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Assessment of the quality of compounded fluconazole capsules marketed in the region of Araraquara (SP, Brazil)

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ABSTRACT

The quality control of drugs has an important role in public health, in ensuring the efficacy and safety of medicines. In the public health system, compounding pharmacies play a vital part. They provide medicines tailored to the individual patient, for example dermatological products and specific doses for children. Unfortunately, many cases of compounded products falling below the minimum quality standard have been reported in Brazil. In this study, the quality of compounded 150 mg fluconazole capsules was assessed and the results were compared with values stipulated in the Brazilian pharmacopoeia. The results suggest that, while it is certainly possible to prepare products meeting pharmacopoeial specifications, there are pharmacies where the quality control is deficient or nonexistent. Fluconazole is an important drug in combatting fungal infections. The use of fluconazole in dosage forms manufactured without high standards of quality control is strongly linked to treatment failure and cases of intoxication, as well as the emergence of resistant microorganisms. This highlights the urgent need for process improvement in compounding pharmacies. There are validated methods that can be successfully employed for routine quality control analysis that can be implemented by any compounding pharmacy.

Keywords: Fluconazole. Compounded medicines. Quality control. Public health.

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INTRODUCTION

Among the available antifungal drug classes, the triazoles are used most extensively. Fluconazole (Figure 1), developed in the 80s, is active against species of Candida and indicated in cases of oropharyngeal, oesophageal, vaginal and systemic candidiasis (Bennett, 2003; Park et al., 2007; Corrêa & Salgado, 2011). It was the first of the triazole drugs and is a white or off-white crystalline powder that melts at 223-224 °C. As was highlighted by Corrêa & Salgado, fluconazole is slightly soluble in water, sparingly soluble in alcohol, soluble in acetone, freely soluble in methanol and very slightly soluble in toluene. It is a weak base, and its ionization constant (pKa), measured in 1.1 M NaOH, is 1.76 ± 0.10 (Corrêa & Salgado, 2011). Its aqueous solubility increases at very high and low pH values.

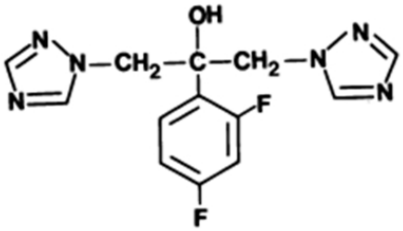

Figure 1. Fluconazole chemical structure (CAS 86386-73-4).

This drug has been approved on prescription in many countries, including Brazil, where it can be found in the form of pharmaceutical capsules. The reference product is Pfizer's branded product, called Zoltec™ in Brazil and Diflucan elsewhere. It is also common to find fluconazole capsules as generic and compounded products in the Brazilian market.

According to Giam and coworkers, compounding is a traditional function of the pharmacist that has declined with the wider availability of manufactured medicines and is now increasingly offered by community pharmacies as a specialized service (Giam et al., 2012).

Compounding pharmacies have an important role, since suitable dosage forms are not always available for specific patient populations, such as infants and children, and must be extemporaneously compounded (Kairuz et al., 2007).

According to Kairuz and coworkers, registered medicines are produced to internationally recognized

standards of Good Manufacturing Practices, while extemporaneous preparation is the manipulation of drugs and excipients for a particular patient using traditional compounding techniques (Kairuz et al., 2007). Some risks arise from compounding practice, including compounding errors, adverse reactions to ingredients and excipients and non-validated stability of the product (Kairuz et al., 2007).

According to the Brazilian food, drug and sanitary surveillance agency ANVISA (Brasil, 2005), the primary role of compounding pharmacies is to meet a specific formulation demand that the pharmaceutical industry either cannot meet or has no interest in manufacturing. Usually, such products are provided as individually prescribed or dermatological formulations. However, nowadays, it is possible to find in compounding pharmacies a wide range of medicines, even those produced on a large scale by the pharmaceutical industry, such as fluconazole. The lower price of compounded products has a strong appeal to consumers and helps to expand this market in Brazil. From 1998 to 2002, the number of compounding pharmacies increased from 2,100 to 5,200 and innumerable prescribed formulations were compounded (Brasil, 2005).

The quality of medicines is vital to patient safety. Drug quality control is necessary and intended to ensure the efficacy, safety and quality of medicines, a crucial role of any pharmacist for public health. Unfortunately, the quality control requirements for compounding procedures are different from those for industrial drug manufacturing processes. Dispensing of low quality products by compounding pharmacies has become a recurrent concern (Brasil, 2005). There are frequent reports of heterogeneous distribution and/or deficient drug release, affecting compounded drugs of various therapeutic classes (Brasil, 2005). As a result, some pharmacies have had their license suspended by the local sanitary agencies.

In 2011, medicines prepared in a compounding pharmacy killed 8 people in the state of Minas Gerais (Brazil). Patients had symptoms of poisoning by drugs against high blood pressure (Jornal Nacional, 2011). In the same year, in São Paulo city, about 45% of the 615 inspections carried out in compounding pharmacies revealed irregularities and 122 of these pharmacies had to remain closed until the problems were resolved (Veja, 2011).

The aim of this study is to discuss the importance of careful monitoring of the quality of compounded medicines, taking compounded fluconazole capsules as an example. Four batches of compounded capsules of 150 mg fluconazole acquired at pharmacies in Araraquara and Sertãozinho cities were tested with respect to their drug contents and physicochemical and antifungal characteristics.

It should be understood that the discussion presented in this study carries no suggestion that compounded products are unsafe. The intention is to highlight the real need for more effective quality control and surveillance of medicines manufactured in compounding pharmacies.

MATERIAL AND METHODS

The four samples of fluconazole 150 mg capsules were given the codenames A, B, C (Araraquara) and D (Sertãozinho), according to the pharmacies and towns where they were acquired. Pure fluconazole (100% purity, Sigma-Aldrich, St. Louis, MO, USA, lot 098k4715) was used as the reference standard and bulk fluconazole (100.3% purity, lot 190508, kindly donated by EMS pharmaceutical company) as the working standard.

A UV-Vis spectrophotometer with internal Chemstation software (HP8453, Agilent, Palo Alto, CA, USA) was used. Other equipment included an analytical balance (H10, Mettler), dissolution tester (SR8-Plus, Hanson), disintegrator (Nova Ética) and digital electronic caliper (727 series, Starrett).

All tests were performed in accordance with the Brazilian Pharmacopoeia 5th edition (BP 5) (Brasil, 2010).

The weight, disintegration and dose uniformity of the capsules were tested in each sample, as specified in the general methods of BP 5 (Brasil, 2010). They were also tested for dissolution, drug content (by derivative UV spectrophotometry) and antifungal potency (by the agar-plate diffusion method), as described in previously validated analytical methods (Corrêa et al., 2012a; Corrêa et al., 2012b).

Dissolution test conditions were 900 mL of 0.1 M HCl medium at 37 ºC, basket apparatus, rotational speed 75 rpm and sampling time 30 min. The drug release was measured by first-order derivative spectrophotometry at wavelength (λ) 268 nm, a previously validated method (Corrêa et al., 2012a). Content uniformity was also assessed by the same derivative analytical method; the working concentration was 250 mg/mL in water.

The antifungal activity was evaluated by the agar diffusion method, with plate cylinders, in a 3x3 design. The growth medium and test organism were Sabouraud agar and Candida albicans (ATCC 90028, in 2% saline). The test concentrations used were 25, 50 and 100 mg/mL. The Petri dishes were incubated at 25 °C for 24 hours. The potency of the drug was calculated by the Hewitt equation (equation 1) (Hewitt, 2004).

Potency (%) = Antilog M x 100 (equation 1)

where:

$$M = F/b$$

$$b = E/I$$

$$E = \frac{1}{4} \times \left[\left(\overline{A3} + \overline{P3}\right) - \left(\overline{A1} + \overline{P1}\right)\right]$$

$$F = \frac{1}{3} \times \left[\left(\overline{A1} + \overline{A2} + \overline{A3}\right) - \left(\overline{P1} + \overline{P2} + \overline{P3}\right)\right]$$

I = Logarithm of the ratio of doses

and A3, A2, A3 and P1, P2, P3 refer to the mean diameters of inhibition zones formed by sample and standard solutions at high, medium and low concentration, respectively.

The results obtained in this study were analyzed statistically.

RESULTS

As highlighted by Corrêa and coworkers, there is strong interference from the placebo constituents (excipients plus capsule shells) in fluconazole determination by UV spectrophotometry, which is greatly reduced by applying the derivative spectrophotometric method (Corrêa et al., 2012b).

The methods used in this study have proved both sensitive and selective (Corrêa et al., 2012a; Corrêa et al., 2012b). It has been successfully demonstrated that they can be used to analyze fluconazole capsules, discriminating the drug without interference from the placebo. Therefore, they were applied here to fluconazole determination in the assay and dissolution tests.

The four batches of compounded fluconazole were analyzed and the results were assessed against the Brazilian Pharmacopoeia specifications (Brasil, 2010). All the results are summarized in Table 1. It can be seen in Table 1 that samples A, B and C were approved, as they passed all the tests recommended in BP 5. On the other hand, sample D was outside the reference limits for weight determination, assay and uniformity of content.

DISCUSSION

Samples A, B and C were approved in all tests. Sample D was approved only in the weight, disintegration and dissolution tests. A solid oral dosage form has to release the drug in the appropriate part of the gastrointestinal tract, so that it can be absorbed. The disintegration of that dosage form is a step in the process of drug release. However, more important than the disintegration is dissolution: the dosage form has to release the drug and it has to be completely dissolved in the gastrointestinal tract, in order to be absorbed. The dissolution performance can be affected by the manufacturing process and the physicochemical characteristics and quality of the raw materials used for the drug and excipients. Markman and coworkers (Markman et al., 2010) stressed that dissolution performance problems can arise from the process of mixing excipients and active ingredients, particle size variations or the rheology of the solids.

The results for capsule weight and the quantity of drug in each capsule should be within a specified range of variation. Large deviations in the weight of the capsules show that the capsule filling procedure is not sufficiently standardized and robust. If the dose unit uniformity test shows a poor result, the drug is not homogeneously distributed in the formulated powder and the manufacturing process is not sufficiently standardized. Wide variation in weight and uniformity of dose can lead to capsules with an

Table 1. Results of quality assessment of fluconazole 150 mg compounded capsules. All tests were carried out in triplicate.

Test	Specifications	Results	Notes
Weight (W, mg; deviation)	W≤300 mg (max.±10.0%); W>300mg (max.±7.5%)	A: 451.91 (2.03) B: 208.3 (1.53) C: 154.7 (3.23) D: 190.1 (6.47)	A,B,C and D: met requirements D: 2 units above upper limit
Uniformity of dosage units (AV; (SD))	AV ≤ 15	A: 0.384 (0.16) B: 8.04 (3.38) C: 7.90 (3.26) D: 18.31 (7.60)	A,B,C: met requirements D: out of specification
Content (% LV; %RSD)	90.0-110.0% LV	A: 93.16 (7.84) B: 105.06 (1.26) C: 90.31 (4.09) D: 89.43 (1.09)	A,B,C: met requirements D: out of specification
Antifungal activity (%)	NR	A: 93.43 B: 87.29 C: 86.49 D: 89.14	B,C,D: low antifungal activity (< 90.0%)
Disintegration (t, min)	Max. 45 min	A: 32 min B: 37 min C: 38 min D: 42 min	A,B,C,D: met requirements
Dissolution (% release, %RSD)	NLT <85% (Q + 5) LV	A: 104.80 (2.18) B: 104.03 (3.10) C: 109.63 (3.65) D: 101.13 (6.05)	A,B,C and D: met requirements D: shows considerable deviation

AV: Accepted value; LV: Label value; NR: not recommended; NLT: not less than; Q: amount of dissolved drug specified in the individual monograph, expressed as a percentage of the amount on the label; RSD: relative standard deviation; t, min: time in minutes; SD: standard deviation.

underdose or overdose of the drug. The recommended doses of drugs are calculated by taking into account the minimum dose required for efficacy with safety and an absence of toxic effects, so that doses outside the recommended range represent a high risk to patient health.

According to the monograph on fluconazole capsules in the updated BP 5, the drug content in the capsules can vary from 90.0% to 110.0% of the declared label value (LV). Except sample D, the samples passed in the content test. Sample D showed a content value below the minimum recommended for the product. Medicines with low doses can contribute to the emergence of fungal resistance and can lead to failure of the treatment.

Equally or more important than the content test, the antimicrobial activity should be assessed for antimicrobial drugs. Unfortunately, the antimicrobial activity test is not recommended for fluconazole in any official compendium. Corrêa and coworkers have demonstrated that the climatic conditions can affect the potency of fluconazole, potentially decreasing its antimicrobial activity during storage, but this cannot be assessed by physicochemical determinations such as chromatographic or spectrophotometric methods (Corrêa et al., 2012c).

Samples B, C and D showed antimicrobial activity lower than 90 % relative to standard solutions. No right value is specified for this test, since it is not officially recommended. For the content test, the accepted range is 90-110%; if we adopt the same range for the antimicrobial activity test, samples B, C and D would be classified as out of specification. Variations in the antimicrobial activity and content results for fluconazole were reported by Corrêa and coworkers in a previous study of the stability of the drug (Corrêa et al., 2012c).

As many cases involving problems with the quality of compounded products have been reported lately (Marcatto et al., 2005; Pissatto et al., 2006; Jornal Nacional, 2011; Veja, 2011) and, in most cases, the non-observance of a quality standard was the main cause, we believe that, to stop the marketing of low-quality pharmaceutical products, it is important that the responsible agencies improve the regulatory inspection of compounded drugs and their quality control. In the specific case of fluconazole, some analytical methods to assess the quality of compounded capsules have been published (Corrêa et al., 2012a, 2012b, 2012c). These quality control analyses should be implemented, to ensure the production of high quality and safe compounded drugs.

The compounding pharmacies are essential to the health care system, in particular because there are specific formulations prescribed for particular patients that are produced only in these pharmacies. Although the present results suggest that it is possible for compounding pharmacies to prepare medicines that meet the specifications of quality, this study also showed that products failing to meet quality specifications are available on the Brazilian market.

Fluconazole is an effective drug in combating fungal infections. The use of fluconazole dosage forms manufactured without high standards of quality may be the cause of therapeutic failure and cases of intoxication, as well as the rise of resistant microorganisms. There are validated methods that can be routinely employed for the quality control analysis of this drug and can be used by any compounding pharmacy (Corrêa et al., 2011; Corrêa et al., 2012a, 2012b, 2012c).

Fluconazole is marketed around the world as branded, generic and compounded products. Recently, many cases involving problems with the compounded products have been reported. In most cases, the non-observance of a quality standard was detected. We believe that to stop low-quality pharmaceutical products entering the market, it is important that the regulatory agencies improve the regulation of compounded drugs and their quality control.

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Conflict of Interest Statement: The authors declare that there search was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

RESUMO

Avaliação da qualidade de cápsulas de fluconazol manipuladas comercializadas na região de Araraquara (SP, Brasil)

O controle de qualidade de fármacos desempenha um papel importante na saúde pública ao garantir segurança e eficácia de medicamentos. No sistema de saúde pública, as farmácias magistrais também são importantes. Elas fornecem medicamentos personalizados como produtos dermatológicos e doses específicas para crianças. Infelizmente, muitos casos de produtos magistrais fabricados fora do padrão mínimo de qualidade têm sido relatados no Brasil. Neste trabalho, a qualidade das cápsulas magistrais de fluconazol 150 mg foi avaliada e os resultados foram comparados com os valores recomendados pela Farmacopeia Brasileira. Os resultados sugerem que é possível manipular produtos que satisfaçam as especificações farmacopeicas, mas estes ainda mostram que há farmácias magistrais onde o controle de qualidade é deficiente ou inexistente. O fluconazol é um fármaco importante no tratamento de infecções fúngicas. Seu uso como forma farmacêutica manipulada sem elevados padrões de qualidade é fortemente relacionado com a falha terapêutica e intoxicações, assim como o surgimento de micro-organismos resistentes. Portanto, a necessidade de melhoria dos processos nas farmácias magistrais se torna mais enfático. Existem métodos validados que podem ser utilizados com sucesso para a análise de rotina de controle de qualidade e que podem ser implementados por qualquer farmácia de manipulação.

Palavras-chave: Fluconazol. Medicamentos magistrais. Controle de Qualidade. Saúde pública.

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