Characteristics, Properties and Analytical Methods of Cefadroxil: A Review

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ABSTRACT

Infections are the second leading cause of mortality worldwide and there are many reasons justifying the need for further studies of antimicrobial agents. Cefadroxil is a drug that has bactericidal activity and broad spectrum of action. Quantitative analyzes about cefadroxil are essential for the understanding of bioavailability, bioequivalence, and therapeutic control, which will ensure the product's characteristics and patients' safety. Thus, this study highlights a brief literature review about the drug and the existing methods developed for the determination of cefadroxil found in official and scientific papers. According to the methods found in literature, liquid chromatography and spectrophotometry of absorption in the ultraviolet region prevailed over the others. Importantly, most of the solvents used for the development of the described analytical methods are toxic to the environment, making it necessary to educate researchers and pharmaceutical companies to use nontoxic solvents to provide environmental-friendly methods and better benefits to equipments and mainly to analysts.

Introduction

Since the mid-1940s, antimicrobials began to have important functions for the control of infectious diseases (Guimarães et al., 2010). There are a wide variety of micro-organisms, and because of this significant difference, antimicrobials must be increasingly studied and known to combat bacterial resistance and restore the balance of infected organisms (Hoefel and Lautert, 2006).

Antimicrobials can have synthetic or natural structures, which are responsible for inhibiting the growth of fungi and bacteria or lead them to death (Guimarães et al., 2010). Among the various existing classes of antibiotics, cephalosporins are derived from the fungus *Cephalosporium acremonium*, and they were first discovered in 1945 by Giuseppe Brotzu in Sardinia and stand out by having bactericidal activity against Gram-positive and Gram-negative bacteria (Climeni et al., 2009; Perera et al., 2001).

Cephalosporins can be classified into five different generations, which differ in the pharmacokinetics, pharmacodynamics, and features that have antimicrobial activity (Fernandes et al., 2013).

Among the first-generation cephalosporins, cefadroxil (CFD) is an effective antibiotic against Gram-positive and Gram-negative bacteria and stands out for presenting high-potential chemotherapeutic oral administration and is widely used for treating bronchitis, tonsillitis, skin infections, soft tissues and ear, gonorrhea, urinary tract, bones and joints (Sharif et al., 2010; Tanrisever and Santella, 1986).

In the Brazilian pharmaceutical market, cefadroxil is marketed as pharmaceutical presentations in the form of tablets with a concentration of 1 g, hard gelatin capsules with a concentration of 500 mg, and powder for suspension with concentrations of 50 mg/mL and 100 mg/mL (Brazil, 2015; Brazil, 2016).

Cefadroxil can be found with the following names: Cefamox® (Bristol-M-Squibb), Cedroxil® (Legrand), Neo Cefadril® (Neo Química), Celoxin® (Vitapan) and Drocef® (Eurofarma), and Cefamox® is a reference product (BPR, 2014). The drug can also be found by the name of cefadroxil (marked "G") as a class of generics produced by companies, such as Abbott, Apotex, Biosintética, Brainfarma, EMS, Eurofarma, Medley, Mepha ratiopharm, Novartis, Ranbaxy, and Teuto, all with record in the National Health Surveillance Agency (ANVISA) for the treatment of infections caused by microorganisms susceptible to cefadroxil (BPR, 2014; Brazil, 2016).

The infections caused by microorganisms vulnerable to cefadroxil reach a large proportion of the population and are very common in society, so the prevalence of cefadroxil sales is much considerable, making studies inevitable, especially to quality control, which has great impact about the quality of medicines, and its data is obtained with the objective to provide information about the composition of material as well as to develop analytical methods (La Roca et al., 2007).

The quality control also needs to ensure safety standards and efficacy of medicinal products in order to avoid risks to the population. Thus, the physicochemical characteristics of drugs must conform to the standards necessary for the proper handling and industrialization of the same to ensure the confidence during treatments about their function (La Roca et al., 2007).

Based on the information and facts that point to the importance of the development of analytical methods, this study will point a review of the characteristics, properties, and analytical methods already developed for the quantification and identification of cefadroxil.
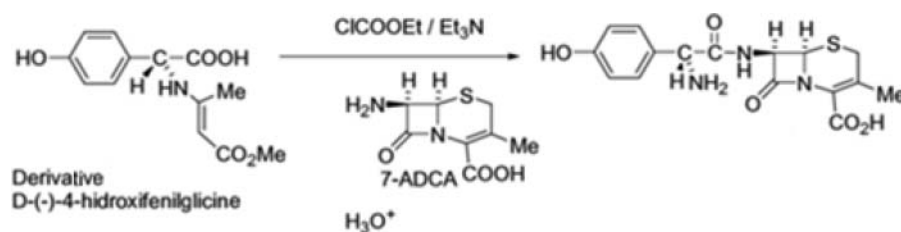
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Figure 1. Synthesis of cefadroxil. (Source: Garcia et al. (2005), p. 255).

Cefadroxil

Structural modification

Cefadroxil (Figure 1) is obtained from a derivative of D-(-)-4-hydroxyphenylglycine with amino group protected in the form of methyl acetoacetate enamine +. The carboxylic group is activated by conversion to an anhydride upon reaction with ethyl chloroform in the presence of triethylamine. The activated derivative then reacts with 7-ADCA, releasing the amine function by acid hydrolysis (Garcia et al., 2005).

Structural forms

Cefadroxil occurs in three forms: anhydrous cefadroxil, hemihydrate cefadroxil, and monohydrate cefadroxil (BP, 2012; EP, 2013; Argentina P., 2003; Brazilian P., 2010; Portuguese Pharmacopoeia, 2007; IP, 2007; JP, 2011; USP 35, 2012). Figure 2 illustrates the existing molecular structure of the active pharmaceutical ingredient.

Action mechanism

Cefadroxil has bactericidal activity by inhibiting the synthesis of the bacterial cell wall; it is much used in the treatment of infections caused by Gram-positive cocci, including pneumococci, streptococci, and staphylococci except for enterococci and methicillin-resistant staphylococci and some Gram-negative bacteria as *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae*, and anaerobic cocci (for example, *Peptococcus, Peptostreptococcus*) (Katzung et al., 2014).

This drug is an antibiotic able to combat skin infections (for example, staphylococcal lesions) or small polymicrobial infections such as soft-tissue abscesses and/or cellulitis, pharyngitis, tonsillitis, gonorrhea, ear infections, urinary infections, and post-surgical infections. However, it is not advised during severe systemic infections (Delucia et al., 2007; Katzung et al., 2014; Tanrisever and Santella, 1986).

Pharmacokinetics and pharmacodynamics

Cefadroxil is the analog p-hydroxy for cephalexin (first-generation cephalosporin), and despite its slightly higher concentration in plasma and urine, it presents *in vitro* activity very similar to that of cephalexin (Delucia et al., 2007; Tanrisever and Santella, 1986).

In pharmaceutical formulations, such as in the form of tablets, capsules, or powder for suspension, cefadroxil is rapidly absorbed after oral administration, and after 1–3 hours it is possible to obtain maximum concentrations of the active substance (AHFS, 2014; DEF, 2015).

Levels of binding protein of cefadroxil in the plasma lie on the boundary between 15% and 20%, and according to biotransformation and excretion, 90% of the active pharmaceutical ingredient is eliminated unaltered in the urine within 24 hours (AHFS, 2014; DEF, 2015).

Physicochemical properties

Cefadroxil is a semisynthetic antibiotic intended for oral administration, white and/or almost white in color, and is chemically designated as (6R,7R)-7-[(2R)-2-amino-2-(4-hydroxyphenyl) acetyl amino]-3-methyl-8-oxo-5-tia-1-azabiciclo[4.2.0]oct-2-eno-2-carboxilic acid (BP 2012; USP 35, 2012).

Its molecular formula is $C_{16}H_{17}N_3O_5S$, and has molecular weight of 363.4 g/mol in anhydrous form, 372.4 g/mol in hemihydrate form, and 381.4 g/mol in monohydrate form (Brazilian P., 2010; Argentina P., 2003).

Cefadroxil has low solubility in water, very slightly soluble in ethanol, and practically insoluble in chloroform and ethyl ether. It has power rating of 950 pg, and not more than 1050 μg/mg for $C_{16}H_{17}N_3O_5S$ in relation to anhydrous substance (Brazilian P., 2010). Its melting point is 197°C and its log p is −0.4 with pKa 3.45 (acid) and 7.43 (basic) (Drug Bank, 2016).

Analytical methods for determining the cefadroxil

The quantification of cefadroxil is extremely important to conduct bioavailability and bioequivalence studies as well as
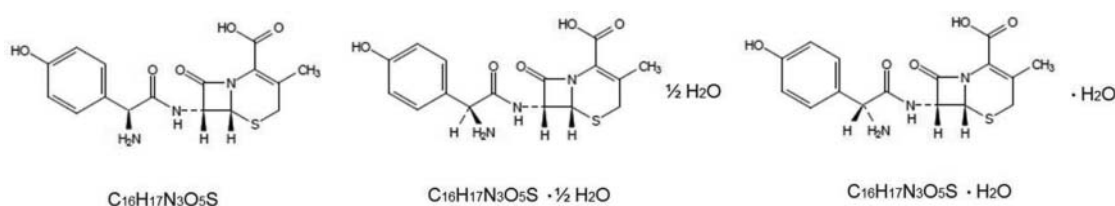

Figure 2. Chemical structure of anhydrous cefadroxil (CAS 50370-12-2), hemihydrate cefadroxil (CAS 119922-85-9), and monohydrate cefadroxil (CAS 66592-87-8), respectively.

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

Method	Conditions	Detection system	Matrices	Reference
HPLC-UV	Column C18 (250 mm × 4 nm). Mobile phase: potassium phosphate monobasic buffer 0.05 M with pH 5.0 and acetonitrile (96:4 v/v).	230 nm	Standard	Argentina Pharmacopoeia (2003); Brazilian Pharmacopoeia (2010); Indian Pharmacopoeia (2007); USP Pharmacopoeia (2012)
HPLC-UV	Column C18 (250 mm × 4 nm). Mobile phase: potassium phosphate monobasic buffer 0.05 M with pH 5.0 and methanol (17: 3 v/v).	262 nm	Standard	Japanese Pharmacopoeia (2011)
HPLC-UV	Column C18 (250 mm × 4.6 nm). Mobile phase: potassium phosphate monobasic buffer 0.05 M with pH 5.0 and acetonitrile (96:4 v/v).	254 nm	Standard	British Pharmacopoeia (2012)
HPLC-UV	Column C18 (100 mm × 4.6 nm). Mobile phase: potassium phosphate monobasic buffer with pH 5.0 and methanol (98:2 v/v).	220 nm	Standard	European Pharmacopoeia (2013) and Portuguese Pharmacopoeia (2007)
HPLC-UV	Column Hypersil C18 (200 mm × 4.6 mm). Mobile phase:potassium phosphate monobasic buffer 0.05 M with pH 3.4 and acetonitrile (87.5:12.5 v/v).	254 nm	Standard	Zhang et al. (1999)
HPLC-UV	Column LiChrosorb RP-8 (250 mm × 4.0 mm). Mobile phase:potassium phosphate monobasic buffer with pH 5.0 and acetonitrile (95:5 v/v).	280 nm	Human urine	Eshra et al. (1993)
HPLC-UV	Column Hypersil C18 (250 mm × 4.6 mm). Mobile phase:potassium phosphate monobasic buffer with pH 5.0 and acetonitrile (96:4 v/v).	254 nm	Tablets	Devaliya and Jain (2009)
HPLC-UV	Column Supelco RP C-18 (250 mm × 4.6 mm). Mobile phase:methanol and disodium hydrogen orthophosphate buffer 0.05 M with pH 3.0 adjusted with phosphoric acid (60:40 v/v).	264 nm	Standard	Anjum et al. (2012)
HPLC-UV	Column C18 (250 mm × 4.6 mm). Mobile phase: potassium phosphate monobasic buffer 0.05 M with pH 5.0 and acetronitrile (94:06 v/v).	225 nm	Tablets	Sharif et al. (2010)
HPLC-UV	Column Purospher BDS C18 (250 mm × 4.6 mm). Mobile phase:ammonium acetate 0.5 M and acetonitrile with pH adjusted to 7.0 using orthophosphoric acid (50:50 v/v).	247 nm	Capsules	Dhoka and Chopade (2012)
HPLC-UV	Column Hypersil C18 (250 mm × 4.6 mm). Mobile phase:potassium phosphate monobasic buffer with pH adjusted to 5.0 using potassium hydroxide 10 M and acetonitrile (96:4 v/v).	230 nm	Standard	Hendrix et al. (1993a)
HPLC-UV	Column Nucleosil AS (200 mm × 4.6 mm). Mobile phase:ammonium dihydrogen phosphate 20 M with pH adjusted to 3.0 with phosphoric acid and water–methanol–acetonitrile (30:35:35 v/v/v).	240 nm	Standard	Lindgren (1987)
HPLC-UV	Column LiChrospher 100 RP-18 (5 mm). Mobile phase:potassium phosphate monobasic buffer 0.02 M with pH adjusted to 3.0 with phosphoric acid and acetronitrile (95:5 v/v).	260 nm	Human urine	El-Gindy et al. (2000)
HPLC-UV	Column Chromolith®-SpeedROD RP-18e (500 mm × 4.6 mm). Mobile phase:acetic acid buffer–sodium acetate with pH 4.0 and methanol–acetic acid (90:10 v/v).	265 nm	Human plasma and urine	Samanidou et al. (2004)
HPLC-UV	Column Spherisorb ODS-2 (250 mm × 4 mm). Mobile phase:acetic acid buffer–sodium acetate with pH 4.0 and methanol (78:22 v/v).	265 nm	Human plasma and urine	Samanidou et al. (2003)
HPLC-UV	Column Altex Ultrasphere Octyl reverse phase C8 (260 mm × 4.6 mm). Mobile phase: monosodium phosphate buffer and methanol with pH 2.6 (80:20 v/v).	240 nm	Human plasma	McAteer et al. (1987)
HPLC-UV	Column C18 (200 mm × 4.6 mm) 10 μm, with pre column stainless-steel screens (150 mm × 4.6 mm). Mobile phase:phosphate buffer 10 M with pH 7.0 and acetonitrile (87:13 v/v).	260 nm	Bovine Plasma	Snippe et al. (1994)
HPLC-UV	Column PLRP-S (250 mm × 4.6 mm). Mobile phase:acetonitrile 0.2 M, sodium 1-octanesulfonate 0.2 M and phosphoric acid with pH 1.4 (10:5:10 v/v/v).	254 nm	Standard	Hendrix et al. (1993b)
HPLC-UV	Column C18 (150 mm × 4.5 mm) 5 μm. Mobile phase:methanol and potassium phosphate monobasic buffer with pH 4.0 (10:90 v/v).	260 nm	Capsules	Rahim et al. (2015)

Table 1. (Continued).

Method	Conditions	Detection system	Matrices	Reference
HPLC-UV	Column C18 (150 mm × 4.5 mm) 5 μm. Mobile phase:potassium phosphate monobasic buffer with pH 4.0 and methanol (96:4 v/v).	260 nm	Human plasma	Rahim et al. (2014)
HPLC-UV	Column Phenomenex Synergi MAX RP C18 (150 mm × 4 mm). Mobile phase:sodium dihydrogen phosphate monohydrate buffer 0.02 M, methanol and acetonitrile (90:8:2 v/v/v).	230 nm	Human plasma	Kano et al. (2012)
HPLC-UV	Column Hypersil C18 (250 mm × 4.6 mm) 5μm. Mobile phase:potassium phosphate monobasic buffer 0.2 M with pH 3.5 adjusted with orthophosphoric acid and acetonitrile (65:35 v/v).	220 nm	Tablets	Rao et al. (2014)
HPLC-UV	Column Purospher® RP-C18 (250 mm × 4.6 mm). Mobile phase:water, methanol and triethylamine with pH 5.5 adjusted with phosphoric acid (85:15:0.1 v/v/v).	258 nm	Tablets	Patel et al. (2014)
HPLC–MS/MS	Column YMC Hydrosphere C18 (150 mm × 4 mm) 5 μm. Mobile phase:acetonitrile in water (0.1%) and formic acid (15:85 v/v).	Electrospray ionization (ESI) and triple quadrupole	Standard	Nygren and Lindahl (2011)
HPLC–MS/MS	Column C18 (150 mm × 2.0 mm) 4 μm. Mobile phase:formic acid and methanol (62:38 v/v).	Positive electrospray ionization (ESI)	Rat plasma and urine	Jin et al. (2014)
HPLC–MS/MS	Column C18 reverse phase. Mobile phase: methanol, acetonitrile and ammonium acetate 2 M with pH 3.5 (25:25:50 v/v/v), 0.8 mL/min.	Quadrupole and atmospheric pressure chemical ionization (APCI)	Human plasma	Nagarajan et al. (2013)
UPLC-UV	Column Acquity UPLC HSS T3 (210 mm × 5 mm) 1.8 μm. Mobile phase: formic acid 0.1% and acetonitrile (10:90 v/v).	254 nm	Standard	Schmidt et al. (2012)
Absorption spectroscopy UV	Dilution with citrate-phosphate buffer pH 6.0 until the concentration 0.002% p/v.	264 nm	Standard	Brazilian Pharmacopoeia (2010); European Pharmacopoeia (2013)
Absorption spectroscopy UV	Dilution with water until the concentration 10 μg/mL.	263 nm	Standard	USP Pharmacopoeia (2012); Japanese Pharmacopoeia (2011)
Absorption spectrophotometry UV–VIS	Dilution with 100 mL of water until the concentration of 10 μg/mL.	475 nm	Tablets	Naveed et al. (2014)
Absorption spectroscopy UV	Dilution 1 mL of sodium hydroxide 1 M in 10 mL of distilled water for 30 minutes.	342 nm	Capsules	Shantier et al. (2010)
Absorption spectroscopy UV	Dilution in distilled water and methanol (50:50 v/v) until the concentration of 100 μg/mL.	264 nm	Standard	Dey et al. (2010)
Absorption spectroscopy UV	Dilution in methanol until the concentration of 100 μg/mL.	257 nm	Tablets	Patel et al. (2010)
Absorption spectrophotometry UV–VIS	Dilution in methanol until the concentration of 200 μg/mL.	578 nm	Tablets	Patel and Patel (2011)
Absorption spectroscopy UV	Dilution in methanol until the concentration of 10 μg/mL.	233 nm	Tablets	Jain et al. (2014)

HPLC-UV: high-performance liquid chromatography with detection by ultravioleta; UPLC-UV: ultra-performance liquid chromatography with detection by ultraviolet; and HPLC–MS/MS: high-performance liquid chromatography coupled with sequential mass spectrometry.

pharmacokinetic parameters for the therapeutic monitoring of the substance.

In this study, there is a predominance of determination by high-performance liquid chromatography (HPLC) and UV absorption spectroscopy.

The advantages of performing quantitative studies by the HPLC technique include the specificity, efficiency, speed (due to shorter analysis time), and accuracy with facility in monitoring technique.

The analytical methods described in the literature for the determination of cefadroxil are shown in Table 1.

As can be seen in Table 1, most of the methods cited above used toxic chemical solvents. Thus, it is extremely important for the development and validation that the analytical methods to be used are chosen so as to decrease the amount of toxic waste produced, because it can cause damage to the equipment used, the environment, and the operators.

So that such problems are minimized, it is necessary to choose equipment that is more sensitive and as specific as the other; has low cost analysis, and consequently reduces energy consumption (the fact that implies directly on the final cost of the product); requires smaller amounts of solvents or that can identify lower concentrations of the same; can recover toxic solvents (for not be discarded in the environment); can educate researchers and pharmaceutical companies to use nontoxic solvents and improve environment in order to reduce the risk on the population and analysts.

Thus, the contribution to the analysis by universities and research centers should be taken into consideration so that the methods can contribute effectively to ensure the quality of medicines and the safety of the same in relation to population.

Conclusion

Cefadroxil is an antibiotic belonging to the cephalosporin class and has bactericidal activity and broad spectrum of action. The significant consumption of this drug contributes to the need to develop new researches about different analytical and bioanalytical methods of the active pharmaceutical ingredient.

Although there are a large number of analytical methods for identification and quantitation of cefadroxil, many use toxic and hazardous solvents. Thus, implementing an innovative vision of ecologically correct methods is very important to improve the productivity of quality control techniques in environmental, social, and economic terms.

Conflict of interest

The authors declare no conflicts of interest.

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