Journal of the Korean Chemical Society
2018, *Vol. 62, No. 5*
Printed in the Republic of Korea
https://doi.org/10.5012/jkcs.2018.62.5.352

Crystal Form of Celecoxib: Preparation, Characterization and Dissolution

Mi-Ryung Jin and Young-Taek Sohn*
College of Pharmacy, Duksung Women's University, Seoul 01369, Korea.
**Email:ytsohn@duksung.ac.kr*
(Received June 11, 2018; Accepted July 24, 2018)

ABSTRACT. Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) is a cyclooxygenase-2 inhibitor used in the treatment of arthritis, acute pain, and dysmenorrhoea. Celecoxib is a Biopharmaceutics Classification System (BCS) class II compound whose oral bioavailability is highly limited owing to its poor aqueous solubility. Several polymorphs of celecoxib have been identified as Form I, Form II, and Form III with melting points of about 162.8 °C, 161.5 °C, and 160.8 °C, respectively. Form IV was generated from the precipitated suspension in the presence of HPMC (Hydroxypropyl methylcellulose) and Polysorbate 80. A rapid rate of dissolution is useful because the rate of dissolution of a drug typically increases its bioavailability. The aim of this study was to investigate the possibility of production of new crystal form of celecoxib that has higher solubility than Form III. New crystal form of celecoxib (Form A) has been isolated by recrystallization and characterized by differential scanning calorimetry (DSC), thermogravimetric (TG) analysis and powder X-ray diffractometry (PXRD). Form A was dissolved faster than Form III. At 30 minutes, the dissolution of Form A was 97.3%, whereas the dissolution of Form III was 82.2% ($p < 0.1$). After storage of three months at 20 °C, in 24% RH (Relative Humidity), the crystal form was not transformed.

Key words: Celecoxib, Polymorphism, Pseudopolymorphism, DSC, PXRD

INTRODUCTION

Pharmaceutical solids can exist in different crystal forms (*e.g.* crystalline, amorphous, or glass) and solvated or hydrated states.[1-2] Crystal forms include polymorphs, solvates, and amorphous forms as defined in the International Conference on Harmonization (ICH) Guideline Q6A.[3]

The crystal form affects properties such as drug absorption, rate of dissolution, elimination rate and stability in galenic preparations.[4-8] Successful utilization of a crystal form of significantly greater thermodynamic activity (*i.e.*, solubility) rather than the more stable modification may provide, in some instances, therapeutic blood levels from otherwise inactive drugs.[9] A thorough understanding of the way in which solid state properties influence solubility, stability, and other properties of the drug substance is critical for the development of profiling strategies and criteria for determining the feasibility of further development.[10]

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide; *Fig.* 1) is a cyclooxygenase-2 inhibitor approved for the management of rheumatism and osteoarthritis.[11] Whether inhibition of COX-2 also plays a dominant role in this drug's anticancer effects is unclear. A recent study of malignant tumor cells showed that celecoxib can inhibit cell growth in vitro, but COX-2 played no role in this outcome. In addition, the anticancer effects of celecoxib have been observed when using cancer cell types that do not contain COX-2.[12] According to US7476744 B2,[13] several polymorphs of celecoxib have been identified as Form I, Form II, and Form III with melting points of 162.8 °C, 161.5 °C, and 160.8 °C, respectively. Form III is a thermodynamically stable crystal form under ambient conditions.

The solubility of celecoxib in water is very low (3.3 mg L^{-1}) and celecoxib is a Biopharmaceutics Classification System (BCS) class II compound with highly limited oral bioavailability due to its poor aqueous solubility. The synthesis

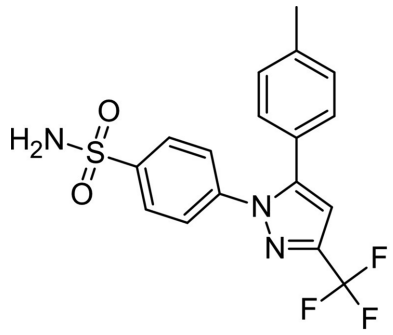


***Figure* 1.** Chemical structure of celecoxib.

of celecoxib salts[14] and production of noncrystalline solid[15-17] have been utilized as an approach to improve the solubility, dissolution rate, and bioavailability. The bioavailability of amorphous celecoxib is double that of crystalline celecoxib in dogs.[16] Unpulverized glass celecoxib remains stable at least 3 months, whereas approximately 70% crystallinity is gained in 100 hours after pulverization.[17] According to US 6964978[16], the amorphous solid has higher bioavailability than the crystalline form, but the stability of the amorphous form is not good because it transforms into the crystalline form.

The aim of this study was to investigate the possibility of production of new crystal form of celecoxib that has higher solubility than Form III.

EXPERIMENTAL

Materials

Celecoxib was supplied by Cadila Pharmaceuticals Ltd., (Ankleshwar, India). Solvents were analytical reagent grade or HPLC grade, used without further purification.

Preparation of Crystal Forms

Form A: A suspension of the starting form in acetone was heated to 45 °C for ten minutes and the solution was filtered to remove most of the precipitates and then left undisturbed for 1 week at -20 °C. The resulting solid was filtered and dried for 1 week in a desiccator to produce Form A.

Methods

Thermal analysis: Thermal analysis methods used in this study included differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis. The DSC data were collected using a Mettler-Toledo DSC 1 STAR^e system (Mettler-Toledo AG, Schwerzenbach, Switzerland) within the temperature range of 30-180 °C at a heating rate of 10 °C/min. Five mg of sample was analyzed using aluminum cells and an empty cell was used as reference. Nitrogen was used as purged gas with a flow rate of 50 mL/min. The TG was carried out using a Mettler-Toledo TGA 1 STAR^e system (Mettler-Toledo AG, Schwerzenbach, Switzerland). Five mg of sample was analyzed within the temperature range of 30-165 °C at a heating rate of 10 °C/min under nitrogen purging (50 mL/min).

Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) patterns were collected under ambient conditions on a D8 focus-Bruker AXS (Bruker AXS GmbH, Karlsruhe, Germany) diffractometer using graphite monochromatized CuKα radiation (λ=1.54178 Å). The isothermal measurement conditions were: target Cu, voltage 30 kV, current 10 mA. The PXRD patterns of the samples were compared based on peak position and relative intensity, peak shifting, and the lack of peaks in certain angular regions.

Dissolution

The dissolution rate of celecoxib was measured using the paddle method of USP XXIV and a dissolution tester (Duksan pure chemical Co., Seoul, Korea). A fixed amount (50 mg, 250-600 μm) of celecoxib crystals was placed into 900 mL of 0.04 M tribasic sodium phosphate buffer with 1% sodium lauryl sulfate and stirred at 50 rpm at 37 ± 0.5C.[18] Next, 1 mL of the dissolution sample was collected at predetermined intervals of 15, 30, 45, 60, 75, 90, and 120 min and placed with an equal volume of fresh media in order to maintain sink conditions. All of the dissolution samples were filtered using a syringe filter (0.45 μm) and analyzed at 254 nm with a X-ma 1000 spectrophotometer (Human Cooperation, Seoul, Korea).

Transformation

An aliquot (100 mg) of each crystal form was placed in a weighing dish and stored at 20 °C in 24% relative humidity (RH). The transformation behavior of the crystal forms was monitored by PXRD and DSC.

RESULTS AND DISCUSSION

The DSC curve, TG curve, and PXRD pattern of the starting form are shown in *Fig*. 2-4. The starting form had a melting point of 162.16 °C (ΔH = 103.1 J/g). The TG curve of the starting form showed no change in weight. The PXRD pattern of the starting form had peaks at 6.5, 10.3, 10.6, 12.6, 14.4, 15.7, 19.2, and 21.1 degrees two-theta. The PXRD pattern of Form I had peaks at 5.5, 5.7, 7.2, and 16.6 degrees two-theta and Form II at 10.3, 13.8, and 17.7 degrees two-theta. US7476744 B2 depicted a comparison of experimental PXRD patterns for Form I, a mixture of Form II and Form III, and Form III. The two-theta data for Form III were not included. The PXRD pattern of Form III in US7476744 B2 had peaks at 5.0, 7.2, 9.5, 10.3, 10.6, 12.6, 14.4, and 15.7 degrees two-theta. According to US7476744 B2, the melting points of Form I, Form II, and Form III are 162.8 °C (ΔH = 72 J/g), 161.5 °C (ΔH = 84 J/g), and 160.8°C (ΔH = 91 J/g). Form III exhibited a complex DSC melting transition, and the melting

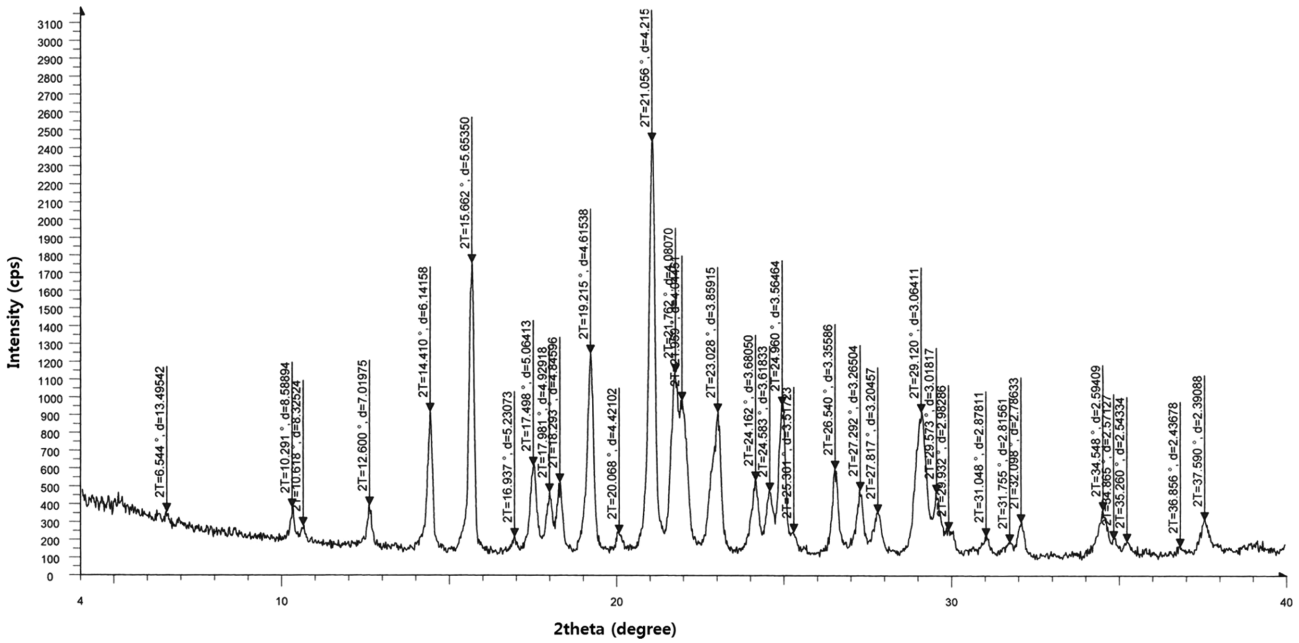


***Figure* 2.** PXRD pattern of Form III.

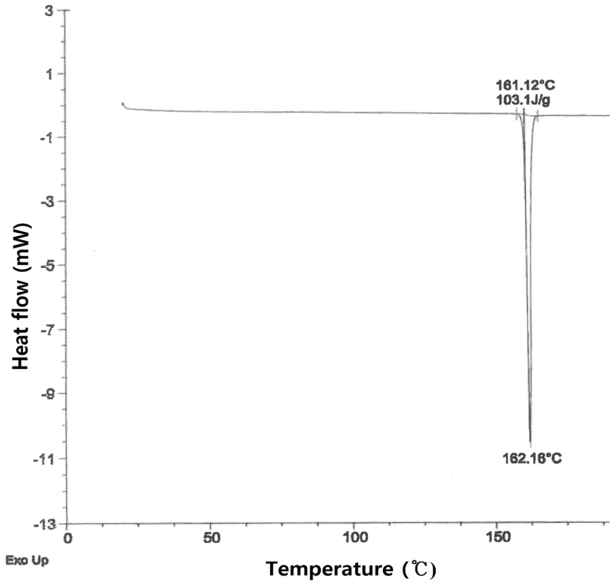


***Figure* 3.** DSC curve of Form III.

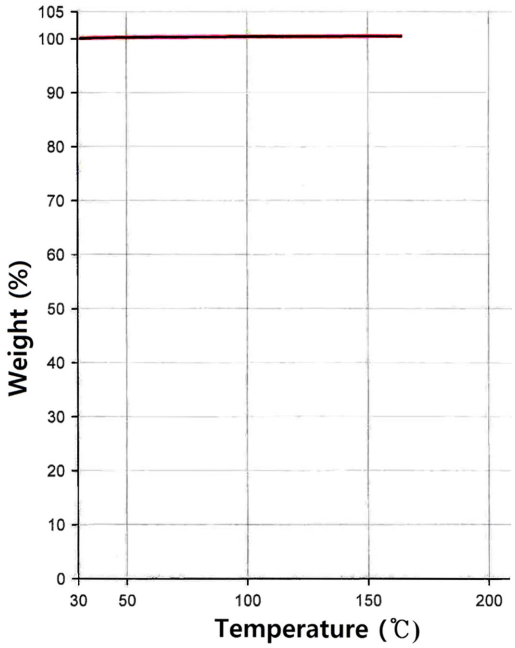


***Figure* 4.** TG curve of Form III.

of Form III was observed at 160.8 °C followed by recrystallization to Form II and subsequent melting of Form II at 162.0 °C. Lu et al[19] generated a new crystal form of celecoxib, Form IV, from the precipitated suspension in the presence of HPMC and Polysorbate 80. The concentration and ratio of the polymer-surfactant are critical for the formation of Form IV. The DSC pattern of Form III in US7476744 B2 had two endothermic peaks, but in the report of Lu et al.[21] Form III had one endothermic peak at 162.4 °C. The DSC and PXRD results confirmed that the starting form is equivalent to Form III.

The crystalline form of celecoxib was marketed although higher bioavailability was found for the amorphous state. The downfall of the amorphous state was its stability. This is due to the structural relaxation which causes devitrification of celecoxib if stored at room temperature.[20] This is

enhanced by mixing it with polymers, such as PVP which helps stabilize the amorphous system.[21] The polymer used forms a composite with the amorphous form and prevents its conversion to the crystalline form. The crystalline form of celecoxib is less pharmaceutically active. Previous studies have investigated the stability and solubility of the drug-polymer amorphous system. If a dopant is employed at levels that will disrupt the crystal lattice, the substance can solidify as an amorphous material.[22] Sometimes solvents exert a similar effect. When a small amount of ethyl acetate is added to a calcium chloride solution prior to the addition of sodium fenoprofen, the calcium fenoprofen that precipitates has a low degree of crystallinity.[23]

Various possibilities were investigated for preparing the crystal form of interest. A suspension of the starting form in acetone was heated to 45 °C for 10 minutes, the solution filtered to remove most of the precipitates and then left undisturbed for 1 week at -20 °C. The resulting solid was filtered and dried for 1 week in a desiccator to produce Form A. The DSC curve, TG curve, and PXRD pattern of Form A are illustrated in *Fig.* 5-7. Form A had a melting point of 162.98 °C (ΔH = 100.5 J/g). The TG curve of Form A showed no change in weight. The PXRD pattern of Form A had peaks at 14.4, 15.7, 16.9, 17.9, 18.2, 19.2, and 21.1 degrees two theta. The PXRD pattern of Form A showed no peak below 14 two-theta angle and had a diffuse "halo"; thus

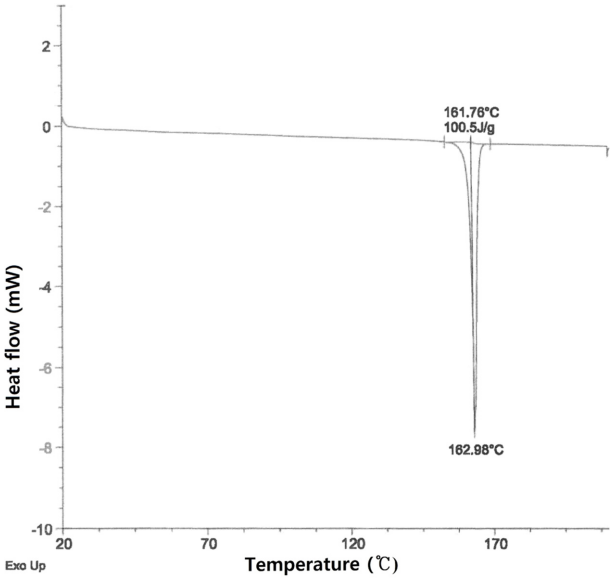


***Figure* 6.** DSC curve of Form A.

Form A lacks the three-dimensional long-range order, but the short-range order (above 14 two-theta angle) is present.

The dissolution patterns of Form III and Form A were studied in 900 mL of sodium phosphate dibasic anhydrous buffer with 1% sodium lauryl sulfate at 37 ± 0.5 °C, stirred at 50 rpm for 120 minutes (*Fig*. 8). Form A was dissolved faster than Form III. At 30 minutes, the dissolution

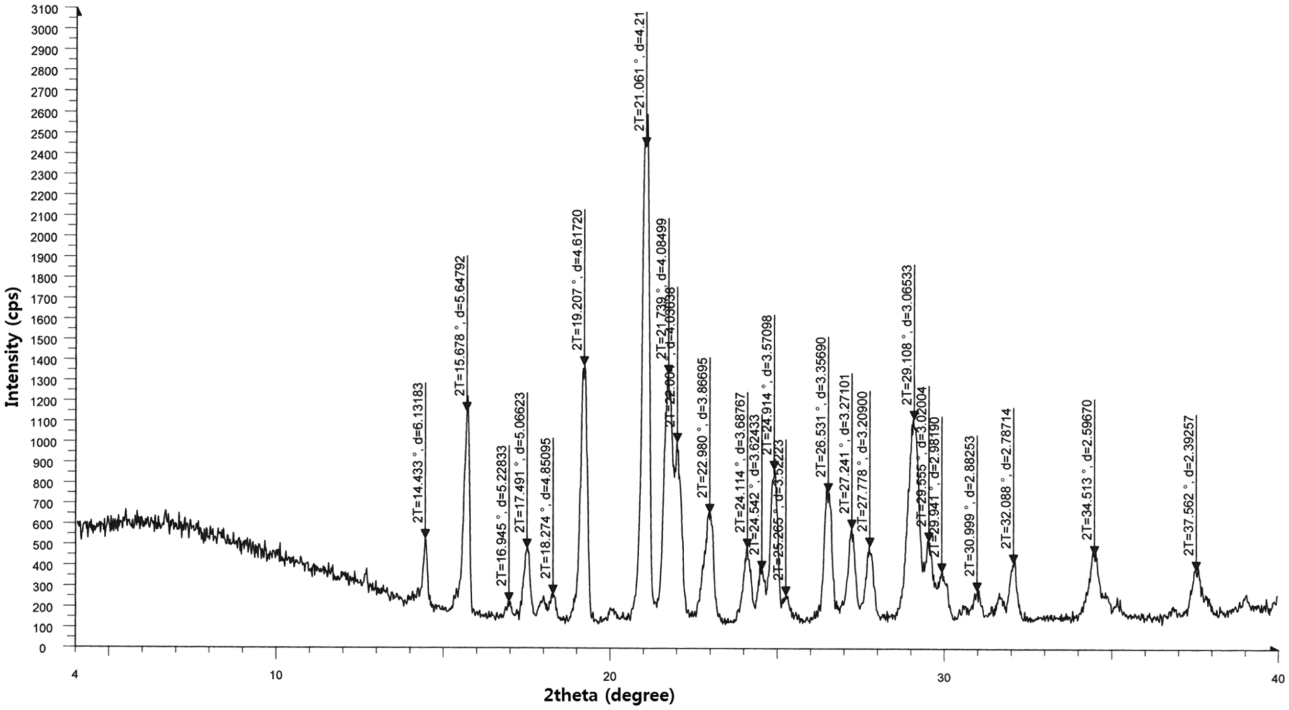


***Figure* 5.** PXRD pattern of Form A.

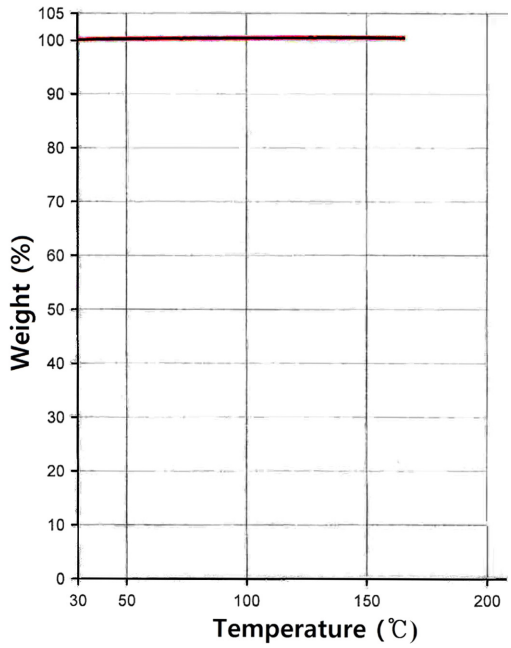


***Figure* 7.** TG curve of Form A.

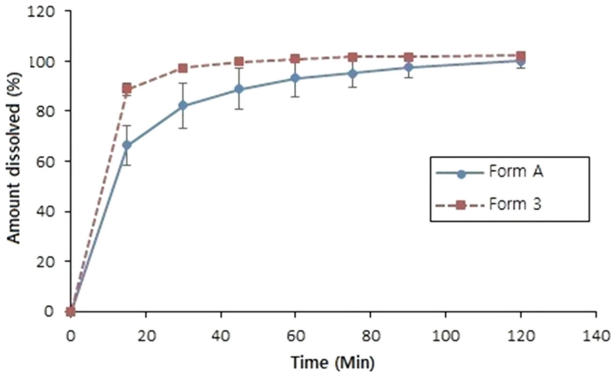


***Figure* 8.** Dissolution patterns of Form III and Form A (n = 3).

of Form A was 97.3%, whereas the dissolution of Form III was 82.2% ($p < 0.1$). All crystal forms were stored at 20 °C in 24% RH. After storage for three months under these conditions, none of the crystal forms showed a change in DSC, TG, and PXRD pattern (data not shown).

CONCLUSION

We undertook the possible production of the new crystal form of celecoxib that has higher solubility than Form III. The PXRD pattern of the crystal form of celecoxib prepared by recrystallization from acetone at -20 °C (Form A) showed no peak below 14 two-theta angle and had a diffuse "halo". The Form A lacks the three-dimensional long-range order, but the short-range order (above 14 two-theta angle) is present. Form A was dissolved faster than Form III. At 30 minutes, the dissolution of Form A was 97.3%, whereas the dissolution of Form III was 82.2% ($p < 0.1$). After storage for 1 month at 20 °C in 24% RH, Form A showed no change in DSC, TG, and PXRD pattern.

Acknowledgments. This work was supported by a research grant from Duksung Women's University (2017).

REFERENCES

1. Fiese, E. F.; Hagen, T. A. In *The theory and practice of industrial pharmacy*, Lachman, L., Lieberman, H. A., Kanig, J. L., Eds.; Lea & Febiger: Philadelphia, 1986; p 171.
2. Wells, J. In *Pharmaceutics,* Aulton, M. Ed.; Churchill Livingstone: Edinburgh, London, New York, Philadelphia, St. Louis, Sydney, Toronto, 2002; p 113.
3. Q6A International Conference on Harmonization; Guidance on Q6A Specifications, *Federal Register* **2000**, *65*, 83041.
4. Kim, S. K.; Bang, H. C.; Sohn, Y. T. *J. Therm. Anal. Calorim.* **2017**, *127*, 1715.
5. Griesser, U. J.; Weigand, D.; Rollinger, J. M.; Haddow, M.; Gstrein, E. *J. Therm. Anal. Calorim.* **2004**, *77*, 511.
6. Dichi, E.; Legendre, B.; Sghaier, M. *J. Therm. Anal. Calorim.* **2014**, *115*, 1551.
7. Seo, H. O.; Sohn, Y. T. *J. Therm. Anal. Calorim.* **2015**, *120*, 749.
8. Tak, S. R; Sohn, Y. T. *J. Therm. Anal. Calorim*. **2016**, *123*, 2477.
9. Di, M. P.; Barthelemy, C.; Palmieri, G. F.; Martelli, S. *Eur. J. Pharm. Sci.* **2001**, *14*, 293.
10. Brittain, H. G. In *Polymorphism in pharmaceutical solids,* Brittain H.G., Ed.: Marcel Dekker: New York, 1999; p 227.
11. Simon, L. S.; Lanza, F. L.; Lipsky, P. E.; Hubbard, R. C.; Talwalker, S.; Schwartz, B. D.; Isakson, P. C.; Geis, G. S. *Arthritis Rheum*. **1998**, *41*, 1591.
12. Chuang, H. C.; Kardosh, A.; Gaffney, K. J.; Petasis, N. A.; Schönthal, A. H. *Mol. Cancer.* **2008**, *7*, 38.
13. Ferro, L. J.; Miyake, P. J. US 7476744 B2, 2009.
14. Morissette, S. L.; Almarsson, Ö.; Peterson, M. L.; Remenar, J. F.; Read, M. J.; Lemmo, A. V.; Ellis, S.; Cima, M. J.; Gardner, C. R. *Adv. Drug Deliv. Rev.* **2004**, *56*, 275.
15. Chawla, G.; Gupta, P.; Hilagavathi, T. R.; Chakraborti, A. K.; Bansal, A. K. *Eur. J. Pharm. Sci.* **2003**, *20*, 305.
16. Hageman, M. J.; Kararli, T. T.; Mackin, L. A.; Miyake, P. J.; Rohrs, B. R.; Stefanski, K. L. US 6964978 B2, 2005.
17. Paradkar, A. R.; Chauhan, B.; Yammamura, S.; Pawar, A. P. *Drug Dev. Ind. Pharm*. **2003**, *29*, 739.
18. Dissolution methods. *US Food and Drug Administration*, **2016**.

19. Lu, G. W.; Hawley, M.; Smith, M.; Geige, B. M.; Pfund, W. *J. Pharm. Sci*. **2006**, *95*, 305.
20. Grzybowska, K.; Paluch, M.; Grzybowski, A.; Wojnarowska, Z.; Hawelek, L.; Kolodziejczyk, K.; Nagi, K. L. *J. Phys. Chem. B*. **2010**, *114*, 12792.
21. Gupta, P.; Kakumanu, V. K.; Bansal, A. K. *Pharm. Res*. **2004**, *21*, 1762.
22. Guillory, J. K. In *Polymorphism in pharmaceutical solids,* Brittain H. G., Ed.: Marcel Dekker, New York, 1999; p 183.
23. Hendriksen, B. A. *Int. J. Pharm*. **1990**, *60*, 243.