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Purification of Dirithromycin. Impurity Reduction and Polymorph Manipulation

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Abstract:

The manufacture of dirithromycin [9*S*(*R*)-9-deoxo-11-deoxy-9,11-[imino[2-(2-methoxyethoxy)ethylidene]oxy]-erythromycin] from commercially available erythromycin A results in a drug substance containing impurities at the level of several percent. A five-step plan for the development of a commercial-scale recrystallization procedure is presented. A purification system for dirithromycin which utilizes the crystalline acetone solvate and exemplifies this plan is described. Physical characterization data for this solvate are included. The solubility of the acetone solvate in water−acetone mixtures is at a maximum at a ratio of 1:9 v/v and exhibits a parabolic relationship with temperature such that, in a solvent composition of 2:1, its solubility is at a minimum at 40 °C. The adduct of erythromycylamine and acetone was found to exist in solution as an equilibrium between the tetrahydro-1,3-oxazine and imine forms.

Introduction

Dirithromycin is one of a new generation of macrolide antibiotics which are derived from erythromycin A. Although its antibiotic activity is similar to that of erythromycin, it offers the advantage of enhanced tissue levels.[1] Dirithromycin is prepared by condensation of erythromycylamine with 2-(2-methoxyethoxy)acetaldehyde[2] or, more conveniently, with its diethyl acetal.[3] The structure of dirithromycin in the solid[4] and solution states[5] has been reported (Figure 1).

Erythromycylamine is derived from the fermentation product erythromycin A *via* its oxime[6] or hydrazone.[7] Erythromycin A is typically not highly pure in its commercial form. The 1995 USP specification for potency is greater than or equal to 85%. Thus, when dirithromycin is produced from commercially available erythromycylamine by processes referenced above, it contains numerous impurities, the sum of which comprises several percent. In addition, since fermentation and chemical batch processes do not produce uniform results, individual batches (lots) of erythromycylamine vary in the total amount of impurities they contain, and even vary somewhat with respect to the identity of some impurities. It was a goal of the present study to develop a purification system for dirithromycin which was tolerant of a wide range of impurity levels. Samples of unpurified dirithromycin (dirithromycin technical) with impurity amounts between 3 and 13% were available and were utilized in this study. Since it is desirable to maximize the purity of bulk drug substances, the major goal of the work described herein was the development of a commercial purification method for dirithromycin which operates in high recovery, uses nontoxic solvents, provides the most stable crystal form of the bulk drug, and minimizes impurities. Ultimately a two-step process was developed to meet these objectives. The first step involves the formation of a crystalline solvate, dirithromycin acetonate, for purification purposes. The second step involves heating a slurry of the acetonate in water to convert the solvate to the stable nonsolvated polymorphic form.

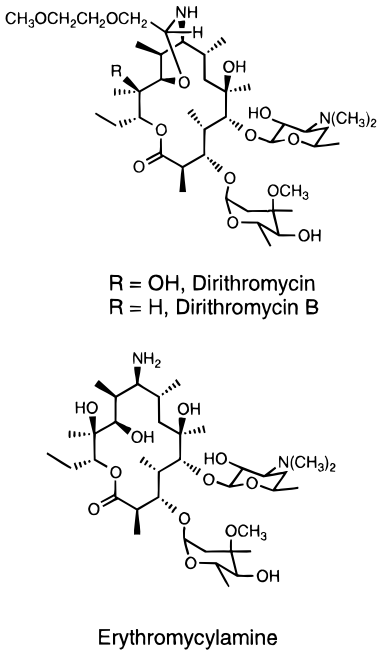

Figure 1. **Structures of dirithromycin, dirithromycin B, and erythromycylamine.**

Results and Discussion

Due to the need for highly pure drugs, the commercial-scale recrystallization of bulk drug substances is routine in the pharmaceutical industry. For this and other projects which require the development of a reliable commercial recrystallization process, the authors have used a five-step approach. These steps are outlined here and exemplified by the details given for the recrystallization of dirithromycin: (1) selection of a solvent system (the quality of the drug substance is the main factor to the considered in this stage); (2) characterization of polymorphic forms; (3) optimization of process times, temperatures, solvent compositions, etc. (both quality and recovery are considered); (4) examination of the chemical stability of the drug during processing; (5) manipulation of the polymorphic form, if necessary.

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Table 1. **Recrystallization of Dirithromycin**

recrystn solvent	recovery (%)	total impurity reduction (%)[a]	dirithromycin B reduction (%)[a]
tert-butyl methyl ether	79	1.50	0.04
tetrachloroethene	76	−0.27	0.10
heptane−toluene	84	0.86	0.04
amyl acetate	31	1.49	0.02
methanol−water	80	0.73	−0.06
ethanol−water	63	1.44	−0.12
acetone−water	90	2.15	0.22
THF−water	83	1.90	0.30
acetonitrile	83	1.38	0.07
EtOAc−Et_3N	60	1.53	−0.27
isopropyl alcohol	63	2.06	0.22

[a] (% impurity in dirithromycin technical) − (% impurity in recrystallized sample).

1. Selection of a Solvent System. Since many of the impurities to be removed from dirithromycin are closely related compounds, a reliable and sensitive method for the determination of impurities in dirithromycin was required. The reverse-phase HPLC method developed by Olsen and co-workers has been shown to resolve all compounds reported here and to be adequately sensitive.[8] It was used throughout this work to quantify both the total impurity level and the level of an individual impurity, dirithromycin B, so named due to its origin in factor B of erythromycin fermentation systems.

The first set of experiments, a screening study, involved small-scale recrystallizations of dirithromycin from several possible solvent systems. The solvents and data are reported in Table 1. In this screening phase, a wide range of solvents were used without regard for practicality to identify solvents and solvent characteristics which could maximize the rejection of impurities. For hydrophobic solvents, these experiments simply involved dissolving dirithromycin technical in warm solvent, cooling the solution, and filtering the product. For hydrophilic solvents, dirithromycin technical was dissolved in the warm organic component and some water was added prior to cooling. Three different starting lots of dirithromycin technical, with total impurities ranging from 3.60% to 4.40%, were used. Therefore, the results are given as the difference in the impurity level before and after the recrystallization. For example, for recrystallization from isopropyl alcohol, the level of total impurities fell from 4.40% to 2.34% upon recrystallization while the amount of dirithromycin B fell from 0.69% to 0.47%. All solvents except tetrachloroethene were able to reduce total impurities. However, some, notably the wet alcohol systems, resulted in an increase in dirithromycin B. The most promising solvent systems were aqueous acetone, aqueous tetrahydrofuran (THF), and isopropyl alcohol. THF was eliminated due to its toxicity. The use of isopropyl alcohol was promising but appeared to limit the recovery of the drug and was more difficult to remove by drying. On the basis of recovery, purification ability, toxicity, and ease of drying, the aqueous acetone system was chosen for further optimization.

2. Characterization of Polymorphic Forms. The Acetone Solvate of Dirithromycin. It was immediately clear that dirithromycin obtained from aqueous acetone recrystallization was a 1:1 solvate with acetone; it had a unique XRPD pattern, and the solution NMR showed 1 equiv of acetone relative to the drug. This solvate of dirithromycin has been reported to be isomorphous with several other solvates that have essentially identical molecular packing in the crystal lattice, including the 2-propanolate.[9] Since the acetonate provided good purification, but was not desirable for use as the final dosage form, a method was developed for generating a pharmaceutically acceptable form (as described later). The initial attempts at generating an anhydrate by gentle drying in a vacuum oven resulted in a product which was a mixture of polymorphic forms. X-ray powder diffraction readily distinguished the acetone solvate from the two anhydrous polymorphic forms (see Figure 2). Polymorphic form 1 is not readily isolated in pure form, as it usually contains detectable levels of the more stable polymorphic form 2 (identified by the asterisks).

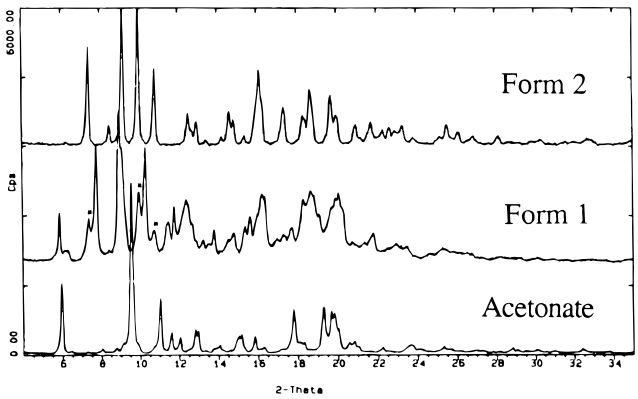

Figure 2. **X-ray powder diffraction patterns of crystal forms isolated from the dirithromycin purification process. Asterisks (*) indicate peaks associated with detectable levels of form 2 being present in the metastable crystal form 1.**

Differential thermal analysis (DTA) of form 1 shows an exothermic solid−solid transition with an onset temperature of 120 °C. This data, combined with the heat of transition rule, indicates that the two polymorphs are related monotropically, with polymorphic form 2 being the thermodynamically more stable form (or else the transition temperature is greater than 120 °C, above which form 1 is more stable).[10] Figure 3 provides a comparison of the DTA data for the polymorphs. Application of the heat of transition rule is based on an assumption that the molecular conformation is the same in the compared polymorphic forms. Based on the determination of the X-ray crystallographic structures of polymorphic form 2 and seven different solvates of dirithromycin, this assumption is most likely valid.[11]

Structural information on several polymorphic forms of dirithromycin, including form 1 and the acetonate, was obtained from solid-state ^{13}C NMR and FTIR analysis and is reported in ref 9. These results indicate that form 1 has two local environments of the lactone carbonyl (two independent molecules in the crystallographic asymmetric unit), one hydrogen bonded and one not. The acetonate has a

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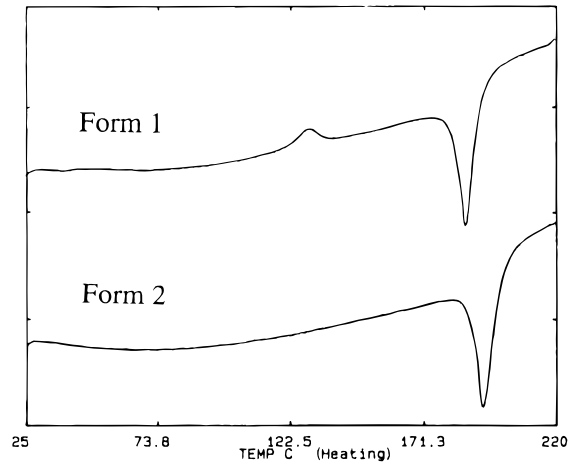

Figure 3. **Differential thermal analysis of polymorphic form 1 (top) and form 2 (bottom). The exothermic transition of form 1 occurs with an onset temperature of 120 °C, whereas the melt of form 2 occurs with an onset temperature of 189 °C.**

single molecular conformer present in its asymmetric unit, and its lactone carbonyl is essentially free of hydrogen bonding.

Thermogravimetric analysis indicates that the acetone is readily lost from the acetone solvate, beginning at room temperature and ending at approximately 120 °C. The total weight loss is dependent upon the drying conditions, but is typically around 6%. A 1:1 solvate of dirithromycin and acetone contains 6.5% acetone by weight.

For additional information on these methods and other means of characterization of polymorphs, please refer to a recent review by Threlfall and references contained therein.[12]

3. Optimization. The Aqueous Acetone Recrystallization. In conjunction with the characterization of the acetone solvate, the optimization of a procedure for recrystallization of dirithromycin from aqueous acetone required the determination of the solubility of the solvate as a function of the water:acetone ratio and temperature. To determine the solubility of dirithromycin as a function of the solvent composition, dirithromycin (form 2) was added to a series of solutions which ranged from 0% to 100% water in acetone (v/v). After equilibration at either 25 or 45 °C, samples were filtered and the concentration in the filtrate was measured by HPLC. The average results from two determinations at each temperature are shown in Figure 4. They indicate that, at both temperatures, the solubility of dirithromycin is at a maximum at a 1:9 water:acetone ratio. Several of the solids from this experiment were dried and analyzed for acetone content by solution-phase NMR; only those from 100% water were form 2; all others contained acetone. Thus, even at water:acetone ratios as high as 4:1, the acetonate is the more stable crystal form in the slurry. At water levels above 60%, the solubility was less than 3 mg/mL, the low end of accurate quantitation in this experiment; therefore no meaningful comparison of the relative solubilities was possible in this range of the plot. All concentrations were measured by the same HPLC method used to quantify the impurities.[8]

To determine the relationship between temperature and solubility of the dirithromycin acetonate at a given solvent composition, a second set of experiments was performed.

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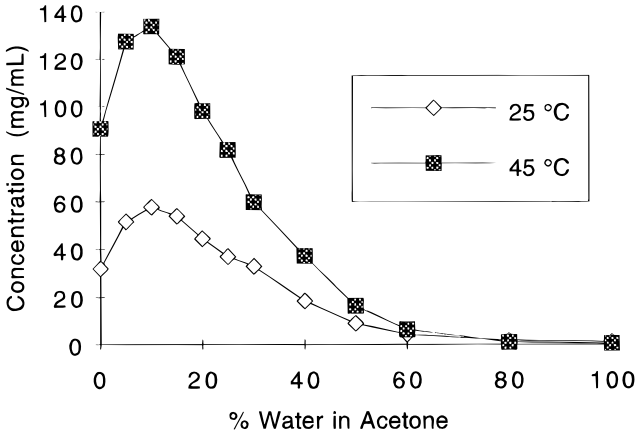

Figure 4. **Solubility of dirithromycin in aqueous acetone.**

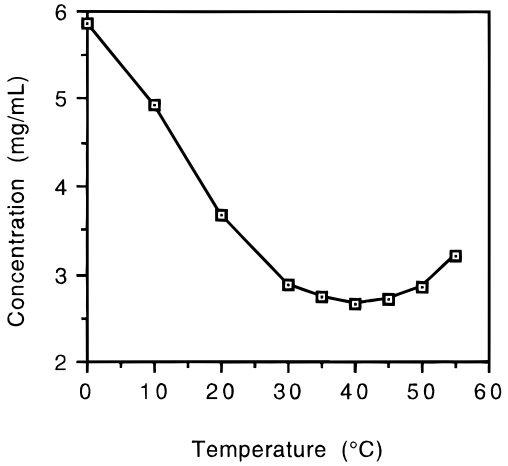

Figure 5. **Solubility of dirithromycin acetone solvate in 2:1 v/v water−acetone.**

Figure 5 shows the results when the solvent ratio was 2:1 water:acetone, v/v, the solvent ratio from which the acetonate is filtered in the optimized procedure. A striking parabolic relationship between solubility and temperature was observed, with a shallow minimum occurring at about 40 °C. This phenomenon was reproducible, and care was taken to avoid vaporization of acetone during the experiments so as to insure a constant solvent composition. The shape and general magnitude of this solubility curve were the same whether actual mother liquors were evaluated during a recrystallization experiment or isolated form 2 dirithromycin was added to aqueous acetone. Although unusual, this behavior is not unprecedented; erythromycin A shows a similar solubility profile.[13] The origin of this unusual solubility behavior is unknown. The residual solid isolated at all temperatures during the solubility study was determined to be the acetonate; therefore, this behavior is not attributed to a change in crystal form. It was also shown that epimerization of dirithromycin in solution was not the cause of this behavior since no significant level of epi-dirithromycin was observed by HPLC in the solution or solid phases.[14] This warrants further investigation.

With the knowledge of the characteristics of the acetone solvate and its solubility, a simple recrystallization procedure

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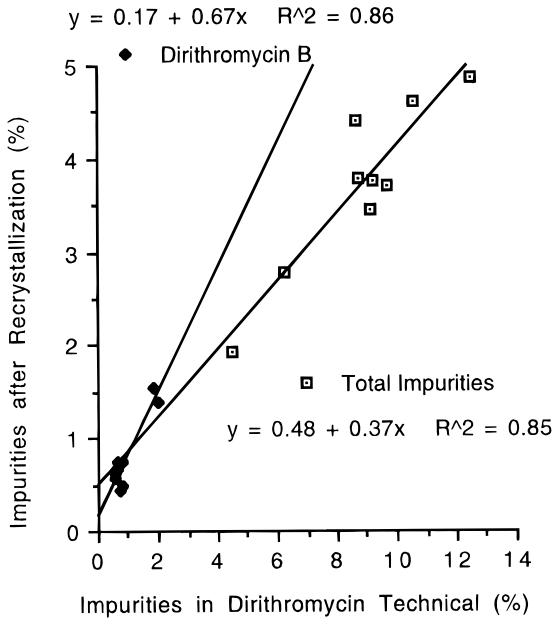

Figure 6. **Impurity reduction by recrystallization of dirithromycin.**

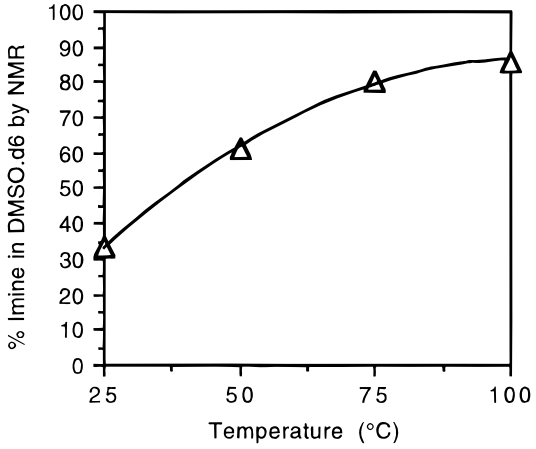

Figure 7. **Imine−tetrahydro-1,3-oxazine equilibrium of erythromycylamine/acetone adduct.**

was designed. It involves dissolution of 1 g of dirithromycin technical in 4.5 mL of 1:9 water:acetone at 55 °C, filtration to remove insoluble impurities, distillation of 1.5 mL of the acetone/water azeotrope, and the addition of 5 mL of water to the warm solution to achieve a water:acetone ratio of about 2:1. This solvent composition was chosen as a compromise between recovery and quality; that is, more water would have given a higher percent recovery but less product per lot in large equipment and would have degraded the ability of the recrystallization to reject impurities. Since the solubility in the mother liquor was at a minimum at 40 °C, the slurry was simply cooled to this temperature and filtered. This procedure produced the acetonate with a recovery of about 90%. This recrystallization to produce the acetonate was designed to increase the purity of dirithromycin; the final manipulation of the crystal form was designed to produce the desired polymorph, not increase the purity. To test the ability of the recrystallization to remove impurities from dirithromycin technical with a wide range of purity, a series of recrystallizations were performed in which the total impurity content in the technical material ranged from 4% to 13% and the range of dirithromycin B was 0.4−1.6%. A typical level of total impurities expected for commercial-scale material was 4.6%; examination of higher levels was performed to insure robustness of the procedure. Figure 6 shows the results, plotted as the total level of impurities in dirithromycin technical versus the level in the recrystallized sample on the *y* axis. The slope of 0.37 indicates that about two-thirds of the total impurities are rejected by this procedure. The figure also shows the same type of data for the levels of the single impurity, dirithromycin B; about one-third of it is rejected by this recrystallization process. This level of purification was deemed sufficient since, with dirithromycin technical containing about 5% total impurities, the amount of impurities after recrystallization would be about 2%, a reasonable level for a semisynthetic antibiotic. As indicated by the regression data shown in Figure 6, the errors associated with this correlation of impurity levels will be somewhat large due to the variability of the raw materials and the difficulty in exactly reproducing crystallization events. Nonetheless, this analysis is an important first step in the establishment of specifications.

4. Examination of Chemical Stability. Although this recrystallization procedure was effective at impurity removal, it did increase levels of erythromycylamine in the drug substance (from about 0.2% in dirithromycin technical). For example, stirring the acetone solvate at 50 °C in water produced about 2% erythromycylamine within 2 h, but continued heating did not change this level. Simple hydrolysis of dirithromycin during the warm aqueous recrystallization was the likely origin of the erythromycylamine; however, examination of the acetone solvate indicated that no increase in erythromycylamine had occurred at this point. In addition, purified dirithromycin did not produce erythromycylamine upon heating at 50 °C in water. These apparent discrepancies were explained by the discovery of an adduct of erythromycylamine and acetone which was eluted too late on the HPLC system in use for detection. With modification of the chromatography by a slight increase in the organic content, these details were clarified. In 1:9 water−acetone at 55 °C, dirithromycin was converted to this adduct in a yield of about 3% after 24 h. Most of this adduct cocrystallized with the dirithromycin acetonate and was quantitatively converted to erythromycylamine within 2 h during the water slurry at 50 °C, the process for crystal form modification, as described below.

To further confirm this hypothesis, a pure sample of the erythromycylamine/acetone adduct was prepared by refluxing erythromycylamine in acetone for an extended time. Although it has not been crystallized, the isolated material does have the correct elemental analysis and high-resolution mass spectrum for $C_{40}H_{74}N_2O_{12}$, erythromycylamine plus acetone less water. This material displayed a single peak by HPLC, but its NMR spectra indicate it to be an equilibrium mixture of two forms. On the basis of both ^{13}C and ^{1}H NMR, the minor component at ambient temperature in DMSO-d_6 is assigned the imine structure mainly on the basis of its carbon frequency of 166.4 ppm. As shown in Figure 7, this isomer predominates above temperatures of about 45 °C. The low-temperature ^{1}H NMR spectrum was regenerated by cooling the sample back to ambient temperature, indicating a true equilibrium. Both isomers were present in solutions in

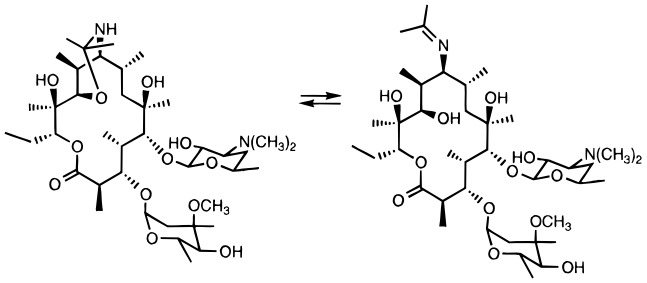

Figure 8. **Erythromycylamine/acetone adduct.**

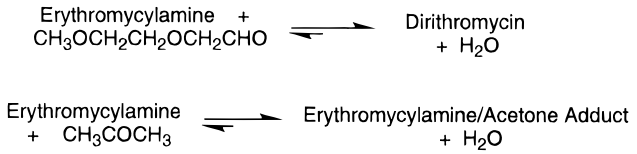

Figure 9. **Equilibrium of erythromycylamine with carbonyl compounds.**

acetone, acetonitrile, and chloroform, in slightly varying ratios. Figure 8 shows the aminal (tetrahydro-1,3-oxazine) and imine forms of the erythromycylamine/acetone adduct that are observed in DMSO-d_6.

The above results with acetone and the high apparent stability of dirithromycin with respect to hydrolysis are best explained by a set of equilibria, as shown in Figure 9. In the absence of another carbonyl compound, only a small amount of dirithromycin (about 0.2%) will hydrolyze during processing. In the presence of excess acetone, however, erythromycylamine will combine with acetone to form the adduct (which is itself an equilibrium mixture of forms).

Two simple and effective methods to minimize the amount of "hydrolysis" of dirithromycin during its recrystallization from aqueous acetone were devised. In the first method, the length of exposure to warm aqueous acetone was minimized. An alternate method is to utilize anhydrous acetone for initial dissolution and filtration and to add water only after removal of most of the acetone by distillation. This latter approach is detailed in the Experimental Section. The recovery and purification capacity of the recrystallization is not compromised by either modification, and levels of erythromycylamine in the final dirithromycin of less than about 0.5% are obtained. This level was deemed acceptable.

5. Manipulation of Polymorphic Form. Because dirithromycin forms solvates with nearly all of the pharmaceutically acceptable solvents, it was nearly impossible to find a method of directly producing the thermodynamically more stable polymorphic form from solution. For this reason, a second step (manipulation) was required with the primary objective of providing the pharmaceutically desirable crystalline modification, polymorphic form 2.

In 2:1 or 4:1 v/v water−acetone, the acetonate is the stable crystal form of dirithromycin. However, it was discovered that if the acetonate was slurried in pure water at 50−70 °C, it rapidly converted to a metastable polymorphic form 1, which subsequently converted to the more stable polymorphic form 2.

In practice, it was not necessary to dry the residual water and acetone from the acetonate prior to the final manipulation. A water rinse of the wet cake was used to remove the excess acetone. This gave a water-wet sample of the acetone solvate which could be slurried in warm water to effect the conversion. Since the acetonate is about 6% acetone by weight and 8.5 mL water is used per gram for the reslurry, the concentration of acetone in the mother liquor after desolvation is less than 1%. At this low acetone activity, polymorphic form 2 is more stable than the acetonate.

To determine the water:acetone ratio at which the two forms are of nearly equal stability, a separate set of experiments was performed. Equal amounts of the solid acetonate and form 2 were combined and added to mixtures of aqueous acetone which ranged from 70% to 100% water, all based on volumes. After rapid agitation of the slurry at 50 °C for 3 h, the solid phase was collected and analyzed by XRPD. For mixtures with 85% or less water, the isolated solid was only the acetonate. When the water content was 90% or greater, the solids were only form 2 by XRPD. When the water content was 87.5%, a mixture of acetonate and form 2 was obtained. Although the precise thermodynamics of this transformation were not defined, this study did provide the needed confirmation that consistent results should be obtained from the optimized process. Namely, the acetonate will always be obtained from 2:1 water−acetone mixtures and form 2 will always be obtained from 99:1 mixtures, since both solvent compositions are far removed from the area of 85−90% water where the forms are isoenergetic. This assumes, of course, that sufficient time and thermal energy for the conversions are provided.

The overall time required for the solution-mediated conversion was dependent upon many common factors such as temperature, stirring rate, and particle size. For example, complete conversion of the acetonate to polymorphic form 2 occurs in less than 17 min at 70 °C, whereas at 40 °C, complete conversion requires approximately 150 min. Due to the potential variability of conversion rate in the final process, an X-ray powder diffraction method is used to determine that the desired form is ultimately produced. The X-ray method detects the less stable polymorphic forms at levels as low as 1% by weight.

Conclusions

In conclusion, an efficient and effective purification process for the reduction of impurities in dirithromycin *via* its acetone solvate has been described. This solvate exhibits an unusual solubility *versus* temperature profile, which is similar to that observed for erythromycin A. By heating this solvate in water, conversion to the more stable anhydrous polymorphic form, designated form 2, occurs. The condensation product of acetone and erythromycylamine can be formed under processing conditions if hydrolysis of dirithromycin occurs; this adduct was found to exist in solution in both its tetrahydro-1,3-oxazine and imine forms.

Experimental Section

X-ray diffraction patterns were collected on a Siemens D5000 diffractometer operated in the step−scan mode with a step size of 0.03 deg·step^{-1} and a count time of 5 s. The diffractometer is equipped with a Cu Kα radiation source, a Kevex silicon drifted lithium solid-state detector, 0.6 mm tube slit, 1.0 mm antiscatter slit, and a 0.1 mm detector slit.

Thermal gravimetric and differential thermal analysis was performed using a Sieko TG/DTA 220 instrument. The

sample (2.697 mg) was placed in a 5 mm aluminum sample pan and heated at a rate of 10 °C/min over a range of 25−220 °C.

Solution NMR spectra were recorded on a Bruker AC300 spectrometer in DMSO-d_6 or $CDCl_3$.

Recrystallization of Dirithromycin. Anhydrous acetone (100 mL) was added to a 250 mL round-bottomed flask fitted with a mechanical agitator and a thermometer. Dirithromycin technical (20.0 g) was added and rinsed into the flask with 60 mL of acetone. The slurry was heated to 55 °C to achieve dissolution and filtered to remove insoluble impurities. The filtrate was added back to the 250 mL flask. A distillation head and condenser were added, and approximately 110 mL of solvent was removed by distillation. Water (100 mL) was added over a 1 h period while the reaction contents were maintained at 55−60 °C. The slurry was cooled to 40 °C, stirred for $^1/_2$ h, and filtered. The cake was rinsed with a solution of acetone and water (1:2) and then with 30 mL of water. The wet cake was added back to the 250 mL flask with 170 mL of water. The slurry was heated at 50 °C for 3 h; the product was collected by filtration at 50 °C, washed with 30 mL of warm water, and dried *in vacuo* at 35−40 °C overnight. The results are given in Table 2.

Erythromycylamine/Acetone Adduct. Erythromycylamine (5.0 g) and 100 mL of acetone were combined, and the solution was refluxed for 1 day to give the amine and the adduct in a 4:96 ratio. Acetone (250 mL) was distilled off and added simultaneously to dry the solution and force the equilibrium to 2.5:97.5. The acetone was removed *in vacuo* to give a foam which contained a small amount of residual acetone by NMR and was about 95% pure by HPLC[8] (the approximate purity of the starting erythromycylamine). HRMS: 774.532, $C_{40}H_{74}N_2O_{12}$ requires 774.525. IR ($CHCl_3$): 3510 (br), 2978, 2940, 1728, 1673, 1457, 1376, 1220, 1053 cm^{-1}. ^1H and ^{13}C NMR in $CDCl_3$, CD_3CN, DMSO-d_6, and acetone-d_6 showed the imine−tetrahydro-1,3-oxazine mixture; full assignments to each were not made. The C1′ protons were used for the variable temperature studies. They were assigned as the doublets at δ 4.57 (imine; DMSO-d_6) and 4.45 (tetrahydro-1,3-oxazine) on the basis of the literature values and $^1H-^{13}C$ correlation spectroscopy.

Table 2. **Recrystallization results**

	potency (%)	total impurities	dirithromycin B (%)	recovery (%)
before	96.4	3.51	0.37	
after	97.9	2.43	0.30	87.4

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