Stability of 3.33 mg/mL Bicalutamide in Syringes or Amber Plastic Bottles following Reconstitution with Sterile Water or Oral Mix Sugar Free at 4°C and 25°C

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INTRODUCTION

Bicalutamide is antiandrogen medication primarily used to treat prostate cancer and is classed by NIOSH as a hazardous drug. Current regulations are based on 'no safe limit' of exposure of any hazardous drug to any person (patient or staff) not prescribed the drug.

A bicalutamide suspension is not commercially available and therefore, a formulation must be compounded for patients who cannot swallow. Compounding a suspension using either crushed tablets or powder requires engineering controls to minimize/eliminate exposure of the operator to bicalutamide particles in the air.

We had previously dispersed bicalutamide tablets in water within a syringe and observed that bicalutamide disintegrates rapidly in water with agitation. However, the lack of stability information had limited the use-before-date to 24 hours and preparation of approximately 300 doses annually prompted a more efficient method of compounding.

The purpose of this portion of the work was to evaluate the stability of bicalutamide dispersions/suspensions during storage in amber polyethylene terephthalate (PET) containers (Jones) and polypropylene (PP) oral plastic syringes (Neomed) over 90 days.

OBJECTIVES

To evaluate the stability of 3.33 mg/mL bicalutamide dispersions/suspensions prepared in sterile water for Injection (SWFI) or suspended in Oral Mix Sugar Free (SF). Dispersions/suspensions were stored at 25°C or 4°C in plastic syringes or amber plastic bottles and stability evaluated over for 90 days.

We also evaluated the rate of 50-mg bicalutamide tablet disintegration in both water and Oral Mix SF, to determine the feasibility of preparing a bicalutamide suspension without previously crushing the tablets.

The concentration of bicalutamide was evaluated using a validated, stability-indicating, liquid chromatographic method using UV detection.

NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
The bicalutamide used in this study was purchased by the Department of Pharmacy, Sunnybrook Health Sciences Centre.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 55% methanol and 45% 0.05 mol/L potassium phosphate (KH_2PO_4) adjusted to pH 7 with 1 M sodium hydroxide which was pumped through 15 cm x 4.6 mm reverse-phase Zorbax SB-CN (Agilent Technologies Canada Inc., Mississauga, Ont.) at 1.0 mL/min. The effluent was monitored at 270 nm.

Assay Validation

A chromatographic separation was developed and evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating bicalutamide from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Dissolution Studies

One 50-mg bicalutamide tablet was placed in 15 mL of SWFI or Oral Mix SF. The mixture was stirred with a magnetic stirrer. Samples were drawn every minute from the SWFI mixture and every 5 minutes from the Oral Mix SF suspension. The bicalutamide concentration determined using the chromatographic method. This study was repeated 3 times for each diluent.

Stability Study

On study day 0, six mixtures of bicalutamide 3.33mg/mL were prepared from bicalutamide tablets (Accord Healthcare Inc; Lot W13809; Expiry: 08/2020) in water or Oral Mix SF. Half of the suspensions were stored at 25°C and half were stored at 4°C. On study days 0, 2, 7, 14, 21, 28, 42, 56, 72 and 90 the bicalutamide concentration was determined using the validated reverse-phase stability-indicating liquid chromatographic method.

Data Reduction and Statistical Analysis

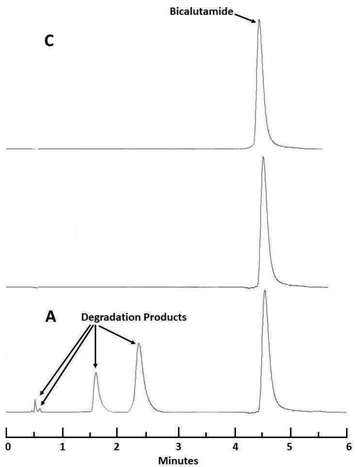
Chemical stability was based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate, determined by linear regression, and the time to achieve 90% of the initial concentration. Multiple linear regression analysis was used to test differences in degradation rate between concentration, diluent and study day.

Figure 1.

Chromatogram A represents a solution of bicalutamide at pH 11.8 after 8 hours of storage at room temperature when 42.82% remained. Bicalutamide degradation followed a first order process with a half life of 6.4 hours under these conditions. After 32 hours 3.15% remained.

Chromatogram B represents the 3.33 mg/mL sample prepared from a tablet on study day zero. Chromatogram C represents the same sample after 90 days storage at room temperature.

Degradation products (at least 4 observed during accelerated degradation) all elute prior to 3 minutes and do not appear following storage at room temperature (Chromatogram C) and do not interfere with quantification of bicalutamide which elutes at 4.5 minutes.



CONCLUSIONS

In preparation of these suspensions, rather than crushing the tablets, it has been shown that disintegration of bicalutamide tablets in SWFI occurs quickly and placing a 50 mg tablet within a syringe and drawing in 15 mL of SWFI may expose the operator to bicalutamide particles in the air. While disintegration of tablets in Oral Mix SF occurs more slowly, adding 15 mL of Oral Mix SF to each uncrushed tablet and allowing sufficient time for disintegration can also minimize exposure to the operator.

Bicalutamide is a stable drug. A suspension of bicalutamide 3.33 mg/mL prepared with tablets in SWFI or Oral Mix SF stored in amber PET bottles or polypropylene syringes retained more than 97% of the initial bicalutamide concentration for 90 days, at both 4°C and 25°C, with 95% confidence.

RESULTS

Table 1. Percent Remaining of the Initial Bicalutamide Concentration [1]

	SWFI[2] 35mL Syringe[3] 4°C	SWFI[2] 35mL Syringe[3] 25°C	Oral Mix SF[4] 35mL Syringe[3] 4°C	Oral Mix SF[4] 35mL Syringe[3] 25°C	Oral Mix SF[4] Amber bottle[5] 4°C	Oral Mix SF[4] Amber bottle[5] 25°C
Nominal Initial Concentration (mg/mL)	3.33mg/mL	3.33mg/mL	3.33mg/mL	3.33mg/mL	3.33mg/mL	3.33mg/mL
Initial Concentration (mg/L)	3.23±1.22	3.24±0.17	3.25±0.56	3.27±0.74	3.30±0.88	3.28±0.52
2	100.33±0.34	99.49±0.37	100.02±0.25	100.59±0.36	100.00±0.35	100.13±0.18
7	100.36±0.33	99.44±0.64	100.32±0.23	98.98±1.23	98.06±0.59	98.86±0.91
14	98.14±0.99	97.10±0.26	97.91±0.65	99.64±0.66	99.46±0.55	96.71±0.07
21	101.29±1.75	100.42±1.09	98.79±0.18	100.80±0.44	95.60±0.97	98.43±0.52
28	101.49±0.64	99.24±0.32	99.38±0.32	100.10±0.33	98.98±0.96	99.47±0.37
42	98.74±1.19	100.09±0.77	97.60±0.10	100.98±0.35	98.04±0.16	99.80±0.31
56	101.01±1.08	98.90±0.77	98.69±0.19	97.83±0.59	98.67±0.87	97.62±0.73
72	101.14±1.52	99.75±1.05	98.00±0.63	100.64±0.74	98.11±0.36	99.70±0.28
90	101.00±1.38	99.27±1.08	99.49±0.33	100.72±0.55	97.88±0.66	100.49±0.47
Degradation Rate (%/day) [Slope]	0.012	0.001	-0.013	0.003	-0.014	0.008
Standard Deviation of Regression (Sy.x)	1.117	0.973	0.941	1.041	1.292	1.254
Fastest Degradation Rate-95% Confidence	-0.0155	-0.0230	-0.0359	-0.0223	-0.0461	-0.0229
Slowest Degradation Rate-95% Confidence	0.0399	0.0252	0.0108	0.0293	0.0180	0.0393
Shortest T-90 in days (95% CI)	644.34	434.11	278.49	447.54	216.78	436.04

1. Concentrations are shown as ± the Coefficient of variation (CV), expressed as a percentage
2. Sterile water for injection
3. Plastic Syringe (Polypropylene, Neomed)
4. Oral Mix Sugar Free – Medisca
5. Amber Plastic bottle (PET, Jones)

Assay Validation

Assay validation demonstrated that degradation products are separated from finasteride (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.02% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.35% within a day and 0.98% between days.

Dissolution Results

Dissolution in SWFI occurred faster the Oral Mix SF. In SWFI, 90% of the complete recovery was obtained in 4 minutes in 3 of 3 tests, whereas in Oral Mix SF, 90% of the complete recovery was obtained in 50 minutes in 3 of 3 tests.

Stability Study Results

Concentrations on each study day are reported in Table 1. During the study period all solutions retained more than 97% of the initial concentration in bottles and syringes at both temperatures and concentrations. The calculated use-before-date, with 95% confidence, averaged 409 days, exceeding the 90-day study period for all temperatures, diluents and container combinations.

Multiple linear regression failed to reveal significant differences in percent remaining due to study day (p=0.96), temperature (p=0.46), diluent (p=0.37) or container (p=0.06). The study was capable of detecting a 0.99% difference.

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