Organic Process Research & Development **2002**, *6*, 855–862

Taking Advantage of Polymorphism To Effect an Impurity Removal: Development of a Thermodynamic Crystal Form of (*R,R*)-Formoterol Tartrate

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Abstract:

The development and large-scale implementation of a novel technology utilizing polymorphic interconversion and crystalline intermediate formation of (*R,R*)-formoterol L-tartrate ((*R,R*)-FmTA, 1) as a tool for the removal of impurities from the final product and generation of the most thermodynamically stable crystal form is reported. The crude product was generated by precipitation of the free base as the L-tartrate salt in a unique polymorphic form, form B. Warming the resultant slurry effected the formation of a partially hydrated stable crystalline intermediate, form C, with a concomitant decrease in the impurity levels in the solid. Isolation and recrystallization of form C provided 1 in the thermodynamically most stable polymorph, form A.

Introduction

Formoterol (Foradil) is a long acting β_2-agonist used as a bronchodilator in the therapy of asthma and chronic bronchitis.[1] The (*R,R*)-enantiomer has been shown to be more active than the other stereoisomers (*R,S*; *S,R;* and *S,S*) of formoterol.[2] (*R,R*)-Formoterol is extremely potent and selective,[3,4] having rapid onset (1−5 min) and long duration, and is 1000 times more active than the (*S,S*) isomer.[5] An outline of the synthetic process for (*R,R*)-formoterol L-tartrate ((*R,R*)-FmTA, **1**) is shown in Figure 1 and has been discussed in detail in other accounts.[6] During development of the process for the production of **1**, two factors grew into issues of great importance: the impurity profile and the crystal morphology of the final product. The results from earlier development work showed that the impurity profile of **1** consisted of impurities **7** and **8** whose abundances ranged from 0.2 to 1.5%, and that traditional crystallization methods could not decrease the level of **8** below 0.2%. This earlier work also indicated that the isolation and crystallization conditions yielded two polymorphic forms: forms A and B, and a stable crystalline intermediate, form C. The requirements for the chemical process necessitated levels of **7** and **8** to be below 0.2% and generation of the product in the most thermodynamically stable crystal form. The difficulty in controlling the level of **8** and the polymorphic nature of **1** required the development of a strategy for the production of (*R,R*)-FmTA with the requisite purity and in the proper crystal form. Herein we describe the development and large-scale implementation of a novel technology utilizing polymorphic interconversions and crystalline intermediate formation of

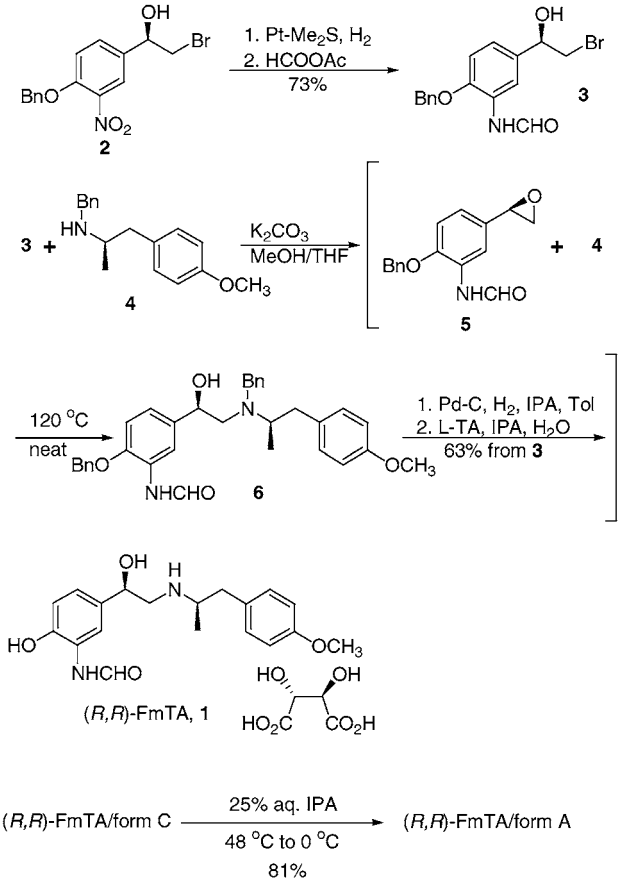

Figure 1. **Synthetic process for the preparation of (*R,R*)-FmTA, form A.**

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10.1021/op025531h CCC: $22.00
Published on Web 10/12/2002

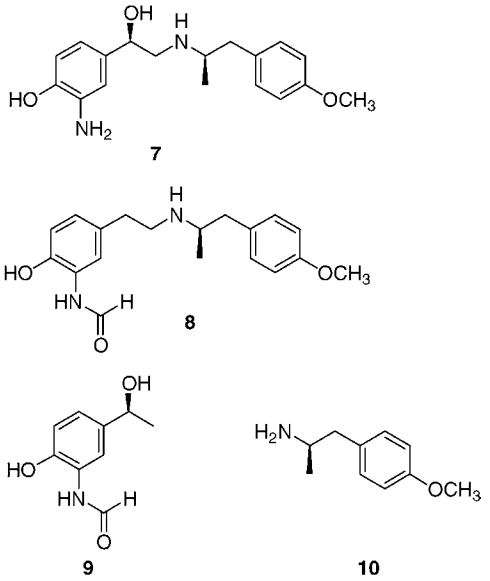

Figure 2. **Impurities in the process for the preparation of (*R*,*R*)-formoterol L-tartrate, form A.**

Table 1. **Impurity profiles of (*R*,*R*)-FmTA isolated product[a]**

entry	isolation	**1** (A%)	**7** (A%)	**8** (A%)	**9** (A%)	**10** (A%)
1	crude product	99.01	0.11	0.64	0.12	0.04
2	recrystallization of crude product	99.43	0.23	0.32	nd	nd

[a] Determined by HPLC analysis.

(*R*,*R*)-FmTA as a tool for the removal of impurities from the final product and generation of the most thermodynamically stable crystal form.[7−12]

Results and Discussions

Purity of 1. A process to provide **1** with the level of any single impurity <0.2% was sought. Initial studies began by characterizing the impurity profile of isolated intermediates and **1** at various stages in the process. As shown in Figure 1, the crude product was isolated as the tartrate salt from **4** via a four-step through-process protocol that entailed: epoxide formation, epoxide opening, debenzylation, and salt formation. Before addition of L-tartaric acid, the crude free-base, as a homogeneous solution in IPA/toluene, contained 25−30% total impurities by HPLC analysis. After addition of an aqueous solution of L-tartaric acid, a thick slurry formed, and the isolated crude product contained the four major impurities **7**−**10** totaling 1% (Figure 2 and Table 1, entry 1). Aniline **7** was formed by hydrolysis of the formamide group of (*R*,*R*)-formoterol, while **8** was generated as a result of dehydroxylation. Compounds **9** and **10** were formed by hydrogenation of the starting bromohydrin **3** and amine **4**, respectively, excess reactants from the previous synthetic steps. After recrystallization of the crude product from 25% aqueous IPA, impurities **9** and **10** were removed, the level of **8** decreased from 0.63 to 0.32%, and the level of **7** *increased* from 0.11 to 0.23% (Table 1, entry 2). The increase in the level of **7** during the crystallization indicated that purification of **1** would be confined to only one crystallization of the crude product. Additionally, the current crystallization process did not provide the final product with adequate purity, requiring further development of the process. Because the preceding steps in the process had been optimized, an improvement in the purity of the final product rested solely on an improvement in the isolation and recrystallization of the crude and final products, respectively.

Table 2. **Impurity profiles of (*R*,*R*)-FmTA isolated products[a]**

entry	isolated product	**1** (A%)	**7** (A%)	**8** (A%)	**9** (A%)	**10** (A%)
1	crude product	99.01	0.11	0.64	0.12	0.04
2	crude product after warming	99.85	0.04	0.11	nd	nd
3	recrystallization of warmed crude product	99.83	0.12	0.05	nd	nd

[a] Determined by HPLC analysis.

Our first approach to the impurity problems was to investigate the behavior of the slurry of crude product at various temperatures. Temperature cycling experiments were performed, cycling the slurry temperature from 22 to 45 °C. After 10−15 cycles, the levels of each impurity **7**−**10** in the solid dropped below 0.10%.[13] In conjunction with the decrease in impurity levels was a thickening of the slurry. The results were repeated when the slurry of the crude product was warmed to 45−50 °C for 1−5 h. As shown in Table 2, impurities **9** and **10** were completely removed from the crude product after warming, and the levels of **7** and **8** were lowered to 0.04 and 0.11%, respectively (entries 1 and 2). Recrystallization provided levels of **7** and **8** easily within the required ranges: 0.12% for **7** and 0.05% for **8** (entry 3). Similar to the results above, the level of **7** rose by 0.08% upon recrystallization, but due to its initially low level, the final level was within the required specification. Also, the slurry thickened as noted before. The results in Table 2 and the concomitant thickening of the slurry indicated that a polymorph interconversion could have occurred during the impurity removal. An investigation of the polymorphic properties of (*R*,*R*)-FmTA was initiated.

Identification of Distinct Crystal Forms and Intermediates. Our initial examinations into the morphology of **1** identified the presence of two distinct crystal forms and a hydrated crystalline intermediate during the impurity removal process: forms A, B, and C. The polymorphs and crystalline intermediate were identified at three stages of the process:

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(13) Temperature cycling has been commonly used for increasing the crystal size of crystalline solids. In our case, the decrease in impurity levels were not linearly dependent on the number of cycles.

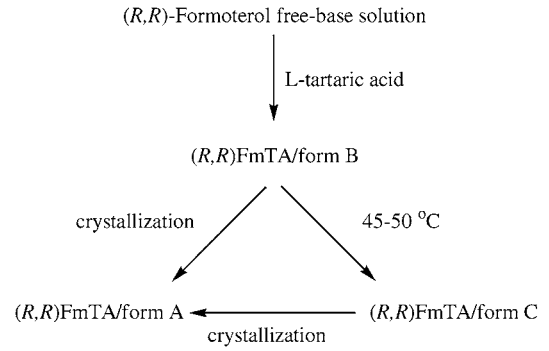


Figure 3. **Polymorph/intermediate interconversion and impurity removal process. (a) (*R*,*R*)-formoterol tartrate/form A. (b) (*R*,*R*)-Formoterol tartrate/form B. (c) (*R*,*R*)-Formoterol tartrate/form C.**

(1) the crude product generated after addition of L-tartaric acid to a solution of the crude free-base (form B), (2) the crystalline intermediate formed after warming the slurry of the crude product to effect the impurity removal (form C),[14] and (3) recrystallization of the intermediate from 25% aqueous isopropyl alcohol (form A). Using the protocol created for the impurity removal (vide supra), the three forms could be generated and interconverted according to Figure 3, demonstrating the concurrency of the impurity removal and polymorph/intermediate interconversions.

Form B. Addition of L-tartaric acid to the reaction solution generated from the four-step through-process protocol produced a slurry of (*R*,*R*)-FmTA. Filtration of the slurry, followed by rinsing the isolated white solid with isopropyl alcohol, gave the morphologically distinct crystalline solid (*R*,*R*)-FmTA/form B. Figures 4b−6b show the IR spectrum (KBr pellet), the DSC trace, and the X-ray powder pattern for the crystalline solid. The most distinct feature of the IR spectrum is the absorbance pattern at 2400−3600 cm^{-1}, especially the pattern centered at 3400 cm^{-1}. In the DSC trace, the sharpness of the endotherm peak at 177 °C with $\Delta H_{fusion} = 136.16$ J/g is particularly noteworthy, and in the X-ray powder pattern, the reflections in the 8−21° 2θ range (tick marks) are the main features of the pattern. The material isolated at this stage in the process provided a stable crystalline white solid that could be stored for long periods (months) without decomposition.

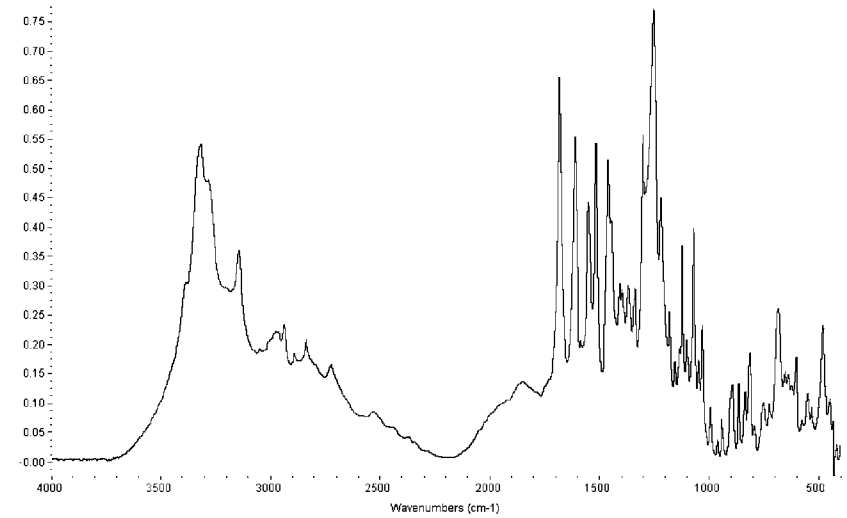
Form C. When the resultant slurry from the through-process protocol was warmed to 45−50 °C for 1−5 h prior to filtration, the slurry thickened. After cooling to room temperature and filtering, a white crystalline solid (*R*,*R*)-FmTA/form C was isolated. Figures 4c−6c show the IR spectrum (KBr pellet), the DSC trace, and the X-ray powder pattern for this crystalline solid. A comparison of these data with the data presented in Figures 4b−6b clearly indicated that this solid was unique from form B. In the IR spectrum, the most readily noticeable pattern is in the 2200−3800 cm^{-1} region. The sharp absorbances at approximately 3500 and 3350 cm^{-1} are characteristic of this polymorphic form and contrast sharply with the pattern shown in Figure 4b. Additionally, the DSC trace portrays several unique features. Specifically, the broad and weak endotherm at 147 °C followed by the stronger transition at 167 °C ($\Delta H_{fusion} =$ 66.19 J/g) was indicative of loss of solvent with subsequent melting. Further analysis by TGA-LOD showed a 0.729% weight loss in the range of 25−140 °C, and a KF measurement showed 0.734% water present in the solid. These data indicate that form C is a hydrated form of (*R*,*R*)-FmTA in a 5:1 (*R*,*R*)-FmTA:water molar ratio. The X-ray powder diffraction definitively proved that this crystalline solid was unique when compared to (*R*,*R*)-FmTA/form B. The pattern is characterized by the sharp reflection at 6.5° 2θ and the reflections in the 17−25° 2θ range (tick marks), and the 2θ values of these peaks are clearly different from those obtained for form B. As shown in Figure 3, simply warming the solution to 45−50 °C effected the conversion of form B to form C.

The novelty of the concomitant impurity removal/interconversion process prompted further investigations. Specifically, the dependence of the process on the solvent system was studied. Generation of the crude product in crystal form B occurred by addition of an aqueous solution of L-tartaric acid to a solution of the free-base in a 3.7:1(w/w) IPA:toluene solvent mixture. After addition of tartaric acid, the resultant slurry consisted of a 17 wt % mixture of (*R*,*R*)-FmTA/form B in a 3.7:1.0:2.0 (w/w/w) IPA:toluene:water solvent mixture. The conversion of form B to form C was effected in this solvent mixture. Our analysis began by examining the effect of toluene on the interconversion.[15] In this context, the isolated crude solid of form B was suspended in a 1.8:1 w/w mixture of IPA:water at a concentration of 17 wt % and warmed to 45−50 °C, and the conversion to form C and the impurity levels were monitored as a function of the amount of toluene in the solvent mixture (Table 3). When the slurry was warmed to 45−50 °C for an extended period, no conversion was observed nor was an impurity removal effected when the amount of toluene in solution was 9 wt % or lower (entries 1−3). However, when the level of toluene was raised to 13 wt %, the impurity removal was observed (entry 4). Further analysis of this sample showed that conversion to form C occurred also. The same results were observed when the level of toluene was raised to the original level, 15 wt % (entry 5). The data show that 13 wt % or more of toluene in the solvent mixture was necessary to cause the impurity removal/interconversion. The results also confirmed that the current solvent ratio, 15 wt % toluene, contained sufficient quantities to ensure the process occurred successfully.

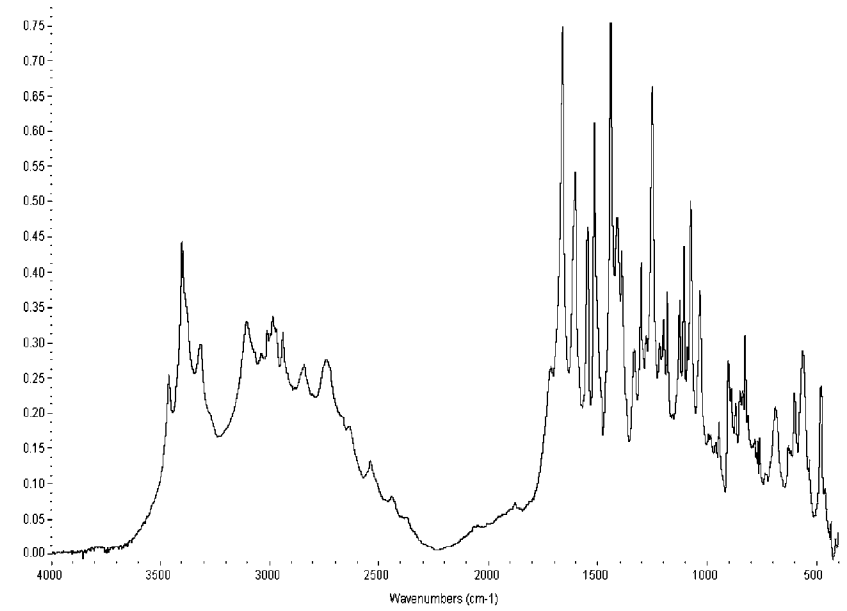
Form A. Crystallization of (*R*,*R*)-FmTA/form B or (*R*,*R*)-FmTA/form C from aqueous IPA generated the same morphologically distinct solid, (*R*,*R*)-FmTA/form A. Under the optimized conditions, dissolution of (*R*,*R*)-FmTA/form C in aqueous isopropyl alcohol at elevated temperatures, followed by cooling to 0−5 °C gave the crystalline solid. The IR spectrum, DSC trace, and X-ray powder diffraction pattern are shown in Figures 4a−6a. The IR spectrum is characterized by the broad absorbance at 3420 cm^{-1} contain-

(14) Although the hydrated intermediate is not a true polymorph, for ease of discussion, this intermediate will be referred to as form C.

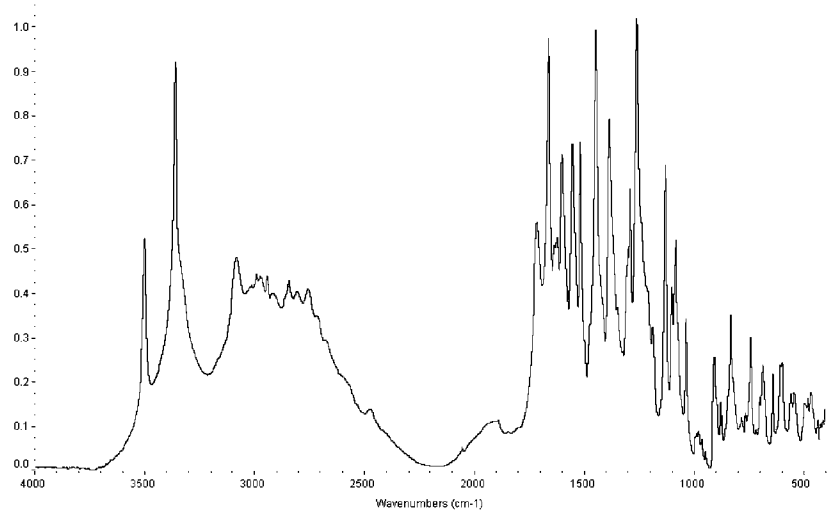
(15) Since form C was determined to be a hydrated intermediate, the water content was not altered in our solvent studies.



(a) (*R*,*R*)-Formoterol Tartrate/Form A

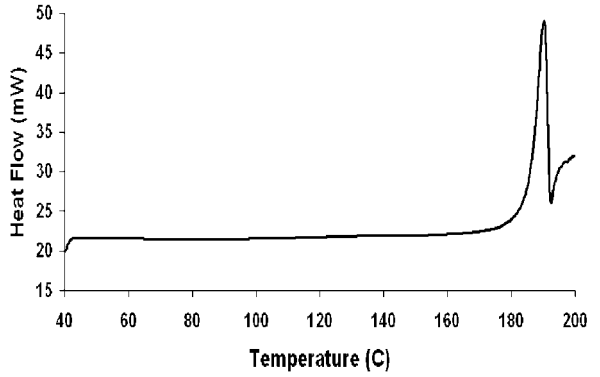


(b) (*R*,*R*)-Formoterol Tartrate/Form B

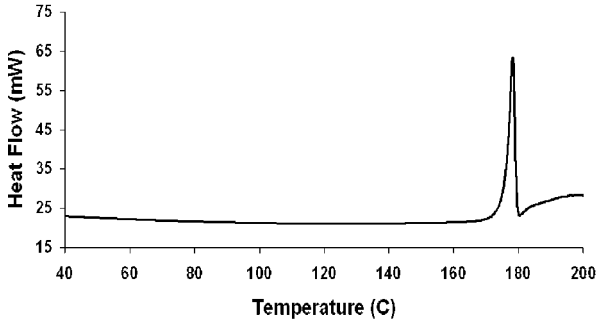


(c) (*R*,*R*)-Formoterol Tartrate/Form C

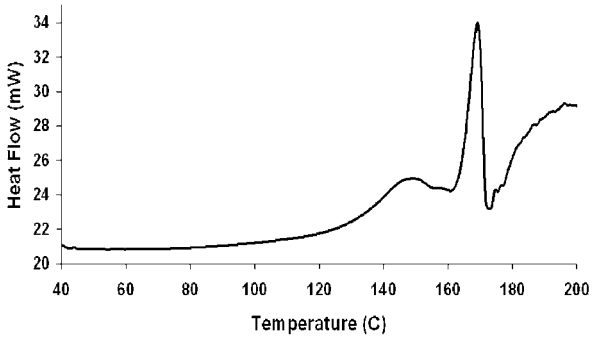
Figure 4. **IR spectra of (a) (*R*,*R*)-formoterol tartrate/form A, (b) (*R*,*R*)-formoterol tartrate/form B, (c) (*R*,*R*)-formoterol tartrate/form C.**



(a) (*R,R*)-Formoterol Tartrate/Form A



(b) (*R,R*)-Formoterol Tartrate/Form B



(c) (*R,R*)-Formoterol Tartrate/Form C

Figure 5. **DSC of (a) (*R,R*)-formoterol tartrate/form A, (b) (*R,R*)-formoterol tartrate/form B, (c) (*R,R*)-formoterol tartrate/form C.**

ing two shoulders, and the absorbances at 3115 cm^{-1} and in the 1400−1800 cm^{-1} range. The DSC shows a strong, sharp endotherm transition at 192 °C with a heat of fusion of 116.04 J/g, and the X-ray powder diffraction pattern contains a unique pattern as shown by the peak at 4.9° 2θ and the peaks in the range of 11−26° 2θ (tick marks). These data clearly determine that the morphology of the solid isolated by crystallization of the crude product was unique. Additionally, forms A and B are enantiotropic.

Polymorph-Controlled Purification and Crystallization Processes. Having established that (*R,R*)-FmTA could be isolated in at least three unique crystal forms, and that an impurity removal and crystal form conversion occurred concomitantly, a process was developed to exploit these phenomena to create a polymorph-controlled purification and crystallization process. Since the purity of the crude product was increased upon conversion of form B to form C and the final product could be isolated in a unique crystal form irrespective of the crystal form of the crude product, a scalable and practical process for this methodology was developed. The optimized process used a controlled manipulation of the polymorphs of (*R,R*)-FmTA as the method for providing the product with <0.2% of any single impurity and in the most thermodynamically stable crystal form A.

Solubility Studies. To properly optimize the process, a study was initiated to determine the solubility of each crystal form in appropriate solvents. Our initial investigations began with a dissolution study of each polymorph. A 17 wt % slurry of the respective solid in 50% aqueous isopropyl alcohol was stirred with warming, and the temperature of dissolution was recorded. The experiment showed that both crystal forms B and C dissolved between 49 and 52 °C and form A dissolved between 65 and 70 °C. The lower solubility of form A in aqueous IPA indicated a controlled process could be developed which would allow for formation of crystal form A while remaining under conditions of high solubility for forms B and C. These initial observations prompted an in-depth analysis of the solubility of crystal form A.

Figures 7 and 8 show the solubilities of (*R,R*)-FmTA/form A as a function of the water content in IPA and as a function of temperature in 25% aqueous IPA, respectively. As expected, from the data in Figure 7, the solubility of (*R,R*)-FmTA increased as the percentage of water increased in the solvent. In IPA only, the solid was nearly insoluble, and in water only, the solid dissolved at a concentration of 1.3 wt % and 2.5 wt % at 0 and 25 °C, respectively. In 25% aqueous IPA (Figure 8), the solubility of the solid as a function of temperature was nonlinear with marginal solubility at 0 °C and a solubility of 3.5 wt % at 60 °C. For comparison, from the initial dissolution studies, form A had a solubility of 17 wt % at 65−70 °C in 50% aqueous IPA (vide supra).

Control of Formation of Impurity 7. A side reaction associated with the dissolution of (*R,R*)-FmTA in aqueous medium was hydrolysis of the formamide group to give aniline **7**, the major impurity in **1**. The rate of hydrolysis increased with temperature and water content in the solvent. As discussed previously, during the warming step for the conversion of crystal form B to form C, the levels of the major impurities decreased in the isolated solid, but the overall the level of **7** (mother liquor) increased. In addition, the level **7** in the final product increased during the final crystallization (Table 1). To control formation of **7**, the hydrolysis of (*R,R*)-FmTA was investigated.

The behavior of the hydrolysis of (*R,R*)-FmTA in water, 25% aqueous IPA, and 50% aqueous IPA was studied. The rates of hydrolysis in water were 0.26% h^{-1} at 60 °C and 0.43% h^{-1} at 70 °C, and in 25% aqueous IPA, the rates decreased to 0.04% h^{-1} at 60 °C, 0.28% h^{-1} at 70 °C, and 1.34% h^{-1} at 80 °C. All rates were linear with respect to concentration. In 50% aqueous IPA at 55 °C, the dissolution temperature of form B at 17 wt % concentration, the rate of hydrolysis was 0.26% h^{-1}. These data show that the rates of dissolution and hydrolysis were proportional to temperature and water content, as expected. A successful crystallization process, therefore, would require conditions that would allow

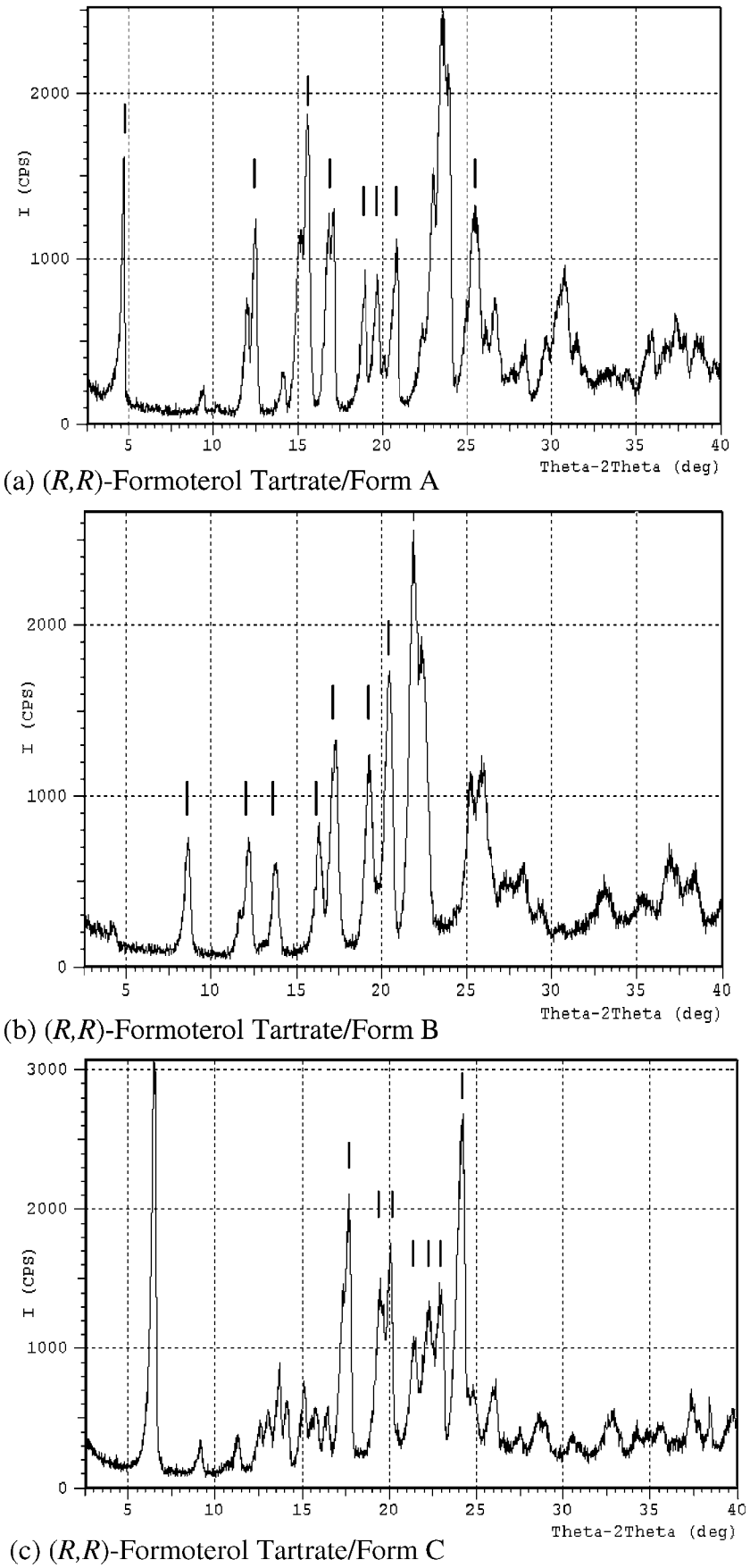


Figure 6. **XRPD of (a) (*R*,*R*)-formoterol tartrate/form A, (b) (*R*,*R*)-formoterol tartrate/form B, (c) (*R*,*R*)-formoterol tartrate/form C.**

for rapid dissolution and minimal hydrolysis at the lowest temperature and lowest water content possible, and provide a product of extremely high chemical and isomeric purity. The process became convoluted because higher water

Table 3. **Impurity Removal from Crude (*R,R*)-FmTA/form B at 45 °C in 70:30w/w IPA/Water[a]**

entry	toluene (wt %)	temp (°C)	time (h)	(*R,R*)-FmTA[b] (A%)	**7**[b] (A%)	**8**[b] (A%)
1	1	44.3	20	99.24	0.04	0.73
2	5	44.3	21	99.21	0.05	0.73
3	9	44.1	22	99.21	0.06	0.72
4	13	45.1	24	99.82	0.04	0.10
5	15	45.2	26	99.77	0.00	0.14

[a] (*R,R*)-FmTA concentration: 17 wt %, initially crystal form B. [b] Determined by HPLC.

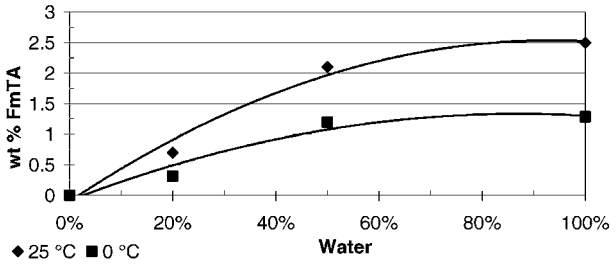


Figure 7. **Solubility of (*R,R*)-FmTA/form A in water/IPA mixtures.**

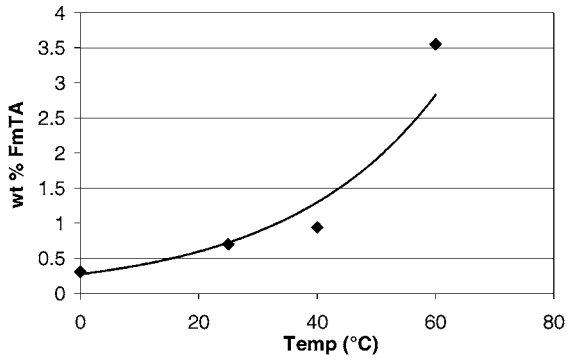


Figure 8. **Solubility of (*R,R*)-FmTA/form A in 25% aqueous IPA.**

concentrations allowed for a lower temperature of dissolution but caused a faster rate of hydrolysis, and lower water concentrations allowed for a slower rate of hydrolysis but required a higher temperature for dissolution. A solution to this dichotomy rested in exploiting the differential solubility of the three forms.

A Polymorph-Controlled Crystallization Process. From the data above, crystal forms B and C dissolved in aqueous IPA at a lower temperature than form A, form C can be generated in higher purity than form B, and form A is the most stable of the three crystal forms. Taking these factors into consideration, the following optimized crystallization process was developed (Figure 9): (1) formation of a slurry of crude (*R,R*)-FmTA/form B by addition of an aqueous solution of L-tartaric acid to a solution of the free-base, (2) in-situ conversion of form B to the highly pure form C, (3) isolation of (*R,R*)-FmTA/form C, (4) dissolution of form C in 50% aqueous IPA (50−55 °C) followed by immediate seeding of the solution with form A crystals (insoluble at 55 °C in 50% aqueous IPA), (5) addition of IPA to decrease the water content to 25% and effect a rapid cooling of the mixture to 40−45 °C, and (6) cooling and isolation of

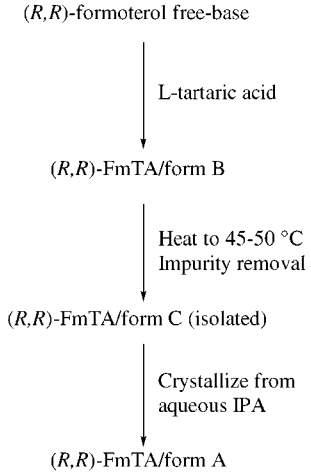


Figure 9. **Optimized process for the polymorph interconversion/impurity removal of (*R,R*)-FmTA.**

(*R,R*)-FmTA/form A. Implementation of this process reproducibly provided (*R,R*)-FmTA/form C with the level of any single impurity <0.1%. Although the level of **7** increased (hydrolysis) during the final crystallization to form A, the process was properly developed to account for the increase and provide **1** with <0.2% of **7** and <0.1% of **8**.

Conclusions

The data shown here demonstrate a novel polymorph/intermediate-controlled purification method for (*R,R*)-FmTA. (*R,R*)-FmTA exists in at least two distinct crystal forms A, and B can be reproducibly manipulated to generate a highly pure crystalline hydrated intermediate, form C. Each crystal form has a unique impurity profile and solubility characteristic that allows for the development of a controlled purification/crystallization process based on their properties. The levels of **7** and **8** were decreased to <0.1% and **9** and **10** were removed upon conversion from crystal form B to form C. Form C (and B) had a greater solubility in aqueous IPA relative to form A, permitting a lower temperature for dissolution of the crude product to control the formation of **7** during the crystallization. The difference in solubilities also provided the ability to isolate the final product in the more stable crystal form A. This process has been performed successfully on numerous batches on pilot-plant scale.

Experimental Section

General. HPLC data were collected on a Waters Alliance HPLC System. The mobile phase consisted of 0.05 M NaH_2PO_4, 0.01 M hexane sulfonic acid, pH 3.0 in a 70/30 mixture with acetonitrile. The data were collected using a flow rate of 1.0 mL/min with 220 nm UV detection on an Agilent SB-CN 5-μm column. DSC data were collected on a Perkin-Elmer DSC7 in a sealed pan at 10 °C/min with a nitrogen flow rate of 30 mL/min. FT-IR data were collected on a Nicolet DX-80 using 16 scans at a resolution of 2 cm^{-1}. The samples were prepared as a 2% ground mixture with KBr, not pulled under vacuum. X-ray powder diffraction analyses were carried out on a Shimadzu XRD-6000 X-ray powder defractometer using Cu Kα radiation (1.5406 Å). The instrument was equipped with a fine-focus X-ray tube.

The tube power was set at 40 kV, 40 mA. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A $\theta-2\theta$ continuous scan at 3°/min (0.4 s/0.02° step) from 4° 2θ to 40° 2θ was used. Samples were prepared for analysis by pressing it with a spatula onto a glass or quartz sample holder.

A detailed experimental procedure for the in situ polymorph conversion/purification and crystallization processes is as follows: To 460 g of a solution of the crude (*R*,*R*)-formoterol free-base in a 3.63:1 (w/w) solution of IPA/toluene (approximately 164 g of (*R*,*R*)-formoterol free-base/L of solution) was added a solution of 40.8 g of L-tartaric acid in 237 g of water. The solution was stirred for 2 h, during which a slurry formed ((*R*,*R*)-FmTA/form B). The mixture was warmed to 45−50 °C until the level of **8** was below 0.15 A% in the solid (2−3 h). Concomitant thickening of the slurry occurred (conversion from crystal form B to crystal form C). The mixture was cooled to 22 °C, and the solid was isolated by filtration and dried to give 109 g of crude product (77% yield).

To the crude product was added 214 g of IPA and 272 g of water. The resultant slurry was warmed until dissolution occurred (50−55 °C). The solution was seeded with 1.1 g of crystals of (*R*,*R*)-FmTA/form A (1%), followed by 545 g of IPA to give a 25% (v/v) aqueous IPA solvent mixture. The solution immediately cooled to 40−45 °C. The solution was stirred for 30 min at 40−45 °C, cooled to 0 °C, and stirred for 2 h. The slurry was filtered to give 93 g (85% yield) of **1** as a white solid.

Acknowledgment

We thank Denise Boas for her assistance in aquiring data.

Received for review March 14, 2002.

OP025531H