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Solid state evaluation of some thalidomide raw materials

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ABSTRACT

Thalidomide presents polymorphism and is a problematic drug due to its poor solubility and difficult tablet processability, which is the dosage form available in Brazil. In most cases, the pharmacopoeias specify do not address solid state characterization of drugs precisely. In this work, different thalidomide commercial samples were characterized by infrared spectroscopy, particle size analysis, scanning electron microscopy, and X-ray diffraction. In addition, the polymorphic forms were quantified for Rietveld analysis and their intrinsic dissolution rates were evaluated. The results demonstrated the market availability of different raw materials which lack of homogeneity due to differences related to crystalline constitution, crystal habit and intrinsic dissolution rate.

1. Introduction

Recently, the thalidomide clinical interest was renewed due to its promising activities as anti-inflammatory, immunomodulatory and antineoplasic agent (Cox et al., 2006; Melchert and List, 2007; Paghdal and Schwartz, 2007). In Brazil, the drug presents restrict distribution within governmental programs and is indicated for the treatment of erythema nodosum leprosum, aphthous ulcerations in patients with human immunodeficiency virus (HIV) infection, chronic-degenerative diseases and multiple myeloma (Brasil, 1997, 2002). In this country, the medicine is produced only as tablets of 100 mg of thalidomide by the State Laboratory Fundação Ezequiel Dias (FUNED). Industrial problems were verified in this laboratory concerning the drug processability as well as its reduced dissolution rate from the tablet formulation.

Racemic thalidomide is a poorly soluble drug in aqueous media (approximately 50 $\mu g\,mL^{-1}$) (Shealy et al., 1968; Hague and Smith, 1988) possibly due to its high crystallinity level (Goosen et al., 2002). Some works reported the existence of two polymorphic forms to thalidomide, named α and β or III and I, respectively (Allen and Trotter, 1971; Caira et al., 1994; Reepmeyer et al., 1994). Reflecting the renewed interest to this issue, Lara-Ochoa et al. (2007) recently evaluated the thermodynamic behavior of each polymorphic form and suggested the formation of the new polymorph (named by the authors of β^*) in particular conditions of heating. However, important information about physicochemical properties attributed to each polymorph, such as dissolution rate, was not found.

The low solubility of thalidomide associated to the existence of polymorphism suggests an evaluation of the relationship between its different physical forms and dissolution behavior.

Solid phase of drugs influences the quality and performance of a solid dosage form, even though the pharmacopeial monographs present few tests to distinguish and characterizes polymorphic phases. Indications of the preferred polymorphic forms are not described and are not encountered indications of the ideal polymorphic form to the effective pharmaceutical dosage form development. In this context, the objective of this work was to characterize and to compare samples of thalidomide raw materials purchased from Brazilian suppliers, evaluating their quality by means of solid state characteristics, employing Fourier transformed infrared spectroscopy (FTIR), X-ray diffraction (XRD), particle size analysis, scanning electron microscopy (SEM) and disk intrinsic dis-

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solution rate (IDR). The crystalline phases were quantified by X-ray diffraction using Rietveld analysis.

2. Materials and methods

2.1. Materials

Seven thalidomide raw materials were purchased from different Brazilian suppliers and were identified as samples T1–T7. Thalidomide reference standards named TR was evaluated in some experiments (United States Pharmacopoeia Convention Center, Batch: F0C107, Rockville, USA).

2.2. Fourier transformed infrared spectroscopy

The infrared spectra were recorded in a FTIR spectrophotometer Shimadzu DR-8001 (Tokyo, Japan) over a range of 3800–500 cm^{-1}. Samples weighing approximately 1.5 mg were mixed with 150 mg of KBr (Vetec, Rio de Janeiro, Brazil) in agate mortar. The mixture was compacted in hydraulic press (PerkinElmer, Waltham, USA) to obtain the KBr disks.

2.3. X-ray diffraction

The phase structures of thalidomide polymorphs were characterized by XRD. For the XRD analysis, the thalidomide raw materials were isolated as a fine powder and placed in the sample holder. The XRD experiments were carried out on a Siemens D5000 diffractometer (Siemens, Berlin, Germany) equipped with a curved graphite crystal using Cu Kα radiation (λ = 1.5406 Å). The diffraction data were collected at room temperature in a Bragg–Brentano $\theta - 2\theta$ geometry. The equipment was operated at 40 kV and 20 mA with a scan range between 8° and 40°. The diffractograms were obtained with a constant step, step size/time de 0.02°2θ/s. The indexation of Bragg reflections was obtained by a pseudo-Voigt profile fitting using the FULLPROF code (Carbajal, 2005).

The α and β thalidomide polymorphism was investigated using X-ray diffraction. The apparent crystallinity was evaluated by means of X-ray diffraction with a profile matching using a full code.

2.3.1. Wide angle X-ray diffraction (WAXD)

The most representative reflections of thalidomide were indexed as monoclinic with space group $P2_1/n$ for α phase and with unit cell parameter a = 8.25 Å, b = 10.06 Å, c = 14.91 Å and β angle = 102.56°. On the other hand, the β phase was indexed as monoclinic with space group $C2/c$ with unit cell parameter a = 20.78 Å, b = 8.06 Å, c = 14.30 Å and β angle = 102.068°. The Bragg reflections at 11.33°, 14.10°, 19.17°, 22.77°, 25.81° and 11.89°, 13.00°, 13.80°, 17.46°, 19.21°, 22.01°, 26.11° correspond to the indexed planes of the monoclinic crystals of α and β thalidomide, respectively.

According to Hermans and Weidingeer (1961), the relative crystallinity is related with the area values by Eq. (1):

$$X_c = \frac{A_c}{A_c + A_a} \quad (1)$$

and the relative apparent crystallinity for α and β phase was obtained by Eqs. (2a) and (2b):

$$X_c^{\alpha} = \frac{A_c^{\alpha}}{A_c^{\alpha} + A_c^{\beta} + A_a} \quad (2a)$$

and

$$X_c^{\beta} = \frac{A_c^{\beta}}{A_c^{\alpha} + A_c^{\beta} + A_a} \quad (2b)$$

where A_c and A_a are the total crystalline and amorphous areas of the diffractogram, respectively and A_c^{α} and A_c^{β} are the areas of α and β phases. The amorphous phase corresponds to a very broad peak with a very large full width of half maximum. Therefore, in order to apply Eq. (1) it is necessary to separate the amorphous and crystalline contributions. In Eqs. (2a) and (2b) the total area of α and β crystalline reflections are used. To calculate the relative crystallinity of the samples, the corresponding crystalline and amorphous areas, A_c and A_a, must be determined. However, there is no well-defined division between the crystalline and amorphous contributions but it is possible to obtain the amorphous peak by interpolating a line between a number of selected points. In addition to the background, a straight line joining the extremities of the diffractogram was assumed. The amorphous halo is subtracted from the original diffractogram and crystalline reflection lines were treated. The areas of these peaks were obtained by a pseudo-Voigt profile fitting using the FULLPROF code. After that, the two contributions were summed and compared with the original diffractogram until a minimal difference was obtained.

The profile agreement factor, R_p, was used to evaluate the quality of the fittings. Bragg's agreement factors, R_b, for each phase were estimated according to Rietveld (1969). The typical errors are about 5% on area determinations and 8% in crystallinity calculations.

2.4. Particle size analysis

The particle size analysis was determined using a laser diffractometer CILAS 1180 (Madison, USA). Approximately 200 mg of samples were dispersed in water and suspended with an ultrasonic system to prevent sedimentation of the particles. The information acquired was analyzed by a computational program and values of mean diameters were obtained.

2.5. Scanning electron microscopy

The crystal habit of the samples was examined by SEM using Jeol 5800 microscope (Tokyo, Japan). The samples were fixed on aluminium stubs using double sided adhesive tape and coated with a thin layer of gold by using a Shimadzu IC-50 sputter coater (Tokyo, Japan) in vacuous before examination.

2.6. Intrinsic dissolution rate

The IDR of the samples was measured with a rotating disk apparatus Flowscience (Cotia, Brazil) in a die of 8 mm diameter (surface area 0.5 cm^2) (USP 31, 2008). 100 mg of samples accurately weighed were compacted in universal testing machine ATS 1105 (Butler, USA) using compaction pressure of 140 MPa in order to form a non-disintegrating compact pellet. Compacted samples had no polymorphic interconversion noted by FTIR. Intrinsic dissolution studies were performed with 1000 mL of dissolution media (HCl 0.225 M and SLS 1%) at 37 ± 0.5 °C and 100 rpm. The sink conditions where maintained in this dissolution method (Pavei et al., submitted for publication). About 5 mL of the test medium was periodically sampled with medium dissolution reposition, and the thalidomide concentration of the aliquot was determined by high-performance liquid chromatography (HPLC) in a Perkin-Elmer Series 200 (Waltham, USA), equipped with a RP-18 Gemini-Phenomenex column (150 mm × 4.6 mm i.d., particle size of 5 μm; 110 Å, Torrance, USA). The mobile phase consisted of 30% (v/v) acetonitrile and 70% (v/v) *orto*-phosphoric acid at 0.1%. Flow rate was 1.5 mL min^{-1}, and the detection wavelength was 237 nm (Pavei et al., submitted for publication). Dissolution assay was evaluated in triplicate.

3. Results and discussion

Thalidomide commercial samples were studied by FTIR, XRD, Rietveld analysis, particle size analysis, SEM and IDR.

3.1. Fourier transformed infrared spectroscopy

The FTIR absorption spectra of the various thalidomide samples are presented in Fig. 1. α and β polymorphic forms of thalidomide show characteristic differences in the detailed shape and intensities related with —NH stretching frequency (above 3000 cm^{-1}) of amide group and —CH stretching frequency (900–690 cm^{-1}) of aromatic ring (Table 1). Reepmeyer et al. (1994) reported characteristic absorption bands in 3196, 3098 and 859 cm^{-1} to the α polymorph and 3277 and 755 cm^{-1} to the β polymorph. According to the results listed in Table 1, the T4 sample presented absorption bands characteristic of the β form and all the other samples were identified as the α form.

3.2. X-ray diffraction

The XRD analysis of thalidomide raw materials (Fig. 2) also indicated differences among to some samples.

The presence of characteristic peaks related to the α or β polymorphic forms was useful to identify of the crystalline phases of the samples. The XRD pattern of samples T1, T2, T3, T6, T7, and TR corresponds to that of α polymorph (Caira et al., 1994; Reepmeyer et al., 1994), with major intensities near 11.33 (7.80), 14.10 (6.27), 19.17 (4.63), 22.77 (3.90), and 25.81 (3.44), representing angle 2θ and interplane distance (d), in parenthesis, respectively. The pattern of sample T4 fits the published data (Caira et al., 1994; Reepmeyer et al., 1994) for polymorph β with d values and 2θ angle near 11.89 (7.44), 13.00 (6.80), 13.80 (6.41), 17.46 (5.07), 19.21 (4.62), 22.01 (4.03), and 26.11 (3.41). The sample T5 exhibited main characteristic peaks associated to the α form, but additional peaks with lower intensities related to the β form are also observed, suggesting some contamination with this polymorph.

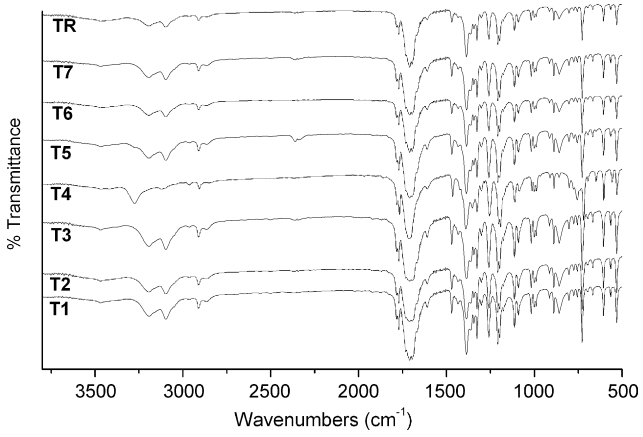

Fig. 1. FTIR spectra of thalidomide raw materials.

Table 1
Main absorbances in the FTIR spectra of thalidomide raw materials.

Sample	Spectral analysis (KBr cm^{-1})	
	νN—H	δC—H
T1	3191; 3091	856
T2	3196; 3096	852
T3	3195; 3091	852
T4	3278	759
T5	3195; 3091	852
T6	3195; 3099	853
T7	3195; 3098	853
TR	3197; 3098	855

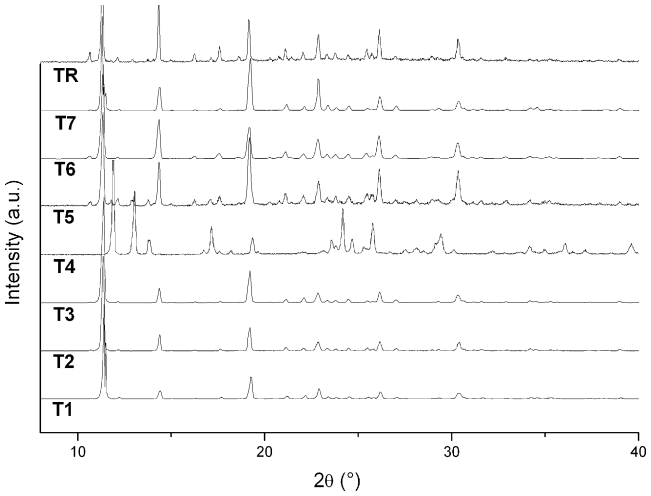

Fig. 2. XRD patterns of thalidomide raw materials.

XRD analysis is not indicated in the thalidomide monograph cited by USP (USP 31, 2008) but it is the best and the most accurate technique for the crystalline structure determination. The XRD pattern of TR sample indicated that it is constituted by α phase, however, reasons for this polymorphic preference concerning the USP thalidomide reference are not disclosed.

3.3. Quantitative analysis of XRD patterns by the Rietveld method

Quantitative analysis of polymorphic composition in a solid state drug is used to guarantee security and efficacy of this compound or to establish and validate process control in pharmaceutics production, where differences between physical properties of polymorphs reflect in pharmaceutical dosage form performance (biodisponibility, stability, etc.) or affect the reproducibility of productive process (Stephenson et al., 2001).

XRD is a precise and currently employed technique to perform quantitative analysis of crystalline solid mixtures. This technique needs diffractograms with diffraction peaks presenting high intensities and resolution. The intensity of a characteristic diffraction peak of a phase is proportional to its weight fraction in a multicomponent mixture. Modern computational techniques applied to the diffractograms allow quantitative analysis of polymorphic forms mixture by comparison between experimental and calculated diffractograms, using data of spatial groups and lattice parameters which correspond to each phase (Vippagunta et al., 2001). A lot of computational methods employed to perform a structural refinement of a compound make use of the Rietveld method (Datta and Grant, 2004).

XRD patterns of thalidomide samples were refined and quantified by Rietveld method using structural parameters to the calculation (Fig. 3). The goodness of fit was evaluated by visual examination of a plot containing the observed and calculated patterns presented in a graphic production obtained at the end of the Rietveld refinements and by analysis of the calculated statistical parameters. The cross-signal indicates an observed XRD pattern and traced lines indicates the calculated pattern. A good match between the two profiles is shown in solid lines and the vertical lines represent the peak position of α or β polymorph.

The Rietveld refinement was efficient to perform the quantification of crystalline phases of thalidomide samples. A lack of fit between the observed and calculated patterns at the maximum

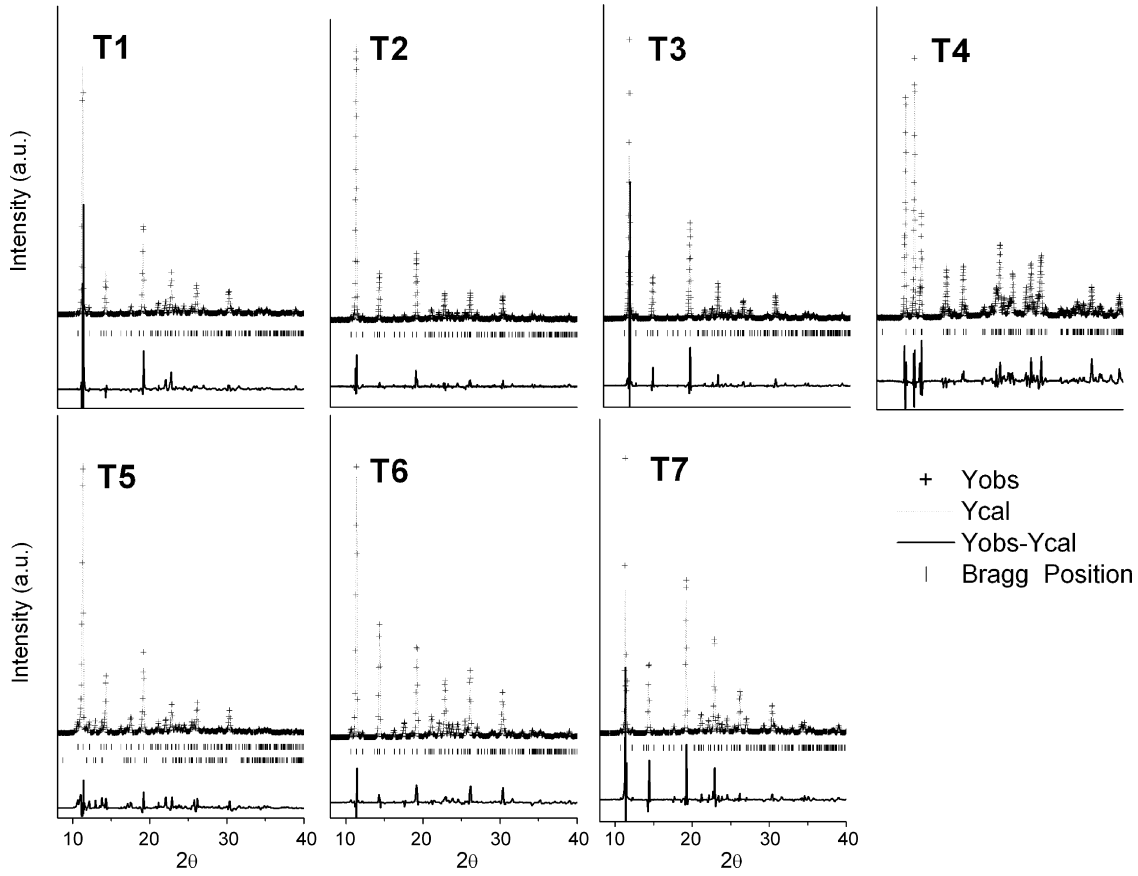

Fig. 3. X-ray patterns and Rietveld refinement to the thalidomide raw materials.

peak intensity to thalidomide refinement resulted in a small contribution to the overall error in the analysis.

The results obtained by Rietveld analysis showed in Table 2 confirmed the α polymorph predominance among the thalidomide samples analyzed. The α phase is encountered in six samples and the β phase only in two samples, mixed to the other phases. The refinement also identified semicrystalline materials in three samples.

The results obtained suggest a lack of periodicity in thalidomide synthetic process forming products with different molecular organization while reflects in distinct physical forms to the same drug. The occurrence of different polymorphic forms as well as the existence of crystalline and amorphous phases impair the reproducibility of the pharmaceutical process and may adversely affect the biopharmaceutical properties of the drug.

According to FDA specification (FDA, 2007), once the crystal state interfere in the physicochemical properties of the drug, the proportion between polymorphic phases must be controlled and the specification observed during the product shelf life (Vippagunta et al., 2001). The polymorphic purity is required to some drugs. As an example, for carbamazepine only the presence of β phase anhydrous is admitted in the drug formulations, being the α anhydrous phase and dihydrate an interference in a final product (Iyengar et al., 2001). In these cases, it is necessary to develop methods of drug synthesis which allows the formation of only a crystalline stable form (Vippagunta et al., 2001). For drugs such as paracetamol, the polymorphic control is necessary to assure the better compressional behavior during the tablet production (Thompson et al., 2004).

Table 2
Polymorphic composition of thalidomide raw materials obtained by Rietveld analysis.

Sample[a]	Composition (%, w/w)		
	α	*β*	Amorphous
T1	100	–	–
T2	100	–	–
T3	100	–	–
T4	–	80	20
T5	96.24	3.76	–
T6	84	–	16
T7	80	–	20

[a] TR: insufficient amount of sample to execute the analysis.

3.4. Scanning electron microscopy and particle size analysis

The particle size analysis demonstrated a similar mean diameter for T1 (52.53 μm), T2 (50.61 μm), T3 (50.44 μm), and T7 (60.29 μm) thalidomide samples. Lower mean particle size was verified in T5 (19.49 μm) and T6 (15.60 μm), while T4 (77.00 μm) exhibited the highest mean diameter.

SEM analysis in Fig. 4 revealed some thalidomide samples with particles presenting distinct crystalline habits. T1, T2, T3, and T7 samples that are composed totally or partially from α form exhibited tabular prismatic habit with a well-defined surface. Apparently, TR sample also has the same crystal habit cited previously, but with a more irregular surface. The β form revealed in the sample T4 presents crystals with characteristic format of big pointed plates. The T5 and T6 samples that present α form as main crystalline fraction exhibited a crystal habit different from those demonstrated to this thalidomide polymorph. Acicular habit with fissures and irregular surface was verified to T5 sample, while it created powder particle adherence. Similar characteristics were encountered at the

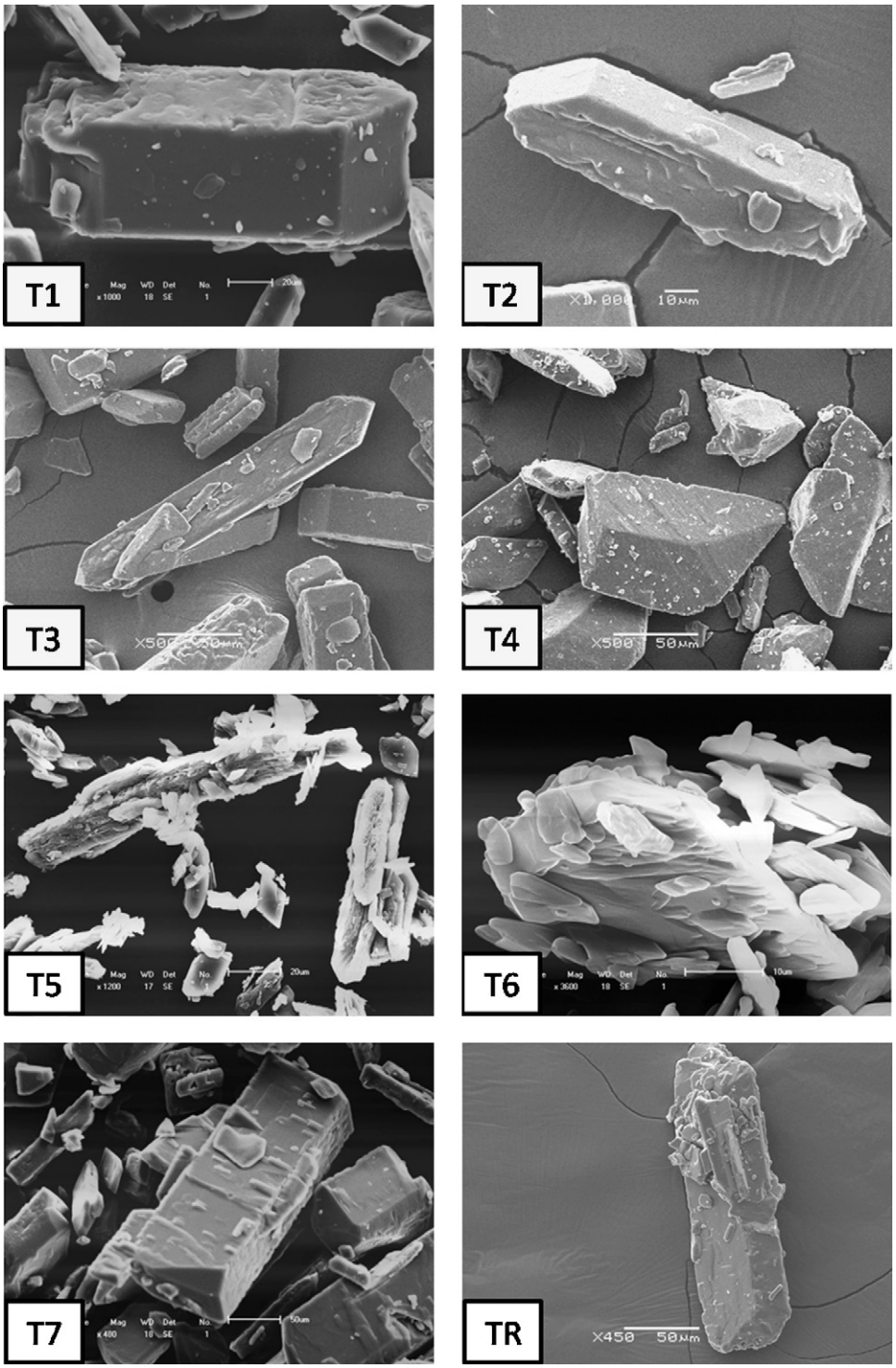

Fig. 4. Scanning electron microscopic photographs of thalidomide raw materials.

T6 sample that is constituted by little agglomerated crystals with plate-shaped habit.

During crystallization process of a substance, external factors can conduct the formation of a special crystalline habit regardless that a compound presents the same internal structure or not. The factors involved are rate of cooling and speed of solution agitation, degree of supersaturation, nature of crystallizing solvent and presence of impurities (Haleblian, 1975; Berkovitch-Yellin, 1985; Shekunov and York, 2000; Tiwary, 2001). These variables can affect crystal growth and consequently crystalline habit, influencing in crystal properties such as particle size, form, purity, imperfections in the structure, and consequently, thermodynamical and mechanical properties of the crystal can be modified (Haleblian, 1975; Shekunov and York, 2000). Hence, in order to obtain a unique crystal form, the standardization of the crystallization conditions is required (Haleblian, 1975).

The commercial thalidomide samples have shown different behavior concerning morphology, crystal habit and particle size. Some samples presented no homogeneity concerning these aspects. One out of four crystal habits was attributed to the β form

Table 3
Comparison between mean values of intrinsic dissolution rate (IDR) presented to the T1, T4, T5 and T6 samples.

Sample	IDR (mg/(min cm^2)) mean[a] ± S.D. (R.S.D.%)
T1	0.0098 ± 0.0006 (6.56)
T4	0.0127 ± 0.0007 (6.18)
T5	0.0103 ± 0.00001 (0.64)
T6	0.0113 ± 0.0003 (3.20)

[a] Statistically significant difference ($n = 3$; ANOVA one-way, $\alpha = 0.05$; $p < 0.05$).

while three were reported to the α form. In this work, bulks with crystal diversification attributed to isomorphic and polymorphic crystals as well. In addition, crystal habit can influence particle orientation, thus modifying the flowing, packing, compaction, compressibility, solubility, and dissolution (Tiwary, 2001; Manish et al., 2005).

Thalidomide samples purchased from different suppliers were approved in conventional pharmacopeial tests (USP 31, 2008), but presented problems relating to industrial production of thalidomide tablets. These problems may be possibly linked to the polymorphism and crystal habit of the samples. However, complementary tests can be carried out to affirm this condition.

3.5. Intrinsic dissolution rate

T1, T4, T5, and T6 samples were selected to disk IDR assay because they are materials with different crystalline or semicrystalline constitution. For T4 sample, the compaction of the powder before the test had demonstrated some difficulty. A tendency of compact lamination and superficial fissures was observed when T4 was compacted to high pressures.

The results obtained by IDR analysis are shown in Table 3 and Fig. 5. The experiments exhibit reproducibility with standard deviation lower then 7% and the dissolution curves were linear according to the coefficients of correlation near 0.99. The linearity of the intrinsic dissolution curves confirms sink conditions (Chan and Grant, 1989).

According to these results, IDR of thalidomide samples presented decreasing classification with respect to the dissolution rate: T4 > T6 > T5 > T1. These values were statistically different when compared with each other (ANOVA). It is possible to observe a higher dissolution rate to the semicrystalline samples when compared to those with crystalline purity.

The presence of disorganized fractions in a solid-element, as amorphous regions, produce zones with higher energetic state than crystalline regions. These imperfections in crystalline lattice lead to the increase in the entropy of system and to the appearance of regions with unbalanced intermolecular forces. These events increasing internal energy and enthalpy of the crystals, which improve some pharmaceutical properties, such as higher dissolution rate. On the other hand, undesirable properties such as increased chemical instability and solid–solid transition can also occur, affecting the quality of the final product (Chow et al., 1984; Saleki-Gerhardt et al., 1994; Agrawal et al., 2004).

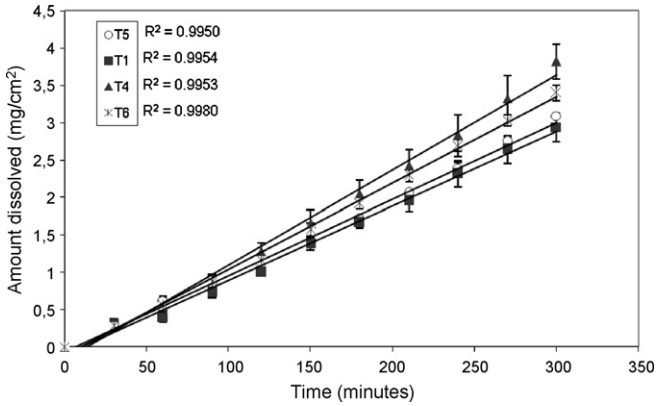

Fig. 5. Intrinsic dissolution curves of T1, T4, T5, and T6. The graphic presents lines obtained by linear regression of the points that express cumulative mean quantities dissolved.

Yu et al. (2004) demonstrated that there is a good correlation between the solubility classification and IDR values of some studied drugs. The authors suggest the existence of a limit value (0.1 mg/(min cm^2)) for classifying high or low IDR relating these results to a solubility classification of drugs.

Based on this criterion, all samples presented a reduced IDR (<0.1 mg/(min cm^2)). In fact, T4 presented a higher solubility, even though it presented a higher particle size, which seems to attribute to the β polymorph higher dissolution. The ID method provides a continuous surface for drug dissolution which eliminates the influence of the particle size; thereby the higher dissolution of the T4 is probably only related to its polymorphism.

4. Conclusions

Solid state characterization of seven commercial thalidomide samples has indicated different polymorphs and mixture of α, β, and amorphous form in some raw materials studied. A lack of homogeneity among the crystal habits analyzed with differences attributed to polymorphic and isomorphic crystals as well. The thalidomide reference standard was constituted by an α phase, but there are no pharmacopoeial indications to the choice of this polymorphic form. This study demonstrated that the selection of a polymorphic form presents no advantage over the improvement of dissolution for thalidomide. The important aspect of this investigation was the verification of a lack of homogeneity between thalidomide commercial samples concerning the polymorphic constitution and the need for investment in additional tests involving solid state characterization by pharmaceutical companies or inclusion of new specifications in the pharmacopoeias including polymorphism investigation. The inclusion of more discriminative studies related to the thalidomide polymorphism is necessary to assure the quality of raw materials. However, future investigations are necessary to perform the selection of the best thalidomide crystalline form for the development of a pharmaceutical oral dosage form containing this drug.

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