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# *In vitro* evaluations of warfarin tablets available in the brazilian market

## Evaluación *in vitro* de tabletas de warfarina disponible en el mercado brasileño

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**Abstract**
The aging of the population has led to an increased use of anticoagulants such as sodium warfarin. This study evaluated the quality of 5 mg warfarin tablets by analyzing eight samples (A1–A8) in accordance with the Brazilian Pharmacopoeia, with the objective of identifying quality deviations and verifying their interchangeability with the reference medication. The samples were subjected to the following quality control tests: average weight, friability (loss <1.5%), disintegration (within 30 minutes), dosing (content between 92.5% and 107.5%), and content uniformity (acceptance value <15). However, sample A3 failed the dissolution test, releasing less than 40% of the active ingredient within 30 minutes. The equivalence assessment indicated that samples A1xA2 (69.97) and A1xA4 (54.43) were interchangeable, whereas samples A3, A5, A6, A7, and A8 were not. The comparison of dissolution profiles using the similarity factor ($f_2$) revealed that several samples exhibited quality deviations, potentially compromising treatment efficacy and safety, and suggesting deficiencies in Good Manufacturing Practices (GMP).

*Keywords:* Anticoagulants; Warfarin; Quality control; Interchangeability; Pharmacopoeia.

**Resumen**
El envejecimiento poblacional ha aumentado el uso de anticoagulantes como la warfarina sódica. Este estudio evaluó la calidad de comprimidos de 5 mg, analizando ocho muestras (A1-A8) según la Farmacopea Brasileña, con el objetivo de identificar desviaciones de calidad y verificar la intercambiabilidad con el medicamento de referencia. Las muestras fueron aprobadas en los ensayos de peso medio, friabilidad (pérdida menor al 1,5%), desintegración (menos de 30 min), dosificación (contenido entre 92,5% y 107,5%) y uniformidad de contenido (valor de aceptación menor a 15). Sin embargo, la muestra A3 reprobó en la prueba de disolución, liberando menos del 40% en 30 min. La evaluación de equivalencia indicó que las muestras A1xA2 (69,97) y A1xA4 (54,43) eran intercambiables, mientras que A3, A5, A6, A7 y A8 no lo eran. La comparación del perfil de disolución mediante el factor $f_2$ reveló que varias muestras presentaron desviaciones de calidad, comprometiendo la eficacia y seguridad del tratamiento, además de indicar fallas en las buenas prácticas de fabricación.

*Palabras clave:* Anticoagulantes; Warfarina; Control de calidad; Intercambiabilidad; Farmacopea.

## Introduction

Human aging involves a series of physical, psychological, and social changes. Physiologically, it results in the gradual decline of organ functions, including reduced immune system capacity, loss of muscle and bone mass, and alterations in the function of vital organs. Psychologically, aging can affect cognition, memory, and the way individuals process emotions and stress (1).

This process is accompanied by an increased use of medications among older adults, as health conditions requiring pharmacological treatment become more prevalent — including the frequent use of oral anticoagulants. These drugs are essential for preventing serious conditions such as thrombosis; however, they also carry a significant risk of bleeding (1).

Warfarin is an anticoagulant widely used in the treatment and prevention of blood homeostasis disorders, including thrombosis, acute myocardial infarction, and other thromboembolic events. Its therapeutic efficacy is directly related to its mechanism of action. To achieve the desired effect, the drug must reach the recommended concentration at the site of action. However, the presence of formulations with quality deviations can compromise therapeutic outcomes (2).

Accelerated stability studies have revealed interactions affecting the solid-state characteristics of warfarin (crystalline/amorphous forms) and the particle size distribution of the active pharmaceutical ingredient (API). Commercial tablets and formulations containing crystalline or amorphous warfarin, as well as binary mixtures of warfarin with various excipients,

were evaluated. Structural changes before and after testing were monitored. The study demonstrated that certain excipients, such as calcium phosphate, can induce the conversion of sodium warfarin to its acidic form, resulting in significant alterations in dissolution behavior—particularly when combined with variations in API particle size. Therefore, the careful selection of both excipients and particle size is critical to ensure the quality and safety of generic sodium warfarin tablets (3). These findings highlight the need for rigorous regulatory oversight to guarantee the quality of pharmaceutical products available on the market (3).

Accordingly, the present study aimed to evaluate whether warfarin tablets from different brands and batches available in Brazil comply with the quality standards established by the Brazilian Pharmacopoeia.

## Materials and methods

### Chemical Reference Substance (CRS) and Samples

The 5 mg sodium warfarin tablet samples used in this study were obtained through donations from the municipal governments of Passo Fundo/RS, Ronda Alta/RS, Serafina Corrêa/RS, and Vanini/RS (five samples), while three additional samples were purchased from local pharmacies. In total, eight samples from different manufacturers and batches were analyzed and labeled A1–A8. Sample A1 was designated as the reference tablet. The warfarin active pharmaceutical ingredient (API), used as the Chemical Reference Substance (CRS), was commercially obtained (Manufacturer: Hangzhou Hyper Chemicals Limited; Batch: WTH-23). The API was previously characterized by Fourier Transform Infrared Spectroscopy (FTIR).

### Quality control tests for the Tablets

The tests conducted followed those described in the Brazilian Pharmacopoeia (4).

### Identification

Identification was carried out following the assay method described in the Brazilian Pharmacopoeia (assay section). The retention time of the principal peak in the chromatogram of the sample solution obtained in the assay was required to correspond to that of the principal peak in the standard solution.

### Weight Determination

Twenty tablets from each sample were individually weighed. The mean tablet weight was calculated, along with the upper and lower specification limits. No more than two units were permitted to fall outside these limits.

### Friability Test

Ten tablets from each sample were weighed and placed in a friabilator (Nova Ética, model 3001) operating at 25 revolutions per minute for 4 minutes. After the test, any powder residue on the tablet surfaces was removed, and the tablets were reweighed. None of the tablets exhibited breakage, chipping, cracking, or shattering. The tablets were considered acceptable if they showed a weight loss of ≤ 1.5%.

### Hardness Test

Tablet hardness was measured using a semi-digital hardness tester (Ethiktechnology). Ten tablets from each sample were tested, and the mean, standard deviation (SD), and relative standard deviation (RSD) were calculated.

### Disintegration Test

Six tablets from each sample were tested in a disintegration apparatus using water maintained at 37 ± 1 °C as the immersion medium. Each tablet was placed in a tube of the disintegration basket, with a disk added to each tube. The time required for complete disintegration was recorded, establishing the maximum disintegration time for uncoated tablets at 30 minutes.

### Assay

The assay was performed by high-performance liquid chromatography (HPLC). A PerkinElmer LC Flexar chromatograph (binary pump Flexar, autosampler Flexar) equipped with a UV detector set at 280 nm and an RP-ACE octadecylsilane silica column (250 × 4.6 mm, 5 µm) was used. The mobile phase consisted of methanol, water, and glacial acetic acid (68:32:1, v/v/v), at a flow rate of 1.0 mL/min. Twenty tablets were accurately weighed and powdered. An amount of powder equivalent to 25 mg of sodium warfarin was transferred to a 25 mL volumetric flask, to which 15 mL of diluent (a mixture of pH 7.4 buffer and acetonitrile (85:15, v/v)) was added. The mixture was sonicated for 20 minutes, then the volume was completed with the same diluent, homogenized, and filtered through a 0.45 µm cellulose membrane filter. The resulting solution was further diluted with the mobile phase to obtain a final concentration of 100 µg/mL. Aliquots of 20 µL of the sample solution and the standard solution were injected separately. Chromatograms were recorded, and the areas under the peaks were measured. The content of sodium warfarin ($C_{19}H_{15}NaO_4$) in the tablets was calculated from the ratio of the responses obtained for the standard and sample solutions. A standard solution was prepared by transferring 25 mg of warfarin CRS to a 25 mL volumetric flask, adding 15 mL of pH 7.4 buffer, and sonicating for 5 minutes to obtain a 1 mg/mL solution. The volume

was then completed with the same buffer and diluted with the mobile phase to yield a final concentration of 100 µg/mL. A resolution solution was prepared by transferring 0.1 g of propylparaben CRS to a 100 mL volumetric flask, adding 50 mL of acetonitrile, and sonicating for 5 minutes. The volume was then completed with acetonitrile and homogenized. From this solution, 2.5 mL were transferred to a 25 mL volumetric flask, followed by the addition of 2.5 mL of the 1 mg/mL warfarin standard solution. The volume was completed with the mobile phase, yielding a solution containing 100 µg/mL each of propylparaben and warfarin. Replicate injections of 20 µL of the resolution solution were performed. The resolution (Rs) between the propylparaben and warfarin peaks was ≥ 2.0, and the relative standard deviation (RSD) for the peak areas of the replicates did not exceed 2.0%.

Uniformity of dosage units

Ten tablets from each batch were weighed individually and placed in 5 mL volumetric flasks. Then, 4 mL of the diluent (as described above) was added, and the mixture was allowed to stand for 20 minutes. The volume was then completed with the same diluent. A 0.5 mL aliquot was taken and transferred to a 5 mL volumetric flask, which was subsequently filled with the mobile phase (as described above). The resulting solutions were injected into the chromatograph. The content of the 10 units was determined, and the mean (X) and standard deviation were calculated to obtain the acceptance value (AV). The following equations were used to calculate AV: if the mean content (X) is between 98.5% and 101.5%, then M = X (AV = k·SD); if X < 98.5%, then M = 98.5% (AV = 98.5 − X + k·SD); if X > 101.5%, then M = 101.5% (AV = X − 101.5 + k·SD). The AV must be less than L1, where L1 = 15 for approval. In addition, no individual result should be less than (1 – L2 × 0.01) M or greater than (1 + L2 × 0.01) M, with L2 equal to 25. A retest with an additional 20 units (n = 30) may be conducted if L1 exceeds 15; however, all individual units must still comply with the individual limit criteria. The acceptance value (AV) is based on the following equation:

$AV=|M-\bar{X}|+ks$

where k is the acceptability constant (for n = 10, k = 2.4), SD is the standard deviation, X is the mean content found, and M is the value to be used when T ≤ 101.5, which is the case for warfarin, and this value will depend on X.

Dissolution Test

The dissolution test was performed using 500 mL of water as the dissolution medium and a paddle apparatus operating at 50 rpm. A total of 56 tablets were placed in the dissolution vessels. At 5, 10, 15, 20, 30, 40, and 60 minutes, 10 mL aliquots of the medium were withdrawn and filtered. After each sampling, an equal volume of fresh medium was added to maintain a constant volume. The procedure followed the same chromatographic conditions described in the Assay section. The amount of $C_{19}H_{15}NaO_4$ dissolved at each time point was calculated by comparing the obtained responses with a calibration curve prepared using the warfarin RCS solution, freshly prepared in the mobile phase on the day of analysis. According to the Brazilian Pharmacopoeia specifications, the acceptance criterion requires that not less than 80% (Q) of the declared amount of $C_{19}H_{15}NaO_4$ be dissolved within 30 minutes.

To assess the pharmaceutical equivalence between formulations, the dissolution profile data were analyzed using the similarity factor ($f_2$), calculated according to the model recommended by the Brazilian legislation (Resolution RDC No. 31/2010 (5), which establishes that the value must fall between 50 and 100 to be considered interchangeable.

$$f_2 = 50 \bullet \log\left\{\left[1+\left(\frac{1}{P}\right)\sum_{i=1}^{P}(R-T)^2\right]^{-1/2} \bullet 100\right\} \quad (1)$$

$f_2$: Similarity factor, Log: Logarithm, P: Collection Time R: Reference Medicine T: Test Medicine.

**Results**

The results of the quality control tests are presented below.

In the identification test, all tablet samples were confirmed as warfarin, based on the correspondence of the retention time of the main chromatographic peaks in each of the eight samples with that of the standard solution (Figure 1). The resolution between the peaks of propylparaben and warfarin was greater than 2.0.

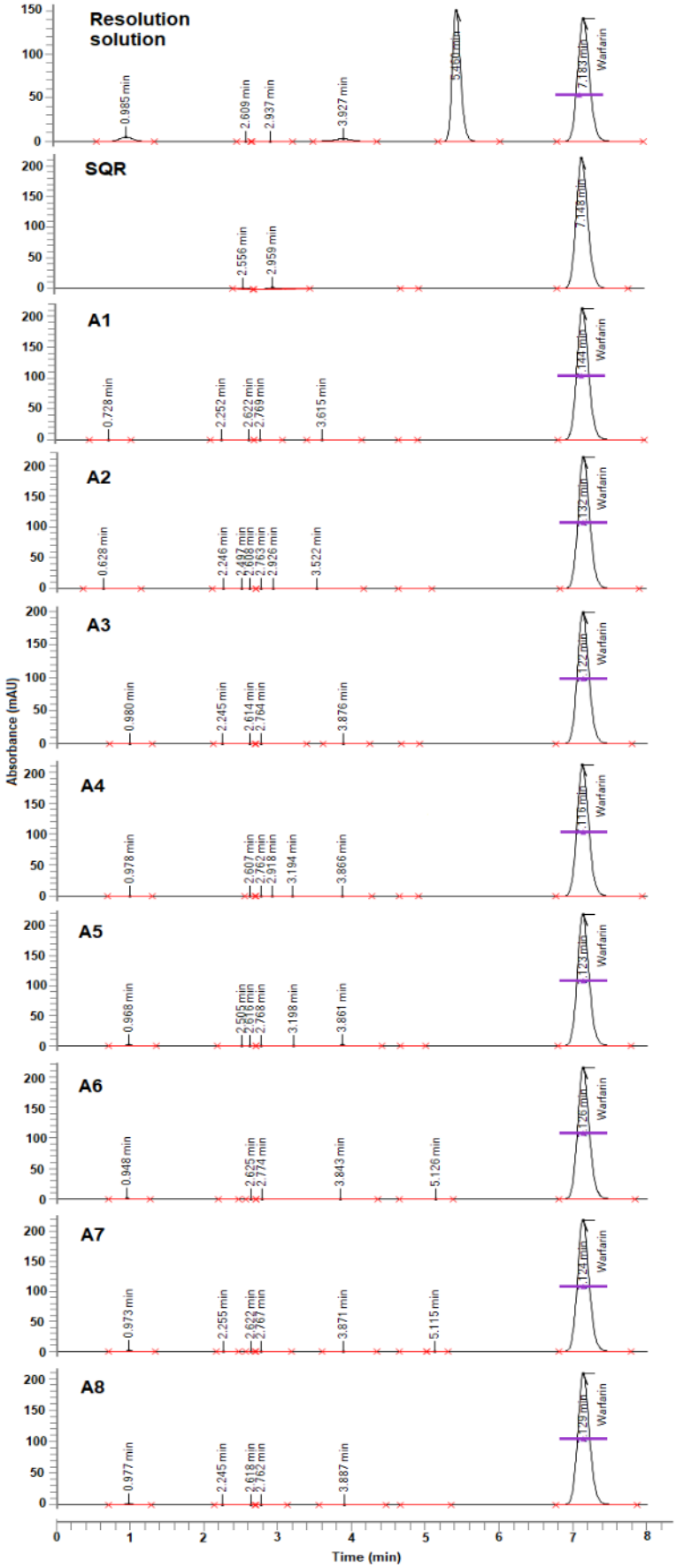


**Figure 1:** Chromatograms of warfarin tablet sample solutions, prepared at a concentration of 100 $\mu$g/m.

For the average weight determination, a variation limit of 7.5% was applied, as the tablets had weights between 80 mg and 250 mg. Upon analyzing the results, it was found that one of the tablets from sample 5 exceeded the upper limit (A5, 0.155 g). Upon analysis, one tablet from sample 5 (A5, 0.155 g) exceeded the upper limit. However, the sample was still considered compliant, since the Brazilian Pharmacopoeia permits up to two units to fall outside the specified limits (4). It is important to note that no individual tablet exceeded or fell below double the specified percentage (15%). Therefore, all samples met the pharmacopoeial requirements and were approved (Table 1).

**Table 1:** Quality control test performed with warfarin tablets.

| Control quality test | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 |
|---|---|---|---|---|---|---|---|---|
| Average Weight (g) | 0.1428 | 0.1419 | 0.1406 | 0.1414 | 0.1401 | 0.1410 | 0.1420 | 0.1408 |
| Upper Limit (g) | 0.1535 | 0.1525 | 0.1512 | 0.1520 | 0.1506 | 0.1516 | 0.1526 | 0.1514 |
| Lower Limit (g) | 0.1321 | 0.1313 | 0.1301 | 0.1308 | 0.1295 | 0.1304 | 0.1314 | 0.1302 |
| Friability (weight loss %) | 0.13% | 0.03% | 0.22% | 0.33% | 0.36% | 0.30% | 0.18% | 0.41% |
| Hardness (N) (n=10) | 64.65 | 52.4 | NR | 56.1 | 39.15 | 46.65 | 51.6 | 46.95 |
| Hardness | 5.62 | 7.36 | NR | 10.43 | 1.64 | 5.82 | 3.07 | 9.02 |
| Hardness RSD (%) | 8.69 | 14.06 | NR | 18.59 | 4.19 | 12.48 | 5.95 | 19.21 |
| Disintegration Time (min:s) | 08:29 | 09:10 | 07:20 | 06:03 | 04:41 | 03:23 | 03:16 | 03:40 |
| Assay (%) (n=3) | 101.10 | 100.65 | 92.88 | 100.33 | 100.68 | 102.94 | 104.34 | 97.10 |
| Assay SD | 1.55 | 0.23 | 0.09 | 0.36 | 4.00 | 2.67 | 0.08 | 1.61 |
| Assay RSD | 1.53 | 0.23 | 0.10 | 0.36 | 3.98 | 2.59 | 0.08 | 1.66 |

SD: Standard Deviation; RSD: Relative Standard Deviation
Sample number 3 was not conducted.

In the friability test, tablets are allowed a maximum mass loss of 1.5% (4). All analyzed samples remained within the established limits and were therefore approved (Table 1).

The hardness test is not an absolute criterion for approval or rejection but serves as an important indicator of a product's consistency and uniformity. All samples complied with the expected parameters (Table 1). Ideally, a relative standard deviation (RSD) of less than 5% is preferred, as it reflects uniformity among the measurements (4). Although sample 8 presented a higher RSD (19.21%), this variation does not entail batch rejection.

The disintegration test also yielded satisfactory results. All tablets disintegrated within the 30-minute limit defined for immediate-release formulations, confirming their suitability for this dosage form (Table 1).

For the assay, a calibration curve was constructed using five standard solutions with concentrations ranging from 80.0 µg/mL to 120.0 µg/mL, each injected in triplicate to ensure precision. The average peak areas were used to calculate the curve, which was reconstructed daily to account for possible experimental variations. For sample analysis, three aliquots from a pool of 20 crushed tablets were diluted and injected into the chromatograph. The practical concentration was determined using the equation of the calibration curve, with the chromatographic peak area being directly proportional to the analyte concentration. The theoretical concentration was defined as 100%, and the practical concentration was expressed as a percentage relative to this value. According to the Brazilian Pharmacopoeia (4), the acceptable content range for warfarin is 92.5% to 107.5%, and all analyzed samples complied with these specifications.

The uniformity of dosage units test was performed using ten tablets per batch. Ideally, the individual doses should exhibit minimal variability. The acceptance value (AV) was calculated according to pharmacopoeial requirements and must be less than 15 for approval (Table 2). The AV calculation depends on both the mean content and the standard deviation of the ten tested units. If the AV exceeds the L1 limit (15), an additional 20 units must be tested. Furthermore, each unit must not contain less than $((1 - (L2 \times 0.01)) \times M)$ or more than $((1 + (L2 \times 0.01) \times M)$, where L2 equals 25.0. Thus, no individual tablet may contain less than approximately 75% or more than approximately 125% of the declared warfarin amount (4). In this assay, all samples met the requirements, with AV values below 15 and individual results within the 75–125% range.

**Table 2:** Result of the Uniformity of dosage units for Warfarin Tablets (n=10).

| SAMPLE | CONTENT % A1 | CONTENT % A2 | CONTENT % A3 | CONTENT % A4 | CONTENT % A5 | CONTENT % A6 | CONTENT % A7 | CONTENT % A8 |
|---|---|---|---|---|---|---|---|---|
| **1** | 98.52 | 104.04 | 99.15 | 110.68 | 97.90 | 96.57 | 88.73 | 102.65 |
| **2** | 98.11 | 94.65 | 96.46 | 95.88 | 100.38 | 93.06 | 102.81 | 101.78 |
| **3** | 99.55 | 103.79 | 102.08 | 102.95 | 96.43 | 102.89 | 105.39 | 98.28 |
| **4** | 99.25 | 100.33 | 109.88 | 95.02 | 101.64 | 89.09 | 106.72 | 98.34 |
| **5** | 101.77 | 102.78 | 105.36 | 102.53 | 100.97 | 91.57 | 105.16 | 97.70 |
| **6** | 98.68 | 97.84 | 105.28 | 105.18 | 105.26 | 97.04 | 105.62 | 101.71 |
| **7** | 97.90 | 98.44 | 92.88 | 103.73 | 101.85 | 94.51 | 101.43 | 93.59 |
| **8** | 97.13 | 104.34 | 98.30 | 108.93 | 98.09 | 94.49 | 107.50 | 97.68 |
| **9** | 102.95 | 98.55 | 91.65 | 110.01 | 111.80 | 89.09 | 102.47 | 107.03 |
| **10** | 99.36 | 99.34 | 97.49 | 105.04 | 102.59 | 91.89 | 105.80 | 100.19 |
| **MEAN** | 99.33 | 100.41 | 99.85 | 103.99 | 101.69 | 94.02 | 103.17 | 99.30 |
| **SD** | 1.78 | 3.22 | 6.13 | 5.07 | 4.38 | 4.15 | 5.43 | 3.65 |
| **AV** | 4.27 | 7.75 | 14.71 | 14.68 | 10.52 | 14.44 | 14.69 | 8.76 |

Dissolution

During the dissolution test, samples were collected at 5, 15, 20, 30, 40, and 60 minutes and analyzed by HPLC. The peak areas obtained were converted into percentage of drug dissolved. According to the Brazilian Pharmacopoeia (4), at least 80% of the declared amount must be dissolved within 30 minutes. The dissolved percentage vs. time (min) data were plotted (Figure 2). All samples released more than 80% of the active ingredient within the first 30 minutes, except for sample A3, which released less than 30% at 30 minutes. Moreover, sample A3 failed to reach 40% dissolution even after 60 minutes, indicating a marked deviation from the established specification. Consequently, sample A3 was disapproved for failing to meet the minimum dissolution requirement.

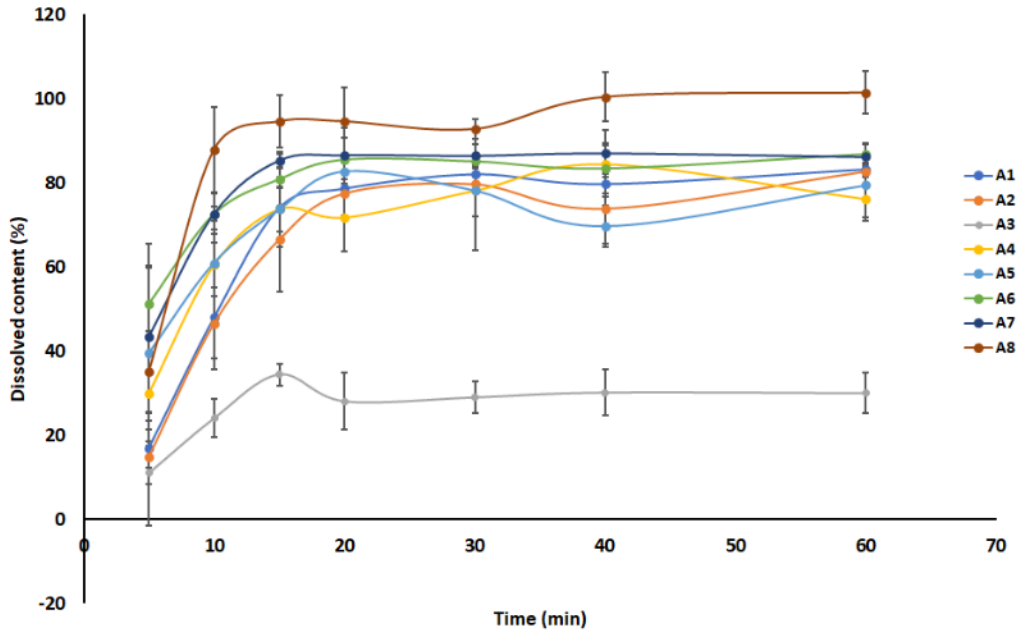


**Figure 2:** Dissolution Profiles of Warfarin Tablet Samples.

Pharmaceutical equivalence is assessed through physicochemical tests, and when necessary, microbiological or biological evaluations. The principal *in vitro* method used to determine equivalence between formulations is the comparative dissolution profile, where the dissolution profile of the reference drug (A1) is compared with those of the other samples using a mathematical model known as the similarity factor ($f_2$– equation 1). According to Resolution RDC No. 30/11, a generic or similar drug must be interchangeable with the reference product. To confirm interchangeability, the $f_2$ value obtained from the comparison must range between 50 and 100 (5).

In addition to the previously mentioned requirements, both the test and reference drugs must fully comply with the individual monograph. In addition to meeting these criteria, both the test and reference formulations must comply with the individual monograph requirements of the Brazilian Pharmacopoeia. In this study, all samples were compared with sample A1 (reference). The results indicated that samples A1×A2 ($f_2$ = 69.97) and A1×A4 ($f_2$ = 54.43) were interchangeable, while samples A3, A5, A6, A7,

and A8 were not, as their $f_2$ values fell below the required range (50–100). Similarly, A2×A3 and A3×A4 comparisons did not meet the established standard (5) (Table 3).

**Table 3:** Similarity Factor ($f_2$) calculated from the dissolution profile results. Sample 1 was used as the reference, and all other samples were compared to it.

| | $f_2$ |
|---|---|
| **A1xA2** | 69.97 |
| **A1xA3** | 18.31 |
| **A1xA4** | 54.43 |
| **A1xA5** | 48.19 |
| **A1xA6** | 38.99 |
| **A1xA7** | 41.12 |
| **A1xA8** | 32.60 |
| **A2XA3** | 19.81 |
| **A3XA4** | 18.56 |

**Table 4.** Summary of the quality control results obtained for the analyzed samples.

**Table 4:** Quality Control results.

| Sample/Test | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 |
|---|---|---|---|---|---|---|---|---|
| Identification | A | A | A | A | A | A | A | A |
| Average Weight | A | A | A | A | A | A | A | A |
| Friability | A | A | A | A | A | A | A | A |
| Hardness | A | A | A | A | A | A | A | A |
| Disintegration | A | A | A | A | A | A | A | A |
| Dosage | A | A | A | A | A | A | A | A |
| Uniformity | A | A | A | A | A | A | A | A |
| Dissolution | A | A | R | A | A | A | A | A |

R= rejected; A= approved

Only sample A3 failed the dissolution test. Regarding interchangeability, samples A2 and A4 were the only ones found to be interchangeable with the reference formulation.

## Discussion

The study revealed that some warfarin samples did not meet quality standards, which may compromise treatment effectiveness and increase the risk of bleeding in patients. Therefore, ensuring both the interchangeability and quality of medications is essential for the safety and well-being of elderly individuals who rely on these treatments.

The main finding of this study was the detection of quality control failures in several warfarin tablet samples available on the Brazilian market. The analyzed samples were subjected to tests established by the Brazilian Pharmacopoeia. In the dissolution assays, sample A3 failed to meet the specified requirements. Moreover, the comparative dissolution profile demonstrated that many samples were not interchangeable with the reference drug—an essential criterion for a product to be considered a generic equivalent. These inconsistencies raise concerns about compliance with good manufacturing practices (GMP) and proper quality control procedures.

Although each batch is expected to undergo rigorous quality testing before marketing, the observed failures suggest that certain products may reach the market with quality deviations and deficiencies in GMP adherence.

The focus on 5 mg warfarin tablets was chosen due to the formulation's low active ingredient concentration—approximately 3% of the tablet's total mass (~150 mg). Such a small proportion of the active pharmaceutical ingredient requires a highly homogeneous blend to ensure accurate dosing and therapeutic efficacy (6). Consequently, potent drugs at low dosages are particularly susceptible to quality deviations, as achieving uniform distribution of the active compound demands a strict and precise mixing process. Another relevant factor is that patients using warfarin frequently experience challenges in stabilizing their INR levels. Before questioning *in vivo* efficacy, it is essential to first verify the *in vitro* quality of the product.

Quality control plays a crucial role in determining the potential interchangeability between reference drugs and their generic, similar, or interchangeable similar counterparts. These products contain the same active ingredient, at the same concentration, dosage form, and route of administration as the reference drug, and are considered equivalent in efficacy and safety—while generally being more affordable (7). It is important to note that generic, similar, and interchangeable similar drugs must demonstrate comparable *in vitro* dissolution profiles to the reference product, as verified by the similarity factor ($f_2$). In addition to *in vitro* assays, generics and interchangeable similar drugs are also subjected to *in vivo* bioavailability and bioequivalence tests during registration. In contrast, similar drugs are exempt from *in vivo* testing (8).

The equivalence test aims to provide an *in vitro* comparison of pharmaceutical equivalence. Generic, similar, and interchangeable similar drugs must exhibit *in vitro* equivalence to the reference formulation, primarily evaluated through pharmacopoeial assays, namely the dissolution profile (5).

Of the eight samples tested in this study, only two (A2 and A4) were interchangeable with the reference product (A1). The remaining samples (A3, A5, A6, A7, and A8) failed to demonstrate interchangeability. The greatest variability occurred within the first five minutes of the dissolution test, and this pronounced initial deviation was responsible for the rejection of several samples, resulting in distinct dissolution profiles. Clinically, this early-stage variation may have limited significance, as it reflects only the initial phase of drug release. Nonetheless, the similarity factor ($f_2$) remains an effective statistical tool for detecting and quantifying differences between dissolution profiles, as it incorporates all sampling time points.

The $f_2$ parameter is therefore essential for assessing dissolution similarity between formulations. It provides a robust statistical measure that considers both the mean values and standard deviations of dissolution data, enabling the reliable determination of whether a generic product can be deemed equivalent to its reference counterpart (9).

Tablet hardness can influence dissolution results. In this study, although the samples exhibited similar average hardness values, a high relative standard deviation was observed—particularly in samples A4 and A8—indicating substantial intralot variability (Table 1). Kokott et al. (10) reported unsatisfactory mechanical resistance results for orodispersible tablets in tensile and compression tests, where only one of the commercial brands analyzed met the requirements of the European Pharmacopoeia, which establishes a maximum disintegration time of three minutes. In contrast, the FDA stipulates a stricter limit of 30 seconds. Although the hardness test is not a definitive acceptance or rejection criterion, it provides important insight into potential inconsistencies in pharmaceutical formulations.

Hardness plays a key role in dissolution efficiency. Tablets with greater mechanical strength, characterized by denser and less porous structures, tend to exhibit slower dissolution rates. This occurs because the dissolution medium encounters greater resistance when penetrating the tablet matrix and releasing the active ingredient (11).

In the dissolution assay, one of the eight samples (A3) failed to meet the established parameters of the Brazilian Pharmacopoeia (4), which requires at least 80% dissolution of the declared amount within 30 minutes. Sample A3 reached only approximately 35% dissolution, indicating a failure in its quality control process (Figure 3).

A study conducted in Indonesia evaluated the quality of reference and generic formulations through physical and chemical tests. The results showed that all samples met the physical and content criteria (90%–110% of the indicated amount). The dissolution profile of branded tablets was similar to that of the innovative product, whereas generic formulations exhibited distinct profiles compared to the reference drug (12).

In the present study, which assessed the quality control of warfarin tablets, unsatisfactory results were observed in the dissolution test. It is important to highlight that, in industrial practice, companies often evaluate dissolution only at the time point specified by the Pharmacopoeia—typically 30 minutes—without conducting a complete profile analysis at multiple time intervals (5, 10, 15, 20, 30, 40, and 60 minutes). This limited approach may lead to inconsistencies across different manufacturing processes. Therefore, there is a clear need to adopt updated and more comprehensive evaluation protocols in drug manufacturing—extending beyond those currently established by pharmacopoeial standards—to prevent potential production failures and quality control issues in commercially available medications. Implementing broader quality assessment procedures could help detect deviations that remain unnoticed under conventional testing.

Many patients using warfarin experience challenges in maintaining stable INR values due to the drug's mechanism of action. However, the findings of this study indicate that dose control issues are not solely linked to *in vivo* variability but also reflect deficiencies in *in vitro* quality control tests.

## Conclusion

Among the analyzed warfarin tablets, some exhibited quality deviations that may compromise both the efficacy and safety of the medications. Of the eight samples evaluated, sample A3 failed the dissolution test, and only two formulations were found to be interchangeable with the reference drug. The lack of pharmaceutical equivalence demonstrated that several generic formulations—and even one reference sample—did not meet interchangeability requirements, indicating potential differences in their *in vivo* performance. Therefore, it can be concluded that quality deviations are present among the analyzed tablets, suggesting deficiencies in good manufacturing practices. These findings raise important concerns regarding the therapeutic efficacy and safety of warfarin products available on the market.

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