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Comparison of Raman spectroscopy vs. high performance liquid chromatography for quality control of complex therapeutic objects: Model of elastomeric portable pumps filled with a fluorouracil solution

Philippe Bourget[a,*], Alexandre Amin[a], Fabrice Vidal[a], Christophe Merlette[a], Frédéric Lagarce[b]

[a] Clinical Pharmacy Department, HU Necker-Enfants Malades, 149 rue de Sèvres, 75743 Paris cedex 15, France
[b] Pharmacy department, Academic Hospital, 4 rue Larrey, Angers, France

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ABSTRACT

This study compares the performance of a reference method of HPLC to Raman spectroscopy (RS) for the analytical quality control (AQC) of complex therapeutic objects. We assessed a model consisting of a widely used anticancer drug, i.e., 5-fluorouracil, which was compounded in a complex medical device, i.e., an elastomeric portable infusion pump. In view of the main objective, the two methods provided excellent results for the analytical validation key criteria, i.e., trueness, precision and accuracy, ranging from 7.5 to 50 mg/mL and in either isotonic sodium or 5% dextrose. The Spearman and Kendall correlation tests (p-value $< 1 \times 10^{-15}$) and the statistical studies performed on the graphs confirm a strong correlation in the results between RS and the standard HPLC under the experimental conditions. The selection of a spectral interval between 700 and 1400 cm^{-1} for both the characterization and quantification by RS was the result of a gradual process optimization, combining matrix and packaging responses. In this new application, we demonstrate at least eight benefits of RS: (a) operator safety, (b) elimination of disposables, (c) elimination of analysis waste, which contributes to the protection of the environment, (d) a fast analytical response of less than 2 min, (e) the ability to identify the solubilizing phase, (f) reduction of the risk of errors because no intrusion or dilution are needed, (g) negligible maintenance costs and (h) a reduction in the budget dedicated to technician training. Overall, we indicate the potential of non-intrusive AQC performed by RS, especially when the analysis is not possible using the usual techniques, and the technique's high potential as a contributor to the safety of medication.

1. Introduction

1.1. Background and purpose

In France, central IV admixtures of chemotherapy treatments (CT) are required by law [1]. This process is currently performed under pharmaceutical liability, especially at hospitals. This requirement represents an important step forward in terms of both the quality and safety of care [2], as well as (a) a strong contribution to the standardization of prescribing practices, (b) a lower exposure of caregivers to chemicals, (c) an improved organization of caregiver workloads and (d) a substantial cost savings [3]. However, we see (a) an increasing number of combined therapies, (b) an increasing number of patients and (c) more individualized and more complex therapeutic regimens. In this multifactorial context, the development of effective tools for the quality control of therapeutic objects (TO)[1] is highly relevant [3]. Our goal is to ensure a high and stable quality in our pharmaceutical preparations for the benefit of patients, caregivers and the environment. Furthermore, a systematic analysis of the production process reveals several critical points; these abnormalities may dangerously weaken the validity of the process. In the course of pioneering studies started 12 years ago at the Gustave-Roussy Institute (Villejuif 94805 cedex, France), we demonstrated the importance of linking the physical

[1] We call therapeutic object(s) (TO(s)) the product resulting from a compounding process, performed by specialized staff, i.e., a) an active principle in solution or in suspension in an appropriate medium, usually normal saline or 5% dextrose solution, and b) an immediately labeled package, possibly pre-connected to an infusion set. The presence of secondary packaging may complete the definition.

* Corresponding author. Tel.: +33 1 42 11 51 88; fax: +33 1 42 11 52 00.
E-mail address: philippe.bourget@nck.aphp.fr (P. Bourget).

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product resulting from a compounding process, which we call TO, to the flow of information [4–8]. This idea occurred to us long before the recent and serious health accidents that were highly publicized in the French media. We designed an analytical quality control (AQC) process that we applied, as systematically as possible, to the three following key parameters: identity, purity and nominal concentration of an active pharmaceutical ingredient (API) in solution or in suspension in a sterile medium. However, experience indicates that a TO cannot be reduced to the API. Under these conditions, the following question is important: is it possible to offer an analytical solution, ideally non-intrusive, that could manage the entire TO, i.e., API, solubilizing matrix and its container?

In this context, the purpose of this study was to develop and validate a Raman spectroscopy (RS) method as an effective tool for the non-intrusive AQC of geometrically complex TO(s). We studied the model of elastomeric portable infusion pumps filled with fluorouracil (5-FU) either in a normal saline solution or in a 5% dextrose solution. This protocol was compared to a reference HPLC method. We also examined how the use of one analytical method vs. another contributes to the security and safety of the administration of medication at the hospital.

1.2. Analytical quality control and Raman spectroscopy

Ideally, the purpose of AQC is to allow the analytical certification of the TO prior to its administration to a patient. In terms of hospital organization, the AQC should be fast, reliable, and fully integrated into the production process and treatment. This is particularly relevant for day care units. However, the need to withdraw a fraction of a TO for analysis purposes should also be considered in terms of security and safety, for both operators and their working environment. For some TOs, withdrawal is difficult, even impossible, e.g., small syringes, autonomous infusion devices (elastomeric portable infusion pumps), and PCA devices. The most frequently used analytical techniques are: (a) chromatographic methods coupled with appropriate detection systems, (b) HPTLC (high performance thin layer chromatography) methods, and (c) coupling of UV/visible light spectroscopic techniques to a Fourier transform infrared spectroscopy detector. Chromatographic methods are powerful, but their implementation is costly and sometimes tedious. They also require specialized skills. We will not detail the strengths and weaknesses of this reference option. According to our criteria, and despite substantial technical improvements, chromatographic methods are not suitable to high-throughput AQC. RS allows for the qualitative and quantitative characterization of an API and its solubilization matrix, without any risk of alteration. However, among the characterization parameters, both the specificity and reliability of the technique must be demonstrated through experimentation; furthermore, some molecules are structurally similar [9]. Finally, we must systematically study the spectral behavior of packaging layers (of varying number and thickness), their contents, and the possible interferences of their respective signatures. For these reasons, the term "contextual analysis" by RS will be used. It is worth to note that quantitative Raman studies of APIs in injectable are very rare [10,11].

2. Materials and methods

2.1. Choosing a suitable API and working conditions

In brief, fluorouracil is a pyrimidine analog that has been used for more than 40 years. This drug is widely used in the treatment of many forms of cancer and often in combination with other anticancer drugs. Some of its main indications are in colorectal and pancreatic cancer. It is also used in the treatment of inflammatory breast cancer, an aggressive form of breast cancer [12]. Most of the protocols involving 5-FU are listed in Table 1. 5-FU is administered at therapeutic concentrations from 12.5 to 50 mg/mL, either in saline or 5% dextrose; the analytical comparison was performed within these two values and in both solvents. To test the analytical performance of RS vs. HPLC and to build robust calibration models, we expanded the range of concentrations from 1.5 mg/L, leading to the production of a large number of calibration TOs and external validation TOs.

2.2. Choosing the medical device

5-FU is usually administered by IV, by means of either an infusion bag (in this case, gravity is used), or a more or less sophisticated electromechanical pump or, finally, by autonomous elastomeric infusion systems that use a combination of the elastomeric material pressure and Hagen–Poiseuille's law. This last option is of particular interest because: (a) these systems are disposable medical devices, (b) their physical structure and their geometry are quite complex, and (c) they are commonly used in both hospitals and in homecare, as well as for ambulatory patients. We selected a pump model widely used in protocols, such as FOLFOX and FOLFIRI (Table 1), i.e., the Infusor® SV2 System (Baxter ref 2C1702KD, batch 09C044 2011-12-31); Fig. 1 is a diagram of the device.

2.3. HPLC analysis

Chromatographic separation was performed on a Dionex Ultimate® 3000 series liquid chromatographic system equipped with a quaternary pump, a variable UV/visible detector, and an autosampler (Dionex, 78960 Voisins le Bretonneux, France). Chromatographic separation was performed on Lichrospher® C18 column (125 mm × 4 mm, dp = 5 μm (Merck, 69008 Lyon, France)). The mobile phase consisting of a mixture of water for injection and KH_2PO_4 (40 mmol/L) adjusted to pH 7.0 with NaOH (10% solution in water), was delivered at rate of 0.8 mL/min. The mobile phase was filtered through a 0.45 μm membrane (Millipore, 67120

Table 1
List of the major chemotherapy protocols that include a continuous infusion of 5-FU and their main parameters of use. LV2, SV2, and LV5 are brand names of Baxter Healthcare.

Protocol name	Dose (mg/m^2)	Time of infusion (h)	Volume (mL)	Infusion system brand name	Ct° max[a] (mg/mL)	Ct° min[b] (mg/mL)
TPF	3750	120	240	LV2	31.3	10.1
GORTEC	2400	96	192	LV2	25.0	8.1
VOKES	4000	120	240	LV2	33.3	10.8
CDDP-5-FU C225	4000	96	192	LV2	41.7	13.5
LOHP 5-FU	5000	120	240	LV2	41.7	13.5
FOLFOX or FOLIRI	2400	46	96	SV2	50.0	16.3
			230	LV5	20.9	6.8
FOLFOX or FOLIRI pediatric use[c]	2400	46	96	SV2	50.0	12.5

[a] Ct° max (recommended): upper limit of concentration into the infusion system for a BSA (body surface area) of 2 m^2.
[b] Ct° min (recommended): lower limit of concentration into the infusion system for a BSA of 1.3 m^2 and a dose reduction of 50%.
[c] Ct° max and Ct° min: recommended values for a BSA of 1 m^2 and a dose reduction of 50%.