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Evaluation of the quality and stability of amoxicillin oral suspension

Blanca Elena Ortega Markman[1], Maria Regina Walter Koschtschak [1], Elizabeth Wu Meihuey[1], Paulo Cesar Pires Rosa[2]*

[1]Physical-chemical Drugs Center. Adolfo Lutz Institute. Diseases Control Coordination of São Paulo, SP, Brazil; [2] Campinas State University – Faculty of Medical Sciences, Department of Pharmacology, Pharmacy Course, Campinas-SP, Brazil.

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ABSTRACT

The laboratory control of diseases frequently receives powders for oral suspension of amoxicillin, with reports of therapeutic ineffectiveness and problems in reconstituting suspensions. The compendial analyzes not shows quality deviations. This fact motivated the study to assess the quality and stability of oral suspensions amoxicillin in the period of use corresponding to the first and seventh days after reconstitution. Six generic drugs were tested along with the referential drug during its intake period, from the first to the seventh day after powder reconstitution for suspension by high performance liquid chromatographic method. The reconstitution of all samples resulted in suspensions with homogeneous aspect. Both pH assay and amoxicillin identification complied with the product's specification. The amoxicillin rates were determined in the 1th and 7th days after the reconstitution of samples through a method for stability detection, developed and validated before. At the 1th day, a generic drug sample presented 78% of the rate declared, below the lowest-value specification (90%). In the 7th day, 3 generic drug samples presented rates below 87%, 83% and 68.1% of the declared value, lower than the minimal specification, thus evidencing pharmacotechnical flaws in the product because of its lack of stability. Percent degradation rates of 3.5%, 4.0%, 6.0%, 9.9%, and 15% amoxicillin in 5 of the generic formulations studied are significant. The present study about amoxicillin oral suspension provides information about the stability during the using period, described for manufacturers. Even though the degradation products have not been identified, they can compromise their safe use, meaning potential risks to the users because of possible toxicity and/or therapeutic inefficacy.

INTRODUCTION

The pharmaceutical forms known as suspensions are two-phase systems, where the solid phase disperses itself in the liquid phase. That pharmaceutical form's attributes make possible the incorporation of low-solubility drugs, of drugs that quickly degrade in water solution, and of excipient modifying the antibiotic's unpleasant taste, added to render such formulations more acceptable (Pharmaceutical Codex, 1994). The suspensions are to present redispersion after shaking, particles' constant size, homogeneous aspect, and microbial resistance, since formulations with inappropriate pharmacotechnique can modify the drug's pharmacokinetics and pharmacodynamics (Pharmaceutical Codex, 1994). The amoxicillin suspensions are indicated for pediatric use because of their high efficacy due to their adequate palatability, easy and quick use, as well as low cost compared to cephalosporin. Amoxicillin is an antibiotic from the penicillin group with an ordinary beta-lactamic structure and antibacterial action against susceptible infections like actinomycoses, biliary tract infections, bronchitis, endocarditis, gastroenteritis, gonorrhea, mouth infections, pneumonia, among others, like in the eradication of *Helicobacter pylori* (Goodman and Gilman, 2007; Martindale, 2005). Amoxicillin is inactivated by the beta-lactamase enzyme, and cases have been reported of cross-resistance with ampicillin. The activity range can be extended with the simultaneous use of a beta-lactamase inhibitor like clavulamic acid. The last, besides reverting amoxicillin resistance in species producing beta-lactamase, has reportedly bettered the amoxicillin action against species considered resistant. Amoxicillin resists the gastric acid and is quickly absorbed after ingestion through the mouth. Foods in the stomach do not seem to decrease the intake's total absorption (Martindale, 2005). The Drugs Center for Physical and Chemical Assays of the Adolfo Lutz Institute of São Paulo, Brazil, has received complaints from users of Health Basic Units reporting therapeutic inefficacy, altered aspect, as well as difficulty to reconstitute the amoxicillin suspensions.

* *Corresponding Author*
Email: paulocpr@fcm.unicamp.br

Thus, a better assessment of the quality of generic drugs available to patients in the public health program should be conducted (Markman *et al*., 2010).

The purpose of this study was to assess both the quality and the stability of amoxicillin oral suspensions of 6 generic drugs, along with the reference drug, during the use corresponding to the 1st and 7th day after reconstitution.

MATERIAL AND METHOD

Initially, have been analyzed suspension powder's aspect, parameters like homogeneity, presence of clusters, powder adherence to the walls of the flasks, and color. Physic-chemical assays, such as pH and amoxicillin suspension's volume determination, have followed the methodologies described United Sates Pharmacopoeia 35th Edition (USP-35, 2012). It was necessary to develop and validate an ultra-violet high-performance liquid chromatography (UV-HPLC) stability-indicating method for the identification, rate determination, and stability verification of amoxicillin through the detection of possible degradation compounds during the using period (7 days), according to the manufacturers' instructions.

The method by HPLC is a great analytical tool that provides separation between pharmaceutical compounds and degradation products (Silva Jr. *et al.*, 2007; Rosa *et al.*, 2013).

The materials used were: placebo (powder excipient for oral suspension), USP tri-hydrated amoxicillin standard, 6 samples of generic drugs' amoxicillin suspension powder, and the reference drug; potentiometer to read the suspensions' pH; Shimadzu Class-VP 10 high-performance liquid chromatographer was tested and certificated by Sinc do Brasil Instrumentação Científica Ltd, according to the performance verification files from Shimadzu Scientific Instruments, provided by Shimadzu Corporation (Japan), specifications and proceedings issued by N.I.S.T. Amoxicillin's retention time (RT) in the method developed was 4.9 minutes. Both amoxicillin standard and amoxicillin suspension under stress (40ºC for 4 hours) presented degradation products with significant areas at the RTs 1.58, 2.84 and 3.17, thus evidencing the method's specificity, (Rosa and Jardim, 2012; Rosa *et al*., 2013). The samples were analyzed in triplicate.

The analysis in different days, using six samples solution and standard solution, were carried out to verify repeatability of the method, by calculated the chromatographic parameters, relative standard deviation (RSD) of assay and evaluation by Fisher Statistical Test.

Results and Discussion

-Five generic drugs samples presented clusters in the oral suspension powder, although previous shaking undid such clusters, and the reconstitution of all powder samples for suspensions following the manufacturers' prescriptions (as described in the label) produced suspensions with homogeneous aspect.

- pH values complied with USP-35 specification (between 5.0 and 7.5), with variations between the first and the seventh day within the range of 0.2 in average, also complying with the product's specification.
- The identification of the antibiotic amoxicillin in the suspensions was positive for the 7 samples.
- Amoxicillin rates in the 1st and 7th day are shown in Table 1.

Table. 1: Stability evaluation of amoxicillin suspensions 250 mg/5mL through the determination of amoxicillin rates in the 1st and 7th day*[1,2].

Amoxicillin % rates determined in the 1st and 7th day after suspension reconstitution according to the declared value, in the Reference (Ref) and in the Generic (G) Drugs							
Day	**Ref.**	**G. 1**	**G. 2**	**G. 3**	**G. 4**	**G. 5**	**G. 6**
1st	95.0	95.0	94.0	98.6	102.0	90.0	78.0
7th	94.0	93.0	90.0	95.1	87.0	83.0	68.1
%Degradation	**1.0%**	**2.0%**	**4.0 %**	**3.5 %**	**15.0%**	**7.0%**	**9.9 %**

*[1] Reference range between 90 and 120% of the declared value, as described both in the amoxicillin oral suspension monograph in the USP-35 and in the manufacturers' specification.

*[2] Means of a method indicating stability comprehending: mobile phase, monopotassic phosphate buffer (0.05 M), and methanol (95:5); 30 ºC, flow rate 1.5 $mLmin^{-1}$; 230 nm; column C-18 RP Select B 250 x 4mm, 5µm.

As shown in Table 1, the results for the 3 suspensions studied reflect problems that may be attributed to the suspensions' formulation and/or the quality of the raw-materials of those formulations. Figure 1, shows the chromatogram of stability evaluation of amoxicillin suspensions 250 mg/5mL in the 7th day. The peaks founded at the retention time between 0.5 until 3.5 minutes were identified as degradation products. No interference from blank, placebo and mobile phase were verified at the retention time of amoxicillin. The parameters of the system suitability, number plates, tailing factor, capacity factor and resolution are according with general chapter chromatography of the American Pharmacopoeia (USP 35, 2012). The analysis of samples solution and standard solution, were obtained in different days for determination of system suitability of the chromatographic method. The value of RSD for six sample in the first day was 1.85 % and in the second day 2.13%. The evaluation by Fisher statistical test showed value of F obtained, 1.18, lower of the F calculated, 5.05, for significance level of 99.0 % (Rosa *et al*., 2013).

The insoluble amoxicillin oral suspension should assure at least 90% activity in 14 days at room temperature. Amoxicillin's stability in the insoluble form is higher than in the solubilized form; oral suspension's stability depends on amoxicillin's loss of solubility (Pranab and Winifred, 1978). The daily determination of amoxicillin in the suspensions stored at room temperature, from the first to the seventh day of use, noted the significant degradation of the assay in some generic medicines. The results of this study demonstrate the importance of verifying the stability of the amoxicillin assay during the period of use, with application of stability indicating methods.

The results comply with the literature, which reports comparative studies between generic and reference antibiotic. Some researches (Del Tacca, 2009), (Steppe, 1997) verified the

non-bioequivalence between the formulations of two generic drugs ant the reference drug in amoxicillin tablets and amoxicillin oral suspensions; furthermore. Challenge the therapeutic efficacy of generic drugs, particularly the injectable antibiotics was studied (Gauzit and Lakdhari, 2012).

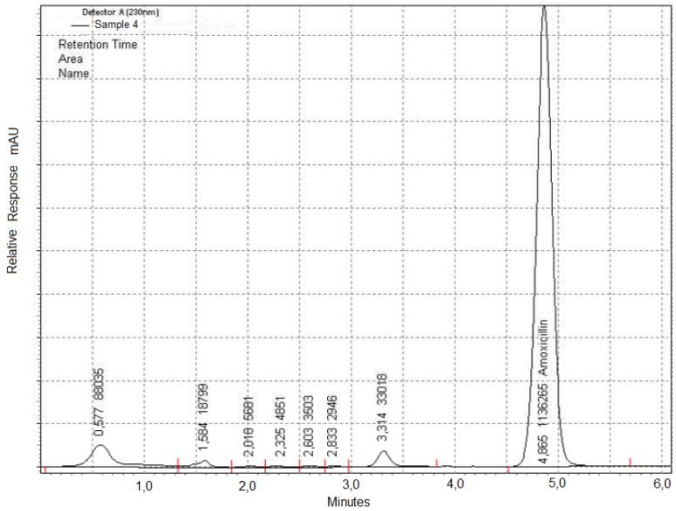

Fig. 1: Chromatogram of stability evaluation of amoxicillin suspensions 250 mg/5mL in the 7th day. Chromatographic conditions: mobile phase, monopotassic phosphate buffer (0.05 M), and methanol (95:5); 30 °C, flow rate 1.5 mLmin-1; 230 nm; column C-18 RP Select B 250 x 4mm, 5µm.

CONCLUSION

Out of the 7 amoxicillin oral suspension samples analyzed, 3 generic drugs presented values below the minimal specification in the 7th day after the reconstitution, thus evidencing flaws in the product's pharmacotechnique because of lack of stability during the using period. Amoxicillin degradation rate (%) in 5 of the formulations studied is significant; although the degradation products have not been identified, they can nevertheless compromise the drug's safe use, meaning potential risks to the users due to possible toxicity and/or therapeutic inefficacy.

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