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Stability of Ergotamine Tartrate Sublingual Tablets

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ABSTRACT

The high moisture content of ergotamine tartrate sublingual tablets poses potential stability problems and safety concerns. The finished product is confined in a protective aluminum foil and could degrade to generate toxic by-products during moisture evaporation and condensation within the package under some storage conditions. This study was initiated to examine the stability of ergotamine tartrate sublingual tablets under various simulated storage conditions. The physical and chemical stability of the product was evaluated over a period of 12 months. Results indicated that no stability problems arose when the product was stored at constant temperature, either ambient or sub-ambient. Experimental results indicated that storage in an environment where the temperature fluctuated widely might lead to poor product stability and should be avoided.

Key words: **ergotamine tartrate tablet, stability.**

INTRODUCTION

Ergotamine, an amide of lysergic acid (Fig. 1), is a α -adrenoreceptor antagonist. It is the drug of choice for symptomatic relief of the pain of migraine and other vascular headaches caused by constriction of the cerebral vessels[1,2]. Ergotamine also exerts oxytocic actions[3], stimulating the smooth muscle of the uterus, but is no longer used clinically as an oxytocic.

Ergotamine tartrate is slightly hygroscopic[4]. In the solid state, it degrades when exposed to light, high temperature and humid conditions. The high moisture content is always a source of potential stability problems in the finished product. The 4-8% moisture content found in sublingual tablets, which is confined in the protective aluminum foil, could potentially degrade the product to generate toxic by-products during moisture evaporation and condensation cycles within the package.

The objective of this study was to examine the stability of ergotamine tartrate sublingual tablets using the temperature cycling method to simulate possible storage situations. We further investigated the stability by exposing the unprotected tablets to laboratory conditions, moisture and fluorescent lighting. The physical stability was eva-

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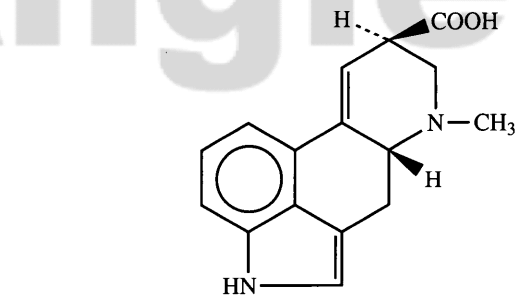
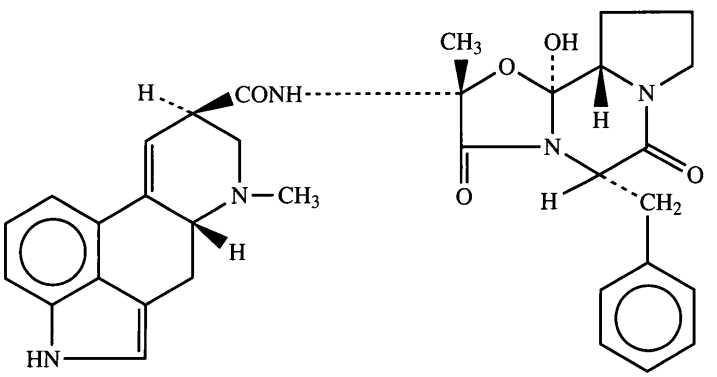


lysergic acid



ergotamine

Figure 1. The ergot alkaloid, ergotamine, is an amide of lysergic acid.

luated by microscopic examination for mold growth on the tablet surface. The chemical stability of the product was evaluated by a stability-indicating HPLC method for the active ingredient.

MATERIALS AND METHODS

I. *Apparatus*

(I)*Liquid Chromatographic System*

An automated HPLC system (Thermo Separation Products, San Jose, CA) consisting of auto injector, variable UV detector, and data processing software was used. The separation of ergotamine and its decomposition products was achieved on a 4.6 mm by 25 cm bonded octadecyl silane column. The mobile phase was acetonitrile and 0.01 M monobasic potassium phosphate (55:45). System suitability and sample analysis were determined using procedures described in the United States Pharmacopeia General Guide Chapter 621 and HPLC monograph for ergotamine tartrate tablets[5].

(II)*Incubator*

The incubator was maintained at 40 ℃ and was purchased from Lab-Line Instruments, Melrose Park, Illinois.

(III)*Optical Microscope*

A 0.7 to 3 X wide mouth optical microscope (Bausch and Lomb, Germany) interfaced with a Polaroid MicroCam (Polaroid Corporation, Cambridge, Massachusetts, USA) was used to examine the tablet surface for mold growth.

II. *Reagents*

Ergotamine tartrate was purchased from Sigma Chemical Company (St. Louis, MO, USA). It was stored at -70 ℃ in a desiccator containing indicating Silica Gel. All chemicals and solvents used were either reagent grade or HPLC grade.

III. *Sample Material*

Ergotamine tartrate sublingual 2 mg tablets, U.S.P., (NDC 59417-120-20 lot KBA exp 12/96) were supplied as 12 containers of 20 unit dose tablets wrapped in aluminum foil strips in a plastic child-resistant container. Each unit package was embossed with the product identification code and warning label indicating it should be protected from light and heat, and kept out of reach of children.

IV. *Analytical Procedure*

The ergotamine tartrate sublingual tablets were subjected to four stability testing procedures, namely, cycling, incubation, refrigeration and exposure to laboratory conditions with the protective aluminum foil removed.

(I)*Cycling Testing*

The ergotamine tartrate tablets, containing almost 8% moisture, were sealed in a protective aluminum foil. The package is highly susceptible to water condensation inside the aluminum foil caused by temperature fluctuations under storage. In time, the moisture on the tablets can degrade the ergotamine producing toxic by-products, and mold may grow on the tablet surface. A two-week cycle of 13 days incubation at 40 ℃ and one day refrigeration at -5 ℃ simulated an extreme temperature fluctuation under storage conditions. This procedure allows 13 days to force moisture out of the tablet and one day for recondensation. Six tablets subjected to the cycling procedure were examined for mold and assayed for ergotamine tartrate and moisture at the start of testing and every three months there- after, i.e. at 3, 6, 9, and 12 months.

(II)*Incubation Testing*

The ergotamine tartrate tablets, sealed in the protective aluminum foil, were incubated at 40 ℃. Six tablets were examined for mold and assayed for ergotamine tartrate and moisture at six and 12 months. By comparing the results of the incubation and the cycling testing, the effect from heating and cooling the tablets can be demonstrated.

(III)*Refrigeration Testing*

The ergotamine tartrate tablets, sealed in the protective aluminum foil, were refrigerated at -5 ℃. Six tablets were examined for mold and assayed for ergotamine tartrate and moisture at six and 12 months. This served as a control for comparing the effect of the other storage and stress testing conditions.

(IV)*Exposed Testing*

In this testing, ergotamine tartrate tablets were removed from the protective aluminum foil and exposed to laboratory moisture and fluorescent lighting conditions. Three tablets were examined for mold and defects using the wide mouth microscope and photographed under magnification using the Polaroid MicroCam at 17, 65, 93, 141 and 365 days.

V. *Examination and Assay Procedures*

At the time of analysis, six tablets (except in the case of the exposed testing tablets) were removed from the testing procedure, examined and assayed. Each tablet was carefully removed from the aluminum foil and physically examined for mold and defects using the wide mouth microscope and photographed under magnification using the Polaroid MicroCam.

The tablets were weighed and heated at 105 ℃ for four hours. Then placed in a desiccator and later weighed again. The loss of weight was recorded. Each tablet was individually placed in a 100 ml volumetric flask containing 50:50 buffer and acetonitrile and sonicated for 20 minutes. The solution was filtered through a 0.45 membrane disk and then injected into the HPLC and compared to an ergotamine tartrate standard similarly chromatographed.

RESULTS AND DISCUSSION

At the start of the study, the ergotamine tartrate tablets were assayed twice on two different days for potency stability testing and found to have 103.8 and 104.0% of declared potency.

Twelve tablets were assayed individually and the average reported.

Typical HPLC chromatograms are shown in Figure 2. The ergotamine tartrate standard eluted at about 5.6 minutes (Fig. 2A) under the above described chromatographic conditions. When ergotamine tartrate standard (Fig. 2B) and tablets (Fig. 2C) were heated at 80℃ for 3 hours in 15 ml acid (pH 4.3), water and base (pH 9.3), a second HPLC peak appeared at about 7.0 minutes retention time. A chromatogram similar to 2B was generated from all acid, water, and base experiments.

Ergotamine tartrate tablets lost an average of 10% potency in all 6 tablets tested during the first 6 months after the start of the cycling testing. The potency declined 7% further in the following 6 months (Fig. 3). At the end of 12 months, six tablets were assayed for potency. The results were 77.2, 81.7, 86.9, 92.5, 92.8, and 94.7% of declared potency with an average of 86.9%. (Fig. 3).

Ergotamine tartrate tablets showed a quick decline in potency to an average of 94% in 6 months when samples were stored at constant temperature of 40℃ (incubation testing). But the loss of potency declined only about 2% more in

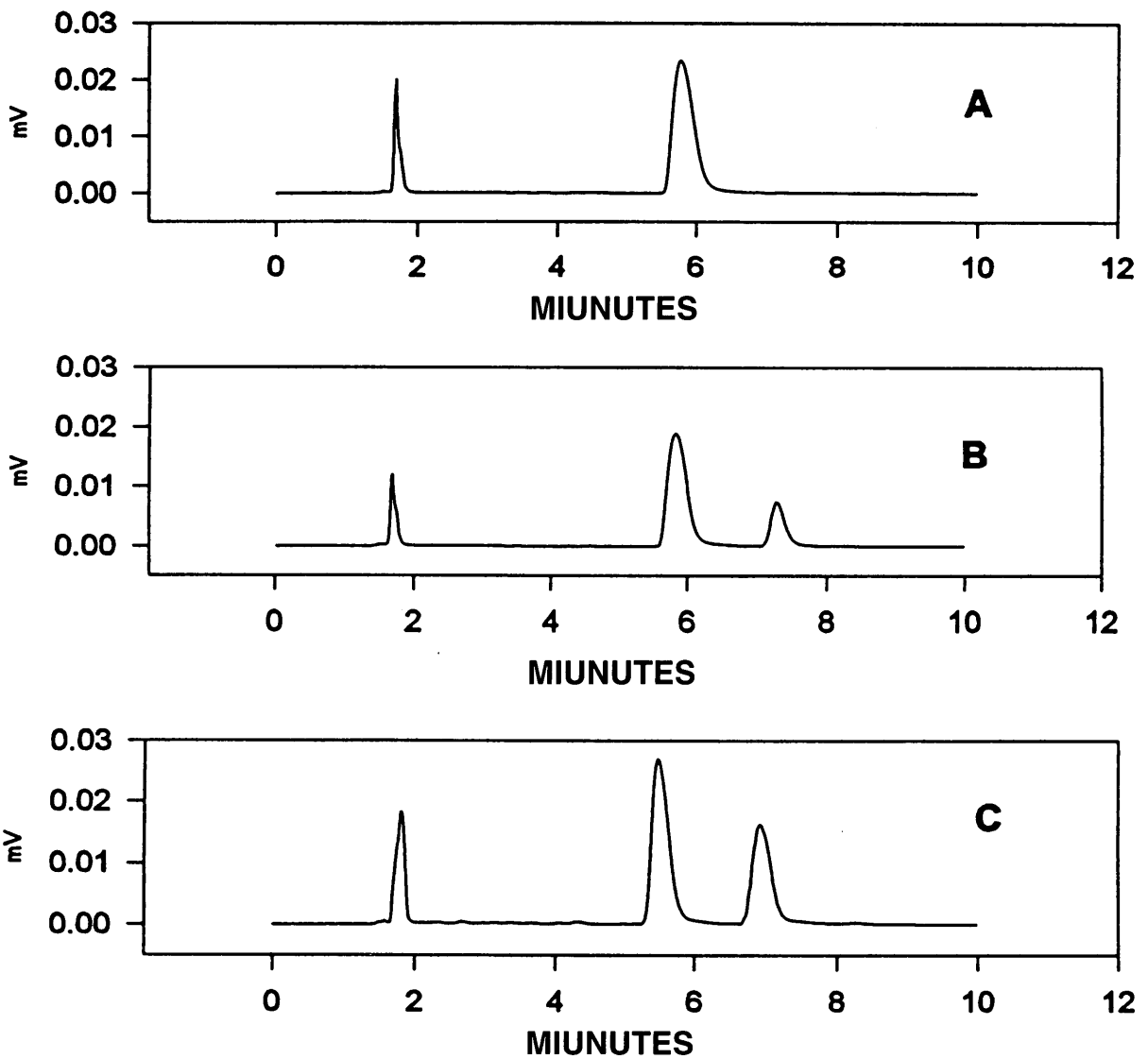


Figure 2. Typical HPLC chromatogram depicting Ergotamine decomposition and the unidentified decomposition product in tablets.

the following 6 months (Fig. 4).

Under refrigeration at -5 ℃, ergotamine tartrate tablets, in unit dosage packages, showed a small decline in potency of only 2.5% in 12 months (Figure 5). Without the protective aluminum foil, and exposed to laboratory moisture and fluorescent lighting conditions, an average of 12% loss of potency occurred in 141 days. But only an additional 1.3% loss of potency was observed from 150 to 350 days (Fig. 6).

No mold was visually detected on any ergotamine tartrate sublingual tablet, either exposed or

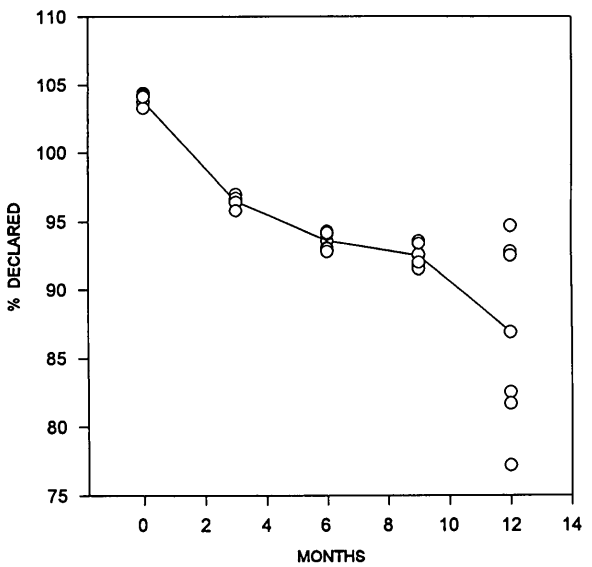


Figure 3. The cycling testing of ergotamine tartrate tablets, by heating for 13 days and refrigeration for one day, shows a rapid decline in potency at 12 months.

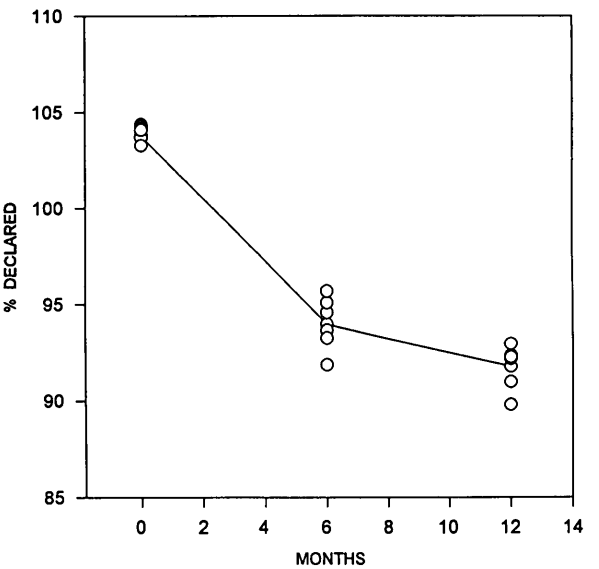


Figure 4. Incubation testing of ergotamine tartrate tablets at constant incubation of 40 ℃, shows a rapid decline in potency from 6 to 12 months.

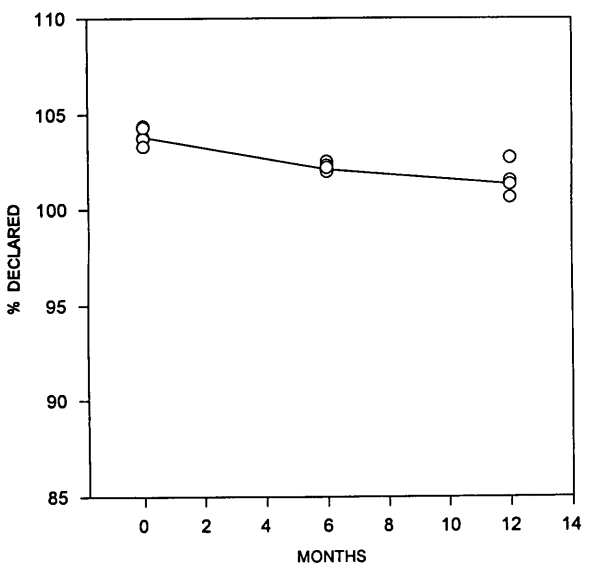


Figure 5. Refrigerated testing of ergotamine tartrate tablets, shows a small decline in potency of only 2.5% with constant refrigeration at -5 ℃.

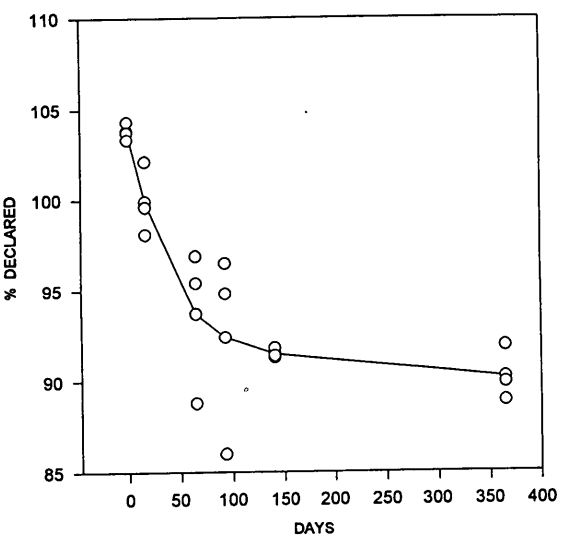


Figure 6. Ergotamine tartrate tablets, without the protective aluminum foil and exposed to laboratory conditions, moisture and fluorescent lighting, has 12% loss of potency in 141 days, but only 1.3% loss of potency from 150 to 350 days.

in the protective aluminum foil, under all stability testing procedures. Also, 12 tablets from the reserve stock of ergotamine tartrate sublingual tablets in the original container, kept at room temperature, were examined for mold at 6 and 12 months. No mold was found on these 24 tablets either.

The product manufacturer determined the tablet moisture content to be 5.46% with limits of 4.0 to 8.0% for assay and 2.0 to 12.0% for stability using Karl Fisher titration. We determined the loss of weight to be 5.3% after heating six tablets for 4 hours which compares well with the manufacturer's claim. In a separate study, our laboratory found a moisture content of 6.5% on stressed tablets from the 40℃ incubation testing procedure and 7.3% on unstressed tablets from the reserve stock held at room temperature by Karl Fisher titration.

CONCLUSIONS

Ergotamine tartrate sublingual tablets are best stored under refrigeration. Constant room temperature storage with protection from sunlight is also satisfactory. Storage in an environment where the temperature fluctuates widely leads to poor product stability and should be avoided.

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Ergotamine Tartrate舌下錠劑的安定性

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摘　要

劑型內高潮濕度對Ergotamine Tartrate舌下錠劑安定性的影響可導致該成品安全問題。由於該成品密封於鋁箔內，在一些儲存環境，錠劑內潮濕水份蒸發及冷凝，可能降級該成品及產生含毒性之副產品，本文針對可能發生之儲存環境，探研此成品一年內之安定性，觀察發現只要保持穩定的儲存溫度，無論在室溫或冷藏，都不會有安定性問題，可是在不穩定，溫度差異大的儲存情況下，那成品的安定性就會受影響，此儲存環境，應以避免。

關鍵詞：Ergotamine Tartrate，舌下錠劑，安定性。