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IN-VITRO RELEASE OF ZINC PYRITHIONE FROM A SHAMPOO BASE AND THE EFFECTS OF VARIOUS ADDITIVES ON ITS RELEASE RATE

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ABSTRACT

Zinc pyrithione has been established as one of the most effective anti-dandruff ingredients for use in shampoo formulations, through various clinical studies. However, the clinical efficacy is dependent upon its release rate from the vehicle and adsorption onto the scalp and hair. In light of these findings, the release of zinc pyrithione from a typical lotion shampoo base was investigated in-vitro. The shampoo formulation consisted of an anionic detergent, an amide and thickening agents commonly used in such products. The additives used included ethanol, dimethylsulfoxide (DMSO), polyethylene glycol-400, propylene glycol and urea at 5%, 10% and 15% by weight of the formulations.

Release experiments were carried out at 37°C, with diffusion cells immersed in beakers containing distilled water adjusted to pH 5.

In general, the presence of the additive ingredient increased the release of zinc pyrithione. Among the samples evaluated, the formulations containing ethanol or propylene glycol gave the highest release rate of the drug. And the rank order for the

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release of the zinc pyrithione was observed to be from the samples with ethanol > dimethyl sulfoxide > urea > polyethylene-glycol-400 > propylene glycol > commercial products.

INTRODUCTION

Dandruff is usually characterised as the excessive scaling of the scalp without clinical signs and symptoms of inflammation(1). This should not be confused with psoriasis and seborrheic dermatitis, because these two skin disorders have distinctive signs of inflammation and also involve other parts of the body as well.

Leyden, et al.(2) have evaluated dandruff by grading on a scale of 0-10, where zero being no traces of visible scaling and 10 as the massive scaling. According to this system, grades 4, 5 and 6 indicate mild, moderate and severe dandruff respectively.

McGinley, et al. have developed a reproducible technique for measuring the numbers of desquamating horny cells (3). The method is referred to as corneococyte count. The sampling technique involves removal of corneocytes in the desquamating loose outer zone, pooled and then mechanically agitated to dispose the cells in the buffered 0.1% triton X-100 test solution and counted in a Fuchs - Rosenthal Hemocytometer.

The coneocytes count is always performed 4 days after a brand shampoo is used and expressed as the quantity of horny cells per square centimeter per 4 days. The count 5 considered as the direct measurement of cells turnover. As a rule, subjects having counts more than 800,000 cells per sq. con. are considered to have moderate to severe dandruff.

Many investigators consider that micro flora, yeasts and bacteria also influence the symptoms of dandruff. Among the organisms commonly found on scalp include anaerobe, p. acnes; yeasts of the genus pityrosporum, and aerobic cocci (4). These organisms are present on the scalp regardless of dandruff and about 45% of them are pityrosporum. However, during the dandruff the amount of these is increased up to 75%, and the dominant yeast is identified to be pityrosporum ovale.

An investigating study (5) was undertaken to evaluate the role of microorganisms by eliminating them one at a time with appropriate antimicrobial agents and finally supressing the entire microflora with combination of these agents. The clinical effects on dandruff were appraised by using the clinical grades and errneocyte counts. The study concluded that the data are strongly antithetical to the belief that the microorganisms play a role in dandruff.

As dandruff is commonly associated with a marked microbaial proliferation, it is usually recommended that antimicrobial especially effective against pityrosporum ovale be incorporated in anti-dandruff formulations. Since during the course of shampooing, the contents of the shampoo remain in contact with the scalp and hair for only a short period of time, therefore, an anti-dandruff agent must immediately be released by the formulation and be of substantive nature. Also, it should be partially adsorbed on the scalp for its therapeutic effect between shampooing (6).

Various agents have been suggested for use in antidandruff shampoos. Among these, zinc pyrithione has been found to be the most suitable and effective antidandruff ingredient for use in shampoo formulation. One of the advantages of this type of substance is its substantivity and tolerance when used externally. The absorption of the zinc pyrithione has been shown to reach maximum at concentration of about 1% in shampoos, but the nature of the vehicle may notably effect the absorption rate as well as the germicide activity (7).

The efficiency of zinc pyrithione has been established through several clinical studies (8, 9, 10, 11, 12, 13, 14, 15 and 16).

Kligman (11) showed that there was no antidandruff activity observed when shampoo containing zinc pyrithione were used for a shorter period of time. Horin (17) demonstated the adsorption of zinc pyritione necessary to treat dandruff depended on pH,

temperature and its concentration in a shampoo base. He also studied the adsorption of zinc pyrithione onto hair and skin as a function of time, pH, temperature and concentration. The study concluded that among other things, the amount of zinc pyrithione adsorbed increased with increasing time.

In light of the previous findings, the purpose of this study was to investigate the in-vitro release of a clinically important antidandruff agent "zinc pyrithione" from a typical shampoo base. Also, to study the effects of various cosmetically acceptable additives at various concentration levels in possibly enhancing its release and to compare against various commercially popular antidandruff shampoos containing the same active ingredient.

EXPERIMENTAL

MATERIALS

Zinc pyrithione was obtained as 48% suspension from Olin Corporation, Stamford, CT. Standapol Es paste, cetiol, Standapol ES-40 concentrate and Euperlan PK-771 were obtained from Henkel Inc., Hoboken, NJ.

PREPARATION OF SHAMPOOS

Each ingredient was accurately weighed in the percentage weight ratio described in Table 1. All ingredients were heated to 80°C ± 5°C and stirred with a lightining mixer except zinc pyrithione for about 15 minutes. The mixture was cooled to 50°C and zinc pyrithione dispersion was slowly added while mixing. Any additive used was also incorporated at this stage of sample preparation.

ANALYTICAL METHOD

All samples were analyzed for zinc pyrithione by a non-published method, "Assay of zinc pyrithione in shampoos by potentiometeric titration with iodine". (18)

CONTENTS UNIFORMITY

All shampoo samples were analyzed for zinc pyrithione contents prior to their diffusion studies. Only samples with zinc pyrithione contents within 100 ± 10% were used for diffusion studies.

TABLE 1

FORMULATION

INGREDIENT	CTFA NAME	% W/W
Standapol CS Paste	(sodium lauryl sulfate (and) sodium cetyl (and) laureth-3)	30.00
Standapol ES 40 Conc.	(sodium myreth sulfate)	2.00
Cetiol LC	(coco-caprate/caprylate)	1.00
Euperlan PK-771	(sodium laureth sulfate (and) glycol stearate (and) cocoamide DEA (and) laureth-10)	3.00
Sodium Stearate	(sodium stearate)	5.00
Methocel HG-4000 (2% solution)	(hydroxypropylmethyl cellulose)	40.00
Zinc Omadine (48% solution)	(zinc pyrithione)	4.00
Water (de-ionized)	water q.s. to	100.00

IN-VITRO RELEASE STUDIES

Accurately weighed 23.5 gm samples of each shampoo was placed in a two ounces glass jar of a 2" diameter with approximate surface area of 3.4 square inches. A semi permeable cellophane membrane with a cut off point of 1000, previously soaked in distilled water for 12 hours was securely fastenend on the lip of the jar with a rubberband and a cotton string.

The samples were then invertedly placed at the center of the beakers containing 150 ml of distilled water. The diffusion surface was arranged to be about ½ cm. below the surface of the diffusion medium as shown in figure 1.

PROCEDURE

Three replica samples of each formulation were placed in three separate beakers, each containing 150 ml of previously heated water to 37°C. Samples were not disturbed until withdrawn for analysis. First beaker was withdrawn after 15 minutes and stirred with a glass rod. The whole solution was then analyzed for the zinc pyrithione content released from the shampoo sample. Second and third beakers were withdrawn from the water bath after

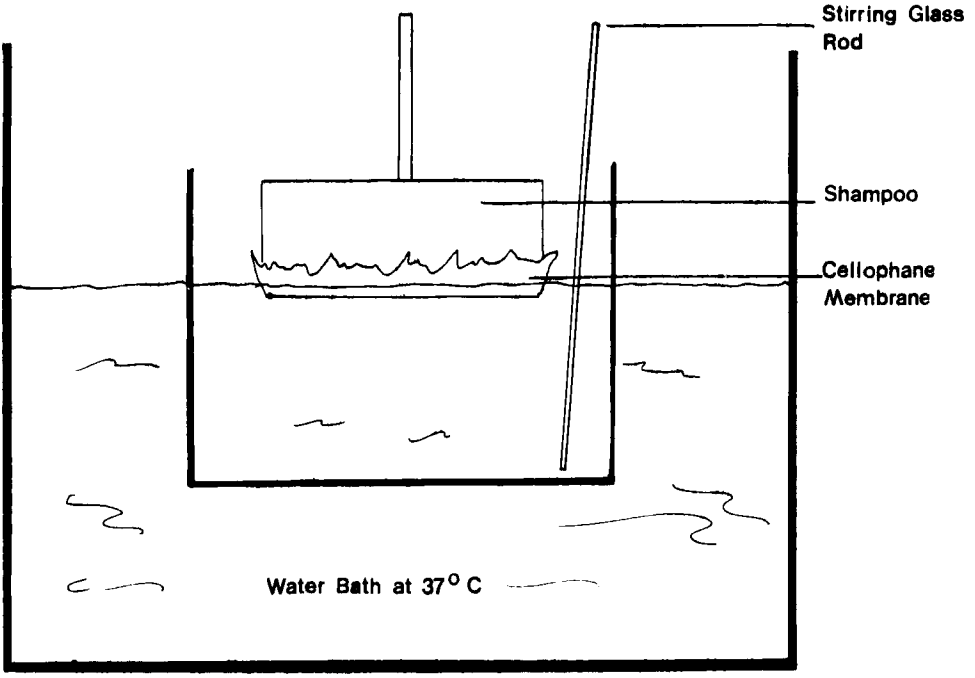

FIGURE 1

Schematic diagram of diffusion apparatus used for release experiment

30 and 45 minutes respectively and analyzed accordingly. Each shampoo sample was run in triplicate. Also, in order to correlate the release rate data with actual use on head, a selected group of samples was diluted with distilled water in a ratio of 1:10 by weight and the diffusion studies were carried out in triplicate as described previously.

RESULTS AND DISCUSSIONS

SOLUBILITY

The solubility of Zinc pyrithione (ZnPT) was determined in the diffusion medium and was found to be 0.0014% ± 0.992 at 36°C, value is expressed at the mean ± SD.

RELEASE OF ZnPT FROM THE SHAMPOO BASES

Table 2 exhibits the in-vitro release data obtained from various samples evaluated. From the data, one observes that the release

TABLE 2

IN-VITRO RELEASE OF ZINC PYRITHIONE

FROM THE VARIOUS SHAMPOO SAMPLES

SAMPLE	Amount Released (mg ± SD) 15 (min)	30 (min)	45 (min)
Commercial Product(s)			
A	1.62 ± .04	2.75 ± .08	2.80 ± .17
B	1.89 ± .27	2.10 ± .30	2.96 ± .27
Experimental			
Control	2.80 ± .08	4.50 ± .15	8.90 ± .55
With Ethanol			
5%	14.50 ± .58	23.90 ± .70	25.80 ± .62
10%	14.50 ± .65	24.50 ± .80	24.80 ± .62
15%	7.30 ± .37	10.00 ± .38	18.90 ± .08
With Propylene Glycol			
5%	2.75 ± .09	3.92 ± .14	8.20 ± .21
10%	2.85 ± .26	7.20 ± .28	9.20 ± .10
15%	3.35 ± .18	8.42 ± .51	14.90 ± .48
With DMSO			
5%	3.25 ± .54	8.35 ± .42	13.82 ± .55
15%	3.90 ± .18	8.85 ± .35	10.30 ± .90
15%	4.82 ± .20	9.30 ± .50	11.90 ± .54
With PEG-400			
5%	2.74 ± .70	8.40 ± .38	11.00 ± .25
10%	3.30 ± .06	9.50 ± .51	12.44 ± .10
15%	2.75 ± .05	5.10 ± .24	8.30 ± .30
With Urea			
5%	3.90 ± .22	7.22 ± .34	13.90 ± .39
10%	4.20 ± .16	8.10 ± .34	14.50 ± .44
15%	8.66 ± .10	10.50 ± .61	16.80 ± .17

of ZnPT from the experimental control is significantly higher than from any of the commercial products included in this study. In addition, the presence of additive ingredients strongly influenced the release of ZnPT in almost all the samples evaluated.

The addition of ethanol to the control formulation of all percentage levels affected the release of ZnPT. Highest release

of the active was found to be from the sample containing 5% ethanol. The release was equally good from the sample containing 10% by wt. of ethanol. Hoever, the amount of alcohol at 15% level did not increase the release of ZnPT as otherwise expected. This could be attributed to the increase in apparent viscosity of the product with increased amount of alcohol used.

The release of ZnPT from the samples containing propylene glycol as the additive was also affected. The sample containing 15% propylene glycol by weight of the formulation gave significantly higher release of the drug compared to the control or the commercial products.

The inclusion of DMSO and polyethylene glycol-400 in the control formulation moderately enhanced the release of ZnPT from the shampoo base. However, the addition of urea as the additive at all concentrations gave a significantly higher release of the drug.

In order to interpret diffusion rate data in terms of meaningful parameters, the data were treated by various kinetic fashions. Release rates of the insoluble drugs in their formulation bases generally follow the well-known equation of Higuchi (19,20) which is,

$$Q = \sqrt{Dt\ (2A - C_s)\ C_s} \qquad \text{Eq. 1}$$

In this equation Q defines the amount of drug released per unit area at time t, A is the concentration of drug expressed in units/cm^3, C_s is its solubility as units/cm^3 in the external phase of the semisolid and D is the diffusion coefficient of drug molecule in the external phase. Because in the semisolid of the suspension types the concentration of the drug is generally greater than its solubility ($A > C_s$), the equation given above can be more simplified to give equation 2,

$$Q = \sqrt{2ADC_s t} \qquad \text{Eq. 2}$$

this theoretically proves that the amount of drug released is

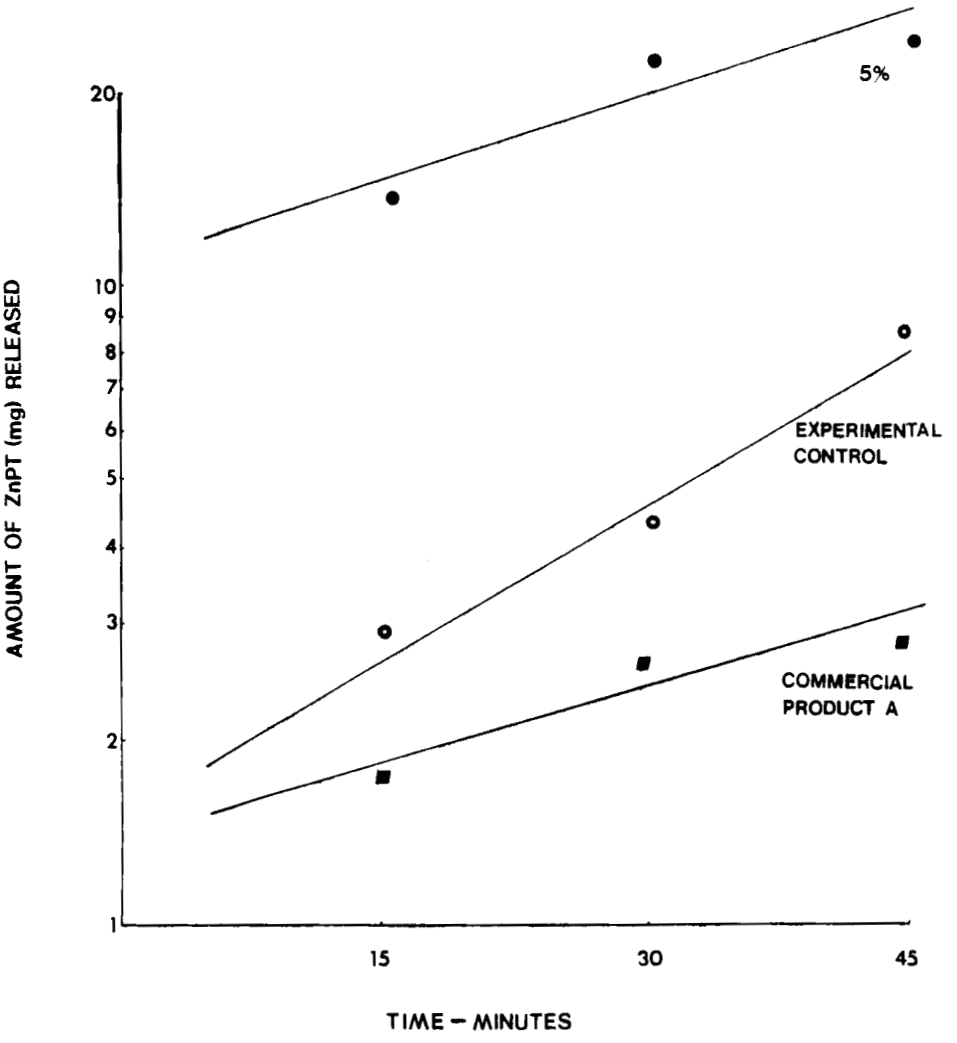

FIGURE 2

Effect of ethanol on the release of zinc pyrithione from a shampoo base plotted in first order kinetic fashion

proportional to the square root of the amount of drug in per unit volume, diffusion coefficient, solubility of the drug and the time.

Therefore, when Q versus t are drawn, generally straight lines are obtained, but they are not always linear (21,22). When the logarithm of the amount of drug released is plotted against the logarithm of diffusion time (23) or the amount released versus

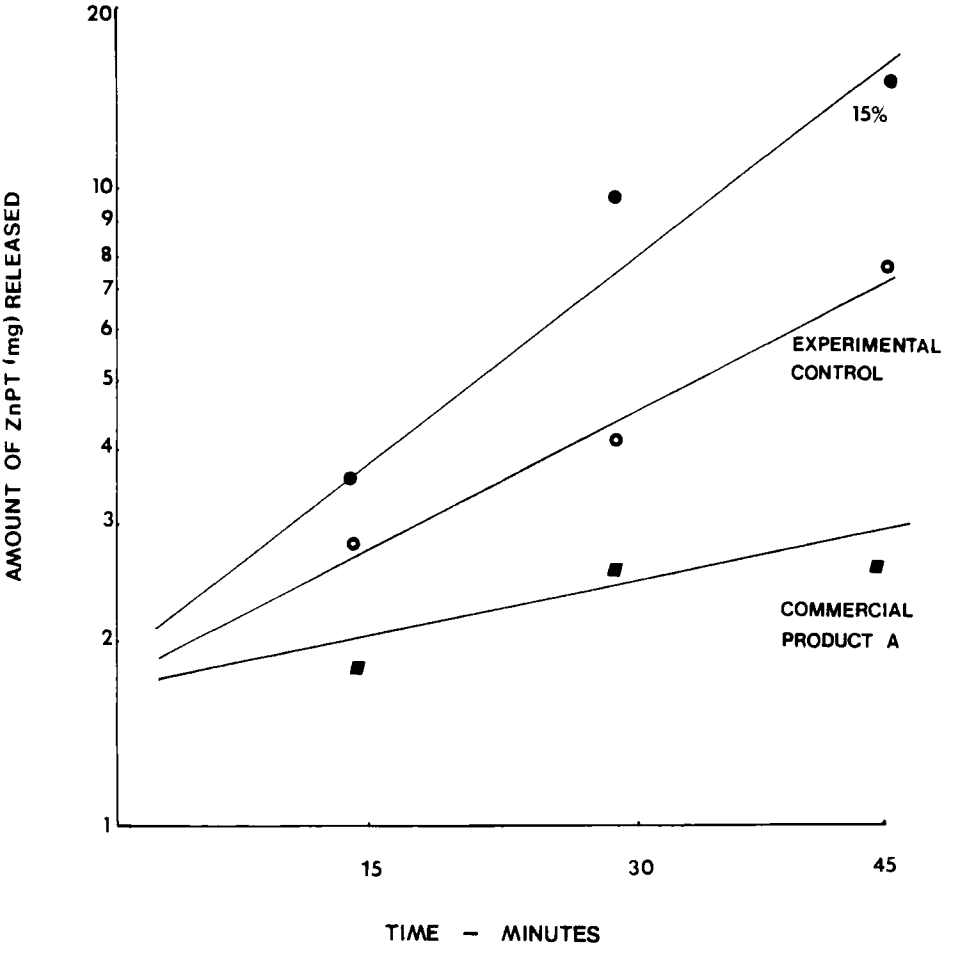

FIGURE 3

Effect of propylene glycol on the release of zinc pyrithione from a shampoo base plotted in first order kinetic fashion

the square root of the time, better fittings are seen in the literature (24,25,26).

The diffusion results were also treated by both first and second order kinetics, and lines with highest correlation coefficients were obtained. In most cases, the regression coefficient values were closer to 1. The release data of zinc pyrithione from the shampoo base containing 5% ethanol as the additive are plotted in Figure 2. According to the statistical

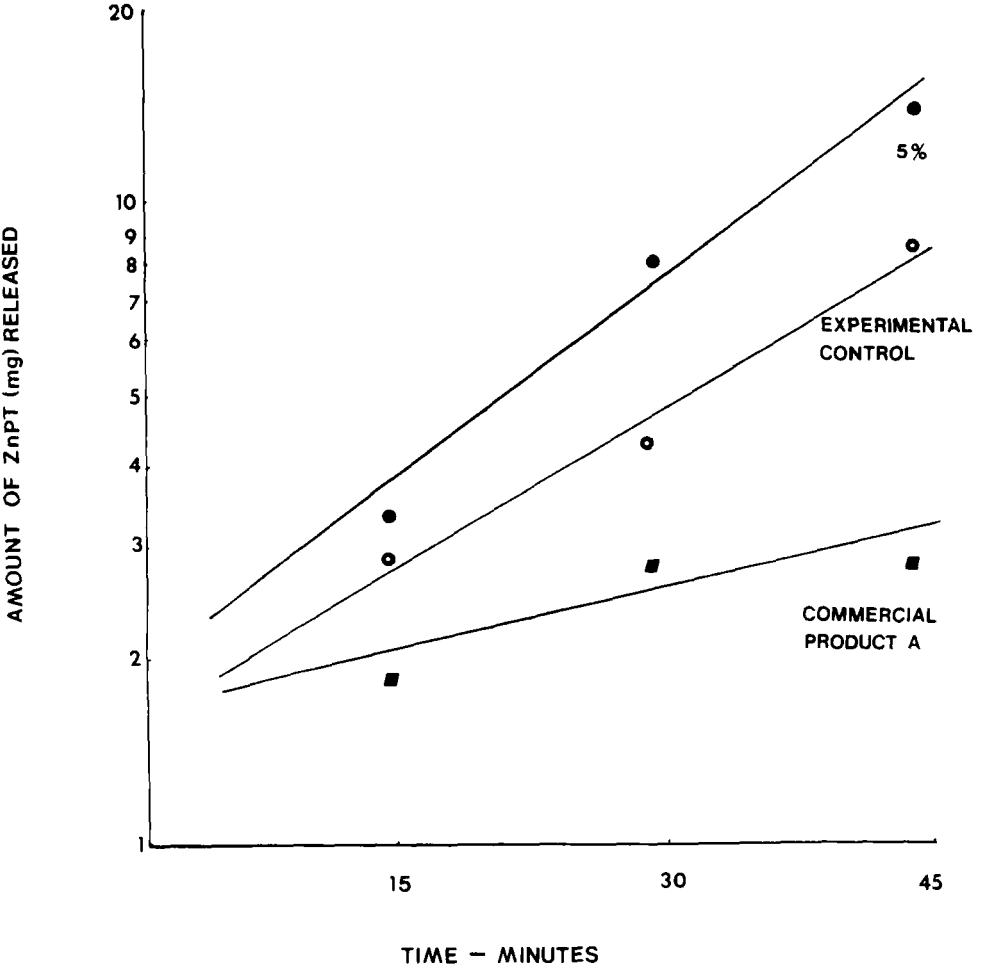

FIGURE 4

Effect of dimethyl sulfoxide on the release of zinc pyrithione from a shampoo base plotted in first order kinetic fashion

evaluation, the released amounts of the drug were significantly higher than either the experimental control or a leading commercial shampoo containing the same amount of zinc pyrithione.

Figure 3. exhibits the effect of propylene glycol on the release of drug from the shampoo base. From this one clearly observes that the release of zinc pyrithione is significantly higher than either the control or the commercial product.

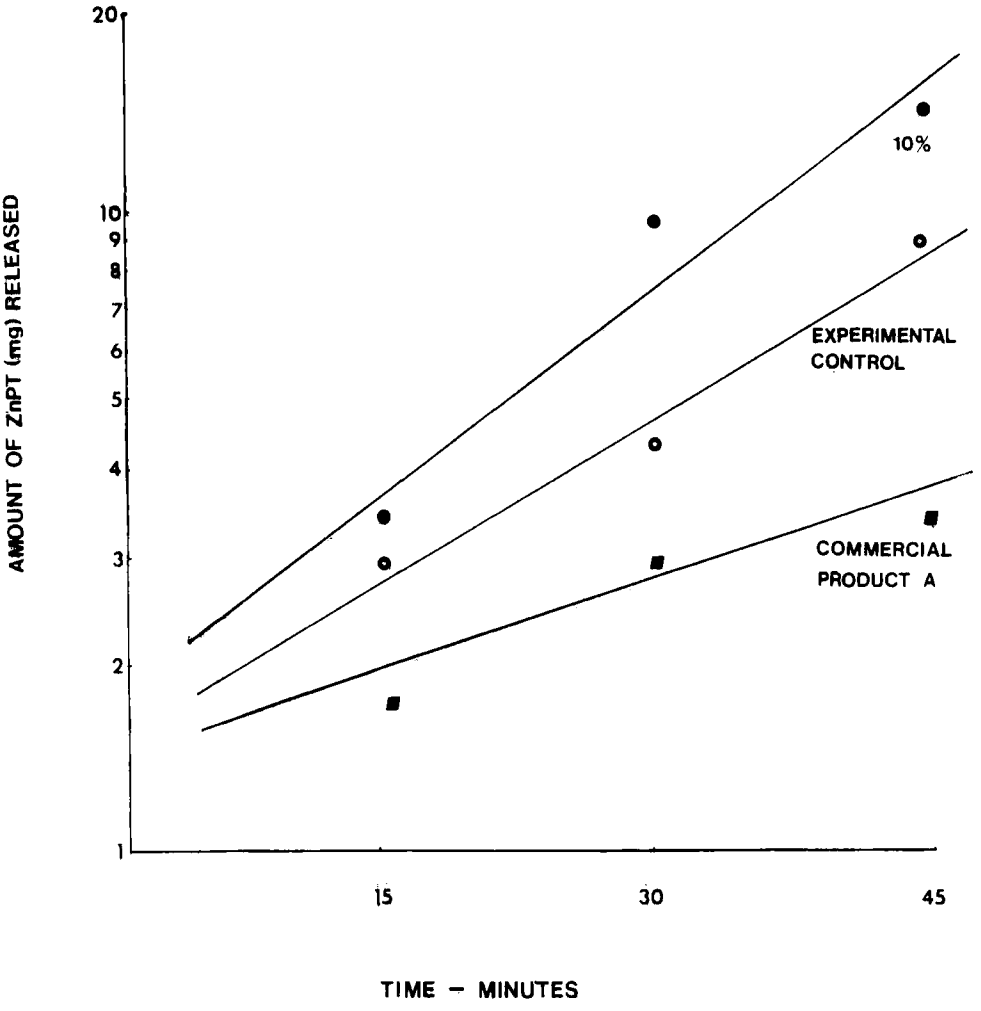

FIGURE 5

Effect of polyethylene glycol-400 on the release of zinc pyrithione from a shampoo base plotted in first order kinetic fashion.

The release from the base containing dimethyl sulfoxide is given in Figure 4. Here again the amount of zinc pyrithione released is significantly higher than either the control or the commercial product. The effects of polyethylene glycol-400 and urea are shown in Figure 5 and 6 respectively. In each case, presence of the additive significantly enhanced the release of

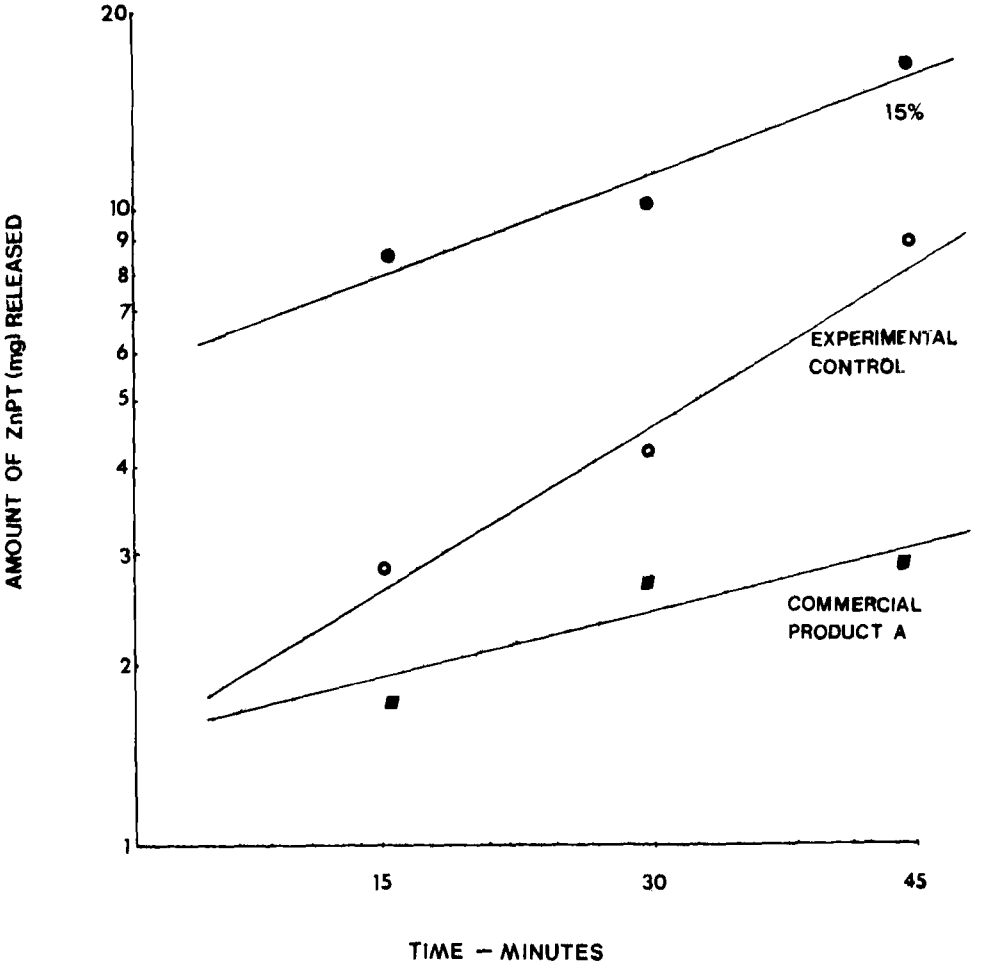

FIGURE 6

Effect of urea on the release of zinc pyrithione from a shampoo base plotted in first order kinetic fashion.

zinc pyrithione from the shampoo base and the amounts released were higher than either the control or the commercial products.

As shown in Table 3, the amounts of the zinc pyrithione released with time were also higher from the diluted samples of shampoo containing various concentrations of propylene glycol. This suggests that the presence of additives does influence the release of zinc pyrithione from the shampoo base with time.

TABLE 3

IN-VITRO RELEASE OF ZINC PYRITHIONE FROM THE DILUTED SHAMPOO CONTAINING (PROPYLENE GLYCOL) AS THE ADDITIVE

SAMPLE	AMOUNT RELEASED (mg ± SD)		
	15 (MIN)	30 (MIN)	45 (MIN)
COMMERCIAL PRODUCT(S)			
A	--	--	1.50 ± 0.35
B	--	--	1.30 ± 0.40
CONTROL	--	--	2.20 ± 0.55
WITH (PG)			
5%	--	--	2.40 ± 0.74
10%	--	--	2.60 ± 0.38
15%	--	--	2.67 ± 0.59

NOTE: EACH READING IS THE AVERAGE OF THREE (3) DETERMINATIONS.

The reasons for the enhanced release of drug from the shampoo bases are likely to be due to the co-solvent effect of various additives on the drug and cause an increase in osmotic pressure of the shampoo bases which could influence the penetration of the drug. Also, this could be attributed to the effects of additives on the rheological properties of the shampoo base.

Although prediction about which base might release the drug best does not seem to be possible for the bases under consideration. But in general, solubility of zinc pyrithione in polyethylene glycol, ethanol, propylene glycol and its water miscibility in the emulsion base may be contributing factors in achieving improved release rates of the drug.

The in-vivo experiments, absorption properties of the drug is as important as the release properties. Therefore, the same results may not necessarily be applicable in vivo. However, it

is possible to expect a certain degree of correlation between the in-vitro findings and in-vivo results. Also, this enables one to screen formulations for "optimum" drug delivery via topical pharmaceutical dosage forms.

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