



Letter

Long-term stability of epinephrine sublingual tablets for the potential first-aid treatment of anaphylaxis

Prompt intramuscular injection of epinephrine in the thigh muscle is the first-aid treatment of choice for anaphylaxis in community settings.¹ However, self-injectable epinephrine has several drawbacks, including replacing the autoinjector annually, even if not used, within their 12- to 24-month shelf-life.¹ In aqueous solutions, epinephrine is unstable in the presence of oxygen, light, heat, and neutral or alkaline pH values.² As a powder, epinephrine should be stored in cool, dry, and opaque containers, according to the US Pharmacopeia (USP) and epinephrine Material Safety Data Sheet.

On the other hand, the sublingual route is a promising alternative for epinephrine administration. We developed rapidly disintegrating sublingual epinephrine tablets (RDSETs), which retain sufficient hardness to withstand shipping and handling but disintegrate rapidly in less than 15 seconds.^{3–5} In a preclinical model, a 40-mg dose had plasma epinephrine concentrations similar to 0.3-mg intramuscular injections in the thigh.^{6–8} The potential of RDSETs as a user-friendly, noninvasive alternative for first-aid emergency treatment of anaphylaxis in a community setting is significant. However, the stability of the RDSETs during manufacturing processes and after long-term storage has not yet been evaluated.

This study's aim was to evaluate long-term epinephrine stability in the RDSETs under conditions at which such tablets may be commonly stored to determine potential shelf-life before use in phase 1 clinical studies.

Three RDSET formulations containing epinephrine bitartrate equivalent to 10 mg, 20 mg, and 40 mg of epinephrine were manufactured by direct compression.^{3–5} Tablet ingredients had low levels of hydroperoxide⁹ and low moisture content. Mixing was performed in a nitrogen-preflushed, opaque glass container, and tablets were compressed immediately. Tablet formulations were quality control tested as promulgated.^{3–5}

After compression, each batch of the 3 tablet formulations was divided into 3 equal quantities and stored in 3 tightly closed, opaque, polytetrafluoroethylene containers with desiccants. The 3 containers were stored at 25°C, 5°C, or 5°C flushed with nitrogen (5°C-N₂). The long-term effect of temperature and oxygen on epinephrine stability in these tablets was evaluated.

Six tablets were randomly removed for epinephrine content analysis using high-performance liquid chromatography (HPLC) with UV detection (Waters, Milford, Massachusetts), according to the USP method,^{3–5} at 6 and 12 months for 10-mg and 20-mg RDSETs and 18 months for 40-mg RDSETs. Three tablets were removed for epinephrine content analysis using HPLC-UV and for absorptivity analysis of epinephrine oxidative products using a Genesys 10-s UV spectrophotometer (Thermo Fisher Scientific, Madison, Wisconsin) according to the USP method¹⁰ at 7 years for 10-mg, 20-mg, and 40-mg RDSETs.

The mean (SD) epinephrine doses in control 10-mg, 20-mg, and 40-mg RDSETs were within USP compendial limits ($\pm 15\%$), confirming that epinephrine stability was not affected by the manufacturing process. Control solutions for epinephrine oxidative products absorptivity measurement were prepared by dissolving placebo tablets in solution spiked with fresh epinephrine bitartrate (absorptivity = 0.001).

Faint yellow discoloration was observed only in the 40-mg RDSETs stored at 25°C for 18 months and 7 years. This finding may indicate minimal epinephrine degradation to adrenolutin, a bright yellow epinephrine oxidative product.^{2,10} However, when RDSETs were dissolved for preparation for HPLC analysis and UV absorbance measurements, no yellow discoloration was visually detected against a white background.

To meet USP standards for epinephrine injections, no discoloration is allowed. Any yellow discoloration after epinephrine solution visual inspection requires measurement of UV absorbance vs control standard solutions.¹⁰ Here, RDSET absorptivity was evaluated even in yellow discoloration absence.

Epinephrine content and absorptivity of oxidative products in stored RDSETs and in controls were compared by 2-way analysis of variance and Tukey-Kramer tests at $P < .05$ (NCSS, Kaysville, Utah). Mean (SD) epinephrine content in 10-mg, 20-mg, and 40-mg RDSETs stored for 6, 12, or 18 months or 7 years at 25°C, 5°C, and 5°C-N₂ did not differ significantly from control RDSETs and was within USP compendial limits for tablets ($\pm 15\%$). The mean epinephrine content was 97% to 100% for the 40-mg RDSET stored for 7 years at all 3 storage conditions. There was no change in the shape of epinephrine chromatography peaks or presence of secondary peaks, confirming absence of epinephrine degradation or oxidative products in RDSETs.

Absorptivity of epinephrine oxidative products in RDSETs (Fig 1) was considerably below 0.2, the USP acceptable level for impurities in epinephrine bitartrate solution.¹⁰ However, absorptivity of RDSETs stored at 25°C was significantly higher than control solutions and those stored at 5°C and 5°C-N₂ possibly because of higher temperature, but the 40-mg RDSET absorptivity was significantly lower than 10-mg and 20-mg RDSETs stored at 25°C (Fig 1). The 10-mg and 20-mg RDSET absorptivity, but not the 40-mg RDSET, stored at 5°C were significantly higher than control solutions, possibly because of the presence of oxygen, which affects epinephrine stability (Fig 1).

No significant difference was found in the absorptivity of the 10-mg, 20-mg, and 40-mg RDSETs stored at 5°C-N₂ and from control solutions. This may be due to RDSET protection from elevated temperature and oxygen (Fig 1). In addition, this finding supports the use of opaque containers and desiccants or proper packaging to reduce RDSET exposure to light and humidity, respectively.

Despite the lack of a significant trend for epinephrine dose effect on absorptivity and thus stability, results may indicate that higher

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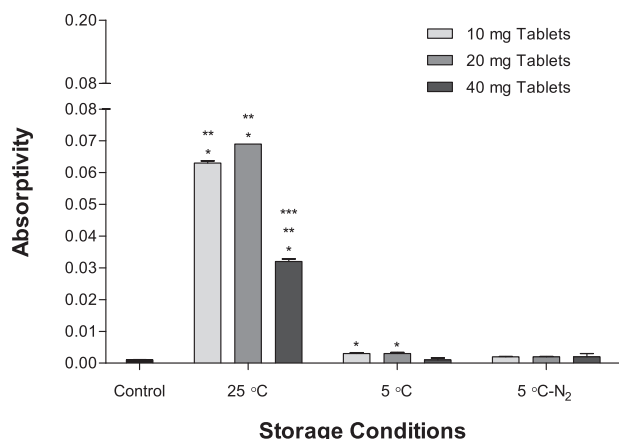


Figure 1. Stability of rapidly-disintegrating sublingual epinephrine tablets (RDSETs) under various storage conditions. Absorptivity of epinephrine oxidative products in the 10-mg, 20-mg, and 40-mg tablet formulations stored at 25°C, 5°C, and 5°C flushed with nitrogen (5°C-N₂) for 7 years was plotted as mean (SD) (n = 3). The absorptivity of the epinephrine oxidative products in all RDSETs was below 0.2, the US Pharmacopeia acceptable level for impurities in epinephrine bitartrate solution. *P < .05 from control (placebo tablets dissolved in solution spiked with fresh epinephrine bitartrate, absorptivity = 0.001). ** P < .05 from epinephrine tablets stored at 5°C and 5°C-N₂. *** P < .05 from 10-mg and 20-mg epinephrine tablets stored at 25°C.

epinephrine content in RDSETs stored under suboptimal conditions has the ability to reduce its own degradation. Lack of discoloration, low absorptivity of epinephrine bitartrate solution from RDSETs, despite stability differences among storage conditions, and absence of a second peak for adrenolutin in the HPLC chromatogram supported by high epinephrine content in RDSETs suggest that epinephrine oxidative products were insignificant or absent. The RDSETs do not contain any antioxidants, such as sodium metabisulfite.^{3–8}

In summary, we found that epinephrine in the RDSETs is stable for at least 7 years even under suboptimal storage conditions. Despite this, efforts should be made to minimize tablet exposure to oxygen, and their storage at lower temperatures improves epinephrine stability. The long-term stability of the RDSETs exceeds the stability of epinephrine solutions in autoinjectors.

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