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Development of a method to determine axitinib, lapatinib and afatinib in plasma by micellar liquid chromatography and validation by the European Medicines Agency guidelines

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ABSTRACT

A method based on micellar liquid chromatography to quantify the tyrosine kinase inhibitors axitinib, lapatinib and afatinib in plasma is reported. The sample pretreatment was a simple 1/5-dilution in a pure micellar solution, filtration and direct injection, without requiring extraction or purification steps. The three drugs were resolved from the matrix in 17 min, using an aqueous solution of 0.07 M sodium dodecyl sulfate – 6.0% 1-pentanol, buffered at pH 7 with 0.01 M phosphate salt as mobile phase, running under isocratic mode at 1 mL/min through a C18 column. The detection was performed by absorbance at 260 nm. An accurate mathematical relationship was established between the retention factor of each drug and the surfactant/organic solvent concentration in the mobile phase, achieved with a limited number of experiments, in order to optimize these factors. A binding behavior of the analytes face to the micelles was found out. The method was successfully validated by the guidelines of the European Medicines Agency in terms of: selectivity, linearity ($r^2 > 0.9995$), calibration range (0.5 to 10 mg/L), limit of detection (0.2 mg/L), carry-over effect, accuracy (− 8.1 to + 6.9%), precision (< 13.8%), dilution integrity, matrix effect, stability and robustness. The procedure was found reliable, practical, economic, accessible, short-time, easy-to-handle, inexpensive, environmental-friendly, safe, useful for the analysis of many samples per day. Finally, the method was applied to the analysis of incurred, using quality control samples in the same analytical run, with adequate results. Therefore, it can be implementable for routine analysis in clinical laboratories.

1. Introduction

For the last years, many tyrosine kinase inhibitor drugs (TKIs) have been developed against several oncogenic diseases, in the frame of targeted therapies, with encouraging clinical results. These small molecules act by blocking specific receptors of tyrosine kinase proteins that are involved in several signal transduction pathways related to tumor cell proliferation and growth, as well as in angiogenesis and suppression of apoptosis [1,2].

Afatinib (Gilotrif®) is an irreversible blocker of several epidermal growth factor receptors (EGFR or ErbB), like HER1 (ErbB1), HER2 (ErbB2), and HER4 (ErbB4). This small molecule was developed by Boehringer Ingelheim (Ingelheim am Rhein, Germany) and was approved by FDA in 2013 as first-line treatment against metastatic non-small cell lung cancer (NSCLC) [3,4]. Axitinib (Inlyta®) is a selective and potent inhibitor of the vascular endothelial growth factor receptors (VEGFR) tyrosine kinase 1, 2, and 3. It was developed by Pfizer (New York, NY, USA) and approved in 2012 by the FDA against metastatic renal cell carcinoma (mRCC) after failure of a previous systemic therapeutic. It has also shown promising results to treat kidney cell cancer, metastatic melanoma, thyroid cancer, and advanced non-small cell lung cancer [3,5,6]. Lapatinib (Tykerb®) is a strong inhibitor of the human epidermal growth factor receptor type 2 (HER2/ERbB2) and epidermal growth factor receptor (HER1/EGFR/ERbB1). It was developed by GlaxoSmithKline (Brentford, UK) and approved in 2007 by the FDA to treat advanced metastatic breast cancer in combination to other chemotherapeutic agents. Its prescription against other solid tumors and metastatic pancreatic cancer is currently under study [3,7,8]. The three drugs are orally administered as tablets [3]. Their main pharmacological and chemical properties are described in Table 1 [3,6,9–13], and the structures can be seen in Fig. 1 [13].

TKI-based therapies show a significant inter- and intrapatient variability clinical response at the same dosage. Indeed, the pharmacokinetics of the TKI depends on many factors: genetics, physiology,

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Table 1
Physicochemical and pharmacological parameters of the studied drugs [3,6,9–13].

Drug	Afatinib	Axitinib	Lapatinib
Chemical group	4-Anilinoquinazoline	Indazole derivative	4-Anilinoquinazoline
Log Po/w	3.8	5.0	5.2
pKa (basic)	8.8	4.8	3.8/7.2
Charge at pH 7	+ 1	+ 1	+ 1
Bioavailability	Unknown	Variable, ≈ 58%	Unknown
Usual treatment	40 mg once daily	5 mg twice daily	1250–1500 mg once daily
Time to steady state	8 days	15 days	6–7 days
Time to peak plasma	2–5 h	2.5–5.1 h	4 h
Half life	37 h	2.5–6.0 h	14.2 h
Route of elimination	85% feces 4% urine	41% feces 23% urine	14% feces 10% urine

pathology, and habits, which affects the bioavailability, metabolism and elimination kinetics. Besides, the TKI have long-term therapies with poor tolerability, undesirable side effects at therapeutic drug exposure, association between plasmatic concentration and efficacy/toxicity, drug-drug interactions, and development of resistance [7–16]. In this context, TDM may be a valuable tool for an effective medical supervision and to ensure the optimal response by the individualization of the treatment. Firstly, it can be used to verify the adherence of the patient. In cases of failure, weak clinical effects, severe toxicity or suspected any factor altering the pharmacodynamics of the drug, the determination of the plasmatic concentration may assist the clinician to properly modify the treatment, by adjusting the dosage or changing the prescribed drug. Therefore, this strategy would improve patient survival and quality of life [1,9,10,14,17,18]. In order to support pharmacological studies in daily clinical practice and in oncology research, a reliable and convenient bioanalytical method to measure the concentration of afatinib, axitinib and lapatinib in plasma is required.

We have previously demonstrated the suitability of micellar liquid chromatography for the rapid analysis of TKIs in plasma, using a hybrid micellar mobile phase and sodium dodecyl sulfate (SDS) as a surfactant [19,20]. Indeed, SDS-micelles and SDS monomers bind to proteins, fats and other biopolymers, provoking their denaturation and solubilization, and the releasing of linked drugs. Therefore, these macromolecules are eluted near the dead time, rather than precipitating in the column, and do not interact with the analytes. Otherwise, hydrophobic small solutes are also solubilized. This avoids the needing of extraction and cleanup intermediate steps to remove harmful compounds and interfering compounds, or recover the analytes, which strongly expedite the experimental manipulation. Therefore, plasma samples can be directly injected, after a simple dilution and filtration, in the column [17,18]. Otherwise, the use of micellar mobile phases also offers benefits for the chromatographic resolution step. The variety of interactions that occurs in the column complicates the retention mechanism and provides a high versatility to MLC, allowing the resolution of mixtures of solutes with different charges and hydrophobicity values using an isocratic elution. The retention factor is highly stable and reproducible, and can be modeled from the composition of the mobile phase, using chemometrics [21,22].

The aim of the work was the development of an analytical method to quantify afatinib, axitinib and lapatinib in plasma by micellar liquid chromatography. The method should provide reliable results and exhibit practical advantages to be used in routine clinical practice, like easy-to-handle, use low amount of hazardous chemicals, inexpensive and able to process many samples in a short time. In order to test the analytical performances, the procedure must be validated by the guidelines of the European Medicines Agency [23]. Finally, its reliability should be demonstrated by analyzing samples of plasma from cancer patients following a therapy based on these drugs. The effect of the composition of the mobile phase on the retention should be also investigated.

2. Experimental

2.1. Standard and chemicals

Solid standards of afatinib free base (purity > 99%), axitinib free base (> 99%) and lapatinib free base (> 99%) were bought from LC laboratories (Woburn, MA, USA). Sodium dodecyl sulfate (> 98.0%), 1-pentanol and dimethyl sulfoxide (DMSO) (HPLC grade) were purchased from Scharlab (Barcelona, Spain). Sodium hydroxide (> 98%) was supplied by from Riedel-deHaën (Hannover, Germany). Sodium dihydrogen phosphate monohydrate (> 98.0%) and hydrochloric acid (37%) came from Panreac (Barcelona, Spain). Ultrapure water was *in-lab* obtained by the purification of deionized water, provided as tap water by the University, using an ultrapure water generator device Simplicity UV (Millipore S.A.S., Molsheim, France). All aqueous solutions were prepared using this water.

2.2. Preparation of solutions and mobile phases

Individual stock solutions of afatinib, axitinib and lapatinib (100 mg/L) were prepared by solving the appropriate mass of the solid standard in dimethyl sulfoxide. The working solutions were prepared by dilution in a micellar solution of 0.05 M SDS buffered at pH 7 with 0.01 M phosphate salt.

The micellar solution (either for dilution or as mobile phase) were prepared as follows: the adequate amount of SDS and $NaH_2PO_4{\cdot}H_2O$

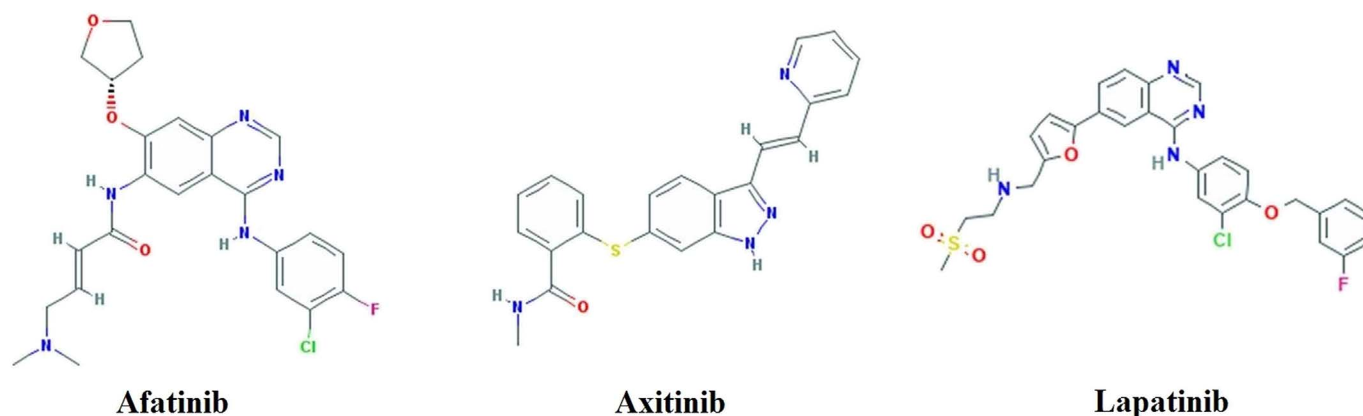

Fig. 1. Structures of the studied anti-cancer drugs.

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