Drug Development and Industrial Pharmacy, 22(9&10), 993-996 (1996)

The Effect of Organic Ligands on the Rate of Loss of Phenylmercuric Nitrate into Rubber Closures and Plastic Containers

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ABSTRACT

The effect of the presence of various organic compounds containing a variety of functional groups on the rate of loss of phenylmericuric (PM) nitrate into plastic containers and rubber closures has been investigated. The presence of organic compounds profoundly influenced the loss of the phenylmercuric nitrate, that loss being dependent upon their chemical structure and concentration. This effect explains the unpredictability of the loss of PM nitrate into polymer matrices from pharmaceutical products.

INTRODUCTION

Phenylmercury (PM) salts, when used as preservatives in pharmaceutical products are subject to considerable loss into plastics (1-6) and rubber closures (7-9). Organomercury compounds are known to complex with a wide variety of both organic and inorganic ligands (10,11), and it has been demonstrated that whereas phosphate buffer may stabilize the loss of PM acetate, the presence of chloride ion may promote it (3).

This paper reports the results of an investigation of the effect on loss of PM nitrate of the presence of water-soluble organic compounds possessing a variety of functional groups which potentially may complex with the PM ion. The object of the study was to assess the extent to which the presence of organic ligands, such as drug and formulation components, may influence the loss of the PM ion due to complexation.

METHODS

Materials and Reagents

PM nitrate was obtained from BDH (Poole, U.K.) and organic ligands from Sigma Chemical (St. Louis, U.S.) and used without further purification. All other chemicals were of analytical reagent grade. Rubber closures (Butyl Rubber, Schubert, Denmark) were cut in

half to fit the glass vials and washed by boiling for 15 min in sodium lauryl sulfate (0.1%), then washed with sodium carbonate (1%), water, hydrochloric acid (1%), disodium edetate (0.1%), water twice, rinsed well with distilled water, and allowed to air-dry prior to use (12).

Assay of PM Nitrate

PM nitrate was assayed by the previously reported method involving high-performance liquid chromatography (HPLC) of the morpholinedithiocarbamate complex (13). Noninterference of the ligand was confirmed by comparative assays of the stock solutions used in the adsorption studies with a blank solution.

Uptake into Rubber Closures

Solutions were prepared containing PM nitrate (1×10^{-4} M) and ligand in phosphate buffer (0.05 M), the pH being adjusted to 6.50 with 0.1 M sodium hydroxide prior to final adjustment to volume. These solutions, 40 ml, and two half-closures were added to 50-ml glass vials with PTFE lined caps and agitated on a horizontal shaker at 2 cps at a temperature of 25°C. The preliminary experiments utilizing a range of ligands were performed using 1×10^{-3} M (10-fold excess) of ligand, 1-ml samples being withdrawn for assay of PM at 42, 90, 140, and 190 hr, and the experiments being performed in duplicate. For the more detailed investigation of L-histidine as a ligand, concentrations of 1×10^{-4}, 2×10^{-4}, 5×10^{-4}, 1×10^{-3}, 2×10^{-3}, and 5×10^{-3} M (corresponding to a 1-, 2-, 5-, 10-, 20- and 50-fold excess of ligand, respectively) were utilized, 1-ml samples being withdrawn at 45, 93, and 142 hr and the experiments being performed in quadruplicate.

Uptake into Polythene Bottles

Solutions were prepared containing PM nitrate (1×10^{-4} M) with an without L-histidine (1×10^{-3} M) in phosphate buffer 0.05 M pH 6.50. Ten milliliters of these solutions were transferred to bottles (medium density polyethylene, B.A.S.S., Germany), which were heat-sealed and stored in sealed glass bottles at 25°C, the bottles being upended at weekly intervals. The contents of 5 containers of each solution were assayed to 180 days at regular time intervals, the vials being weighed after filling to enable an assessment of moisture loss to be made.

RESULTS AND DISCUSSION

While the coordination chemistry of PM has received little attention, the properties of the analogous compound methylmercury has received detailed investigation and displays the ability to complex with a wide variety of organic and inorganic ligands (10,11). Organic compounds were chosen which are water soluble and possess a variety of functional groups capable of undergoing complexation with the PM ion. Table 1 lists the compounds investigated and the results of a preliminary investigation involving uptake into rubber closures using a 10-fold excess of ligand. All experiments display-

Table 1

Influence of Organic Ligands on the Rate of Loss of Phenylmercury into Rubber Closures: Moles of Phenylmercury Remaining Versus Time

	y Intercept (moles $\times 10^{-6}$)	Slope (moles $hr^{-1} \times 10^{-8}$)	Correlation Coefficient
Control	4.01	-1.24	0.996
L-Histidine	4.01	-0.56	0.999
Adenosine	4.04	-0.94	0.998
Cytosine	3.99	-1.09	0.999
Citrate	4.00	-1.13	0.999
L-Serine	4.08	-1.15	0.988
Glycine	4.02	-1.17	0.999
L-Aspartic acid	4.05	-1.35	0.999
Cytidine	4.11	-1.35	0.982

ed a linear relationship between concentration of PM remaining and time, and from this the rate of uptake, in moles per hour, could be calculated. The most effective compound at reducing losses was the amino-acid L-histidine, for which the rate of uptake was approximately half that of the control containing no ligand. This may be explained by the fact that organomercury compounds complex strongly to the imidazole ring (11) and, being an ionized species, the resulting complex would be expected to be highly water soluble.

A more detailed investigation was undertaken of L-histidine at a range of ligand-to-PM mole ratios (Table 2). The effect of the L-histidine was saturable, with no enhancement of effect beyond a fivefold excess of L-histidine to PM ion.

The study was extended to an investigation of the effect of a 10-fold excess of L-histidine on the uptake of PM into medium-density polyethylene containers (Fig. 1). Under the storage conditions employed in the study the maximum moisture loss was 0.25% for any one container, and no attempt was made to correct the determined levels of PM for this factor. No statistically significant differences ($p = 0.001$) were noted between those containing L-histidine and the control samples.

Table 2

Effect of L-Histidine Concentration on the Rate of Loss of Phenylmercury into Rubber Closures: Moles of Phenylmercury Remaining Versus Time

Mole Ratio, Hist/PM	*y* Intercept (moles × 10^{-6})	Slope (moles hr^{-1} × 10^{-8})	Correlation Coefficient
Control	3.98	-1.25	0.999
1	3.99	-1.16	0.999
2	4.02	-1.05	0.999
5	4.02	-0.64	0.994
10	4.00	-0.62	0.999
20	4.01	-0.67	0.993
50	4.00	-0.68	0.999

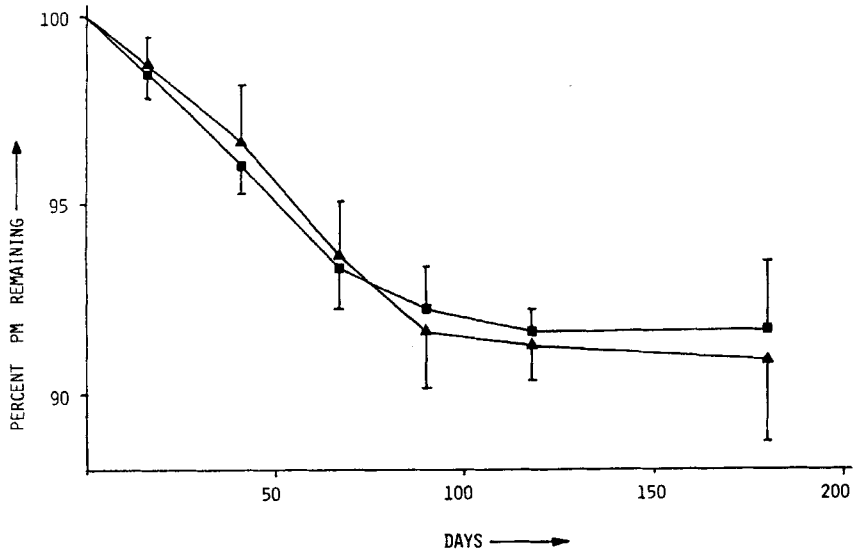

Figure 1. Plot of percentage of phenylmercury remaining versus time for storage of a solution of phenylmercuric nitrate (1×10^{-4} M) with (- ▲ -) and without (- ■ -) L-histidine (1×10^{-3} M) in medium-density polyethylene bottles.

Other workers have noted differences in loss of PM into plastic containers and rubber closures which have been dependent upon the nature of other components such as chloride and buffer components in the solution (3–5). The failure of the L-histidine to modify the uptake characteristics of the PM into medium-density polyethylene is difficult to rationalize giving consideration to its effect upon uptake into rubber closures. Losses of organomercury compounds such as the PM ion and the ethylmercuric ion of thiomersal in ophthalmic products are highly dependent upon the presence of buffer components, and the nature and concentration of the drug incorporated into the formulation and complexation with formulation components must play a major role in influencing this loss.

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