Stability of a Simple Finasteride 0.33 mg/mL Suspension Using Tablets in Water and an Oral Mix Vehicle

William Perks, Shirley Law, John Iazzetta, Nathan Ma and Scott Walker

Sunnybrook Health Sciences Centre, Department of Pharmacy and the [3]Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

Sunnybrook HEALTH SCIENCES CENTRE when it matters MOST

INTRODUCTION

Finasteride is a hazardous drug, classed as a NIOSH group 3 drug because of its reproductive risk. 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 finasteride 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 finasteride particles in the air.

We had previously dispersed finasteride tablets in water within a syringe and observed that finasteride disintegrates rapidly in water with agitation. However, the lack of stability information had limited the use-before-date to 24 hours and preparation in excess of 1300 doses in one year made this an inefficient formulation.

Therefore, we extended the observation of rapid tablet disintegration to an evaluation of disintegration-dissolution studies of the 9 available finasteride tablet formulations in water and Oral Mix products. This study revealed that a suspension of finasteride could be prepared without crushing the tablets prior to placement in either water or Oral Mix. Placing the whole uncrushed tablets in Oral Mix and shaking, resulted in complete disintegration within an hour.

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

OBJECTIVES

To evaluate the stability of finasteride 0.33 mg/mL suspensions prepared in Oral Mix (OM), Oral Mix Sugar Free (SF) and sterile water and stored in PET plastic bottles. In addition, finasteride 0.33 mg/mL suspension was prepared in sterile water and stored in PP amber oral plastic syringes over 90 days. During the study, suspensions were stored at 23ºC and 4ºC.

The concentration of finasteride was evaluated during storage 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 finasteride 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 50% acetonitrile and 50% 0.05 mol/L phosphoric acid adjusted to pH 3 with triethylamine (1.6 mL/L) which was pumped through 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelcosil; Supelco, Toronto, Ontario) at 1.0 mL/min. The effluent was monitored at 258 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 finasteride 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.

Stability Study:

On study day 0, six suspensions of finasteride 50 mg/150 mL (0.33 mg/mL) were prepared from finasteride powder in Oral Mix Sugar Free (SF). Another 6 suspensions were prepared from whole uncrushed finasteride tablets mixed in Oral Mix and Oral Mix SF and stored in PET bottles. As well, six finasteride 5 mg/15 mL suspensions (0.33 mg/mL) were prepared from a whole uncrushed finasteride 5mg tablet mixed with 15mL of water in a 20 mL PP syringe. Half of the suspensions were stored at 23ºC and half were stored at 4ºC. On study days 0, 1, 3, 7, 14, 28, 38, 49, 63 and 90 the finasteride concentration was determined using the validated reverse-phase stability-indicating liquid chromatographic method.

Data Reduction and Statistical Analysis

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence, was also greater than 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the a priori cut-off for significance.

Interested in a copy of this poster or other Sunnybrook Posters?

Scan the QR code or go to : http://metrodis.org/SB_PPC
And download the poster from this site.

CONCLUSIONS

Finasteride 0.33 mg/mL suspensions prepared with tablets in OM and SF or pharmaceutical grade powder in SF stored in PET bottles retained more than 94% of the initial finasteride concentration for 90 days with 95% confidence.

The finasteride 0.33 mg/mL formulation prepared with tablets in sterile water at stored in a PP syringe also retained more than 94% of the initial concentration. The beyond use date applied to this formulation should take into account the potential for microbial contamination due to the lack of preservatives in this formulation.

The formulation using pharmaceutical grade finasteride powder and Sugar-Free Oral Mix is pharmaceutically the most elegant, but like any formulation using powder or crushed tablets, the operator may be exposed to hazardous particles unless prepared in a powder containment cabinet to ensure the operator's protection.

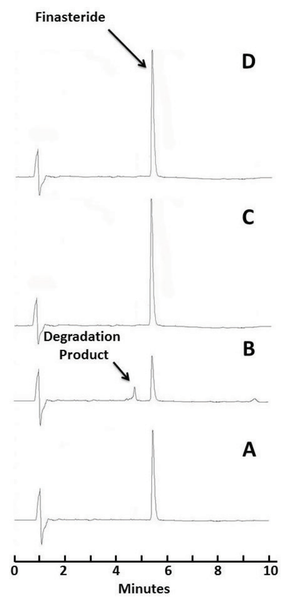
RESULTS

Table 1. Percent Remaining of the Initial Finasteride Concentration.

Study Day	Sterile Water-Tablet 4C	Oral Mix Tablet 4C	Oral Mix SF Tablet 4C	Oral Mix SF Powder 4C	Sterile Water-Tablet RT	Oral Mix Tablet RT	Oral Mix SF Tablet RT	Oral Mix SF Powder RT
Initial concentration (µg/mL)	324.17	325.39	326.16	331.16	327.15	329.26	327.62	331.63
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
1	99.29	99.02	99.18	99.58	99.57	99.19	99.46	99.42
3	99.71	99.50	99.41	99.89	100.07	99.75	100.03	99.77
7	97.90	97.69	97.60	98.07	98.25	97.93	98.20	97.95
14	98.36	98.08	98.01	98.59	98.73	98.22	98.55	98.49
28	102.17	101.84	100.78	101.95	103.12	102.95	102.94	101.94
38	98.78	98.69	98.25	98.96	99.10	98.56	99.19	98.89
49	98.78	98.53	98.30	98.75	99.19	98.70	99.49	98.67
63	97.77	97.37	97.15	97.35	98.04	97.40	98.12	97.19
90	97.93	97.24	96.94	97.54	97.72	97.27	97.53	96.75
Degradation Rate (%/day)	-0.017	-0.021	-0.025	-0.023	-0.020	-0.023	-0.019	-0.029
Std Dev Regression (Sy.x)	1.308	1.311	1.056	1.232	1.503	1.593	1.484	1.291
T-90 – Days	576.75	445.10	373.38	417.75	508.48	421.45	526.59	349.60
Shortest T-90 (95% CI)-Days	201.84	184.50	194.14	183.79	174.05	158.45	177.94	163.53

Figure 1.
Chromatogram A represents a solution of 0.20 mg/mL finasteride in water at pH 2.3 prior to incubation at 93C. Chromatogram B was observed after the 0.20 mg/mL solution at pH 2.3 had been incubated at 93C for 578 hours. 45.2% of the initial finasteride was observed to remain. Chromatogram C represents the 0.20 mg/mL sample prepared from a tablet on study day zero. Chromatogram D represents the same sample after 90 days storage at room temperature.

The degradation product eluting at 4.8 minutes observed in the accelerated study, does not appear following storage at room temperature and does not interfere with quantification of finasteride, which elutes at 5.5 minutes.



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 3.20% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.83% within a day and 2.44% between days.

Concentration Results

Concentrations on each study day are reported in Table 1. During the study period all solutions retained more than 95% of the initial concentration in bottles and syringes at both temperatures and concentrations. The calculated use-before-date, with 95% confidence, averaged 180 days, exceeding the 90 study period for all temperatures and formulation combinations.

Analysis of variance revealed significant differences in percent remaining due to study day ($p < 0.001$), temperature ($p < 0.001$) and formulation. The study was capable of detecting a 0.24% difference in concentration due to study day, temperature, concentration or container. The average difference due to temperature or formulation is 0.28%.