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Long-term physico-chemical stability of 5-fluorouracile at standardised rounded doses (SRD) in MyFuser® portable infusion pump

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Management of chemotherapies is a strategic issue for european healthcare. Dose-banding enables to reduce waiting time of patients in day care units and drug wastage. The aim of this study was to assess the stability of 5-Fluorouracile (5-FU) at standardised rounded doses of 4 and 5 g in MyFuser® portable infusion pump for in-advance preparation. Ten MyFuser® (4 and 5 gr 5-FU added to NaCl 0.9%) were prepared under aseptic conditions and stored at room temperature (23 ± 2 °C) for 28 days then at 30 °C for three days. Physical stability tests were periodically performed: visual and microscopic inspection, pH measurements and optical densities. The concentration of solutions was measured by High Performance Liquid Chromatography/UV detector. Results confirm the stability of 5-FU at selected SRD of 4 g and 5 g with NaCl 0.9% in MyFuser® for at least 28 days at room temperature and three days at 30 °C, allowing in-advance preparation.

Keywords: Dose-Banding; 5-FU; Chromatography; stability study; portable infusion pump; CIVAS

Introduction

The constant increase of the number of cancer[1] leads hospitals to wonder about their therapeutic management of this pathology. A main concern in oncology remains the cytotoxic drug dosing. As far as we know, "the recommended dose for a specific patient is the highest dose associated with an acceptable toxicity"[2]. The historical calculation of chemotherapy doses is based on Body Surface Area (BSA) but the concept of dose-banding gradually arises as another option because of the weak correlation between BSA doses and the efficacy and toxicity of the drugs. As Plumridge et al. described, dose-banding must be understood as a "system whereby through agreement between prescribers and pharmacists, doses of intravenous cytotoxic drugs, calculated on an individualized basis that are within defined ranges or bands are rounded up or down to predetermined standard doses. The maximum variation of the adjustment between the standard dose and the doses constituting each band is 5% or less"[3]. The usage of dose-banding remains restricted in Belgium so that stability studies are needed on the horizon of implementation.

Dose-banding enables in-advance preparation of ready-to-use cytotoxic drugs in centralised intravenous admixture services (CIVAS)[4,5] where physicochemical and bacteriological quality[6] are assured. It relieves nursing staff from the tasks of infusions preparation and reduces the risk of errors. The centralised preparation of standardised rounded doses (SRD) allows to reduce the waiting time of patients in day care units and to reuse returned mixtures in order to limit wastages[7,8].

This study focuses on 5-Fluorouracile (5-FU) dose-banding applied to a recent type of portable diffuser MyFuser® XM 2.5 ml/h from Canox

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(Canox Medical device SRL, Capurso, Italy) composed of an elastomeric infusion pump. It is not implantable, not programmable, single-use and allows the ambulatory infusion of drugs. 5-FU is an antimetabolite drug that exerts its anticancer effects through inhibition of thymidylate synthase and incorporation of its metabolites into RNA and DNA. It is used by oncologists to treat colorectal, head and breast cancers[9]. Portable eslastomeric pumps are already used in the day care unit. They lighten chemotherapy by allowing patients to go back home for the 48 hours of administering.

The literature offers lots of references about the stability of 5-FU in various conditions. For example, the stability of the drug has been tested in sodium chloride PVC bags, in portable infusion pumps, in combination with other drugs and at various temperatures[10–14]. Despite those works, there are still little paper concerning stability of 5-FU at concentration of dose-banding[15] and the stability of 5-FU at standardised dose in portable infusion pump has never been assessed.

The aim of this work is to study the physico-chemical stability of 5-FU in MyFuser® within the scope of dose-banding prepared in advance at standard rounded doses of 4 and 5 g.

Materials and methods

Solutions preparation

Ten Myfuser® from Canox (lot F15B050) were prepared under aseptic conditions and stored at room temperature (23 ± 2 °C) for 28 days to match to the usual preservation times in the CIVAS and then at higher temperature (30 °C into a heating chamber) for three days (28 + 3 days) to exceed real-life conditions when infusors are weared by patients during 48 h. Likewise, infusors were not protected from the light during storage.

Five MyFuser 4 g (MyFuser4) were composed of 80 ml 5-FU (50 mg/ml, Teva Pharma, lot 3490715) and 35 ml 0.9% sodium chloride solution (Macopharma, lot 15L03G) for a final concentration of 34.78 mg/ml and five MyFuser 5 g (MyFuser5) were composed of 100 ml 5-FU (50 mg/ml, Teva Pharma, lot 3490715) and 15 ml 0.9% sodium chloride solution (Macopharma, lot 15L03G) for a final concentration of 43.47 mg/ml.

Aliquots were withdrawn following a precise schedule to perform physicochemical stability tests at room temperature (23 ± 2 °C) (3 times a week during the first two weeks then 2 times a week during the two following weeks) and at 30 °C (twice a day for 3 days). Aliquots dedicated to the physical study were straight analysed while those dedicated to chemical study were frozen at −80 °C.

Chemical stability

Chromatographic conditions

5-FU solution concentrations were measured by high liquid performance chromatography (HPLC), (Alliance, model 2695, Waters Association, Milford Massachusetts) coupled to a photodiode array (model 996, Waters Association, Milford Massachusetts) set at 300 nm and a processing module (Empower 3 Software, Waters Association, Milford, MA, USA). The reversed-phase column was a C18 (Hyperclone™ 3 µm ODS 100 × 4.6 mm, Phenomenex, H16-097915) in association with a pre-column (C18, 4 × 3 mm, Phenomenex, PRD 060439) kept at 35 °C. The mobile phase was made up of 5% methanol and 95% phosphate buffer 0.01 M (pH 7.5) at a flow rate of 1.0 ml/min.

Standard solutions

One calibration curve was prepared in triplicate using five levels of standards (50 mg/ml, 40 mg/ml, 35 mg/ml, 30 mg/ml and 20 mg/ml), based on the commercial solution of 5-FU (50 mg/ml) diluted in distilled water. Standards were injected in the system after a hundred-fold dilution.

Quality control solutions

Three quality control solutions (45 mg/ml, 37.5 mg/ml and 25 mg/ml) were prepared for each run, based on the commercial solution of 5-FU (50 mg/ml) diluted in distilled water. Controls were injected in the system after a hundred-fold dilution.

Samples

Aliquots dedicated to the chemical study were defrosted by batch just before chromatographic analyses to meet an organisational need on the technical floor. The chemical analyse was made in triplicate after a hundredfold dilution.

Validation of the chromatographic method

The chromatographic method was validated following the ICH Q2(R1) guidelines[16].

The three quality control solutions were used to calculate within (n = 10) and between (n = 9) day reproducibility.

The linearity was evaluated by two fold serial dilutions (n = 10) in purified water from a 5-FU solution of 50 mg/ml.

Limits of detection (LOD) and quantification (LOQ) were determined using 10 blanks (mobile phase) measurements. LOD and LOQ were calculated as follows:

LOD = mean + 3 x standard deviation.

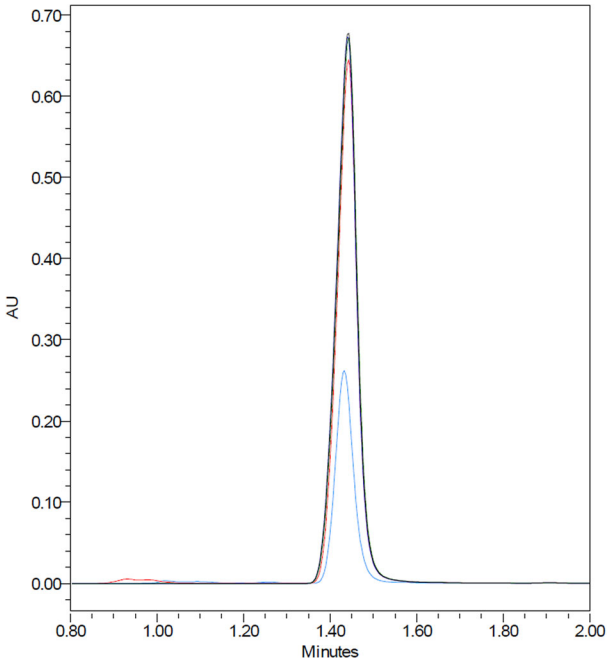

Figure 1. Forced degradation chromatogram of 5-FU after 4 days at 23 ± 2 °C: natural t0 (black), natural t4 (green), acid t4 (dark blue), alkaline t4 (red), oxidant (light blue).

LOQ = mean + 10 x standard deviation.

A degradation study was performed to assess the stability-indicating capability of the method. Vials of 5-FU (50 mg/ml) were prepared in neutral, acidic (HCl 0.2M), alkaline (NaOH, 0.2M) and oxidative (H2O2, 3%) conditions. Acidic and alkaline solutions were neutralised before injection. Solutions were injected immediately after preparation and after 2 and 4 days of preservation at room temperature (23 ± 2 °C) and at 60 °C.

pH

The pH of each solution was measured with a glass electrode pH-meter (inoLab, WTW GmbH, Weilheim, Germany).

Statistical analyses

The measurements were done in four different assays, which results in an inter-assay variability that could substantially interfere with the estimation of the evolution of concentration over time. This inter-assay variability was measured through a linear mixed model with concentration a the dependent variable, SRD and storage times at room temperature (23 ± 2 °C) and 30 degrees as independent variables and assay as a random intercept. A corrected concentration was then obtained by substracting the assay effect from the raw concentration. In the main analysis we used the corrected concentration. However, in a sensitivity analysis, we used the uncorrected data in order to verify that the corrected concentrations does not lead to overoptimistic conclusions, which is not the case as the uncorrected stability is systematically longer than the corrected one (data not shown).

As defined in ICH Guidelines[16], the shelf life of a product was defined as "the earliest time at which the 95% confidence limit for the mean intersects the proposed acceptance criterion". Therefore, a unilateral 95% confidence interval on the mean was used to determine the earliest time at which the product concentration fall under 90% of the initial concentration or 95% of the initial concentration when any signs of physical instability exist.[17].

However, as stated by the Shelf-Life Working Group of the Product Quality Research Institute, the definition of the shelf life should be based on "an acceptably small proportion of product exceeding an acceptance criterion"[18]. We thus used the 95% unilateral prediction interval in addition to the confidence interval to cover, on average, 95% of the distribution.

In order to compute these confidence and prediction intervals, we used a linear regression model for each SRD with the corrected concentration as the dependent variable and the storage time at room temperature (23 ± 2 °C) and 30 degrees as the independent variables.

Physical stability

At each time, solutions were visually inspected in front of black and white backgrounds in order to detect colour changes, opacity or visible particles and a spun aliquot (5 minutes at 2150 g, Heraeus multifuge 1S, Thermo Scientific, USA) was examined under the microscope (Jenamed, Carl Zeiss, Germany) with a 12.5x objective to detect particles.

The optical densities were monitored (Genesys 10 UV, Spectronic Unican) at three wavelengths (350, 410 and 550 nm) to follow the apparition of turbidity as an indicator of the apparition of subvisible particles[17].

Results

Validation of the HPLC method

The within and between day reproducibility remained below 6%.

The concentrations were linear over the range 0.098 – 50 mg/ml with a calculated determination coefficient (r^2) of 0.999.

Limits of detection and quantification were both < 0.001 mg/ml.

The degradation test showed a diminution of the main peak (±20%), demonstrating the stability-indicating capability of the method[18]. The Figure 1

Table 1. Evolution of the relative concentration of 5-FU during storage and conditions of administering. RT = Room temperature (23 ± 2 °C), Mean(sd) = observed relative concentration (reference = initial concentration), Fitted. = estimated relative concentration, LL95CI = 95% Confidence interval on the mean, LL95PI = 95% Prediction interval.

SRD		Day	Mean	SD	Fitted	LL95CI	LL95PI
4 g	RT	0	3723	22	100,0	99,1	95,8
		2	3814	32	100,0	99,1	95,8
		4	3788	34	100,0	99,2	95,8
		7	3808	38	99,9	99,3	95,7
		9	3744	37	99,9	99,3	95,7
		11	3724	42	99,9	99,3	95,7
		15	3810	31	99,9	99,4	95,7
		17	3755	60	99,8	99,3	95,7
		22	3928	48	99,8	99,2	95,6
		24	3732	63	99,8	99,1	95,6
		28	3754	160	99,7	98,9	95,5
	30 °C	29	3635	26	98,2	97,5	94,0
		30	3674	37	96,6	95,6	92,4
		31	3600	76	95,0	93,5	90,6
5 g	RT	0	4033	39	100,0	98,8	94,8
		2	4154	42	99,7	98,6	94,5
		4	4157	25	99,3	98,4	94,2
		7	4005	103	98,8	98,0	93,7
		9	3984	16	98,5	97,8	93,4
		11	4087	50	98,2	97,5	93,1
		15	4283	57	97,5	96,9	92,4
		17	4023	37	97,2	96,6	92,1
		22	4110	18	96,4	95,6	91,3
		24	3963	52	96,0	95,2	90,9
		28	3895	166	95,4	94,4	90,2
	30 °C	29	3781	53	93,6	92,8	88,5
		30	3820	107	91,9	90,6	86,7
		31	3740	74	90,1	88,3	84,7

illustrates the degradation after 4 days at room temperature (23 ± 2 °C).

Chemical stability

In the MyFuser4 condition, the relative concentration remained higher than 90% of the initial content during the 28 + 3 days of storage following both confidence and prediction intervals. In the MyFuser5 condition, the relative concentration remained higher than 90% of the initial content during 28 + 2 days of storage following confidence interval and during 28 + 0 days of storage following prediction interval.

Results are resumed in Table 1.

Physical stability

There was no colour change, opacity or particles observed in the solutions during the 28 + 3 days of storage. No subvisible particle was detected by microscopic examination.

The evolution of the pH did not show any significant change during the 28 + 3 days of storage (Table 2). The absolute optical densities remained stable over the study period (Table 2).

Discussion

The literature includes various stability studies about 5-FU in different conditions.

With in-advance preparation in mind, it was necessary to assess the best conditions for long term storage of 5-FU. Some studies pointed out the risks of crystallisation of 5-FU in sodium chloride 0.9% when stored in a cold room[13,14] but Martel's study[13] showed a stability of at least 14 days in PVC bags stored at 21 °C and ambulatory pump reservoir stored at 33 °C. Our study confirmed the stability of the drug in a recent elastomeric silicone reservoir at room temperature (23 ± 2 °C) for a longer period of 28 days.

Stiles et al.[11] studied the stability of three commercially available 5-FU aqueous solutions (50 mg/ml) into portable infusion pump at 25 and 37 °C, simulating infusion conditions. At 25 °C, the simulated infusion showed a fine precipitate in the tubing of the Roche® brand FU 48 to 96 hours after the pumping beginning. In our study, no precipitate appeared. This is possibly related to the difference of excipient between the brands (Teva® vs Roche®). At 37 °C, their results indicated the stability of the drug in all tested brands for a seven-day period. In this study, the stability at 30 °C in a heating chamber differs according to the dose of 5-FU studied. The MyFuser4 is stable during the study period (28 + 3) but the MyFuser5 shows a restricted stability (28 + 2 and 28 + 0) at 30 °C. This difference in stability can be explained by the higher concentration in the 5 g diffusers.

In addition, in this study, two different statistical methods have been used to determine the stability duration: the confidence and prediction intervals. Both methods match ICH guidelines but they have a different clinical significance in this context. The use of the confidence interval shows an average stability for all solutions studied over the study period while the prediction interval on the mean ensure that each solution studied keeps 90% of its initial content for the study period. The use of the prediction interval is then more stringent than the use of the confidence interval on the mean.

Finally, the products possibly released into the 5-FU solution from the elastomeric infusion pump have not been studied. The stability to heat and light was neither assessed given that those parameters have already been studied[19].

Establishing the long-term stability of a drug is of considerable interest to the hospital pharmacy service: this allows the preparation of the drug to be disconnected from its dispensation. In advance preparation gives the possibility of mass

Table 2 Evolution of the Optical densities and pH during storage and conditions of administering.

		Optical densities (Mean ± SD)			
Diffuser	Dose (g)	350 nm	410 nm	550 nm	pH (Mean ± SD)
MyFuser	4	0.023 ± 0.003	0.002 ± 0.001	0.000 ± 0.002	8.8 ± 0.1
	5	0.028 ± 0.003	0.003 ± 0.001	0.000 ± 0.002	8.9 ± 0.1

production, which generates savings. In addition, it also makes it possible to limit the waiting time between prescription and dispensation for patients. This study is the first to assess the stability of 5-FU at standardised doses combined with portable infusion pump conditions.

Conclusion

According to the physical and chemical results of our study, Teva Pharma brand 5-FU is stable in MyFuser4 for at least 28 days at room temperature (23 ± 2 °C) and for at least three days at 30 °C. These results allow the in-advance preparation of Teva Pharma brand 5-FU at selected SRD of 4 g in MyFuser® device for dose-banding usage.

Teva Pharma brand 5-FU in Myfuser5 for at least 28 days at room temperature (23 ± 2 °C). The extra days stability at 30 °C vary from zero to two days according to the statistical method applied.

Notes on contributor

Mélanie Closset is a medical doctor (2009) with a master degree in ethic (2015). She's in charge of the department of clinical biochemistry of the medicine laboratory at CHU UCL Namur. She's PhD student since 2018 and she is collaborating with the department of pharmacy on stability studies about injectable drugs.

Sabrina Onorati is a laboratory technologist since 2016. She's working at the department of clinical biochemistry of the medicine laboratory at CHU UCL Namur. She collaborated with the department of pharmacy on stability studies about injectable.

Marie-Lise Colsoul is a Bioengineer. PhD student at the Catholic University of Louvain since 2018, she is also in charge of the chromatographic department of the medicine laboratory at CHU UCL Namur. She is collaborating with the department of pharmacy on stability studies about injectable.

Nicolas Goderniaux is a laboratory technologist. He's working at the department of clinical biochemistry of the medicine laboratory at CHU UCL Namur and is collaborating with the department of pharmacy on stability studies about injectable.

Benoît Bihin is biologist. PhD Student at the university of Namur since 2011, he is also lecturer of biostatistics courses. He works at the CHU UCL Namur as biostatistician since 2014 and is a member of the Drug Stability Research Group.

Jacques Jamart is medical doctor (1972) and surgeon (1978) then received a master degree in statistics (1984). He worked in experimental surgery mainly in the field of organ preservation for transplantation and more recently as biostatistician and head of Scientific Support Unit (1993) of University Hospital of Mont-Godinne. He is also emeritus professor at Catholic University of Louvain(2009) and at University of Namur (2010).

Laura Soumoy is hospital pharmacist. She has been working at the CHU UCL Namur since 2014 and is now chief of the department of Pharmacy since 2019. Since 2017, she is also a member of the Drug Stability Research Group in the same CHU.

Professor Jean-Daniel Hecq is Hospital pharmacist and doctor in pharmaceutical sciences. He worked at the CHU UCL Namur from 1979 to 2019 and was chief of the department of Pharmacy from 1989 to 2019. He is also the coordinator of the Drug Stability Research Group in the same CHU and the author since 39 years of a Belgian electronic database so entitled "Stability of injectable drugs in infusion".

Pascal Odou is professor at the Faculty of Pharmacy of Lille (2004) in hospital pharmaceutical technologies. He is also the director (2015) of the Research Group on injectable forms and associated technologies (ULR 7365). In addition to these academic functions, he is since 2010, also the pharmacist in charge of the pharmaceutical department of the University Hospital of Lille.

Professor Laurence Galanti, MD, PhD is co-director of the department of laboratory medicine at CHU UCL Namur, in charge of clinical biochemistry on the site of Mont-Godinne. She holds several positions in national and international scientific organizations. Her research focused on clinical application of biomarkers of exposition to tobacco smoke and on the stability of injectable drugs in collaboration with the department of pharmacy.

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