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CRYSTAL FORMS OF A CAPSAICIN DERIVATIVE ANALGESIC DA-5018

*E.-A. Lee and Y.-T. Sohn**

College of Pharmacy, Duksung Women's University, 419, Ssangmun-Dong, Dobong-Gu, 132-714 Seoul, Korea

DA-5018 is a new capsaicin derivative and has analgesic effect. The objective of this work was to investigate the existence of polymorphs and pseudopolymorphs of DA-5018 and the transformation of crystal forms. Eight crystal forms of DA-5018 have been isolated by recrystallization and characterized by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TG).

The PXRD and DSC patterns of the eight crystal forms were different respectively.

In the dissolution studies in simulated intestinal fluid at 37±0.5°C, the solubility of Form 2 was the highest. And the solubility in water decreased in rank order: Form 2>Form 3>Form 1>Form 5>Form 7>Form 4>Form 6>Form 8.

Eight crystal forms were shown to have a good physical stability at room temperature for 60 days.

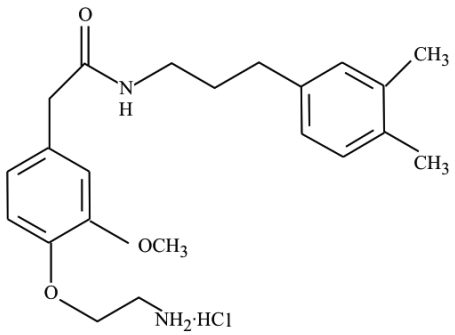
Keywords: *crystal form, DA-5018, dissolution, DSC, polymorphism, pseudopolymorphism, PXRD, TG, transformation*

Introduction

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid-state [1–4]. The pharmaceutical importance of this phenomenon lies in the fact that different polymorphic forms exhibit unique physicochemical properties include solubility/dissolution rates which can influence bioavailability [5] and stability in galenic preparations [6–8]. The successful utilization of a crystal form of significantly greater thermodynamic activity (i.e., solubility) than the stable modification may provide, in some instances, therapeutic blood levels from otherwise inactive drugs.

The presence of this phenomenon in pharmaceuticals is particularly common and a recent report lists over 500 examples of pharmaceuticals that exhibit polymorphism [9]. Various techniques are currently utilized to characterize polymorphs including powder X-ray diffraction (PXRD), hot-stage microscopy (HSM), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, solid-state nuclear magnetic resonance (SSNMR) spectroscopy, and thermogravimetric analysis (TG) [10–15].

The compound DA-5018 (Scheme 1), {3-(3,4-dimethylphenyl)}-d-(2-aminoethoxy)-3-methoxyphenyl acetamide, is a capsaicin derivative analgesic developed by DongA Pharmaceutical Co. Ltd., Korea. In the case of a new drug substance, it is important that crystal form data should be generated prior to the initiation of pivotal clinical studies and primary stability batches. Companies have experienced market shortages because they have observed unpredicted changes in crystal form, which ultimately resulted in problematic quality release and stability testing of the finished dosage form. The aim of this study was to investigate the existence of polymorphs and pseudopolymorphs of DA-5018 and the transformation of these crystal forms.



Scheme 1 Chemical structure of DA-5018

Experimental

Materials

DA-5018 was provided from DongA Pharmaceutical Co. Ltd., Korea. Other extra pure chemicals were purchased from a reagent commercial company.

* Author for correspondence: ytsohn@duksung.ac.kr

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Preparation of crystal forms

Form 1

Form 1 is the donated one and standard. Standard was always stored at 0–2°C condition.

Form 2

A suspension of Form 1 in formic acid was heated to 30°C for 10 min. The solution was filtered to remove most nuclei and then left undisturbed for one week at room temperature. The resulting solid was filtered and dried for one week in the desiccators to give Form 2.

The preparation methods of Forms 3–8 are summarized in Table 1.

Table 1 Preparation of crystal forms

Form	Solvent	Cooling temp.
2	Formic acid	Room temp.
3	Formic acid	–2°C
4	Formic acid	–70°C
5	Ethylacetate	Room temp.
6	Acetic acid	Room temp.
7	Chloroform	Room temp.
8	Acetonitrile	Room temp.

Methods

Powder X-ray diffraction

Powder X-ray diffraction patterns under ambient conditions were collected on Rigaku DMAX-IIIA (Japan) diffractometer using graphite monochromatized CuK_α radiation (λ=1.54178 Å). The measurement conditions were isothermal.; target, Cu; voltage, 30 kV, current, 10 mA. The PXRD patterns of the samples were compared with regard to peak position and relative intensity, peak shifting, and the presence or lack of peaks in certain angular regions.

Thermal analysis

Thermal analysis methods used in this study included differential scanning calorimetry, thermogravimetric analysis. DSC patterns were recorded with a Mettler DSC-12E (Mettler, Switzerland). TG analysis was performed on all samples indicated by DSC as being possible solvates or hydrates. TG patterns were recorded with a SEIKO I SSC-5000 (SEIKO, Japan). Samples of 5 mg were weighed in pierced aluminum pans with heating rate of 10°C min^{-1} and temperature range from 30 to 300°C.

Transformation

A certain amount (20 mg) of polymorphs was taken and placed in weighing dish. They were stored in desiccator of 0% Relative Humidity (silica gel, 20°C), 52% Relative Humidity (saturated solution of $Na_2Cr_2O_7 \cdot 2H_2O$/20°C) and 95% Relative Humidity (saturated solution of Na_2HPO_4/20°C).

The transformation behavior of polymorphs was monitored by powder X-ray diffraction (XRD) analysis, DSC and TG.

Dissolution

The dissolution rate of DA-5018 crystal forms was measured according to the dissolution test (paddle method) of the Korean Pharmacopoeia 8th Edition.

A fixed amount (30 mg, 250–600 μm) of DA-5018 crystal forms was put into 1 L of simulated intestinal fluid (0.2 mol L^{-1} KH_2PO_4 250 mL+0.2 mol L^{-1} NaOH 118 mL+distilled water ad 1 L) and stirred at 150 rpm at 37±0.5°C. At an appropriate intervals, an aliquot (1 mL) was withdrawn with a syringe and filtered with 0.45 μm syringe filter. And then it was analyzed spectrophotometrically at 210 nm.

Results and discussion

Differential scanning calorimetry curves of Form 1, 2, 3, 4, 5, 6, 7 and 8 are illustrated in Figs 1 and 2. The DSC curve of Form 1 shows two endothermic peaks, one endothermic peak at 104°C and the second endothermic peak at 113.9°C. The DSC curve of Form 2 shows two endothermic peaks, one endothermic peak at 119.4°C and the second endothermic peak at 142.7°C. Form 3 shows two endothermic peaks, one endothermic peak at 98.6°C and the second endothermic peak at 112°C. Form 4 shows three endothermic peaks, one endother-

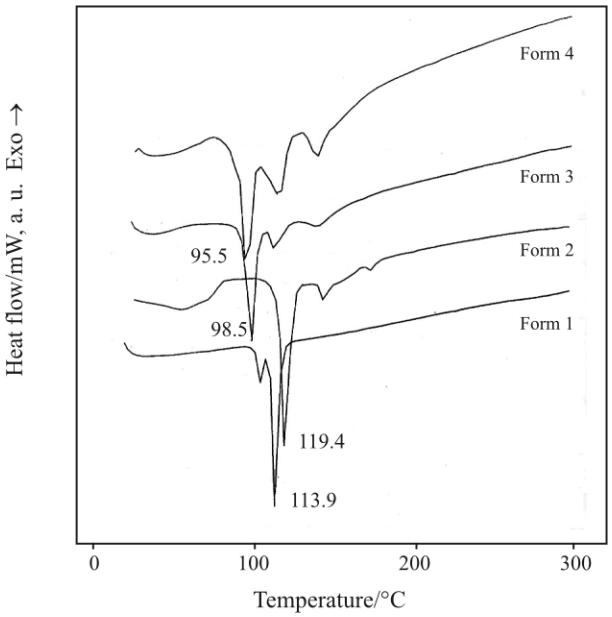

Fig. 1 DSC curves of Forms 1–4

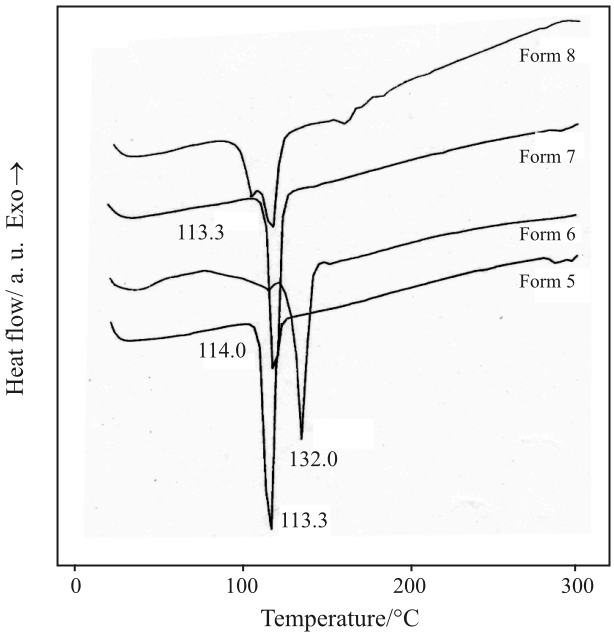

Fig. 2 DSC curves of Forms 5–8

mic peak at 95°C and the second endothermic peak at 115.1°C and the third endothermic peak at 139.6°C. The DSC curve of Form 5 shows one endothermic peak at 113.3°C. The DSC curve of Form 6 shows one endothermic peak at 132°C. The DSC curve of Form 7 shows one endothermic peak at 11°C. Form 8 shows three endothermic peaks, one endothermic peak at 101.6°C and the second endothermic peak at 113.3°C and the third endothermic peak at 123.1°C. From the TG data (not shown) it was confirmed that eight crystal forms are neither solvates nor hydrates.

The powder X-ray diffraction patterns of Form 1, 2, 3, 4, 5, 6, 7 and 8 are illustrated in Figs 3 and 4 and they showed differences.

The DSC, TG and PXRD results confirmed the existence of eight crystal forms of DA-5018.

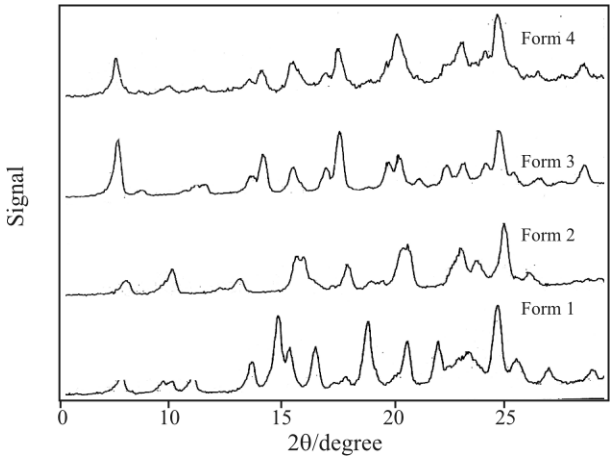

Fig. 3 Powder X-ray diffraction pattern of Forms 1–4

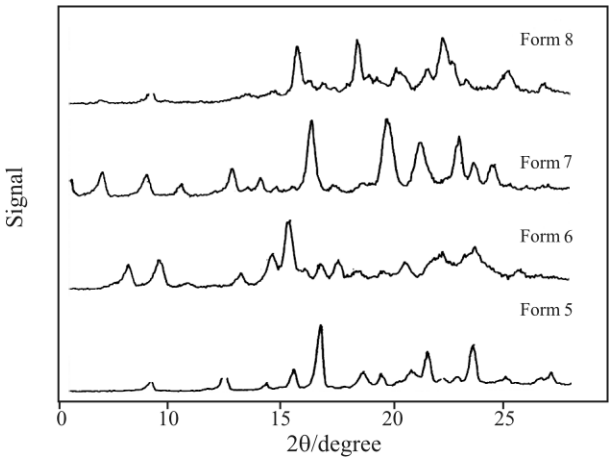

Fig. 4 Powder X-ray diffraction pattern of Forms 5–8

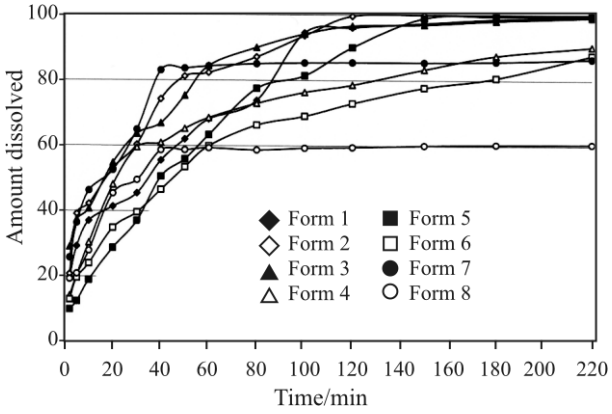

Fig. 5 Dissolution patterns of eight crystal forms of DA-5018

After storage of 60 days at 0% Relative Humidity (silica gel, 20°C), 52% Relative Humidity (saturated solution of $Na_2Cr_2O_7 \cdot 2H_2O$/20°C) and 95% Relative Humidity (saturated solution of Na_2HPO_4/20°C), eight crystal forms showed no change in DSC, TG and PXRD patterns. And it was confirmed that eight crystal forms were shown to have a good physical stability at room temperature for 60 days.

The dissolution patterns of eight crystal forms of DA-5018 are illustrated in Fig. 5. In the dissolution studies in simulated intestinal fluid at 37±0.5°C, the solubility of Form 2 was the highest. And the solubility in water decreased in rank order: Form 2>Form 3> Form 1>Form 5>Form 7>Form 4> Form 6>Form 8.

Conclusions

Eight crystal forms of DA-5018 were prepared by recrystallization from different solvents. The crystal forms were characterized by PXRD, DSC and TG. After storage of 60 days at 0% RH, 52% RH and 95% RH, eight crystal forms showed no transformation. In the dissolution studies in simulated intestinal fluid at 37±0.5°C eight crystal forms showed difference.

References

1 J. Haleblian and W. McCrone, J. Pharm. Sci., 58 (1969) 911.
2 R. Hüttenrauch, Acta Pharm. Technol., 34 (1988) 1.
3 J. Haleblian, J. Pharm. Sci., 64 (1975) 1269.
4 M. Kuhnert-Brandstätter, Informationsdienst A.P.V., 19 (1973) 73.
5 Y. T. Sohn, J. Kor. Pharm. Sci., 58 (2004) 443.
6 T. Matsumoto, N. Kaneniwa, S. Higuchi and M. Otsuka, J. Pharm. Pharmacol., 43 (1991) 74.
7 Y. Matsunaga, N. Bando, H. Yuasa and Y. Kanaya, Chem. Pharm. Bull., 44 (1996) 1931.
8 A. Pyne, K. Chatterjee and R. Suryanarayanan, Pharm. Res., 20 (2003) 802.
9 A. Grünenberg, Pharmazie in unserer Zeit, 26 (1997) 224.
10 A. Burger, Acta Pharm.Technol., 28 (1982) 1.
11 J. O. Henck, U. J. Griesser and A. Burger, Pharm. Ind., 59 (1997) 165.
12 D. Singh, P.V. Marshall, L. Shields and P. York, J. Pharm. Sci., 87 (1998) 655.
13 Y. T. Sohn, J. Therm. Anal. Cal., 89 (2007) 799.
14 M. A. F. Souza, M. M. Conceicao, M. C. D. Silva, L. E. B. Soledade and A. G. Souza, J. Therm. Anal. Cal., 87 (2007) 859.
15 R. S. Barbieri, A. K. C. Dias, S. F. da Silva, V. R. Terra and E. P. de Lima, J. Therm. Anal. Cal., 79 (2005) 255.

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