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Captopril 25 mg tablets stability assessment in different primary packaging materials

Avaliação da estabilidade de comprimidos de captopril 25 mg em distintos materiais de embalagem primária

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ABSTRACT

Introduction: Packaging is used to provide protection and information, from the production to the administration of a formulation. It is essential to define the primary packaging, for keeping the therapeutic efficacy of drugs, safety of users and for protecting drugs from instability. **Objectives:** The main objective of this study was to assess the stability of captopril 25 mg tablets in different primary packaging materials. **Method:** The characterization (IR, DSC and physical tests) of the packaging materials used for captopril was carried out prior to the manufacture of tablets. Tablets were also characterized by physical-chemical analysis, comparative dissolution profile and stability studies. **Results:** The characterization of packaging materials was crucial for understanding the behavior of captopril when packed in each material. Materials with significant barrier, as blisters PVC/PVdC 90 g.m^{-2} and hard aluminum and PVC/PE/PVdC and hard aluminum showed satisfactory results in a second stage, S2. On the contrary, lower barrier materials as blisters PVC/PVdC 40 g.m^{-2} and hard aluminum did not present dissolution analysis S2. **Conclusions:** The aluminum strip presented the best results. And the batch in glass bottle, although packaged in excellent material, was disapproved in accelerated stability.

KEYWORDS: Packaging; Stability; Captopril; Tablets

RESUMO

Introdução: A embalagem farmacêutica é utilizada para prover proteção e informação, da produção à administração de uma formulação. É essencial que seja feita uma avaliação criteriosa da embalagem destinada a um medicamento, a fim de manter a eficácia terapêutica e a segurança dos usuários e de proteger o medicamento de possíveis instabilidades. **Objetivo:** O objetivo principal deste estudo foi avaliar a estabilidade de comprimidos de captopril 25 mg em distintos materiais de embalagem primária. **Método:** A caracterização (IV, DSC e testes físicos) dos materiais de embalagem utilizados para o captopril foi realizada anteriormente à fabricação dos comprimidos. Os comprimidos foram caracterizados por análise físico-química, perfil de dissolução comparativo e estudos de estabilidade. **Resultados:** A caracterização da embalagem foi decisiva para compreender o comportamento do captopril quando acondicionado em cada material. Materiais com barreira expressiva, como blísteres de PVC/PVdC 90 g.m^{-2} e alumínio duro e PVC/PE/PVdC e alumínio duro demonstraram resultados satisfatórios em um segundo estágio (S2), enquanto materiais de menor barreira, como blísteres de PVC/PVdC 40 g.m^{-2} e alumínio duro, não apresentaram análise de dissolução S2. **Conclusões:** O lote em *strip* de alumínio apresentou os melhores resultados. E o lote em frasco de vidro, apesar de acondicionado em excelente material, foi reprovado na estabilidade acelerada.

PALAVRAS-CHAVE: Embalagem; Estabilidade; Captopril; Comprimidos

INTRODUCTION

In the form of 25 mg plain tablets, captopril is part of the Brazilian National List of Essential Medicines (Rename). An angiotensin-converting-enzyme inhibitor, it is used to control mild, moderate and severe high blood pressure, alone or in combination with other classes of antihypertensive agents[1,2].

High blood pressure has a high economic and social cost for health systems and is considered one of the main causes of morbidity and mortality in most developed countries. Its worldwide prevalence is approximately 30%, and it is an important risk factor for stroke, ischemic heart disease and heart failure[3].

In Brazil, cardiovascular diseases account for 33% of deaths with known causes. These diseases were the primary cause of hospitalization in the public sector between 1996 and 1999 and accounted for 17% of hospitalizations of individuals aged 40 to 59 and 29% of those aged 60 or older[4].

Progress in scientific research shows that the safety and efficacy of medicinal products cannot be attributed solely to the intrinsic pharmacological properties of the drug. Factors related to their physico-chemical properties, as well as those related to fillers, primary packaging materials, in addition to the manufacturing process, have been considered responsible for changes in the effect of the medicines, since they can affect the bioavailability of the drugs[5].

This article presents an investigation based on stability studies of captopril 25 mg tablets, packaged in different primary packaging materials, since product stability monitoring tests showed dissolution results in S1 below the values specified by BP 5th Ed, under conditions of 30 ± 2ºC/75 ± 5% RH, after the period of three months. With this trend towards dissolution tests in S2, it was necessary to evaluate carefully whether the possible causes of the problem correlated with the primary packaging material that was used.

METHOD

Packaging material characterization

Physico-chemical and microbiological analysis

The packaging materials (PVC/PVdC films 40 g.m^{-2}, PVC/PVdC 90 g.m^{-2}, PVC/PE/PVdC, aluminum strip + polyethylene, hard aluminum, glass bottle and polypropylene cap) were analyzed according to the methods described below and the results were compared to the standard specifications for each material. The materials were evaluated as shown in Chart 1.

Identification: we added two drops of 5% potassium hydroxide methanol solution and two drops of pyridine to the samples. A dark-brown-colored solution would indicated the presence of PVdC in the samples.

Color: the material was visually compared to the specification.

Total weight: two pieces of material were cut into a square of 10 x 10 cm. The weight of each sample (w1 and w2) was determined in a Shimadzu analytical balance (model AUN 220D) and then the weight in g.m^{-2} was calculated according to Equation 1, where w was the weight in grams and 0.01 m^2 was the sample area.

$$\textit{Weight calculation} = \frac{\frac{p1+p2}{2}}{0{,}01\ m^2} \quad (1)$$

Total thickness: assessed with the aid of a Digimess micrometer (model DM-A0050).

Width: measured using a Starrett caliper (model DM-A0082).

Coil external and internal diameter: measured with a steel ruler of 1,000 mm.

Dimensional stress: we measured the tension in the transverse and longitudinal direction of two 10 x 10 cm plates of the material. The directions were marked with a pen. The plates were stored in a VWR Brand 1.400 E vacuum oven at 130°C for 5 min. After this period, the directions were measured and the variations were calculated.

Cut: we measured whether the cut was regular, with no narrow and/or wide areas.

Coiling: we checked whether the tension allowed the layers to slide and whether the number and color of the splices met the specifications.

Primer weight: the primer was removed from each square - previously cut for total weight analysis - with cotton soaked in ethyl acetate rubbed on the full extension of the aluminum. For hard aluminum, in addition to the removal of the primer layer, the friction process also extracted the thermosetting resin. The weight of each sample was determined and calculated according to Equation 1. The calculation of the subtraction of the total weight from the result found in this item resulted in the isolated weight of the primer for the aluminum + polyethylene strip and in the weight of the thermosetting resin and primer for the hard aluminum sample.

Aluminum weight: 70 mL of ethyl acetate P.A., 20 mL of acetic acid P.A. and 10 mL of ethyl alcohol P.A. were homogenized. The solution had enough volume for the sample squares (from the previous analysis) to be immersed. After 24 hours in the solution, the samples were washed and rubbed to obtain complete separation of polyethylene and aluminum. Then, the aluminum underwent a drying process in an oven (at 60º C) for five minutes. It was then weighed and the results were recorded, according to Equation 1. For the hard aluminum, the method used in the previous item for the removal of the primer layer and the thermosetting resin provided the isolation of the aluminum, and the aluminum weight was determined through Equation 1.

Polyethylene weight: calculated by subtracting the aluminum weight + polyethylene weight (without the primer) from the isolated aluminum weight (result obtained in the previous analysis).

Aluminum thickness was determined using the micrometer in samples obtained after aluminum isolation.

Chart 1. Physico-chemical parameters per packaging material.

	PVC/PVdC* 40 g.m^{-2}	PVC/PVdC* 90 g.m^{-2}	PVC/PE/PVdC**	Aluminum strip + polyethylene	Hard aluminum	Glass bottle	Polypropylene cap
Identification	X	X	X				
Color	X	X	X			X	X
Total weight	X	X	X	X	X		
Total thickness	X	X	X	X	X		
Width	X	X	X	X	X		
Diameter	X	X	X	X	X		
Stress	X	X	X				
Cut	X	X	X				
Coiling	X	X	X	X	X		
Primer weight				X	X		
Aluminum weight				X	X		
Polyethylene weight				X			
Aluminum thickness				X	X		
Print				X	X		
Primer application				X	X		
Primer performance				X	X		
Volume						X	
Dimensions						X	X
Weight						X	X
Chemical resistance						X	
Microbial limit						X	

* PVC: Polyvinyl chloride; PVdC: Polyvinylidene chloride.
** PVC: Polyvinyl chloride; PE: Polyethylene; and PVdC: Polyvinylidene chloride.

Print: compared to the standard specified pantone color and to the current graphic art.

Primer application: we verified whether the application was on the specified side.

Primer performance test: a strip of adhesive tape was pasted to the print and removed afterward. With this, we were able to check whether there was any paint release.

Total volume: we added drinking water to ten units of bottles up to the height of the bottleneck. The water was then transferred to a graduated cylinder so we could read the volume of each bottle.

Dimensions: the height of the bottle, of the end, the external diameter of the body, the internal diameter of the end, over the screw and the safety ring were analyzed in ten units of bottles, with a caliper. Also with a caliper, screw diameter, external diameter, groove and total height were measured in ten units of caps.

Weight: ten units of bottles and caps were weighed on analytical balance.

Chemical resistance: reagents and solutions of 0.01 M sulfuric acid (H_2SO_4) and methyl orange were prepared. Twenty bottles were filled with drinking water. They were capped with aluminum and taken to a Baumer autoclave at 121 ± 2°C for 60 min. A 5 mL fraction was withdrawn from each bottle until we obtained 100 mL of the aqueous extract. To this extract we added 5 drops of methyl orange. It was then tittered, while still warm, with 0.01 M H_2SO_4 solution. At the same time, the test was performed in blank. The results were compared to the standardized specification for H_2SO_4 per ML of aqueous extract.

Microbial limit: we analyzed samples of 20 units of bottles; the results were compared to the standardized specification, according to methodology developed internally by the microbiology laboratory for microbial count test, pathogen identification and microbiological analysis of packaging material.

Other identification techniques

The plastic materials in the form of films were submitted to the characterization by differential scanning calorimetry (DSC) and infrared spectroscopy.

Therefore, we were able to qualitatively compare the plastic films listed for the packaging of captopril 25 mg tablets.

Differential Scanning Calorimetry (DSC)

To obtain the DSC curves, a mass between 5.0 and 10.0 mg of plastic films was carefully weighed in aluminum crucibles, which were sealed with aluminum caps and automatically drilled. The tests were carried out in a Mettler Toledo, model 822e, under a dynamic atmosphere of nitrogen with flow rate of 80 mL per min. They were performed using a thermal cycle and a heating rate of 10 K per min, with initial heating of 25 to 120°C, followed by cooling to -40°C and finally a second heating up to 200°C.

The results of onset and midpoint were compared with results of the Klöckner Pentapharm® standards, previously analyzed and with values available in the literature for some polymers.

Infrared spectroscopy

We used a Thermo-Nicolet spectrometer (model Nicolet 6700) equipped with detector, laser and OMNIC 7.0 software. Small amounts of plastic were placed in direct contact with the crystal of the attenuated total reflectance (ATR) accessory.

The ATR technique can be used to analyze solids like films or sample parts, as long as they can be homogeneously adhered to the crystal. The parameters were entered in the software and then the spectrum scan was performed.

Parameters comprise: the spectrum band (4,000 to 600 cm-1); the number of spectrum scans (32 scans); the used resolution of 4 cm-1; and the unit – the spectra were acquired in transmittance percentage (%T).

Formulation and control

Captopril 25 mg tablets (test captopril) were manufactured with the following qualitative composition: captopril (Shandong Weifgang, China), 102 microcrystalline cellulose (Blanver, Brazil), cornstarch (Cargill, Brazil), spray dried lactose monohydrate (Foremost Farms, USA) and micro-powdered stearic acid (Casa da Química, Brazil).

Initially, a single batch of 84 kg or 600,000 single tablets of captopril 25 mg was manufactured. The raw materials were weighed separately. The spray dried lactose monohydrate, captopril, the cornstarch and the 102 microcrystalline cellulose were passed through a vibrating sieve equipped with 16 mesh (1 mm opening) screens and transferred to a 200-liter RENARD "V" mixer. The micro-powdered stearic acid was passed in 30 mesh screens (1.875 mm opening) and added to the "V" mixer. Then, the Fette 2090i compressing machine was set to produce the tablets.

We did the quality control according to the following criteria: appearance (circular, white, flat, grooved and 7.0 mm diameter), thickness (2.5-3.0 mm), mean weight (140.0 mg ± 5% [133 mg-147mg]), individual weight (140.0 mg ± 7.5% [130 mg-150 mg]), hardness (39-137 N), friability (maximum 1%) and disintegration (maximum 30 min in water at 37º C, with disc), pursuant to BP 5th Ed.

Additionally, we assessed the criteria of identification through high performance liquid chromatography, content (22.5-25.0-27.5 mg per tablet (90% to 110% of the declared value), unit dose uniformity, captopril disulfide (maximum 3.0%) and dissolution (Q = 80% in 20 min), pursuant to BP 5th Ed. A comparative dissolution profile was also done according to Anvisa RDC n. 31, of August 11, 2010.

Because they are standardized in the Brazilian Pharmacopoeia, we will present only the assays with greater prominence, such as: content, unit dose uniformity, purity tests, dissolution test and dissolution profile.

All methods of evaluation of the tablets were validated according to the criteria established in Anvisa RDC n. 899, of May 29, 2003, whose results were not presented here because they are not directly related to the evaluation exposed in this article.

Content

In compliance with BP 5th Ed, we prepared the mobile phase (methanol, water and phosphoric acid), the sample solution (capsules of captopril 25 mg ground and added to the mobile phase) and the standard solution (captopril standard, captopril disulfide solution and mobile phase).

We used a Hitachi high performance liquid chromatograph (Lachrom model), with C18 column (250 x 4.6 mm [5µm]), with a Varian UV/VIS spectrophotometer detector (Cary 100), at 220 nm wavelength, with fl of 1.0 mL/min and injected volume of 20 µL, with relative retention times of 0.5 for captopril and 1.0 for captopril disulfide. The resolution between the peaks should be maintained at least 2.0 and the maximum relative standard deviation of 2.0. The injections of the solutions were done, the chromatograms were recorded and the averages of the areas for standard solution and sample solution were determined.

Uniformidade de doses unitárias (variação de conteúdo): va ≤ 15.0

The sample was prepared by disintegrating the captopril 25 mg tablets into a mixture of ethanol and water. For the standard solution, standard captopril was added to the mixture of ethanol and water.

Solutions were read and the absorbance values were recorded. The mean absorbance was determined for standard and sample solution. The procedure was performed according to BP 5th Ed.

The absorbance values of the sample solutions were measured in a spectrophotometer at the wavelength of 212 nm, using a mixture of ethanol and water (1:1) for zero adjustment (white). The amount of captopril in each tablet was calculated based on the readings we obtained.

Captopril disulfide purity tests/limit (maximum 3.0%)

Pursuant to BP 5th Ed, the mobile phase (methanol, water and phosphoric acid), we prepared the standard captopril disulfide solution (captopril disulfide and mobile phase) and the sample solution (captopril 25 mg tablets powdered and added to the mobile phase). The solutions were injected, the chromatograms were recorded and the area of the peak relative to the captopril disulfide obtained in the sample solution should not be higher than the area of the peak relative to the captopril disulfide obtained in the standard solution of disulfide, at most 3.0%.

Dissolution test and comparative dissolution profile

For the dissolution test, we used Varian apparatus (model VK 7.025) type 1, basket, with dissolution medium of 0.1 M hydrochloric acid, 900 mL, rotation of 50 rpm, for 20 minutes at the temperature of 37 ± 0.5 °C. The comparative dissolution profile was made with the reference drug, Captosen® 25 mg, by Pharlab

Indústria Farmacêutica S.A. We compared the percentage of drug release (test and reference) at the following time intervals: 5, 10, 15, 20 and 40 min, without replacement of the medium.

According to Anvisa RDC n. 31/2010, comparatives dissolution profiles should only use the simulation factor (f2) calculation, which corresponds to the measure of similarity between the dissolved percentages of both profiles. However, when the active substance has high solubility and the formulation has immediate release and very fast dissolution for both drugs, according to the RDC, the f2 factor may not be discriminant, therefore, there would be no need to calculate it[7].

Captopril is classified in the biopharmaceutical classification system as a class II drug of low solubility and high permeability. As captopril has rapid dissolution, calculating the similarity factor (f2) was not necessary.

Following the comparative dissolution profile, the dissolution efficiency (DE) was defined by the area under the curve (AUC), at a given time, expressed as the percentage of the area of the rectangle (AUC_{TR}) corresponding to 100% dissolution, in the same period of time, by the trapezoid method. It was calculated from the percentage curves of dissolved captopril versus time (dissolution profile), yielding the area under the curve (AUC) and the total area of the rectangle (AUC_{TR}). The DE is calculated by the ratio between these two parameters and expressed as a percentage (Equation 2).

$$ED = \frac{ASC_{(0-t)}}{ASC_{TR}} * 100\% \quad (2)$$

Chart 2. Experimental packaging batches

Packaging batches	Packaging material
Batch 1	Hard aluminum and PVC/PVdC blister 40 $g.m^{-2}$
Batch 2	Hard aluminum and PVC/PVdC blister 90 $g.m^{-2}$
Batch 3	Hard aluminum and PVC/PE/PVdC blister
Batch 4	Aluminum + polyethylene strip
Batch 5	Amber glass bottle with polypropylene cap

Packaging

After production and satisfactory results in the physico-chemical analyses of captopril 25 mg tablets and their packaging materials, 5 kg or 35,714 tablets were set aside for packaging in different primary packaging materials, as shown in Chart 2.

Batch 5, in an amber glass bottle with a polypropylene cap, was designed to enrich the comparative analysis of the results, since this procedure does not expose the product to the natural sealing temperatures of a packaging process in blister and strip.

Stability studies

The characteristics of the batch of captopril 25 mg (test captopril) were evaluated by an accelerated and long-term stability study when packaged in different primary packaging materials.

The studies were conducted in a Weiss climatic chamber, as specified by Anvisa RDC n. 1, of July 29, 20058.

Microbiological studies

Microbiological studies were conducted according to BP 5th Ed, method 5.5.3.1 - Microbiological tests for non-sterile products.

For the total count of aerobic microorganisms (bacteria and fungi), Petri dishes (containing casein-soy agar and Sabouraud dextrose agar, respectively) were examined for microbial development and number of colonies (CFU). The results were expressed as CFU/g of product. If microbial growth was not observed in either of the two dishes, the result should be described as <10 CFU/g.

In order to investigate *Escherichia coli* using casein-soybean broth, MacConkey broth and MacConkey agar, we checked whether there was growth of pink to reddish colonies surrounded or not by zone of bile precipitate, which would indicate the likely presence of *E. coli*. If there was growth of these colonies, the identification would have to be done through complementary tests. The search result for *E. coli* was described as present or absent.

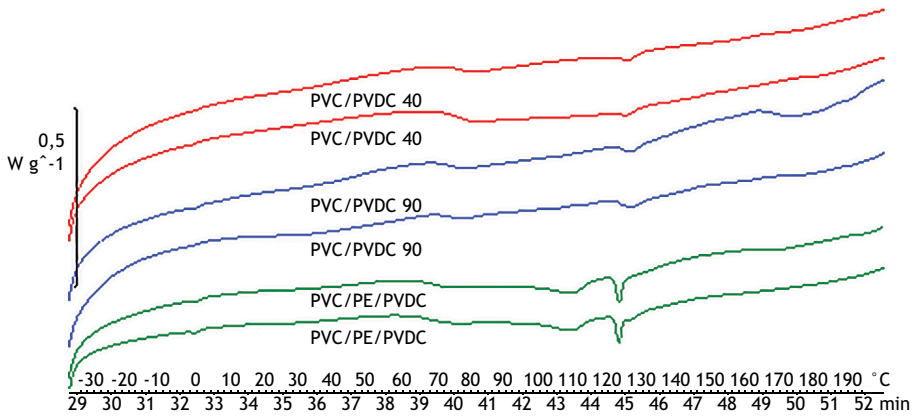

Figure 1. DSC curves of plastic materials.

RESULTS AND DISCUSSION

Results of characterization analyses of the packaging materials used in the packaging of captopril 25 mg tablets

The physico-chemical analyses conducted for the packaging materials presented satisfactory results, with approval in all the parameters, according to standardized specifications.

The results of the DSC analysis can be observed in Figure 1 and Table 1.

According to Table 1, the results found were compared with standards made available by Klöckner Pentapharm®, which allowed the identification of the plastic films through the proximity of the onset and midpoint values.

The evaluated plastic materials showed curves typical of amorphous substances, which do not present melting, but rather glass transition intervals, where the softening of the materials occurs, with an ideal temperature to mold the pouches in the case of the blisters[9,10.]

In the materials with lamination of two polymers (PVC/PVdC), two glass transition intervals were verified, as well as in three-polymer laminates (PVC/PE/PVdC), three glass transition intervals.

The method used for DSC analysis provided for initial heating, followed by cooling, reheating it to start the duplicate analysis of each material. The heating followed by the cooling allowed us to extinguish any thermal history of the material, enabling better visualization of each interval in the second heating.

By comparing the data with information available in the literature, it was also possible to verify the identification of each polymer layer through onset values (start of phase change or change of baseline). For PVC, onset was close to the range of 64.1 to 73.0ºC, which are similar values to those reported by Araújo and Pires[11], which ranged from 59.0 to 74.0º C, and Pita[10], with a maximum of 87.0°C. For PE, the onset was near 101.7°C, as found by Soares et al.[12] and Kämpf[9]. Since the polymeric materials were laminated, one can interfere with the glass transition temperature of the other, upward or downward[9,10,11,12].

For PVdC, the onset ranged from 121.3°C to 127.0°C according to the Klöckner Pentapharm® standard, which has its onset at 122.5°C.

In the triplex (PVC/PE/PVdC) the enthalpic relaxation was more evident. Enthalpic relaxation is the energy captured during softening, with molecule movement, as demonstrated by the "inverted peak" signal, in which the baseline after the glass transition interval does not return to the original baseline. This is typical of amorphous materials, where there is a difference in the heat capacity of the beginning and of the end[9,10].

The different weights of the duplex materials (PVC/PVdC 40 g.m^{-2} and PVC/PVdC 90 g.m^{-2}) did not promote significant differences in results that could discriminate one material from the other. However, DSC analysis enabled us to compare materials and to differentiate a duplex laminate (PVC/PVdC) from a triplex laminate (PVC/PE/PVdC).

The results of infrared (IR) spectroscopy analyses can be observed in Figure 2. Spectrum analysis allowed identification of the functional groups of the plastic films. The bands allowed the identification of the materials comparing these experimental values with those presented in the literature for each material.

In Figure 2, graphs (a) (b) and (c), peak values of transmittance were compared with values found in the literature, which present specific approximate bands of PVC and PVdC (laminate layers PVC/PVdC 40 g.m^{-2}, PVC/PVDC 90 g.m^{-2}and PVC/PE/PVdC) between 638 and 604 cm-1, corresponding to the C-Cl stretch vibrations, typical of these molecules. Moreover, the literature presents other bands typical of PVC and PVdC that can be observed in the experimental results, such as the identification of alkane groups, between 2,962 and 2,885 cm-1 (CH_2 and CH); 1,430 cm^{-1} (CH); from 1,330 to 1,250 cm^{-1} (CH in CH-Cl) in the PVC layer); 1,000 to 1,200 cm^{-1} (C-C) and 962 cm^{-1} (CH_2)[10,13].

In chart (c), typical PE bands of 2,851 to 2,920 cm^{-1}, with a larger (less weak) expression can be observed at 2,917 cm^{-1}, when compared to charts (a) and (b). These bands close to 2,900 cm^{-1} may relate to the stretching of the C-H groups.

The IR spectroscopy of the plastic materials did not enable us to make great distinction among the materials, since PVC, PE and PVDC are basically composed of the same functional groups, generating the expression of the same bands. However, it enabled us to prove the chemical composition of the laminates we used.

Table 1. Results of DSC analysis of plastic materials

Plastic materials	1st glass transition PVC*		2nd glass transition PE**		3rd glass transition PVdC***	
	Onset	Midpoint	Onset	Midpoint	Onset	Midpoint
Standards	74.8	78.4	109.6	112.4	122.5	124.8
PVC/PVdC 40 g.m^{-2}	73.0	77.0	NA	NA	127.0	128.1
PVC/PVdC 90 g.m^{-2}	71.4	75.3	NA	NA	122.7	125.3
PVC/PE/PVdC	64.1	68.2	101.7	107.3	121.3	121.4

*PVC: Polyvinyl chloride;
**PE: Polyethylene;
***PVdC: Polyvinylidene chloride.

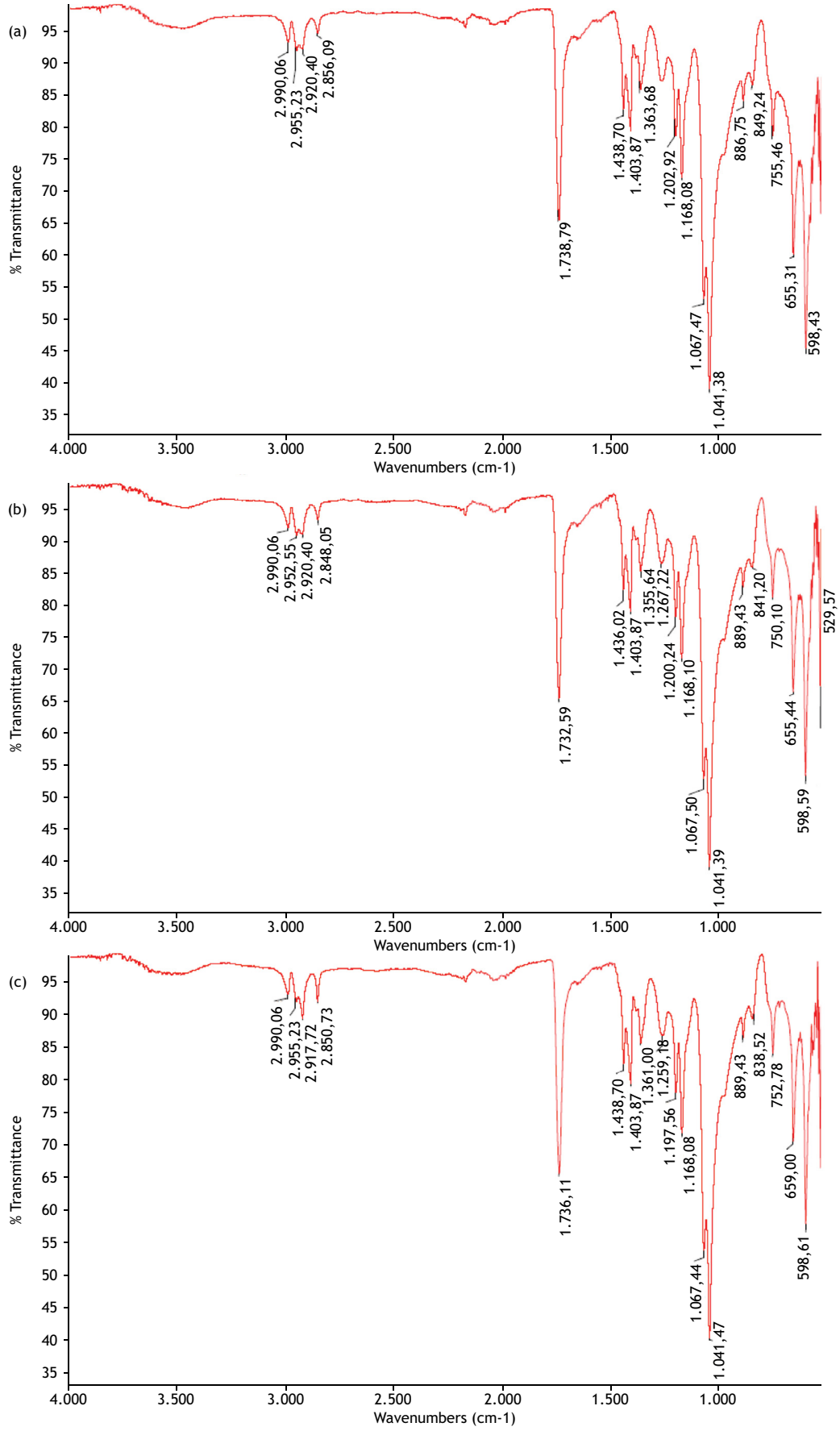

Figure 2. Infrared spectroscopy of PVC/PVdC 40 g.m-² (a), PVC/PVdC 90 g.m-² (b) and PVC/PE/PVdC (c).

Results of physico-chemical analyses of captopril 25 mg tablets

The content analyses carried out to evaluate the final mixture content of the six samples collected in the V-type mixer were approved in their results.

Likewise, the results of the physico-chemical analysis of captopril 25 mg tablets, performed at time zero, were also satisfactory, as observed in Table 2.

With these results obtained at time zero, we could verify that the product was in accordance with the requirements specified in BP 5th Ed.

The result of the comparative dissolution profile performed between captopril test tablets and tablets from two batches of the reference drug, Captosen®, is shown in Figure 3.

The captopril test drug demonstrated a similar dissolution profile as that of the reference drugs, as can be observed in Figure 3. The percentage of drug released after 10 min was similar for the different samples (95.17% to 104.94%), although the start of the release was slightly different. At the time of 20 min, the test drug released approximately 103.21% of captopril, whereas the reference drugs released 101.02% and 98.79%, respectively, for Captosen® 1 and Captosen® 2.

The three curves tend to overlap in the chart, demonstrating homogeneity in the in vitro dissolution process. The highest standard deviation (SD) of the dissolution percentages of the six vats analyzed was observed in the 15 min time for the Captosen® 1 sample, with a SD of 2.71%, whereas, for test captopril, the highest SD was 2.51% at 5 min. Both coefficients of variation are allowed for the first collection points, according to Anvisa RDC n. 31/2010.

The data obtained was used to assess the dissolution efficiency (DE). With the calculation of the DE, we could determine the actual amount of drug dissolved in the medium and thus get a better prognosis for in vivo results.

As shown by the results in Table 3, DE calculations for test captopril, Captosen® 1 and Captosen® 2 were expressed as percentages, with satisfactory results between 90.15% and 94.13%.

Results of the formulation characterization (after the packaging process)

The results of accelerated and long-term stability studies can be seen in Tables 3, 4, 5, 6 and 7.

For batch 1, packaged in PVC/PVdC blisters 40 g.m^{-2} and hard aluminum (duplex blister of smaller weight), the currently registered primary packaging material for captopril 25 mg, the results of stability studies were satisfactory, according to Table 3, with approval in the dissolution test in S1, with standard deviation (%) of 3.7 between the evaluated months.

In Table 4, the highlighted results were outside the values specified by BP 5th Ed, which describes that in S1 none of the six tablets analyzed should show dissolution rates lower than 85% (Q + 5%).

However, an analysis of S2 is allowed, in which 12 tablets were analyzed (S1 + S2) and in no tablet dissolution results were found to be lower than 65%, with the average being higher than 80%. Batch 2 (in duplex blister of higher weight) was then approved in S2, within 6 months of accelerated stability.

For the other parameters assessed in this batch during the stability studies, the results were satisfactory, as specified by BP 5th Ed.

Also with satisfactory result in S2 in the dissolution assessment, in the 9-month time, under conditions of long-term stability, there is the batch of test captopril packaged in PVC/PE/PVdC blister and hard aluminum (batch 3 - triplex blister), as shown in Table 5.

Materials with a significant barrier, such as the PVC/PVdC blister 90 g.m^{-2} and hard aluminum (batch 2) and PVC/PE/PVdC blister and hard aluminum (batch 3) showed satisfactory results in S2. On the other hand, lower barrier materials, such as the PVC/

Table 2. Results of the analysis of the tablets at time zero.

Test	Specification	Result
Description	Circular, flat and grooved tablet	In accordance
Color	White	In accordance
Identification	High performance liquid chromatography	In accordance
Uniformity of doses by content uniformity	VA: max. 15.0	9.2
Captopril disulfide	Maximum 3%	0.1%
Content	22.5-25.0-27.5 mg per tablet	25.4 mg per tablet
Average weight	140 mg	143 mg
Mean weight variation	133 to 147 mg	140 to 147 mg
Thickness	2.5 to 3.0 mm	2.9 mm
Hardness	39 to 137 N	90 N
Diameter	About 7.0 mm	7.0 mm
Result: Approved		

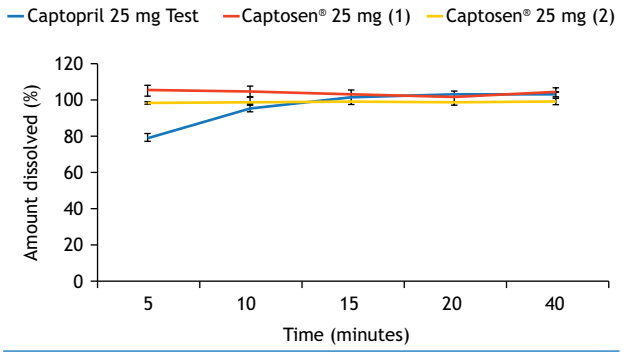

Figure 3.Comparative dissolution profile performed between test captopril tablets and tablets from two batches of the reference drug, Captosen®.

PVdC blister 40 g.m-2 and hard aluminum (batch 1), did not have dissolution analysis in S2.

We verified that in a given analysis time, results in S2 appear, but this was not repeated in the following times, since the results were approved in S1. In order to assess the occasional occurrence of S2 better, we suggest a detailed investigation of content uniformity during validation of the mixing step.

It is noteworthy that the trend to S2 stages already observed in the follow-up studies of captopril 25 mg continued to be detected by accelerated and long-term stability studies, even with the drug packaged in different primary packaging materials.

Literature descriptions[14,15] demonstrate the expected behavior for batch 4 as seen in Table 6, where the captopril test tablets were packed in aluminum strip with satisfactory dissolution results (in S1). Such behavior reaffirms that aluminum/aluminum packages offer better protection to the drug when compared to plastic packaging. The absence of micro-holes in the structure, the use of a lower sealing temperature, a high barrier to moisture, oxygen and/or light may have led to more effective results[14,15].

This batch was the one that presented the best results. It proved more stable over time, as we can see in Figure 4, which summarizes the dissolution behavior of the captopril batches in the different packages during the long-term stability studies, conducted at a temperature of 30 ± 2°C and relative humidity of 75 ± 5%.

Table 7 shows the results of the captopril disulfide percentage above the value specified by BP 5th Ed, maximum of 3%, when the batch was packed in an amber glass bottle (batch 5).

The captopril content under these same conditions, despite occurring within the specified range (22.5 to 27.5 mg per tablet), decreased from 25.2 mg per tablet in month 3 to 24.1 mg per tablet in month 6 in accelerated stability. Under long-term stability conditions, it decreased from 25.4 mg per tablet in month 3 to 24.3 mg per tablet in month 18 and 23.6 mg per tablet in month 24, which may be related to an increase in captopril disulfide.

Captopril degradation leads to the formation of captopril disulfide. Copper and iron are the main catalysts of this reaction and,

Chart 3. Results of the dissolution efficiency (DE) of test captopril, Captosen® 1 e Captosen® 2.

	Mean DE ± SD (%)
Captopril 25 mg Test	90.15 ± 1.23
Captosen® 25 mg (1)	94.13 ± 2.27
Captosen® 25 mg (2)	90.29 ± 0.82

like other contaminants, they can be present in the formulations, which may be related to the contact with production equipment or primary packaging materials, as well as contaminants of the fillers themselves. The captopril degradation reaction may lead to a decrease in the active ingredient content, affecting the indicated therapy and causing undesirable effects in the body[16].

In order to assess the presence of copper and iron in the fillers used in the formulation and in the active material, the receipt analysis reports of these materials were analyzed and we verified that all the materials were approved according to BP 5th Ed.

Since the amber glass contains iron oxide, this component may have migrated to the captopril tablets packed in this material, catalyzing the degradation to form the captopril disulfide17.

Another trigger of this degradation may have been oxygen. Captopril, when packed in glass bottles, may be degraded by the presence of oxygen in the headspace or by the moisture permeability of the polypropylene cap. In this case, batch 5, packed in a glass bottle, may also have undergone oxidative degradation as it obtained the highest moisture content recorded among the tested materials, reaching 6.7% RH in month 6. Still for batch 5 we observed a decrease in tablet hardness, possibly related to moisture.

Research has shown that moisture and its interactions can have effects on the stability of various drugs and directly affect the tablet properties. When absorbed by the tablets, moisture can cause softening of the cohesive points, jeopardizing the initial hardness of the pharmaceutical form[18,19].

Therefore, batch 5, despite having excellent barrier material and amber pigmentation, which adds potential photoprotection, was not approved after the 6th month of accelerated stability, based on the specifications of BP 5th Ed. However, batch 5 was monitored until the end of the study so we could observe its behavior over time.

CONCLUSIONS

Continuous monitoring of process variability is in line with modern quality systems and the Good Manufacturing Practices model for pharmaceutical companies.

In this context, the present study, in addition to monitoring the tendency or frequency of captopril approval at S2 in dissolution tests, contributes to filling the literature gap on the influence of primary packaging on the stability of medicines, since little has been published on that matter.

Table 3. Stability of captopril 25 mg tablets in PVC/PVdC blister 40 g.m-² and aluminum (batch 1

TEMPERATURE	30 ± 2°C/75 ± 5% UR							40 ± 2°C/75 ± 5% UR	
ANALYSIS	INITIAL	3 months	6 months	9 months	12 months	18 months	24 months	3 months	6 months
DESCRIPTION: White, flat, grooved and odorless circular tablet	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
PACKAGING: Appearance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
HARDNESS: Informative	90	69	67	72	71	71	73	57	60
MOISTURE: Informative	-	5.1	5.6	6.5	6.0	5.4	6.1	5.1	6.0
DISINTEGRATION: Maximum 30 min	03'12"	01'05"	01'08"	00'55"	00'57"	00'56"	00'55"	00'51''	01'10"
DISSOLUTION: Q = 80% / 20 min	104.0	102.6	98.6	99.5	108.3	102.4	102.1	100.0	91.9
CAPTOPRIL DISULFIDE: Maximum 3.0%	0.1	0.6	0.9	1.1	1.5	2.2	2.5	1.3	2.3
Content: 22.5 -25.0 - 27.5 mg/tablet	25.4	25.1	24.4	25.1	26.0	25.1	24.8	25.2	25.5
(90% to 110% of the declared value)	101.6	100.4	97.6	100.4	104.0	100.4	99.2	100.8	102.0
MICROBIAL LIMIT	INITIAL	OBSERVATIONS: -						INITIAL	06 months
Total Aerobic Bacteria (max 1000 CFU/g)	<10	<10							
Fungi and Yeasts (max 100 CFU/g)	<10	<10							
Pathogen E. coli (absence in 1 gram)	absent	<10 absent absent							

Table 4. Stability of captopril 25 mg tablets in PVC/PVdC blister 90 g.m-² and aluminum (batch 2).

TEMPERATURE	30 ± 2°C/75 ± 5% UR							40 ± 2°C/75 ± 5% UR	
ANALYSIS	INITIAL	3 months	6 months	9 months	12 months	18 months	24 months	3 months	6 months
DESCRIPTION: White, flat, grooved and odorless circular tablet	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
PACKAGING: Appearance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
HARDNESS: Informative	90	70	71	78	69	73	80	60	57
MOISTURE: Informative	-	5.4	5.7	6.6	5.7	5.5	6.0	4.0	6.0
DISINTEGRATION: Maximum 30 min	03'12"	01'29"	01'30"	01'10"	01'04"	01'02"	01'02"	01'37''	00'55"
DISSOLUTION: Q = 80% / 20 min	104.0	100.0	96.8	100.2	95.6	99.7	98.0	99.6	90.0 S2*
CAPTOPRIL DISULFIDE: Maximum 3.0%	0.1	0.5	0.7	0.9	1.1	1.6	1.7	1.0	2.4
Content: 22.5 -25.0 - 27.5 mg/tablet	25.4	25.2	24.8	25.0	26.0	25.1	24.8	25.5	25.6
(90% to 110% of the declared value)	101.6	100.8	99.2	100.0	104.0	100.4	99.3	102.0	102.4
MICROBIAL LIMIT	INITIAL	OBSERVATIONS: * S1: 92.4-90.7-82.8-78.6-86.9-92.5 / S2: 95.0-87.1-93.9-87.1-95.5-97.6						INITIAL	06 months
Total Aerobic Bacteria (max 1000 CFU/g)	<10	<10							
Fungi and Yeasts (max 100 CFU/g)	<10	<10							
Pathogen E. coli (absence in 1 gram)	absent	<10 absent absent							

Table 5. Stability of captopril 25 mg tablets in PVC/PE/PVdC blister and aluminum (batch 3).

TEMPERATURE	30 ± 2°C/75 ± 5% UR							40 ± 2°C/75 ± 5% UR	
ANALYSIS	INITIAL	3 months	6 months	9 months	12 months	18 months	24 months	3 months	6 months
DESCRIPTION: White, flat, grooved and odorless circular tablet	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
PACKAGING: Appearance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
HARDNESS: Informative	90	72	72	76	74	68	74	57	58
MOISTURE: Informative	-	5.0	5.7	6.6	5.6	5.2	5.9	5.0	6.0
DISINTEGRATION: Maximum 30 min	03'12"	02'00"	00'58"	00'55"	00'52"	01'17"	00'53"	01'20"	01'02"
DISSOLUTION: Q = 80% / 20 min	104.0	102.9	100.6	95.4 S2*	100.3	102.3	101.1	97.2	92.9
CAPTOPRIL DISULFIDE: Maximum 3.0%	0.1	0.4	0.7	0.8	1.6	1.5	1.9	0.8	2.2
CONTENT: 22.5 -25.0 - 27.5 mg/tablet	25.4	25.3	25.5	25.0	25.4	25.2	25.6	25.6	26.7
(90% to 110% of the declared value)	101.6	101.2	102.0	100.0	101.6	100.8	102.3	102.4	106.8
MICROBIAL LIMIT	INITIAL	OBSERVATIONS: * S1: 100.0-98.4-95.7-72.9-96.5-97.1 / S2: 100.0-103.0-99.0-100.0-87.0-95.0.						INITIAL	06 months
Total Aerobic Bacteria (max 1000 CFU/g)	<10	<10							
Fungi and Yeasts (max 100 CFU/g)	<10	<10							
Pathogen E. coli (absence in 1 gram)	absent	<10 absent absent							

Table 6. Stability of captopril 25 mg tablets in aluminum strip (batch 4).

TEMPERATURE	30 ± 2°C/75 ± 5% UR							40 ± 2°C/75 ± 5% UR	
ANALYSIS	INITIAL	3 months	6 months	9 months	12 months	18 months	24 months	3 months	6 months
DESCRIPTION: White, flat, grooved and odorless circular tablet	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
PACKAGING: Appearance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
HARDNESS: Informative	90	85	80	93	91	85	97	79	74
MOISTURE: Informative	-	4.7	5.7	6.2	5.1	4.9	5.2	4.8	5.6
DISINTEGRATION: Maximum 30 min	03'12"	02'15"	02'10"	02'35"	00'44"	01'17"	01'22"	01'15"	01'16"
DISSOLUTION: Q = 80% / 20 min	104.0	98.7	97.0	98.0	103.3	99.7	99.2	100.7	99.3
CAPTOPRIL DISULFIDE: Maximum 3.0%	0.1	0.4	0.7	0.7	0.8	0.5	0.5	0.5	0.7
CONTENT: 22.5 -25.0 - 27.5 mg/tablet	25.4	24.9	25.4	25.6	25.3	25.2	25.5	25.5	25.1
(90% to 110% of the declared value)	101.6	99.6	101.6	102.4	101.2	100.8	102.1	102.0	100.4
LIMITE MICROBIANO	INITIAL	OBSERVATIONS: -						INITIAL	06 months
Bactérias Aeróbicas Totais (máx 1.000 UFC/g)	<10	<10							
Fungos e Leveduras (máx 100 UFC/g)	<10	<10							
Patógeno *E.coli* (ausência em 1 grama)	absent	<10 absent absent							

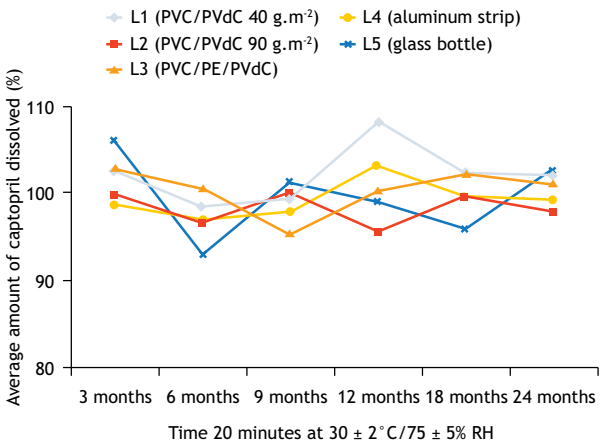

Figure 4. Amount of captopril dissolved per batch.

The frequency of S2 stages already observed in the follow-up studies of captopril 25 mg continued to be detected in accelerated and long-term stability studies, even with the medicine packaged in different primary packaging materials. Of the approved batches, the behavior of the batch of captopril 25 mg packaged in aluminum strip (batch 4) was the only one that reinforced the expected performance that aluminum/aluminum packages offer better protection of the drug when compared to plastic packages.

For other blister batches, there is no objective reason why the batches packaged in better barrier materials, like PVC/PVdC blister 90 g.m-²and hard aluminum (batch 2) and PVC/PE blister/PVdC and hard aluminum (batch 3), present lower dissolution results than the batch packaged in lower barrier material such as PVC/PVdC blister 40 g.m-² and hard aluminum (batch 1).

We therefore suggest opportunities for further and more detailed studies to evaluate the formulation and the manufacturing process of this type of packaging.

Consequently, we could conclude that although these materials have a significant influence on the packaged medicine behavior, the tendency of S2 analysis during the dissolution studies, observed for some tablets, cannot be related to the physico-chemical constitution of the primary packaging materials.

The in-depth characterization of the primary packaging materials and the DSC and IR analyses, complementing the physico-chemical tests, were essential to compose the specification, to prove the physico-chemical constitution, to differentiate the barrier and protection properties of each material or each component of a laminated material and to relate them to the results of the stability studies, helping us understand the final result.

Through the knowledge of these properties, the benefits that each primary packaging material can provide to the packaged medicine and the study of the results demonstrated in this study, we could conclude that the primary packaging is not responsible for the tendency of S2 in the dissolution of the tablets.

Tabela 7. Estabilidade de comprimidos de captopril 25 mg em frasco de vidro (lote 5).

TEMPERATURE	30 ± 2°C/75 ± 5 % UR							40 ± 2°C/75 ± 5% UR	
ANALYSIS	INITIAL	3 months	6 months	9 months	12 months	18 months	24 months	3 months	6 months
DESCRIPTION: White, flat, grooved and odorless circular tablet	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
PACKAGING: Appearance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance	in accordance
HARDNESS: Informative	90	65	61	78	71	70	77	54	56
MOISTURE: Informative	-	5.0	6.7	6.3	5.9	5.0	5.8	4.9	6.7
DISINTEGRATION: Maximum 30 min	03'12''	01'31''	00'50''	01'10''	01'05''	00'59''	01'20''	01'13''	00'55''
DISSOLUTION: Q = 80% / 20 min	104.0	106.2	93.1	101.3	99.1	95.9	102.8	93.4	99.2
CAPTOPRIL DISULFIDE: Maximum 3.0%	0.1	0.5	1.0	2.0	2.8	4.2*	4.9*	1.8	4.0*
CONTENT: 22.5 -25.0 - 27.5 mg/tablet	25.4	25.4	25.1	24.9	24.4	24.3	23.6	25.2	24.1
(90% to 110% of the declared value)	101.6	101.6	100.4	99.6	97.6	97.2	94.4	100.8	96.4
LIMITE MICROBIANO	INItIAL			OBSERVATIONS: *Results above specified.				INITIAL	06 months
Bactérias Aeróbicas Totais (máx 1.000 UFC/g)	<10				<10				
Fungos e Leveduras (máx 100 UFC/g)	<10				<10				
Patógeno *E.coli* (ausência em 1 grama)	absent				absent				

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.