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Development and Validation of an Innovative Method for the Determination of Cefadroxil Monohydrate in Capsules

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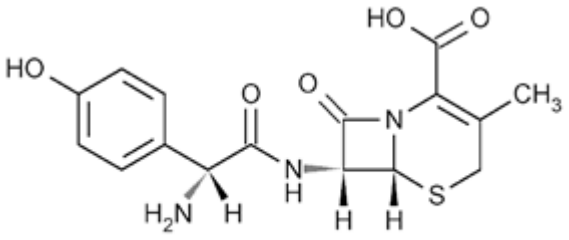
Abstract This paper describes the development and validation of an innovative method using Fourier Transform Infrared (FT-IR) transmission spectroscopy for the determination and quantification of cefadroxil monohydrate in capsules. The method was validated with no use of organic solvents and it is in accordance to the International Conference on Harmonisation guidelines, presenting great advantage over other analytical methods, because of the great contribution to the environment, green chemical and pharmaceutical industries. The method can be quantified by measuring the absorbance of the band corresponding to the carbonyl present in the drug molecule, in the region between 1800 and 1700 cm^{-1}, where it shows accuracy, linearity, precision, robustness and selectivity, being linear over a range of concentrations from 1.5 to 2.5 mg with correlation coefficients of 0.9990 and limit of detection and quantitation of 0.37 and 1.11 mg, respectively. This FT-IR method presents simple execution, low cost analysis and it is environmentally friendly, therefore it is very useful for routine quality control analysis of this drug.

Keywords Cefadroxil, Infrared, Green Chemistry, Spectroscopy, Quantitative

1. Introduction

The cefadroxil (Figure 1) is a semi-synthetic antibiotic belonging to the class of first-generation cephalosporins (DEVALIYA & JAIN, 2009; DEY et al., 2010). Its mechanism of action is due to inhibition of the synthesis of the cell wall of mainly Gram-positive bacteria being widely used for treatment of infections such as pharyngitis, tonsillitis, gonorrhea, skin infections and soft tissue, ear and urinary tract (TANRISEVER & SANTELLA, 1986).



M.M 363.39

Figure 1. Chemical structure of anhydrous cefadroxil (CAS 50370-12-2)

There are two known forms of cefadroxil beyond the anhydrous substance: the monohydrate form (CAS 66592-87-8) and the hemihydrate form (CAS 119922-85-9) (ARGENTINA PHARMACOPOEIA, 2003; BP, 2012; BRAZILIAN PHARMACOPOEIA, 2010; EF, 2013; IP, 2007; JP, 2011; PORTUGUESE PHARMACOPOEIA, 2005; USP 37, 2014).

The cefadroxil is marketed in Brazil in the form of capsules with concentration of 500 mg, tablet with concentration of 1 g and powder for suspension with concentration of 50 and 100 mg/mL (BRAZIL, 2016a, BRAZIL, 2016b).

Various analytical methods are described in the literature to determine and quantify the cefadroxil (MARCO & SALGADO, 2016). Among them, there are the high performance liquid chromatography (DHOKA & CHOPADE, 2012; EL-GINDY et al., 2000; HENDRIX et al., 1993; LINDGREN, 1987; MCATEER el al., 1987; NAGARAJAN et al., 2013; RAO et al., 2014; SAMANIDOU et al., 2003; SAMANIDOU et al., 2004; SHARIF et al., 2010); ultra performance liquid chromatography (SCHMIDT & STEINER, 2012); UV absorption spectroscopy (JAIN et al., 2014; PRADIP et al., 2015); capillary electrophoresis (ANDRASI et al., 2007; AUDA et al., 2009; GÁSPÁR et al., 2002; HANCU et al., 2013; HANCU et al., 2015; HERNÁNDEZ et al., 2003; LI et al., 1998; LIU et al., 2006; MRESTANI et al., 1997; MRESTANIA et al., 1998; SHALAEVA et al., 2008; SOLANGI et al., 2007) and chemiluminescence (ALY et al., 1998; SUN et al., 2004; THONGPOON et al., 2006). However, the majority of these methods use toxic organic solvents which are harmful to the environment and operators, contributing and involving directly in the formation of toxic

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waste from industries and clinical laboratories.

Investing in original and innovative analytical methods contributes to the environmental and economic impacts, favoring directly to green chemistry to present social benefits with sustainable production and good management practices (ANASTAS, 2016; HODGES, 2016; NIES, 2016). Thus, an alternative method was developed and validated, presenting other advantages over the existing analytical methods for analysis of cefadroxil monohydrate capsules, because it uses no organic solvents and presents the great contribution to green chemistry. The method is according to the ICH and presented accuracy, linearity, precision, robustness and selectivity (ICH, 2005).

The transmission spectroscopy with Fourier transform infrared (FT-IR), is a technique widely used by industries, research and areas of organic and inoganic chemical because it is simple, reliable, easy to perform and safe for the determination and quantification drugs (CORRÊA & SALGADO, 2014; KOGAWA & SALGADO, 2013; KOGAWA et al., 2014; KOGAWA et al., 2016; MORENO & SALGADO, 2012; TÓTOLI & SALGADO, 2012; VIEIRA et al., 2012).

By presenting advantages over other analytical techniques, the FT-IR spectroscopy is the most widely used because it is and more sensive and rapid than the dispersive infrared spectrometer, because it measures at once the energy absorbed to sample at each wavelength through a beam of transmitted infrared light (PAVIA et al., 2010).

Thus, the objective of this study was to propose na analytical method to quantify the cefadroxil monohydrate capsules, in oder to ensure favorable analyzes to the environment and the green chemistry, being able to be used as an alternative for routine analyzes in the quality control.

2. Material and Methods

2.1. Chemicals

The cefadroxil monohydrate reference chemical substance (RCS) with purity of 93.027% and cefadroxil monohydrate 500 mg capsules, were kindly donated by the pharmaceutical company EMS (Hortolândia, SP, Brazil).

The mixture of adjuvants was prepared in the laboratory in accordance with the appropriate amounts of cefadroxil monohydrate 500 mg capsules. The magnesium stearate, croscarmellose sodium and talc were properly homogenized.

The potassium bromide (KBr) (Synth, Brazil) were of analytical grade and was used for the preparation of pellets. Prior to its use, it was ground and dried at 120°C until constant weight.

Dilutions of 1:10 and cefadroxil monohydrate and KBr were performed to minimize possible weighing error.

2.2. Instrumentation and Analytical Conditions

2.2.1. Equipments

An FT-IR spectrometer (Shimadzu®, Kyoto, Japan, IR Prestige-21 model), was used and the spectral region was consisted of 4000 - 500 cm^{-1} at intervals of 2 cm^{-1}. The band corresponding to group carbonyl in the molecule of drug, was selected using the support of IR Solution software, which was consisted in the spectral region between 1800-1700 cm^{-1}.

2.2.2. Obtaining of Analytical Curve

Equivalent amounts of 1.5, 1.7, 1.9, 2.1, 2.3 and 2.5 mg of cefadroxil monohydrate RCS were previously diluted in KBr (1:10 w/w) and after diluted in KBr again to obtain sufficient quantities of 150 mg of pellets. After adding the powders, the homogeneous mixture was submitted to mechanical pressing for 10 minutes, to prepare translucent pellets.

2.2.3. Preparation of Cefadroxil Monohydrate RCS Pellets

Aliquots of powder equivalent to 1.9 mg of cefadroxil monohydrate RCS (19.0 mg diluting 1:10 in KBr) were properly homogeinized in 131 mg potassium bromide, to form pellets of 150 mg. The determinations of the substance were performed in triplicate in absorbance.

2.2.4. Preparation of Cefadroxil Monohydrate Sample Pellets

Twenty capsules cefadroxil monohydrate 500 mg for determining the average weight were used and subsequently they were homogenized. Aliquots were weighed equivalent to 1.9 mg of cefadroxil monohydrate sample (19.0 mg diluting 1:10 in KBr) being properly homogeinized in 131 mg potassium bromide, to form 150 mg pellets. The determinations of the substance were performed in absorbance in triplicate.

2.2.5. Preparation of Adjuvants Present in Capsules of Cefadroxil Monohydrate Pellets

A mixture of adjuvants present in the sample of capsules was performed in the usual concentrations, to assess the possibility of interference in spectrophotometric analysis of cefadroxil monohydrate in the infrared region. Magnesium stearate, croscarmellose sodium and talc were homogenized and diluted 1:10 in KBr for the formation of peletts of 150 mg. The determinations of the substances were performed in triplicate and the readings were performed in absorbance.

2.3. Method Validation

The method was validated according to the International Conference on Harmonisation guidelines showing: accuracy, linearity, precision, robustness, selectivity, detection limit and quantitation limit.

2.3.1. Linearity

The linearity of the method was evaluated by linear regression analysis, which is calculated by the square minimum method and statistical analysis was by ANOVA. To validate the method, six concentrations (1.5, 1.7, 1.9, 2.1, 2.3 and 2.5 mg) of cefadroxil monohydrate were used, the

method it was performed by three different days.

2.3.2. Selectivity

The adjuvants present in the cefadroxil monohydrate capsules showed no significant interference with the method infrared spectroscopy (FT-IR). It is allowed to verify this statement in Figure 3.

2.3.3. Accuracy

The accuracy of the method was performed by testing for recovery, to which was added known amount of standard in known quantity of sample (ICH, 2005). The method was performed at three different levels (R1, R2, R3), being prepared in triplicate on three different days. Table 1 shows the preparation of the tablets for the recovery test method.

2.3.4. Precision

The precision of the method was obtained according to two different criteria: intraday (repeatability) and interdays and between analysts (intermediate). The intraday precision was made out by preparation and analysis of six pellets cefadroxil monohydrate at a concentration of 1.9 mg/150 mg on the same day and about the same working conditions. The interday precision and among analysts was made out by preparation and analysis of six pellets cefadroxil monohydrate at a concentration of 1.9 mg/150 mg, on three different days and about the same working conditions. At the end of testing, the standard deviations of the measurements were observed.

2.3.5. Robustness

Robustness is a parameter that evaluates the reliability of the method in relation to small proposital changes and/or changes in working conditions. The parameters varied were: compression of the pellets time two minutes down and above the usual working time compression; compressive strength, ranging four kN down and above the usual working compression and potassium bromide trade mark. The evaluation was performed by factorial design 2^3 and Table 3 shows the parameters of the evaluation of the robustness by factorial design 2^3 of the analytical method for cefadroxil monohydrate analysis.

2.3.6. Detection and Quantitation Limits

The limits of detection and quantification were based and calculated according to the standard deviation and interception curve slope. Three different curves were performed to obtain the data necessary to calculate. The values were calculated using the equations 1 and 2.

$$\text{Equation 1. } LD = 3.3 \times (SD/a)$$

$$\text{Equation 2. } LQ = 10 \times (SD/a)$$

Where:
a = inclination of the analytical curve
SD = intercept standard deviation

3. Results and Discussion

The validation of analytical and bioanalytical methods is fundamental in the process of good manufacturing practices, since it reproduces reliable, precise and accurate results responsible for ensuring the effectiveness of pharmaceuticals.

Research on quality control certify the results by adopting the processes, equipment, procedures, materials, activity and developed systems ensuring quality when associated with the product, while at the same time, essential for pharmaceutical companies in relation to finished products (BONFILIO et al, 2010;. BRAZIL, 2006; BRAZIL, 2003).

In order to reduce the environmental impacts on the environment and operators, industries should and can replace the analytical methods using organic solvents by methods that present a significant reduction of these substances and/or that do not employ, in order to also ensure safety needed on the technique of choice in compared to what propose to analyze.

Spectroscopy in the mid-infrared region is widely known for identifying compounds such as food, cosmetics and medicines (MORENO & SALGADO, 2012). The molecule when absorbed, presents frequency by infrared radiation absorbing natural vibrational frequency, which originates in an increase of the amplitude of this vibration movement in the chemical bonds of molecules (PAVIA et al, 2010; TÓTOLI & SALGADO, 2012).

In addition to getting great advantage over the environmental impacts due to non-use of organic solvents, this technique provides easy implementation, speed the analysis, lower economic costs, minimal or no pre-treatment in the samples, allowing the presence of impurities when present in the samples and providing optimal resolution and accurate results in quantitative analysis, especially in drugs and/or substances that present incompatibilities with solvents.

Thus, we chose to develop and validate an innovative method by infrared spectroscopy for the analysis of the monohydrate cefadroxil, due to non-use of organic solvents, allowing quantify the drug and certify the security of the method bringing a great alternative to pharmaceutical industries and laboratories of quality control.

The method can be quantified by measuring the absorbance of the band corresponding to the carbonyl presents in the drug molecule, in the region between 1800 and 1700 cm^{-1}, presenting accuracy, linearity, precision, robustness and selectivity.

3.1. Linearity

The analytical curve was made on three consecutive days, showing mean values of absorbances in the region of 1800-1700 cm^{-1} in relation to concentrations between 1.5 to 2.5 mg/pellet as shown in Figure 2. The correlation coefficient (R) was of 0.9990 and statistical analysis was calculated by ANOVA and the calculated showed ($P < 0.05$),

F calculated (0.83) lower than F critical (3.26), determining excellent linearity of the method.

3.2. Selectivity

The adjuvants present in the pharmaceutical preparation (capsules) of cefadroxil monohydrate did not show specific absorption bands, that is, there is no interference with the results obtained for the quantification of the drug. This statement can be understood through the spectral analysis shown in Figure 3.

Table 1. Preparation of pellets for the test of recovery of infrared spectrometry method for cefadroxil monohydrate

	CFD sample (mg) (dilution 1:10, w/w in KBr)	CFD RCS (mg) (dilution 1:10, w/w in KBr)	%	Final theoretical concentration (mg/pellets)	KBr amount (mg)
Sample	15	---		1.5	135.0
R1	15	1	80	1.6	134.0
R2	15	5	100	2.0	130.0
R3	15	9	120	2.4	126.0
Standard	---	15		1.5	135.0

CFD: cefadroxil

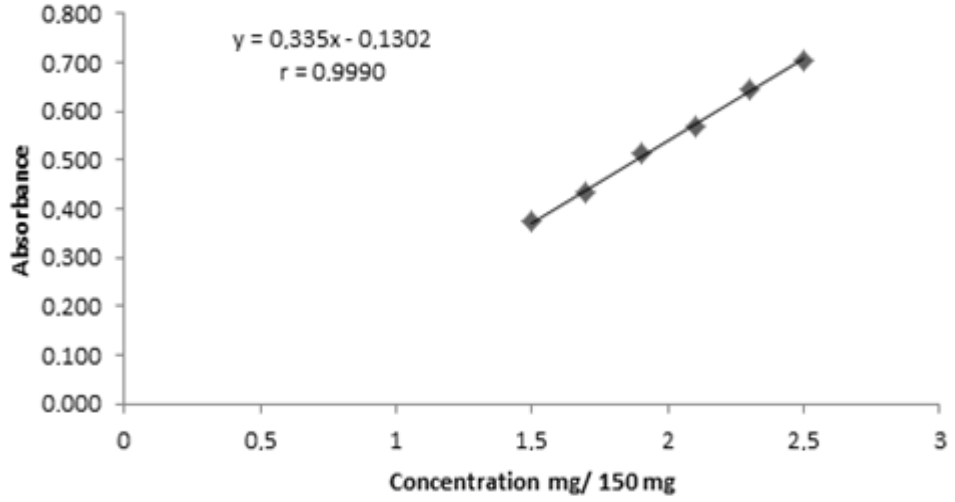
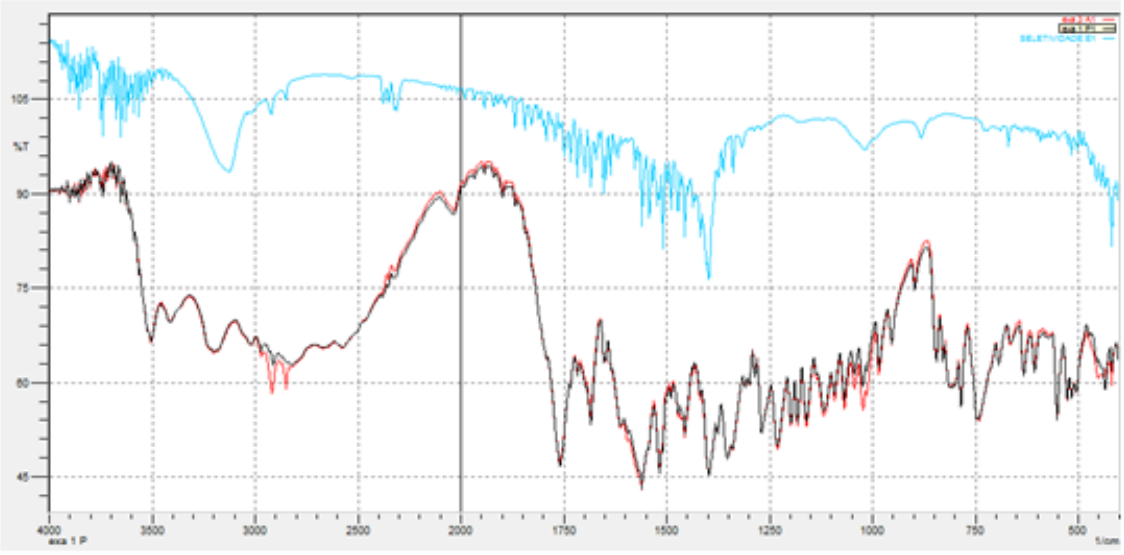


Figure 2. Graphical representation of the calibration curve of cefadroxil monohydrate by spectrophotometric method in the infrared region



Spectrum red: cefadroxil monohydrate sample; spectrum black: cefadroxil monohydrate RCS and spectrum blue: excipients present in the capsules cefadroxil monohydrate.

Figure 3. Overlap absorption spectra in the infrared region cefadroxil monohydrate SQR, cefadroxil monohydrate capsules and adjuvants

3.3. Precision

The repeatability of the analytical method showed reliability to be analyzed the % relative standard deviation obtaining a value (2.61%) lower than (5%). The intermediate precision was performed by two analysts and by two different days, could being proven through statistical analysis with the mean values obtained in the analysis by different analysts. Table 2 shows the comparative analysis and statistical findings.

Table 2. Determination of precision for test-F and t-test between analysts of spectrophotometric method in the infrared region

Test-F: Two samples for variance	Test-t: Two samples assuming equal variances
F^{cal} 1.60 < 6.39 F^{crit}	t^{cal} 0.87 < 2.30 t^{crit}
P^{value} 0.32 > 0.05	P^{value} 0.40 > 0.05

3.4. Robustness

The robustness of the method was evaluated by variation of absorbance values found in eight trials. Thus, sixteen translucent pellets with concentration referring to 1.9 mg cefadroxil monohydrate were read (Table 3). Subsequently, it was determined the analysis of variance for each contrast (Table 4), and it was observed that the changes did not present significant interference in the proposed method, that is, all values (P-value) are higher than (0.05), representing the reliability of the method even with small variations in working conditions.

Through Pareto graphic (Figure 4), it was observed values of effects to evaluate the possible interactions between factors. The data presented allowed to verify that there were no interactions statistically significant for a (P-value) of 0.05, that is, neither of the altered factors interfered significantly in the quantification of the drug. Although the demonstration of the robustness of the method it has been adequate for the analysis, it is important to note that the factors (mark KBr and analysis time) when combined presented greater variations in the results, finding evident in Figure 4.

3.5. Accuracy

The accuracy of the method was adequate and presented experimental concentration values very close to the actual values, obtaining rates very close to 100% recoveries. Table 5 shows the data obtained in the recovery test.

3.6. Detection and Quantitation Limits

The limits of detection and quantification were calculated to determine the sensitivity of the method. The value found for the detection limit was 0.37 mg and the quantitation limit was 1.11 mg. This values indicate the reliability of the method for the determination and quantification of cefadroxil monohydrate 500 mg capsules.

Table 3. Evaluation of the parameters of robustness by factorial design 2^3 of the analytical method for cefadroxil monohydrate analysis by spectrophotometry in the infrared region

Test	Time (minutes)	Strength (kN)	Mark KBr	Abs. I	Abs. II	Average	RSD (%)
1	8	76	Synth	0.496	0.494	0.495	0.28
2	12	76	Synth	0.494	0.520	0.507	3.63
3	8	84	Synth	0.532	0.496	0.514	4.95
4	12	84	Synth	0.513	0.497	0.505	2.24
5	8	76	Dinâmica	0.513	0.508	0.511	0.69
6	12	76	Dinâmica	0.523	0.506	0.515	2.33
7	8	84	Dinâmica	0.494	0.495	0.495	0.14
8	12	84	Dinâmica	0.491	0.508	0.500	2.41

Table 4. Analysis of variance for robustness spectroscopy in the infrared region

Source of variation	df	SS	SA	F	F tabulated	value-P
Factor 1	1	0.00004	0.00004	0.2031	5.3177	0.6640
Factor 2	1	0.00005	0.00005	0.2764	5.3177	0.6131
Factor 3	1	0.00000	0.00000	0.0056	5.3177	0.4739
Factor interaction 1 and 2	1	0.00010	0.00010	0.5642	5.3177	0.9418
Factor interaction 1 and 3	1	0.00001	0.00001	0.0508	5.3177	0.8272
Factor interaction 2 and 3	1	0.00058	0.00058	3.2496	5.3177	0.1090
Factor interaction 1, 2 and 3	1	0.00012	0.00012	0.6827	5.3177	0.4325
Treatments	7	0.00089	0.00013	0.7189	3.5005	0.6617
Residue	8	0.00142	0.00018	-	-	-

Factor 1 = time of compression (minute) / factor 2 = Strength (kN) / Factor 3= mark KBr
df= degrees of freedom / SS= Sum of Squares/ SA= square average / F= test statistic F

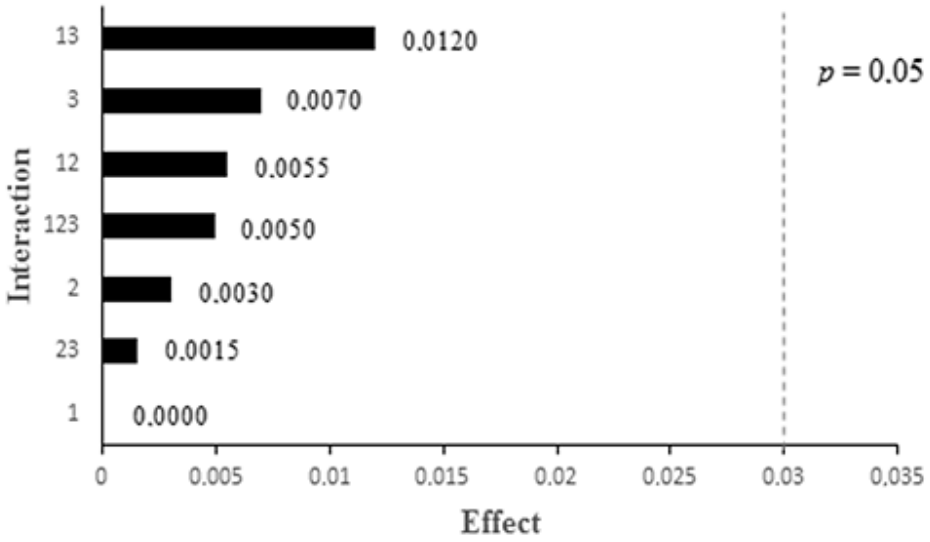


Figure 4. Pareto graphic of the interactions of the robustness variable for the spectrophotometric method in the infrared region

Table 5. Determination of the accuracy of the analytical method for analysis cefadroxil monohydrate by spectrophotometry in the infrared region

	CFD RCS added (mg)	CFD RCS found (mg)	Recovery[1] (%)	RSD[2] (%)	Average recovery (%)
R1	1	0.99	99.42	1.85	
R2	5	5.07	101.41	0.63	100.35
R3	9	9.02	100.23	1.15	

CFD: cefadroxil monohydrate

4. Conclusions

The validated method using Fourier transform infrared (FT-IR) transmission spectroscopy for quantitation of cefadroxil monohydrate capsules presented excellent results in parameters employed. Its advantages over other existing methods are clear in relation to the simplicity of execution, no use of organic solvents, low cost, minimal preparations of samples, using simple reagents and no formation of toxic waste to the environment by pharmaceutical companies. The developed and validated method can be easily applied in routine analysis for cefadroxil monohydrate analysis, as well as the study shows great possibility of application of FT-IR spectroscopy for the determination and quantification of other drugs.

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