NIMESULIDE: DISSOLUTION PROFILE, VALIDATION OF ANALYTICAL METHODS FOR CAPSULES, AND ASSESSMENT OF PRODUCT QUALITY

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Received: 04 Sep 2015 Revised and Accepted: 18 Nov 2015

ABSTRACT

Objective: The main objective of this paper was to evaluate the quality of similar (S, n=3) and generic (G, n=3) tablets and compounding capsules (C, n=6) containing nimesulide (100 mg).

Methods: The parameters investigated (weight, nimesulide content, uniformity of dosage units, disintegration, friability and hardness (tablets) and dissolution profile) were evaluated against the Brazilian Pharmacopeia and a reference compound (for tablets). Nimesulide content, determined by a UV/visible spectrophotometric method, and dissolution test were validated for compounding capsules.

Results: All formulations had a mean weight coefficient of variation lower than 5%. Three compounding formulations contained less than 95 mg nimesulide, with C1 (88.5 mg) also showing a lack of dosage unit uniformity. Disintegration times were lower than 5 min for all samples and friability less than 0.5% for all tablet formulations. The hardness of the reference product (25.5N) was lower compared to the other tablet samples (30-80.3N). All tablet formulations reached 75% release after 5 min of the dissolution test, but none of the compounding formulations reached the minimum 75% release after 45 min, probably due to inadequate excipient composition and amount. On average, excipient accounted for 46.3% of the capsule weight (against 74% in tablets), and some of the products did not contain water-soluble substances to promote dissolution.

Conclusion: The results of this study indicate a lack of quality in compounding nimesulide products, which could jeopardize patients’ health and treatment.

Keywords: Nimesulide, Dissolution profile, Validation, Capsules, Tablets, Compounding pharmacy.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications in the world [1]. Nimesulide (fig. 1) is a cyclooxygenase-II selective NSAID derived from sulfonanilide [2]. The drug has analgesic, anti-inflammatory and antipyretic effects, and is used mainly in the treatment of acute pain, osteoarthritis and primary dysmenorrhea [2-4].

According to the Biopharmaceutics Classification System (BCS), nimesulide is a class II drug, with low solubility and high permeability, which means that dissolution is the rate-limiting step for drug absorption [4, 5]. The dissolution profile of a drug formulation measured in the laboratory is related to its in vivo release, and can predict how they are absorbed, ensuring appropriate bioavailability and therapeutics [5-8].

Nimesulide is found in commercial dosage forms such as suppositories, drops, suspensions, granules, and tablets. Compounding formulation of nimesulide in gelatin capsules is also widely prescribed in Brazil due to the advantages of therapeutic individualization, combined drugs and lower costs. Compounding pharmacies represent an important market sector, which has been expanding in Brazil and other countries. This expansion, however, is not always followed by quality assurance, potentially affecting the therapeutic efficacy of the drug, and thus posing a risk to human health [9-11].

To ensure the quality of its products, compounding pharmacies, like other pharmaceutical product manufacturers, must comply with Good Manufacturing Practices, legal requirements, and regulatory standards. These pharmacies must have a quality control system implemented to offer safe and appropriate products to patients, who expect a medication of the same quality as the industrial product, approved and supervised by the competent authorities. However, it is not always known whether compounding products were manufactured by trained personnel, who followed validated processes using properly calibrated and cleaned equipment, with ingredients obtained from approved sources and whether appropriate laboratory testing was performed to verify the compounding drug potency, purity, and quality. Furthermore, the shelf-life of compounding products is normally not verified to assure their original strength and purity over time [11, 12].

The current Brazilian legislation concerning compounding pharmacies includes the control of the raw material and water, and analysis of content and dose uniformity of the final product [13]. However, dissolution and disintegration tests are not required. This paper reports the validation of a dissolution test for compounding capsules containing nimesulide 100 mg and a spectrophotometric method for the quantification of nimesulide content in the formulations. Compounding and industrialized formulations were evaluated for their physical and chemical properties with respect to pharmacopeia specifications.

![Fig. 1: Nimesulide](image)

**Molecular mass**: 308.1 g/mol  
**pKa**: 6.56  
**water solubility**: 10 µg/ml
MATERIALS AND METHODS

Chemicals

Nimesulide European Pharmacopoeia reference standard was obtained from Fluka® (100% reported purity). Anhydrous potassium phosphate monobasic, sodium hydroxide, phosphoric acid 85%, and polysorbate 80 were purchased from Dinaíca® (São Paulo, Brazil). Water was purified by reverse osmosis system.

Two nimesulide stock solutions were prepared for this work. A stock solution at 200 μg/ml prepared in NaOH 0.01 M (SS1), and a stock solution at 150 μg/ml prepared in 7.4 pH potassium phosphate buffer + tween 80 at 2% (SS2).

Tested formulations

Similar (S1, S2, S3), generic (G1, G2, G3), and reference (R; Nisulid® Ache Laboratórios Farmacêuticos, Brazil) tablets containing nimesulide 100 mg were obtained commercially. Their compositions are described in Table 1. The compounding gelatin capsule formulations C1, C2 and C3 and their placebo were donated by three different pharmacies. C4 and C5 were purchased from two pharmacies in Brasilia (Federal District, Brazil) (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Excipient formulation composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>G1</td>
</tr>
<tr>
<td>G2</td>
</tr>
<tr>
<td>G3</td>
</tr>
<tr>
<td>S1</td>
</tr>
<tr>
<td>S2</td>
</tr>
<tr>
<td>S3</td>
</tr>
<tr>
<td>C1</td>
</tr>
<tr>
<td>C2</td>
</tr>
<tr>
<td>C3</td>
</tr>
</tbody>
</table>

R= reference formulation; G= generic formulation; S= similar formulation; C= compounding formulation

Nimesulide determination

Nimesulide content was determined according to the Brazilian Pharmacopoeia (2010) for tablet formulations. The method was validated in this study for capsule formulations.

Twenty tablet units (R, G and S formulations) or the content of 20 capsules (C formulations) were homogenized, a sample containing approximately 100 mg of nimesulide transferred to a 100 ml volumetric flask, the volume completed with 0.01 M NaOH, the solution filtered using an 80 g/cm² filter (Prolab®), and an aliquot diluted with 0.01 M NaOH to a final concentration of 2 μg/ml. Three aliquots of this final solution were taken to determine the content of nimesulide using a UV/Vis spectrophotometer (1650PC; Shimadzu®) at 392 nm against a nimesulide calibration curve in 0.01 M NaOH (0.4 to 3.0 μg/ml) prepared from SS1.

To determine the content of nimesulide in the dissolution test, the withdrawn aliquots were filtered, 1 ml diluted to 100 ml with water, and nimesulide content determined against a calibration curve prepared in water from SS2 (0.45 to 2.25 μg/ml).

Method validation for nimesulide in gelatin capsules (compounding formulations)

All validation parameters were evaluated according to International Conference on Harmonization guidelines [14].

Linearity of the spectrometric response was evaluated for nimesulide calibration curves at 0.4, 1.0, 1.6, 2.0, 2.4 and 3.0 μg/ml prepared in 0.01 M NaOH from SS1, and at 0.45, 0.75, 1.2, 1.5, 1.8 and 2.25 μg/ml prepared in water from SS2. Each solution was prepared in triplicate. The absorption at 392 nm of the resulting solutions was measured.

Specificity was evaluated by comparing the spectrum of the C1, C2 and C3 excipients and excipient plus gelatin capsule with the spectrum of nimesulide standard solutions at 2 and 1.5 μg/ml, prepared in 0.01 M NaOH (from SS1) and in water (from SS2), respectively. Spectrophotometric scans for each solution were obtained from 300 to 600 nm.

Precision was assessed by estimating repeatability and intermediate precision. Repeatability was evaluated through the coefficient of variation (CV) from the recovery data of formulations C1, C2 and C3 (6 replicates for each) prepared at a theoretical concentration of 2 μg/ml in 0.01 M NaOH (from SS1) and of 1.5 μg/ml in water (from SS2). Intermediate precision was evaluated with data obtained on two different days.

Accuracy was assessed by recovery data. Known amounts of the nimesulide standard were added to solutions of the C1, C2 and C3 excipients at final concentrations of 1.6, 2.0 and 2.4 μg/ml in 0.01 M NaOH (80, 100 and 120% of the nominal assay of nimesulide), and at 1.2, 1.5 and 1.8 μg/ml in water (from SS2). The absorption at 392 nm was measured, and percentages recovered at each concentration level were calculated.

Robustness of the nimesulide determination method was assessed by checking the results using 80 or 200 g/cm² filters to prepare the 0.01 M NaOH solutions. Stability of the standard solution at 2 μg/ml with 0.01 M NaOH was also evaluated for a 4-hour period.

Robustness of the dissolution method was assessed using dissolution medium prepared with two different potassium phosphate brands and nimesulide standard solutions in water (prepared from SS2). Withdrawn aliquots were filtered with 80 or 200 g/cm² filters. Stability of the standard solution diluted with water at concentration of 1.5 μg/ml was evaluated for a 4-hour period.

Uniformity of dosage units

The assessment of this parameter was based on the drug content results and individual weight of 10 units for each product. The test estimated the drug content in each unit. An acceptance value (AV) was calculated as an approval criterion, according to Brazilian Pharmacopoeia specifications [15]. This value had to be below the reference limit of 15.0. When this was not the case, it was necessary to carry out the test with an additional 20 units and the AV calculated with all 30 units. Table 2 shows the equations used in these calculations.

Disintegration of tablet formulations

Disintegration time was evaluated in an Ethic technology model 301-1 (Brazil) disintegrator using six units of each formulation and purified water at 392 nm against a nimesulide calibration curve in 0.01 M NaOH (0.4 to 2.25 μg/ml) prepared from SS1.
water at 37±1°C as immersion media [15-17]. Disintegration time was reached when all six units were disintegrated in the tester.

Friability and hardness of tablet formulations

Friability was tested with 20 accurately weighted tablets and placed in the drum of a friabilator (Nova Etica® 300 apparatus). The tablets were rotated at 25 rpm for 4 min, removed, accurately re-weighted, and the percentage weight loss calculated [16]. Hardness (Nova Etica® 298-AT apparatus) was individually assessed for 10 tablets of each formulation and the results expressed as mean values in Newtons (N) [15, 16].

Dissolution test

Dissolution tests were conducted in a Nova Etica® 299/6 apparatus, using basket for capsules or paddle for tablet formulations, and 900 ml of 7.4 pH potassium phosphate buffer+tween 80 at 2% as dissolution medium. Twelve units of each formulation were used in each test. The tests were conducted at 37 °C at 75 rpm, with 5 ml samples taken at 5, 10, 15, 20, 30 and 45 min (with medium dissolution replacement) after test initiation, and the nimesulide content determined spectrophotometrically.

Table 3 shows the physical properties of the formulations investigated in this study. In all cases, the CV of the mean weight (n=20) was lower than 5%. According to the Brazilian Pharmacopeia (2010), for tablets with a mean weight higher than 250 g, no more than two in 20 units tested should have a variation higher than±5% the mean weight, and for compounding capsules weighing lower than 300 mg, this variation should not exceed±10%.

RESULTS AND DISCUSSION

Method validation for capsule formulations

Currently, the pharmacopoeia method to measure nimesulide concentration is only available for tablet formulation, and in this study the same method was validated for capsule formulations, used in compounding pharmacies. The method was validated using nimesulide dissolved in 0.01 M NaOH (to measure the concentration in the formulation) and buffer/water (concentration after the dissolution test). Nimesulide calibration curves prepared in both media showed correlation coefficients higher than 0.999 for all replicates (n=3).

Specificity of nimesulide measurement in the spectrophotometer was shown in the range of 300 to 600 nm (fig. 2), with no significant absorption due to the excipient (0.01 M NaOH) and the excipient plus capsules (in 7.4 pH potassium phosphate buffer).

The precision of the spectrophotometric measurement was shown through the repeatability (n=6) and intermediate precision (n=12), with CV values below 5% in both cases. The method showed to be accurate, with recovery within the accepted range (95 to 105%) for all 3 concentration levels and different combinations of excipients.

The method was shown to be robust since the results of nimesulide content were not significantly different when the final solution was filtered using an 80 or 200 g/cm² filter paper (data not shown).

Stability of the reference standard solutions prepared in 0.01 M NaOH and potassium phosphate buffer was confirmed for a 4-hour period, with variations in concentration of the solutions of 0.9 and 0.5%, respectively (data not shown).

Characteristics of nimesulide formulations

Table 3 shows the physical properties of the formulations investigated in this study. In all cases, the CV of the mean weight (n=20) was lower than 5%. According to the Brazilian Pharmacopoeia (2010), for tablets

Table 2: Equations used to the calculation of f 1  and f 2  values and uniformity of dosage units

<table>
<thead>
<tr>
<th>Definition</th>
<th>Equations</th>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual drug content in each</td>
<td>[ f_1 = \frac{\sum_{i=1}^{n}</td>
<td>R_i - T_i</td>
</tr>
<tr>
<td>Acceptance value</td>
<td>[ f_2 = 50 \times \log \left( 1 + \frac{1}{n} \sum_{i=1}^{n} [R_i - T_i]^2 \right)^{-0.5} \times 100 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ X_i = w_i \times \frac{A}{W} ]</td>
<td>w_i: individual weight of each unit; A: drug content (%); W: mean weight (n=20).</td>
</tr>
</tbody>
</table>

Tablet dissolution profile comparison

In order to compare the dissolution profiles obtained for the tablet formulations, the difference factor (f 1 ), the similarity factor (f 2 ), and dissolution efficiency (DE) were determined. The DE was calculated from the area under the dissolution curve at time t: (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time [18, 19]. Statistical treatments of DE results were based on variance analysis and t-test.

The f 1  factor measures the percent error between two dissolution curves over all time points. It is zero when the compared profiles are identical and increases proportionally with the dissimilarity between the two dissolution profiles. The f 2  factor is a logarithmic transformation of the sum-squared error of differences between the compared products over all time points (table 2). It is 100 when the profiles are identical and tends to 0 as the difference increases. Two dissolution profiles are considered similar if f 1  is between 0 and 15 and f 2  is between 50 and 100 [18, 19].
All formulations were within these parameters, indicating weight homogeneity within the product lots. On average, the excipient accounted for 73.9% of the total weight for tablet formulations (67.8-75.2%), and 46.3% for compounding, showing a large variation among the formulations (17.1% for C1 to 65.4% for C3). Most likely, the results for the compounding capsules are due to the excipient composition in formulations, which is a key parameter to guarantee disintegration and dissolution of solid dosage forms (table 1), an issue that will be discussed further in this paper.

Mean nimesulide content (n=3) in tablet formulations ranged from 95.9 to 103.6 mg (table 3), within the maximum ±5% deviation range of the reported label content (100 mg), specified in the Brazilian Pharmacopoeia [15]. Three compounding formulations (C1, C2 and C4) did not comply with the Pharmacopoeia, with respective values of 88.9%, 94.3% and 91.9%. It is possible to correlate this observed quality deviation of the compounding formulations with inaccurate weighting, uncalibrated balances, and operators with the lack of proper training, or loss of the drug during the encapsulation process. Furthermore, the inadvertent acquisition of low-quality raw ingredients by the compounding pharmacy can be a very important source of products with inadequate active content.

The result of the uniformity of dosage unit test was unsatisfactory for formulation C1, with a final calculated AV of 19.7, higher than the pharmacopoeia specification (lower than 15.0). This deviation may be due to lack of homogenization of the active ingredient and excipient mixture, a major step during the manipulation process to yield the same amount of drug in every single unit of the product. Uniformity of content in solid dosage forms is a key parameter, especially with regard to compounding pharmacies, due to component segregation, which can decrease homogeneity of the blended powder. It is known that manipulation processes vary amongst different establishments [20], and it is important to validate the process and apply Good Manufacture Practices in order to yield quality products.

Disintegration times were lower than 5 min for all formulations tested (table 3), in agreement with the Pharmacopoeia that specifies a maximum of 30 min for tablets, and 45 min for capsules [15]. Friability, which indicates the ability of the tablets to withstand abrasion in packing, handling and transporting (in % of mass loss), was less than 0.5% for all tablet formulations, within the Brazilian (maximum of 1.5%) and the US (maximum of 1.0%) pharmacopoeia specifications. Hardness, which measures the strength of the tablet to withstand pressure, ranged from 30 to 80 N. Although this is only an informative test [16], there was a large variation among the tablet formulations, with the reference product presenting the lowest value and variability (25.5 N, CV of 5.1%), and could reach 80.3 N (CV of 20.9%) for a similar formulation (table 3).

Comparing the therapeutic performance of two pharmaceutical products containing the same drug represents an approach to evaluate possible interchangeability between innovator and similar formulations [22]. The absorption of a drug after oral administration depends on the release from a dosage form, dissolution under physiological conditions and intestinal permeability [23]. As the first and second stages are critical in the absorption process, in vitro dissolution is a relevant approach to predict in vivo therapeutic performance of a pharmaceutical product [19, 21], especially when dealing with BCS class II drugs such as nimesulide.

Table 3: Characteristics of the nimesulide formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight, mg (CV, %)</th>
<th>Nimesulide, mg (CV, %)</th>
<th>Disintegration time</th>
<th>Friability, %</th>
<th>Hardness, N (CV, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>40.37 (0.37)</td>
<td>10.21 (1.11)</td>
<td>1'41&quot;</td>
<td>0.33</td>
<td>25.5 (5.1)</td>
</tr>
<tr>
<td>G1</td>
<td>45.51 (2.4)</td>
<td>103.6 (0.63)</td>
<td>2'25&quot;</td>
<td>0.22</td>
<td>73.2 (12.8)</td>
</tr>
<tr>
<td>G2</td>
<td>39.95 (0.6)</td>
<td>100.9 (0.53)</td>
<td>56&quot;</td>
<td>0.21</td>
<td>30.0 (13.1)</td>
</tr>
<tr>
<td>G3</td>
<td>40.06 (2.0)</td>
<td>99.4 (0.75)</td>
<td>1'30&quot;</td>
<td>0.04</td>
<td>76.5 (6.4)</td>
</tr>
<tr>
<td>S1</td>
<td>399.4 (2.0)</td>
<td>99.0 (1.04)</td>
<td>1'16&quot;</td>
<td>0.12</td>
<td>80.3 (20.9)</td>
</tr>
<tr>
<td>S2</td>
<td>392.0 (0.78)</td>
<td>97.9 (0.66)</td>
<td>1'16&quot;</td>
<td>0.13</td>
<td>77.0 (10.5)</td>
</tr>
<tr>
<td>S3</td>
<td>298.6 (1.1)</td>
<td>95.9 (0.50)</td>
<td>1'15&quot;</td>
<td>0.33</td>
<td>72.3 (19.3)</td>
</tr>
<tr>
<td>C1</td>
<td>107.3 (2.8)</td>
<td>88.9 (0.62)</td>
<td>1'15&quot;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C2</td>
<td>170.5 (2.8)</td>
<td>94.3 (0.53)</td>
<td>2'25&quot;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C3</td>
<td>277.3 (1.9)</td>
<td>96.0 (1.05)</td>
<td>1'50&quot;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C4</td>
<td>259.3 (2.7)</td>
<td>91.9 (0.63)</td>
<td>2'33&quot;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C5</td>
<td>169.5 (4.1)</td>
<td>102.1 (1.04)</td>
<td>2'41&quot;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CV= coefficient of variation; a20 units; b mean of three determinations; c10 units; R= reference formulation; G= generic formulation; S= similar formulation; C= compounding formulation.

Fig. 3: Dissolution profiles of nimesulide 100 mg in the reference and generic tablets (A), reference and similar tablets (B) and in the compounding formulations (C)
Dissolution profiles of the tablet formulations are shown in fig. 3 (A and B). According to the Brazilian Pharmacopeia, at least 75% of the drug should be released from the tablet during the 45 min of the test [15]. In this study, all tested tablet formulations reached 75% release after 5 min of the assay.

A statistical comparison between two dissolution profiles has the purpose of testing the possibility of interchange ability between the reference, and a similar or generic product [22]. The results in table 3 show that the dissolution efficiency (DE) of formulations S3, G2 and G3 were statistically different from formulation R (*P<0.005). Two dissolution profiles are considered similar if $f_1$ is between 0 and 15, and $f_2$ is between 50 and 100. The $f_2$ factor was not calculated for formulations G1, G2, G3, S1 and S2 due to the fast release of the drugs (over 85% within 15 min of the assay), when $f_2$ loses its discriminatory power [17]. Table 4 shows that only formulation S3 was not similar to formulation R, due to a low $f_2$ (47.2).

Although products C1 and C3 contain some substances that increase poor water-soluble drug dissolution (sodium lauryl sulfate and sodium croscarmellose), the formulation performance still did not comply with pharmacopeia specifications (about 50% release after 45 min of the assay; fig. 3C). This indicates that the proportion of the excipients in the formulation was probably not adequate to obtain an optimal dissolution of the capsule.

Although the excipient composition of C4 and C5 were not available for this study, it is possible to assume that the C4 formulation contained suitable excipients that promoted nimesulide release and improved its dissolution. This product had the most satisfactory dissolution performance among the capsules. Furthermore, as previously shown, the proportion of excipients to the total compounding formulation weight was low in most cases (17% for C1), which might also have had a significant impact on the dissolution profiles. The selection of suitable excipients in an appropriate proportion is critical for reaching satisfactory dissolution performance and, therefore, adequate bioavailability.

CONCLUSION

Nimesulide is a BCS class II drug and, since dissolution in vitro represents the rate-limiting step for drug bioavailability, it is of major importance that dissolution tests are conducted during formulation development and quality control of the final product. Inadequate drug dissolution greatly compromises the expected effect on the organism, resulting in poor therapeutic efficacy, and may represent a risk to a patient’s health. The results of this study showed that none of the tested compounding formulations showed an adequate dissolution profile, probably due to inadequate excipient composition. Brazilian legislation for compounding products should include dissolution tests to assure the therapeutic efficacy of the final product. Furthermore, compounding establishments should be closely monitored to ensure their compliance with the regulation.

ACKNOWLEDGEMENT

The authors thank the Catholic University of Brasilia, its technicians, and Dr. Samara Haddad Simões for allowing the use of the Quality Control Laboratory.

CONFLICT INTERESTS

Declared none.

Table 4: Dissolution efficiency (DE; n=12) difference factor ($f_1$) and similarity factor ($f_2$) for tablet formulations

<table>
<thead>
<tr>
<th>Product</th>
<th>DE (mean±sd)</th>
<th>$f_1$</th>
<th>$f_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>83.91±1.48</td>
<td>2.75</td>
<td>-</td>
</tr>
<tr>
<td>G1</td>
<td>86.5±2.68</td>
<td>7.65</td>
<td>-</td>
</tr>
<tr>
<td>G2</td>
<td>85.4±3.3*</td>
<td>5.63</td>
<td>-</td>
</tr>
<tr>
<td>G3</td>
<td>76.7±0.83*</td>
<td>3.37</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td>85.3±1.67</td>
<td>3.58</td>
<td>-</td>
</tr>
<tr>
<td>S2</td>
<td>89.1±2.33</td>
<td>10.84</td>
<td>47.24</td>
</tr>
<tr>
<td>S3</td>
<td>87.7±2.67*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

sd= standard deviation; * significantly different from the reference compound R (*P<0.005)

REFERENCES


