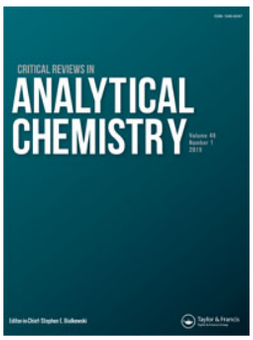

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Flucloxacillin: A Review of Characteristics, Properties and Analytical Methods

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ABSTRACT

Bacterial resistance is a growing and worrying factor. The high reproducibility of these resistant microorganisms tends to influence the development of new drugs and research related to product quality control. Among the existing antimicrobials, flucloxacillin (FLU) was designed for oral and injectable administration with bactericidal activity. FLU sodium is the form used in pharmaceutical formulations. It is an antimicrobial resistant against penicillinase, an enzyme responsible for cleaving the beta-lactam ring of penicilins, which leads to inactivity of the drug. Qualitative and quantitative analyzes are essential to ensure quality of pharmaceuticals and health of the population. It is important that quality control is effective and appropriate, only then we can win the battle against microbial resistance. In this work, we want to highlight tthe characteristics of FLU as an important antibiotic and methods for the determination of FLU in pharmaceutical products and biological matrices. Among the analytical methods described in the literature for the determination of FLU, high performance liquid chromatography (HPLC) stands out. Anyway, this method uses toxic solvents (e.g. acetonitrile) long columns, which provide long runs, as well as produces large amounts of waste. Currently, the priority changed to develop ecologically correct, conscious and sustainable methods. This new view on analytical methods should be applied to FLU analyzes and used to develop and improve existing methods.

KEYWORDS

Analytical methods; flucloxacillin; quality control; sustainable method

Introduction

Increasingly, studies related to antimicrobial agents are intended to contribute to the treatment of infectious diseases and to combating antimicrobial resistance, due to the reproducibility of microorganisms and the development of superbugs.[1,2]

Penicillins are broad-spectrum antimicrobial agents and are used for the treatment of numerous infections. They are mainly active against Gram-positive bacteria.[3] Penicillins are classified into several subcategories, which are differentiated by their chemical structures and antimicrobial activities. The effect of flucloxacillin sodium (FLU) in the class of isoxazolepenicillins, which are active penicillins against penicillinase-producing strains, has a molecular chain modification that differentiates its action spectrum.[4]

FLU is commonly used for the treatment of serious infections of the skin, soft tissue and the respiratory tractas well as endocarditis and osteomyelitis caused by methicillin susceptible to *S. aureus*. FLU is widely recommended in Europe and Australia for the treatment of staphylococcal infections. In the United Kingdom, FLU is the most commonly prescribed oral antimicrobial for the treatment of staphylococci.[5]

In 1970, Sutherland and collaborators[6] showed that FLU was as active as dicloxacillin and oxacillin, and it was slightly more active than cloxacillin. In addition, FLU proved to be effective against penicillin-resistant staphylococci.

Compared to vanomycin FLU is preferred in the treatment of serious diseases produced by resistant bacteria. Due to this important factor, it is extremely relevant to study the main characteristics of the drug, as well as the existing methods in the literature for the identification and/or quantification of this antimicrobial agent.[5]

The activities carried out in quality control are certified by the validation of the analytical methods. The equipment as well as the inputs involved in the production process also present quality certification.[7]

The study on antimicrobial agents increases the need for the development and production of these drugs, such as FLU, thereby increasing the demand and accountability of the Quality Control (QC) sector for pharmaceutical inputs and finished products in laboratories and industries. Quality control aims to guarantee the quality of the product and ensure the health of the patient.[7]

The literature showed varied methods for the evaluation of FLU, such as spectrophotometry in the ultraviolet and visible region, high performance liquid chromatography and coupled to mass spectrometry, capillary electrophoresis and even microbiological method as diffusion in agar.[3,5,8,10,19,20,22,26,31,99]

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Therefore, the main objective of this review was to identify and analyze the analytical methods described in the literature to FLU. Considering the importance, that flucloxacillin sodium presents in the current antimicrobial treatment. This review showsthe characteristics, properties and highlight the analytical methods for quantification and determination of FLU in both pharmaceutical products and biological samples described in the literature. For this purpose, the search focused on the following databases: PubMed, Scopus and Web of Science whose period ranged from 1977 to 2017.

Flucloxacillin

Flucloxacillin (FLU) is an antimicrobial that belongs to the semi-synthetic isoxazolpenicillins group. It is an antimicrobial resistant to penicillinase, an enzyme responsible for cleaving the beta-lactam ring, making the other drugs inactive against microorganisms.[8] In this work, we focused on aspects related to form, structural modification, mechanism of action, pharmacodynamics, pharmacokinetics and pharmaceutical properties, as well as methods for FLU analysis are presented below.

Structural form

There are two forms of flucloxacillin: flucloxacillin sodium (FLU, Figure 1) and flucloxacillin magnesium octahydrate. Flucloxacillin sodium (FLU) is the form used in pharmaceutical formulations.[9,10]

Structural Modification

FLU belongs to the class of semi-synthetic penicillin isoxazole; its structure was modified by the addition of a bulky structure in the lateral group (Figure 2), which acts as a steric hindrance and prevents the approach of betalactamases. The synthesis of FLU is described in patent U.S. 3239307.[11]

Mechanism of action

The mechanisms of action of antimicrobials can act on the interference of cell wall synthesis, inhibition of protein synthesis, interference in DNA synthesis and inhibition of metabolic pathway.[12]

FLU inhibits the cell wall biosynthesisofGram positive microorganisms, being a bactericidal drug. The penicillins in general act in this way, preventing the reproduction of bacteria, more specifically inhibiting the synthesis of peptideoglycan, by inhibiting the enzymes transpeptidases.[13] It should be noted that the indiscriminate use of antimicrobials contributes to bacterial resistance, which has become a worldwide health problem.[14]

Pharmacokinetics and pharmacodynamics

FLU is used in the treatment of infectionsof susceptible microorganisms; its bioavailability is 50–70% after oral administration and its absorption by the intestine is rapid. This drug, can be used orally, intravenously, intramuscularly, intrapleural, intraarticularly and by nebulization.[15,16]

FLU is an organic compound, acid in aqueous solution with pKa 2.76, determined at 37°C in 0.15 M KCl.[17] It has a half-life of approximately 1 hour. FLU can be found in bone tissues, breast milk, pleural and sinuvial fluid; it crosses the placenta and does not diffuse easily in cerebrospinal fluid.[4]

Physicochemical properties

FLU is a semi-synthetic product derived from fermentation, white or almost white, hygroscopic and crystalline. The solubility of FLU is characterized as very soluble in water and methanol, and soluble in ethanol (96%). The chemical name of FLU is (2S,5R,6R)-6-[[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazole-4-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid.

Its molecular formula is $C_{19}H_{16}ClFN_3NaO_5S.H_2O$ and molecular weight is 493.869 mol/L.[10] It has LogP 2.58 and pKa (acid) 3.75.[17]

Quality control

The development of analytical methods for quality control of drugs and pharmaceuticals is a necessity for industries and laboratories. This maintains the excellence of products and the confidence of the consumer.[18]

Among the analytical methods for determination and quantification of FLU, there are physical-chemical and microbiological methods, which are presented in Table 1.[19–42]

The development of green and eco-friendly methods gained attention over the last yearsin the quality control of drugs; the objective is to develop analytical processes that generate less negative impacts on the environment.[43]

Analytical methods for determination and quantification of FLU

This review provides details about methods of quantification and determination of FLU. Several methods such as high-performance liquid chromatography (LC), high-performance liquid chromatography coupled with mass spectrometry

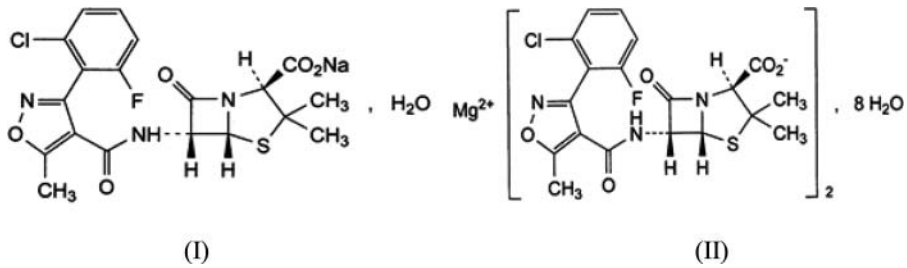

Figure 1. Chemical structures of flucloxacillin sodium (I) e flucloxacillin magnesium 3 octahydrate (II).

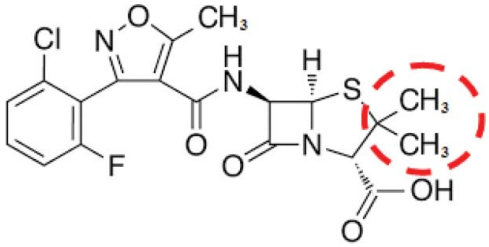

Figure 2. Chemical struture of flucoxacilin (CAS 5250-39-5), focusing the bulky 7 structure.

(LC-MS), spectrophotometry in the ultraviolet and visible regions (UV/ Vis), nuclear magnetic resonance (NMR), gas chromatography (GC), gas chromatography coupled with mass spectrometry (GC-MS), polarography, potentiometry and agar diffusion methods are presented in Table 1.

Determination of the concentration of flucloxacillinin biological fluids or matrices other than blood or urine such as pharmaceutical dosage form may be found in the literature. They range from reference substance, capsules, tablets, oral suspension, and powder for oral suspension to FLU associated with another antimicrobial.Biological samples range from plasma, serum, lymph, urine, skin blister, subcutaneous tissue, muscle to heart valve tissue.[3,10,20,21,26,30,32,40,42,89,91,102,104,108,109]

Among the methods for quantification and characterization of FLU, LC stands out in relation to the others, representing 45% of the total number of methods published in the literature, as shown in Figure 3. Figure 4 shows a graphical representation of the amount of solvents used in the methods of LC and UV for FLU determination described in the current literature.

The information presented is useful for researchers, especially those involved in the development of different dosage forms and for the quality control of FLU and combination with other drugs.

Analytical awareness relevant to FLU analytical methods

A current approach involves the application of analytical methods with concepts of green chemistry. These methods bring the idea of techniques to be less environmentally aggressive, aiming at the concepts of prevention and sustainability, minimizing the consumption of reagents and energy, as well as the generation of waste in the industry. These are fundamental characteristics to be followed during the development of green and eco-friendly analytical methods.[18,43]

Currently, there is an increasing interestrelated to the development of non-aggressive methods to the environment and with low toxicity to the human and animal health. We can cite the principles of green chemistry, where it is essential to execute and ensure that environmentally friendly processes are being carried out.[43,44,47,58–60,85,113] These aspects and principles involve broad improvment of the production, such as prevention of waste generation with planning for the choice of processes, which will avoid waste of products, time and expenses; reduction of the products' toxicities, causing in safety to the operators and environment. The energy demand of chemical processes, that could be minimized with the use of performed under room temperature and pressure conditions to reduce energy expenditure. Analytical methods could be monitored in real time to avoid the formation of hazardous substances in order to considering the minimization of potential accidents, such as leaks, explosions and fires; aiming at greater occupational and environmental safety.[113] New methods and techniques that are able to reduce and eliminate the use and generation of hazardous substances in all stages of chemical analysis are the main objective of the Green Analytical Chemistry (GAC).[43,116] GAC is based mainly on the elimination or minimization of the use of chemical substances, on the minimization of the consumption of electricity, on the correct handling of the generated analytical residues and on the greater safety of the operators.[113]

Thus, in general, the methods of analysis for drugs and medicinesare deficient in green, clean and sustainable aspect; therefore, the development of new methods with this new concept has gained space in the laboratories of development of green methods. Moreover, analytical methods play an important role in the pharmaceutical field, being present since the stages of initial drug synthesis until post-marketing steps.[44–48]

Gas chromatography is considered greener than liquid chromatography as it does not require solvents for separation. On the other hand, liquid chromatography offers more possibilities of "greening". One alternative is the replacement of toxic solvents with "green" solvents. A green solvent, ethanol for example, is one that offers no risks to the health of the analyst, offers safe handling and biodegradability. It respects the environment, avoiding depletion of ozone and less emission into the air, in addition to involving renewable resources. Production processes, possibility of recycling and cost of energy should also be considered in the evaluation of how a solvent is green.[49,119]

In addition to ethanol, other solvents are recommended as isopropyl alcohol, *n*-butanol, ethyl acetate, isopropyl acetate, butyl acetate, anisole, sulfolane and water.[117] Organic solvents should be replaced with water, when possible, or the mixing of organic solvents with water could be considered. However, when this is not possible an alternative is the use of supercritical CO_2, which is non-toxic and does not contribute to climate change. Ionic liquids are also a good choice, since they suffer very little evaporation and therefore are not lost to the atmosphere.[118] The analytical techniques can contribute to important information concerning drugs, including the development of new drugs, design of new dosage form and quantification of active content in the commercialized pharmaceutical products. In this aspect, it is important to show pharmacokinetic parameters for therapeutic monitoring of the drug are also related with analytical techniques behavior.[18,50,51]

Reviews play an important role in the academic and industrial sector.[114,115] They contribute with relevant informative concerning drugs and pharmaceutical products.[44,45,52–57] Review work, like this one, helps analysts in developing new and better analytical methods because they provide an overview of what already exists in the literature.

In the context of analytical conditions, most of the methods reported in the literature have used water, phosphate buffer, acetonitrile and methanol as mobile phase in isocratic or gradient elution. In our laboratory, researches aim to develop new methods focused in green analytical chemistry such as liquid

Table 1. Analytical methods described in the literature for determination of flucloxacillin.

Method	Conditions	Detection	LOD–LOQ	Type of studied sample	Reference
VIS	Copper sulphate	400 nm	NA	CRS	[19]
Agar diffusion	*S. aureus* ATCC 6538 P. Concentration found: after 250 mg: 5.7 μg/mL after 500 mg: 11.4 μg/mL	NI	NA	serum	[8]
Agar diffusion	*Sarcina lutea* ATCC 9341. Concentration found/active: 1.0 μg/mL	NI	NI	FLU metabolite in urine and mouse serum	[20]
UV	Water	220 nm	NI	FLU submitted to radiation	[103]
NMR	silica gel Polygram Sil N-HR/UV254 Solvent: Mercapto mercury methanol: acetone (50:50) D_2O (solvent) with 3-trimethylsilil propionic acid	254 nm	NI	FLU submitted to radiation	[103]
HPLC	Column LiChrosorb RP-8, 250 × 4.6 mm, 5 μm, ODS (500 × 2.1 mm). MP: 0.02 M ammonium acetate pH 6.6: ACN (100: 34)	220 nm	NA	plasma, serum and urine	[89]
Polarography	Mercury electrode, platinum wires against electrode Solvent: water	220 nm	NA	CRS	[21]
HPLC	Column LiChrosorb RP-18, 250 × 4.6 mm. *MP*: aqueous solution of TBAB 5 mM + 1/120 M Na_2HPO_4 + 1/120 M KH_2PO_4: ACN (3:1), pH 7.48	254 nm	NA	urine	[22]
GC-MS	Column GC: 1.5% OV-17% coated in Chromosorb W (100–120 mesh) (100 × 2 mm). *MP*: Helium gas	254 nm	NA	urine	[22]
HPLC	Column: Spheriosorb C_{18}, (250 mm), 5 μm, with pre-column Spheriosorb C_{18} (75 mm), 5 μm. MP: methanol: sol. TF 0.04 M, pH 7.0 (45:55)	220 nm	NA	Serum, lymph, blister and urine	[91]
HPLC	Column Partisil PXS 10/25 C_{18} MP: Aqueous methanol solution at 42, 35 or 28% containing 0.01% sodium bicarbonate	220 nm	NA	Powder subjected to radiation γ at 18.8 °C	[98]
HPLC	Column: Hypersil ODS 100 × 2 mm, 5 μm. MP: ACN:water (40:60), with TF solution 10 mM, pH 2.0	220 nm	LOD 0.1 μg/mL	plasma	[92]
Agar diffusion	*Bacillus subtilis* ATCC 6633 Concentration found/active: (a) 125.2–4.4 μg/mL (b)14.7 $\leq$ 0.2 μg/mL (c) 14.2 $\leq$ 0.2 μg/mL (d) 15.4–3.7 μg/mL	NI	NI	Serum (a), subcutaneous tissue (b), muscle (c) and heart valve tissue (d), collected at time 0–12h	[104]
NMR COSY	Frequency of resonance: H-NMR: 13–400 MHz F-NMR: 50–376 MHz	NI	NI	Rat urine	[102]
HPLC	Column: Brownlee RP_{18}VeloSep 400 × 3.2 mm, 3.0 μm. *MP*: ACN:TF solution 0.01 M pH 7.0 (18:82)	220 nm	0.05–0.3 mg/L	plasma	[23]
Agar diffusion	*Bacillus subtilis* ATCC 6633 Concentration found/active: 123.6 mg/L after 1 h of administration 17.4 mg/L after 6 h of administration	NI	NI	Rat serum	[105]
HPLC	Column Phenomenex Resolve C_{18}, 300 × 3.9 mm, 5 μm. MP: ACN: Na_2HPO_4 mM and $(CH_3)_4NCl$ 10 mM (water), pH 5.0	220–240 nm	NI	CRS	[90]
HPLC	Column: ND. MP: ND	230 nm	NA	serum	[93]
Agar diffusion	*S. aureus* ATCC 25923. Concentration found/active:27 mg/L, after 12 g/day	NI	NI	serum	[93]
VIS	Molybdenum thiocyanate (binary complex)	467 nm	NA	capsules	[24]
VIS	Pyrocatechol violet 0.2–44 μg/mL	641 nm	NA	capsules, syrup and amoxicillin association	[107]
VIS	DDQ TCNQ 10–80 μg/mL (DDQ) and 5–35 μg/mL (TCNQ)	460 nm (DDQ) 840 nm (TCNQ)	NA	capsules	[109]
VIS	*p*-nitrophenol (I), 2,4 dinitrophenol (II), 3,5 dinitrosalicilic acid (III), picric acid (IV), picric acid (V)	446 (I), 435 (II), 442 (III), 473 (IV), 439 (V)	NA	powder for injection, syrup and capsules	[25]
HPLC	Column TSK-Gel ODS-80 TM, 150 × 4.6 mm, 5 μm	232 nm	NA	capsules	[106]

HPLC-MS/MS	Column YMC Pack NH_2, 100 × 5 mm, 5 μm YMC Pack ODS AM, 150 × 2 mm, 5 μm. *MP*: A: water: ACN: TFA (1000:20:1) B: ACN: water: TFA (800:200:1).	triplequadrupole	LOD 0.03 ng/mL	antifungal drug contaminated with FLU	[3]
HPLC	Column Zorbax 300 SCX, 250 × 4.6 mm, 5 μm. MP: dihydrogen ammonium phosphate 0.025 M (pH 2.6): ACN (95:5)	225 nm	LOQ 0.2 μg/mL	FLU associated with amoxicillin in injectable preparation	[26]
VIS	2,3 dichloro5,6 diciane-*p*-benzoquinone; potassium iodate	460; 522 nm	NA	capsules	[27]
VIS	Iodine/starch/carreador (sol. TF 0.2 M, pH 6.5 (1:1:3)	842 nm, 415 nm	NA	capsules	[108]
VIS	Chloranilic acid; dichloroquinone 4 chloroimide; 2,3 dichloro 5,6 diciane-*p*-benzoquinone; TCNQ	520;450;455;842 nm	NA	capsules	[101]
HPLC	Column: C_8, 250 × 4.6 mm, 5 μm. *MP*: sodium perchlorate 0.02 M: ACN (75:25)	240 nm	NA	plasma	[94]
HPLC	Column Alltima ODS C_{18}, 250 × 4.6 mm, 5 μm, ODS C_{18} 300 × 4 mm. *MP*: ACN:sol. TF 10 mM (64.5: 35.5)	220 nm	NA	plasma	[29]
HPLC	Column C18. MP: sol. TF pH 6.2: ACN	220 nm	NA	plasma and urine	[95]
VIS	sudan III	566 nm	NA	Capsules, syrup, powder for injection + amoxicillin association	[28]
HPLC	Column Hypersil ODS, 250 × 4.6 mm, 5 μm. MP: ACN: sol. TF (0.27%), pH 5.0 (25:75) Silica gel C_{18}, 5 μm	225 nm	NI	API	[9,88]
VIS	Iodine	362 nm	2.47 × 10–1–8.15 × 10–2 μg/mL	human urine	[30]
HPLC	Column LUNA SCX, 250 × 4.6 mm, 5 μm. *MP*: mixture of buffer (prepared from 0.001 M diammonium hydrogen orthophosphate and 0.04 M tetra butyl ammonium bromide pH adjusted to 7.0 ± 0.1 with orthophosphoric acid) and acetonitrile in the ratio (99:10 v/v), at 1 mL/min	254 nm	NI	capsules	[33]
HPLC	Column Kromasil C18 250 × 4.6 mm, 5 μm. *MP*: Na2HPO4 0.020 M: ACN (75:25)	225 nm	0.08–0.25 μg/mL	capsules	[31]
HPLC	Column C18, 150 × 4.6 mm, 5 μm. *MP*: pH 5.0 phosphate buffer and ACN at 1.5 mL/min	225 nm	NI	oral suspension	[32]
HPLC	Column Waters X Bridge C18 300 × 4 mm, 2.5 μm. *MP*: ACN: sol. TF 100 mM pH 3.0 (75: 25)	210 nm	NA	plasma	[96]
HPLC	Column Waters X Bridge C18 300 × 4.6 mm, 2.5 μm. MP: ACN: sol. TF pH 3.0 (25:75)	220 nm	NA	Plasma and urine	[97]
UV	Water	274 nm	2.35–7.12 mg/L	capsules	[5]
Agar diffusion	*Staphylococcus aureus* ATCC 5923. Concentration found/active: 1.5 to 6.0 μg/mL	NI	NI	capsules	[34]
Potentiometry	Membrane consisting of Aliquat 336S-flucloxacillin as an electroactive material in poly vinyl chloride matrix membrane plasticized with orthonitrophenyl-octylether or dioctylphthalate	NI	NI	capsules	[36]
LC-MS/MS	Column UPLC BEH C18, 1.7 μm, 50 × 2.1 mm; *MP*: 0.1% formic acid and acetonitrile (40:60)	255 nm	NA	plasma	[100]
HPLC	Column Lichrosorb 10 RP-1 C18 column 250 × 4.60 mm, 5 μm. *MP*: 40% v/v redistilled methanol and 60% v/v 0.02 M potassium dihydrogen phosphate, KH_2PO_4 (pH 3.70) at 1 mL/min	255 nm	0.003029–0.009178% w/v	capsules	[35]
GC	Column Elite-5 fused silica capillary column 30 m × 32 mm Gas: N2	Flame ionization	NI	capsules	[38]

(*Continued on next page*)

Table 1. (*Continued*).

Method	Conditions	Detection	LOD–LOQ	Type of studied sample	Reference
LC-MS/MS	Column Phenomenex, Part 00B-4462-AN, 2.6 μm, 2.1 × 50 mm. *MP*: water: ACN, each containing 0.1% at 0.3 mL/min	254 nm	LOQ 0.25 μg/mL	plasma	[99]
HPLC	Column C_{18}, 250 × 4.6 mm. MP: buffer di-potassium hydrogen phosphate (pH 3 with ortophosphoric acid): methanol (70: 30% v/v) at 1 mL/min	225 nm	0.018 −0.06 μg/mL	tablets	[40]
HPLC	Column Phenomenex® Bondclone 10 C_{18} (300 × 3.9 mm, 5 μm). *MP*: 60% methanol and 40% KH_2PO_4 buffer adjusted to a pH of 5 with 1 M sodium hydroxide solution.	225 nm	0.00437–0.0132% w/v	capsules	[41]
VIS	Mercury imidazole	346 nm	NI	capsules, injetion solution	[10]
HPLC	Column Hypersil ODS, 250 × 4.6 mm, 5 μm. MP: ACN: sol. TF (0.27%), pH 5.0 (25:75) Silica gel C_{18}, 5 μm	225 nm	NI	capsules and injectable solution	[10]
HPLC	Column Phenomenex C_{18}, 300 × 3.9 mm, 10 μm; *MP*: methanol and acetate buffer pH 5.0 (60:40) at 1.1 mL/min	254 nm	0.104–0.316 mg/mL	capsules	[42]
VIS	Mercuric-imidazol	346 nm	NI	CRS	[10]

ACN = acetonitrile; Amox = amoxicillin; CRS = chemical reference substance; TLC = thin layer chromatography; HPLC = high performance liquid chromatography; Na_2HPO_4 = potassium dihydrogen phosphate; $(CH_3)_4NCl$ = tetramethylammonium chloride; DDQ = 2,2-8,8 dichloro-5,5- diciano-*p*-benzoquinone; *MP* = mobile phase; GC–MS = gas chromatography coupled with mass spectrometry; NMR = nuclear magnetic ressonance; TCNQ = 7,7,8,8- tetracyanoquinodimethane; TF = phosphate buffer solution; UV = UItraviolet spectrophotometry; VIS = visible spectrophotometry; LOD = limit of detection; LOQ = limit of quantification; NI = not informed; NA = not available.

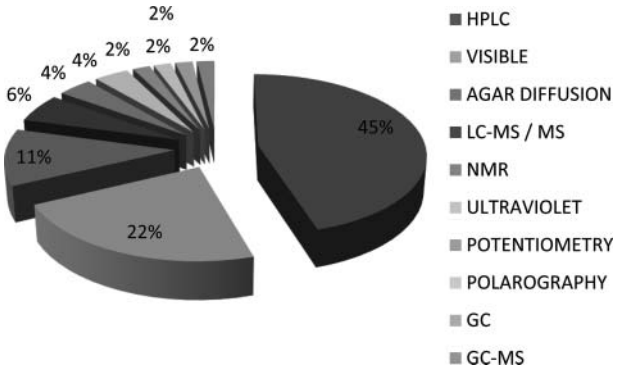

Figure 3. Distribution of analytical methods described in the literature for 2 determination of FLU.

chromatographic techniques using lower toxicity solvent for both environment and human..[61–84]

The HPLC methods for FLU determination still rely on toxic solvents, such as methanol and acetonitrile,[85] and buffer solutions, which reduce the life of the equipment and column, require more cleaning time and therefore more solvents to clean, besides having little time of use, which requires new preparations, and more time for this.[72]

Although FLU can be analysed withtitration and spectrophotometric methods that are theoretically inexpensive, simple to perform and quick to release results butthey have disadvantages that put them at the margins of green chemistry and sustainability. Titration requires large quantities of samples, around mg. Spectrophotometric methods in the ultraviolet and visible regions are excellent for routine analyzes, but the used solvent must be carefully chosen because the aliquots used are around mL, while in HPLC and CE are μL and Nl.[59,86]

Microbiological methods for assessing the potency of FLU as agar diffusion shown in Table 1 are time-consuming and require 20 hours for release of results; in addition to the larger volume of material used. Turbidimetric assay, another type of microbiological method, is more rapid, with results in 4 hours and the evaluationof the results is performed with an spectrophotometric apparatus whereas the evaluation of agar diffusion assay has to be done manually, which can present a higher error or differences from one analyst to another.[56,71,72,76,78,82] However, FLU still lacks this type of innovation.

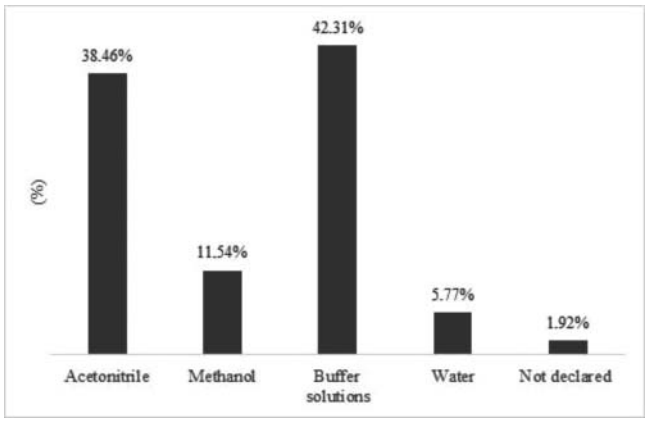

Figure 4. Graphical representation of the amount of solvents used in the methods of 6 HPLC and UV for FLU determination.

Therefore, FLU could have ecologically correct methods and at the same time effective. This is possible and a need of the current pharmaceutical chemistry. Some pharmaceutical products present methods by HPLC using ethanol as solvent and other methods by spectrophotometry in the ultraviolet region using only water as diluents.[81,84,110–112] Perhaps this is the way for green analysis of FLU. Multidimensional thinking is valued nowadays. In addition, analytical methods must to providing reliable results, be fast, low cost and not harmful to the analyst or the environment. The investing in the principles of green analytical chemistry will bring numerous benefits to the environmental, economic and personal future.[113]

Conclusion

Flucloxacillin is a restricted-use antimicrobial indicated for patients with severe and advanced diseases. In Europe and Australia, it is used in the treatment of staphylococcal infections. In the United Kingdom, FLU is the most commonly prescribed oral antimicrobial for the treatment of staphylococci. In Brazil, FLU is still little known, since it was recently included by ANVISA in the List DCB 2005 updated by Resolution 111.[87]

The significant consumption of FLU generates the need to develop analytical and bioanalytical methods according to the new reality of the chemical industry for the identification and quantification of FLU, as fast and low cost methods, as well as being neither harmful to the analyst nor to the environment. Among the analytical methods described for the determination of FLU, high performance liquid chromatography stands out, but the methods use toxic solvents, buffer solutions, long columns, which provide long runs and retention times, as well as large amounts of waste. Therefore, the priority to develop ecologically correct, conscious and sustainable methods is very important, current and necessary for the quality control of FLU, optimizing the productivity without harming the environment and the health of the operators. The conclusion must not necessarily choose an ecologically correct class, but analyze the whole set, method, solvents, accessories, time, cost, waste and everything else that involves this analysis.

Antibiotics can save countless lives. Therefore, it is imperative that quality control is effective and appropriate. Only then, we can win the battle against microbial resistance.

Conflict of interest

The authors declare no conflicts of interest.

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