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Physicochemical stability of Fluorouracil Accord in three different concentrations in portable elastomeric infusion pumps

Author byline as per print journal: *Irene Krämer, PhD; Frank Erdnuess, PhD; Judith Thiesen, PhD*

Study objectives: To determine the physicochemical stability of Fluorouracil Accord 50 mg/mL solution for injection or infusion in three different types of elastomeric infusion pumps over 42 days, either undiluted (50 mg/mL) or after dilution with 0.9% sodium chloride or 5% glucose solution to concentrations of 0.1 mg/mL and 25 mg/mL.
Methods: Test solutions were aseptically prepared with Fluorouracil Accord (5-FU) 50 mg/mL either transferred to Surefuser+ (Nipro), Easypump (B Braun), or Folfusor SV 2.5 mL/h (Baxter) elastomeric pumps. Test solutions were stored light-protected in the refrigerator (2°C–8°C) (0.1 mg/mL, 25 mg/mL 5-FU) and without light protection at 20°C–25°C (0.1 mg/mL, 25 mg/mL, 50 mg/mL 5-FU). At predetermined time points, storage conditions were changed, and test pumps kept for an additional period of 7 days at 30°C to simulate infusion conditions. Physicochemical stability was assessed by pH measurement, visual inspection and high-performance liquid chromatography (HPLC) analysis.
Results: Physicochemical stability of undiluted and diluted Fluorouracil Accord in elastomeric infusion pumps was demonstrated for a 42-day storage at 2°C–8°C or at room temperature plus additional 7 days at 30°C.
Conclusion: Fluorouracil Accord solutions in elastomeric infusion pumps may be prepared in advance and stored over a period of 42 days at room temperature (concentration range 0.1 mg/mL to 50 mg/mL 5-FU) or at 2°C–8°C (concentration range: 0.1 mg/mL to 25 mg/mL 5-FU) plus 7 days at 30°C.

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Introduction

Fluorouracil is a pyrimidine antimetabolite that competes with uracil for incorporation into DNA, thereby blocking the cellular enzyme thymidylate synthetase. It is mainly used in combination with calcium or sodium folinate and oxaliplatin (FOLFOX [1]) or irinotecan (FOLFIRI [2]) for the treatment of various types of cancer, primarily colorectal, oesophageal, stomach, and anal cancers. In these regimens, high-dose fluorouracil is continuously infused via portable elastomeric pumps.

Physiochemical stability of several commercially available 5-FU products in elastomeric infusion pumps is reported for up to 28 days [3–5]. The summary of product characteristics of Fluorouracil Accord 50 mg/mL injection establishes its physicochemical stability over a 24-hour period when diluted to 0.98 mg/mL 5-FU with 0.9% sodium chloride or 5% glucose solution and stored at 25°C, regardless of the container material used [6].

Study objectives

The objective of the study was to determine the physicochemical stability of Fluorouracil Accord 50 mg/mL in three types of elastomeric infusion pumps (Surefuser+ (Nipro), Easypump (B Braun), Folfusor SV 2.5 mL/h (Baxter)) at three concentrations (50 mg/mL (undiluted), 0.1 mg/mL, and 25 mg/mL (diluted with 0.9% sodium chloride or 5% glucose solution)) and stored at room temperature or under refrigeration for 42 days followed by 7 days at 30°C .

Methods

5-FU test solutions were prepared under EU Class A conditions and in accordance with the principles of Good Manu facturing Practice . Using the European Medicines Agency (EMA) licensed Fluorouracil Accord 50 mg/mL solution for injection or infusion (batch numbers PP00022 and PP00667) and three types of elastomeric infusion pumps, a total 15 different test solutions were prepared. The test solutions were stored at 20°C– 25°C without light protection (0.1 mg/mL, 25 mg/mL, 50 mg/mL 5-FU) or at 2°C– 8°C protected from light (0.1 mg/mL, 25 mg/mL 5-FU). At predetermined time points, see Table 1, a defined number of pumps were transferred to 30°C conditions and stored for an additional seven days (simulated infusion). Test samples were withdrawn at the end of the simulated infusion period and analysed.

Table 1: Storage conditions and sampling time points of Fluorouracil Accord test solutions in three types of elastomeric infusion pumps

Type of elastomeric pump (manufacturer)	5 FU-Concentration (mg/mL)	Type of Diluent	Transfer time points to 30°C (day)	
			20°C–25°C, normal room light	2°C–8°C, protected from light
Surefuser+ (Nipro)	0.1	0.9% NaCl	0, 14, 28, 42*	0, 14, 28, 42*
		5% glucose	0, 14, 28, 42*	0, 14, 28, 42*
	25	0.9% NaCl	0, 14, 28, 42*	0, 14, 28, 42*
		5% glucose	0, 14, 28, 42*	0, 14, 28, 42*
	50	undiluted	0, 14, 28, 42*	n.a.
EasyPump (B Braun)	0.1	0.9% NaCl	0, 14, 28, 42*	0, 14, 28, 42*
		5% glucose	0, 14, 28, 42*	0, 14, 28, 42*
	25	0.9% NaCl	0, 14, 28, 42*	0, 14, 28, 42*
		5% glucose	0, 14, 28, 42*	0, 14, 28, 42*
	50	undiluted	0, 14, 28, 42*	n.a.
Folfusor SV 2.5 mL/hr (Baxter)	0.1	0.9% NaCl	0, 14, 28, 42*	0, 14, 28, 42*
		5% glucose	0, 14, 28, 42*	0, 14, 28, 42*
	25	0.9% NaCl	0, 14, 28, 42*	0, 14, 28, 42*
		5% glucose	0, 14, 28, 42*	0, 14, 28, 42*
	50	undiluted	0, 14, 28, 42*	n.a.

*At each time point, test pumps were transferred for additional 7 days to 30°C storage conditions; test samples were taken at the end of the storage period (x days plus 7 days).
n.a.: not analysed.

The physical stability analysis of all test solutions was determined by pH measurements (using a glass electrode calibrated with standard buffer solutions) and by visual inspections under standard laboratory light for any changes in colour, clarity, or the presence of particulate matter.

The chemical stability was assessed via high-performance liquid chromatography (HPLC) assay, which has been validated for linearity of the analytical response and acceptable precision [7]. The assay was proven to be stability-indicating for non-specific degradation of the parent drug. Acceptance criteria were set at a concentration of ±10 % of the initial concentration [7]. In addition, related substances were analysed. Peaks in the HPLC chromatograms were identified by their relative retention times according to the 5-FU main peak, and concentrations were calculated. Acceptance criteria for the peaks were set as follows [7]:

- Barbituric acid (impurity A): </= 0.1%
- 5-hydroxy uracil (impurity B): </= 0.2%

- Single unknown impurity: </= 0.1%
- Total impurities: </= 0.8%

Results

Fluorouracil Accord solutions in elastomeric infusion pumps remained physically and chemically stable for 42 plus 7 days, regardless of the concentration (0.1 mg/mL, 25 mg/mL, 50 mg/mL), vehicle solution (undiluted, 0.9% sodium chloride, 5% glucose solution), and storage condition (20°C– 25°C without light protection, 2°C–8°C light protected) used. The HPLC assays revealed only slight variations in 5-FU concentrations when test pumps were stored at 2°C– 8°C, see Tables 2-4. 5-FU concentrations in test pumps stored at 20°C– 25°C increased over the storage period, predominantly in solutions in Easypumps, see Tables 2, 3 and 4. Several peaks of related substances were observed in the HPLC chromatograms, but none exceeded the set limits. Two were identified as 5-hydroxyuracil (impurity B) and barbituric acid (impurity A). Single peaks of unknown impurities amounted to less than 0.08%, and total impurities amounted to less than 0.3% of the main peak (not shown in the tables). Neither colour changes, turbidity, nor visible particles were noticeable during visual inspection.

Table 2: Physicochemical stability of Fluorouracil Accord solutions in Surefuser+ (Nipro) stored at 2°C–8°C (light protected) plus 7 days at 30°C or at 20°C–25°C (normal room light) plus 7 days at 30°C

Concentration	Diluent	Time/ Specification	Fluorouracil concentration remaining (%); Initial concentration set as 100%	
			90%–110% of initial concentration	
			Initial storage at 2°C–8°C, light protected	Initial storage at 20°C–25°C, normal room light
0.1 mg/mL	0.9% NaCl	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	101.01	100.71
		28 d + 7 d at 30°C	100.95	101.43
		42 d + 7 d at 30°C	100.44	105.40
	5% glucose	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	100.09	99.84
		28 d + 7 d at 30°C	100.18	100.40
		42 d + 7 d at 30°C	99.23	101.09
25 mg/mL	0.9% NaCl	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	101.82	101.38
		28 d + 7 d at 30°C	103.53	102.16
		42 d + 7 d at 30°C	99.21	102.98
	5% glucose	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	101.17	105.19
		28 d + 7 d at 30°C	102.50	104.67
		42 d + 7 d at 30°C	101.34	102.27
50 mg/mL	undiluted	0 (initial)	n.a.	100.00
		14 d + 7 d at 30°C	n.a.	103.70
		28 d + 7 d at 30°C	n.a.	104.72
		42 d + 7 d at 30°C	n.a.	101.14

n.a.: not analysed.

Table 3: Physicochemical stability of Fluorouracil Accord solutions in EasyPump (B Braun) stored at 2°C–8°C (light protected) plus 7 days at 30°C or at 20°C–25°C (normal room light) plus 7 days at 30°C

Concentration	Diluent	Time/ Specification	Fluorouracil concentration remaining (%); Initial concentration set as 100%	
			90%–110% of initial concentration	
			Initial storage at 2°C–8°C, light protected	Initial storage at 20°C–25°C, normal room light
0.1 mg/mL	0.9% NaCl	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	101.38	102.77
		28 d + 7 d at 30°C	104.13	103.95
		42 d + 7 d at 30°C	101.31	105.23
	5% glucose	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	100.50	101.77
		28 d + 7 d at 30°C	101.11	103.10
		42 d + 7 d at 30°C	100.85	104.51
25 mg/mL	0.9% NaCl	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	103.25	101.41

(Continued)

Table 3: Physicochemical stability of Fluorouracil Accord solutions in EasyPump (B Braun) stored at 2°C–8°C (light protected) plus 7 days at 30°C or at 20°C–25°C (normal room light) plus 7 days at 30°C (*Continued*)

Concentration	Diluent	Time/ Specification	Fluorouracil concentration remaining (%) Initial concentration set as 100%	
			90%–110% of initial concentration	
			Initial storage at 2°C–8°C, light protected	Initial storage at 20°C–25°C, normal room light
		28 d + 7 d at 30°C	105.35	107.22
		42 d + 7 d at 30°C	104.60	103.80
	5% glucose	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	102.23	103.66
		28 d + 7 d at 30°C	102.37	107.76
		42 d + 7 d at 30°C	101.04	105.44
50 mg/mL	undiluted	0 (initial)	n.a.	100.00
		14 d + 7 d at 30°C	n.a.	104.83
		28 d + 7 d at 30°C	n.a.	109.86
		42 d + 7 d at 30°C	n.a.	108.50

n.a.: not analysed.

Table 4: Physicochemical stability of Fluorouracil Accord solutions in Folfusor SV 2.5 mL/hr (Baxter) stored at 2°C–8°C (light protected) plus 7 days at 30°C or at 20°C–25°C (normal room light) plus 7 days at 30°C

Concentration	Diluent	Time/ Specification	Fluorouracil concentration remaining (%) Initial concentration set as 100%	
			90%–110% of initial concentration	
			Initial storage at 2°C–8°C, light protected	Initial storage at 20°C–25°C, normal room light
0.1 mg/mL	0.9% NaCl	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	100.70	100.42
		28 d + 7 d at 30°C	100.72	100.40
		42 d + 7 d at 30°C	100.04	101.03
	5% glucose	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	99.85	99.53
		28 d + 7 d at 30°C	99.68	99.97
		42 d + 7 d at 30°C	99.69	100.07
25 mg/mL	0.9% NaCl	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	102.75	101.73
		28 d + 7 d at 30°C	100.93	101.02
		42 d + 7 d at 30°C	102.42	101.07
	5% glucose	0 (initial)	100.00	100.00
		14 d + 7 d at 30°C	102.84	102.24
		28 d + 7 d at 30°C	101.42	101.63
		42 d + 7 d at 30°C	102.21	99.58
50 mg/mL	undiluted	0 (initial)	n.a.	100.00
		14 d + 7 d at 30°C	n.a.	104.94
		28 d + 7 d at 30°C	n.a.	104.25
		42 d + 7 d at 30°C	n.a.	100.15

n.a.: not analysed.

Conclusion

The physicochemical stability of Fluorouracil Accord 50 mg/mL in three types of elastomeric infusion pumps (Surefuser+, Nipro; Easypump, B Braun; Folfusor SV 2.5 mL/h, Baxter) at three concentrations (50 mg/mL undiluted, 0.1 mg/mL, 25 mg/mL, diluted with 0.9% sodium chloride, 5% glucose solution) was proven for 42 days storage, plus an additional 7 days of storage at 30°C to simulate infusion conditions.

Thus, Fluorouracil Accord infusion solutions in elastomeric pumps, with a concentration range of 0.1 mg/mL to 50 mg/mL, can be prepared in advance in pharmacy-based cytotoxic preparation units and stored for up to 42 days prior to administration. Samples were withdrawn after an additional 7 days of storage at 30°C to simulate elevated temperature conditions during administration. Storage at 2°C– 8°C is preferred due to enhanced microbiological stability and reduced evaporation of the vehicle solution.

Analysis was performed and documented by an accredited external laboratory. Results were carefully checked for plausibility and cautiously interpreted.

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Authors

Professor Irene Krämer, PhD
Frank Erdnuess, PhD
Judith Thiesen, PhD

Department of Pharmacy, University Medical Center of the Johannes Gutenberg University Mainz, 1 Langenbeckstraße, DE-55131 Mainz, Germany

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Author for correspondence: Judith Thiesen, PhD, Department of Pharmacy, University Medical Center of the Johannes Gutenberg University Mainz, 1 Langenbeckstraße, DE-55131 Mainz, Germany

Disclosure of Conflict of Interest Statement is available upon request.

Generics and Biosimilars Initiative (GaBI)
Tel: +32 474989572 | Fax: +32 14 583 048