Chapter 11

Quality Control of Formulated Medicines

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1. Introduction

A pharmaceutical drug is technically obtained or prepared for prophylactic, curative, palliative or diagnostic purposes. The final product must meet quality standard, be safe and effective. In Brazil, there is a high demand for formulated drugs. This is mainly due to their lower price compared to manufactured drugs, evidenced by the rapid growth – an increase of 350% from 1998 to 2010.

Even after the ANVISA's (Agency National Health Surveillance) establishment of the new handling standards to be followed by the magistral pharmacies, several serious cases, including death reports, caused by the consumption of formulated drugs have recently become public [1-5].

Other problems related to this subject occurred in 2004, when deaths caused by manipulated medicines of low therapeutic index (clonidine and levotiroxine) led ANVISA to modify the regulation for manipulated medicines. The concentration of each compound was not totally assured and the contamination by impurities, not included in the original formula, were present in the final product.

In a previous work, we have also observed the presence of impurities – such as metals - in different kinds of medicines. The ingestion of metals, even at low levels, can be very harmful to humans. Besides this, the long-term uptake of some drugs is also risky. This should require attention and surveillance from the public health-related agencies [6-10].

The quality and safety of drugs must follow the specifications described in the official compendia - among them, the pharmacopoeias. Medicines cannot contain impurities or

other substances that endanger the patient's health. According to the second edition of the Brazilian Pharmacopoeia National Formulary [1], to ensure safety, efficacy and quality of the handled products it is necessary correct calculations, exact measurements, and adequate conditions and procedures of preparation. The prudent judgment of the pharmacist, who must be a qualified professional for this purpose, is another fundamental aspect. Additionally, an appropriate profile with a proven stability must be sought in the literature [11-14].

The requirements of sanitary legislation and quality control of raw materials for magistral solid preparations are:

- raw material: character sensory, solubility, pH determination, melting point, density, weight and volume; analysis report of manufacturer/supplier;
- raw material of vegetal origin: organoleptic characters, solubility, pH determination, melting point, density, weight and volume, evaluation of vendor analysis report;
- manipulated product: solid dosage forms: description, appearance and organoleptic characteristics, determination of average weight

The legislation also determines that all pharmacies must perform analyzes every two months of at least one of the formulas containing drug(s) ≤ 25 mg of drugs. The priority is to those that contain ≤ 5 mg of drugs. The legislation establishes special quality control requirements for preparations of substances with low therapeutic index, like hormones, antibiotics and cytotoxic drugs, homeopathic products, and sterile products. The raw materials used in sterile preparations must also be analyzed [15-17].

The Legislation on Good Practices for Handling does not require impurity tests for the raw materials received by the pharmacies. It is only necessary to check the certificate of a qualified supplier – issued in accordance with methods described in the pharmacopoeia, which are only suitable for the detection of some elements (Ag, As, Bi, Cd, Hg, Mo, Pb, Sb, and Sn) [18].

Quality control tests for the products handled do not include detection and quantification of impurities. Moreover, the analysis required for formulated preparations allow limited conclusions about the quality of the process, since they do not testify the homogeneity of the active principle directly, but only as to the uniformity of filling of the capsules. So, a particular formulation can have the acceptance criteria for average mass, standard deviation and coefficient of variation but not the uniformity of this active content in the capsules [19].

Periodic reviews performed every two months for formulated drugs do not statistically have significant value, so that a reliable conclusion about the quality of formulated drugs can not be reached [20]. The analysis of thirty batches of 20 mg of Sinvastatin medicine manipulated in pharmacies of Belo Horizonte, showed that only fourteen of them, met the quality standard required by pharmacopeia. Thus, the therapeutic efficacy of 53% of the analyzed products can not be totally dependable [21].

In this study, the quality of medicines Omeprazole and Enalapril Maleate from five (5) different magistral pharmacies was evaluated according to the methodology described in pharmacopoeia. The analyses for mass determination, identification of active principle, content, content uniformity and related compounds were performed.

The target drugs, Omeprazole and Enalapril Maleate, were chosen because of their representativeness of consumption and availability of related reference data in the pharmacopoeias.

In order to evaluate the presence and concentration of chemical elements, the technique used in this study was neutron activation analysis (NAA), applying the k_0-standardization method [23-25]. The neutron activation analysis is a very sensitive and reliable multielemental technique, suitable for determination of the elements such as: As, Ba, Br, Ca, Ce, Cl, Co, Cr, Eu, Fe, Hf, Mg, Mn, Na, Sb, Sc, Sm, Ti and Zn, in different drugs [14]. The technique is based on the principle that when the material is irradiated by neutrons, some elements with suitable nuclear characteristics become radioactive isotopes. Thus, the concentration of each element can be determined by counting the respective radiation emitted by the corresponding radionuclide [26].

The results described here are part of a wider project which also includes the analyses of Fluoxetin and Sinvastatin medicines and will be published briefly.

2. Quality control of formulated drugs

2.1. The pharmacopeia

The 5th edition of the Brazilian Pharmacopoeia [27] defines quality control as: "The set of measures to ensure, at any time, the batch production of medicines and other products that meet the standards of identity, activity, content, purity, efficacy and safety." According to Resolution RDC Nº. 67, October 8, 2007 [15], which provides the Technical Regulation establishing the Good Handling Practices in Pharmacies (Good Compounding Practices) quality control of magistral and officinal preparations, is given by the completion of at minimum, the tests described in Table 1, according to the Brazilian Pharmacopoeia or other Official Compendium recognized by the National Health Surveillance Agency (ANVISA).

Results of tests must be recorded in the same order of handling, in addition to other relevant information. The pharmacist must evaluate the results to approve or not the preparation for dispensing. Each pharmacy is responsible for the quality of magistral preparations that handles, keeps, transports and dispenses. Raw materials should be checked in its receipt and moved to quarantine soon after, until the release of the reports of quality control. In the absence of pharmacopoeia monograph, the scientific literature should be used as a reference, and only with the lack of literature, the specification provided by the supplier may be used. All results must be written and stored [15].

Preparation	Test
Solid	Description, appearance, organoleptic characteristics, average mass
Semi-solid	Description, appearance, organoleptic characteristics, pH (where applicable), mass
Non-sterile liquid	Description, appearance, organoleptic characteristics, pH, mass or volume before filling

Table 1. Tests for quality control of magistral drugs

However, some studies also show that the rule of Good Practices on Handling does not answer and does not guarantee the quality of compounded drugs [20].

2.2. Analyses performed

The analyses of quality control were performed at the Laboratory for Quality Control of Chemical Physics Drug, and Cosmetic Sanitizing of the Ezequiel Dias Foundation (FUNED). The following tests were performed [15,27,28]:

- Aspect;
- Identification ;
- Labeling;
- Content;
- Related compounds;
- Dosage uniformity;
- Unit Change in mass;

The test of aspect is just a visual description of the product to be analyzed, coloration of the capsule and its content.

The test of identification allows determining the presence of the active principle in the product analyzed. It is performed through the high performance liquid chromatography (HPLC) [28].

The analysis of content aims to verify whether the drug has a dose of active ingredient on the label provided and used to quantify the active ingredient in the product analyzed. This test is performed according to the pharmacopoeia for each product, and may be performed in the ultraviolet and visible spectrophotometry, by high performance liquid chromatography, among other methods. The test uses usually ten to twenty capsules and each capsule analyzed separately, but the "pool" of these. There are limits specified in the monograph, which should be within the active drug, usually 90 to 110%. Results below the limit can result in ineffective therapy and above, intoxication, depending on the drug analized [28].

The analysis of related compounds determines the amount of by-products of synthesis of the substance and / or its degradation products and / or contaminants from the process of

obtaining the substance which can be normally found within a specified limit. This test is done only when specified in the pharmacopoeia.

The variation of the mass allows checking the uniformity of mass between units within a batch. For products in hard capsules should be weighed individually, twenty units, the contents of each one should be removed, properly cleaned and reweighed. The mass content of each capsule is determined by mass difference between the full and the empty capsule. Then the average mass of the contents can be determined. For hard capsules, the limit of variation is ± 10% of the mass corresponding to less than 300 mg. If the mass corresponds to 300 mg or more, the maximum range is ± 7.5%. It cannot be tolerated more than two units outside the limits specified in the official compendia, but none can be above or below twice the percentages indicated [27].

The uniformity of dosage units evaluate the uniformity of distribution of active component units in a single batch can be determined by two methods: mass variation and content uniformity. The mass variation test is only applicable in specific cases. The test for content uniformity is based on the content of each active ingredients in a number of unit doses in order to determine whether the content is within specified limits, being applicable in all cases [28].

3. Methodology

3.1. High performance liquid chromatography

In this study the identification tests, content, related compounds and content uniformity was performed by high performance liquid chromatography (HPLC) according to the specifications of literature [28]. The chromatograph Shimadzu detector was coupled to molecular absorption spectrophotometry in the ultraviolet-visible Perkin Elmer Lambda 25 model, Class-VP software. All chemical reference substances (SQR) were purchased from USP (The United States Pharmacopeia).

To analyze the Enalapril Maleate, L7 C_8 column (4.6 mm x 25 cm x 5 mm) was used. Isocratic elution was performed with a buffer monobasic sodium phosphate pH 2.2 /acetonitrile at a ratio of 75:25. Solvents and solutions were degassed in ultrasonic bath (Elma Transsonic Digitals) and filtered through a Millipore membrane of 0.45 micrometers. Chromatography was performed at 50°C, flow rate of 2 $mL.min^{-1}$, with injections of 50 μL, detection at 215 nm and running time of 30 min. The calculations were based on the content of the samples obtained areas of the areas of the SQR of Enalapril Maleate. For related compounds the content of diketopiperazine compounds and enalaprilat was also calculated.

For omeprazole, L7 C_8 column (4.6 mm x 15 cm x 5 mm) was used. Elution was performed by mixing two solutions – solution A (6 g of glycine in 1500 mL water, pH 9) and solution B (acetonitrile and methanol, 85:15 ratio) – as shown in Table 3. Solvents and solutions were degassed in ultrasonic bath (Elma Transsonic Digitals) and filtered through a Millipore membrane of 0.45 micrometers. Chromatography was performed with a flow of 1,2 $mL.min^{-1}$, with injections of 10 μL, detection at 305 nm and running time of 30 min. The cal-

culations were based on the content of the samples obtained areas of the areas of the SQR of omeprazole.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0 – 20	88 → 40	12 → 60	Linear gradient
20 – 21	40 → 88	60 → 12	Linear gradient
21 – 25	88	12	Isocratic

Table 2. Parameters of elution of the HPLC analysis of Omeprazole

3.1.1. Results and discussion

a. Appearance, Identification and Labeling

Both, Omeprazole and Enalapril Maleate samples, showed similar aspects as their samples: hard capsule containing white pellets for Omeprazole, and hard capsule containing white powder varying only the color of the hard capsule used by each pharmacy. All samples, Omeprazole and Enalapril Maleate, were satisfactory for labeling and identification, confirming that the identity of the material was in accordance with the label from its packaging. In addition, all labels contain information provided by RDC Resolution Nº 67, October 8, 2007 [15]:

1. Name of the prescriber;

2. Name of the patient;

3. Registration Number of the formulation;

4. Data handling and shelf life;

5. Formulation components and their quantities;

6. Number of units;

7. Dosage;

8. Identification of pharmacy, full address and federal registration;

9. Name and professional register of the responsible person.

b. Related substances (Enalapril Maleate)

The test for related substances is performed only when described in the pharmacopeia of the compound to be analyzed, or another official compendium regulated by ANVISA [28]. For the Enalapril Maleate it is specified that no more than 5% of diketopiperazine and enalaprilat can be found in the final product. All samples of Enalapril Maleate were satisfactory for this analysis and the results are shown in Table 5.

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Pharmacy	Enalaprilat (%)	Diketopiperazine (%)	Enalaprilat + Diketopiperazine (%)
A	0.66	0.82	1.48
B	0.16	0.07	0.23
C	0.53	0.87	1.40
D	0.05	0.001	0.055
E	1.18	2.77	3.95

Table 3. Content of related compounds of Enalapril Maleate

c. Content

The reference values for the content of both drugs should not be less than 90% nor exceed 110% of the declared value, 10 mg and 20 mg for omeprazole and enalapril, respectively. The results for content of active ingredient are described in Table 6.

It can be observed that four from the five samples of omeprazole were unsatisfactory; two of them with content above the permissible and the other two with the content below. For the samples of enalapril, two were unsatisfactory, one exceeding the limit and the other with recommended content lower than expected, as showed in Table 6.

Pharmacy	Omeprazole (10 mg/caps)	Enalapril Maleate (20 mg/caps)
A	(11.3 ± 0.4) mg/caps or 112.7% declared	(18.5 ± 0.2) mg/caps or 92.6% of declared
B	(8.4 ± 2.2) mg/caps or 84.4% declared	(20.5 ± 0.1) mg/caps or 102.7% declared
C	(6.9 ± 2.6) mg/caps or 68.7% declared	(18.5 ± 0.1) mg/caps or 92.5% declared
D	(11.2 ± 0.1) mg/caps or 111.5% declared	(11.2 ± 4.3) mg/caps or 56.0% declared
E	(11.0 ± 0.2) mg/caps or 109.6% declared	(16.9 ±1.2) mg/caps or 84.7% do declared

Table 4. Final content of Omeprazole and Enalapril Maleate

d. Uniformity of the dosage unit

All Omeprazole samples were considered unsatisfactory for uniformity of the dosage unit. Three samples were satisfactory for Enalapril Maleate. The results for uniformity of dosage unit are described in Table 7 as contained in the final analysis report issued by FUNED. Variations in dose uniformity should not exceed 15% [28].

e. Mass Variation

The acceptable limit for the analysis of variation in mass of capsules, weighing less than 300 mg is ± 10% above the average mass, and it is tolerable no more than two units outside the specified limit and any unit may be above or below twice the percentages indicated. Thus, only a sample of Omeprazole was considered unsatisfactory. The results for the samples of Omeprazole and Enalapril Maleate are presented in Tables 8 and 9, respectively [27].

Pharmacy	Omeprazole (10 mg/caps)	Enalapril Maleate (20 mg/caps)
A	18.7%	7.8%
B	24.0%	14.2%
C	47.9%	10.6%
D	15.6%	14.0%
E	15.8%	46.5%

Table 5. Dose uniformity of the capsules of Omeprazole and Enalapril Maleate

Pharmacy	average weight (mg/caps.)	Lower	Higher
*A	220.4 ± 1.2	2.4	1.6
B	226.8 ± 5.8	9.5	8.7
C	210.0 ± 4.9	9.7	7.5
*D	119.0 ± 2.1	6.5	10.9
**E	120.7 ± 2.9	10.9	7.9

*One unit above the limit. ** Two units above the limit. Caps, capsules

Table 6. Variation (%) in mass of the capsules of Enalapril Maleate (20 mg/caps)

Pharmacy	average mass (mg/caps.)	Lower	Higher
*A	108.3 ± 3.0	7.1	15.1
B	195.4 ± 1.8	4.6	3.0
C	175.9 ± 3.0	9.1	4.7
**D	107.0 ± 7.0	15.3	40.8
***E	105.0 ± 2.1	10.6	7.2

*Two units above the limit. ** Four units above the limit. Unsatisfactory. *** One unit above the limit.

Table 7. Variation (%) in mass of the capsules of Enalapril Maleate (20 mg/caps)

From the ten samples analyzed, seven were rated as *unsatisfactory*, considering the analysis of aspect, mass variation, identification, related substances, uniformity of dosage units, content and labeling.

It was observed that, if only the official established procedures (description, appearance, organoleptic characteristics and average mass) were considered from the seven samples rated as unsatisfactory, just one would be classified in this status. The remaining six samples would erroneously be rated satisfactory, meaning that would be approved for human consumption [18].

Some factors may cause deviations, inherent to the handling process of drugs in capsules, such as the loss of substance during the grinding, mixing and filling the capsules. Miscalculations and weight of the formulation components, errors inherent to the operator and the use of damaged equipment may also compromise the process and therefore the quality of the final product [29].

The results of Omerazole and Enalapril Maleate were analyzed by ANOVA followed by Tukey's test for uniformity of content and unit dose. Results were considered significantly different at $p < 0.05$.

3.2. Neutron activation analysis

3.2.1. Material and methods

All samples of Omeprazole and Enalapril Maleate were purchased in the market of the Belo Horizonte, state of Minas Gerais, Brazil from five (5) different magistral pharmacies.

Due to operational reasons, Jožef Stefan Institute (JSI) performed analyses only from three (3) different pharmacies from the sampling group. Due to same operational reasons, the JSI did not analyze the short half-lives radionuclides of elements like Al, Cl, Mg, Mn and Ti.

The samples of Omeprazole and Enalapril Maleate performed by the JSI were packed in polyethylene capsules in plastic bottle containing 20 capsules each. Whole powder mass from 20 capsules was taken to prepare homogenized samples, which was transferred in clean polyethylene bottle. In the samples of Omeprazole performed by CDTN, just one the mass of one capsule taken randomly was considered by each sample. The difference of procedures carried out by both Institutes was due to operational reasons.

Both institutes CDTN/CNEN and JSI followed the same procedure to prepare the samples. The aliquots of each sample were manually crushed or ground using an agate mortar with pestle, whenever necessary, to avoid any contamination. In most cases, unless the amount of material did not allow it, two replicates were taken and weighed in polyethylene vials. It is relevant to emphasize that no additional chemical sample preparation was performed. At CDTN/CNEN and IJS, the samples were irradiated together with several Al–0.1% Au disks as neutron flux monitors, according to the k_0-standardisation method procedure [23,24,30].

Table 10 shows the characteristics of the applied technique such as the parameters f (thermal to epithermal fluxes ratio) and the α (parameter which measures the epithermal flux devia-

tion from the ideal (1/E) distribution), needed for the k_0-method, the irradiation times and gamma spectrometry systems at each Institute.

3.2.2. Results and discussion

The obtained results of NAA from the medicines Omeprazole and Enalapril Maleate are showed in the Tables 11 to 13.

The technique applied was suitable for determining 20 chemical elements – Al, Br, Ca, Cl, Co, Cr, Fe, Mg, Mn, Na, Sb, Sc, Sm, Sr, Ta, Th, Ti, U and Zn – in a large range of concentration, without any chemical process. The elements Cl, Fe, K, Mg, Mn, Na, and Zn could be expected in this kind of samples. Other elements, not considered essential, for the human being such as As and Sr, found in lower concentration compared to Cl, Fe, K, Mg, Mn, Na, and Zn can also represent a health problem in a long term consumption. Even essential elements were determined but in high concentrations, like Fe may be toxic.

High concentration of elements such as Cl, Ca, Mg, Na and Ti are expected because they are frequently components of excipients in the preparation of pellets. The presence of Mg is due to the excipients usually used: magnesium is a component of magnesium estearate ($Mg[C_{18}H_{35}O_2]$), a lubricant for tablets and capsules and opadry, coloring agent, respectively [26]. Mg also is present in magnesium silicate ($Mg_3SiO_4(OH)_2$] Na is a component of sodium laurilsulfate, ($[CH_3(CH_2)_{10}(CH_2O)(SO_3)Na]$ and sodium bicarbonate $NaHCO_3$. Ca is added as excipient as calcium phosphate and Ti as titanium dioxide, TiO_2. Fe comes from red iron oxide, used as excipient as well [10,13]. The impurities such as Br, Co, Cr, Hf, La, Sb, Sc, Sm, Sr, Ta, Th and U, are probably original from the raw material and/or from the process of production and manipulation of the medicine. All elements determined not foreseen in the original formula can be considered as impurities.

	INSTITUTE	
	CDTN/CNEN	**JSI**
Thermal Flux (neutrons cm^{-2} s^{-1})	6.4x 10^{11}	1.1x 10^{12}
k_0-standardisation parameters		
f	20.4	28.6
α	0.197	- 0.011
Irradiation time (h)	8	13
Detector nominal efficiency (%)	50	40
Software used for:	Genie 2000	Genie 2000
Acquisition spectra	(CANBERRA)	(CANBERRA)
Spectra Analysis	HyperLab	HyperLab
Concentration calculation	Kayzero for Windows, V.2.42	Kayzero for Windows, V.2.42
Sample mass (mg)	200-250	240-250

Table 8. Experimental information of neutron activation analysis

The data presented in Tables 12, 13 and 14 cannot be compared directly because the samples analyzed are not from the batch, but the results are, in general, very similar. Most results determined by the CDTN in one capsule of Omeprazole taken randomly were also determined by the JSI in the homogenized samples, except for the elements Br, Cr and La. The concentrations of the elements determined by both institutes have, in general, the same magnitude.

The discussion about toxicity levels and possible consequences for humans being is very difficult, due to the low concentration of the elements and limitations on the studies available in the literature. For most trace elements, there are just some available data on acute and chronic toxicity in experimental animals, not sufficient data to assess the risks to the human health on a long term daily intake [22].

4. Conclusion

The obtained results of samples of omeprazole and enalapril from five different magistral pharmacies of Belo Horizonte, Brazil, confirm the concern about the quality and safety for consumption of formulated medicines. They represent a preliminary part of a more complete investigation, still under way.

From the ten samples analyzed, seven were considered unsatisfactory. Most of the problems found through analyses Omeprazole and Enalapril Maleate medicines, like the variation of active principle mass, mass variation and dosage unit, come from the inadequacy of procedures for handling the ingredients in the pharmacy.

Problems can also be caused by the quality of the raw material used and inefficient or inexistence of test for checking the material. Diversified impurities reinforce the hypothesis that these elements are not controlled by the quality system. It also suggests that quality control over the purity of medicines in general should be established, as well as the concentration limits for the impurities, at least for some elements like As, Cd, Cu, Hg, Pb and Sn, already foreseen for food in the Brazilian legislation.

The possible harmful and/or toxicological effects for the human health as a consequence of long term use of the formulated medicines represent an important concern for the authorities of the public health system. Recent cases of contamination and death in Brazil due to the consumption of inadequate formulated medicines has been enhancing the debate about the quality of the magistral pharmacy.

In conclusion, the results point out the necessity of prompt and efficient actions by the authorities of the health public system to assure the quality of formulated medicines. The aim of this work is just to provide evidences in order to contribute with this initiative.

	Pharmacy														
Element	**A**			**B**			**C**			**D**			**E**		
Al	532	±	20	260	±	10	305	±	11	452	±	17	335	±	12
Br	DL			0.60	±	0.03	DL			DL			DL		
Ca	17740	±	793	9379	±	446	11230	±	512	19600	±	880	14260	±	190
Cl	806	±	48	313	±	18	262	±	18	490	±	30	514	±	31
Co	0.5	±	0.1	0.3	±	0.1	0.3	±	0.1	DL	±		0.10	±	0.01
Cr	11.7	±	0.5	7.9	±	0.3	6.7	±	0.3	11.6	±	0.5	13	±	1
Fe	65	±	5	64	±	11	47	±	10	49	±	11	51	±	5
Mg	4643	±	192	449	±	28	390	±	28	998	±	57	697	±	47
Mn	2.8	±	0.3	1.4	±	0.1	DL			1.8		0.2	2.2		0.2
Na	8134	±	326	4003	±	144	3918	±	140	6838	±	241	6718	±	247
Sb	0.09	±	0.01	0.41	±	0.02	0.04	±	0.01	0.06	±	0.01	0.13	±	0.01

Table 9. Elemental concentration ($mg.kg^{-1}$) for Omeprazole (CDTN/CNEN)

	Pharmacy														
Element	**A**			**B**			**C**			**D**			**E**		
Sc	0.03	±	0.01	0.03	±	0.01	0.01	±	0.01	0.02	±	0.01	0.02	±	0.01
Sm	DL			0.02	±		DL			0.02		0.01	DL		
Sr	DL			DL			DL			21	±	4	DL		
Ta	0.02	±	0.01	0.14	±	0.01	DL			0.15	±	0.01	0.09	±	0.01
Ti	2748	±	105	1483	±	55	897	±	34	2124	±	79	1907	±	71
U	DL			0.22	±	0.01	DL			DL			0.4	±	0.1
Zn	3.4	±	0.4	1.8	±	0.3	DL			2.9	±	0.4	2.5	±	0.3

* DL – Lower than the Detection Limit

Table 10. Elemental concentration ($mg.kg^{-1}$) for Omeprazole (CDTN/CNEN)

	Pharmacy								
Element	**A**			**B**			**C**		
Br	0.19	±	0.01	0.17	±	0.01	0.22	±	0.01
Ca	16453	±	592	14908	±	540	12817	±	467
Ce	DL			DL	±		0.09	±	0.01

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	Pharmacy								
Element	**A**			**B**			**C**		
Co	0.18	±	0.01	0.016	±	0.001	0.51	±	0.02
Cr	0.52	±	0.03	0.26	±	0.02	0.59	±	0.04
Fe	102	±	4	53	±	2	265	±	9
Hf	0.020	±	0.001	0.009	±	0.001	0.021	±	0.002
La	0.019	±	0.002	0.030	±	0.004	0.040	±	0.002
Mo	0.34	±	0.05	DL	±		DL		
Na	6616	±	232	5988	±	210	4836	±	169
Sb	0.014	±	0.001	0.012	±	0.001	0.011	±	0.001
Sc	0.013	±	0.005	0.010	±	0.001	0.022	±	0.001
Sm	DL			DL			0.0052	±	0.0003
Sr	22.3	±	1.1	17.4	±	1.0	9.0	±	1.0
Ta	0.34	±	0.01	0.076	±	0.003	0.42	±	0.02
Th	0.012	±	0.002	DL			0.027	±	0.002
U	0.09	±	0.01	0.14	±	0.01	0.053	±	0.004
Zn	0.60	±	0.1	0.4	±	0.1	0.7	±	0.1

* DL – Lower than the Detection Limit

Table 11. Elemental concentration ($mg.kg^{-1}$) for Omeprazole (JSI)

	Pharmacy								
Element	**A**			**B**			**C**		
Br	0.13	±	0.01	0.47	±	0.02	0.24	±	0.02
Cr	0.07	±	0.01	0.15	±	0.01	0.10	±	0.01
Na	12540	±	439	271	±	10	72480	±	2538
Sc	0.0009	±	0.0001	0.0007	±	0.0001	0.0054	±	0.0002
Sb	0.09	±	0.01	0.41	±	0.02	0.04	±	0.01
Th	DL			DL			0.015	±	0.001
Zn	0.49	±	0.04	DL			0.015	±	0.001

* DL – Lower than the Detection Limit

Table 12. Elemental concentration ($mg.kg^{-1}$) for Enalapril Maleate (JSI)

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