride and phosphate formulations in solvent B showed poorer stability than in the other solvents irrespective of the type of container, while formulations in solvent C showed the best stability. In addition, the effect of the pH on the stability of the formulations was determined, and it was clear that at pH values below 4 the stability of all formulations decreased.

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INTRODUCTION

Pharmacists in hospitals and community settings have for some time been preparing topical clindamycin prescriptions for treating acne vulgaris by incorporating the content of six to eight 150 mg clindamycin hydrochloride capsules into alcohol or other solvents. Orr et al. (1) suggested as a solvent an "ideal vehicle" consisting of isopropanol 70%, propylene glycol 10% and water 20%. To our knowledge, however, very little information regarding the stability of these and/or other topical clindamycin formulations has been published. It was decided to prepare topical solutions of clindamycin hydrochloride (I) and clindamycin phosphate (II) with three different vehicles, study their stability in glass and plastic containers at different temperatures and compare the results with a standard topical clindamycin solution.

EXPERIMENTAL

Materials

Clindamycin hydrochloride[1], Clindamycin phosphate[2], solvent A (70% isopropanol, 10% propylene glycol and 20% water; pH=5.5)[3], solvent B (48% isopropanol, polyoxyethylene ethers, acetone, salicylic acid and allantoin; pH=2.9)[4], solvent C (40% alcohol, acetone, polysorbate 20, fragrance and water; pH=5.0)[5], "standard" (50% isopropyl alcohol, propylene glycol and water; pH= 5.0)[6], and methanol, HLPC grade. All other chemicals were reagent grade or better and used without further purification.

Formulations

Appropriate quantities of (I) (1 mg of clindamycin HCl is equivalent to 858 mcg of clindamycin base) or (II) (1 mg

of clindamycin phosphage is equivalent to 785 mcg of clindamycin base) were dissolved in each solvent to prepare 1 liter quantities of 1% solutions of (I) and (II). To achieve complete solubility the preparations were mixed up to 24 hours with the aid of a magnetic stirring bar. At no time was heat used for fear of altering the compounds' stability.

Stability Studies

The rate of degradation of (I) and (II) in all solvents was determined at 25°, 40°, and 50°C. Portions of each formulation were placed in 2 ounce screw cap plastic (polypropylene) and glass bottles. In addition, the "standard" was treated under the same conditions and was used as a control. Each bottle was analyzed for clindamycin by utilizing HPLC.

Preparation of Standards

Standard solution of (I) was prepared by dissolving 116 mg in 10 ml of the vehicle being tested in a 100 ml volumetric flask. A methanol-water (25:75) solution was added to volume. The standard solution of (II) was prepared by dissolving 123 mg of (II) in 10 ml of the vehicle being tested. A methanol-water solution (45:55) was added to bring to volume.

Mobile Phase

The mobile phase for (I) was prepared by mixing 1 gm of dioctyl sodium sulfosuccinate, 1 gm formic acid, 125 ml water and brought to 500 ml total volume with methanol. The mobile phase for (II) was prepared by mixing 1 gm EDTA, 200 ml water, adjusted to a pH of 5.8 with 5N NaOH, 275 ml methanol and brought with water to 500 ml total volume.

HPLC

Samples were analyzed using a high-performance liquid chromatograph equipped with a universal liquid chromatographic injector, a UV (254 nm) absorbance detector and a strip-chart recorder connected to a Waters differential refractometer. The samples were chromatographed at room temperature on a microparticulate (μBondapac C-18) reverse-phase HPLC column. The flow rate was adjusted to 1 ml/minute with a column. pressure of 42.18 kg/cm.^{2} The chart speed was 0.5 cm/minute; the attenuation of the refractive index detector was 9.6 x 10^{-5} units full scale which is equal to the 4x reading on the Waters differential refractometer. The ratio on the peak heights of (I) and (II) to that of the standard (I) and (II) was used to calculate the concentrations based on a calibration curve prepared from standard samples.

Calculations

Peak height ratios were obtained by dividing the peak heights of (I) and (II) by the peak heights of the standards of (I) and (II). Calibration curves from known concentrations were prepared by plotting the peak height ratios versus the (I) and (II) concentrations. The values of the unknown concentrations of the (I) and (II) samples were read directly from the graph.

RESULTS AND DISCUSSION

Typical chromatograms obtained with (I) and (II) in solvents A, B, and C, and the "standard" preparation are shown in Fig. 1 and 2.

The stability of (I) and (II) in all solvents was determined in both glass and plastic containers at three

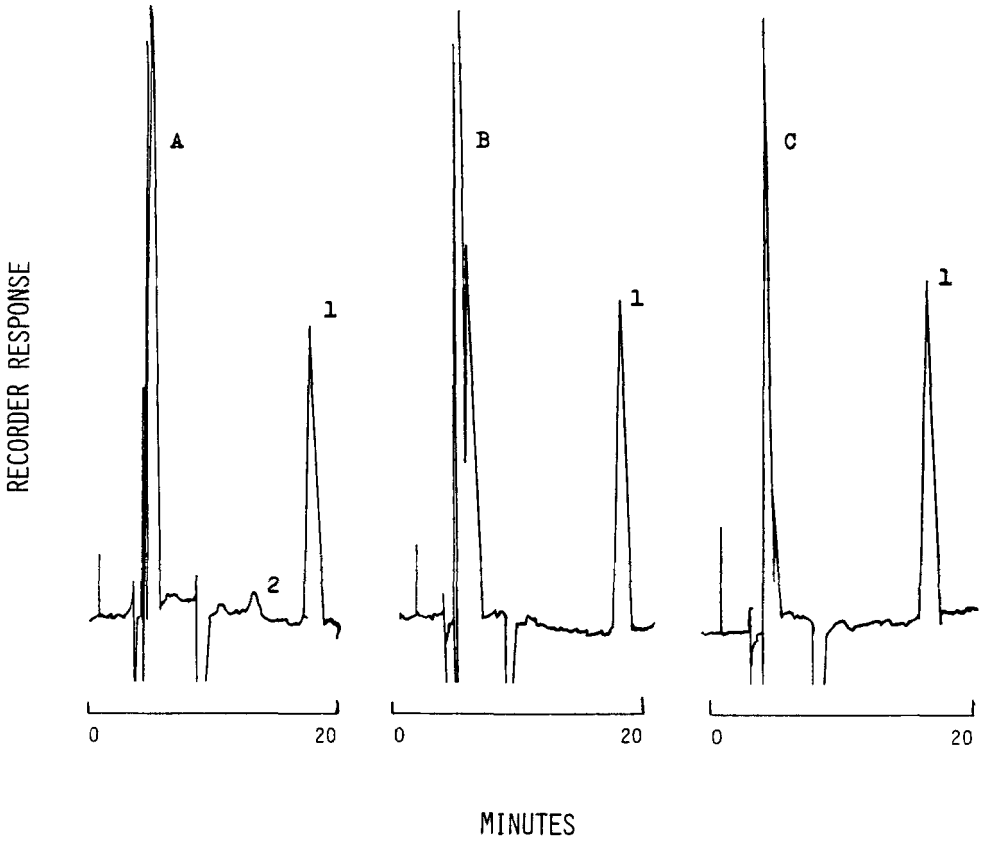

FIGURE 1

Chromatogram of Clindamycin Hydrochloride. Key: (A) Solvent A - Major peak is clindamycin (1) and minor peak is Clincamycin B (2) which differs in that an ethyl group replaces the n-propyl group of clindamycin; (B) Solvent B; (C) Solvent C.

different temperatures (25° 40°, and 50°C). The data are shown in Table 1; stability data at 50°C with plastic containers could not be obtained due to the destruction of plastic (polypropylene) container at this elevated temperature. It is apparent from Table 1 that the stability of (I) in glass containers at 25°C decreases in the order C > A > B, while in plastic bottles the order is A, C > B. The stability at all other temperatures in glass and plastic con-

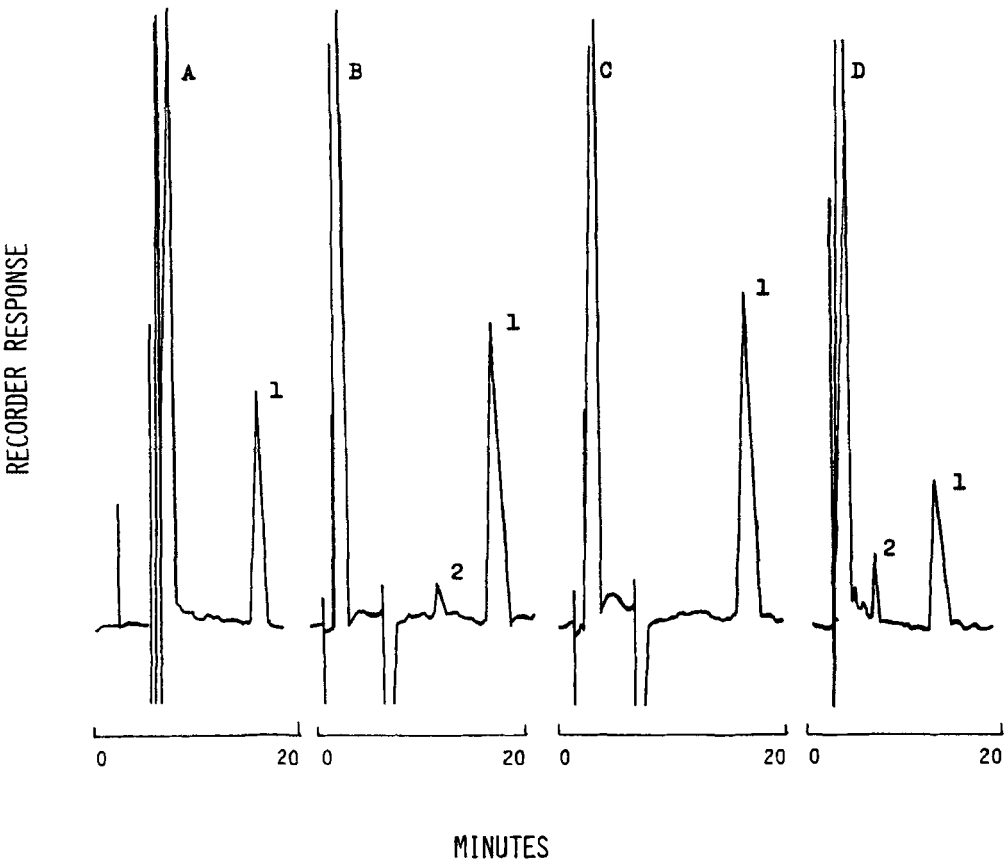

FIGURE 2

Chromatogram of "standard" and clindamycin phosphate. Key: (A) "standard;" (B) solvent A; (C) solvent B; and (D) solvent C; 1, clindamycin 2-phosphate; 2, a mixture of clindamycin 3-phosphate and clindamycin 4-phosphate.

tainers is of the same order of magnitude. The stability of (II) in glass containers decreases in the order: standard > A, C > B at 25°C, while in plastic containers the order is: C > A > B. The stability at all other temperatures for both containers is the same, with the exception of the standard which showed an increase in stability of two months over the other preparations.

Table I. Stability of (I) and (II) In Different Solvents

Time (in months) Required for Less than 90% of the Active Ingredient to Remain in Solution

	(I)					(II)				
	Glass			Plastic		Glass			Plastic	
Solvent	Temperature					Temperature				
	25°	40°	50°	25°	40°	25°	40°	50°	25°	40°
A	10	4	2	10	4	12	4	2	10	2
B	8	4	2	8	4	10	4	2	6	2
C	12	4	2	10	4	12	4	2	12	2
Standard	--	-	-	--	-	13.6	6	2	--	-

Polypropylene is a straight chain hydrocarbon of waxy character, and it has the lowest density (0.91) of all plastics. It contains antioxidants, antistatic agents and processing aids (such as agents that allow the bottles to be released more easily from their molds) that could affect the stability of clindamycin.

According to Oesterling (2), there are three important pathways of clindamycin degradation: Pathway A: the triglycoside is hydrolyzed to 1-dethiomethyl-1-hydroxylincomycin and methylmercaptan; this pathway is predominant at pH values below 4. Pathway B: the amide hydrolysis; this occurs through the entire pH range and is presumably especially important in solutions of very high or very low pH. Pathway C: hydrolysis

Table 2. Effects of pH on the Rate Constant ($month^{-1}$) of (I) and (II) at Room Temperature

		(I)		(II)	
Solvent	pH	Glass	Plastic	Glass	Plastic
A	5.5	7.19×10^{-3}	1×10^{-3}	6.14×10^{-3}	11.5×10^{-3}
B	2.9	1.36×10^{-2}	1.57×10^{-2}	1.06×10^{-2}	$1.43. \times 10^{-2}$
C	5.0	6.67×10^{-3}	6.9×10^{-3}	8.64×10^{-3}	9.21×10^{-3}
Standard	5.0	----	-----	5.18×10^{-3}	----

to lincomycin at pH's between 5 and 9; this reaches a maximum rate at high pH's when the tertiary amino function is essentially completely unprotonated. It is clear from Table 2 that the decomposition of (I) and (II) in solvent B at a pH of 1.9 will follow pathway A which requires a pH below 4. The decomposition of (I) and (II) in the other solvents that have pH values close to 5 will follow pathways B and/or C. In addition, since pH 5 is not the optimum pH for these two pathways, the rates of the decomposition will be expected to be low. This is verified by the data of Table 2.

The rate constants were calculated by using first order kinetics and utilizing plots of the log of the concentrations remaining against time (months). The activation energies were calculated by using the Arrhenius equation and plotting the log of each rate constant versus the reciprocal of absolute temperature. The data for all treatments are shown in Tables III and IV. Note again that throughout the experiments relative better stability was obtained in glass than in plastic containers as can be seen in Tables 3 and 4.

Further analysis of the data, however, by utilizing a one way ANOVA for an independent measures was conducted to identify if there were any differences between glass ($\bar{x}$ = 28.7) and plastic($\bar{x}$ = 24.22) containers.

The results listed in Table 5 show that F (1, 11) = 2.72, p> 0.05, indicating that a difference of magnitude (28.7 - 24.22) or greater would be observed by chance 12.75% of the time, assuming that the true (unobserved) difference is zero.

Table 3. Rates of Decomposition and Energies of Activation of Clindamycin Hydrochloride

Vehicle	Container	K_{RT}	$K_{40°C}$	$K_{50°C}$	ΔEa (Kcals/mol)
A	Glass	7.19×10^{-3}	1.88×10^{-3}	3.47×10^{-3}	28.00
	Polypropylene	1.00×10^{-3}	1.96×10^{-3}	---	27.00
B	Glass	1.36×10^{-2}	2.75×10^{-2}	4.2×10^{-2}	20.10
	Polypropylene	1.57×10^{-2}	2.96×10^{-2}	---	18.00
C	Glass	6.67×10^{-3}	6.56×10^{-2}	3.65×10^{-2}	29.90
	Polypropylene	6.90×10^{-3}	1.86×10^{-2}	---	27.60

Table 4. Rates of Decomposition and Energies of Activation of Clindamycin Hydrochloride

Vehicle	Container	K_{RT}	$K_{40°C}$	$K_{50°C}$	ΔEa (Kcals/mol)
Standard	Original	5.18×10^{-3}	6.15×10^{-2}	3.78×10^{-2}	35.00
A	Glass	6.14×10^{-3}	1.83×10^{-2}	3.58×10^{-2}	31.00
	Polypropylene	11.5×10^{-3}	3.08×10^{-2}	---	28.00
B	Glass	1.06×10^{-2}	2.62×10^{-2}	4.37×10^{-2}	25.00
	Polypropylene	1.43×10^{-2}	2.97×10^{-2}	---	22.00
C	Glass	8.64×10^{-3}	2.65×10^{-2}	6.28×10^{-2}	32.00
	Polypropylene	9.21×10^{-3}	2.53×10^{-2}	---	29.00

Table 5. Analysis of Variance for Glass and Plastic Containers

Source of Variance	SS	δf	MS	F
Variance	1	64.939	64.939	2.72[a]
Error	II	262.948	23.901	
Total	12	327.888		

ACKNOWLEDGEMENTS

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FOOTNOTES

1. The Upjohn Co., Kalamazoo, MI, Lot #U-21251F(471PB)
2. The Upjohn Co., Kalamazoo, MI, Lot #U-28508E(779PB)
3. Ideal Solvent
4. Owen Laboratories, Dallas, TX, (Ionax® Lot #9H151)
5. Texas Pharmaceutical Co., San Antonio, TX (Sebanil® Lot #822P)
6. The Upjohn Co., Kalamazoo, MI, (Cleocin® Lot #0190M)
7. Fisher Scientific, Fair Lawn, NJ 07410

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1. R.J. Orr, N.C. Lacima, L.S. Peters and G.L. Flynn, Am. Pharm., NS 18, Oct., Nov. 1978.
2. T.O. Oesterling, J. Pharm. Sci., 59, 63 (1970).