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Characterization of nimesulide and development of immediate release tablets

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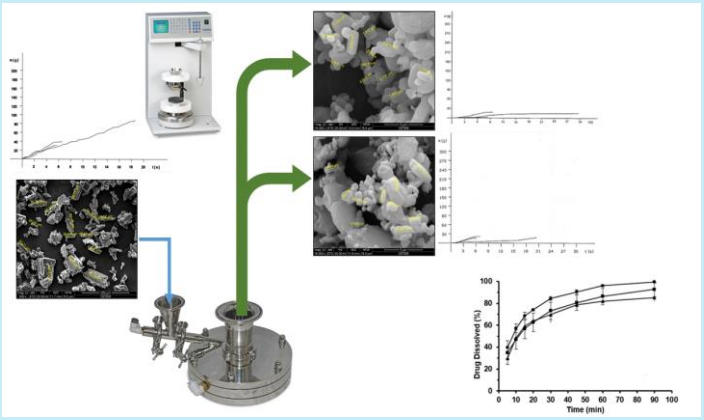
ABSTRACT: This paper aims to characterize nimesulide raw materials from different manufacturers and to develop immediate release tablets, in order to register a generic product. Also, raw material characteristics and the tablets final properties were investigated in order to establish a different specification for quality control. Two micronized and one non-micronized nimesulide samples were obtained from different manufacturers and were characterized by thermal analysis, spectroscopic techniques, morphological analysis, flowability and biopharmaceutical evaluation. The samples belong to the same polymorph. The formulations design and the choice of the production process were carried out based on the results obtained in the characterization assessments. The proposed formulations showed different dissolution behavior. One formulation was selected and then the dissolution was evaluated in different dissolution media containing varying concentrations of surfactant, in order to verify if the concentration of 2% (v/v) of polysorbate 80, recommended by the Brazilian Pharmacopoeia, would be overestimating the bioavailability of the drug. The results showed that the percentage of surfactant present in the dissolution medium directly impacts the amount of dissolved drug. The selected formulation demonstrated promising results to proceed with the bio batches manufacture and the pharmaceutical equivalence study.



1. Introduction

Nimesulide is a nonsteroidal sulfonamide and belongs to the class of anti-inflammatory drugs (NSAIDs) that demonstrates a selectivity for COX-2 (cyclo-oxygenase-2) and, therefore, has anti-inflammatory, analgesic and antipyretic activities[1,2]. When administered in recommended dosage demonstrates low incidence of side effects and is better tolerated than other NSAIDs, such as diclofenac, ketoprofen, naproxen and piroxicam[1].

Nimesulide is a sulfonanilide derivative, with a melting point around 143 °C[2,3]. According to the literature, it is a weakly acidic (pK_a approximately to 6.5), attributed to the presence of a sulfonamide group[1,2]. It is practically insoluble in water (about 10 µg/mL) and soluble in methanol and ethanol at room temperature[4]. Based on Biopharmaceutics Classification System (BCS), nimesulide is considered a class 2 drug, characterized by low solubility and high permeability. Thus, its dissolution may represent a limiting step in drug absorption process[3].

According to one study reported in the literature, crystallization of nimesulide in different organic solvents affects some physicochemical properties such as melting point, solubility and dissolution profile, indicating the existence of

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polymorphs[5]. Other studies describe the existence of two polymorphs of nimesulide: form I (usually used in the pharmaceutical industry) and form II[6,7].

Some studies discuss the characterization of nimesulide and demonstrated that DSC and X-ray diffraction techniques are promising in identifying polymorphs of nimesulide[7]. Additionally, the literature contains several studies using spectroscopy in the form of infrared complementary to other analytical techniques[7-10].

In terms of biopharmaceutical evaluation, a study obtained different values of intrinsic dissolution rate of nimesulide polymorphs I and II. However, the analysis of the graph in this study demonstrates that there was no linearity, affecting the results obtained in IDR[7]. Other studies using the intrinsic dissolution with this drug were not found, as well as studies using the wettability test. Allied to such trials, the powder dissolution has been used in biopharmaceutical evaluation[11,12], because there are some important factors that can impact on the assay results, for example, wettability, crystallinity, particle size and surface area[13].

The formulation studies evaluated the nimesulide tablets dissolution profile and found that drug release is not achieved even by testing the presence of surfactant at different concentrations in the dissolution medium[14,15].

Reducing the particle size of the drug to microparticles has been shown to significantly increase the dissolution and bioavailability of drugs. This is achieved by increasing the contact surface, which has a positive impact on the dissolution rate and possibly absorption[16]. One method to reduce particle size is by micronization[17] however, although there are advantages regarding the optimization of the dissolution of drugs with low solubility, micronizing should be carefully considered, because this can result in low density problems and inadequate flow. Accordingly, with respect to flowability, the literature reports a previous study evaluating the fluidity, in which it was demonstrated that nimesulide has no good flow properties[9].

The objective of this study was the characterization of nimesulide samples from different manufacturers and the development of immediate release tablets, in order to register a generic product. It was also tried to make some correlation between raw material characteristics and the final properties of the tablets in order to establish a different specification for quality control.

2. Materials and methods

2.1. Materials

Samples of nimesulide from three different manufacturers were coded as NM1 (sample non-micronized), NM2 and NM3 (micronized). The excipients microcrystalline cellulose 101 (Mingtai), lactose monohydrate 80 (DFE Pharma), sodium lauryl sulfate (Nuclear), docusate sodium (Shin-Etsu Chemical), sodium starch glycolate (Ecadil), low substituted hydroxypropyl cellulose (Shin-Etsu Chemical), polyvinylpyrrolidone K-30 (Boai Niki) and magnesium stearate (Magnesia), previously tested and approved according to the USP[18], were used. Standard sample of nimesulide was supplied by National Institute for Quality Control in Health, with purity of 99.80% and Nisulid®, Aché Laboratory, as the reference medicine.

2.2. Evaluation of the active pharmaceutical ingredient according to pharmacopoeia criteria

Samples NM1, NM2 and NM3, were analyzed according to the methodologies described in the Brazilian Pharmacopoeia[4]. The tests included identification, which used the method of infrared spectroscopy (spectrometer infrared model Nicolet 6700 FT-IR, Thermo Scientific), heavy metals, loss on drying, sulfated ash and dosing. This last one, followed the recommendations established in the method B of the Brazilian Pharmacopeia, which uses spectrophotometry absorption in the ultraviolet (LAMBDA 25, PerkinElmer) and the absorbance readings were performed at 392 nm.

2.3. Differential scanning calorimetry (DSC)

The DSC analysis was performed with a differential exploratory calorimeter instrument model 60, Shimadzu. The samples were weighed (about 3 mg) and encapsulated in aluminum crucibles with lid closed. The DSC curves were obtained under heating rates of 5, 10, 20 and 40 °C/min over a temperature from 25 to 200 °C, a flow rate of 50 mL min^{-1} of argon gas. Assays

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were performed in triplicate. Different heating rates were used.

2.4. Fourier transform Infrared spectroscopy

The FTIR spectra were record using a Thermo Scientific, model Nicolet 6700 FT-IR, over a range from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}. IR samples were analyzed directly without sample preparation.

2.5. X-Ray Powder Diffraction

The XRPD patterns of the samples were record on an X-ray D8 diffractometer (Bruker) equipped with Lynxeye XE detector and with Cu as tube anode (Kα radiation with λ = 1.5418 Å). The diffraction patterns were record under the following conditions: voltage 40 kV, 40 mA and fixed divergence slit using configuration of 2θ range from 4 to 50°, with a step size of 0.02° and a step time of 0.1 s. The identification of the crystal structure was performed using the database Cambridge Structural Database (CSD)[19] and calculated XRD pattern was prepared using the program Mercury 3.7[20].

2.6. Determination of particle size distribution using laser diffraction analysis

Particle size distribution was obtained by the laser diffraction method with a Malvern equipment, Model 2000E Mastersizer, using the liquid mode, a measurement range of 0.1-500 µm and obscuration between 17 and 23%. The suspension of 500 mg of nimesulide was prepared with an aqueous solution containing 0.5% polysorbate 80, in a total of around 30 mL. It was necessary to use ultrasound (USC 2800A, Unique) with speed 10.

2.7. Scanning Electron Microscopy (SEM)

To study the morphology of NM samples, SEM was performed on a Quanta 400 microscope (FEI), at a voltage 10 kV, using 500 and 16000x magnification. Small amounts of sample were adhered on a metal stub using double-sided adhesive carbon tape, which were then vacuum-coated (0.6 mbar) with a thin layer of gold in a BAL-TEC SCD 005 sputter coater at room temperature.

2.8. Wettability

The analysis was conducted with a tensiometer Krüss, DSA 100 at room temperature by sessile drop method. Approximately 300 mg were compressed in the form of discs using 800 psi for 1 min with the aid of a hydraulic press. The liquid drop (water saturated with nimesulide) was dispensed onto the surface of the sample and the images were captured immediately. The instrument calculated the contact angle by fitting mathematical expression to the shape of the drop.

2.9. Powder dissolution

Powder dissolution was performed with a dissolutor Distek, model 6100, and the conditions were as follows: 900 mL of potassium phosphate buffer solution adjusted to pH 7.4, with 2.0% polysorbate 80 (w/w) at 37 ± 0.5 °C and stirred with apparatus II (paddle) at 75 rpm rotating speed. Approximately 100.0 mg of nimesulide were added directly to the vessels and aliquots of 10 mL were collected after 5, 10, 15, 20, 30, 45, 60 and 90 min, without replacing the medium. Aliquots were filtered through 45 µm polytetrafluoroethylene filter, diluted and the absorbance measured in a spectrophotometer (LAMBDA 25, PerkinElmer) at a wavelength of 392 nm. The tests were performed in triplicate. A comparison of the dissolution profiles dispersion was made by calculating the difference factor (F1), the similarity factor (F2) and the dissolution efficiency (DE). The DE values were submitted to statistical analysis of variance (one-way ANOVA) followed by Tukey test and considered significant $p < 0.05$.

2.10. Determination of flowability

The evaluation of the flowability was carried out by the bulk and tapped density, Carr index, Hausner ratio, repose angle and flow through an orifice determination. The densities were determined according method I of USP[18], using the equipment Tap Density Tester (Nova Ética). The values were used to calculate the Carr's index and Hausner ratio. For the determination of repose angle and flow through an orifice was used Granulate GTB Tester Equipment (Erweka) with different diameter orifices and rotation speed to determine the optimal test conditions and

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discriminate the flowability profiles of the samples.

2.11. Formulation design

The galenic batches were prepared in amounts about 600 to 800 g. The wet granulation was conducted with a high shear granulator capacity 4 L (TMG 1/6, Glatt), for the initial powder mixture and the wetting with the binder solution. After the granulation, the wet mass was passed through a mesh of 4 mm using the oscillating granulator (K-70, Lawes). The drying of the granulate was performed in a fluidized bed (midi Glatt, Glatt), at a temperature of 45 °C under a controlled flow. The end point was determined by drying the residual humidity using an infrared balance (IV2500, Gehaka) and was established a range between 2 and 3%. After drying, the granulate was normalized with a mesh of 1.5 mm in the oscillating granulator. Then, this granulate was transferred to a V-blender, capacity 2 L (66/10, Lawes), to perform the mixing of the excipients that were added in the extra granular phase. Finally, the compression was performed on a rotating compressor (2000 10PSC, Lawes), fitted with punches of 10 mm flat. The process control was carried out by checking the weight, hardness, friability and disintegration of the tablets. For such determinations was used the following equipments: semi-analytical balance, capacity 200 g (Sartorius), portable durometer (TBH100, Erweka), friability tester (TA10, Erweka) and disintegrator (301-1, Nova Ética).

2.12. Evaluation of galenic batches

The tablets were analyzed by the average weight, hardness, friability and disintegration, conducted as described in Brazilian Pharmacopoeia[4], and the comparative dissolution profile, was carried out with the Nisulid® reference drug.

2.13. Dosing

The analysis was performed according to the Brazilian Pharmacopoeia[4], which quantifies the nimesulide content in tablets by ultraviolet absorption spectrophotometry at a wavelength of 392 nm. The assay was performed in triplicate with the standard solution and the sample solution.

2.14. Dissolution profile

Initially, the dissolution profiles were performed using the conditions recommended by the Brazilian Pharmacopoeia[4], with the reference product and the galenic batches who presented the results of physical tests (hardness, disintegration and friability) most promising. The analytical conditions were: 900 mL of potassium phosphate buffer, pH 7.4, containing 2.0% (v/v) polysorbate 80 and stirred with paddle at a rotation speed of 75 rpm. Aliquots of 10 mL were removed after 5, 10, 15, 20, 30 and 45 min, without replacing the medium, maintaining sink conditions throughout the test. The amount of drug dissolved was determined by reading on a spectrophotometer (UV-1800, Shimadzu) in the ultraviolet region at a wavelength of 392 nm. Then, one of the galenic formulations, which showed the same type of dissolution to the reference product has been selected to perform additional dissolution profiles studies. For this, was used the dissolution medium potassium phosphate buffer, pH 7.4, containing polysorbate 80 in concentrations of 1.0% and 0.5%. The others analytical conditions were maintained. The dissolution profiles were compared using dissolution efficiency (DE) and their values were submitted to statistical analysis of variance (one-way ANOVA) followed by Tukey test and considered significant $p < 0.05$.

3. Results

3.1. Evaluation of the active pharmaceutical ingredient according to pharmacopoeia criteria

The results of heavy metals, loss on drying, sulfated ash and dosing match the specifications of the Brazilian Pharmacopoeia[4] and are presented in Table 1.

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Table 1. Results of heavy metals, loss on drying, sulfated ash, dosing, contact angle of NM1, NM2 and NM3 samples.

	Sample		
	NM1	NM2	NM3
Heavy metals (ppm)	< 20 ppm	< 20 ppm	< 20 ppm
Loss on drying (%)	0.19	0.21	0.34
Sulfated ash (%)	0.04	0.03	0.03
Dosing (%)	99.5	99.2	99.6
Contact angle (°) (average ± SD)	80.7 ± 1.7	79.1 ± 3.0	78.8 ± 3.3

3.2. Differential scanning calorimetry (DSC)

The DSC curves obtained for NM1, NM2 and NM3 samples, measured at a heating rate of 5 °C/min showed a single sharp endothermic peak at approximately 149 °C in accordance with the melting point measurements (Figure 1). The same results were obtained in the DSC curves for NM1 sample under other conditions as 10, 20 and 40 °C min^{-1}. In addition, NM2 and NM3 showed identical results. For NM1, NM2 and NM3 samples, the baseline of DSC curves was similar and display that the thermal capacity was not changed by micronization process.

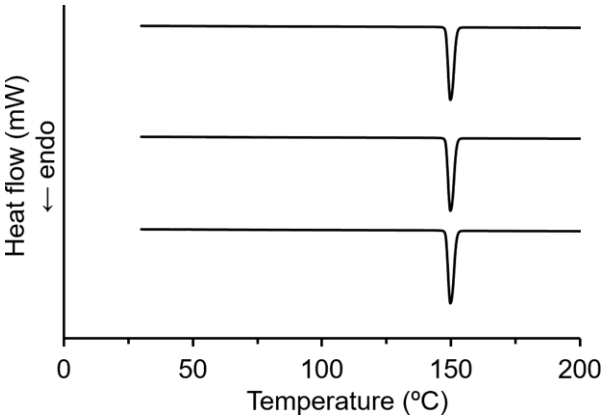

Figure 1. DSC curves from bottom to top NM1, NM2 and NM3 samples at a heating rate of 5 °C/min.

3.3. Infrared Spectroscopy

The FTIR spectra of all samples were equivalent (data not shown). The IR spectrum showed the ν_{NH} at 3278 cm^{-1}, a band at 1149 cm^{-1} assigned to the symmetric deformation of SO_2 group, ν_{NO2} stretching frequencies at 1330 cm^{-1} and 1588 cm^{-1} and a band at 1246 cm^{-1} assigned to the ν_{COC}. Except for the ν_{NH} and ν_{NO2} (at 1588 cm^{-1}), that presented weak intensity peaks, all the others functional groups of nimesulide demonstrated medium intensity peaks.

3.4. X-Ray Diffraction

The X-ray diffraction patterns of NM1, NM2 and NM3 samples (Figure 2) presented characteristic peaks at approximately 2θ = 17.07, 18.14, 19.35 and 21.60°. The samples comparison data clearly showed that the micronization process did not change the NM structure. The results were compared with the data of NM polymorphs I and II calculated from CSD and are also shown in Figure 2.

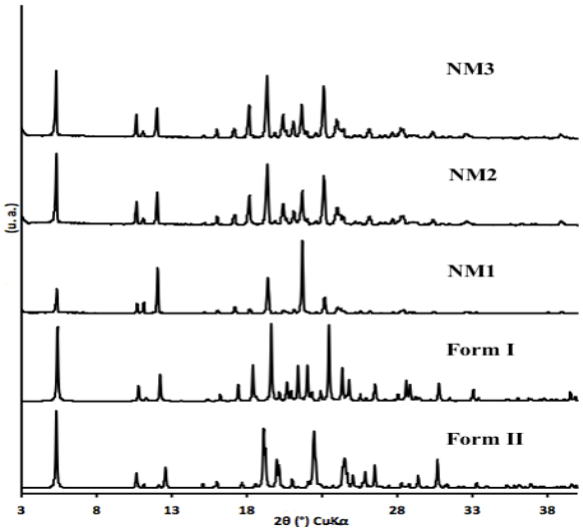

Figure 2. X-Ray diffraction patterns of the samples NM1, NM2 and NM3 and calculated patterns of the polymorphs I and II of nimesulide obtained from the CDCC (The Cambridge Crystallographic Data Centre).

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3.5. Particle size distribution using laser diffraction

The average size of particles results, the values of particles smaller than 10% (d10), 50% (d50), and 90% (d90) and the results of dispersibility indices (span) was obtained with the samples from different manufacturers of nimesulide. The NM3 sample showed the smallest particle size (d10 = 1.28; d50 = 6.57 and d90 = 20.61), followed very closely by the NM2 sample (d10 = 2.09; d50 = 8.46 and d90 = 20.89) and, finally, the non-micronized sample (NM1) showed the largest particle size (d10 = 10.34; d50 = 33.85 and d90 = 76.52). Comparison of dispersibility indices indicate that NM3 sample has the greater nonuniformity of particle size distribution (DI = 2.94), followed by NM2 sample (DI = 2.22) and, finally, NM1 sample (DI = 1.96). The particle size distribution graphs are shown in Figure 3.

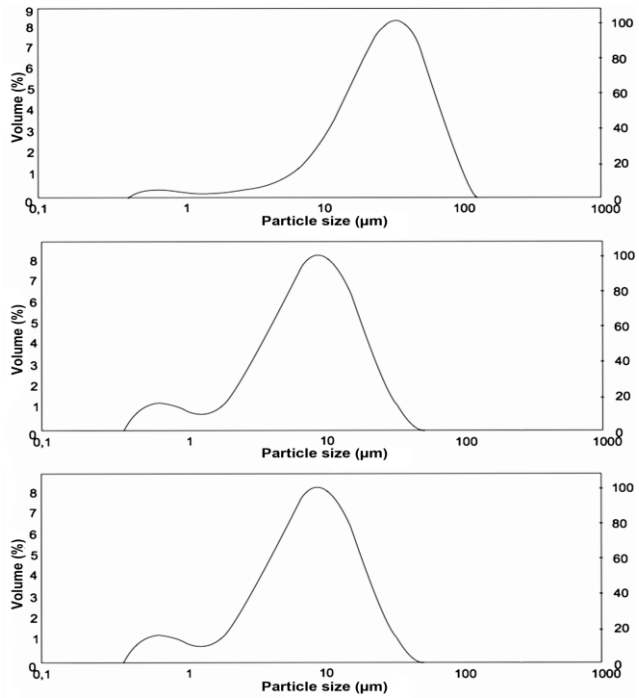

Figure 3. Particle size measurements obtained by LASER diffraction from bottom to top NM1, NM2 and NM3 samples.

3.6. Scanning electron microscopy (SEM)

The images of the samples under study, obtained by SEM at 500x magnification for NM1 and 16.000x for NM2 and NM3 samples, are shown in Figure 4. The NM1 sample presented the highest particle sizes between 25.2 and 103.5 µm, which was previously expected because is the IFA non-micronized, while the micronized NM2 and NM3 samples showed particles in the range of 364.8 nm to 3.5 µm (Figure 4 B, C). The micronization process led to the formation of aggregates.

3.7. Wettability

Table 1 presents the results for all samples, being observed that, using the method of the sessile drop and water as wetting agent, they were all near 80°.

3.8. Powder dissolution

Comparison of dissolution dispersion profiles of NM1, NM2 and NM3 samples is shown in Figure 5 and the values of F1, F2 and DE were established. The F1 and F2 values (15.26 and 46.23, respectively) confirm that the NM1 and NM3 samples showed the greatest differences between the profiles. The result of F1 for the micronized samples (NM2 and NM3) also showed a high value (12.36) and a considerably borderline result for the F2 parameter (50.55). Less expected, the F1 and F2 values that showed the greatest similarity was when the dissolution profiles of NM1 (non-micronized) and NM2 (micronized) were compared (3.33; 69.29). The DE values were statistically analyzed by ANOVA and significant differences were detected ($p < 0.05$). However, when using the Tukey test, it was found that there were no significant differences between the DE values of NM1 and NM2 profiles (DE = 71 ± 2 and 74 ± 5, respectively), while the significant differences were encountered between the profiles NM1 and NM3, NM2 and NM3 (DE = 83 ± 1).

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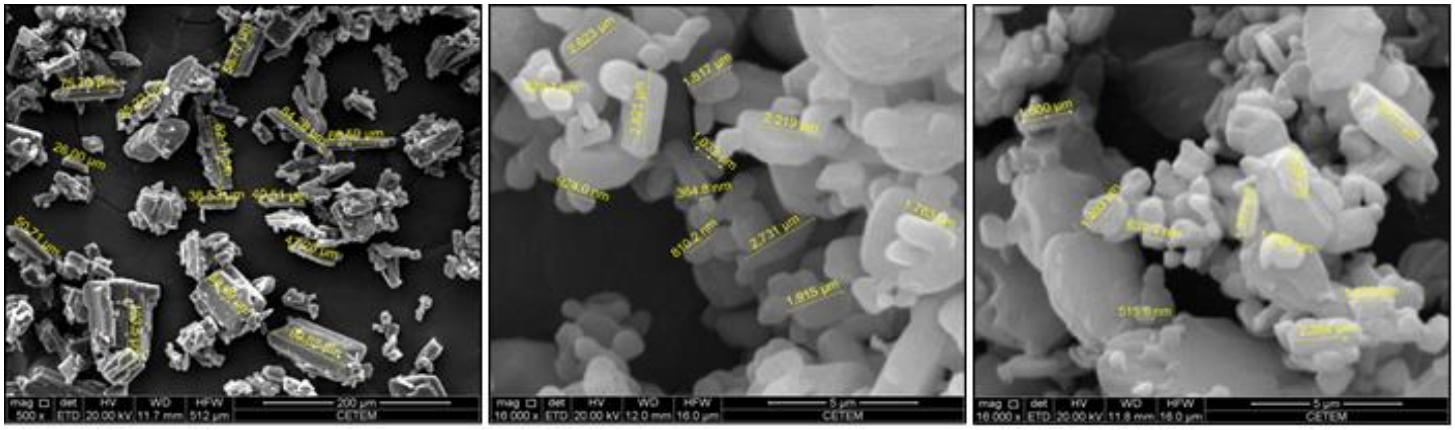

Figure 4. Scanning electron microscopy of the samples NM1, NM2 and NM3 from top to down, with measurements with increase of 500, 20Kv for NM1 and 16.000 X for NM2 and NM3.

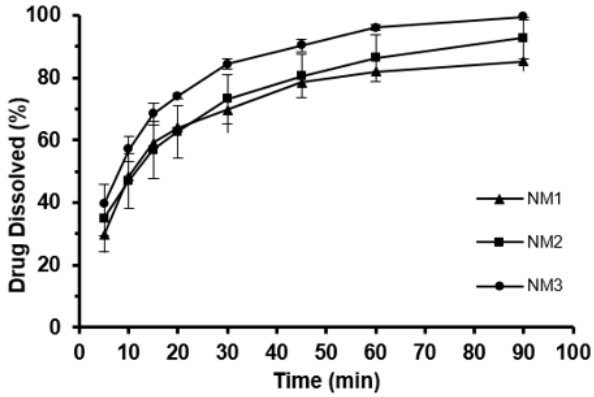

Figure 5. Powder dissolution profiles of NM1, NM2 and NM3 samples in 900 ml of potassium phosphate butter, pH 7.4, containing 2.0% polysorbate 80 (V/V), using paddle apparatus at 75 RPM.

3.9. Determination of flowability

3.9.1. Bulk and tapped density, compressibility index and Hausner ratio

The values obtained in bulk and tapped densities tests and the flow ratings of nimesulide samples found for the compressibility index and Hausner ratio were established according to the recommendations by USP[18] and are shown in Table 2. Densities obtained for the sample NM1, although slightly larger, still represent lower density values. The lower values for the densities of NM2 and NM3 samples are consistent with their smaller size particles.

Table 2. Data obtained from the DSC curves Tonset, Tpeak and enthalpy (ΔH) for the samples NM1, NM2 and NM3 in different heating rates.

Properties	**Sample**	**Heating rate (°C/min)**			
		5	10	20	40
T_{onset} ± SD (°C)	NM1	148.3 ± 0.3	148.5 ± 0.3	149.0 ± 0.6	150.8 ± 0.7
	NM2	147.9 ± 0.3	148.2 ± 0.4	148.8 ± 0.5	149.8 ± 0.4
	NM3	147.6 ± 0.2	147.8 ± 0.3	148.6 ± 0.4	149.8 ± 0.3
T_{peak} ± SD (°C)	NM1	149.8 ± 0.3	150.8 ± 0.3	152.5 ± 0.5	157.0 ± 0.6
	NM2	149.2 ± 0.3	150.1 ± 0.3	151.4 ± 0.5	153.5 ± 0.5
	NM3	149.1 ± 0.2	149.4 ± 0.3	151.2 ± 0.4	154.0 ± 0.3
ΔH ± SD (J/g)	NM1	121.6 ± 0.3	111.8 ± 0.4	112.2 ± 0.6	120.1 ± 0.7
	NM2	111.8 ± 0.4	110.7 ± 0.8	111.7 ± 0.5	116.7 ± 0.6
	NM3	109.7 ± 0.3	109.7 ± 0.4	107.6 ± 0.5	113.0 ± 0.4

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3.9.2. Determination of repose angle and flow through orifice

The repose angle could not be determined due to the poor flowability of the samples. The graphs obtained by the flow through orifice are shown in Figure 6 and the results are featured in Table 2.

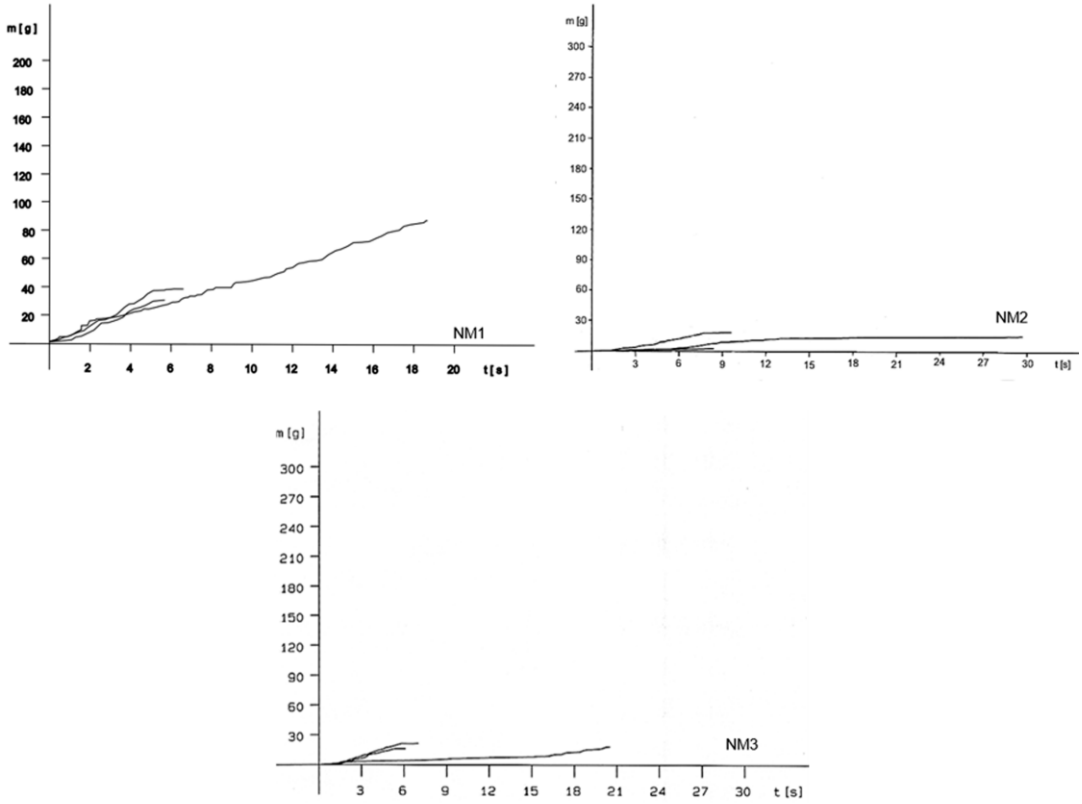

Figure 6. Graphs oof low through orifice of NM1, NM2 and NM3 samples.

3.10. Development and evaluation of nimesulide tablets obtained in galenic batches

The design of the galenic formulations batches was conducted with the excipients commonly used in the pharmaceutical industry, besides the excipients present in the reference product formulation. The excipients lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycollate, docusate sodium, hydrogenated vegetable oil and magnesium stearate are present in the formulation of Nisulid®. The galenic batches used the same excipients except by the hydrogenated vegetable oil and formulations with polyvinylpyrrolidone K-30 and pregelatinized starch as a binder in place of hydroxypropylcellulose, and sodium lauryl sulfate, as the surfactant, instead of sodium docusate were also tested. The galenic batches (Table 3) used only the micronized samples, NM2 and NM3, due to the better results in powder dissolution than the API non-micronized (Figure 5).

3.10.1. Physical parameters of the tablets and dosing

The results of weight, hardness, friability and dosing were all satisfactory. The disintegration test showed some unsatisfactory results, represented by L5 batch with a relatively high disintegration time (L5 = 9’ 30”), especially when compared to the reference product, (1’ 15”) besides L6 that was out of specification (L6 = greater than 30’). Therefore, it was decided not to perform the dissolution profiles of these batches.

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Table 3. Flowability measurements of NM1, NM2 and NM3 samples (n=3).

Properties	Sample		
	NM1	NM2	NM3
Bulk density ± SD (g/mL)	0.45 ± 0.01	0.20 ± 0.02	0.19 ± 0.02
Tapped density ± SD (g/mL)	0.69 ± 0.01	0.28 ± 0.02	0.26 ± 0.02
Compressibility index (rating)	34.78 (very poor)	26.53 (poor)	27.69 (poor)
Hausner ratio (rating)	1.53 (very poor)	1.36 (poor)	1.38 (poor)
Repose angle	ND	ND	ND
Flow through orifice (s/100 g* – RSD %)	18.8 (17.0-21.3) ± 11.78%	61.0 (32.7-112.0) ± 72.69%	189.6 (52.7-323.1) ± 71.34%

ND not determined

* The results expressed are the average obtained regarding the determination in triplicate samples. The values in brackets refer to the range found in the analysis, with minimum and maximum values.

3.10.2. Dissolution profile

3.10.2.1. Dissolution profiles conducted according to the criteria of the Brazilian Pharmacopoeia

Initially, the dissolution profiles were performed with the galenic batches L1, L2, L3, L4, L7 and the reference product using the conditions recommended by the Brazilian Pharmacopoeia[4] and are shown in Figure 7. In these tests, the reference product showed values greater than 85% of dissolution in 15 minutes, while only L2 and L3 batches showed a very fast dissolution profile, same behavior of the reference product. The statistical analysis has shown that DE values of L2 and L3 dissolution profiles (DE = 84.95 and 84.02, respectively) are not significantly different ($p > 0.05$). However, it was decided to select the L2 batch for the evaluation of the influence of the surfactant in the medium dissolution recommended by the Brazilian Pharmacopoeia (polysorbate 80 2.0%) in different concentrations.

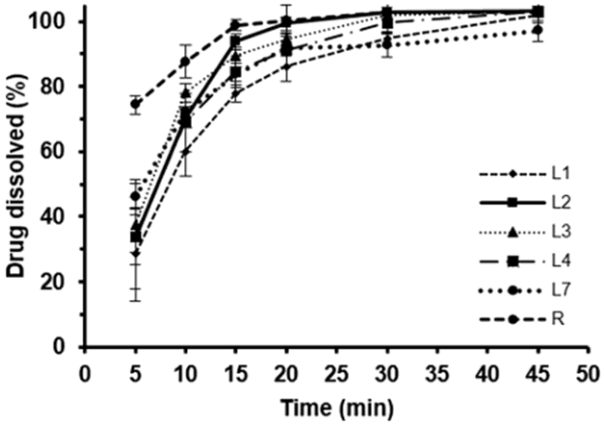

Figure 7. Overlap of L1, L2, L3, L4, L7 dissolution profiles and the reference product (R) using the pharmacopoeic parameters (BF 5, 2010).

3.10.2.2. Dissolution profile in potassium phosphate buffer, pH 7.4, containing different concentrations of polysorbate 80

The curves of dissolution profiles containing different concentrations of polysorbate 80 obtained with the tablets of L2 batch and Nisulid® is illustrated in Figure 8. The presented results show a reduction in drug release as the concentration of polysorbate 80 has been reduced. In all assessed surfactant concentrations, the test product and the reference product remained values above 85% over 15 minutes maintaining the very rapid dissolution classification and making it unnecessary the determination of F2. The dissolution efficiency was calculated to compare dissolution profiles. There was a reduction in DE when the concentration of the surfactant was gradually removed from the dissolution medium.

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This occurred for both the L2 batch (DE = 84.95; 82.21 and 80. 41, respectively with 2.0% polysorbate, 1.0% and 0.5%) as for the reference product (DE = 90. 83; 90. 53 and 87.05, in the same conditions). Statistical analysis by ANOVA revealed that the dissolution profiles are statistically different ($p < 0.05$) and the Tukey's test identified that in each condition evaluated (polysorbate 80 2.0%, 1.0% and 0.5%), the dissolution profile of L2 batch was statistically different from the reference product. The sodium lauryl sulfate present in the formulation would enhance the percentage of this surfactant in the dissolution medium at a maximum of 0,1%.

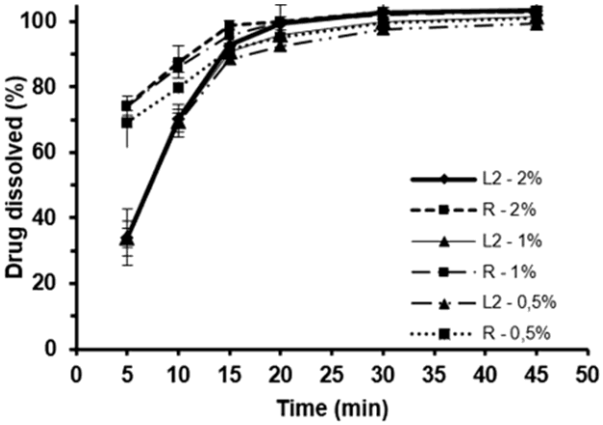

Figure 8. Overlap of dissolution profiles of L2 batch and the reference product (R) in potassium phosphate buffer, pH 7.4, containing different concetrations of poysorbate 80 (2.0%, 1.0% and 0.5%).

4. Discussion

The pharmacopoeia tests related to the heavy metals determination, loss on drying, sulfated ash and dosing, performed with NM1, NM2 and NM3 samples were approved by the specifications of the Brazilian Pharmacopoeia 2010 (Table 1). The differences between the dosing of galenic batches (approximately 95%) and the reference product (100.16%) are assigned to the manual transfers of high shear for oscillating granulator, and hence to the fluidized bed, procedures that, in industrial scale, occur in an automatic way.

The DSC curves of NM1, NM2 and NM3 showed a single endothermic event close to 149 °C (Figure 1). The evaluation of the T_{onset}, T_{peak} and ΔH values obtained in different heating rate showed slightly lower values to the micronized samples (NM2 and NM3, around 110-120 J/g). This phenomenon is widely described in the literature regarding DSC[21].

Previous studies reported the melting point of NM form I over the range of 148.9 to 151.0 °C and enthalpy (ΔH) of 102.97 J/g and 127.4 J g^{-1} [9,22,23]. These studies used different analysis conditions of each other and from this work, especially regarding the purge gas, heating rate and the types of crucible. Thus, although the results are very close to the literature data, such differences limit a more reliable correlation.

A study reported that NM form I is the most thermodynamically stable and has a transition temperature over the range of 144-147 °C (ΔH = 107.63 J/g)[7]. Otherwise, polymorph II has an endotermic event at 140 °C and suffers a transition to polymorph I (melting point at 144 °C and ΔH = 105.97 J/g)[6,7]. The DSC curves (Figure 1) of all NM samples showed similar thermal behavior to that of polymorph I.

There are not major differences between the FTIR spectra of NM1, NM2 and NM3 samples that could be used to distinguish among polymorph I and II. Only the characteristic bands of nimesulide were identified, so although this technique is often used to discriminate between polymorphs in this case it was inconclusive[7,10].

The X-ray powder diffraction is the standard method to distinguish between different polymorphs. In the case of nimesulide, there are noticeable differences in the peak position of form I (2θ = 17.15, 18.13, 19.34 and 21.66°) and form II (2θ = 18.91, 22.15 and 26.14°)[6]. In addition, diffraction patterns in the CSD revealed peaks at 2θ = 17.38, 18.38, 19.62 and 22.00° for form I and 2θ = 19.10, 22.44 and 25.84° for form II. The XRPD patterns of nimesulide samples analyzed correspond to the form I, although the NM1 (non-micronized sample) have shown differences in peak intensities (Figure 2). Besides, the literature mentions the occurrence of preferred orientation in X-ray diffraction of nimesulide samples, resulting in peaks of different intensities, but always in the same position, which characterizes the same crystalline arrangement.

A review of the particle size distribution graphs (Figure 3) allows to observe the presence of more than one population of particle sizes, primarily evidenced in micronized samples (NM2 and NM3) below 1 μM, which represents a bimodal distribution curve. Often, micronization causes difficulties in a good dispersion, assigned to cohesive interparticle properties and electrostatic forces provided by the particles that are subjected to this process. The sample NM1

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non-micronized has a particle size population below 5 µm, but less significant compared with the population of particle sizes below 1 µM detected in micronized samples.

During the development of a solid dosage formulation, the knowledge of the size and distribution of particle size can be used to guide the selection of a process by direct compression or wet granulation. The results obtained from laser diffraction were used together with the results of the flowability evaluation in order to complement the choice of manufacturing process of nimesulide tablets.

The data obtained by SEM confirmed the results of particle size distribution by laser diffraction, in which NM1 sample also showed much higher particle sizes compared to the NM2 and NM3 samples (Figure 4). Additionally, the presence of a population of particles with sizes close to 1 µM in NM2 and NM3 samples and 5 µm in NM1 sample, observed in the particle size distribution by laser diffraction, were also observed in the SEM. The image of NM1, although demonstrating a certain variability in their morphology, shows elongated particles. The images of NM2 and NM3 micronized samples showed greatest similarity regarding the particle sizes and can also be observed the formation of aggregates (Figure 4B and C).

The results of the wettability test were all close to 80° (Table 1) and, in accordance with literature, the values close to 90° predict a poor wettability[24]. Although the literature does not present studies applying wettability test with nimesulide, some works with other drugs were conducted, in which the results of the contact angles were correlated with water solubility[25,26,27].

When the aim is the development of a tablet formulation, the low solubility of the drug is an aspect that reflects negatively on its bioavailability. The powder dissolution tests served as an important tool to complement the biopharmaceutical evaluation of nimesulide samples. The literature revealed some studies using powder dissolution tests with nimesulide samples and the results have a certain proximity to that found in this study[22,28]. However, the studies referenced used different analytical conditions, especially with regard to the dissolution medium and the rotation apparatus, which compromise the correlation results.

Differently from the laser diffraction results, which showed a very small difference between NM2 and NM3, in the powder dissolution, these samples did not demonstrate similar behavior, which can be verified by NM3 superior performance relatively to NM2 (Figure 5). The non-micronized sample (NM1) presented larger particle sizes when compared to micronized samples and, however, in the powder dissolution, NM1 showed values near NM2. Thus, other factors that impact the powder dissolution results should be considered as the presence of electrostatic charge and the trend to agglomerate, which could undertake the performance of NM2 sample.

It was also not possible to establish a direct relationship of the results obtained in the wettability with the results of powder dissolution because, as mentioned above, the values of contact angles provided by the samples of nimesulide were very close (Table 1).

The evaluation of flowability brought together the results of different methods in order to make more complete the understanding of the flow properties of the samples under study. The densities obtained for the NM1 are low (Table 2), showed values slightly higher the other samples. The literature shows results of bulk and tapped density for nimesulide samples near to that of the non-micronized NM1. However, for the tapped density, the referenced study used a different method, making questionable the correlation to the results presented here[13]. The lower values for the densities of NM2 and NM3 can be explained by the effect of the micronization process, which results in powders having greater adhesion between the particles and therefore a greater tendency to agglomerate. The result is a poor flow material with low apparent density.

The determination of the compressibility index and Hausner ratio showed that all samples did not have good flow properties (Table 2). Considering that the higher values for compressibility index and Hausner ratio indicate stronger interparticle interactions and undesirable flow characteristics[29], it would be expected that micronized samples, NM2 and NM3, would demonstrate the worst results of flow. However, they presented better flowability rating than that exhibited by the sample NM1 (non-micronized).

One possible explanation for the discrepancies between the results found in the various flowability assessments lies in the qualitative scale of classification for flow properties adopted by official compendia, for example, the US

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Pharmacopeia. Thus, the CI and HR parameters have low discriminatory power, especially for the poor flow samples.

The repose angle and the flow through orifice tests were carried out in the same equipment. The tests with NM1, NM2 and NM3 samples were conducted using the following funnel openings 10, 15 and 25 mm. However, no flow was detectable. Then there was used the opening of 15 mm and tested four (4) speeds available on the machine (1, 2, 3 and 4). The NM1 sample showed flowability with speed 1 (one), but for the NM2 and NM3 samples, it was necessary to use the speed 4, maximum permitted by the equipment. The different experimental conditions undertake, somehow, the discussion of results. Still, it is possible establish some considerations concerning the flow properties of the samples under study.

The results confirmed the estimation of poor flow for this API, previously provided by other tests. Plus, it is also possible verify that no reproducibility was observed in the tests performed in triplicate. The NM1, non-micronized, revealed superior flow properties compared to the other samples. It is also possible assign a worse flow for NM3 sample, which also showed less uniform behavior (Figure 6).

In general, all samples showed erratic flow behavior, which indicates that an unstable formation and destruction process of the arc dominates the flow process. This process is also evidenced by the standard in “steps” where the powder flow rate accelerates periodically, probably due to the destruction of the formed ar.

It is known that the micronization process promotes a tendency to increased electrostatic charge. Thus, NM2 and NM3 samples have two important properties that contribute to a poor flow: low-density particles and, supposedly, high electrostatic charge. Unfortunately, for this work, it was not possible to assess electrostatic density.

The results obtained in flow assessment tests allow identify a discrepancy between the determinations of the CI and HR and flow through orifice. The flow through orifice provided more realistic results, demonstrating, numerically, the characteristic of poor flow for nimesulide. As mentioned above, HR and CI values may not be discriminatory and may cause unreal results flow to powders that are particularly characterized by poor flow. Furthermore, the samples NM1, NM2 and NM3 have particle sizes that are considered small (< 80 µM) besides low density values, which are factors related to the high cohesion of its particles. In this way, it is understandable that the flow evaluation methods may have discordant results.

Based on the results presented in flowability assessments, particle size distribution and SEM and considering the aim of the development of a solid dosage formulation, the direct compression process becomes less suitable than the wet granulation, due to the high possibility of problems related to the flow in the hopper and inadequate die filling that promotes, consequently, nonuniformity of mass and content.

The average weight values found for galenic batches are close to the average weight displayed for the reference product (about 400 mg) and the results were all satisfactory. The tablet hardness results obtained with the galenic batches showed correlation with those of friability, in which the L2, L3, L5, L6 and L7 batches showed the lowest hardness values (close to 5.0 kgf) and the higher friability values (near 0.42%) and the tablets obtained with the L1 and L4 galenic batches demonstrated higher strength, both to rupture (hardness assay about 7.0 kgf) and abrasion (friability percentage about 0.35%).

L2 and L3 batches have the same formulation and the same process by only changing the manufacturer of API (Table 3). The differences in results of particle size and hardness were not significant, preventing a direct correlation between these tests.

The L4 batch has the same qualitative and quantitative excipients that can influence the compressibility from the L2 and L3 batches but showed higher hardness (mean = 7.1 kgf). The difference was in the granulation process (Table 3) including a higher time to addition the granulating solution and a longer mixture for the L4 batch. Possibly, these process variations allow adequate wetting of the powders, resulting in stronger granules and, consequently, in longer disintegration time and slower dissolution compared to the values shown by L2 and L3 batches.

Regarding disintegration test, L1 batch has the same qualitative composition of L2 and L3, but the surfactant (sodium lauryl sulfate) was used in different ways. L1 showed the highest values in hardness assay (7.5 kgf). These differences had a negative impact on the disintegration of the tablets obtained with this batch (L1 = 6’ 40”), which had twice the disintegration time of L2 and L3 batches

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(L2 = 3’ 18” and L3 = 3’ 10”). The L4 batch used another surfactant (sodium docusate) and its disintegration time (4’ 10”) was higher than the L2 and L3 batches. L5 and L6 formulations are closest qualitatively of the reference product, but showed more extensive disintegration times and L6, in this assay, was disapproved (L5 = 9’ 30” and L6 = greater than 30’). Obviously, this cannot attribute similarity or difference by not being aware of the percentages of each agent in the reference product formulation. The L7 galenic batch used different binder and surfactant and had the shortest disintegration time (1’ 23”). Regarding Nisulid®, the tablet format is convex which facilitates the maintenance of abrasion resistance, observed by the low value friability (0.27%), although its hardness is lower (4.9 kgf) as compared to galenic batch. The disintegration time of the reference product was 1’ 15”.

Accordingly, it can be concluded that the step in which the surfactant is added to the formulation, as well as tablet hardness, directly alter the disintegration time and, therefore, can be used as auxiliary tools to discriminate between nimesulide formulations.

In the dosing assay, all galenic batches showed results close to 95% of the labeled value, and for Nisulid® tablets there was obtained 100.2%. All results meet the specification preconized in the Brazilian Pharmacopoeia.

The dissolution profiles achieved in pharmacopoeia conditions demonstrated that the formulations of the L2 and L3 batches and the reference product exhibited very rapid dissolution with results of the amount of dissolved drug above 85% in 15 minutes and thus the value of F2 loses its discriminative relevance.

Whereas L2 and L3 batches are formulations that differ only in the API manufacturer, it is interesting correlate the results obtained in the dissolution profile and the data obtained in API characterization, particularly in particle size, wettability and powder dissolution assessments. The results of particle size analysis by laser diffraction and wettability were quite close. However, in the powder dissolution, NM3 showed dissolution of approximately 10% higher than NM2 and further such profiles showed statistically significant differences ($p < 0.05$). Although NM3 biopharmaceutical properties were higher than observed with NM2, the L2 and L3 formulated product showed near dissolution results and statistical analysis of ED values showed similarity between these profiles ($p > 0.05$).

The dissolution efficiency values were calculated and L2 batch had the highest result (DE = 84.95), although quite near the value presented by L3 (DE = 84.02). L4 and L7 shown next values (L4 = 80.92 and L7 = 79.67) and the L1 batch showed the lowest DE value (76.61). The DE values were subjected to statistical analysis by ANOVA and Tukey test, and it was found that all galenic batches formulations and Nisulid® differ significantly ($p < 0.05$) and the L2 and L3 batches do not present significant differences between the DE values ($p > 0.05$). The L4 batch showed a dissolution profile similar to those of L2 and L3, but with lower dissolution mean values and, particularly at 15 minutes, there was not reached 85% (although it was close), which results in the classification as a rapid dissolving formulation, distinct from that presented by Nisulid® and by the L2 and L3 batches. As occurred with L4, L7 not reached 85% drug release within 15 minutes, despite having very close behavior (Figure 7) and it is also classified as a rapid dissolving formulation.

An interesting feature of the L7 dissolution profile lies in the result obtained in the first sampling time, which was superior in almost 10% when compared with the result obtained with L3. One possible explanation is the dual nature of the pregelatinized starch, that acts not only as a binder but also as a disintegrate, which may be maximizing the release of the API in this initial time. The result of the disintegration assay (83 s) confirms this hypothesis, considering the smallest time shown.

Although the statistical analysis has shown that DE values of L2, L3 and L4 batches are not significantly different ($p > 0.05$), it was decided to select the L2 batch for complementary tests. Even if the L2 has showed the greatest dissolution of values, there is a considerable difference between L2 and the reference product in the first sampling times ($t = 5$ min and $t = 10$ min).

In terms of bioequivalence, the literature reports that nimesulide has rapid oral absorption[2]. A Brazilian study evaluated the bioequivalence of nimesulide tablets and Nisulid® and there were found for C_{max} values equivalent to 5.30 and 4.52 ng mL^{-1} and T_{max} of 2.23 and 3.32 h, respectively, for the reference and test products[30].

Analyzing such data from the literature and based on the dissolution assessments designed to

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simulate physiological conditions and provided tools for the *in vitro* evaluation of bioavailability, the evaluation of C_{max} and T_{max} would not represent bioequivalence problems. This is because, after 45 min (lower time to reach C_{max} than those presented by the literature) L2 batch and the reference product already reach the same percentage of dissolution; so, it is expected the same release between the drug (test and reference) *in vivo* assays.

The AUC parameter requires a more careful analysis. Another study, mentioned a nimesulide bioequivalence study that showed disapproved results, having been previously approved in the pharmaceutical equivalence, which reinforces the alert for the interpretation of the results of this drug dissolution profiles[31]. Whereas nimesulide is a class II drug in the BCS, which the dissolution is the limiting step for the absorption, it becomes mandatory a careful design of the dissolution test.

Thus, even if the medium is preconized by the Brazilian Pharmacopoeia containing 2.0% polysorbate 80[4], it was considered important evaluate the behavior of the L2 batch using the same potassium phosphate buffer established for Brazilian Pharmacopoeia but containing different concentrations of surfactant.

The presented results show a reduction in drug release amounts as the concentration of polysorbate 80 has been reduced. Still, in all assessed surfactant concentrations, the test and the reference product values remained above 85% over 15 minutes, maintaining the very rapid dissolution classification and making it unnecessary the F2 calculation. However, the dissolution efficiency was calculated as a tool to compare dissolution profiles. Again, there was observed a reduction of the obtained values of DE as the concentration of the surfactant was gradually reduced in the dissolution medium. This occurred for both the L2 batch as for the reference product. Statistical analysis by ANOVA revealed that the dissolution profiles are statistically different ($p < 0.05$) and Tukey's test identified that in each condition evaluated (2.0%, 1.0% and 0.5% polysorbate 80), the dissolution profile of L2 batch is statistically different from the reference product.

The literature reports a study evaluating the dissolution profile of nimesulide tablets in a medium of phosphate buffer pH 7.4 containing different concentrations of polysorbate 80. The highest release value was in the presence of 2.5% surfactant, obtaining around 90% of dissolution in 60 min[21]. Another study evaluating the dissolution of commercial nimesulide tablets in sodium phosphate buffer pH 7.4 supplemented with 1.0% polysorbate 80 did not obtain values above 90% in 60 min[15].

Since both studies do not provide information about the composition of the test product, outcome differences found comparing with those showed here can be attributed to probable differences in formulations, given that the excipients can act in direct mode in the dissolution process. In addition to the important contribution of excipients in the rate and extent of dissolution, aspects such as, for example, the API particle size are striking features in the dissolution of solid dosage forms. These physicochemical properties were not available in the referenced work, limiting further discussion.

The *in vitro* dissolution tests are used in quality control of medicines and the development of new formulations. Depending on the drug class, such as nimesulide (Class II in the BCS), the results of a dissolution study can be closely related with in vivo performance. For these drugs, difficulties in selecting the dissolution medium are constantly found, which must reproduce the physiological conditions to ensure an *in vitro-in vivo* correlation and to discriminate different formulations[28].

5. Conclusions

Differential scanning calorimetry and X-ray diffraction showed that all samples tested (NM1, NM2 and NM3) presented polymorph I. The characterization of particle size showed good correlation with the density results and flow through orifice in which the micronized samples showed worse flow behavior when compared with the non-micronized sample. The scanning electron microscopy confirmed the results of size and particle size distribution carried out by laser diffraction.

Although the wettability results were very close, the powder dissolution identified small differences between the samples, demonstrating that the dissolution of the NM3 sample (micronized) was superior to the others. The micronized samples exhibited higher IDR than the non-micronized one (NM1) and, in this case, surface properties such as roughness and microstructural factors may be involved.

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Although the results have shown a reduction in drug release as the surfactant concentration has been reduced in the dissolution medium of both products (test and reference), the classification as a very rapid dissolution formulation was maintained. Batch L2 was selected for further work toward product registration.

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