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Article

Pharmaceutical evaluation of compounded furosemide capsules and excipient performance

Pabllo Adelino Estevam Barbosa[1], Roberto Bentes Rozário[1], Tatiane Pereira de Souza[1], Kátia Solange Cardoso Rodrigues dos Santos[1]*

[1]*Faculty of Pharmaceutical Sciences, Federal University of Amazonas, Manaus, AM, Brazil*

Compounding pharmacies play an important role not only in compounding personalized formulations, but also preparing drugs at the same concentration and dosage as those from commercial manufacturers. The excipients used in compounding are generally standardized for many drugs, however they do not consider the intrinsic properties, such as the poor water solubility, of each substance. The excipient performance of commercially available compounded furosemide capsules in 7 compounding pharmacies from Manaus was evaluated and compared them to the performance of the reference medicinal product (Lasix® tablets) and 2 batches of capsules made in-house (T2 and T4) with a standardized excipient. All batches were subjected to tests for weight variation, assay, uniformity of dosage units, disintegration and dissolution profile. Of the 7 different compound formulas acquired in the compounding pharmacies, only 2 passed all tests. Most formulas passed the tests for weight determination, disintegration time and assay, however batches from 2 establishments failed in regards to the uniformity of the content and 5 batches failed the dissolution test. The reference medicinal product was approved in all tests, as were the T2 capsules made in-house with drug-excipient ratio 1:2. These results confirm the importance of the excipient composition, especially for poorly soluble drugs.

Keywords: Drug compounding. Quality control. Capsules. Furosemide. Excipients.

INTRODUCTION

The U.S. Food and Drug Administration (FDA) defines drug compounding as a practice in which a licensed pharmacist or a compounding pharmacy's technician under the supervision of a licensed pharmacist combines, mixes, or alters ingredients to create a medication which is tailored to meet the needs of an individual patient (FDA, 2017). In Brazil, the Brazilian Health Regulatory Agency (ANVISA) regards compounding as a set of pharmaco-technical operations for preparing compounded medicines (ANVISA, 2007).

Traditional pharmaceutical compounding plays a valuable role in providing access to medications for individuals with unique medical needs, which cannot be met by a commercially available product (Gudeman *et al*., 2013). These products may be liquid and/or flavored products for children, dye-free products, products without specific allergens, noncommercial formulations, and other customized products (Guharoy *et al*., 2013), including veterinary drugs. However, consumers, attracted by the lower cost, also seek compounding pharmacies to obtain compounded versions of commercially available manufactured formulas (Markman, Rosa, Koschtschak, 2010; Machado *et al*., 2012).

To introduce new drugs on to the market, pharmaceutical companies go through the pre-formulation stage, in which the impact of the excipient composition on drug dissolution is studied (Narang, Boddu, 2015). In contrast, the compounding pharmacist is free to choose excipients for its compounded drugs, and these are not always the same excipients used by all compounding pharmacies. Traditionally, the effect of excipients on drug product performance was considered of minor importance, due to their pharmacological inactivity (Zarmpi *et al*.,

***Correspondence:** K. S. C. R. dos Santos. Faculdade de Ciências Farmacêuticas. Universidade Federal do Amazonas. Manaus, AM, Brasil. E-mail: katiasantos@ufam.edu.br. ORCID: 0000-0002-1054-2853

2017), however, excipients usually constitute a major component of solid dosage forms and their use contributes to the stability and release of the active pharmaceutical ingredient (API) (Pifferi, Santoro, Pedrani, 1999). Nowadays, though, desirable excipient properties include this functionality, and therefore this variability affects the formulation's performance and drug bioavailability (Dave *et al*., 2015).

According to a census conducted by the Brazilian Association of Compounding Pharmacists (ANFARMAG), in 2018, there were 7545 pharmacies specialized in medication compounding in Brazil and hard-capsule compounding plays an essential role, since this type of product is easy to be manually produced. Nevertheless, bioavailability of the drugs compounded in hard capsules is not always optimized and choosing the appropriate excipients is a key factor in order to improve the dissolution kinetics of active pharmaceutical ingredients (Lamolha *et al*., 2014). The proper choice of excipients during manufacturing or compounding has become even more important since the advent of Biopharmaceutical Classification System (BCS), which has significantly advanced pharmaceutical science by providing a quantitative methodology, based on drug solubility, drug permeability and drug product dissolution, for the identification of products with little risk of bioequivalence failure (García-Arieta, 2014).The BCS framework developed by Amidon *et al*. (1995) divided drugs into 4 categories: Class I. High solubility-high permeability drugs; Class II. Low solubility-high permeability drugs; Class III. High solubility-low permeability drugs; and Class IV. Low solubility-low permeability drugs. This classification serves as a guide for selecting drugs that must be compounded with hydrophilic excipient to improve their dissolution rates.

The Collegiate Board Resolution (RDC) Nº.67/2007 (ANVISA, 2007), partially altered by RDC Nr. 87/2008 (ANVISA, 2008), ruled that all excipients used in compounded medicines must be standardized by pharmacies according to technical knowledge. Before this change occurred, a very common and incorrect practice in the compounding sector was the standardization of a mixture of adjuvants in order to make a single excipient to be used for compounding most formulations (Thompson, Davidow, 2009). Any pharmaceutical substance, either drug or pharmacotechnical adjuvant, has intrinsic individual properties, such as solubility, stability, hygroscopicity, incompatibility, powder flowability, among others. Therefore, the use of a single kind of excipient for all formulations is not recommended, and may interfere in the dissolution of the API, especially one with low water solubility. Thus, the selective addition of excipients in accordance with the specific characteristics of each drug, case by case, becomes the best practice (Ullmann, 2017).

To improve the dissolution and the consequent bioavailability of poorly soluble drugs (BCS classes II and IV drugs), the chosen diluents should preferably be hydrophilic, since their affinity with the aqueous medium can increase the drug dissolution rate. The use of disintegrating and wetting agents can also be useful to facilitate the drug dissolution from solid dosage forms (Machado *et al.,* 2012; Aulton, Taylor, 2013), though it is not advisable to use hydrophobic adjuvants, such as magnesium stearate (Ferreira, 2008).

In Brazil, there have been few studies conducted to evaluate compounding practice and some of them have revealed quality deviations for compounded capsules of diacerein (Conceição *et al.,* 2012), furosemide (Machado *et al*., 2012), hydrochlorothiazide (Oliveira, Yoshida, Silva, 2014; Aglio, 2016; Cruz, 2017), ranitidine (Silva *et al*., 2018) and simvastatin (Markman, Rosa, Koschtschak, 2010; Marques-Marinho *et al*., 2011). In this study, furosemide was selected as the model API since it is a poorly water-soluble molecule (BCS class III drug) and excipient composition must be optimized in order to improve the drug dissolution.

The goal of this study was to investigate the excipient performance of commercially-available compounded furosemide capsules obtained from 7 compounding pharmacies in Manaus, Amazonas state, Brazil (in alphabetic order: Amazônia Fórmula, Artesã, Bioexata, Fórmula Farma, Pharmacy, Pharmapele and Top Pharma). Once obtained, the data was compared with the performance data for the reference medicinal product (Lasix® tablets) and data for the capsules made in-house (T2 and T4) with a standardized excipient which

was specifically formulated to facilitate the dissolution of furosemide, as described in the literature (Villanova, Sá, 2010).

MATERIAL AND METHODS

Compounded capsules of furosemide (batches with 100 capsules of furosemide 40 mg) were ordered from 7 compounding pharmacies located in Manaus, Amazon state, Brazil, and were arbitrarily assigned numerical designations to maintain anonymity. A reference-product batch in tablet form (Lasix® from Sanofi Aventis, Batch: L626964) was purchased for comparison purposes. Furosemide (Brazilian Pharmacopeia Reference Standard - BP-RS) (Batch: 1002) was purchased from National Institute of Quality Control in Health at the Oswaldo Cruz Foundation (INCQS-FIOCRUZ). Furosemide was also purchased from Pharma Nostra (Batch:14094906D) and all excipients and reagents were pharmacopeial and analytical grade, respectively. Equipment employed in tests were: analytical balance EVEN BL-220AB-BI (USA); UV Spectrophotometer EVEN IL-592 (USA); Disintegrating Apparatus NOVA ÉTICA NE-3007 (Brazil) and Dissolution Testing Apparatus NOVA ÉTICA 299/6 (Brazil).

Preparation of Furosemide Capsules Containing the Standard Excipient

The composition of the standard excipient, proposed and tested by Villanova and Sá (2010) for furosemide (Table I), was prepared by mixing pre-sieved powders in a mortar using the geometric dilution method, and then further sieved and conditioned in a capped bottle.

The tapped density of furosemide and excipient powders were determined by Carr's method (1965) and then employed to calculate drug and excipient masses. The resulting formulas were then weighed to fill capsules No.4 (T4) and No.2 (T2), with capacities of 0.21 mL and 0.37 mL, respectively. After the mixing of drug and excipient powders by geometric dilution, capsules were produced using a manual capsule-filling machine.

TABLE I - Composition of the tested excipient to prepare capsules compounded in-house (T2 and T4)

Adjuvant	Quantity (% w/w)	Function
Colloidal silicon dioxide	1.0	Lubricant and adsorbent
Sodium lauryl sulfate	1.5	Lubricant and wetting agent
Sodium starch glycolate	5.0	Disintegrant
Microcrystalline cellulose	25.0	Hydrophilic diluent
Starch	Up to 100.0	Hydrophilic diluent

In vitro quality control tests

All tests were performed according to protocols described in the Brazilian Pharmacopoeia (Farmacopeia Brasileira, 2019), except for the dissolution profile, for which the concentration of the drug at the time of collection was calculated according to the methodology described by Aronson (1993), and shown in a graph depicting the percentage of drug dissolved according to the quantity of time that had elapsed.

Weight determination

To begin with, 20 capsules were individually weighed on an analytical balance. Then, each capsule was opened and its powder content was removed. The capsule was weighed again after being properly cleaned with a brush. The net weight of the contents of each capsule was calculated by subtracting the weight of the capsule from the respective gross weight. Tablets of the reference product were weighed directly. The mean of individual weights ($\bar{m}$), standard deviation (SD) and coefficient of variation (CV) of all batches were determined according to Equations 1, 2 and 3, respectively.

Equation 1

$$\bar{m} = \frac{m_1 + m_2 + \cdots + m_{20}}{20}$$

Equation 2

$$SD = \sqrt{\frac{\sum(m_n - \bar{m})^2}{n-1}}$$

Equation 3

$$CV = \frac{SD}{\bar{m}}$$

Assay

The contents of 20 capsules were mixed in a mortar. In the case of the reference tablets, the 20 units were crushed and also mixed in a mortar. The amount of powder equivalent to 0.2 g of furosemide was calculated and diluted with NaOH 0.1 M in a volumetric flask to prepare 500 mL of stock solution in triplicate. An aliquot of 1 mL was transferred to a volumetric flask and diluted with NaOH 0.1 M to result in 50 mL of furosemide solution at a theoretical concentration of 8 μg.mL^{-1}. A standard solution (using the furosemide reference standard) was prepared at the same concentration. All solutions were analyzed in an UV spectrophotometer at 271 nm using NaOH 0.1M solution for baseline correction. From the measured absorbance, the experimental concentration of furosemide in each replicate was calculated (Equation 4) and the percentage of the labeled amount (or dose) of furosemide could be evaluated (Equation 5), since the estimated concentration allows us to calculate the furosemide mass present in the total volume of the stock solution.

Equation 4

$$C_{exp} = \frac{A_r \cdot C_S}{A_S}$$

Where: C_{exp} – Experimental concentration of furosemide in replicate; A_r – Measured absorbance of the replicate; C_S – Experimental concentration of furosemide (BP-RS) in standard solution; A_S – Measured absorbance of the standard solution.

Equation 5

$$D_b\% = \frac{mf_r \cdot 100}{mf_L}$$

Where: D_b% – percentage of the labeled amount (or dose) of furosemide in the batch (mixed content of 20 units); mf_r – calculated mass of furosemide in the replicate; mf_L – mass of furosemide declared on the label.

Uniformity of dosage units

The uniformity of dosage units was performed by the weight variation method, in which it is assumed that furosemide was homogeneously distributed between the dosage units. The furosemide content per dosage unit was calculated from the measured weight values for the first 10 replicates and the drug content estimate for the batch in assay, according to Equation 6. The mean drug content of these 10 replicates was employed to calculate the acceptance value by Equation 7. When a batch failed the first step of this test, 20 other new replicates were performed in a second stage in order to sample 30 replicates in total. New values for mean of individual contents and acceptance value was calculated. It is important to note that, in the second stage, the maximum and minimum deviations must be calculated according to Equations 8 and 9, respectively, and none of the 30 sample replicates must be outside the deviation range.

Equation 6

$$D_r\% = \frac{mc_r \cdot D_b\%}{\bar{m}}$$

Where: D_r% – percentage of the label claim of furosemide in the replicate; mc_r – weighed mass of the powder content in the replicate; D_b% – percentage of the label claim

of furosemide on a representative sample of the batch (mixed content of 20 units);($\bar{m}$ - mean weigth of the powder content.

Equation 7

$$AV = |M - \overline{D_r\%}| + k \,.\, SD$$

Where: AV – acceptance value; $\overline{D_r\%}$ - mean of percentage of the label's stated quantity of furosemide in replicates; M – reference value (if 98.5% ≤ $\overline{D_r\%}$ ≤ 101.5%, then M = $\overline{D_r\%}$; if $\overline{D_r\%}$ < 98.5%, then M = 98.5%; if $\overline{D_r\%}$ > 101.5%, then M = 101.5%, k – acceptability constant (if the number of samples was 10, then k = 2.4; if the number of samples was 30, then k = 2.0); SD = standard deviation of percentage of the stated amount of furosemide on the label amount (or dose) in replicates.

Equation 8

$$D_{max} = [1 + (L2 \,.\, 0.01)] \,.\, M$$

Where: D_{max} – value of maximum deviation for D_r% of each replicate; L2 –maximum allowed range for deviation in the second stage (it is constant = 25); M – reference value (if 98.5% ≤ $\overline{D_r\%}$ ≤ 101.5%, then M = $\overline{D_r\%}$; if $\overline{D_r\%}$ < 98.5%, then M = 98.5%; if $\overline{D_r\%}$ > 101.5%, then M = 101.5%).

Equation9

$$D_{min} = [1 - (L2 \,.\, 0.01)] \,.\, M$$

Where: D_{min} – value of minimum deviation for D_r% of each replicate; L2 – limit value in the second stage (it is constant = 25%); M – constant (if 98.5% ≤ $\overline{D_r\%}$ ≤ 101.5%, so M = $\overline{D_r\%}$; if $\overline{D_r\%}$ < 98.5%, so M = 98.5%; if $\overline{D_r\%}$ > 101.5%, so M = 101.5%).

Disintegration Test

To determine the time necessary for the complete disintegration of capsules or tablets, 6 units of each batch were placed in the baskets of the disintegrating apparatus, which used disks and distilled water at 37 ± *2* °C as a medium. The taken for complete disintegration to occur was observed and expressed as a mean of 6 replicates.

Dissolution Test

Dissolution testing experiments were performed in a dissolution testing apparatus using paddles rotating at 50 rpm and the addition of 900 mL of pH 5.8 phosphate buffer at 37 ± 2 °C as dissolution medium. In the first step, 6 replicates of each batch were assayed. After 60 minutes, a 10 mL aliquot was withdrawn and filtered with a 0.45 µm pore-size syringe filter. Then, samples were diluted with pH 5.8 phosphate buffer and their respective absorbance levels were measured using an UV spectrophotometer at 271 nm, using pH 5.8 phosphate buffer for baseline correction. A calibration curve constructed with furosemide (BP-RS) (r^2 = 0.9993) was used to convert the sample UV absorbance data to the furosemide concentration in the dissolution medium. Batches were approved if all replicates dissolved 85% of the labeled concentration within 60 minutes. When a batch failed the first step of the test, 6 other new replicates were performed under the same conditions in order to calculate the mean amount of dissolved drug (considering the 12 replicates). If this mean value was greater than 80% of the labeled concentration and none of the replicates had dissolved to less than 65% of the labeled content, batches were approved. If this criterion was still not met, 12 more replicates were carried out in a third stage in order to calculate the new mean amount of dissolved drug (considering the 24 replicates). To be approved in this last stage, batches had to present a mean value which was greater than 80% of the labeled concentration and no more than 2 replicates had to have dissolved to less than 65% of the labeled content.

Dissolution Profile

To construct the dissolution profile, dissolution testing experiments were carried out under the same conditions as described above. Aliquots of 10 mL were withdrawn from the dissolution medium (the same volume was replaced with a fresh solution of pH 5.8 phosphate buffer) at 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes.

After a filtration step using a 0.45 µm pore-size syringe filter, all samples were diluted with pH 5.8 phosphate buffer and the respective levels of absorbance were measured using an UV spectrophotometer at 271 nm, with pH 5.8 phosphate buffer for baseline correction. The same calibration curve constructed for dissolution test was also used to convert the sample UV absorbance data to the furosemide concentration data in dissolution medium.

RESULTS AND DISCUSSION

Furosemide is a Class IV drug according to BCS, which means that it is a drug which has low water solubility and a low permeation rate in biological membranes. In order to improve the percentage of the drug dissolved in the medium and, consequently, the bioavailability of these drugs, it is necessary to work on the excipient composition. The ideal excipient improves the wettability via the dissolving medium and favors the breakdown of the pharmaceutical form, thus preventing the drug forming lumps with a dry core (Zvonar *et al.*, 2010).

Villanova and Sá (2010) conducted studies on the formulation of excipients for various drugs with water solubility problems. For furosemide, they proposed an excipient (Table I) composed of microcrystalline cellulose and corn starch as hydrophilic diluents, colloidal silicon dioxide as a glidant, sodium lauryl sulfate as a wetting agent and sodium starch glycolate as a super disintegrant. The excipient indicated in the literature was used in the compounding of our in-house capsules in order to compare the performance of the excipients utilized by compounding pharmacies in Manaus. For our in-house capsules, 2 formulations were manipulated: one that used capsule No. 4 (capacity: 0.21 mL), where furosemide represented 48% of the mass of the content (T4), and another that used capsule No. 2 (capacity: 0.37 mL), where furosemide represented 25% of the mass of the content (T2), that is, in the smaller capsule, the drug/excipient ratio is practically 1:1, whereas in the larger capsule, the proportion was 1:3, further diluting the dose of the drug in the excipient mass.

The composition of the excipients utilized by the 7 studied compounding pharmacies (P1, P2, P3, P4, P5, P6 and P7), as shown in Table II, was obtained from the establishments via direct contact with the pharmacist or owner, however, the percentages of each component were not informed. The composition of the excipient used in the manufacture of the reference tablet (R) was obtained from the package insert.

TABLE II - Declared excipient composition of furosemide capsules contained in compounding capsules (P1, P2, P3, P4, P5 P6 and P7) and the reference medicinal product (R) compared to our in-house capsules (T2 and T4)

Adjuvant	Function	Sample								
		P1	P2	P3	P4	P5	P6	P7	T2/T4	R
Magnesium stearate	Lubricant		X	X	X			X		X
Coloidal silicon dioxide	Adsorbent, glidant		X		X	X		X	X	
Sodium lauryl sulfate	Lubricant, wettingagent				X			X	X	
Sodium starch glycolate	Disintegrant								X	
Talc	Diluent, lubricant			X	X			X		X
Starch	Diluent, disintegrant		X	X	X	X		X	X	X
Mannitol	Diluent	X								
Microcrystalline cellulose	Diluent, Disintegrant		X	X		X	X		X	
Lactose	Diluent						X			X

Of the 7 pharmacies evaluated, 5 of them used starch in the compounding of the drug, this being the most commonly employed component. In the compounding of the sample from P1, only one diluent (mannitol) was used as an excipient, which may demonstrate lack of concern or lack of knowledge about the care that should be taken when choosing adjuvants that must be present in Class IV drug formulations, since it is well established that this class should prioritize the use of hydrophilic diluents, disintegrating agents and wetting agents to accelerate the dissolution of drugs (Villanova, Sá, 2010). Pharmacies P4 and P7 used the most components to produce the excipient. However, none of them chose a disintegrant, such as sodium starch glycolate or croscarmellose sodium, which are recommended to facilitate the dissolution of Class IV drugs. Another observation that stands out was the high use of magnesium stearate as a lubricant, since this adjuvant, due to its hydrophobic characteristic, usually reduces, or even compromises, the dissolution time (Joshi, Duriez, 2004) and must be avoided in drugs with water solubility problems.

The determination of the mean weight is an important measure to infer if the distribution of the powder in the capsules was carried out homogeneously in the filling stage (Aulton, Taylor, 2013), This has an impact on dosage rigor, since heavier or lighter capsules may contain, respectively, more or less drug mass. According to the Brazilian Pharmacopoeia, a batch of capsules or pills will pass this test when no more than 2 units are found outside the range. In the case of our study, this is ± 10% for capsules with a mean weight less than 300 mg (P1, P2, P3, P4, P5, P6, P7, T2 and T4) and ± 7.5% for tablets with a mean weight between 80 and 250 mg (R). According to Figure 1, batches from P1, P2, P5, P7, T2, T4 and R passed the test, since all 20 units tested fell within the calculated range. Although batches from P4 and P6 present, respectively, 1 and 2 units outside the range, they were still approved in the tests since, according to the Brazilian Pharmacopoeia, up to 2 units outside the ± 10% variation limit are tolerated, provided that they are within double the percentage indicated ($\overline{X}$ ±20%). However, the batch from P3 failed the weight determination, since it presented 3 units outside the calculated range.

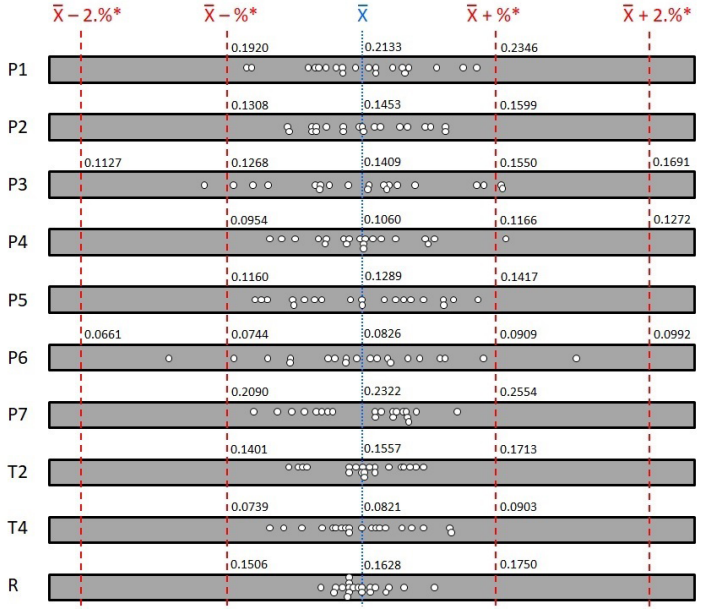

FIGURE 1 - Individual weight distribution of the 20 units of tested capsules and tablets. The dotted line delimits the mean weight ($\overline{X}$) and the dashed lines indicate the maximum ($\overline{X}$ + %) and minimum ($\overline{X}$ – %) variation limits, as well as double the maximum variation limit ($\overline{X}$ + 2. %) and minimum ($\overline{X}$ – 2. %), though the latter should be observed only when there are up to 2 units outside the first range.

*% = 10 for the capsules (P1, P2, P3, P4, P5, P6, P7, T2 e T4) and % = 7.5 for the tablet (R).

Although it is not recommended by the Brazilian Pharmacopoeia, standard deviation and the coefficient of variation were calculated to corroborate the analysis of the quality of the compounding of the capsules regarding the distribution of the powders (Table III). The batches with the lowest coefficient of variation values were observed for R (1.43%) and T2 (2.94%) and are consistent with the distribution of unit values which are very close to the mean, as shown in Figure 1. The highest coefficient of variation was observed for P6 (6.63%) and P3 (6.46%), and explain the occurrence of, respectively, 2 and 3 capsules outside the first range of ± 10%.

TABLE III - Mean weight calculated for all studied batches

Sample	Mean ± SD (g)	CV (%)
P1	0.2133 ± 0.0097	4.53
P2	0.1453 ± 0.0054	3.74
P3	0.1409 ± 0.0091	6.46
P4	0.1060 ± 0.0045	4.23
P5	0.1289 ± 0.0066	5.16
P6	0.0826 ± 0.0055	6.63
P7	0.2322 ± 0.0092	3.98
T2	0.1557 ± 0.0046	2.94
T4	0.0821 ± 0.0030	3.67
R	0.1628 ± 0.0023	1.43

SD = standard deviation; CV = coefficient of variation or relative standard deviation.

The analysis of the composition of the excipients used by compounding pharmacies (Table II) shows that P6 did not use any adjuvants to improve the flow of the powders. Furthermore, on the scale of flowability (Hoag, 2017), lactose is characterized as a powder with fair to passable flow properties (Jain, Ahmad, Khar, 2012). The absence of lubricant or glidant, associated with the deficient lactose flow properties, explains the lack of homogeneity in the distribution of powders in the filling stage of the P6 capsules. In the case of batch P3, since powders with flow problems were not used, the failure in the test may have been due to an error by the compounding pharmacy technician or pharmacist. A significant proportion of the pharmacies (4 establishments) used colloidal silicon dioxide in their formulation, which may explain the good weight uniformity observed in these formulations. The use of the glidant improves the flow, causing free flow of the powder into the capsule, without the need to force it in or hit the tray so that the powder settles inside the capsule, which leads to a better distribution. It is also important to report that the content of the P2 capsules was quite compacted, which suggests that too much force was used to insert all the powder in the capsule, and this can cause a delay in the dissolution of the drug, and negatively affect the dissolution profile.

According to the monograph for furosemide in the Brazilian Pharmacopeia, each dosage unit must contain a minimum of 90% and a maximum of 110% of the amount of furosemide as declared on the label. Table IV shows that only batch P6 failed in this regard, since it had a content of 81.62%, which is below the minimum limit of 90%. All others were approved for having furosemide levels within the specified limit (90 to 110%). The low concentration of drug in this sample may be the result of an error in weighing due to poorly calibrated scales or an error caused by the technician. To minimize this problem, it is of fundamental importance that the calibration of the scales is incorporated into the daily routine, and the team, periodically evaluated and trained to improve their skills. The low content detected could also be due to the loss of powder during the encapsulation step. In this case, the encapsulation yield (or percentage of loss) must be calculated and, according to ANFARMAG (2015), when the powder loss is greater than 4%, it is of fundamental importance that the handler weighs excessively equivalent drug excess mass losses so that the capsules contain the labeled dose.

TABLE IV - Furosemide content as a mean percentage of label's claim for compounded batches (P1 to P7), batches made in-house (T2 and T4) and batch of the reference medicinal product (R)

Sample	Furosemide content (%)			
	Replicates			Mean ± SD
	1	2	3	
P1	96.32	93.11	94.72	94.72 ± 1.61
P2	97.47	101.15	96.09	98.24 ± 2.61
P3	105.06	107.12	105.51	105.90 ± 1.09
P4	105.97	108.04	95.17	103.06 ± 6.91
P5	91.27	97.70	94.26	94.41 ± 3.22
P6	85.06	75.87	83.92	81.62 ± 5.01
P7	103.22	98.85	93.34	98.47 ± 4.95
T2	106.05	103.06	104.67	104.67 ± 1.50
T4	97.70	101.61	102.76	100.69 ± 2.65
R	104.60	103.91	103.68	104.60 ± 0.48

SD = standard deviation.

The uniformity of dosage units test was determined by the Weight Variation method. Table V shows the results obtained in the first stage of the test, where the content of 10 units of capsules or tablets is estimated. If the calculated acceptance value (AV) is less than maximum allowed acceptance value (L1 = 15), the batch is approved, as can be observed for batches P1, P2, P4, P7, T2, T4 and R. Batches that did not meet this criterion (P3, P5 and P6) proceeded to the second stage of the test, where a new AV value was calculated from the estimated content for 30 capsule units. This should not be higher than L1. In addition, to be considered approved in the second stage, the batch must also not have any individual content greater than D_{max}, or less than D_{min}. Only batch P5 was approved in the second stage with an AV less than 15 (14.52). Batches P3 and P6 failed with AV values of 17.08 and 27.98, respectively, with P6 still showing 2 units (69.33% and 70.02%) lower than D_{min} (73.88%).

TABLE V - Amount of furosemide as a percentage of the labeled dose (D_r%) in first and second stage, calculated by weight variation test

Sample	1st Stage (n = 10)		2nd Stage (n = 30)			
	D_r% ± SD	AV	D_r% ± SD	AV	D_{max}	D_{min}
P1	93.64 ± 4.13	14.77	—	—	—	—
P2	97.12 ± 4.14	11.31	—	—	—	—
P3	104.69 ± 7.47	21.12	105.26 ± 6.66	17.08	126.88	76.13
P4	101.89 ± 5.06	12.55	—	—	—	—
P5	93.34 ± 4.89	16.90	92.86 ± 4.44	14.52	123.13	73.88

TABLE V - Amount of furosemide as a percentage of the labeled dose (D_r%) in first and second stage, calculated by weight variation test

Sample	1st Stage (n = 10)		2nd Stage (n = 30)			
	D_r% ± SD	AV	D_r% ± SD	AV	D_{max}	D_{min}
P6	80.69 ± 4.51	28.63	81.54 ± 5.51	27.98	123.13	73.88**
P7	97.35 ± 4.36	11.62	—	—	—	—
T2	106.01 ± 2.90	11.47	—	—	—	—
T4	99.55 ± 4.15	9.97	—	—	—	—
R	102.88 ± 1.88	5.90	—	—	—	—

SD = standard deviation; AV = acceptance value; D_{max} = value of maximum deviation; D_{min} = value of minimum deviation.

*The number of asterisks refers to the number of units below D_{min}

Failure in this test points to two probable situations: (1) inefficiency in the mixing stage between drug powders and adjuvants, since the 40 mg dose of furosemide was not well-distributed among the units or (2) incorrect weighing which interfered with drug content per dose unit. Batch P3 seems to fit in the first situation, since it presented an excessive amount of furosemide (content was 105.90 ± 1.09%). However, batch P6 seems to fit both situations, since the estimated furosemide content in 30 units fluctuated between 69.33 to 94.52% and had the lowest content (81.62% - Table IV) among the establishments studied, which demonstrates a problem in weighing the drug. In order to obtain a homogeneous and uniform mixture, it is preferable that the density and particle size of the powders are similar. This factor is particularly important, when a drug delivered in low dosage is mixed with excipients of a larger amount (Yalkowsky, Bolton, 1990).

The disintegration test reflects the time that the pharmaceutical form takes to achieve the complete disintegration of the tablets or dissolution of the casings, in the case of the capsules. The Brazilian Pharmacopoeia recommends that immediate-release tablets containing furosemide should be completely disintegrated in a maximum of 30 minutes, while the capsules should occur within 45 minutes. Figure 2 shows the mean time taken for the disintegration of the studied samples. As expected, the tablets (R) were the first to disintegrate, with a time of 1m50s ± 26s, and were thus approved in the test. Among the approved capsule batches, P2 showed the fastest disintegration (3m 36s ± 39s) and T4, the slowest (15m 41s ± 6m 02s). The only batch that failed the test was P6, which had a mean disintegration time of 46m 47s ± 14m 31s, and the last replicate to dissolve took 67m 42s for complete disintegration. Some factors can interfere with the speed of disintegration of the gelatinous casings, such as composition, humidity, thickness of the gelatinous layer and the presence of a coating to purposely modify the yield of the drug (Aulton, Taylor, 2013). Faced with such a discrepant result, the pharmacy was consulted to collect information about the type of capsule used for compounding P6. The pharmacist responsible for the establishment explained that, because they were out of ordinary capsules on the day of compounding, they filled the prescription with gastro-resistant capsules. This explains the long time for disintegration, since the test was carried out in a neutral aqueous medium and gastro-resistant capsules resist acidic pH levels and disintegrate more quickly in more alkaline pH levels. In any case, this substitution should be discouraged, since, in the absence of a specification in a medical prescription regarding the need for a modified release, all solid forms must be prepared for immediate release. In addition, the delay in the disintegration of the pharmaceutical form affects the dissolution of the drug, also delaying the start of pharmacological action and the plasma levels of the drug (Gullapalli, Mazzitelli, 2017).

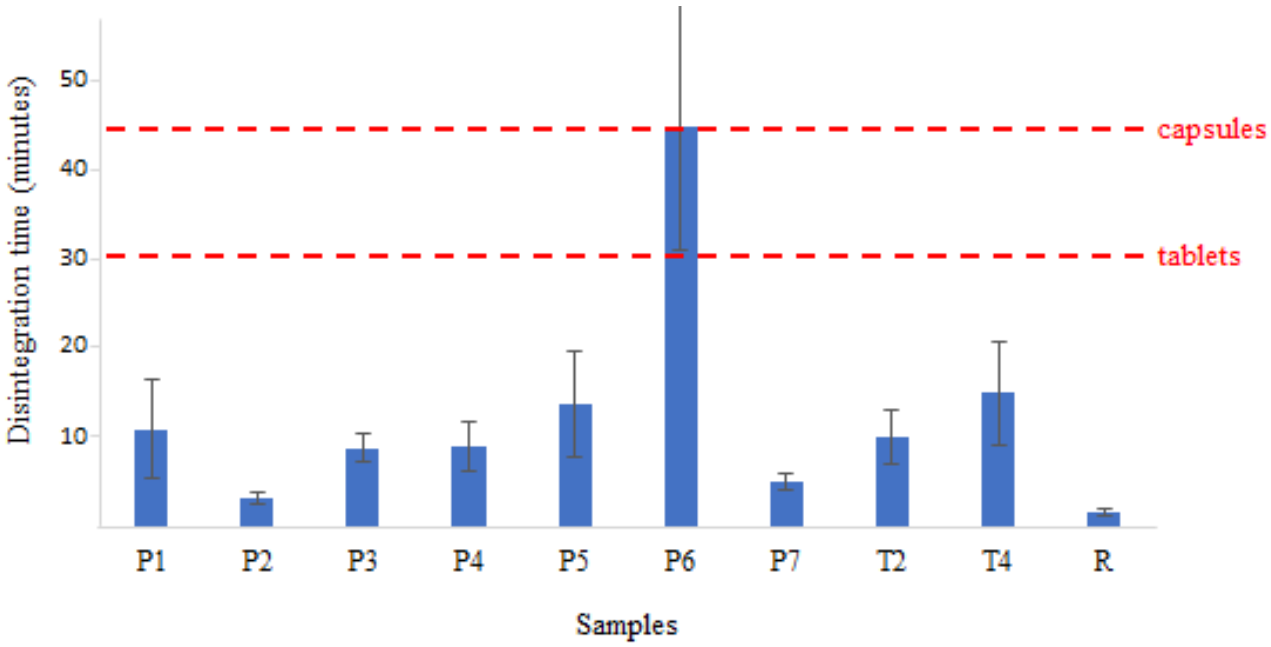

FIGURE 2 - Mean (n = 6) disintegration time for the capsules (P1, P2, P3, P4, P5, P6, P7, T2 and T4) and tablets (R). Dashed lines represent the maximum time allowed by the Brazilian Pharmacopoeia for the dissolution of 40 mg tablets (30 minutes) and capsules (45 minutes) of furosemide.

The Brazilian Pharmacopoeia provides a specific monograph for furosemide tablets, but not for furosemide capsules. As both are intended for the immediate release of furosemide, the experimental conditions recommended in the pharmacopoeia for furosemide tablets were also used for the compounded furosemide capsules. The complete test consists of 3 steps (Table VI). To be approved in the first stage, each of the 6 units tested must have dissolved 85% of the amount of furosemide declared on the label. Only R passed the first stage for having completely released the furosemide content in 30 minutes. Samples P5 and T2 were not approved at this stage because, despite having a mean time of above 85%, they presented one (82.20%) and two (83.34 and 84.88%) replicates below 85%, respectively. The other samples had means ranging from 79.10 to 17.21%.

TABLE VI - Mean furosemide dissolution based on the percentage of the amount of furosemide declared on the label for compounded batches (P1 to P7), batches made in-house (T2 and T4) and batch of the reference medicinal product (R) after 60 minutes of testing

Sample	Mean of Dissolved Furosemide ± SD (%)		
	1st Stage (n = 6)	2nd Stage (n = 12)	3rd Stage (n = 24)
P1	64.96 ± 6.43 ***	65.62 ± 6.02 ******	—
P2	59.19 ± 2.71 ******	59.23 ± 2.95 **********††	—
P3	70.28 ± 4.63 **	70.27 ± 4.73 ****	—
P4	79.10 ± 10.80 *	80.97 ± 10.95 **	81.24 ± 10.85 ***
P5	86.59 ± 2.26	86.79 ± 1.93	—
P6	17.22 ± 2.14 ††††††	17.09 ± 1.90 †††††††††††	—

TABLE VI - Mean furosemide dissolution based on the percentage of the amount of furosemide declared on the label for compounded batches (P1 to P7), batches made in-house (T2 and T4) and batch of the reference medicinal product (R) after 60 minutes of testing

Sample	Mean of Dissolved Furosemide ± SD (%)		
	1st Stage (n = 6)	2nd Stage (n = 12)	3rd Stage (n = 24)
P7	63.24 ± 4.32 ***	62.69 ± 3.49 *********	—
T2	87.49 ± 2.78	88.79 ± 2.46	—
T4	45.99 ± 5.42 ††††††	—	—
R	109.03 ± 2.69	—	—

* The number of asterisks refers to the number of units below 65%
† The number of crosses refers to the number of units below 55%

For batch approval in the second stage of the dissolution test, the new mean calculated for the 12 replicates must be greater than 80%, and none of the units tested must have dissolved less than 65% of the amount of furosemide declared on the label. Samples P5 and T2 meet this criterion and were approved in the second stage. Batch P4 presented a mean of 80.97%, but was not considered approved because one of the 12 units presented a content of below 65% (63.61%). In stage 3, the new mean calculated for 24 replicates must still be greater than 80%, but tolerates up to 2 units below 65%, however, none of them must be less than 55% of the amount of furosemide declared on the label. The P4 sample failed to comply with this criterion, because, despite a mean of above 80% (81.24%), 3 units revealed a content of below 65% (62.17; 63.61 and 64.19%). All other batches failed in the second stage, without the need to perform the third stage, since all of them presented more than 2 units below 65%, with P2 and P6 also presenting units below 55%.

In addition to the dissolution test, curves were constructed with the dissolution profile of all batches (Figure 3).

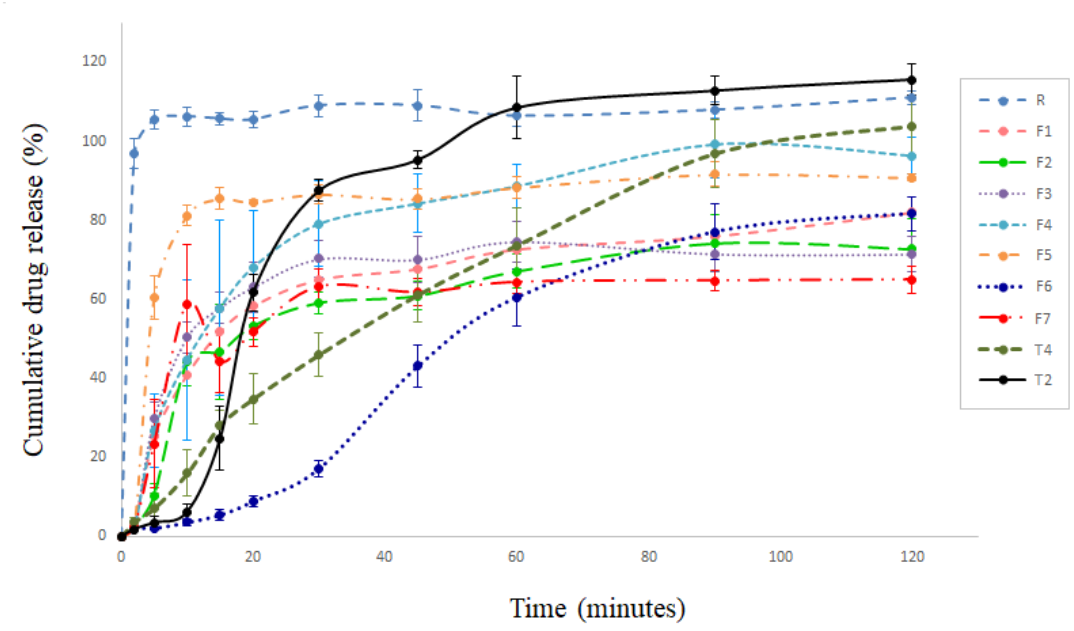

FIGURE 3 – Dissolution profile (n = 6) for the capsules (P1, P2, P3, P4, P5, P6, P7, T2 and T4) and tablets (R) of furosemide.

In the first 5 minutes, all the furosemide contained in R was already dissolved. In terms of the curve profile, the P5 sample was the one that came closest to the behavior of reference medicine, because, within 10 minutes, the drug content had already solubilized, though only reaching a level around 95%. In the other formulations, the speed of dissolution of the furosemide was slower. Some reached the maximum level over time, such as P4 in 90 minutes, and T4 and T2, which were manipulated with the excipient as standardized in the literature, and reached the level maximum in 90 and 60 minutes, respectively. It can also be observed that the P7 capsules were the ones with the lowest percentage of dissolved drug, around 64%, and reached the plateau in 90 minutes, while P6 had the lowest dissolution speed, probably delayed by the incorrect use of the gastroresistant capsules.

The importance of choosing the correct formulation components and optimizing their concentration is necessary since the speed and extent of the released drug can be substantially altered as a result of pharmaceutical adjuvants (Castro *et al*., 2003). Therefore, attention should be paid to the type, quantity and quality of adjuvants to be used in the formulation. Studies have found that identical active ingredients have a variable dissolution rate when handled differently, depending on the excipient and/or concentrations involved (Markman, Rosa, Koschtschak, 2010; Marques-Marinho *et al*., 2011; Machado *et al*., 2012; Oliveira, Yoshida, Silva, 2014). In certain cases, several capsule formulations have caused a difference in percentage of the drug dissolved in the medium, which can decrease or even inhibit the pharmacological effect of the drugs. Therefore, it is necessary to establish criteria regarding the use of excipients.

Different excipient standards were used by the pharmacies analyzed, and P4 and P7 used a standard excipient formulation called DILUCAP, which is composed of magnesium stearate (0.05%), colloidal silicon dioxide (1%), sodium lauryl sulfate (1 %), talc (30%) and starch (qs 100%) (Ferreira, 2008). This excipient is often used by compounding pharmacies to meet most medical prescriptions. However, with the advent of BCS, DILUCAP is not a suitable excipient formulation for compounding Class II and IV drugs (due to its low water solubility), since talc and magnesium stearate have hydrophobic characteristics, which can limit the speed and extent of dissolution of the active ingredient. In spite of this, after 60 minutes, of all compounding pharmacies, P4's capsules were the ones that reached the highest percentage of dissolved furosemide in the medium, whereas P7's capsules were those that demonstrated less dissolution. The performance of DILUCAP, and its variation between the extremes, shows how erratic the dissolution of furosemide via this excipient can be. However, it is worth noting that batch and manufacturer differences can also interfere with the functionality of excipients (Dave *et al*., 2015; Elder, Kuentz, Holm, 2015).

Capsules P1, P5 and P6, which did not use magnesium stearate, had higher percentages of drug dissolution over time. Samples P2, P3 and P7 show the impact of magnesium stearate on the complete dissolution of the furosemide. This is especially noteworthy since all of these batches had levels of 98.24; 105.90 and 98.47% furosemide, respectively (Table IV), but only allowed the maximum dissolution of 72.75; 71.49 and 64.97%, respectively, during 120 minutes of the test.

Despite being most commonly used in the preparation of tablets, disintegrating agents have recently been included in capsule formulations to aid in the disintegration and distribution of capsule contents in the stomach (Evans *et al*., 2005). Super-disintegrants, such as croscarmellose and sodium starch glycolate, act by swelling due to water absorption, which increases their original volume by several times. Crospovidone, another super-disintegrant, acts differently by absorbing water via capillary action and regains its normal structure releasing an amount of energy capable of breaking the tablet (Aulton, Taylor, 2013).

Wetting agents with surfactant activity, such as sodium lauryl sulfate, are added to the formulation to facilitate wetting by gastrointestinal fluids and facilitate the dissolution and absorption of drugs (Ferreira, 2008). This is due to the ability of the surfactant to reduce the solid/liquid interfacial tension, allowing the dissolution medium to wet the solid more efficiently, which contributes to the dissolution of the drug (Thompson, Davidow, 2009). To optimize the dissolution of poorly soluble drugs, such as furosemide, the best results are obtained by using soluble diluents together with a wetting agent, such as 1% sodium lauryl sulfate (Aulton, Taylor, 2013).

The excipient standardized by Villanova and Sá (2010) is indicated for the delivery of low water-solubility drugs because it has, in addition to hydrophilic diluents (starch and microcrystalline cellulose), a disintegrating agent (sodium starch glycolate and croscarmellose sodium), a wetting agent (sodium lauryl sulfate) and a non-hydrophobic lubricant (colloidal silicon dioxide). Its impact on the dissolution of furosemide was observed in T2 and T4. The first capsule compounded was T4, which, despite the presence of the standardized excipient, failed the dissolution test because it did not meet the criterion of allowing the dissolution of 85% of the declared amount in 30 minutes; it reached an average of 45.99% (Table VI). However, the dissolution profile reveals that, despite the prolonged time (90 minutes), this excipient was able to guarantee the dissolution of 100% of the delivered dose, which was not seen with the excipients of the other manipulated capsules. As previously discussed, the ratio of drug to excipient in T4 is 1:1, that is, the hydrophobic characteristics of the drug molecule are not being completely compensated by the excipient when they are mixed in equivalent amounts. While there is an increase in the volume of the capsule in T2, the dose of the drug to be delivered continues to be the same. However, there is more space to be filled with excipient, which increases by 3 times the proportion of excipient in relation to the furosemide. This causes the drug particles to become more diluted in the excipient bed and further away from each other, decreasing the chances of aggregation and favoring the performance of adjuvants in improving the dissolution of the furosemide. As can be seen in Figure 3, in 30 minutes more than 80% of the dose was already dissolved and, in 60 minutes, the dissolution of furosemide was already complete and equated to R.

Table VII summarizes the approvals and failures of the batches studied in all the pharmacopeial tests to which they were submitted.

TABLE VII: Summary of approvals and failures for all batches of products analyzed

Quality test	P1	P2	P3	P4	P5	P6	P7	T2	T4	R
Weight determination	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
Assay	✓	✓	✓	✓	✓	X	✓	✓	✓	✓
Uniformity of content										
S1	✓	✓	X	✓	X	X	✓	✓	✓	✓
S2	—	—	X	—	✓	X	—	—	—	—
Disintegration	✓	✓	✓	✓	✓	X	✓	✓	✓	✓
Dissolution										
S1	X	X	X	X	X	X	X	X	X	✓
S2	X	X	X	X	✓	X	X	✓	X	—
S3	X*	X*	X*	X	—	X*	X*	—	X*	—

S = stage of the test.
*S3 was not performed experimentally because S1 and S2 already presented unit values that would not meet the acceptance criteria of S3.

In addition to R, the only approved capsules in all requirements were P5 and T2 capsules, although both failed in Stage 1 of the dissolution test. However, T2 performed markedly better than P5, in respect to:

- lowest coefficient of variation in the weight determination (2.94% versus 5.16%);
- highest dosage of the drug in the content test (104.67 ± 1.50 versus 94.41 ± 3.22);
- approval in the first stage of the content uniformity test, whereas P5 only achieved approval in the second stage;
- shortest disintegration time of the capsules (the last sextuplicate disintegrated within 14 minutes and 56 seconds versus 18 minutes and 54 seconds of P5);
- dissolution of 100% of the declared dose in 60 minutes of testing, while P5 established a level of around 91% by the end of the 120 minutes of the test.

This study evaluated furosemide capsules purchased from 7 compounding pharmacies and found most of them to vary significantly from the acceptance criteria of the licensed product. The results confirm the importance of the appropriate choice of adjuvants that will compose the excipient, especially in the delivery of drugs with poor water solubility (Class II and IV). The study proved that the excipient standardized by Villanova and Sá (2010) is suitable for providing complete dissolution of furosemide in the medium, provided that it is added in a proportion which is greater than 50% in relation to the drug.

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