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Quality control of ranitidine hydrochloride compounded capsules

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Abstract. The class of medicines most used for the treatment of gastric disorders is histamine H2 receptor inhibitors, reducing the gastric acid secretion. Ranitidine hydrochloride is one of the most used agents of this class, usually found as 150 and 300 mg tablets. Dispensing extemporaneous compounds has been shown as alternative when patient seeks for medicines with personalized doses or lower cost, resulting in a progressive increase of this type of medicine. Aiming to evaluate the quality of extemporaneous compounding, this work verified the quality of ranitidine hydrochloride capsules from three compounding pharmacies (F1, F2 and F3) of the state of Mato Grosso. Trials were conducted according to Brazilian Pharmacopeia. Results showed that compounded capsules from F1 and F3 met the Brazilian Pharmacopeia specifications while the F2 ones were out of specification limits. Therefore, it was observed that it is needed a strict control over the compounding process to assure quality, effective and safe products.
Keywords: control, quality, ranitidine hydrochloride, capsule, compounding.

Introduction

The digestive system can be divided into two main parts: the alimentary tract and accessory organs. On embryologic grounds, the Gastrointestinal (GI) tract should be divided into upper (mouth to major papilla in the duodenum), middle (duodenal papilla to transverse colon), and lower (mid-transverse colon to anus). Associated with the alimentary tract are the following accessory organs: salivary glands, teeth, tongue, pancreas, liver and gallbladder (Tortora & Derrickson, 2012).

Disorders in the digestive system lead to the occurrence of several diseases, mainly peptic diseases, in other words, diseases determined by dysfunction in chloric and peptic balances and their actions, such as: gastro esophageal reflux disease (GERD), peptic ulcer disease (PUD) and functional dyspepsia (FD) (Silva, 2008).

The symptoms related to these gastric disorders include epigastric pain, postprandial discomfort, retrosternal heartburn, heartburn, regurgitation, dysphagia, odynophagia and in some cases patients may have nausea and vomiting (Silva, 2008).

The pharmacological approach for the treatment of these disorders uses H2 receptor antagonists, proton pump inhibitors, antacids and, if necessary, antibiotics, in addition to the recommendation of a healthy diet without irritants, avoid the use of drugs that can attack the gastric mucosa and minimize anxiety situations. (Rang & Dale, 2011; Bertaccini & Coruzzi, 1989; Hoogewerf & Pasricha, 2006; Silva, 2008).

Among other medicines, H2 receptor antagonists are the most widely used ones, with cimetidine, ranitidine, famotidine and nizatidine available on the market. Among these drugs, ranitidine hydrochloride is the most prescribed one, available in concentrations ranging from 75 to 300 mg (Barros et al., 2010). In order to have dosages individually customized, the trade in compounding products has been increasing, since the patient may have a medicine prepared for his needs and at a lower price. (Barros et al., 2010).

The compounded drugs offer advantages over the industrialized ones, however there are still some obstacles that hinder the growth of this sector, and the biggest one is the lack of credibility of the product compounded by the absence of strict quality control (Zarbielli, Macedo & Mendez, 2007).

In this respect, the development of studies regarding the analysis of compounding products aims to obtain specific data on the safety of these medicines, indicating their final quality.

The Brazilian Pharmacopeia (Brasil, 2010) establishes the limits of acceptability and the tests that must be performed to guarantee the quality of products. According to the Resolution of the board of directors - RDC N°. 67, OCTOBER 8, 2007 (Brasil, 2007), compounding pharmacies must perform, at least, description, appearance, organoleptic characteristics and average weight tests for solid dosage forms. In order to oversee the compounding process, content determination and content uniformity of the active ingredient of at least one formula must be performed every three months of the pharmaceutical unit containing the drug in a quantity equal to or lower than 25 mg (Brasil, 2007; Gianotto et al., 2008).

Therefore, due to the increase in the number of compounding pharmacies in the state of Mato Grosso along with the fact that ranitidine hydrochloride is a widely used drug in the public network for GERD, the goal of this work was to evaluate the quality of ranitidine hydrochloride capsules produced in three compounding pharmacies in the state of Mato Grosso.

Methods

Samples

Ranitidine hydrochloride capsules 300 mg, produced in three compounding pharmacies in Sinop - MT, identified by the letters: F1, F2 and F3.

Ranitidine reference substance (SQR)

Arte Farma provided Ranitidine hydrochloride reference substance with assigned purity of 99.0 %.

Reagents

All reagents used were of analytical grade: distilled water, hydrochloride acid (Synth®), methanol (Synth® and Neon®).

Identification

Fourier transform infrared spectroscopy (FTIR) was used to identify ranitidine hydrochloride in three different capsule formulations using an Affinity-1 Fourier Transform infrared spectrophotometer (Shimadzu®). Spectra were recorded at room temperature at range 3500-500 cm^{-1}. After recording a background spectrum, potassium bromide pellets containing around 1-2% of ranitidine hydrochloride were prepared and immediately analyzed by FTIR spectrophotometer. For each sample, 20 scans were recorded with 4 cm^{-1} resolution.

Weight variation

This test was performed according to the Brazilian Pharmacopoeia (Brasil, 2010). Twenty capsules of each pharmaceutical product (F1, F2 and F3) were weighed individually using an analytical balance. The average weight, standard deviation and variation coefficient were further calculated. For capsules weighing less than 300 mg the variation limit is 10%, while for those with a weight greater than 300 mg, the variation allowed is 7.5%. None of the units tested could be above or below twice the indicated percentages (Brasil, 2010).

Disintegration test

The disintegration time of capsules was performed according to the Brazilian Pharmacopoeia (Brasil, 2010). Six capsules of each product (F1, F2 and F3) were placed in each compartment of the disintegration apparatus basket and acrylic disks were added afterwards. The basket was attached to the device and then subjected to vertical movements using water as immersion fluid at 37° C ± 2 ° C until complete disintegration of the capsules. The requirement of the Brazilian Pharmacopoeia is met if all capsules tested are completely disintegrated in less than 45 minutes (Brasil, 2010).

Drug content

The content of the products was estimated using spectrophotometer (FEMTO, CIRRUS 80 MB) according to the Brazilian Pharmacopoeia (Brasil, 2010). The content of 20 capsules of each pharmaceutical product (F1, F2 and F3) was mixed and the weight equivalent of 0.125 g average weight was transferred to a 250 mL volumetric flask, 150 mL of water was added, and the flask was sonicated for 30 min. The flask was filled up with water; the total volume was filtered and then diluted to 0.00125% (p/v). The standard was prepared at the same concentration. The absorbance of standard and samples were determined at wavelength 314 nm.

Uniformity of dosage units

For the uniformity of dosage units test, it was used the method described in the Brazilian Pharmacopoeia (Brasil, 2010), using 10 capsules of each pharmaceutical product, quantified individually, according to the drug content.

Dissolution test

In vitro dissolution test was carried out using a discriminative dissolution method described in general methods of the Brazilian Pharmacopeia (Brasil, 2010). The dissolution conditions were: distilled water (900 mL) and a paddle stirring apparatus at rate 50 rpm.

Ten milliliters of dissolution medium (controlled at 37.0 ± 0.5 °C) were sampled after 45 min, and the samples were analyzed by spectrophotometric method. Six samples of each product were assayed. The absorbance was measured at 314 nm using the same solvent for zero adjustment. The amount of ranitidine hydrochloride dissolved in the medium was then calculated, comparing the readings obtained with that of the 0.00125% (w / v) ranitidine hydrochloride SQR solution, prepared in the same solvent. For this assay, not less than 80% (Q) of the declared amount

of ranitidine dissolved in 45 minutes is acceptable (Brasil, 2010).

Results and discussion

Compounding pharmacies have a great variety of products to meet the specific needs of each patient. The main challenge is to provide a quality product with assured therapeutic effectiveness and safety to the patient (Santos, 2011). Capsules fit in one of the most commercialized pharmaceutical forms in compounding pharmacies, due to their easy production and dosage adjustment, according to the patient's need (Ferreira, 2008). Other relevant characteristic of capsules is their bioavailability, usually dissolving quickly, allowing the active ingredient to reach the site of action fast (Manganelli, Ely & Contri, 2016).

The FTIR results clearly showed that the absorption bands of all samples are coincident with ranitidine hydrochloride reference standard. These results confirmed the unequivocal identification of $C_{13}H_{22}N_4O_3S$ on analyzed samples (Figure 1).

The weight determination indicates if the units of a batch show weight homogeneity. Thus, the average weight is one of the main quality control indicators in the routine of a compounding pharmacy, able to show the inefficiency in the compounding technique used (Santos, 2011). The individual weight of the capsules from the three compounding pharmacies (F1, F2 and F3) are shown in Table 1, and it was observed that all capsules produced by the three compounding pharmacies had variations in their weights within the limit allowed. Compounding pharmacy F1 had the lower variation among the capsules, while F3 had the highest. It is worth mentioning that weight variation may compromise the amount of active ingredient in each capsule.

The disintegration test is a quality parameter that aims to find out the necessary time required to completely disintegrate a solid pharmaceutical form (Brasil, 2010). Higher or lower values may compromise the medicine bioavailability (Villanova, Oréfice & Cunha, 2010).

The Brazilian Pharmacopeia (Brasil, 2010) establishes for the disintegration trial of ranitidine hydrochloride tablets that they have to be completely disintegrated in max 45 minutes, with water at 37 ± 1 ºC as immersion liquid, the same parameters are taken for capsules. The time for disintegration of the capsules was 4 (four) minutes, within the limit established by Brazilian Pharmacopeia (Table 2).

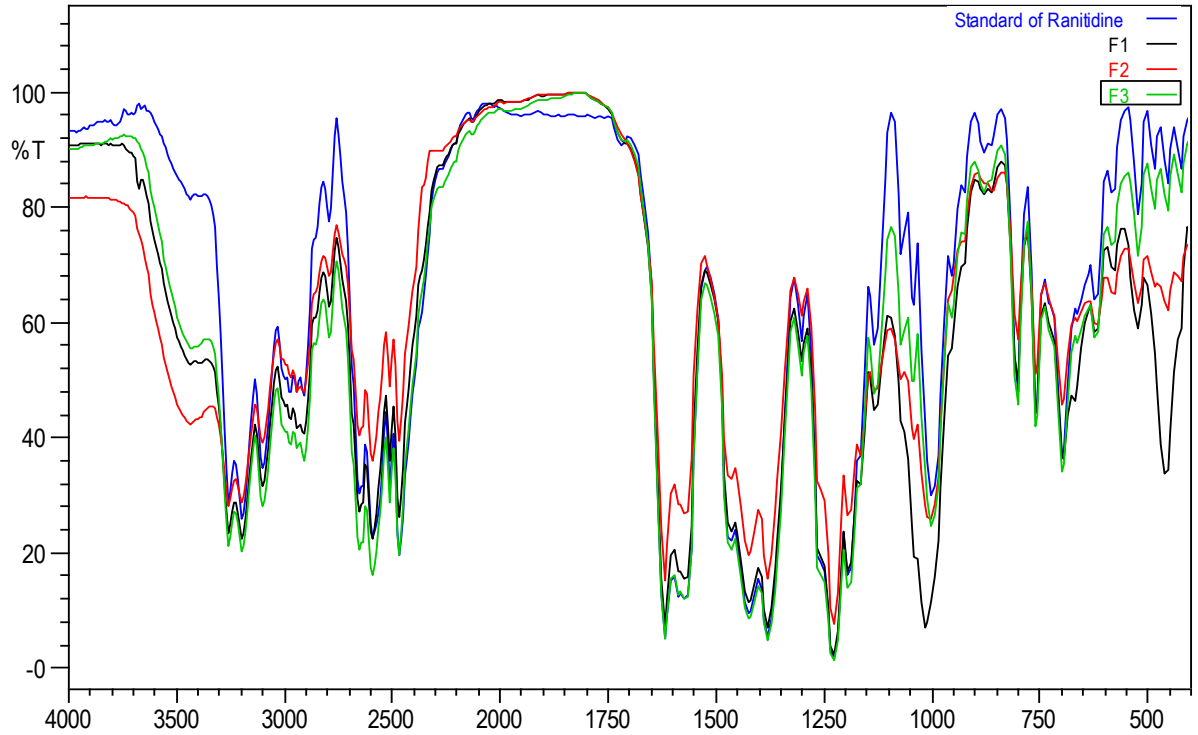

Figure 1: FTIR of standard ranitidine hydrochloride (SQR) and of the capsule samples containing ranitidine hydrochloride from three compounding pharmacies (F1, F2 and F3).

Table 1. Individual weight, average weight, standard deviation and coefficient of variation of ranitidine hydrochloride capsules compounded in three pharmacies in the state of Mato Grosso (F1, F2 and F3)

Capsule	F1 Individual weight (mg)	F2 Individual weight (mg)	F3 Individual weight (mg)
1	0.4578	0.4546	0.3515
2	0.4555	0.4836	0.3315
3	0.4601	0.4572	0.3457
4	0.4498	0.4801	0.3491
5	0.4535	0.4904	0.3554
6	0.4606	0.4724	0.3668
7	0.4554	0.4531	0.3459
8	0.4609	0.4751	0.3585
9	0.4550	0.4500	0.3505
10	0.4705	0.4821	0.3555
11	0.4562	0.4807	0.3527
12	0.4575	0.4493	0.3333
13	0.4475	0.4698	0.3491
14	0.4599	0.4672	0.3656
15	0.4519	0.4659	0.3359
16	0.4512	0.4534	0.3430
17	0.4591	0.4846	0.3446
18	0.4541	0.4622	0.3616
19	0.4538	0.4784	0.3674
20	0.4554	0.4592	0.3328
Average weight	0.4566	0.4685	0.3498
Standard deviation	0.0053	0.0127	0.0108
CV (%)*	1.1591	2.7107	3.0885

CV: coefficient of variation

Frequently, the identification and quantification method used is ultraviolet spectrophotometry, once it provides practicality, low cost, simple interpretation of results and relative sensitivity and specificity (Galo & Colombo, 2009). This method has as principle the absorption of energy according to the molecular structure and its concentration (Silverstein, Bassler & Morrill, 2006).

It was performed the absorption spectrum of the reference chemical substance (SQR) and the samples (Figure 2), between 200 and 400 nm wavelength, to quantify the ranitidine hydrochloride in capsules of the three compounding pharmacies. The absorption spectrum showed two maximum absorptions, one at 223 nm and another at 308 nm. It was decided to determine the content of ranitidine hydrochloride at 308 nm, since in this wavelength the active ingredient is most stable, according to the Brazilian Pharmacopeia (Brasil, 2010). In addition, according to Hohnjec et al. (1981), at the wavelength 223 nm it may occur interaction with the excipients used in the formulation, not verified in the capsules of the three pharmacies analyzed.

Table 2. Disintegration of the sample capsules containing ranitidine hydrochloride from three compounding pharmacies (F1, F2 and F3) in the state of Mato Grosso

Product	Disintegration time (minutes)
F1	4
F2	4
F3	4

The dosage test establishes the concentration of the active ingredients in the samples analyzed (Brasil, 2007) and the spectrophotometric determination is usually used as a quantification method for drugs, demonstrating practicality, low cost, simple data interpretation and relative sensitivity and specificity (Galo & Colombo, 2009).

According to the Brazilian Pharmacopeia (Brasil, 2010), ranitidine hydrochloride tablets must have a minimum of 90,0%, and maximum of 110,0% of the active ingredient amount declared, the same is considered for capsules.

For the determination of ranitidine hydrochloride in capsules it was used SQR 99.0% purity and the results are shown in Table 3.

It was observed that capsules from the compounding pharmacy F2 did not show minimum acceptance values, 90% of content, established by Brazilian Pharmacopeia (Brasil, 2010). This can be due to a lack of uniform homogenization, mistaken calculation of the drug, no accuracy in the procedure from the operator and even from the polyvinyl chloride (PVC) manual encapsulator, majorly found in compounding pharmacies, which might be damaged over time, compromising the final product in its weight uniformity among the capsule units and differences in its dose uniformity (Silva & Silva, 2014; Aulton, 2005).

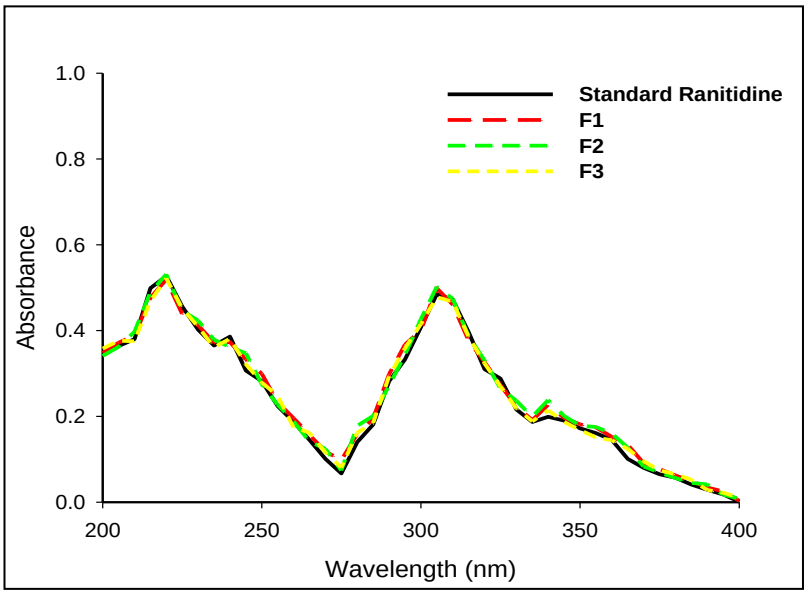

Figure 2: Absorption spectrum of the ultraviolet region of standard ranitidine hydrochloride and sample capsules obtained from three compounding pharmacies (F1, F2 and F3) in the state of Mato Grosso.

Table 3. Dosage of ranitidine hydrochloride capsules from compounding pharmacies F1, F2 and F3 in the state of Mato Grosso

	Standard	F1	F2	F3
Concentration (μgmL $^{-1}$)	6.25	6.58	5.120	5.870
Content (%)	99.0	104.2	81.1	93.0
Standard deviation	0.0040	0.0056	0.0025	0.0049

The uniformity of unitary doses allows the evaluation of the distribution of amount of drug among the batch units (Brasil, 2007). For the capsules to be in accordance with the Pharmacopeic standards, three major parameters are decisive: the choice of shell, the mixing and filling techniques and the characteristics of the drug to be compounded, given that in these compounding steps the majority of the quality deviation happens (Allen, Popovich & Ansel, 2008). It is noticed in the compounding processes that the weight of pharmaceutical forms do not guarantee that they will have the same amount of active ingredient, since the mixing process may not be homogeneous (Ferreira, 2008). According to Segundo Santana (2014), the non-uniformity in the drug distribution may result in sub dose or excessive dose capsules, causing therapeutic inefficiency or side effects, respectively.

The unitary dose uniformity test was performed by content uniformity and is shown in Table 4. The capsule content from the three compounding pharmacies evaluated had acceptance values (VA) lower than 15.0, in other words, within the test acceptance limit.

The VA calculus takes into consideration two fundamental aspects: the average of the active ingredient content and the standard deviation of the results obtained. For the samples to be approved, it is necessary that the average content of the units meet the closest value of the label, in other words 100%, and the individual content of the units show controlled variation (Brasil, 2007).

Table 4. Content uniformity of the ranitidine hydrochloride capsule samples from three compounding pharmacies (F1, F2 and F3) in the state of Mato Grosso

Capsules	F1 Individual content (%)	F2 Individual content (%)	F3 Individual content (%)
1	101.60	91.08	93.61
2	102.00	88.23	94.88
3	104.48	92.35	95.51
4	103.84	94.25	93.93
5	103.52	92.66	91.71
6	107.36	92.98	94.25
7	104.80	95.83	97.73
8	106.08	93.93	92.98
9	102.24	93.30	97.42
10	106.40	96.78	92.35
Average	104.23	93.14	94.44
D.P.R	1.97	2.39	2.00
V.A	7.52	10.12	7.85

D.P.R= relative standard deviation V.A= acceptance value

It can be observed that all samples obtained from the three compounding pharmacies passed the test for showing acceptance values under 15.

Capsules obtained from pharmacy F2, although showed acceptance value under 15 (V.A.= 10,12), did not pass the dosing test, suggesting that the compounding procedure is not being adequate, in other words, it is not following the Good Manufacturing Practices (Brasil, 2007), compromising the therapeutic treatment.

Some authors (Marcatto et al., 2005; Miotto & Adams 2004; Pissato et al., 2006) have reported that several compounded products show satisfying results for weight determination, however they do not pass the unitary dose uniformity and/or dosing tests. This fact is often unnoticed by the compounding pharmacies, once they usually are non-routine tests, being outsourced by pharmacies. In addition, it is given priority in these tests to drugs that contain amount of active ingredient equal or lower than 25 mg, required by ANVISA at RDC 67/2007 and 87/2008.

For a drug to fulfill its therapeutic effect, it is necessary to be dissolved in the organic fluids and, afterwards, be absorbed (Alves, 2017; Marcílio, 2017). The pharmaceutical technology adjuvants, although inert pharmacologically, may influence the speed of the active ingredient release (Gonzalez et al., 1995). The absorption of tablets as well as capsules depends on the drug dissociation from its presentation form, also on the disintegration and dissolution, in physiological conditions. Due to the criticality of the two first steps, dissolution *in vitro* is a test that aims to verify the drug performance *in vivo* (Scheshowitsch, 2007). For this reason in the quality control of pharmaceutical forms administered via oral, the dissolution test is one of the most important tests (Marcílio, 2017).

Results of the samples from the three compounding pharmacies are shown in Table 5 and all samples passed the test for presenting dissolution over 80% of the ranitidine hydrochloride declared amount, as stated in the Brazilian Pharmacopeia (Brasil, 2010).

All samples showed dissolution over 80%, in accordance with the Brazilian Pharmacopeia (Brasil, 2010), however the standard deviation over 5% observed mainly in pharmacy F2, showed the non-uniformity in this process, also evidenced through other tests (dosing and unitary dose uniformity tests).

The quality control parameters analyzed in this study showed that ranitidine hydrochloride capsules obtained from pharmacies F1 and F3 are in accordance with the Pharmacopeic specifications, while the ones from F2 are not. The disapproval of the products from pharmacy F2 demonstrates the lack of homogeneity in the compounding technique used. It is recommended, therefore, a better qualification of employees and suppliers, as well as a strict quality control in order to offer effective and safe products.

Table 5: Percentage dissolved of the ranitidine hydrochloride capsule samples from the three compounding pharmacies (F1, F2 and F3) in the state of Mato Grosso

Capsule	F1 % dissolved	F2 % dissolved	F3 % dissolved
1	95.30	93.08	110.08
2	102.69	103.43	98.26
3	103.43	110.08	93.82
4	105.64	99.73	94.56
5	104.91	109.34	96.04
6	107.12	95.30	99.73
Average	103.18	101.83	98.75
D.P	4.17	7.08	5.98

D.P= standard deviation

Conclusion

It was verified, from the results obtained, that ranitidine hydrochloride capsules from the compounding pharmacies F1 and F3 were approved in all tests set by the Brazilian Pharmacopeia. Capsules compounded by pharmacy F2 were reproved at dosing test. These results indicate the need for reviewing the compounding procedures, which involve the raw material analysis, weighing process, powder mixing, encapsulating process and storage of compounded formulations, aiming to obtain quality products, assuring treatment efficacy and safety.

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