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Effervescent vitamin C tablets and its quality control

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Abstract. Ascorbic acid (vitamin C), a potent antioxidant, is not synthesized by the human body and is obtained from food and pharmaceutical formulations. As a pharmaceutical product, it is available as a solution, powder, granules and tablets. Effervescent tablets are the most consumed since the isolated form or associated with other substances. It is commercially available from several suppliers, which makes its evaluation fundamental to ensure the quality, efficacy and safety of the patient in face of over-the-counter medication. Quality control is essential in the final product, as many products do not have the desired quality, compromising its validity and action. The present study aimed to evaluate effervescent vitamin C tablets from three different brands. The quality tests were carried out according to the parameters recommended by the Brazilian Pharmacopeia. The content was determined by the titrimetric and spectrophotometric method, as there is no official methodology for effervescent vitamin C tablets. All brands were approved in the quality tests used, guaranteeing and demonstrating the company's commitment to the population that consumes it.
Keywords: ascorbic acid, quality control, effervescent tablets

Introduction

Oral dosage forms are the most used for medication administration due to their ease of administration, transport and greater stability, when compared to liquid and semi-solid forms. Among oral solids, tablets are more common due to the relatively simple manufacturing process, with high productivity and low cost (LACHMAN et al., 2010). However, when the tablet requires a large amount of active substance, its administration is difficult due to its size and an option for these cases is effervescent tablets (ANSEL, 2007).

Effervescent tablets are prepared by compacting granulated effervescent salts that release carbon dioxide in contact with water. Therefore, it is necessary to be dissolved or dispersed in water before administration. (BRANYFIELD, c2017; CAMPOS, ALVES and SILVA, 2012). The use of these effervescent formulations has been growing due to advantages such as: good stability, masking of unpleasant taste, possibility of working with high doses, efficient administration in patients with difficulty in swallowing, in addition to increasing the bioavailability of the drug (ASLANI e SHARIFIAN, 2019; CRISTINA, 2012; LINDBERG, 2007). As a disadvantage, we can mention the need for packaging to be impervious to moisture and light, which makes the medicine more expensive. On the other hand, depending on the active substance, it contributes to the stability of the product during the shelf life (CRISTINA, 2012).

Quality control of pharmaceutical forms is an indispensable condition, since it is the sector responsible for guaranteeing the quality and effectiveness of the medicine, which will be marketed (GIL, 2010; PINTO et al., 2010; UNITED STATES PHARMACOPEIA, 2007).

For effervescent drugs, in addition to the tests for identification, purity, drug content and those inherent to the pharmaceutical form, such as hardness, friability, average weight, uniformity of unit doses, two tests stand out: the disintegration test / dissolution, and the pH of the solution obtained after the disintegration (GIL, 2010; UNITED STATES PHARMACOPEIA, 2007). This test also collaborate to verify the release of carbon dioxide into the solution functioning as a buffer system, due to the balance generated between the acid component and the corresponding salt. (ANSEL, 2007; WORLD HEALTH ORGANIZATION, 2011). Also, the disintegration and dissolution happen simultaneously.

The pH after disaggregation must be constant or with slight variations between tablets in the same batch. Heterogeneity or large variations in values during the tests probably suggest that there is heterogeneity in the distribution of raw materials

before compression, which may influence the stability and flavor of the final product (ANSEL, 2007; GENNARO, 2014).

Among the effervescent drugs sold, are tablets containing ascorbic acid (Vitamin C). Vitamin C is water-soluble and has low stability against oxidation, requiring care in its production, storage and use (ALVES, JAIME, GONÇALVES, SUZUKI, 2008; DELVIN, 2011). As vitamin C is a widely marketed product not only under medical guidance, it is expected that the proposed trust will exist, regardless of the brand or supplier company. Loss of quality interferes with the success of the treatment and / or exposes users to exacerbation of adverse or undesirable events, since the active substance can be altered during storage, by the action of light, moisture and heat (PRISTA et al., 1995).

Thus, due to the concern with health, the ease of marketing vitamin supplements, the wide variety of suppliers and prices, the work aimed to verify the quality of effervescent tablets from three brands available in the market in 2019

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Methods

Samples

Samples from three brands that produce effervescent vitamin C at a dose of 1 g were analyzed. The tablets were purchased in the municipality of Sinop - MT, in 2019. The tablets of each supplier were from the same manufacturing batch and, for ethical reasons, the names of the manufacturers of the drugs were not informed, being called products, X, Y and Z.

Reference chemical substance (RCS)

The RCS used was 99.7% pure ascorbic acid (Proquimios).

Reagents

All reagents used were of analytical grade: soluble starch (Synth), sulfuric acid (Proquimios), hydrochloric acid (Synth), resublimated iodine (Isofar), potassium iodide (Neon), sodium thiosulfate (Isofar), potassium dichromate (Isofar), 1,10-Phenanthroline (Vetec) and iron sulfate heptahydrate (Dynamic).

Equipments

The equipment used was: analytical balance (Shimadzu - model AUY220), durometer (Logen - model LSD-DI), infrared spectrophotometer with Fourier transform (FTIR) (Affinity - 1 - Shimadzu), digital pH meter (Del lab - model DLA -PH), stopwatch (Dinloo - XL-009A), UV-visible spectrophotometer (PG Instruments - model T80).

Vitamin C tablets were analyzed according to the tests described below.

Drug identification test

Infrared absorption spectrophotometry with Fourier transform (FTIR) was used. The spectra were obtained using potassium bromide tablets containing about 1–2 % vitamin C, which were recorded at room temperature in the range of 2000 - 500 cm^{-1}. For each sample, 20 scans were recorded with a resolution of 4 cm^{-1}. The test is considered positive if the samples showed absorption maximums at the same wavelengths and with the same relative intensities as those observed in the ascorbic acid (RCS) spectrum, prepared in an identical manner.

Measurement of average weight

Twenty effervescent tablets from each supplier were individually weighed to calculate the average weight, standard deviation and coefficient of variation. According to the Brazilian Pharmacopeia (BRASIL, 2010), tablets containing more than 250 mg, can have a maximum of two tablets outside the specified limits of +/- 5.0%, and no sample can contain unit weight above or below double of the percentage indicated (BRASIL, 2010).

Hardness

Ten units were submitted to the test, using the durometer, in order to verify their resistance against a force applied diametrically. According to the Brazilian Pharmacopoeia, the minimum acceptable is 3 kgf (BRASIL, 2010).

Friability

Ten tablets of each pharmaceutical product were weighed and placed in a friabilometer. After 100 rotations carried out for 4 minutes (25 rpm), the tablets were removed from the equipment and any residue or dust will be removed and weighed again. Friability was calculated by the difference between the initial weight and the final weight of the tablets. Tablets with losses of less than 1.5% of their weight are considered acceptable. Chipped or split-layer tablets were not considered for calculating the percentage of friability (BRASIL, 2010).

Disintegration time

To perform the test, a tablet was added to a beaker containing 200 mL of water at a temperature of 15 – 25 ^{0}C. The test was performed in six times. According to the World Health Organization (WHO), gas bubbles must be released and when the gas release ends, the granules must be disaggregated and dissolved or dispersed in water in less than five minutes (WORLD HEALTH ORGANIZATION, 2011).

Determination of pH

The pH was determined in the six solutions resulting from the effervescence test, using a pH meter previously calibrated with buffer solutions (BRASIL, 2010).

Dosing and uniformity of unit doses

Effervescent tablets containing ascorbic acid do not have an official monograph, therefore, dosing was carried out following two methods: titrimetric

and spectrophotometric. The tests were performed in triplicate.

The dosage performed by the titrimetric method is that indicated by the Brazilian Pharmacopeia for tablets and that was used for effervescent tablets (BRASIL, 2010). For the test, 20 tablets were totally powdered and weighed. Then, 0.2 g of weight equivalent of ascorbic acid was dissolved in a mixture of 100 ml of water and 25 ml of sulfuric acid 1 mol.L^{-1}, which was then titrated with 0.05 mol.L^{-1} iodine solution using starch solution as indicator. (BRASIL, 2010).

The spectrophotometric method was performed according to Silva et al (2019), in which an iron (III) and 1.10-phenanthroline complex is reduced by ascorbic acid, resulting in a red-orange complex with strong absorption in the wavelength of 510 nm.

For both methods, the acceptance value of 90 to 110% was adopted as established for the pharmaceutical form of ascorbic acid tablets (BRASIL, 2010)

The uniformity assay for unit doses was the same as for dosing, only being performed individually with 10 effervescent tablets.

Results and discussion

The identification test performed by FTIR showed that all products contain vitamin C (Figure 1), as they as they presented the same absorption bands as SRQ ascorbic acid.

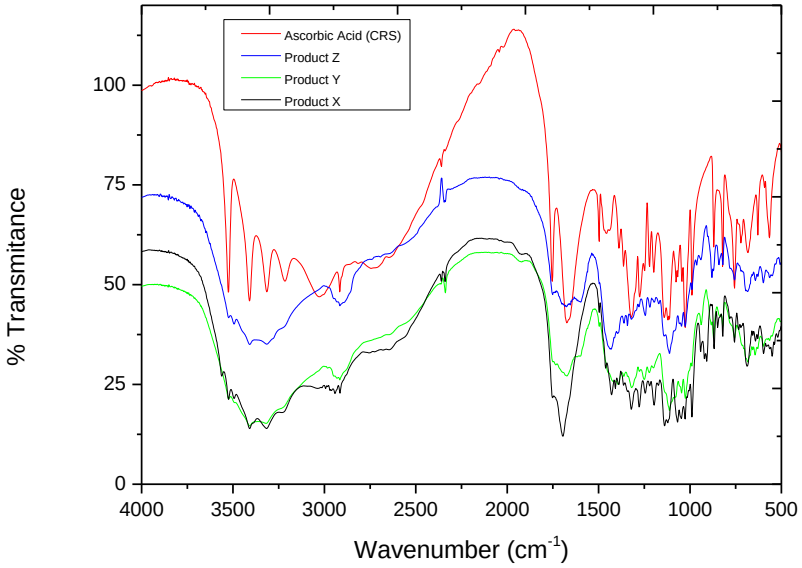

Figure 1. Spectrometry of the RCS ascorbic acid infrared region and samples of effervescent tablets containing vitamin C (X, Y and Z product).

The average weights of the samples are shown in Table 1. All samples showed values according to the established by the Brazilian Pharmacopeia (BRASIL, 2010). The product named X had the lowest relative standard deviation (0.53%), while product Y the largest deviation (2.43%), showing a greater dispersion of weights from one tablet to another.

The hardness test allows to verify the resistance of the tablet to crushing or even rupture under a subjected pressure and its result is expressed in kgf (kilogram-force). The Brazilian Pharmacopeia (BRASIL, 2010) establishes only the minimum value of 3.0 Kgf that the tablets must have. It is an important test for tablets that can interfere with production, packaging, transport and handling operations. A tablet with a very high hardness can break down very slowly or even not break down, on the other hand, a tablet with a hardness below the limit can break down too quickly (ANSEL, 2007).

Both situations can result in an ineffective drug release and action. The results of the hardness test are shown in Table 2, where it was found that all products passed the hardness test because they had values above 3.0 kgf.

The friability test reflects the resistance of the tablet to wear when subjected to mechanical shocks resulting from industrial processes and everyday actions, such as production, packaging, storage, transport and distribution, and even handling by the patient (LACHMAN et al. , 2001). There is usually a relationship between hardness and friability, where a high hardness can result in reduced friability and vice versa (STORPIRTIS, 2009). The Brazilian pharmacopoeia (BRAZIL, 2010) and the American pharmacopeia (UNITED STATES PHARMACOPEIA, 2007) reported that effervescent tablets may have different specifications regarding

friability, which makes it essential to choose the packaging material to ensure quality, stability and the shelf life of tablets with high friability.

Table 1. Individual weight, average weight and relative standard deviation of effervescent vitamin C tablets (products X, Y and Z).

Tablet	Individual weight (g)X	Individual weight (g)Y	Individual weight (g)Z
1	3.970	3.809	3.336
2	3.949	3.729	3.308
3	3.929	3.810	3.273
4	3.952	3.791	3.259
5	3.964	3.716	3.298
6	3.956	3.758	3.290
7	3.944	3.645	3.226
8	3.992	3.704	3.230
9	3.966	3.815	3.284
10	3.949	3.799	3.238
11	3.997	3.785	3.170
12	3.939	3.845	3.205
13	4.016	3.768	3.227
14	3.972	3.775	3.263
15	3.969	3.709	3.177
16	3.988	3.601	3.181
17	3.937	3.733	3.261
18	3.971	3.602	3.270
19	3.973	3.558	3.280
20	3.997	3.934	3.240
Average weight	3.966	3.744	3.251
Standard deviation	0.023	0.091	0.045
R.S.D (%)	0.58	2.43	1.38

R.S.D. (%) = Relative standard deviation.

Table 2. Hardness of the samples of effervescent tablets of vitamin C of products X, Y and Z.

Tablet	X (kgf)	Y (kgf)	Z (kgf)
1	8.25	> 20.38	17.08
2	6.06	15.19	> 20.38
3	12.82	> 20.38	> 20.38
4	17.51	11.54	19.07
5	7.47	> 20.38	> 20.38
6	15.37	15.95	17.75
7	18.61	13.98	15.37
8	10.81	17.21	> 20.38
9	> 20.38	12.49	14.51
10	17.88	18.17	17.77

The results corroborated with Andrade (2017), where the analysis of the tablets showed a loss greater than 1.5% in the friability test, showing that the loss of material may be related to the excipients, which are sensitive to mechanical action due to their effervescent mechanism that it should dissolve quickly. To prevent loss and breakage of the tablets, the packages are tubes. The effervescence time allows you to check the time (in minutes) that effervescent tablets take to disintegrate and dissolve completely in the water. This type of tablet is prepared by compacting some salts that release carbon dioxide in contact with water (BRANYFIELD, c2017). Thus, the disintegration and dissolution of the effervescent tablets occurs by the release of carbon dioxide and, when the gaseous release ends, the granules must be disaggregated and dissolved in water in less than 5 minutes.

Tablets not disintegrated or incompletely dissolved in water after effervescence suggest manufacturing flaws, such as, for example, a very high hardness, which makes the tablet not fully disintegrate in water, which may influence the content and action of the drug (ÓRFÃO, 2016).

The water temperature influences disintegration and dissolution. Low temperatures result in an increase in time, so it is set at a temperature between 15 to 25 ° C for the disintegration and dissolution process to occur (LINDBERG, 2007).

The three products (X, Y and Z) at the temperature of 20 ^{0}C disintegrated and dissolved within the established limit of 5 minutes (Table 3). The results found are similar to those of Aslani (2014). This author evaluated Amoxicillin effervescent tablets and found that the analyzed samples disintegrated in less than 5 minutes, a condition for effervescent tablets. The disintegration and dissolution time for this type of pharmaceutical form is essential for its administration, since they are ingested right after the total disintegration / dissolution.

Table 3. Disintegration and dissolution time of samples of effervescent vitamin C tablets of products X, Y and Z at 20^{0}C .

Tablet	X	Y	Z
1	2 min 10 s	1 min 57 s	1 min 28 s
2	2 min 15 s	1 min 46 s	1 min 27 s
3	2 min 10 s	1 min 56 s	1 min 22 s
4	1 min 57 s	1 min 53 s	1 min 37 s
5	2 min16 s	1 min 59 s	1 min 23 s
6	2 min 04 s	1 min 51 s	1 min 18 s
Average	2 min 02 s	1 min 54 s	1 min 26 s

The pH must remain constant or with small variations between tablets in the same batch. Vitamin C has a slightly acidic characteristic, since it is a weak acid (pKa = 4.04 at 25 ºC) (DAMODARAN, 2010) and must be maintained to maintain its stability (ROSA, 2007).

The maintenance of pH is important so that the vitamin does not degrade when exposed to variations such as a very acidic pH, hydrolysis or a basic pH may occur, resulting in oxidation of ascorbic acid, in addition to light, humidity, temperature, oxygen, resulting in chemical transformations to the tablet that become dangerous under these conditions (ROSA, 2007; SURINI, 2017). The pH is one of the main factors that affect the stability of ascorbic acid (PATHY, 2018)

In addition, the pH must be in balance with the pH of the stomach (pH = 1.4) and the intestine (pH = 7.5) (BRUNTON, 2012) to favor its absorption. An interesting aspect is the buffering capacity of excipients of effervescent forms, since gastric pH tends to increase after ingestion of this type of pharmaceutical form (LEE, 2012; IPCI, 2016).

The pH results after the disintegration / dissolution of the tablets are shown in Table 5. All products showed a pH between 4.5 to 5.0, which is suitable for this type of formulation to guarantee the stability of the solution at the time of its administration.

Table 5. The pH values and relative standard deviation of effervescent tablets containing vitamin C from products X, Y and Z..

Tablet	X	Y	Z
1	4.63	4.49	4.72
2	4.59	4.47	4.80
3	4.65	4.50	4.90
4	4.60	4.52	4.95
5	4.63	4.53	4.74
6	4.58	4.54	4.87
Average	4.61	4.51	4.83
R.S.D. (%)	0.58	0.57	1.90

R.S.D. (%) = Relative standard deviation.

The dosage of medications is essential for the administration of correct doses, in order to ensure that the quantity of the declared active ingredient is within the established after being subjected to all stages of production (GIL, 2010).

The drug content must respect the limits established by the Pharmacopeia (BRASIL, 2010) because levels above the established may cause adverse effects such as overdose, toxicity, on the other hand, a level below the minimum will not result in the expected action of the medication.

It is worth mentioning that two tests were performed to determine the dosage (titrimetric and spectrophotometric), whose objective was to analyze the possible difference between the methods, since there is no official methodology for this dosage form, in addition to ensuring the reliability of the results obtained.

The results of the analyzes are shown in Table 6 and 7, verifying that all products had an ascorbic acid content between 98.1 and 105.7%. The results found were similar to Andrade (2017), who reported levels between 97.51% and 101.67%, using the titrimetric method. According to the parameters adopted for ascorbic acid tablets, effervescent tablets were within the limit.

There was no difference between the methods used ($p < 0.05$), showing that effervescent tablets can be evaluated by both methods. The data corroborated with the study by Silva et al. (2019).

The uniformity of the tablets represents the guarantee of the quantity of active ingredient in each unit. Factors such as hardness, excipients used, homogeneity, weight, loss of tablet powder influence the efficiency of the drug, that is, uniformity checks the quality in the drug's production stages (LACHMAN et al., 2010).

Table 6. Content and relative standard deviation of samples of effervescent tablets of vitamin C of products X, Y and Z obtained by titration..

	X	Y	Z
Ascorbic acid (%)	98.1	100.4	98.8
R.S.D. (%)	0.57	1.55	1.36

R.S.D. (%) = Relative standard deviation.

Table 7. Content and relative standard deviation of samples of effervescent tablets of vitamin C, products X, Y and Z obtained by spectrophotometry in the visible region.

	X	Y	Z
Ascorbic acid (%)	104.6	105	105.7
R.S.D. (%)	0.43	0.118	0.773

R.S.D. (%) = Relative standard deviation.

For the uniformity test of unit doses, the titrimetric method was chosen since there was no difference between the methods used. The test was performed by weight variation and the results are shown in Table 8. The three products had an acceptance value of less than 15, which is the limit established by the Brazilian Pharmacopeia (BRASIL, 2010), ensuring that all products have the declared amount of vitamin C and the homogeneity of the pharmaceutical form in each tablet.

Table 8. Uniformity and relative standard deviation of samples of effervescent vitamin C tablets of products X, Y and Z.

Tablet	X (%)	Y (%)	Z (%)
1	95.0	96.4	96.4
2	97.5	95.9	95.9
3	96.7	99.7	96.3
4	98.0	93.4	96.8
5	98.0	97.2	97.6
6	97.6	98.0	98.0
7	97.5	100.0	93.4
8	97.0	101.7	94.6
9	97.9	97.6	95.1
10	97.8	95.9	93.8
Average	97.30	97.58	95.79
R.S.D. (%)	0.94	2.47	1.61
AV	3.39	6.69	6.41

R.S.D. (%) = Relative standard deviation.
AV = Acceptance value

Therefore, the batches of the three brands were approved in the quality tests, showing pharmacotechnical efficacy, product stability and guarantee of safety to the user during its validity period.

Complying with quality standards is essential for any medication to result in an effective treatment, in addition to guaranteeing the quality of the product, contributing to the safety and reliability of the patient.

Conclusion

The analyzes to determine the quality of effervescent tablets containing ascorbic acid from three companies met all the necessary requirements for approval in the quality tests, as there is no method for effervescent tablets in Brazilian Pharmacopoeia. In addition, the assay tests were similar, showing the possibility of using two methods that are simple and low cost.

The results were important, since vitamin C pills are over-the-counter and widely purchased by the population, since there is no effective control over consumption, the dose used and or even adverse effects.

In this way, quality control must always be in place to ensure the safety of the final product.

References

ALVES, RMV., JAIME, SBM., GONÇALVES, MP., SUZUKI, PW. Embalagens plásticas e de vidro para produtos farmacêuticos: avaliação das propriedades de barreira à luz. Revista de Ciências Farmacêuticas Básica e Aplicada. 29(2): 169-180, 2008.

ANDRADE, AS. Controle de qualidade físico-químico de comprimidos efervescentes de ácido ascórbico 1g disponíveis nas farmácias de Santo Antônio de Jesus. 46p. (Trabalho de Conclusão de Curso) - Faculdade Maria Milza, Governador Mangabeira, Brasil, 2017.

ANSEL, HC., POPOVICH, NG., ALLEN, LV. Formas farmacêuticas e sistemas de liberação de fármacos. (8 ed.) Artemed, São Paulo, p. 249-268, 2007.

ASLANI, A., SHARIFIAN, T. Formulation, characterization and physicochemical evaluation of amoxicillin effervescent tablets. Advanced Biomedical Research. 3: 5-7, 2014.

BRANYFIELD, A. Martindale: the complete drug reference. (38 ed.) Farmaceutical Press, London. 4160p. 2017.

BRASIL. Farmacopeia Brasileira. Agência Nacional de Vigilância Sanitária. Brasília. (5 ed.) v. 1. 546p. 2010.

BRASIL. Farmacopeia Brasileira. Agência Nacional de Vigilância Sanitária. Brasília. (5 ed.) v. 2. 904p. 2010.

BRUNTON, LL., CHABNER, BA., KNOLLMANN, BC. Goodman: as bases farmacológicas da terapêutica de Goodman & Gilman. (13 ed.) Artmed, Porto Alegre. p. 819-829, 2012.

CAMPOS, DA., ALVES, ND., SILVA, TD. Estudo de pré-formulação e desenvolvimento de pó efervescente contendo ácido acetilsalicílico. Farmácia & Ciência 3: 20-33, 2012.

CRISTINA, HPD. Formas farmacêuticas efervescentes uma abordagem alternativa. 91p. (Dissertação de Mestrado) – Universidade de Lisboa, Lisboa, Portugal, 2012.

DAMODARAN, S., PARKIN, KL., FENNEMA, RO. Química de alimentos de Fennema. (4 ed.) Artmed, Porto Alegre, p. 366-367, 2010.

DELVIN, TM. Manual de Bioquímica: com correlações clínicas. (7 ed.) Edgarder Blücher, São Paulo, p. 1099-1111, 2011.

IPCI, K., ÖKTEMER, T., BIRDANE, L., ALTINTOPRAK, N., MULUK., NB., PASSALI, D., LOPATIN, A., BELLUSSI, L., MLADINA, R., PAWANKAR, R., CINGI, C. Effervescent tablets: a safe and practical delivery system for drug administration. ENT Updates 6(1): 46-50, 2016.

GENNARO, AR. Remington: a ciência e a prática da farmácia. (20 ed.) Guanabara, Rio de Janeiro, p. 885-914, 2014.

GIL, ES. Controle físico-químico de qualidade de medicamentos. (3 ed.) Pharmabooks, São Paulo, 512p. 2010.

LACHMAN, L., LIEBERMAN, HA., KANIG, JL. Teoria e prática na indústria farmacêutica. (2 ed.) Fundação Calouste Gulbenkian, Lisboa. 1531p. 2010.

LEE, R. Effervescent tablets – key facts about a unique, effective dosage form. Tablets and Capsules. p. 1-4, 2004. Disponível em https://www.amerilabtech.com/wp-content/uploads/2012/01/EffervescentTabletsKeyFacts.pdf/ accessed on December 22, 2019.

LINDBERG, NO., HANSSON, H. Effervescent Pharmaceuticals in Encyclopedia of Pharmaceutical Technology 12: 1454-1465, 2007.

ÓRFÃO, MK., ALVES, JO., VALLADÂO, AS., BONFILIO, R. ANDRIGHETTI, CR., RIBEIRO, EB., VALLADÃO, DMS. Controle de qualidade de comprimidos de hidroclorotiazida comercializados no município de Sinop. Scientific Eletronic Archives 10(5): 124-132, 2016.

PATHY, K. Process for Preparation of Vitamin C and Method for Determination of Vitamin C in Tablets. SciFed Journal of Chemical Research (1): 11-13, 2018.

PINTO, TJA., KANEKO, TM., OHARA, MT. Controle biológico de qualidade de produtos farmacêuticos, correlatos e cosméticos. (3 ed.) Atheneu, São Paulo, p. 3-8, 2010.

PRISTA, LN., ALVES, AC., MORGADO, R. Tecnologia (5 ed.) v. 1. Farmacêutica Calouste Gulbenkia, Porto. 786p. 1995.

ROSA, JS., GODOY, RLO., NETO, JO., CAMPOS, RS., MATTA, VM., FREIRE, CA., SILVA, AS., SOUZA, RS. Desenvolvimento de um método de análise de vitamina C em alimentos por cromatografia líquida de alta eficiência e exclusão iônica. Ciência Tecnologia Alimentos 27(4): 837-846, 2007.

SILVA, RS., PEDROSO, AV., JESUS, PC., GELINSKI, JMLN., BORGES, EM. Determinação de Vitamina C em Suplementos Alimentares Utilizando Métodos Volumétricos e Espectrofotometria de Absorção Molecular. Revista Virtual de Química 11(1): 155-179, 2019.

SURINI, S., WARDANI, MRW., SAGITA, E. Evaluating Of Effervescent Tablets Containing Grape Seed (Vitis Vinifera L.) Extract as a Nutraceutical. International Journal of Applied Pharmaceutics 9(1): 150-153, 2017.

STORPIRTIS, S., GONÇALVES, JE., CHIANN, C., GAI, MN. Biofarmacotécnica. Koogan, Rio de Janeiro. p. 12-28, 2009.

UNITED STATES. United States Pharmacopeia. Pharmacopeial Convention. Rockville, USA. 2007.

WORLD HEALT ORGANIZATION. Revision of monograph tablets. 2011. Disponível em http://www.who.int/medicines/publications/pharmacopoeia/Tabs-GeneralMono-rev FINAL_31032011.pdf/ accessed on January 8, 2020.