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Preliminary assessment of the quality of the fluoxetine commercialized by pharmacies of manipulation from the city of Belo Horizonte/Brazil

Avaliação preliminar da qualidade da fluoxetina comercializada por farmácias de manipulação em Belo Horizonte/MG

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ABSTRACT

In this study, fourteen samples of fluoxetine being commercialized by thirteen different establishments of the network of magistral pharmacies in the City of Belo Horizonte/MG were assessed. The sampling corresponds to 47,0% of the total 30 different units of preparation of the city, which corresponds to about 180 points of sale. Analyses for determining weight, identification, active ingredient content and uniformity of dosage units were performed by the State Foundation Ezequiel Dias (FUNED /MG) based on methodologies described by reference pharmacopoeias. Irregularities, on the labeling and the content testing, were observed in some samples. It was also investigated, through the technique of neutron activation analysis (NAA), the presence and concentrations of metals and other inorganic impurities. The results showed the presence of elements such as As, Br, Cr Co, Cr, Hf and others, that even at low concentrations, may be harmful to human health if consumed steadily for a long term.

KEYWORDS: Quality Control; Fluoxetine; Good Practice of Manipulation; Sanitary Surveillance

RESUMO

Neste trabalho, foram avaliadas 14 amostras de fluoxetina comercializadas por 13 estabelecimentos diferentes da rede de farmácias magistrais em Belo Horizonte/MG. A amostragem obtida representa 47,0% do total de 30 unidades de preparação distintas na cidade e corresponde a cerca de 180 pontos de venda. Foram realizadas análises de determinação de peso, identificação, teor de princípio ativo e uniformidade de doses unitárias. As análises foram realizadas pela Fundação Estadual Ezequiel Dias (Funed/MG) com base nas metodologias descritas nas farmacopeias de referência. Foram observadas irregularidades em algumas amostras como na rotulagem e ensaio de teor. Foi também investigada a presença e concentração de metais e outras impurezas inorgânicas através da técnica de análise por ativação neutrônica (AAN). Os resultados mostraram também a presença de elementos como As, Br, Co, Cr e Hf que, mesmo em baixas concentrações, podem ser prejudiciais à saúde humana se consumidos de forma constante durante longo prazo.

PALAVRAS-CHAVE: Controle de Qualidade; Fluoxetina; Boas Práticas de Manipulação; Vigilância Sanitária

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INTRODUCTION

Fluoxetine ($C_{17}H_{18}F_3NO$) is a selective serotonin reuptake inhibitor (5-HT) with serotonergic action and one of the most commonly prescribed antidepressants currently available. Selective serotonin reuptake inhibitors are used to treat several psychiatric disorders, like depression, anxiety, panic attacks and obsessive-compulsive disorder[1].

Compounded fluoxetine occupies an increasingly significant market share. This is in part due to the alternative of customized prescription and dosage, including association with other drugs, and a lower cost in comparison with the reference products. For these reasons, compounding pharmacies play an important social role in the supply of drugs to the population[2,3,4,5,6,7]. Additionally, several studies have shown that compounded drugs have good acceptance among the population[8,9,10,11,12,13,14].

Because of some clear signs of excess consumption and misuse, notably for weight loss, fluoxetine is part of the "Resultados 2009" report of the Brazilian Agency of Sanitary Surveillance (Anvisa)[15], with data from the National Controlled Products Management System (SNGPC). According to SNGPC data, in 2009 the consumption of compounded fluoxetine was higher than the consumption of its manufactured version in Brazil. Minas Gerais was classified as the third state with the highest consumption of fluoxetine hydrochloride-based compounded products. However, the limitations of the study should be considered[15].

Several problems related to compounded drugs make a more rigorous assessment of the quality and safety of these products necessary in the context of public health[16,17,18]. There is a growing trend in increasing quality requirements, which involve ethical and regulatory issues, but also an increasingly competitive pharmaceutical market[17].

Several studies have confirmed a number of problems in the production and marketing of compounded drugs, including preparations containing fluoxetine hydrochloride[16,17,18,19,20,21]. These quality problems are related to several factors, such as: the use of inadequate compounding processes, failure to carry out analyses that attest to the quality and conformity of the raw materials, and the lack or insufficiency of professional training[22,23,24].

The main cause of quality issues inherent in the capsule drug compounding process is the loss of powder during the grinding, sieving, blending and filling operations of the hard gelatin shells. Errors in calculation and weighing of formulation components, mistakes made by the pharmacists and the use of damaged or poorly calibrated equipment can also affect the process and consequently the quality of the final product. Problems related to the mixing and granulometric variation of the raw materials can lead to variations in content uniformity, since these variables influence the pharmacotechnical parameters of solid pharmaceutical products[26,27,28].

Furthermore, some studies have also shown the presence of inorganic impurities in compounded drugs and in raw materials used in compounding pharmacies[29,30]. It is known that continuous exposure to certain elements can lead to various health problems. In addition to their inherent toxicity, these elements may worsen some pathologies and influence the stability of certain drugs. The consequence is the decrease in the bioavailability of the active ingredient and interference in the absorption of essential elements[28,29,30,31,32,33,34,35].

Inorganic impurities observed in medicinal products are inadvertently introduced during the manufacturing process, in the storage of the raw material or of the finished product[19,36]. However, elemental evaluation of compounded drugs is not required by the current legislation. According to RDC n. 67/2007[37], compounding pharmacies should follow some procedures to individually analyze the batches of raw material they receive. This includes the verification of organoleptic characteristics, pH, average weight, viscosity, alcohol content or grade, density, volume, active ingredient content, dissolution and microbiological purity.

In this work, we analyzed the physico-chemical quality and the presence of inorganic contaminants in samples of compounded fluoxetine marketed in compounding pharmacies of the city of Belo Horizonte, Brazil. The objective was to provide the responsible bodies with information to help them improve control mechanisms and ensure adequate quality and safety for consumers.

METHOD

We analyzed a total of 14 samples from 13 different stores. For the physico-chemical quality evaluation, we considered nine samples (A-I); for inorganic contamination, five samples (A, J-M) were considered. The samples (A-I) were collected by the Sanitary Surveillance of the state of Minas Gerais (VISA/MG) as part of the quality control program for compounded drugs conducted by the Ezequiel Dias Foundation (Funed/MG) in partnership with VISA/MG. Funed/MG's Laboratories for Quality Control of Medicines, Sanitation and Cosmetics are part of the network of Laboratories of the Public Health Center of Minas Gerais (Lacen/MG). All of them are accredited with the Brazilian Network of Health Analytical Laboratories (Reblas), the National Institute of Metrology, Standardization and Industrial Quality (Inmetro) and the National Accreditation Organization (ONA). In 2011, it was officially recognized by the World Health Organization (WHO) as a reference in the quality control of medicines for the Americas.

Each sample contained 15 to 40 mg/capsule of fluoxetine hydrochloride. Samples (J-M) were acquired anonymously using a medical prescription obtained especially for this project. In this case, each sample contained 10 mg/capsule of fluoxetine hydrochloride. Because of operational limitations, it was not possible to carry out both physico-chemical and inorganic contamination analyses in the same set of samples.

Data from 2013 indicated the existence of 180 compounding pharmacies or stores in the city of Belo Horizonte. However, several points of sale are part of the same network of pharmacies and the

compounded products are obtained from the same laboratory. The number of different compounding units is smaller than 30. Since the 13 establishments are part of different pharmacy networks, our sampling covers 33% of all establishments. The choice was made according to the geographical location, which reflects different customer profiles and price ranges. These are possible impact factors in the quality of compounded products. The samples were obtained between June and July and the analyses were carried out between October and December of 2013.

The physico-chemical quality control analyses were performed at the Laboratory of Physical and Chemical Quality Control (determination of weight, identification, content of active principle, related compounds – when applicable – and unit dose uniformity) of the Medicine, Sanitation and Cosmetic Service of Funed's Octávio Magalhães Institute, considered as the Central Laboratory of Public Health of Minas Gerais. Analyses of physico-chemical quality control, appearance and labeling were performed according to the tests and methodologies described in Table 1.

The analysis of active ingredient content was made by high performance liquid chromatography (HPLC) (Figure). In the fluoxetine assay, the contents of five capsules were mixed.

The unit dose uniformity test evaluates the amount of active component in individual units of the batch and verifies whether this quantity is uniform in the tested units.

The aspect analysis describes the physical characteristics of the drug, for example, white and green hard capsule containing white pellets. In the case of compounded drugs, it is a purely descriptive analysis. In comparison, manufactured drugs are analyzed based on the data contained in the drug registration in Anvisa.

The label check confirms whether the required information is in accordance with RDC n. 67/07[37]. This information includes prescriber's name, patient's name, formulation registration number in the Prescription Book, date of compounding, expiration date and more. Detailed description of the methodology employed in all analyses can be found in the work of Melo[40].

The determination of inorganic impurities was carried out at the Center for the Development of Nuclear Technology (CDTN) and at the Nuclear and Energy Research Institute (IPEN) in São Paulo, Brazil, using the neutron activation analysis technique (NAA)[23]. The experimental parameters used in each laboratory are described in Table 2. The main advantage of NAA is the possibility of determining several elements simultaneously at lower costs and in a shorter time[23].

We did pharmacopoeia tests for determination of weight, identification, content and uniformity of unit doses to evaluate the physico-chemical quality of the drugs[36,37].

The product labeling analysis was also carried out according to the current Good Compounding Practices document: RDC n. 67/2007[37]. All analyses were carried out from March 2011 to February 2013.

Table 1. Tests performed by the Ezequiel Dias State Foundation - Funed and references.

Test	Methodology (Reference)
Aspect	-
Labeling	RDC n. 67 (2007)[37]
Determination of weight	Brazilian Pharmacopoeia V (2010)[38]
Identification	USP 34 (2010)[39]
Content	USP 34 (2010)[39]
Uniformity of unit doses	USP 34 (2010)[39]

RESULTS AND DISCUSSION

Of the nine label analyses we carried out, pharmacies A to I, only one, pharmacy C, was satisfactory. The pharmacy samples found to be unsatisfactory did not present the components of the formulation and their respective amounts in the primary packaging, which is required by RDC n.67/2007[37]. Additionally, in the samples of pharmacies A, D, G and I, there were mistakes in the presentation of information identifying the establishment, such as: absence, error or duplication of addresses, absence or error of CNPJ, no identification of the head pharmacist. This information is important to promote the correct use of medicines and the packages must comply with the current legislation[43].

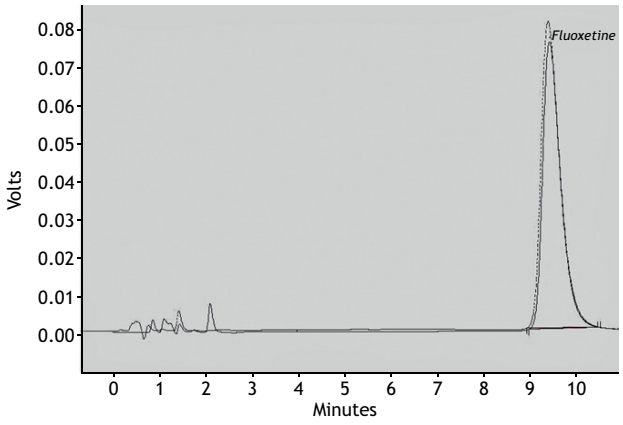

Figure. Fluoxetine content test chromatogram.

Table 2. Experimental parameters used in the NAA performed by the CDTN and IPEN Institutes.

Experimental data	CDTN	IPEN
Reactor/Power	TRIGA IPR-R1/100kW	IEA-R1/5MW
Gamma spectrometry	HPGe (Canberra GC 2018)[41]	HPGe (Canberra GC 2018)[31]
Data acquisition system	Gennie 2000, v.3.1 (Canberra)[42]	Gennie 2000, v.3.1 (Canberra)[42]
Mass of samples (mg)	200-250	180
Number of samples analyzed	3	5
Thermal flow ($cm^{-2}.s^{-1}$)	6,4 x10^{11}	5,0 x10^{11}
Irradiation time (h)	8	18

AAN: Neutron activation analysis; CDTN: Nuclear Technology Development Center; IPEN: Energy and Nuclear Research Institute.

Regarding the aspect, the hard capsules of fluoxetine hydrochloride were of various colors and contained white powder. All the analyzed samples were satisfactory for the tests of identification of the active principle and weight determination, as presented in Table 3.

In relation to the content assay presented in Table 4 we can see that the samples from pharmacies A and I were unsatisfactory. Samples considered to be unsatisfactory, with an active ingredient content of less than 90% of the declared value, are worrying because this may lead to ineffective pharmacological treatment, with absence or modification of the expected therapeutic response[38,44]. According to the current health-related legislation, analyses of description, appearance, organoleptic characteristics and average weight are necessary for sound compounded preparations. No content testing is required in the routine compounding of these preparations.

However, as evidenced by the results obtained in this study, the analyses required by the health-related legislation are not sufficient to attest to the quality of compounded drugs.

After all, if only the parameters required by the legislation were considered, the drugs in establishments A and I, satisfactory in determining weight but unsatisfactory in content, would be considered fit for consumption and could lead to risks to patients' health.

The results for the unit dose uniformity assay (content uniformity) were satisfactory for all samples, as shown in Table 5.

This assay enables us to measure the amount of active component in individual units of the batch – while the assaying evaluates a pool of the drugs – and verify whether this amount is uniform in these units. The content uniformity test is based on assaying the individual content of active substances in a number of individual unit doses (10 or 30 capsules) to determine whether the content is within specified limits.

In Table 5, VI_{min} is the minimum individual value found, VI_{max} is the maximum individual value found, $\bar{A}$ is the average of the individual values expressed in % of the declared value, σ is the relative standard deviation and AV is the acceptance value, calculated to be the determinant value for approval or rejection in the assay.

Comparing the results of the acceptance value among the samples of the different establishments, we can observe that, although satisfactory in this test, the samples from pharmacies A and I presented closer values to the acceptable limit (AV < 15). This can be explained by the fact that the units we tested had a less homogeneous content. Samples from pharmacies A and I failed this test.

The results of the investigation of inorganic impurities using the NAA[36] technique are presented in Tables 6 and 7. Because of logistic limitations, it was not possible to carry out the analyses in the two laboratories with the same set of samples. This fact confirms the heterogeneity of the samples and explains the differences observed in the results of the two laboratories for the concentrations of the same element in different samples from the same pharmacy.

Contamination of medicinal products by inorganic impurities can occur due to many reasons, like the introduction of raw materials, reagents, catalysts, solvents, electrodes, pipes and other types of equipment used in the synthesis process, exposure to particles in the air or in some container, among others[45]. The presence of elements such as Ca, Mg and Na may be expected since these are components of a variety of fillers, like sodium metabisulfite, sodium lauryl sulfate, magnesium stearate, calcium phosphate and the like[46]. Other elements found in pigments such as Fe in iron oxide and dyes such as Ca and Na, calcium salt, calcium carbonate and sodium salt may be in the raw materials present in the synthesis of the active ingredient[37]. Non-essential elements considered to be impurities such as As, Br, Cl, Cr, Mn, Sb, Sc, Th and Zn found

Table 3. Results of determination of mean weight of fluoxetine hydrochloride in mg/capsule and the maximum and minimum variations, in %, per pharmacy.

Pharmacy	AW (mg/capsule)	D_{max}	D_{min}	Result
A	157.1 ± 2.4	5.5	6.7	Satisfactory
B	130.7 ± 1.8	6.6	3.6	Satisfactory
C	154.5 ± 1.5	4.3	4.8	Satisfactory
D	136.1 ± 1.8	4.9	6.2	Satisfactory
E	129.2 ± 2.1	8.4	7.8	Satisfactory
F	115.6 ± 1.5	6.7	3.4	Satisfactory
G	246.1 ± 1.4	1.8	1.9	Satisfactory
H	114.6 ± 1.2	4.3	3.9	Satisfactory
I	88.0 ± 1.9	7.5	7.2	Satisfactory

AW: Average weight; D_{max}: Maximum variation; D_{min}: Minimum variation.

Table 4. Results of the labeled contents (T_R) and measured (T_M) in mg / capsule and T_M in % of fluoxetine hydrochloride in the samples from pharmacies A-I.

Pharmacy	T_R	T_M (mg/capsule)	T_M (%)	Result
A	15	13.1 ± 2.1	87.5	Unsatisfactory
B	20	18.9 ± 0.9	94.7	Satisfactory
C	20	19.5 ± 0.5	97.5	Satisfactory
D	20	20.3 ± 1.3	101.4	Satisfactory
E	20	19.2 ± 0.9	96.2	Satisfactory
F	20	20.1 ± 1.0	100.6	Satisfactory
G	40	38.0 ± 0.6	95.0	Satisfactory
H	20	21.1 ± 0.6	105.5	Satisfactory
I	20	17.0 ± 0.4	85.0	Unsatisfactory

T_R: labeled content; T_M: measured content.

Table 5. Uniformity of unit dose results for fluoxetine hydrochloride.

Pharmacy	$VI_{min.}$ (%)	$VI_{max.}$ (%)	$\bar{A}$ (%)	σ	AV	Result
A	88.5	97.3	91.9	3.1	14	Satisfactory
B	91.1	97.3	94.6	2.1	8.9	Satisfactory
C	100.3	106.9	103.1	2.2	10	Satisfactory
D	95	106.4	99.4	3.3	8.9	Satisfactory
E	90	109	98.6	4.7	11.3	Satisfactory
F	96.9	103.7	100.2	2.6	6.4	Satisfactory
G	92.4	96.4	94.0	1.2	7.4	Satisfactory
H	100.2	111.4	105.9	3.6	13	Satisfactory
I	85.8	96.3	92.3	3.8	14.7	Satisfactory

AW: Average weight; D_{max}: Maximum variation; D_{min}: Minimum variation.

Table 6. Results of NAA performed by IPEN for samples A to M, and EMEA specification. Values in ppm (μg.g^{-1}).

Element	A	J	K	L	M	EMEA specification
	Concentration ± Uncertainty	Concentration ± Uncertainty	Concentration ± Uncertainty	Concentration ± Uncertainty	Concentration ± Uncertainty	
As	< 0.02	< 0.02	0.10 ± 0.01	< 0.02	< 0.02	-
Br	7.3 ± 0.1	3.8 ± 0.1	1.6 ± 0.0	6.3 ± 0.0	0.6 ± 0.0	-
Ca	117 ± 19	90 ± 9	112 ± 16	53.5 ± 5.8	53 ± 6	-
Cl	53,653 ± 1,358	12,913 ± 325	8,863 ± 203	14,208 ± 322	17,098 ± 418	
Cr	0.19 ± 0.01	2.4 ± 0.1	0.5 ± 0.1	0.7 ± 0.1	0.3 ± 0.1	25
Fe	< 1.3	11.9 ± 0.4	226 ± 2	5.1 ± 1.0	3.4 ± 0.2	1,300
Mg	< 183	< 183	13,858 ± 333	< 183	< 183	
Mn	< 0.63	< 0.63	3.9 ± 0.8	< 0.6	< 0.6	250
Na	5.2 ± 0.3	1,674 ± 30	259.5 ± 5	95 ± 11	135 ± 11	-
Zn	0.25 ± 0.01	1.0 ± 0.1	1.0 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	1,300

NAA: Neutron activation analysis; IPEN: Energy and Nuclear Research Institute; EMEA: European Medicines Agency.

Table 7. Results of NAA performed by CDTN for samples of fluoxetine from pharmacies J, K and N and EMEA specification. Values in ppm (μg.g^{-1}).

Element	J	K	N	EMEA specification
	Concentration ± Uncertainty	Concentration ± Uncertainty	Concentration ± Uncertainty	
Al	166 ± 6	325 ± 12	226 ± 8	-
Br	5.9 ± 0.2	1.1 ± 0.1	2.1 ± 0.1	-
Cl	7,843 ± 283	5,771 ± 218	5,883 ± 213	-
Co	0.11 ± 0.01	0.44 ± 0.02	0.10 ± 0.01	-
Cr	0.95 ± 0.11	1.4 ± 0.1	1.7 ± 0.1	25
Fe	33 ± 5	491 ± 19	49 ± 6	1,300
Hf	0.15 ± 0.01	0.19 ± 0.02	0.19 ± 0.01	-
K	87 ± 4	100 ± 16	26 ± 3	-
La	0.060 ± 0.001	0.10 ± 0.01	0.05 ± 0.01	-
Mg	< 124	15,160 ± 951	< 73	1,300
Mn	< 0.7	4.4 ± 0.3	< 0.4	250
Na	1,115 ± 4	126 ± 44	440 ± 15	-
Sb	0.13 ± 0.01	0.23 ± 0.01	0.13 ± 0.01	-
Zn	0.20 ± 0.07	2.47 ± 0.09	0.79 ± 0.3	1,300

NAA: Neutron activation analysis; CDTN: Nuclear Technology Development Center; EMEA: European Medicines Agency.

in the samples are likely to originate from the processes of production of raw materials and handling of the drug[30,31,33]. RDC n. 67/2007[37] does not require that contaminants be analyzed in the raw materials received by the pharmacies.

We observed that, considering the intake limits specified by the European Medicines Agency (EMEA) for some elements like Cr, Fe, Mn and Zn, all samples had lower concentrations and seemed satisfactory[37,45].

However, the assessment of inorganic impurities and a possible long-term effect of exposure to low concentrations of some elements, considering the use of continuous use of some drugs, should not be ruled out by exposure to other sources like food, water, air, and others. In addition, there are several interfering variables, like bioavailability of the elements, physiological conditions, health status, age, gender, diet and genetic variation of the exposed organism. Heavy metals typically have a chronic toxicological impact that can be difficult to detect and attribute to a single root cause[37,45,46,47,48].

CONCLUSION

Preliminary results obtained with samples marketed by compounding pharmacies in Belo Horizonte confirm the concern with the quality of compounded preparations containing fluoxetine hydrochloride.

Only one of nine samples presented satisfactory results in the label analysis. Two samples failed the content test and two were approved in the uniformity test, but with acceptance values (AV) that were very close to the limit. These results confirm the need for more investment and more initiative from the stakeholders to ensure the quality of compounded drugs.

The investigation of the presence of inorganic contaminants in the samples revealed the presence of several non-essential elements, like As, Br, Cl, Cr, Mn, Sb, Sc, Th and Zn. Other elements normally present in drug samples such as Fe, Ca and Na were also found in the samples.

Even at low concentrations, the presence of these elements reinforces the need for quality control of compounded drugs as well as the quality of their raw material.

The legislation does not require the determination of possible contaminating inorganic elements. In any case, it would not be feasible to perform it in each and every compounding pharmacy. As far as we know, the certificates of origin of raw material do not bring information about that either. Therefore, it is important that sanitary surveillance services and partner laboratories be able to perform this task by sampling the raw material that is received.

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Conflict of interest

The authors report that there is no potential conflict of interest with peers and institutions, political or financial, in this study.