Stability of 5-fluorouracil at 4°C, 25°C, and 33°C stored in Nipro SureFuser+ Ambulatory Balloon Infusers

Nathan H Ma[1], Lauren F Charbonneau[1], Shirley Law[1] and Scott E Walker[1,2]

Department of Pharmacy, Sunnybrook Health Sciences Centre [1], and the Leslie Dan Faculty of Pharmacy, University of Toronto [2], Toronto, Ontario.

INTRODUCTION

5-fluorouracil is one of the most commonly used antineoplastic agents. It is generally used in combination with other antineoplastic agents to treat a wide range of cancers including breast, gastrointestinal, genitourinary, gynecological and head and neck.

Depending on the regimen, 5-fluorouracil can be administered by direct intravenous injection, or diluted with 5% dextrose in water and infused over 24 hours. If the infusion time is >24 hours, 5-fluorouracil can by administered using an elastomeric infusion pump to allow the patient to receive the medication in an outpatient setting.

The introduction of the Nipro SureFuser+ Ambulatory Balloon Infusers raised the question whether 5-fluorouracil is compatible with the infuser and whether the drug will remain stable.

OBJECTIVES

The first objective of the study was to evaluate the stability of 5-fluorouracil undiluted and diluted with 5% dextrose to concentrations of 5 and 30 mg/mL and stored in Nipro SureFuser+ Ambulatory Balloon Infusers at 4°C and 25°C over 60 days.

The second objective was to evaluate stability of 5-fluorouracil when stored in Nipro SureFuser+ Ambulatory Balloon Infusers over 7 days undiluted and diluted with 5% dextrose to concentrations of 5 and 30mg/mL and stored at 33°C.

The concentration of 5-fluorouracil was evaluated during storage at each temperature using a validated, stability indicating, liquid chromatographic method using UV detection.

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

Scan the QR code or Go to http://metrodis.org/SB_PPC2015.html and download the poster from this site.

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 stability study, SureFuser+ Ambulatory Balloon Infusers and 5-fluorouracil used in this study was supplied by CardioMed through an unrestricted research grant.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of 100% 0.05M potassium phosphate monobasic which was pumped through 150mm x 4.6mm reverse-phase C18, 5µm column (Supelcosil ABZ+; Supelco, Toronto, ON) at 1.0 mL/min. The effluent was monitored with UV detection at 262nm.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and specificity. The system was shown to be capable of separating 5-fluorouracil 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, Sandoz 5-fluorouracil (Lot: LD8236, Expiry: Oct-22) was used to prepare 36 Nipro SureFuser+ Ambulatory Balloon Infusers (Lot: 20B11P, Expiry: Jan 31, 2023). Twelve infusers were prepared with undiluted (50 mg/mL) 5-fluorouracil, twelve were filled with 5-fluorouracil diluted with D5W to 30 mg/mL, and the last twelve with 5-fluorouracil diluted with D5W to 5 mg/mL. Four infusers of each concentration were stored at 4°C, 25°C and 33°C. Three infusers were used to evaluate 5-fluorouracil concentration and the fourth was visually inspected for physical compatibility.

For infusers stored at 4°C and 25°C, concentration and physical inspection were completed on study days 0, 2, 4, 7, 14, 21, 28, 42, 49, and 60. Concentration and physical inspection were completed on study days 0, 1, 2, 3, 4, and 7 for infusers stored at 33°C.

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) with 95% confidence. Chemical stability was calculated using the lower limit of the observed degradation rate with 95% confidence and the time to achieve 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate between the different storage temperatures and concentrations. The 5% level was used as the *a priori* cut-off for significance.

RESULTS

Assay Validation

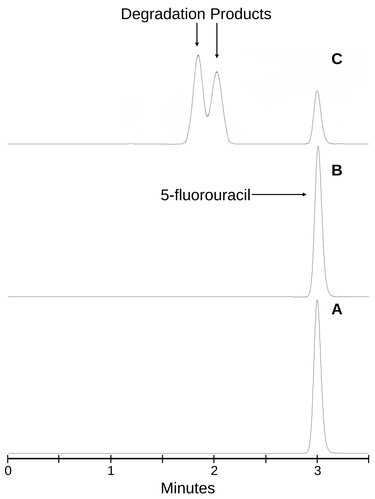
Assay validation demonstrated that degradation products are separated from 5-fluorouracil (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 1.15% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.34% within a day, 0.88% between days and the standard deviation of regression averaged 0.82.

Figure 1. Representative Chromatograms

Chromatogram A represents a solution of 50 mg/mL 5-fluorouracil on day 0. Chromatogram B shows the same sample after 60 days of storage at 25°C with 97% remaining.

Chromatogram C represents a solution of 5-fluorouracil at pH 1.52 after storage at 90°C for 45 hours with 34.6% of the initial concentration remaining.

5-fluorouracil eluted at 3 minutes and degradation products eluted at 1.87 and 2.06 minutes.



Concentration Results

The percent remaining of the initial concentration on each study day are reported in Tables 1 and 2. Solutions stored in the fridge (4°C), at room temperature (25°C), and in the incubator (33°C) retained more than 97% of their initial concentrations. The time to achieve 90% of the initial concentration, with 95% confidence, exceeded the 60 day study period for solutions stored in the fridge (4°C) and at room temperature (25°C) as well as the 7 day study period for the infusers stored at 33°C.

Precipitation was noted in the infusers containing undiluted 5-fluorouracil at day 60, but the precipitate was resolubilized after storage at room temperature for two days.

Analysis of variance revealed significant differences in percent remaining due to study day ($p<0.01$), diluent ($p<0.01$) and temperature ($p<0.01$), but not concentration ($p=0.18$). The study was capable of detecting a 0.93% difference in concentration due to study day, temperature, concentration or container.

CONCLUSIONS

When stored in Nipro SureFuser+ Ambulatory Balloon Infusers, 5-fluorouracil undiluted or diluted with 5% dextrose to concentrations of 5 and 30 mg/mL is stable for at least 60 days when stored at 4°C or 25°C and at least 7 days when stored at 33°C.

Table 1. Percent Remaining[1] of the Initial 5-fluorouracil Concentration when stored in Refrigerator (4°C) and at Room Temperature (25°C).

Diluent	D5W[2]	D5W[2]	Undiluted	D5W[2]	D5W[2]	Undiluted
Temperature	4°C	4°C	4°C	25°C	25°C	25°C
Nominal Initial Concentration (mg/mL)	5	30	50	5	30	50
Initial Concentration (mg/mL)	5.10±0.14	30.55±0.09	50.72±0.12	5.11±0.28	30.45±0.75	50.71±0.23
Study day 0	100.00	100.00	100.000	100.000	100.000	100.000
Study day 2	99.98±0.09	102.37±1.16	99.73±0.93	99.33±0.47	102.18±1.22	102.73±1.07
Study day 4	99.80±0.12	100.93±0.11	100.62±0.76	99.29±0.16	101.11±0.78	101.46±1.99
Study day 7	99.59±0.29	100.42±1.04	100.59±0.22	100.46±1.17	101.47±0.75	101.49±1.80
Study day 14	99.98±0.45	99.13±0.29	100.31±0.32	99.90±0.49	98.97±1.54	102.38±1.94
Study day 21	99.18±0.49	101.56±0.41	100.44±0.42	99.37±0.76	102.18±1.83	100.35±1.67
Study day 28	98.14±0.39	98.92±0.58	99.16±0.29	97.90±1.31	99.79±1.07	99.55±1.23
Study day 42	99.23±0.40	101.58±0.96	99.84±1.22	98.60±0.51	100.32±0.60	98.10±1.00
Study day 49	98.69±0.47	98.31±0.16	98.59±0.33	98.38±0.45	98.51±0.73	97.10±1.16
Study day 60	98.36±0.35	98.71±0.89	99.25±1.15	98.01±1.34	98.67±0.96	97.08±0.65
Degradation Rate (%/day) [Slope]	-0.026	-0.033	-0.022	-0.032	-0.041	-0.080
Intercept (Percent of Initial Concentration)	99.90	100.94	100.36	99.86	101.25	101.93
Correlation coefficient (r)	-0.810	-0.504	-0.698	-0.793	-0.634	-0.884
Standard Deviation of Regression (Sy.x)	0.433	1.285	0.516	0.564	1.131	0.961
Standard Error in Slope (Sb)	0.0068	0.0201	0.0081	0.0088	0.01766	0.0150
Confidence Interval for slope	0.0156	0.0463	0.0186	0.0203	0.0407	0.0346
Fastest Slope 95% Confidence	-0.0420	-0.0794	-0.0408	-0.0526	-0.0816	-0.1148
Upper Limit 95% Confidence	-0.0108	0.0131	-0.0036	-0.0121	-0.0002	-0.0456
Shortest T-90[3] in Days (95% CI)	237.96	125.98	245.01	189.98	122.54	87.08

1. Concentrations are shown as mean ± coefficient of variation (CV), expressed as a percentage
2. Dextrose 5% in water
3. Time to achieve 90% of initial concentration

Table 2. Percent Remaining of the Initial 5-Fluorouracil Concentration in Nipro SureFuser+ Ambulatory Balloon Infusers when stored in incubator at 33°C.

Diluent	D5W[2]	D5W[2]	Undiluted
Temperature	33°C	33°C	33°C
Nominal Initial Concentration (mg/mL)	5	30	50
Initial Concentration (mg/mL)	5.04±0.20	30.40±0.13	50.51±0.003
Study day 0	100.00	100.00	100.00
Study day 1	99.36±0.22	99.14±0.27	99.50±0.40
Study day 2	102.42±0.33	100.78±0.33	101.79±1.25
Study day 3	100.69±0.08	99.98±0.15	102.68±1.45
Study day 4	101.27±0.31	99.91±0.90	102.96±0.22
Study day 7	102.28±0.16	100.71±0.40	103.66±0.95
Degradation Rate (%/day) [Slope]	0.333	0.122	0.602
Intercept (Percent of Initial Concentration)	100.062	99.739	100.056
Correlation coefficient (r)	0.674	0.503	0.891
Standard Deviation of Regression (Sy.x)	1.013	0.583	0.853
Standard Error in Slope (Sb)	0.182359	0.105044	0.153558
Confidence Interval for slope	0.50631	0.29165	0.42635
Fastest Slope 95% Confidence	-0.1736444	-0.1693591	0.1761520
Upper Limit95% Confidence	0.8390	0.4139	1.0288
Shortest T-90[3] in Days (95% CI)	57.59	59.05	56.77

1. Concentrations are shown as mean ± coefficient of variation (CV), expressed as a percentage
2. Dextrose 5% in water
3. Time to achieve 90% of initial concentration