

1-2017

A Pilot Stability Study of Dehydroepiandrosterone Rapid-dissolving Tablets Prepared by Extemporaneous Compounding

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Publication Information

Rush, Steven D.; Vernak, Charlene; and Zhao, Fang (2017). "A Pilot Stability Study of Dehydroepiandrosterone Rapid-dissolving Tablets Prepared by Extemporaneous Compounding." *International Journal of Pharmaceutical Compounding* 21.1, 83-87.

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Abstract

Dehydroepiandrosterone supplementation is used to treat a variety of conditions. Rapid-dissolving tablets are a relatively novel choice for compounded dehydroepiandrosterone dosage forms. While rapid-dissolving tablets offer ease of administration, there are uncertainties about the physical and chemical stability of the drug and dosage form during preparation and over long-term storage. This study was designed to evaluate the stability of dehydroepiandrosterone rapid-dissolving tablets just after preparation and over six months of storage. The Professional Compounding Centers of America rapid-dissolving tablet mold and base formula were used to prepare 10-mg strength dehydroepiandrosterone rapid-dissolving tablets. The formulation was heated at 100°C to 110°C for 30 minutes, released from the mold, and cooled at room temperature for 30 minutes. The resulting rapid-dissolving tablets were individually packaged in amber blister packs and stored in a stability chamber maintained at 25°C and 60% relative humidity. The stability samples were pulled at pre-determined time points for evaluation, which included visual inspection, tablet weight check, United States Pharmacopeia disintegration test, and stability-indicating high-performance liquid chromatography. The freshly prepared dehydroepiandrosterone rapid-dissolving tablets exhibited satisfactory chemical and physical stability. Time 0 samples disintegrated within 40 seconds in water kept at 37°C. The high-performance liquid chromatographic results confirmed that the initial potency was 101.9% of label claim and that there was no chemical degradation from the heating procedure. Over six months of storage, there were no significant changes in visual appearance, physical integrity, or disintegration time for any of the stability samples. The high-performance liquid chromatographic results also indicated that dehydroepiandrosterone rapid-dissolving tablets retained >95% label claim with no detectable degradation products. The dehydroepiandrosterone rapid-dissolving tablets investigated in this pilot study were physically and chemically stable during preparation and over six months of storage at 25°C and 60% relative humidity.

Keywords

fsc2017

Disciplines

Pharmacy and Pharmaceutical Sciences

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ABSTRACT

Dehydroepiandrosterone supplementation is used to treat a variety of conditions. Rapid-dissolving tablets are a relatively novel choice for compounded dehydroepiandrosterone dosage forms. While rapid-dissolving tablets offer ease of administration, there are uncertainties about the physical and chemical stability of the drug and dosage form during preparation and over long-term storage. This study was designed to evaluate the stability of dehydroepiandrosterone rapid-dissolving tablets just after preparation and over six months of storage. The Professional Compounding Centers of America rapid-dissolving tablet mold and base formula were used to prepare 10-mg strength dehydroepiandrosterone rapid-dissolving tablets. The formulation was heated at 100°C to 110°C for 30 minutes, released from the mold, and cooled at room temperature for 30 minutes. The resulting rapid-dissolving tablets were individually packaged in amber blister packs and stored in a stability chamber maintained at 25°C and 60% relative humidity. The stability samples were pulled at pre-determined time points for evaluation, which included visual inspection, tablet weight check, *United States Pharmacopeia* disintegration test, and stability-indicating high-performance liquid chromatography. The freshly prepared dehydroepiandrosterone rapid-dissolving tablets exhibited satisfactory chemical and physical stability. Time 0 samples disintegrated within 40 seconds in water kept at 37°C. The high-performance liquid chromatographic results confirmed that the initial potency was 101.9% of label claim and that there was no chemical degradation from the heating procedure. Over six months of storage, there were no significant changes in visual appearance, physical integrity, or disintegration time for any of the stability samples. The high-performance liquid chromatographic results also indicated that dehydroepiandrosterone rapid-dissolving tablets retained >95% label claim with no detectable degradation products. The dehydroepiandrosterone rapid-dissolving tablets investigated in this pilot study were physically and chemically stable during preparation and over six months of storage at 25°C and 60% relative humidity.

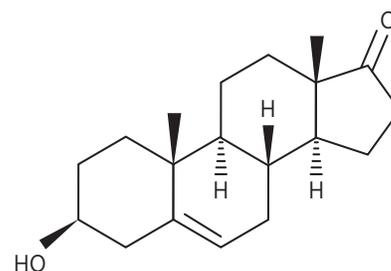
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INTRODUCTION

Dehydroepiandrosterone (DHEA) is an important steroid produced primarily by the adrenal gland. Its chemical structure is shown in Figure 1. DHEA and its sulfate conjugate (DHEAS) are the most abundant circulating steroid hormones in the body and serve as a reservoir for the biosynthesis of other more potent sex hormones, such as testosterone and estradiol.¹⁻³

FIGURE 1. CHEMICAL STRUCTURE OF DEHYDROEPIANDROSTERONE.



Recent studies reveal that DHEA is a neurosteroid with important functions in the mammalian brains.⁴⁻⁶ Levels of DHEA and DHEAS peak in early adulthood and decline steadily afterwards at a rate of about 10% per decade.² Supplementation of DHEA has been proposed to treat a wide variety of conditions, such as sexual dysfunction, decline in cognitive functions, osteoporosis, and infertility.^{2,7-9} However,

many claims are still awaiting evidence from adequately powered, long-term clinical trials. DHEA is regulated as a dietary supplement in the U.S., and commercial products are available as oral capsules/tablets, intra-oral spray, and transdermal creams/gels. However, quality issues of these commercial products have been revealed by independent laboratory analysis, and patients are recommended to obtain DHEA supplements from compounding pharmacies.²

With the recent introduction of special molds and base formulas, rapid-dissolving tablets (RDTs) are gaining popularity among compounded dosage forms. DHEA in RDT dosage forms can offer ease of administration for general patients and serve as an effective option for patients who cannot swallow tablets or have absorption issues (e.g., due to gastric bypass). However, the new excipients, compounding methods, and physical properties of RDTs are significantly different from those of the conventional solid dosage forms, such as compressed tablets or hard-gelatin capsules. There are new uncertainties about the drug and dosage form stability during preparation and over long-term storage.

FIGURE 2. APPEARANCE OF RAPID-DISSOLVING TABLETS AFTER THEY ARE RELEASED FROM THE MOLD.



This pilot study was designed to evaluate the chemical and physical stability of a representative DHEA RDT formulation immediately after preparation and over six months of storage. Such information will aid the compounding pharmacists in establishing proper storage conditions and beyond-use dates of similar DHEA RDT preparations.

MATERIALS AND METHODS

MATERIALS

All ingredients for the RDTs were purchased from Professional Compounding Centers of America (PCCA) (Houston, Texas), and they include DHEA micronized powder (Cat 55-2960), RDT powder base (Cat 30-3269), steviol glycosides (Cat 30-4539), acesulfame potassium (Cat 30-4398), and peppermint oil flavor (Cat 30-3462). The 96-cavity RDT mold (Cat 35-3791) and the blister packs with adhesive label backing (Cat 35-2512 and Cat 35-2671) were also obtained from PCCA. For high-performance liquid chromatography (HPLC) analysis, a reference standard of DHEA bulk drug substance (Lot A0329093; Cat AC154980100), 0.45- μ m

TABLE 1. DEHYDROEPIANDROSTERONE RAPID-DISSOLVING TABLET FORMULA.

INGREDIENT	AMOUNT PER RDT	AMOUNT PER BATCH (96 RDTs)
DHEA micronized powder	10 mg	0.960 g
RDT base powder	625 mg	59.992 g
Steviol glycosides	3 mg	0.288 g
Acesulfame potassium	4 mg	0.384 g
Peppermint oil flavor	-0.04 drop	4 drops
Total (excluding flavor)	642 mg	61.6 g

DHEA = dehydroepiandrosterone; RDT = rapid-dissolving tablet

PVDF syringe filters, and acetonitrile (Cat A998-4) were purchased from Fisher Scientific (Hanover Park, Illinois); Type I purified water was obtained using a Milli-Q system from Millipore (Billerica, Massachusetts).

RAPID-DISSOLVING TABLETS FORMULA AND COMPOUNDING

The formula of 10-mg DHEA RDTs is listed in Table 1. In addition to the drug and RDT base, small amounts of two artificial sweeteners and a flavor were included. For each batch preparation, the ingredients were mixed thoroughly and press-filled into the cavities of a RDT mold. The filled RDT mold was heated in a convection oven at 100°C to 110°C for 30 minutes. The resulting RDTs were cooled to room temperature and immediately released from the mold. A representative picture of the RDTs at this stage is shown in Figure 2. The RDTs were cooled for an additional 30 minutes, packaged into blister packs, and sealed with an adhesive label backing.

STABILITY STUDY

For the stability study evaluation, the packaged RDTs were stored in a stability chamber maintained at 25°C ± 2°C and 60% ± 5% relative humidity (RH). Samples were withdrawn for analysis at 0, 2, 4, 9, 13, and 26 weeks. At each time point, twelve RDTs were taken out of the blister packs and subjected to visual inspection for color, shape, and physical defects. Their weights were also measured to monitor any potential moisture uptake. Six RDTs were then analyzed by the *United States Pharmacopeia (USP)* disintegration test, using a Varian VK 100 model (Cary, North Carolina) with water as the media.¹⁰ Three RDTs were analyzed by the stability-indicating HPLC method described below.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

The HPLC analysis was performed using a model LC-2010A system with LC Solution software from Shimadzu Scientific Instruments (Marlborough, Massachusetts). A Hypersil ODS-2 C18 column (150 × 4.6 mm, 5 μ) from Fisher Scientific (Cat 31605154630) was used and maintained at 30°C. The mobile phase consisted of acetonitrile:water 45:55 (v/v), and the flow rate was 0.8 mL/min. The sample injection volume was 25 μL, and the ultraviolet detection was set at 207 nm. Under these HPLC conditions, the retention time of the drug was approximately 8.0 min. A representative HPLC chromatogram is shown in Figure 3.

For the potency and stability analysis, three RDTs from each time point were aggregated and crushed to a fine powder in a glass mortar and pestle. Three samples of about one-half tablet weight were weighed out and placed in to Class-A, 25-mL volumetric flasks. The flasks were brought to volume with the mobile phase, and the nominal DHEA concentration was about 0.2 mg/mL. The samples were shaken vigorously for the drug to fully dissolve. Ap-

proximately a 2-mL aliquot of each sample was withdrawn and filtered through a PVDF 0.45-μm syringe filter into an HPLC vial for analysis. Each sample was analyzed by three replicate injections. The average DHEA RDT potency and percent label claims were calculated for each stability time point. The HPLC chromatograms were also carefully inspected for potential degradation products.

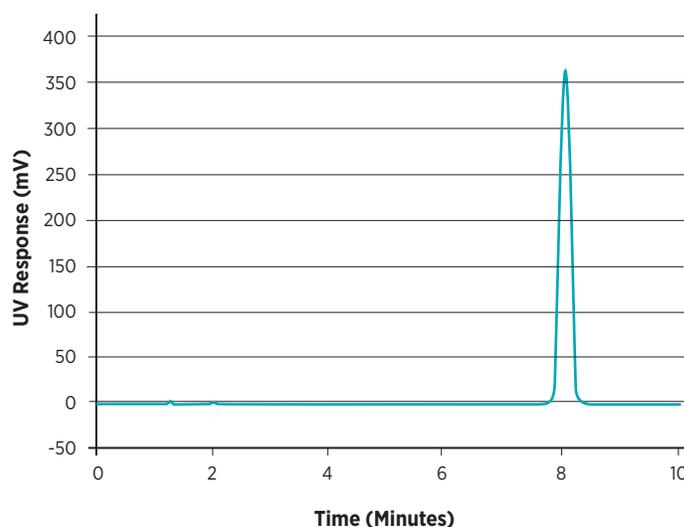
For calibration purpose, DHEA standard solutions were prepared at 0.12, 0.16, 0.20, 0.24, and 0.28 mg/mL. A five-point standard curve was generated on each analysis day. The curves were found to be linear over the concentration range of the standards with a regression coefficient (r) of 0.99 or better. The precision of the method was established by multiple injections of the mid-point standard (0.2 mg/mL) throughout each analysis day. The intra-day and inter-day coefficients of variation were within 0.2% and 1.1%, respectively. Additionally, a blank RDT sample was prepared and analyzed on each analysis day to confirm that there was no interference from the RDT excipients.

FORCED DEGRADATION STUDY

In order to verify that the above HPLC method was stability indicating, four DHEA solution samples at 0.2 mg/mL were prepared for a forced degradation study. Samples 1 and 2 were adjusted to pH 2 and 12 with hydrochloric acid and sodium hydroxide, respectively. Samples 3 and 4 were each spiked with hydrogen peroxide for a final concentration of 3%. Samples 1 through 3 were incubated at 60°C in a convection oven, and Sample 4 was kept on a windowsill (ambient room temperature) and exposed to direct sunlight.

All four samples were analyzed at initial time, 3 hours, 24 hours, 72 hours, and 7 days using the HPLC method described above. No

FIGURE 3. A REPRESENTATIVE HIGH-PERFORMANCE LIQUID CHROMATOGRAM OF 0.2-MG/ML DEHYDROEPIANDROSTERONE.



significant degradation was observed for Samples 1 or 2 after 7 days. Sample 3 degraded by 62% after 3 hours, and Sample 4 degraded by 91% after 7 days. The degradation peaks in both samples were well separated from that of the parent drug. Based on these results, the HPLC method was considered as stability indicating and deemed suitable for the proposed stability study of the DHEA RDTs.

RESULTS AND DISCUSSION

The DHEA RDT formulation exhibited satisfactory chemical and physical stability during the compounding process. All resulting RDTs appeared as white and round tablets with no visible physical defects. The weight of twelve RDT samples averaged 637 mg (99.2% nominal value). The disintegrate time of the six RDTs ranged from 5 seconds to 40 seconds. The HPLC results showed that the initial potency was 101.9% of label claim. No new peaks were observed in the HPLC chromatograms, which suggested that DHEA, in this solid RDT formulation, was chemically stable against the 30-minute heating process at 100°C to 110°C employed during compounding.

Over 26 weeks (six months) of storage at 25°C/60% RH, the visual appearance remained mostly unchanged, and all stability samples retained their physical integrity with no obvious visual defects. No significant tablet weight gain was observed, suggesting that there was minimal moisture uptake by the DHEA RDTs in the blister packs. The disintegration time also remained at 5 seconds to 40 seconds for all stability samples. As shown in Table 2, the HPLC results indicated that DHEA RDTs retained >95% of label claim throughout the six months of storage. No significant degradation products were detected by the stability-indicating HPLC method.

According to *USP* <795>, in the absence of established stability data, the beyond-use date is recommended as 180 days (~ six months) for non-aqueous formulations.¹¹ RDTs are a relatively new dosage form which may present unique stability challenges chemically and physically. For example, the compounding method for the formulation used in this study involves heating at 100°C to 110°C, which is not typically used in compounding conventional solid dosage forms such as powders or capsules. Heating can lead to potential chemical instability of the drug and physical form change (e.g., crystalline to amorphous). By design, the RDT matrix is presumably more hygroscopic and porous than traditional compressed tablets. The increased exposure to moisture and oxygen may also accelerate drug degradation during storage. With these considerations, it is prudent to conduct a stability study on a new drug RDT formulation and generate actual data to support the beyond-use date.

The results from this pilot study confirmed that DHEA in the current RDT formulation is chemically stable against the heating step at 100°C to 110°C during compounding and remains stable over six months of storage at 25°C/60% RH. The additional data

TABLE 2. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY RESULTS OF DEHYDROEPIANDROSTERONE RAPID-DISSOLVING TABLETS STABILITY SAMPLES.

TIME (WEEK)	% LABEL CLAIM*
0	101.9 ± 0.32
2	101.0 ± 3.01
4	103.8 ± 2.95
9	100.2 ± 1.32
13	96.8 ± 0.33
26	99.4 ± 1.50

*Mean ± standard deviation (n=3)

from visual inspection, weight check, and disintegration test also verified that the DHEA RDTs retained their physical integrity and rapid-dissolving property during this storage period.

Several limitations of this study should be pointed out. This study evaluated only the RDT base formula and packaging materials from one commercial supplier. The recommended storage condition was limited to one temperature/humidity. Finally, the disintegration test only confirmed that the tablet, not necessarily the drug, was dissolving rapidly in an aqueous environment. Nevertheless, the results from this pilot study will be useful for the design of a comprehensive stability study in the future.

CONCLUSION

A pilot stability study was conducted on the 10-mg strength DHEA RDTs prepared using the RDT base formula and mold from PCCA. The DHEA RDTs was found to be stable chemically and physically during the compounding procedures and over six months of storage at 25°C and 60% RH.

ACKNOWLEDGMENT

The authors would like to thank the pharmacists Merideth Bodah, PharmD, and Katie Shaw, PharmD, as well as the staff of Vernak Farms Pharmacy, for their assistance in the formulation development and sample preparation.

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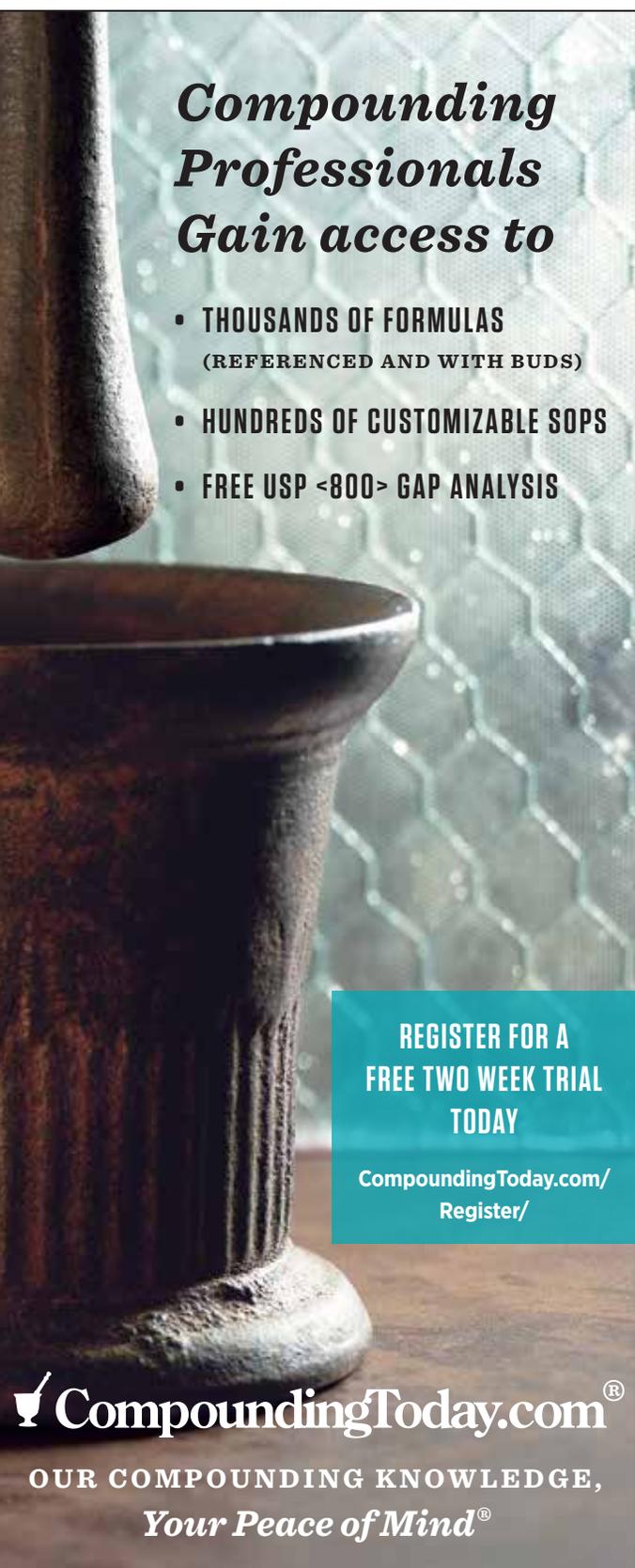
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