ARTICLE
https://doi.org/10.22239/2317-269x.01134

Detection of quality deviations in compounded formulation: acetic acid solution, ketoconazole syrup and T4 thyroid hormone capsules

Detecção de desvios de qualidade nos medicamentos manipulados: solução de ácido acético, xarope de cetoconazol e cápsulas de hormônio tireoidiano T4

Fernanda Fernandes Farias[I,*]
Helena Miyoco Yano[I]
Eliana Della Coletta Yudice[II]
Marcos Paulo Guilherme[I]
Valéria Adriana Pereira Martins[I]
Luz Marina Trujillo[I]
Maria Cristina Santa Bárbara[I]
Blanca Elena Ortega Markman[I]

ABSTRACT

Introduction: Incorrect doses of the active ingredient in compounded formulations make up common errors in the compounding process, which can cause harm to the patient's health, reflecting the possible absence of Good Compounding Practices (GCP). **Objective:** To report quality deviations in acetic acid solution, ketoconazole syrup and T4 capsules. **Method:** Identification by chemical reactions and by HPLC, content by titration and HPLC, pH by potentiometry. **Results:** Positive identification for acetic acid with 98.20% content compatible with glacial acetic acid, in disagreement with the prescription of 5% solution. The ketoconazole content of 16.20 mg/mL found in the syrup corresponds to 81.00% of the declared value, the minimum specification is 90.00%; pH 8.0; positive identification for anionic surfactant component in the syrup. The results found for T4 capsules were 177,70 µg for 25 µg capsules and 174, 44 µg for 200 µg capsules, corresponding to 710,96% and 87,22% of the declared content, respectively, in disagreement with the specifications of 90.00% and 110.00%. **Conclusions:** The study illustrated the detection of quality deviations in compounded drugs from different pharmacies, due to pharmacotechnical misconceptions, lack of quality control and lack of GCP implementation. Frequent inspection prevents health risks to the population.

KEYWORDS: Compounding Formulations; Health Surveillance; Pharmaceutical Assistance; Public Health

RESUMO

Introdução: Doses incorretas do ativo nas preparações magistrais configuram erros comuns na manipulação, podendo ocasionar agravos à saúde do paciente, refletindo possível ausência das Boas Práticas de Manipulação (BPM). **Objetivo:** Relatar desvios de qualidade nos medicamentos solução de ácido acético, xarope de cetoconazol e cápsulas de T4. **Método:** Identificação por reações químicas e por CLAE, teor por titulação e CLAE, pH por potenciometria. **Resultados:** Identificação positiva, para ácido acético com teor de 98,20% compatível com ácido acético glacial, em desacordo com a prescrição de solução a 5%. O teor de cetoconazol de 16,20 mg/mL encontrado no xarope corresponde a 81,00% do declarado, com especificação mínima de 90,00%; pH 8,0; identificação positiva para tensoativo aniônico componente saponáceo, no xarope. Os resultados encontrados: cápsulas de T4 de 25 µg foi de 177,70 µg e as de 200 µg foi de 174,44 µg, correspondendo a 710,96% e 87,22% do teor declarado, respectivamente, em desacordo com a especificação de 90,00% a 110,00%. **Conclusões:** O trabalho ilustrou a detecção de desvios de qualidade em medicamentos manipulados de diferentes farmácias, decorrentes de erros farmacotécnicos, ausência de controle de qualidade e falta de implementação das BPM. A frequente fiscalização previne riscos sanitários à população.

PALAVRAS-CHAVE: Medicamentos Manipulados; Risco Sanitário; Desvios da Qualidade; Saúde Pública

[I] Centro de Medicamentos, Instituto Adolfo Lutz (IAL), São Paulo, SP, Brasil

[II] Centro de Laboratório Regional - Santo André, Instituto Adolfo Lutz (IAL), São Paulo, SP, Brasil

***** **E-mail:** farmafernanda@gmail.com

Received: Fev 19, 2018
Approved: Jul 02, 2018

INTRODUCTION

Compounding pharmacies are public health establishments whose purpose is to produce individualized medical prescriptions. The Resolution of the Collegiate Board of Directors (RDC) n. 67, of October 8, 2007, of the Brazilian National Health Surveillance Agency (ANVISA), established Good Compounding Practices (GCP) that require establishments to follow standard operating procedures (SOPs), the use of raw materials from qualified suppliers and the internal quality control of the compounding process[1].

Usually, compounded drugs have a lower cost when compared to manufactured drugs. That is one of the reasons that promoted the growth of these medicines in Brazil and in the world. In addition, they are individualized preparations according to the medical prescription; the distinctive feature of a compounded pharmacy is that it meets the patient's individual needs, considering risk/benefit[2].

A study by the Federal Council of Pharmacy in 2016 had already estimated more than 8,000 compounding pharmacies with about 60 million prescriptions filled annually[3,4]. However, according to the literature, the safety and clinical efficacy of these medicines often fall short of expectations, because they are not subject to the same quality control analyses as manufactured drugs. Manufactured drugs undergo destructive analytical techniques in assays like identification, content, uniformity of unit doses, dissolution, among others, during and after its manufacturing process[1].

Incorrect doses of the active substance in the formulation of compounded drugs is one of the most common errors in the compounding process and can cause serious health problems for the patient. This fact reflects the lack of GCP according to RDC n. 67/2007[1].

There are several reports in the literature about errors in compounded drugs that caused health problems to users, like what happened in Brasília in 2003, with compounded clonidine capsules. They contained a dose a hundred times higher than that stated on the label, which resulted in poisoning and death of the user, since that was a low therapy index and high potency drug[5].

In the state of Santa Catarina, a study was carried out to evaluate the compliance of 25 mg captopril capsules compounded by four different pharmacies. Two samples presented an unsatisfactory result for the mean weight of the capsule contents, probably due to problems in the encapsulation, and this may interfere with the therapeutic dose[6].

In 2007, in the state of São Paulo, studies by Markman et al.[7] detected serious deviations of quality in materials and capsules containing thyroid hormones (T3 and T4), with technical complaints from several Brazilian states. The values found for T3 and/or T4 overdose led patients to hospital admission and even death due to poisoning, exposing the technical limitations of compounding processes, as well as the lack of quality control of these finished products. The use of improperly compounded medicinal products may pose health risks.

In 2010, the Adolfo Lutz Institute (IAL) of São Paulo received repeated complaints from consumers of compounded T3 and T4 formulas. One of the samples showed serious errors in the doses for compounded T3 and T4 in milligrams versus the prescription, which should have been in micrograms. The results also demonstrated oscillations between ineffective therapeutic doses and overdoses, indicating lack of GCP enforcement and exposure of patients to health risks[8].

In 2011 a pharmacy in Belo Horizonte compounded capsules containing secnidazole 500 mg (antifungal). After ingestion, several patients had symptoms of low blood pressure, bradycardia, chest pain, cyanosis and feeling of faint. These symptoms led to hospitalization and some deaths. The investigation of the Health Surveillance and the technical police identified that the antifungal secnidazole had been replaced with antihypertensive amlodipine besylate, whose usual dose is 5 to 10 mg/capsule[9,10].

Among other compounded samples received and analyzed by the IAL, many presented quality deviations such as drug absence, underdose and/or overdose. Overdosage of colchicine was found in compounded capsules, causing poisoning of the patient. In another sample of 1% silver nitrate ophthalmic solution received with the complaint of lack of therapeutic effect, tests identified drug underdosage[12].

Label error is another quality deviation that may lead to inaccuracy in the administration of the medicinal product[13]. The verification of adulteration of controlled-use raw material in the facilities of a compounding pharmacy was another non-compliance found[14].

The Center for Medicines, Cosmetics and Sanitizers of the IAL, Central Laboratory of Public Health of São Paulo, in partnership with the Health Surveillance and Pharmacovigilance Services, corroborates the promotion of health in the state of São Paulo and other Brazilian states, through quality assurance of samples of consumer products, medicines, cosmetics, *inter alia*, usually sent by Health Surveillance services with technical complaints from users and legal proceedings[15].

In 2015, IAL's Nucleus of Physical and Chemical Tests in Medicines (NFQM) received requests from other cities in the state of São Paulo through their local Health Surveillance Services, to perform analyses of three compounded drugs. Thus, this study aims to report the results found in the analyses performed on these drugs, as well as the occurrences reported below:

a) Acetic acid solution: physician from a Clinic of Medical Specialties (AME) of the State Department of Health of the state of São Paulo prescribed a 5% acetic acid solution. This had been prepared in a compounding pharmacy and labeled as glacial acetic acid concentrate. However, in the clinic where the formulation was applied onto the genitals of the patient, according to the treatment prescribed by the physician, the information on the label was not previously checked by the health professional.

The patient immediately felt severe pain due to the burn in the area where the acid was applied. This occurrence, as well as the strong odor of the product, led the physician to discontinue treatment and contact the compounding pharmacy, which reported that the product had been bottled without proper dilution of the acid.

b) 20 mg/mL ketoconazole syrup was prescribed for oral administration, to a pediatric patient who, immediately after ingestion, presented nausea and vomiting. The patient's mother was suspicious so she decided to try the syrup. She tasted the unpleasant flavor and noticed the production of froth when rubbing the liquid in the palm of her hand.

c) T4 L-thyroxine capsules: formulations at the concentrations of 25 µg and 200 µg T4/capsule were compounded by a pharmacy that did not have legal authorization for compounding these hormones, according to Annex III of the GCP of hormones, antibiotics, cytostatics and substances subject to special control under RDC n. 67/2007.

METHOD

Materials, reagents and equipment

Analytical balance Metller Toledo® model AL 204, potentiometer Q-400M1 Quimis®, Waters high performance liquid chromatograph®, Empower processor, C18 column with 5 µm particles and 250 x 4.6 mm Lichrospher of Merck®, high efficiency liquid chromatograph from Shimadzu®, CLASS-VP 10 processor, L10 column, 5 µm and 250 x 4.6 mm particles from Nucleosil Macherey-Nagel®, Merck® phosphoric acid, chemical reference substances Levothyroxine T4 and ketoconazole of the American Pharmacopoeia and Brazilian Pharmacopoeia respectively, ultrapurified water in the Purelab Classic DI Elga® system, Durapore PVDF membrane filter unit with 0.45 µm pore, 13 mm diameter Millipore®, Synth® oxalic acid, Electrochemical® sulfuric acid, Vetec® ethyl alcohol, Synth® sodium hydroxide, Synth® ferric chloride, Vetec® hydrochloric acid, QEEL® phenylephthalein, Dinâmica® ammonium acetate, methanol HPLC grade Vetec®, Merck® phosphoric acid PA, Merck® acetonitrile HPLC grade, Merck® 0.004 molar solution of hyamine.

Analytical procedure

The aforementioned samples from (a) and (b) were submitted to analyses according to the methods described in the Brazilian Pharmacopeia[16] and sample C was according to the U.S. Pharmacopeia. The tests performed are listed in the Table, as well as the identification and content analyses for anionic surfactant[17,18] (detergent) in the syrup identified as ketoconazole.

Research, identification and content of the acetic acid solution

- Acetate anion identification reactions

Two 10-mL aliquots of the sample were heated in different containers. In an aliquot, 10 mL of oxalic acid TS was added to verify the evolution of acid fumes with the characteristic odor of acetic acid; to the other aliquot we added 1 mL of sulfuric acid TS and 1 mL of ethanol to investigate the production of the characteristic odor of ethyl acetate.

Table. Tests done on the compounded drugs.

	acetic acid solution	ketoconazole syrup	T4 L-thyroxine capsule
Aspect	X	X	X
Content weight			X
pH		X	
Identification	X	X	X
Content	X	X	X
Uniformity of unit doses			X

5 mL of the sample was diluted in 10 mL of water; the pH adjustment was performed to about 7 with 1.0 M sodium hydroxide solution; 5 drops of ferric chloride TS were added to verify the development of dark red color, which disappears after addition of drops of 0.1 M hydrochloric acid, according to the Brazilian Pharmacopeia[16].

- Anion acetate content

The acetic acid content was determined by direct titration of the acetate anion in the sample, using the 1.0 M sodium hydroxide VS and phenolphthalein solution as the indicator.

Solution identified as a ketoconazole syrup

- Determination of pH

pH solution reading in digital potentiometer.

- Ketoconazole content

The ketoconazole content in the analyzed sample was determined by high performance liquid chromatography, UV-Vis 232 nm detector, C18 chromatographic column, mobile phase composed of methanol and 0.5% (w/v) ammonium acetate (95: 05 v/v), 10 µL injection volume, isocratic mode and 1.0 mL/min flow rate. The chromatograms were processed by the Empower Waters control system. The concentrations of standard solution and sample solution were 0.1 mg/mL ketoconazole in methanol.

- Determination of the anionic surfactant

Since the solution of the sample had froth, typical of detergent substances or anionic surfactants, the extraction of this substance was done with chloroform. The chloroform extract was subjected to neutralization titration using as a titrant the 0.004 M solution of Hyamine (alkyl dimethyl benzyl ammonium chloride) and dimidium bromide as the indicator[17,18].

T4 compounded capsules

Identification and L-thyroxine content in the capsules were determined by high performance liquid chromatography as described in the U.S. Pharmacopeia[19]. A UV-Vis detector was used at wavelength 238 nm, column oven at a temperature of 27° C, injection volume of 20 µL, column packed with silica chemically attached to nitrile-L10

groups. The mobile phase consisted of water acidified with 0.05% (v/v) phosphoric acid and acetonitrile (52:48), the diluent used was the mobile phase, flow rate of 1.6 mL/min. The solutions prepared at the final concentration of 0.01 mg/mL L-thyroxine (T4) for the standard and samples were filtered and injected into Shimadzu's high efficiency liquid chromatograph. The chromatograms were processed by the SCL-10A-VP control system. The determination of uniformity of dosage units per capsule content was performed in the same chromatographic system and in accordance with the acceptance criteria of the Brazilian Pharmacopeia[16].

RESULTS AND DISCUSSION

(a) Solution identified as acetic acid

Description of the sample: sample contained in amber vial with broken seal, the liquid had transparent appearance, without visible particles in suspension, with a strong typical odor of acetic acid. It was labeled as: "glacial acetic acid, use according to medical advice, external use, name and address of the pharmacy".

Acetate anion was identified in the sample by the release of acid fumes with typical acetic acid odor and typical of ethyl acetate odor, and with the production of a dark red color that disappeared after addition of some drops of hydrochloric acid[16].

The content of acetic acid found was 98.2% (w/w) compatible with the value for glacial acetic acid (concentrate)[16] and as declared on the label of the compounded product. However, the formulation prescribed by the physician was a solution of acetic acid diluted to 5%; the compounded formulation labeled as a concentrate was administered by the health agent to the patient in a mucosa, causing hospitalization due to severe burns with severe pain.

b) Syrup identified as a ketoconazole syrup

Ketoconazole was identified by comparing the retention time of the main peak of the chromatogram of the sample solution with the retention time of the main peak of the chromatogram of the standard solution. The content found was 16.2 mg/mL ketoconazole, 81.00% of the label value of 20 mg ketoconazole/mL, with an unsatisfactory result in relation to the reference value[16] of the Brazilian Pharmacopeia, which is 90.00% to 110.00% of the declared value.

The sodium lauryl sulfate (SLS) anionic surfactant, determined on the sample identified as ketoconazole syrup, is a chemical used in various cosmetics, personal care products and pharmaceutical formulations as a wetting, emulsifying and lubricating agent, at concentrations that are appropriate to each formulation. The content of 20.27% w/w of surfactant in the sample is neither compatible with pharmaceutical formulations, nor would it comply with Normative Resolution n. 1, of November 27, 1978[19] which was repealed. That Resolution approved the standards to be complied with by detergents and similar products, specifying that the product was considered concentrated when it had a minimum content of 10.00% and a maximum of 15.00% w/w of active substance. The current RDC n. 40[20], published on June 5, 2008, does not establish minimum and maximum content for anionic surfactant for cosmetic and sanitizing formulations. The results found for this compounded formulation, which the label describes as a pharmaceutical form of ketoconazole syrup for oral administration, displays serious compounding mistakes, as well as lack of quality control of the compounded products.

The pH of the sample was determined to be 8.0.

c) T4 L-thyroxine capsule

The identification of the thyroid hormone T4 for the samples constituted of compounded capsules with 25 µg and 200 µg of T4 was satisfactory. The result of the T4 content in the capsules with 25.00 µg were 177.70 µg per capsule, which means 710.96% of the declared content. In the 200 µg capsules, the content found was 174.44 µg of T4, which corresponds to 87.22% of the declared content. Both formulations were in disagreement with the reference values between 90.00% and 110.00% of the declared value established in the American Pharmacopeia[21].

The uniformity of dosage unit assay evaluates the drug distribution at each unit dose. The percentages found in relation to the declared value for samples composed of T4 capsules were: (a) dose of 200 µg - 80.61% ; 91.78%; 92.29%; 78.68%; 87.00%; 104.01%; 85.43%; 101.98%; 77.78%; 72.66%; Acceptance Value (AV) of 36.16; (b) dose of 25 µg - 760.14%; 811.12%; 575.57%; 707.97%; 720.24%; 647.83%; 705.68%; 751.58%; 689.80%; 739.48%; AV 764.98.

According to the Brazilian Pharmacopeia[16], the product meets the unit dose uniformity test if the Acceptance Value calculated for the first ten tested units is not greater than *L*1, where L1 = 15. However, both have AVs above that threshold, which shows lack of uniformity.

Some 200 µg capsules had values below the minimum allowed (90.00%). This quality deviation could cause therapeutic inefficacy in the treatment. The overdoses found for 25 µg capsules with values up to 811.12%, where the maximum permitted value is up to 110.00% in relation to the declared value, may cause poisoning and other damages to the user's health. The results showed a great variability of dosage in the two samples, indicating the absence of GCP and lack of a quality assurance system.

CONCLUSIONS

This work illustrates the detection of quality deviations in compounded drugs from different pharmacies due to pharmaceutical and technical errors. The study also reveals the absence of minimum quality control tests in the compounded products that must be performed in the compounding pharmacy or in an outsourced laboratory with technical competence. This suggests the absence of GCP enforcement.

The results can also be attributed to the lack of calibration and/or suitability of the equipment used in the compounding process, lack of training and education of the technical staff, lack of SOPs throughout the compounding process, from the receipt and evaluation of the medical prescription to the production and dispensation of the compounded drugs, in addition to the lack of quality assurance procedures for the compounded drugs.

Because of these occurrences and other episodes, it is the responsibility of the health authorities to keep constant supervision of compounding pharmacies, to verify the implementation of GCPs, as well as the establishment of a documented and monitored Quality Assurance System, as required by RDC n. 67/2007. In this way, it is possible to guarantee the quality of the compounded drugs in order to prevent health risks to the population.

REFERENCES

1. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução Nº 67, de 8 de outubro de 2007. Dispõe sobre Boas Práticas de Manipulação de Preparações Magistrais e Oficinais para Uso Humano em farmácias. Diário Oficial União. 9 out 2007.
2. Silva ACP, Oliveira CVS, Cavalheiro MVS, Miranda MCC. Desafios para a rede nacional de laboratórios de vigilância sanitária: o caso dos medicamentos manipulados. Cienc Saúde Coletiva. 2010;15(3):3371-80. https://doi.org/10.1590/S1413-81232010000900012
3. Conselho Federal de Farmácia - CFF. Dados 2016. Brasília, DF: Conselho Federal de Farmácia; 2016[acesso 6 jul 2017]. Disponível em: http://www.cff.org.br/pagina.php?id=801&menu=801&titulo=Dados+2016
4. Paes M. Manipulação de remédios vem registrando expansão. Brasília, DF: Conselho Federal de Farmácia; 2013[acesso 6 jul 2017]. Disponível em: http://www.cff.org.br/noticia.php?id=1280
5. Erros e episódios que não podem se repetir na manipulação de medicamentos. Portal Educação. 2017[acesso 7 ago 2017]. Disponível em: https://www.portaleducacao.com.br/conteudo/artigos/enem/erros-e-episodios-que-nao-podem-se-repetir-na-manipulacao-de-medicamentos/44373
6. Marcatto AP, Lamim R, Block LC, Brasolin TMB. Análise de cápsulas de captopril manipuladas em farmácias. Rev Cienc Farm Básica Apl. 2005;26(3):221-5.
7. Markman BEO, Koschtschak MRW, Auricchio MT. Otimização e validação de método farmacopeico para verificar possíveis desvios de qualidade de matérias-primas e cápsulas manipuladas contendo hormônios tireoideanos. Rev Inst Adolfo Lutz. 2007;66(3):268-74.
8. Magnelli RF, Markman BEO, Koschtschak MRW, Wu EM, Oliveira DM, Oliveira ES. Problemas reincidentes na manipulação de fármacos de baixo índice terapêutico. Bol Inst Adolfo Lutz. 2010;7(79):6-11.
9. Fundação Ezequiel Dias - FUNED. Intoxicação medicamentosa: avaliação confirma presença do anti-hipertensivo no lugar do antifúngico. Belo Horizonte: Fundação Ezequiel Dias; 2017[acesso 2 nov 2017]. Disponível em: http://www.funed.mg.gov.br/noticias/intoxicacao-medicamentosa/
10. BulasMed. Besilato de anlodipino: Novartis. 2015[acesso 2 nov 2017]. Disponível em: http://www.bulas.med.br/bula/7341/besilato+de+anlodipino.htm
11. Yano HM, Bugno A, Auricchio MT. Intoxicação por colchicina em formulação manipulada. Rev Inst Adolfo Lutz. 2008;67(3):234-6.
12. Yano HM, Trujillo LM, Farias FF, Del Bianco MB, Guardia RCA, Auricchio MT. Superdosagem de solução oftálmica de nitrato de prata 1% em produto manipulado. Bol Inst Adolfo Lutz. 2011; 21(2):39-40.
13. Yano HM, Guardia RCA, Farias FF, Del Bianco MB, Auricchio MT. Problematização de rotulagem em produtos farmacêuticos manipulados de acordo com a legislação vigente. Bol Epidemiol Paul. 2011;8(88):23-6.
14. Yano HM, Farias FF, Del Bianco MB, Auricchio MT, Oliveira JGA, Gomes PF et al. Adulteração de matéria-prima de uso controlado, encontrada em farmácia de manipulação, pela autoridade sanitária. Bol Epidemiol Paul. 2012;9(101):16-23.
15. Secretaria de Estado da Saúde. Instituto Adolfo Lutz - IAL. São Paulo: Secretaria de Estado da Saúde; 2017[acesso 15 dez 2017]. Disponível em: http://www.ial.sp.gov.br/
16. Agência Nacional de Vigilância Sanitária - Anvisa. Farmacopeia Brasileira. 5a ed. Brasília, DF: Agência Nacional de Vigilância Sanitária; 2010.
17. Longman GF. The analysis of detergents and detergents products. London: John Wiley & Sons; 1977.
18. Instituto Nacional Controle de Qualidade em Saúde - INCQS. Procedimento Nº 65.3110.014, de 26 de outubro de 2015. Determinação de Tensoativo aniônico e catiônico: Revisado 11, Manual 4.3. Rio de Janeiro, Instituto Nacional Controle de Qualidade em Saúde; 2015.
19. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução Normativa Nº 1, de 27 de novembro de 1978. Aprova as Normas a serem obedecidas pelos detergentes e seus congêneres. Diário Oficial União. 27 nov 1978.
20. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução RDC Nº 40, de 05 de junho de 2008. Aprova o Regulamento Técnico para produtos de limpeza e afins harmonizado no âmbito do Mercosul através da Resolução GMC Nº 47/07. Diário Oficial União. 6 jun 2009.
21. The US Pharmacopoeial Convention The US Pharmacopoeia. 40th. ed. Rockville: The US Pharmacopoeial Convention; 2017.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.