DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 7(4), 397-403 (1981)



# THERMAL STABILITY OF VARIOUS EPINEPHRINE FORMULATIONS

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## ABSTRACT

The effects of prolonged heat exposure on the stability of various epinephrine formulations (maleate, fumarate, HCl, and bitartrate) were studied with respect to mass loss and pressor potency. Mass loss was relative to length of incubation and was accompanied by discoloration in HCl and bitartrate. Fumarate and maleate demonstrated least loss of mass and little discoloration. Pressor potency was significantly reduced, relative to length of heat exposure, in HCl and bitartrate, but remained elevated in fumarate and maleate. Thus, the latter formulation demonstrate the highest thermostability.

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[2]This work was supported by Nephrone Company, Seattle, WA 98104.

## INTRODUCTION

It is well known that clinically used hydrochloride and bitartrate salts of l-epinephrine (U.S.P.) undergo spontaneous decomposition during prolonged storage. Oxidation and recemization are manifested by a gradual discoloration from yellow to dark brown. These two complex processes have been the subject of numerous studies ever since epinephrine was isolated and its structure determined in the early 1900's. The analytical problems associated with stability studies have proved difficult to overcome, and have been investigated by many authors (1-5).

Previous studies demonstrated that when maleate, fumarate, hydrochloride, and bitartrate salts of epinephrine were subjected to prolonged exposure to ultraviolet light (253.4 nm), the first two substances were more stable against oxidation than either l-epinephrine hydrochloride or l-epinephrine bitartrate (6). The present studies were undertaken to investigate the effects of temperature on the stability of various epinephrine salts and their comparative pharmacodynamic potencies.

## MATERIALS AND METHODS

Drugs. The following drugs were used: Maleate, fumarate, HCl salts of dl-epinephrine[1], l-epinephrine bitartrate (U.S.P.)[2].

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[1]Burton Pharmaceuticals, Seattle WA.

[2]City Chemical Company, New York, NY.

The concentrations of all drug formulations used in these experiments were expressed on the basis of their l-base forms.

Thermal stability of various epinephrine formulations. Following desiccant exposure with a Mettler analytical balance (Model 20HT), various salts of epinephrine were weighed to the precise equivalent of 1 g epinephrine base. The individual drug was then placed in a preweighed Eppendorf tube (heat resistant) and incubated up to 20 days at 95°C constant temperature (±0.2°C) with an Eppendorf microthermostat. The various salt forms of epinephrine were removed from the Eppendorf tubes on days 2, 4, 6, 8, 15, and 20 of incubation, immediately placed in a desicator overnight, and then weighed.

Comparative pressor effects of various epinephrine formulations following heat exposure. Twenty-eight cats of either sex, weighing between 2.5-3.5 kg, were anesthetized with sodium pentobarbital (30 mg/kg) administered intraperitoneally. The left femoral artery and right femoral vein of each cat were cannulated. The animals were then atropinized (1 mg/kg). One of the various incubated epinephrine formulations was administered to each animal (2 μg/kg) via the femoral vein, while blood pressure was recorded from the cannulated left femoral artery using a transducer and Sanborn 321 dual channel carrier amplifier recorder.[1] A tracheal cannula was routinely inserted and artificial respiration was administered when necessary.

[1]Hewlett-Packard, Palo Alto, CA.

## RESULTS AND DISCUSSION

The thermal stabilities of different epinephrine formulations were found to be significantly different. Figure 1 demonstrates the comparative overall mass changes of epinephrine formulations. It is apparent that the rate of mass loss for all formulations are relatively linear with time, with the exception of the bitartrate salt of epinephrine. The rate of mass loss for fumarate, maleate, and HCl salts of epinephrine were 0.4 mg, 0.73 mg, and 2.6 mg $day,^{-1}$ respectively. On the other hand, the initial rate of mass loss for epinephrine bitartrate was 13.3 mg $day^{-1}$; subsequently, the rate of mass for loss bitartrate was much slower (0.45 mg $day^{-1}$). Fumarate and maleate salts were significantly more stable at the 95°C temperature than either bitartrate or HCl epinephrine formulations. Furthermore, mass loss of both HCl and bitartrate was accompanied by a discoloration of the drugs to dark brown as early the 4th day of incubation. In contrast, the color of fumurate and maleate epinepheine formulations ranged from slightly yellow to white at the same duration of heat exposure. Thus, epinephrine fumarate formulation was found to be the most temperature resistant.

Pressor effects of various epinephrine formulations following temperature exposure are shown in Figure 2. There are no significant differences in the respective pressor effects prior to incubation of these drugs at 95°C. In pretreatment animals, the mean arterial blood pressure was 105 $\pm$ 12 mm Hg. The comparative arterial blood pressure of each animals was determined following

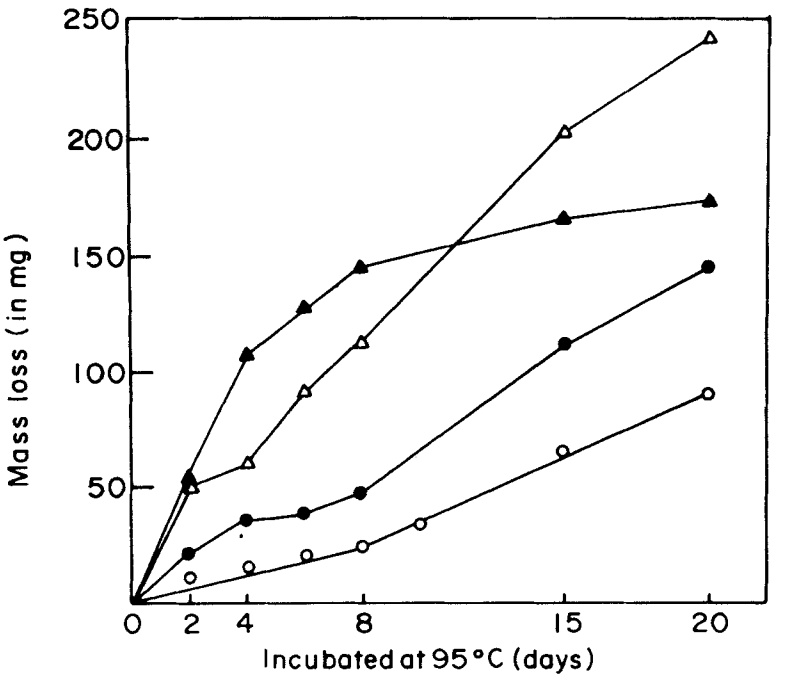


FIGURE 1

Thermal effects on maleate, fumarate, hydrochloride, and bitartrate salt of epinephrine. Each point represents the mean of duplicate experiments. dl-epinephrine fumarate (o); dl-epinephrine maleate (●); l-epinephrine bitartrate (Δ), and dl-epinephrine HCl (▲).

administration of various epinephrine formulations (2 μg equivalent l-epinephrine base) at day 0, 2, 4, 6, 8, 15, and 20 of exposure of each drug to heat. As early as 2 days following heat exposure, HCl formulation lost approximately 40% of its original pressor potency. By 4 days, the pressor potency of HCl and bitartrate formulations were decreased significantly to 19 and 75% of their

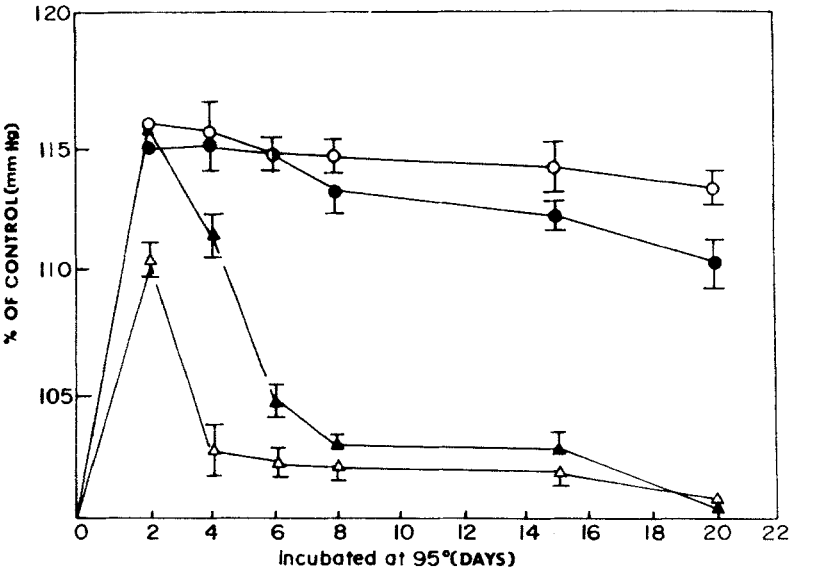


FIGURE 2

A comparative pressor effect of various epinephrine formulations. Blood pressure (mm Hg) was determined via the femoral artery of cats and each point represents the mean (± S.D.) of 4 animals. dl-epinephrine fumarate (O); dl-epininephrine maleate (●), dl-epinephrine HCl (Δ); and l-epinephrine bitartrate (▲).

respective control potencies. In contrast, no significant changes are observed with either fumarate or maleate formulations. By 8 days, the pressor potencies of HCl and bitartrate formulations were further diminished to only 13 and 18% of their respective control potencies, and remained relatively constant for another 7 days. By 20 days, however, both HCl and bitartrate formulations had no detectable pressor effects. An increase in epinephrine HCl and

bitartrate dose from 2 μg to 10 μg per dose failed to demonstrate any appreciable blood pressure changes. By contrast, the pressor potency of epinephrine fumarate and maleate remained approximately 90 and 73% of their respective controls.

The exact mechanism of thermostability for fumarate and maleate salts of epinephrine has not been investigated in the present study. However, thermostability may be attributed to a melting point which is higher in fumarate and maleate than in the other formulations. In conclusion, the thermostability of epinephrine fumarate and maleate appears to be significantly superior to that of the other two formulations.

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