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Research Article

Development and Validation of a Discriminative Dissolution Test for Nimesulide Suspensions

Laís Bastos da Fonseca,[4,5] Márcio Labastie,[2] Valéria Pereira de Sousa,[1] and Nadia Maria Volpato[1,3]

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Abstract. The dissolution test for oral dosage forms has recently widened to a variety of special dosage forms such as suspensions. For class II drugs, such as nimesulide (NMS), this study is very important because formulation problems may compromise drug bioavailability. In the present work, tests with four brands of commercially available NMS (RA, TS, TB, and TC) have been performed in order to study their dissolution at different conditions. The suspensions have been characterized relatively to particle size, pH, and density besides NMS assay and the amount of drug in solution in the suspension vehicles. The dissolution study was conducted using the following media: simulated intestinal fluid, pH 6.8, containing polysorbate 80 (P80) or sodium lauryl sulfate (SLS); phosphate buffer, pH 7.4, with P80 and aqueous solution of SLS. Concerning the quantitative analysis, the UV–VIS spectrophotometry could have been used in substitution to high-performance liquid chromatography since the methodology had been adequately validated. The influence of the drug particle size distribution was significant on the dissolution profiles of NMS formulations, confirming to be a factor that should be strictly controlled in the development of oral suspensions.

KEY WORDS: dissolution; nimesulide; particle size; suspension; validation.

INTRODUCTION

The dissolution test for immediate or controlled release in solid oral dosage forms has recently widened to a variety of novel or special dosage forms such as suspensions, chewing gums, transdermal patches, implants, and others. In these cases, because of the different characteristics of the products, their sites, and forms of application, it is essential to give appropriate consideration to the following in the development of the test method: apparatus selection, dissolution medium composition, agitation, and temperature. The process validation should demonstrate that the new method will guarantee accurate, precise, and reproducible data, ensuring acceptable drug product quality and allowing for interpretation of the product's *in vivo* performance (1).

Up to this moment, very few works on suspension dissolution tests were reported, evidencing a lack of information on that pharmaceutical dosage form. Although suspensions are disperse systems, the drug absorption is also a function of the dissolution rate. Several factors influence the drug dissolution rate, including: (a) the drug physicochemical properties (particle size); (b) formulation characteristics (additives); and (c) dissolution method (apparatus type, medium pH, and surfactant type) (2).

Nimesulide (NMS) is a non-steroidal anti-inflammatory drug. The drug has pK_a values around 6.5 (3,4) and is sparingly soluble in water (~10 μg/mL). According to the Biopharmaceutical Classification System, NMS can be classified as a class II drug (low solubility and high permeability); therefore, the drug dissolution may be a rate-limiting step in the drug adsorption process (5). For water-insoluble drugs, difficulties are usually found in selecting a proper dissolution medium, with suitable volume and composition, as well as a good discriminating power. For some low-solubility compounds, adequate dissolution cannot be achieved with aqueous solutions within physiologic pH ranges (1.2–6.8). For these compounds, an aqueous solution containing a surfactant may be used to enhance the drug solubility and/or to obtain the sink conditions (6,7). The best medium to be chosen should include the one with the best discriminating ability.

The purpose of this study was to develop and validate a method for a dissolution test for NMS suspensions with different characteristics using UV–VIS spectrophotometry for the quantitative drug analysis in substitution to high-performance liquid chromatography (HPLC) in order to compare the dissolution rate of different suspensions.

[1] Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil.
[2] Departamento de Medicamentos, INCQS/FIOCRUZ, Rio de Janeiro, Brazil.
[3] Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
[4] Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Av. Pau Brasil s/n, Edifício CCS, Bloco Bss sala 34–Ilha do Fundão, Rio de Janeiro, Rio de Janeiro CEP: 21941-590, Brazil.
[5] To whom correspondence should be addressed. (e-mail: lfonseca@far.fiocruz.br)

MATERIALS AND METHODS

Materials

In the present study, four commercial NMS suspensions from different origins were employed and are described as follows: product RA, labeled to contain 10 mg/mL dosage of NMS (Nisulid® batch no. 41133, Brazil); product TS, labeled to contain 10 mg/mL of the drug (batch no. 501, Brazil); product TB, labeled to contain 10 mg/mL of NMS (batch no. 2213, Brazil); and product TC, labeled to contain 50 mg/mL of the drug (batch no. 013, Brazil). The first one is the Brazilian reference product; the others are similar brands. Nimesulide reference substance was kindly provided by Schering-Plough Produtos Farmacêuticos (batch no. 012K1278, Brazil).

The reagents employed were obtained from different local distributors. Monobasic sodium phosphate was purchased from Merck® (Rio de Janeiro, Brazil); monobasic potassium phosphate, monobasic sodium phosphate monohydrated, sodium hydroxide, and polysorbate 80 (P80) were purchased from Vetec® (Rio de Janeiro, Brazil); sodium lauryl sulfate (SLS) was obtained from Synth® (Rio de Janeiro, Brazil); dibasic sodium phosphate was purchased from Proquímios® (Rio de Janeiro, Brazil).

The samples for dissolution procedure were filtered by 10-μm polyethylene filters, assembled to sampling tubes, followed by immediate membrane filtration through a 0.45-μm pore polyvinylidene fluoride Millex® filter (Millipore, São Paulo, Brazil).

Particle Size Analysis

The drug particle size distribution was obtained through laser diffraction analysis (Shimadzu, model SALD 2101). The medium used was HCl 0.01 N added with 0.01% of polysorbate 80 and saturated with NMS in order to avoid any solubilization of the drug from suspensions.

Nimesulide Quantification

NMS was determined in the commercial suspensions by an HPLC system (Shimadzu Scientific Instruments, Japan) comprising a diode array UV detector (SPD-M10A VP), a pump (LC-10AD VP), and an automatic injector (SIL-10AD VP). A reverse phase column Shim-pack CLC-ODS (M) (250×4.6 mm, 5 μm) was used with a mobile phase consisting of water, acetonitrile, and acetic acid (45:55:1, *v*/*v*/*v*) at a flow rate of 1.5 mL/min. The injection volume was 20 μL, and a wavelength of 300 nm was used for detection. NMS presented a retention time of 7.3 min in the conditions above.

On the other hand, NMS present in the different dissolution media tested in this work was measured in an UV–VIS spectrophotometer (Varian UV–VIS Carry 50, USA) at 395 or 397 nm after appropriate dilution and treatment of samples with NaOH 1 N added to the volumetric flasks at 1:10 (*v*/*v*). Such procedure was conducted in order to promote the molecule complete ionization and, consequently, to furnish specificity to the assay due to a batocromic effect (red shift) in the maximum absorption wavelength. The methodology was validated and employed in order to substitute the HPLC system.

Validation

The NMS analysis through UV–VIS spectrophotometry for the dissolution test had been previously validated concerning specificity, linearity, accuracy and reproducible results, quantification and detection limits, as well as possible drug adsorption on the filters. Due to the absence of a placebo batch, specificity was inferred by comparing the results obtained with spectrophotometry and HPLC used to the NMS assay in the suspensions, and the accuracy was evaluated through the standard addition method. Additionally, the specificity was also evaluated through the standard addition assay (8).

Linearity was evaluated by analyzing five NMS different concentrations in the range from 5 to 30 μg/mL. In order to perform this analysis, four standard curves were prepared for each dissolution medium, one per day. The method linearity was measured by linear regression analysis.

Accuracy was evaluated through the standard addition method as follows: a standard solution (SS) containing 50 μg/mL of NMS in suitable dissolvent was prepared. For products RA, TB, and TS, 3.0-mL samples were taken from the homogenized suspensions and transferred into a 100-mL flask added with 50 mL of methanol. The remaining volume was completed with dissolution medium. For the TC product, the 3.0-mL sample was transferred into a 250-mL flask added with 120 mL of methanol, and once again, the remaining volume was completed with dissolution medium. From these mixtures, 2.0-mL samples were taken and transferred into ten 50-mL flasks in which 5 mL NaOH 1 N had been previously introduced. One flask remained only with the sample; the other flasks received the SS in three different amounts: 3.0 mL (25% of the nominal NMS concentration), 5.0 mL (42%), and 10.0 mL (83%). The volume of the flasks was completed with the dissolution medium. All the preparations were run in triplicate for the four products tested. This procedure was applied to simulated enteric fluid (SEF), pH 6.8, plus P80 1.5% and aqueous solution of SLS 1%.

Precision was assessed in terms of relative standard deviation (RSD) by comparing the results from three determinations of the suspensions through UV–VIS spectrophotometric analysis in SEF, pH 6.8, plus P80 1.5%, aqueous solution of SLS 1% or phosphate buffer, pH 7.4, plus P80 1.0% as dissolvent.

Limit of detection (LOD) and limit of quantification (LOQ) were estimated based on the analytical curve parameters (8). They were calculated for all dissolution media investigated in this work.

For filter adsorption, two standard NMS solutions (5 and 15 μg/mL) were prepared in SEF, pH 6.8, with P80 1.5% and aqueous solution of SLS 1%. Three samples of 5 mL each, from the solutions, were filtered. The filtration procedure was exactly the same as that employed in the dissolution test where new filters were connected in the syringes and introduced into the NMS standard solutions to retire the sample. Both filtered and non-filtered samples were analyzed at the UV–VIS spectrophotometer in order to evaluate the possible waste of the drug adsorbed on the filters.

Table I. NMS Solubility at Different Dissolution Media (13,14)

Dissolution media	[NMS] (μg/mL)
Water	10.1
Water plus SLS 1%	103.6
SEF, pH 6.8	30.1
SEF, pH 6.8, plus P80 0.5%	83.6
SEF, pH 6.8, plus P80 1%	147.7
SEF, pH 6.8, plus P80 1.5%	230.5
SEF, pH 6.8, plus SLS 0.5%	111.3
SEF, pH 6.8, plus SLS 1%	170.7
Phosphate buffer, pH 7.4	62.6
Phosphate buffer, pH 7.4, plus P80 1%	229.6
Phosphate buffer, pH 7.4, plus P80 1.5%	300.0
Phosphate buffer, pH 7.4, plus SLS 1%	163.4

Dissolution Study

Since NMS is a weak acid with low water solubility, the pH range of the media tested was established at 6.8–7.4, avoiding lower pH values. Solubility values (Table I) for NMS were used as a selection criterion so that large amounts of surfactant would not necessary. The dissolution media used were: SEF, pH 6.8, with polysorbate 80 (P80) at the concentrations of 1% and 1.5% (*w*/*v*); phosphate buffer, pH 7.4, with P80 at 1% (*w*/*v*) which were prepared according to USP 29 (9); and water with SLS at 1% (*w*/*v*) and modified SEF, pH 6.8, with SLS 0.5% (*w*/*v*) prepared with 49.0 g of monobasic sodium phosphate monohydrated and 42.0 g of dibasic sodium phosphate in 6,000 mL of distilled water, adjusting pH with NaOH 1 N or HCl 1 N for 6.8±0.1 and completing the volume to 7,000 mL with distilled water.

The amount of suspension (containing about 100 mg of NMS) introduced in the vessels was assessed by weighting a syringe before and after the sample introduction and based on the density of each product, which was previously determined.

The dissolution study was conducted using 1,000 mL of different media maintained at 37°C, with the paddle method and stirring rate of 25 and 50 rpm (dissolution test system model VK7010, VANKEL). Sampling was manual and performed at 5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, and 300 min at 25 rpm; however, when employing 50 rpm, probing in collect was interrupted after 180 min. For analytical determinations, samples were diluted 1:10 in the dissolution medium with the addition of 1 mL of NaOH 1 N. The drug absorption intensity was measured in UV–VIS spectrophotometer at the maximum wavelength of each medium (about 396 nm).

RESULTS AND DISCUSSION

Particle Size Analysis

Results for particle size analysis are presented in Fig. 1 and are summarized in Table II, also indicating the upper limit diameters for the respective population (10%, 50%, and 90% of particles). As observed, RA and TS formulations presented similar size distribution (average diameter, d_m= 3.4 μm), while TC showed the greatest particle size (d_m= 27.57 μm) and TB an intermediate size (d_m=7.19 μm). The size distribution differences between suspensions allowed an analysis of the dissolution conditions tested in order to enhance the discriminatory power of the method for different formulations.

Validation

The NMS analysis by UV–VIS spectrophotometry with the alkalinization of the samples was adequate for drug quantification in all dissolution media tested, achieving good results, with reduction in cost and analysis time. Figure 2 shows the batocromic effect (red shift) in the maximum absorption wavelength of NMS due to the complete ionization of the molecule by adding NaOH at a final concentration of 0.1 N. A hypercromic effect is also observed.

Specificity was assured as described in Table III, which shows that most results for NMS spectrophotometric assay, in the suspensions of products, have not been statistically different from that obtained by using the reference method (HPLC) when using different solvents (dissolution media). Exception occurred with the TC product in which the results were considered significantly different ($p<0.05$) from the control method. However, the deviation observed is less than

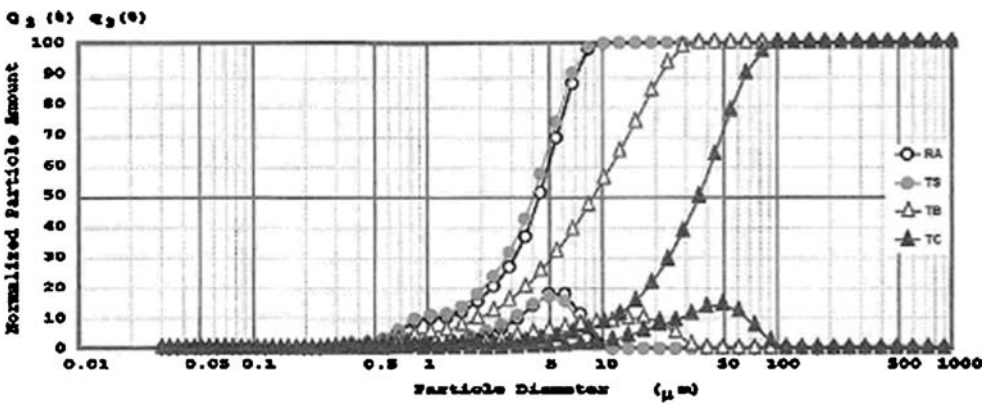

Fig. 1. Nimesulide particle size distribution normalized by the total amount of particles in the test for the suspensions dosage forms studied: products RA, TS, TB, and TC

Table II. Particle Size Distribution for the Suspension Dosage Forms Studied

Samples	Particle diameter (μm)					
	Average ± SD	Median	Mode	10%	50%	90%
RA	3.40±0.32	4.18	4.94	0.94	4.18	6.88
TS	3.35±0.32	4.09	4.94	0.95	4.09	6.79
TB	7.19±0.42	8.69	17.22	1.88	8.69	21.13
TC	27.57±0.36	33.20	48.79	10.32	33.20	61.71

1%, and the values obtained through the spectrophotometric analysis are lower than those achieved with the HPLC method. Furthermore, the results have been considered satisfactory as far as specificity is concerned.

Linearity was evaluated through the analysis of five different NMS concentrations ranging from 5 to 30 μg/mL. Four standard curves for each medium, in 4 days, were prepared. The method has showed linearity with a good fitting (R^2>0.999), correlation coefficient of 0.9999 to 1.0000, and intercept not different from 0 (p>0.05).

The accuracy was assessed by the standard method procedure since placebo formulation was not available as mentioned above. These results are presented in Tables III and IV in which it can be assured that the methodology used was exact once the data for the three levels of the standard addition method have been found within the range from 98.0% to 102.0 % (10).

The method precision was assessed from results of repeated suspensions assay (three times) in the SEF media, pH 6.8, with P80 1.5%, aqueous solution of SLS 1%, and phosphate buffer, pH 7.4, with P80 1%. As evidenced in Table III, the method is precise for the NMS quantification in the formulations tested since the relative standard deviation was lower than 1.0% in all cases. Tables IV and V corroborate the good precision of the spectrophotometric method.

The LOD and LOQ for the five different media employed provided results ranging from 0.5 to 0.9 μg/mL for LOD and from 1.7 to 2.8 μg/mL for LOQ.

In the dissolution test, it should be guaranteed that the drug would not be adsorbed on the filters used. In the NMS concentrations tested, there was a loss of 0.13% of the solutions with concentration of 5 μg/mL in both media evaluated and a loss of 0.07 and 0.25% of the NMS concentration of 15 μg/mL in aqueous solution of SLS 1% and SEF, pH 6.8, with P80 1.5%, respectively. It is recommended that the maximum loss of solute through adsorption on the filters is 2% according to Fortunato (11) and 5% according to Lindenberg *et al.* (12). Therefore, the results have shown that the filters used in the present work have not retained considerable amount of material since no significant drug loss was observed in the analysis.

Dissolution Tests

The percent quantification of NMS dissolved in the dissolution tests was performed based on the weight of suspensions added into each vessel. The amount of NMS added was calculated based on the weight difference between full and empty syringes, relating it to the formulation density and the concentration of the products, as observed in

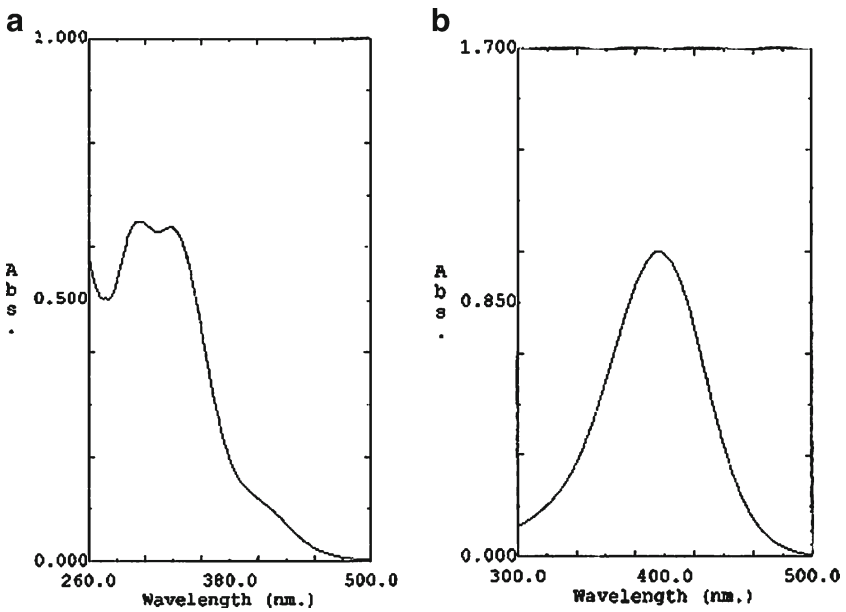

Fig. 2. UV spectrum of NMS reference substance at 20 μg/mL in medium SEF, pH 6.8, plus P80 1.5% **a** without NaOH 0.1 N and with **b** NaOH 0.1 N

Table III. Comparison of the Results for NMS Assay in the Suspension Dosage Forms Employing Two Methods: HPLC and UV Spectrophotometry with Different Solvent Media (n=3; average results followed by RSD in parenthesis)

Products	Results for NMS assay (%) by HPLC	Results for NMS assay (%) by UV spectrophotometry		
		SEF, pH 6.8, plus P80 1.5%	Water plus SLS 1.0%	Phosphate buffer, pH 7.4, plus P80 1.0%
RA	100.19	101.10[a] (0.12)	100.58[NS] (0.18)	100.26[NS] (0.07)
TS	99.38	99.89[NS] (0.14)	99.75[NS] (0.16)	99.46[NS] (0.07)
TB	107.53	107.21[NS] (0.10)	106.99[NS] (0.11)	107.09[NS] (0.08)
TC	102.84	101.99[a] (0.19)	101.76[a] (0.14)	101.55[a] (0.10)

NS non-significantly different from HPLC result (α=0.05)
[a] Significantly different from HPLC result (p<0.05)

Table IV. Results for the NMS Recovery Test Employing SEF, pH 6.8, plus P80 1.5% by UV Spectrophotometry in the Products RA, TB, TS, and TC Evaluated

Solution	Amount of standard added (μg)	Total amount recovered			
		Average mass (μg) recovery ± SD (%)			
		RA	TB	TS	TC
Sample without standard addition[a]	–	585.2	631.37	595.5	620.4
Level 1 of standard addition[b]	154.8	740.0	786.1	750.0	774.8
		100.0±0.01	100.0±0.00	99.9±0.09	99.8±0.11
Level 2 of standard addition[b]	257.9	842.5	889.1	852.8	878.0
		99.8±0.12	99.9±0.05	99.8±0.10	99.9±0.06
Level 3 of standard addition[b]	515.8	1100.2	1146.5	1111.0	1136.2
		99.9±0.08	99.9±0.08	100.0±0.05	100.0±0.09

SD standard deviation
[a] Without replicate
[b] Done in triplicate

Table V. Results for the NMS Recovery Test Employing SEF, pH 6.8, plus SLS 1.0% by UV Spectrophotometry in the Products RA, TB, TS, and TC Evaluated

Solution	Amount of standard added (μg)	Total amount recovered			
		Average mass (μg) recovery ± SD (%)			
		RA	TB	TS	TC
Sample without standard addition[a]	–	557.0	642.8	566.9	485.8
Level 1 of standard addition[b]	150.6	705.9	794.5	718.5	665.7
		98.9±0.11	100.5±0.45	100.7±0.21	100.0±0.06
Level 2 of standard addition[b]	250.9	807.8	896.1	820.0	753.5
		99.9±0.05	100.9±0.04	100.9±0.04	100.0±0.30
Level 3 of standard addition[b]	501.9	1060.0	1146.3	1068.7	982.8
		100.2±0.00	100.3±0.03	100.0±0.02	99.0±0.05

SD standard deviation
[a] Without replicate
[b] Done in triplicate

Table VI. Mean Amount of Suspension Added to the Vessels and Resulting Dose of NMS for the Dissolution Profiles, Calculated from the Formulation Density, Labeled Concentration and Assay Result (n=30)

Products	Suspensions mean amount added ± SD (g)	Density (g/mL)	Calculated volume added (mL)	Labeled conc. (mg/mL)	Added dose by labeled conc. (mg) = A	Assay result by HPLC (%)	Added dose by assay result (mg) = B	Difference (A − B)
RA	11.83±0.31	1.1742	10.07	10	100.75	100.19	100.94	−0.19
TS	11.78±0.44	1.1441	10.30	10	102.96	99.38	102.32	+0.64
TB	10.82±0.27	1.0782	10.04	10	100.35	107.53	107.91	−7.56
TC	2.30±0.06	1.1143	2.06	50	103.20	102.84	106.13	−2.93

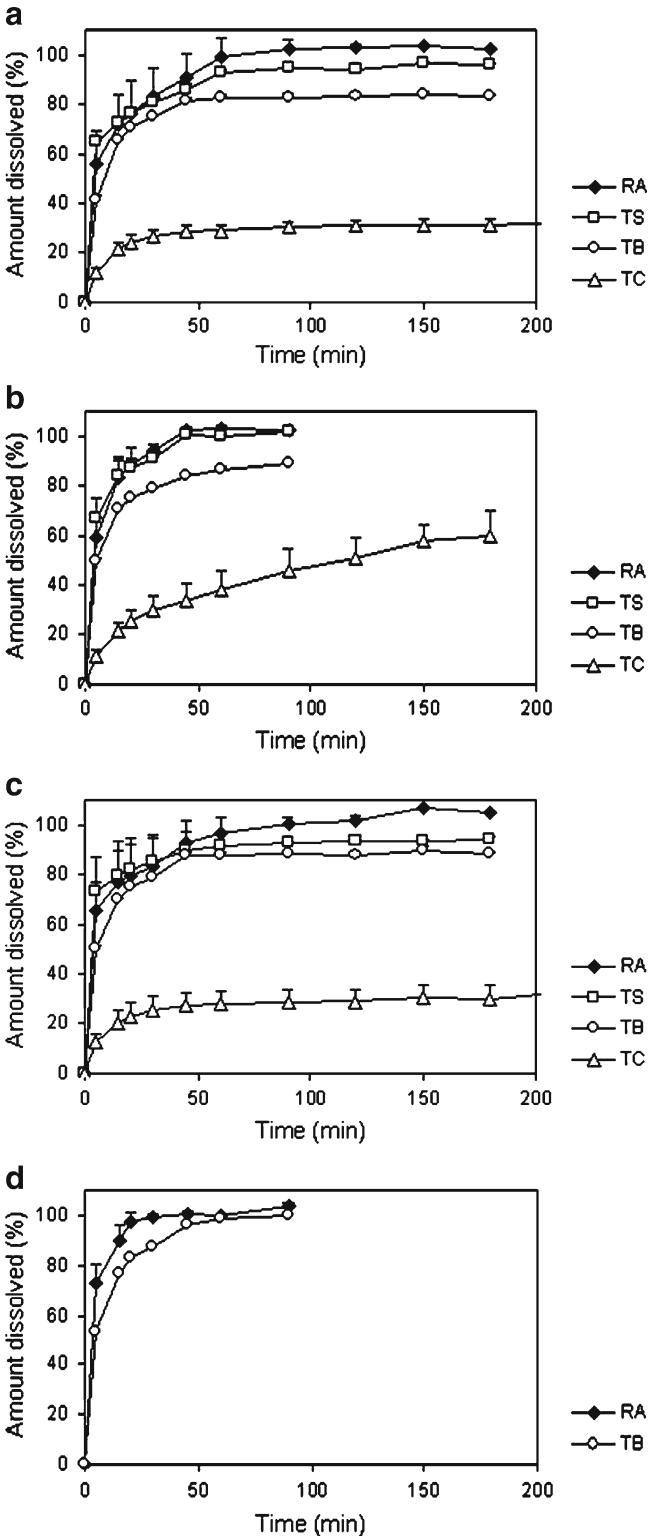

Fig. 3. Dissolution profiles of suspensions obtained in SEF, pH6.8, plus P80 1.0% employing **a** 25 rpm and **b** 50 rpm and in SEF, pH 6.8, plus P80 1.5% also employing **c** 25 rpm and **d** 50 rpm (average values ± SD)

Table VI. This procedure has been adopted to overcome variations of volume imprecision measured in common syringes. In the sole case of product TB in which concentration of NMS was 107.5% of the labeled value, dissolved percents were computed based on the actual NMS concentration obtained from the assay test. In the last column of Table VI where the differences between labeled and actual concentrations are presented for each product, the difference

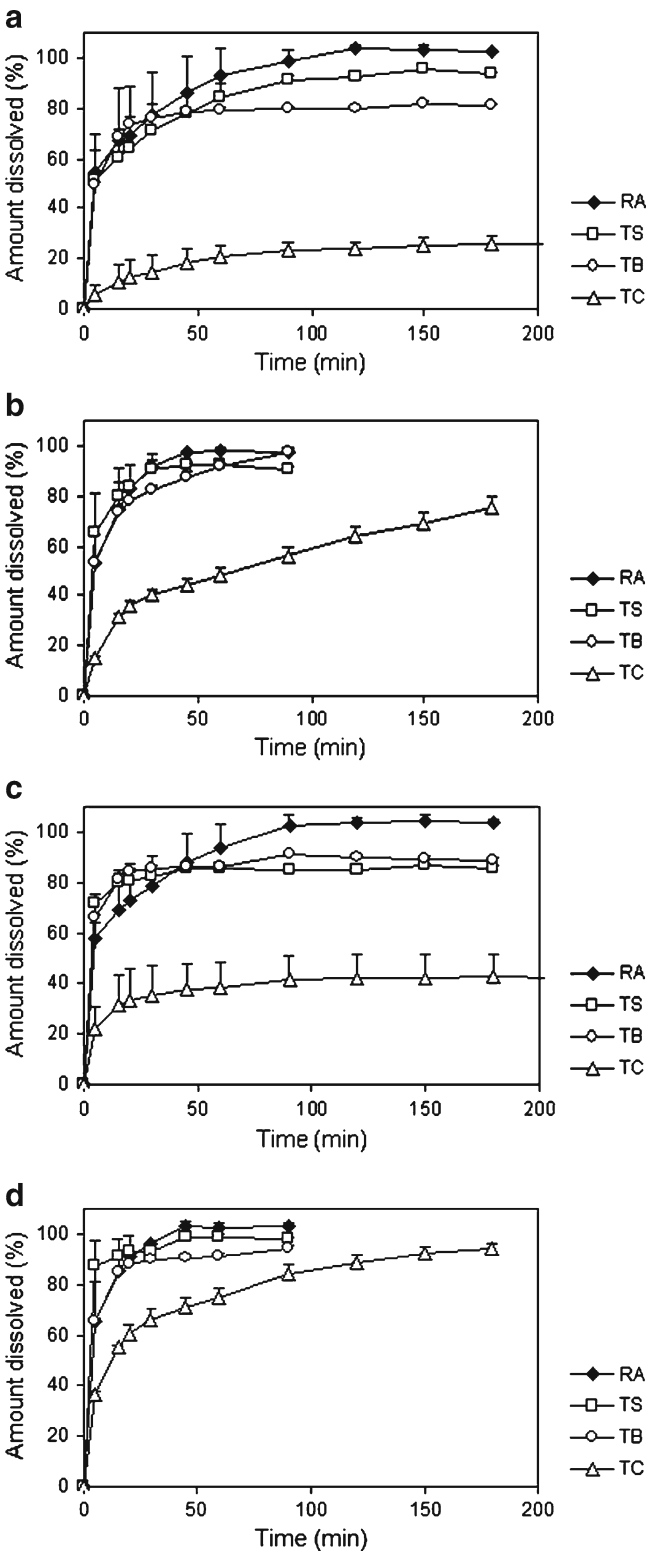

Fig. 4. Dissolution profiles of suspensions obtained in water plus SLS 1.0% (measured pH 7.38) employing **a** 25 rpm and **b** 50 rpm and in phosphate buffer, pH 7.4, plus P80 1.0% also employing **c** 25 rpm and **d** 50 rpm (average values ± SD)

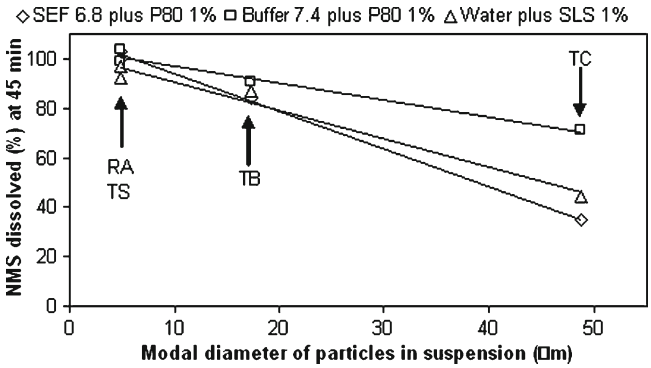

Fig. 5. Correlation between the amount of NMS dissolved at 45 min in three different media at 50 rpm and the drug particle size determined for the products represented by their modal diameter value (RA=4.9 μm; TS=4.9 μm; TB=17.2 μm; and TC=48.8 μm)

higher than 5% for product TB justifies this correction. The use of the declared value, in this case, would imply an overestimation of the NMS dissolved amount.

In Figs. 3 and 4, the dissolution profiles of the suspensions are presented according to the different conditions tested. Although the sink condition was not reached (Table I) (13,14), the NMS complete dissolution was achieved for products RA and TS in most conditions evaluated. Product TB did not present complete dissolution in almost all conditions tested; however, at least 80% of its content was dissolved. On the other hand, TC presented a totally different performance. These results could be related to NMS particle size in the products, as presented in Fig. 1. The diverse drug particle size distribution could be evidenced in different conditions of the dissolution tests performed. It is worth mentioning that for all products studied, the fraction of NMS soluble in the suspension vehicles, determined after suitable filtration, was lower than 5 μg/mL, corresponding to 0.05% of the labeled concentrations.

With a 25-rpm stirring rate, a stagnation of the dissolution process was visible, mainly for TB and TC formulations, a case in which a non-dissolved residual powder was observed in the bottom of the vessels at the end of the experiment, for all media tested. This behavior was not so intense under a 50-rpm stirring rate. This has led us to conclude that stirring at 25 rpm was not enough to disperse the largest drug particles and was not capable of promoting the complete dissolution of the drug in the media within the evaluated time. Thus, the stirring rate of 50 rpm was more adequate for the dissolution method without, however, accelerating excessively the process.

The effect of particle size expressed by modes can be correlated with percents of dissolved drug after 45 min, as illustrated in Fig. 5 for three different media. The more the dissolution is favored, the less discriminatory the method will be, as observed in the case of phosphate buffer, pH 7.4, with P80 1% as dissolution medium. Since the particle size distribution cannot be considered normal, the mode (rather than the mean) characterizes better the NMS suspensions.

The effect of increasing P80 from 1% to 1.5% in SEF, pH 6.8, medium on the dissolution profiles is not clearly visible even with the NMS solubility increasing from 147 to 230 μg/mL (Table I) (13,14). This behavior was evidenced for both 25- and 50-rpm stirring rates and seems to indicate that concentrations beyond 1.0% (*w*/*v*) of polysorbate 80 are not necessary.

The medium phosphate buffer, pH 7.4, with P80 1% produced the highest NMS dissolution rate. This can be attributed not only to the presence of the surfactant but also to the more favorable pH. Although out of the range currently recommended (1.2–6.8) for products containing weakly acid drugs, it was used to confirm its weak discriminating power for the formulations studied (6,15). In contrast, the aqueous solution medium of SLS 1%, even presenting a similar pH (about 7.38), favored more differenced dissolution profiles among the products, which is easily related to the lower NMS solubility (103.6 μg/mL) in this medium.

CONCLUSIONS

The UV–VIS spectrophotometric determination of NMS in dissolution media with alkalinization of samples presented satisfactory results based on the validation of data obtained, in accordance to international guidelines, and were adequate for the study of NMS suspensions dissolution.

The best quality control conditions for NMS suspensions was reached with a dissolution medium SEF, pH 6.8, containing the non-ionic surfactant polysorbate 80 at 1% as optimized concentration, paddle method at 50 rpm, which presented a good discriminatory power between products with different characteristics.

Despite the world regulatory agencies requiring validated dissolution test for suspensions pharmaceutical forms, nowadays, there are very few papers in the literature and official compendia (pharmacopeias) about this topic, so this work reached its goal of furnishing dissolution conditions for appropriate evaluation of this dosage form containing nimesulide.

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