DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(5), 665-690 (1986)



# CHARACTERIZATION OF COMMERCIAL LOTS OF ERYTHROMYCIN BASE

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## ABSTRACT

The physical properties of five commercial lots of erythromycin base were evaluated with the object of characterizing the bulk chemical. The materials were investigated by thermal analyses, IR spectroscopy, X-ray powder diffractions, equilibrium solubility in distilled water, and dissolution rates in phosphate buffer pH 7.5. Among the lots examined, three were found to be polymorphic variants of crystalline dihydrate, one a crystalline anhydrate and the other an amorphous solid. The different crystalline dihydrates displayed considerable variation in thermal properties but showed similar equilibrium solubilities in distilled water. At a given temperature, crystalline anhydrate has a higher aqueous solubility compared to the dihydrates. All crystalline forms of erythromycin showed rapid **in vitro** drug release from loosely-filled capsules. In contrast, the amorphous form exhibited a high equilibrium solubility but slower dissolution rate, a result attributable to its poor wettability. Contact angle measurements

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performed on powder compacts of the solid confirmed the hydrophobic nature of the amorphous form, an inference based on the high and stable contact angles formed. Under similar test conditions, low contact angles and rapid spreading of liquid film were noted for the crystalline dihydrates. The previously reported observations of lower solubility with increasing temperature was confirmed in the current studies for all forms of erythromycin base.

## INTRODUCTION

Erythromycin, a macrolide antibiotic is widely used in the treatment of respiratory and soft tissue infections (1). The free base form of the drug constitutes the active component in a number of marketed oral solid pharmaceutical products (2). The chemical structure of the compound is shown in Figure 1.

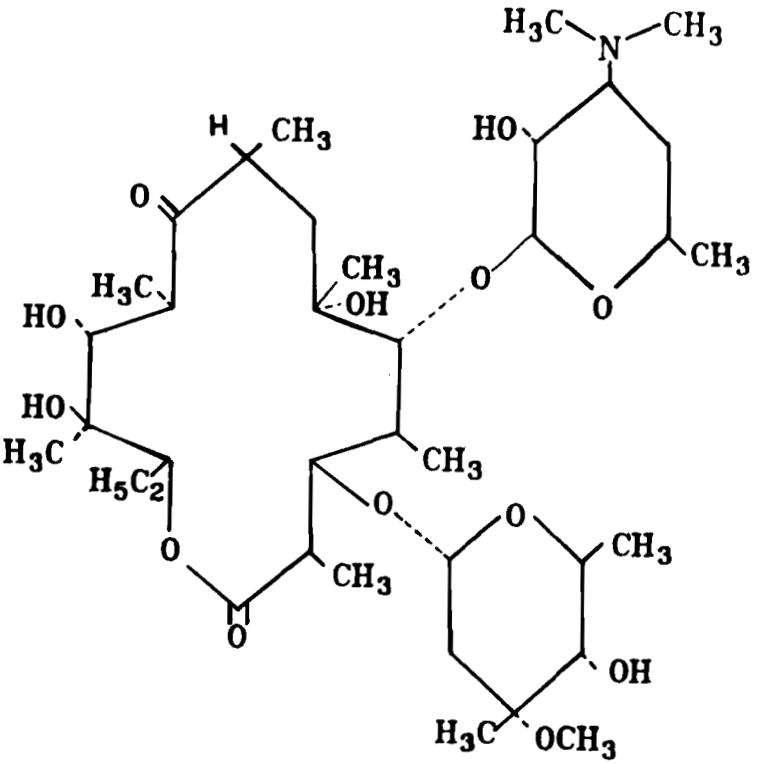


FIGURE 1

Chemical Structure of Erythromycin

A number of reports are available in the pharmaceutical and chemical literature detailing the physicochemical properties of erythromycin base (3,4,5). There is a consensus that the drug can exist in a number of polymorphic states, as a solvate, hydrate or anhydrous form, depending upon its history, method of preparation and solvents employed in the final crystallization step. Pelliza, Nebuloni and Gallo (6) studied the different crystal forms of the compound by differential thermal analysis. They characterized two crystal forms, one melting at 190° C and the other at 138° C, and an amorphous form. Allen et al. (7) described the properties of three different forms of hydrates and designated them as dihydrate, monohydrate and anhydrate. They characterized these forms through surface area measurements, thermal analyses, X-ray patterns and **in vitro** dissolution rates. They showed that significant differences exist in the dissolution properties of the different hydrates. Subsequently, Fukumori and coworkers (8) discounted the existence of the monohydrate and suggested that the monohydrate described previously was only a desolvation product of a chloroform solvate.

A review of the literature on this subject revealed that studies on the physicochemical properties of erythromycin base are largely confined to materials that are specially prepared and processed in the research laboratories. Similar information on the commercially marketed lots of bulk drug is often lacking. During manufacture of erythromycin products, significant variations in the physical properties of bulk raw material are often encountered among materials supplied by different manufacturers and among different lots supplied by the same manufacturer. The purpose of this investigation was to characterize some of the commercial lots of erythromycin base in order to obtain information that could be of value in setting specifications on the bulk chemical. The properties examined included thermoanalytical, infrared spectroscopy, X-ray powder diffraction, aqueous solubility, dissolution rate, and wettability.

## EXPERIMENTAL

### Materials

Erythromycin base bulk materials were used as received, The five lots examined were designated in this study as $A^1$, $B^2$, $C\text{-}1^3$, $C\text{-}2^4$, $C\text{-}3^5$. All other chemicals were reagent grade.

## METHODS

### Thermal Analysis

Hot stage microscopic examination was carried out using a microscope[6] at a magnification of 100X and a hot stage[7] at a heating rate of 2° C/min and 10° C/min.

Differential Scanning Calorimetric (DSC) analysis was performed using a DSC instrument[8] under nitrogen atmosphere at the indicated rates. Thermogravimetric Analysis (TGA) was performed on a thermoanalytical system[9] under a nitrogen atmosphere at a heating rate of 2.5° C/min. Preliminary experiments indicated that data obtained at this setting was more reproducible than when the instrument was run at faster rates.

### X-Ray Analysis

X-ray powder diffractograms were obtained on a diffractometer[10] at a scan speed of 1°/min.

### Infrared Spectroscopy (IR)

IR measurements were recorded on Nujol mulls using an infrared spectrophotometer[11].

### Solubility Studies

Equilibrium solubilities of different lots of the drug substance were determined in distilled water and in 0.2 M phosphate buffer pH 7.5 at an ionic strength of 0.5 adjusted with potassium chloride. Excess solid was added to the solvent in a stoppered glass container immersed in a constant temperature bath[12]. The container was shaken vigorously on a mechanical shaker[13] for 1-2 hours. These time periods were judged to be adequate for the samples to attain equilibrium based on preliminary experimentation. Longer equilibration times were shown to result in significant degradation of the drug substance (9). At the end of equilibration period, the suspension was filtered using a 0.45 μ pore size filter[14] and the filtrate was assayed.

All buffer solutions were prepared with potassium salts since they were reported to offer better stability relative to sodium salts (9).

### Dissolution Studies

The dissolution rates of erythromycin bulk powders were determined according to the procedure outlined in USP XX Method I. The basket rotation was 50 rpm and the temperature of the dissolution fluid was maintained at 37° C. Nine hundred milliliters of 0.2 M phosphate buffer pH

7.5, ionic strength 0.5 served as the dissolution medium. A No. 0 size clear hard gelatin capsule containing 250 mg of bulk powder (loose-pack) with no added excipients was used .

In order to eliminate particle size effects, all powders tested were passed through a 200 mesh sieve prior to hand filling into capsules. At 15 minute intervals up to one hour, 3 ml of filtered dissolution medium was withdrawn and assayed for the amount of drug in solution. The withdrawn volume was not replaced with fresh medium since theoretical calculations have shown that the cumulative error involved in not replacing the medium is less than 2%. Each experiment was carried out in triplicate and the results averaged.

Analysis of Drug Samples

To measure the drug concentration in solution, an assay procedure described by Ford et al. (10) was used. It is based on the principle that a stable yellow chromophore is produced when an aqueous solution of erythromycin is heated with concentrated hydrochloric or sulfuric acid. The intensity of the resulting yellow color is proportional to the amount of drug substance in solution.

Procedure

The test sample was diluted with distilled water to contain 10-100 µg/ml of erythromycin base. It was transferred to a 50 ml volumetric flask, and 30 ml of concentrated hydrochloric acid was added. The flask was stoppered, mixed thoroughly and heated on a water bath for about 30 minutes at 50° ± 2° C. The solution was cooled by placing the flask in an ice bath for about 2 minutes. It was allowed to come to room temperature and made up to volume with distilled water and mixed. The absorbance of the clear yellow solution was measured on a spectrophotometer[15] at a wavelength of 482 nm using 1-cm cuvettes. A reagent solution prepared exactly as above but omitting the drug served as the blank solution in these measurements.

A plot of the absorbance of solution versus concentration was linear in the concentration range 10-100 µg/ml.

Wettability

The wettability of different lots of erythromycin base was assessed by direct measurement of contact angle made by a saturated solution of the

drug on a powder compact using a goniometer[16]. The powder compacts were made on a hydraulic press[17] at an applied pressure of 7,500 psi using a standard 1-1/8 " plunger. The faces of plunger and base were covered with polytetrafluoroethylene (Teflon) sheets to facilitate ejection of the compact. About 2.5 g of powder was used to prepare each compact. The solid surface was wiped clean with a brush or gently blown with air to remove any particles which might affect the smoothness of suface. In order to prevent dissolution or disruption of the compact during contact angle measurements, a saturated solution of erythromycin base in distilled water or phosphate buffer pH 7.5 was used as the test liquid (11). All measurements were carried out at 25° ± 0.1° using the environmental chamber attachment of the instrument. A constant volume of liquid (0.01 ml) was used for drop formation with the aid of micro-syringe attachment. When the base assembly was tilted there was a tendency for the liquid drop to spread on the compact rather than roll over. It was therefore not possible to measure the advancing and receding angles separately. Where possible, the angles formed on both sides of the drop were noted.

In all instances, zero time represented the value measured within 20 seconds after the deposition of the liquid. The drops were placed on different locations in the compact for each new measurement. The reported contact angles are the averages of 12 separate determinations (six for each compact).

## RESULTS AND DISCUSSION

TGA curves of the different lots of erythromycin base studied are shown in Figures 2 and 3.

For samples from Lots A, B, and C-1, weight changes occurred over a narrow temperature range 40-80° C, suggesting that moisture was present in these materials in bound form within the crystal lattice. The weight loss of approximately 4.6%, is nearly equal to stoichiometric value of 4.5% calculated for a dihydrate. On the other hand, Lots C-2 and C-3 displayed weight loss over a wider temperature range (30-125° C), suggesting the presence of loosely bound surface moisture in the solid. The weight loss was 1% for Lot C-2 and 1.9% for Lot C-3.

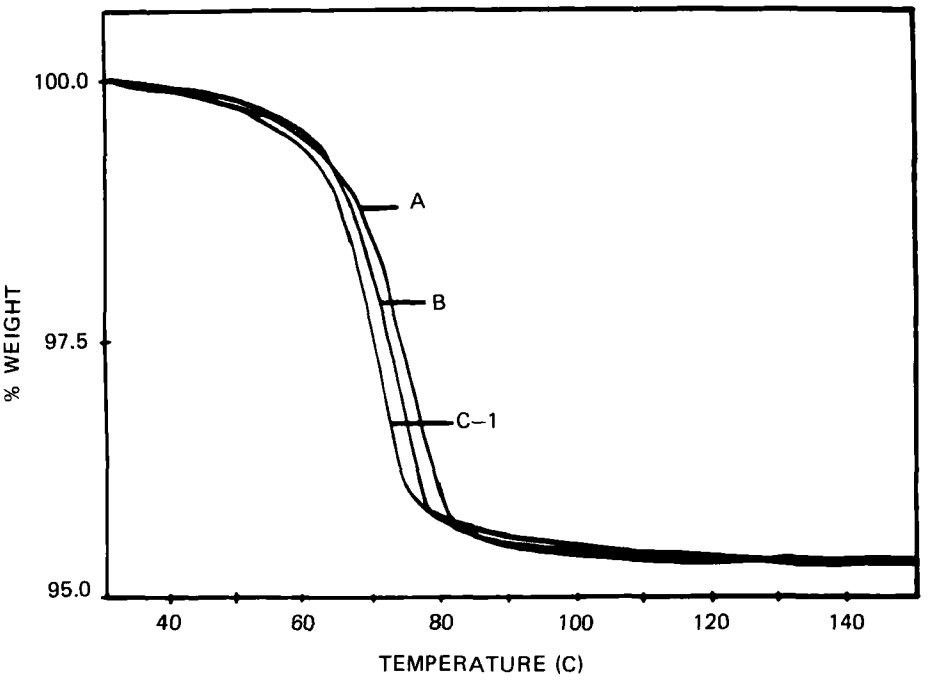


FIGURE 2
TGA Thermal Curves of Erythromycin Base, Lots A, B, and C-1 at a Heating Rate of 2.5° C/min.

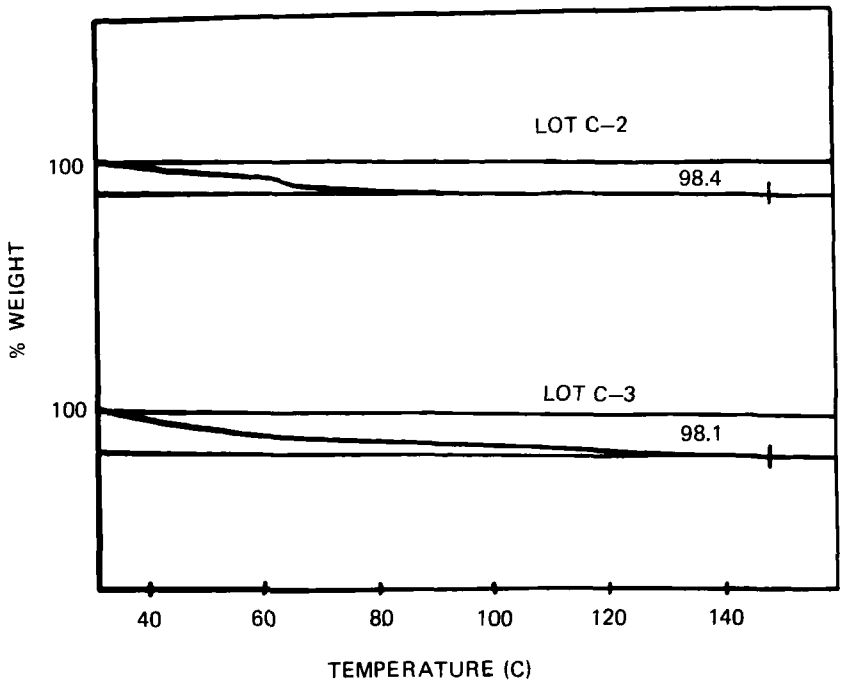


FIGURE 3
TGA Thermal Curves of Erythromycin Base of Lots C-2 and C-3 at a Heating Rate of 2.5° C/min.

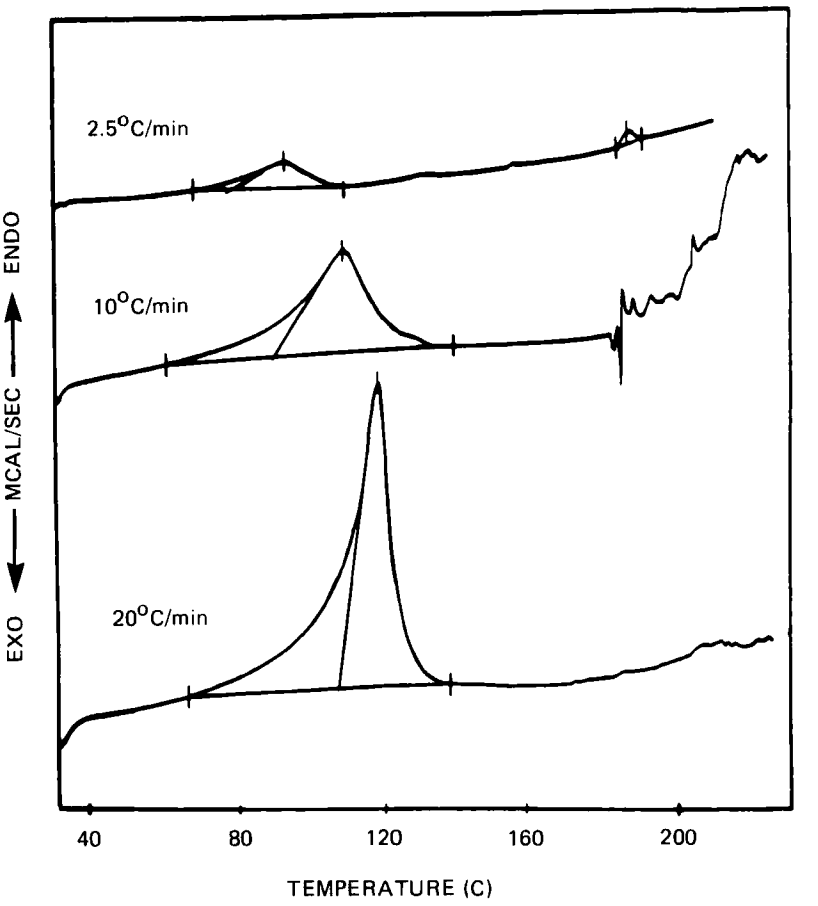


FIGURE 4
DSC Curves of Erythromycin Base of Lot A at Heating Rates, 2.5° C/min, 10° C/min, 20° C/min.

Results of DSC analysis of Lots A, B. and C-1 at three different heating rates 2.5° C, 10° C and 20° C per minute are presented in Figures 4,5 and 6. In all cases, faster heating resulted in higher melting temperatures and more pronounced endothermic peaks. This is to be expected since heat flow into the test sample is faster than heat removal from the sample. Under these conditions, the solid is not completely in a state of equilibrium.

Although all three lots A, B, and C-1 were described by the suppliers as dihydrates, they displayed different DSC thermal curves, indicating that they represent different polymorphic forms of the dihydrate. In all three

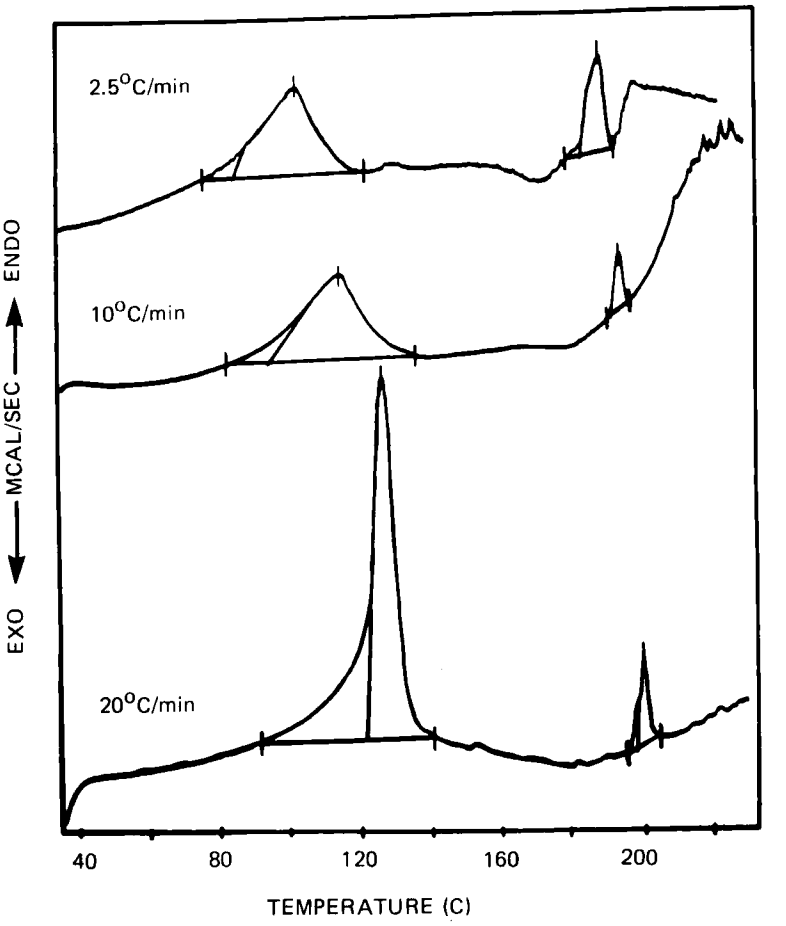


FIGURE 5
DSC Curves of Erythromycin Base of Lot B at Heating Rates, 2.5° C/min, 10° C/min and 20° C/min.

cases, a peak for desolvation results in formation of amorphous material which subsequently melts into an isotropic liquid. At higher temperatures, crystalline transformation of the melt and subsequent melting of the crystal phase occurs. This was most pronounced with Lot C-1, where after dissolution, a total rearrangement to a crystalline phase (exothermic peak at 151.3° C) was observed. With samples from Lots A and B, conversion to a crystalline phase occurs only to a limited extent partly because of insufficient time for recrystallization, particularly when heated at 10°

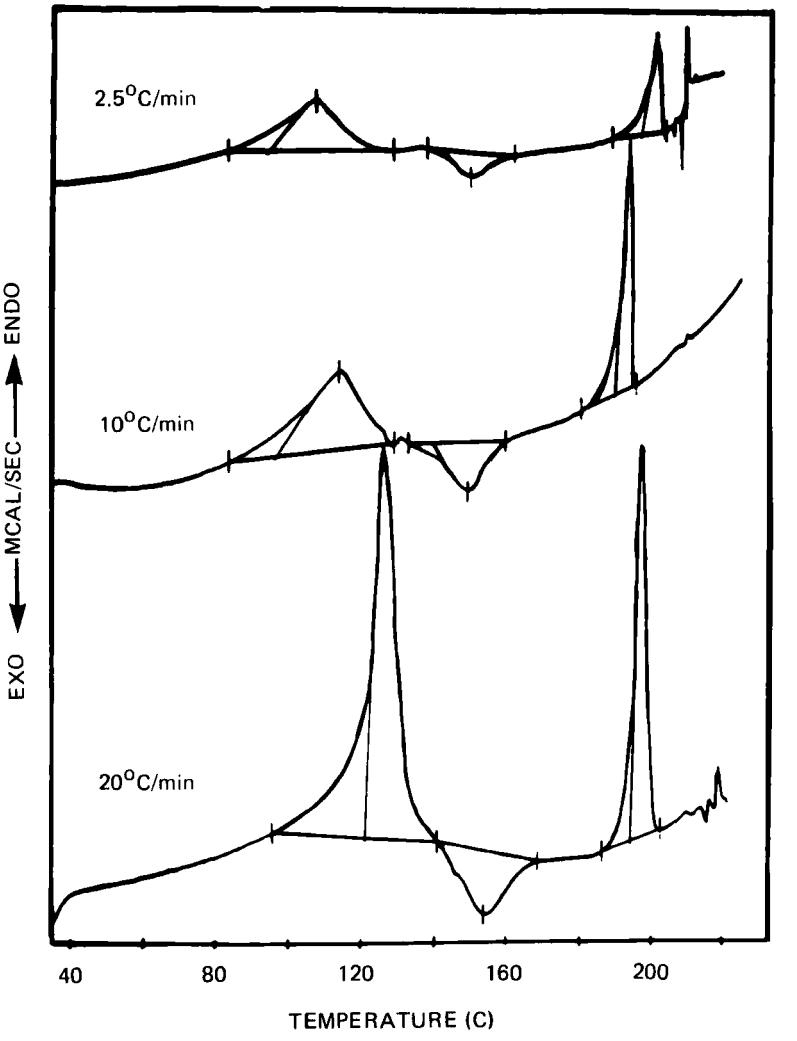


FIGURE 6
DSC Curves of Erythromycin Base of Lot C-1 at Heating Rates, 2.5° C/min, 10° C./min, 20° C/min.

C/min. In fact, unless the sample is heated at a slower speed, e.g. 2.5° C/min, only a single endothermic maximum corresponding to desolvation is observed in the temperature range 30°-200° C for Lot A.

The reaction sequence for the different hydrates as a function of temperature are:

Lots A and B

Rapid Heating

E $2H_2O$ ⟶ E amorph + $2H_2O$

E amorp ⟶ E isotropic liquid

Slow Heating

E $2H_2O$ ⟶ E amorph + $2H_2O$

E amorph ⟶ E cryst. (limited extent)

E cryst ⟶ E isotropic liquid

E amorph ⟶ E isotropic liquid

Lot C-1

Slow and Rapid Heating

E$2H_2O$ $\xrightarrow{95° - 130° C}$ E amorp + 2 $H_2O$

E amorph $\xrightarrow{140° - 160° C}$ E cryst.

E cryst $\xrightarrow{190° - 198° C}$ E isotropic liquid

During hot stage examination, no changes were apparent in the samples until about 125° C. The absence of changes at the desolvation temperatures under thermomicroscopy is a significant feature of Lots A, B, and C-1. Loss of birefringence and melting of the sample were noted between 125° - 135° C for all dihydrate samples tested. For Lot C-1 melting at 135° C was followed by the appearance of a new crystalline phase in the temperature range 140-155° C, while for Lots A and B only a small portion of the melt recrystallized. The recrystallized anhydrate melts at about 190° C and decomposes beyond 205° C.

Based on the results of thermoanalytical studies, the sequential changes that transpire when a sample of erythromycin dihydrate is heated in

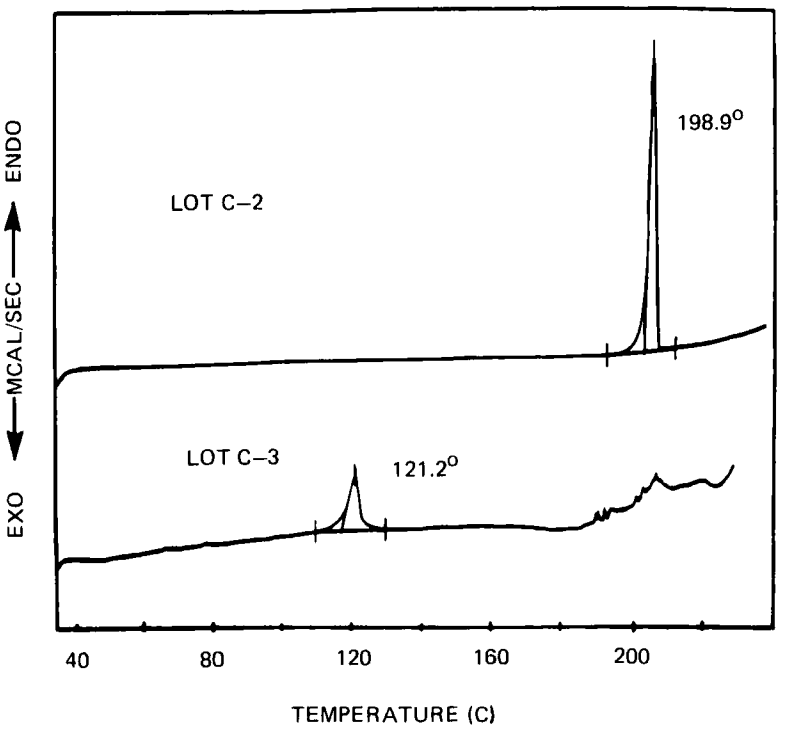


FIGURE 7
DSC Curves of Erythromycin Base of Lots C-2 and C-3 at a Heating Rate of 10° C/min.

the temperature range 30°-200° C can be described as (a) dehydration with formation of amorphous solid (b) melting of the amorphous solid (c) formation of a new crystalline phase from the melt and (d) melting of the crystalline phase. Thermogravimetric analysis can reveal only desolvation process since weight changes occur only during the loss of solvent. DSC curves contain peaks due to desolvation as well as formation and melting of the crystalline phase depending upon the particular polymorph involved and the rate of heating. Because of the small energy changes involved in the melting of amorphous solid, this step is not likely to give rise to major peaks in the DSC thermal curves and desolvation overlaps melting process (12). However, melting of the amorphous solid can be clearly seen under hot stage microscopic examination. A new crystalline phase formation from the melt and subsequent melting of these crystals were apparent in Lot C-1 and to a limited extent with Lots A and B by this technique.

Lot C-2 shows a single melting endothermic peak at about 195° C under all heating rates indicating that the material is mostly a crystalline anhydrate with a small amount of adsorbed moisture (Figure 7). This was confirmed by observations during thermomicroscopy.

Samples of Lot C-3 showed melting at about 125° C under hot stage examination and a small peak at 121° C under DSC. This may be attributed to a small amount of dihydrate present in the sample. Commercial lots are usually mixtures of hydrates and it is to be expected that characteristics of dihydrate may be present with this lot to a limited extent.

Effect of Particle Size on the DSC Curves

Fine powders of the dihydrates were generated by manually grinding the solids in a mortar. The average particle size of the powders was reduced from about 100 microns to less than 2.5 microns, an estimate based on visual microscopic observation. DSC analysis performed on these samples showed no significant differences in their DSC profiles from the original samples at both slow and fast heating rates. This is in contrast to observations made on other compounds (13,14) where particle size reduction resulted in transformation into another crystal form or into an amorphous phase.

X-Ray Diffraction Analysis

X-ray powder diffraction patterns obtained on samples of lots of the drug substance are shown in Figure 8. The most striking pattern was observed for Lot C-3, where the lines are broad and diffuse, signifying that the material is mostly noncrystalline solid. Also, no marked differences were seen in the X-ray patterns between Lots A, and C-2 suggesting that with crystalline erythromycin, X-ray analysis is not useful in distinguishing different hydration states of crystalline erythromycin base.

Infrared Absorption Spectra

There were no significant differences in the infrared absorption spectral characteristics among the dihydrates Lots A, B, and C-1. The spectra of Lots C-3, C-2 and A are shown in Figure 9. In Lot C-2, a crystalline anhydrate , the peaks due to free lactone at 1740 $cm^{-1}$ and hydrogen bonded hydroxyl group at 3500 $cm^{-1}$ were shifted from the corresponding values in the dihydrate samples. Lot C-3 is characterized by broad undifferentiated peaks at 3400 $cm^{-1}$ and 2900 $cm^{-1}$, and an absence of

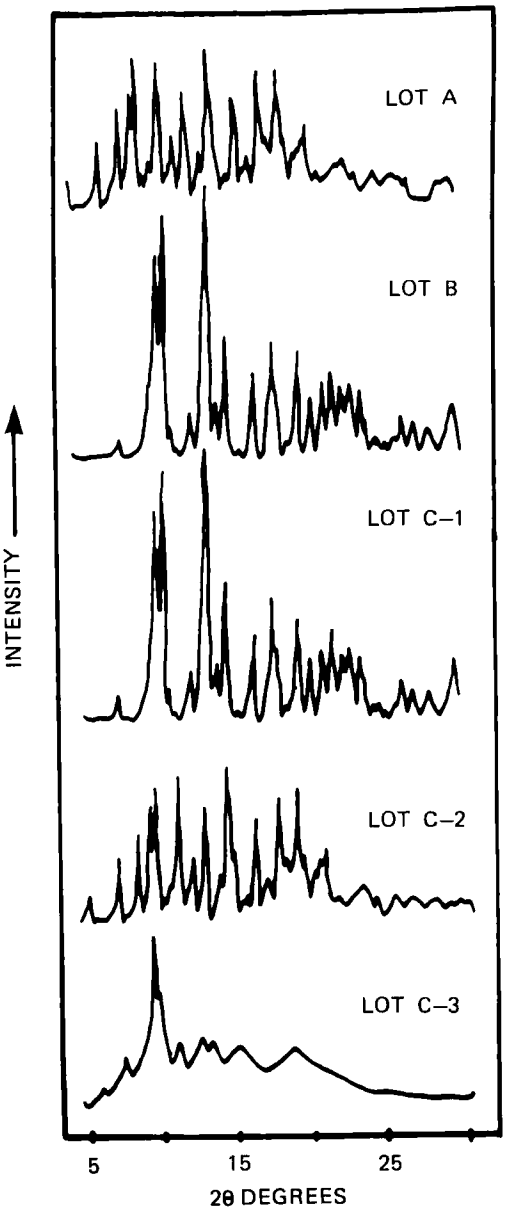


FIGURE 8
X-Ray Powder Diffractograms of Different Lots of Erythromycin Base.

shoulder at 1640 $cm^{-1}$ and 1710 $cm^{-1}$. The broad peaks confirm the amorphous nature of the material and indicate that the molecule can assume a variety of orientations.



## Solubility Studies

The equilibrium solubilities of different lots of erythromycin base in distilled water at 25° C and 37° C are shown in Table I. The differences in the solubilities among the dihydrates are small. The crystalline anhydrate has a higher solubility than the three dihydrates at both temperatures. The exact solubility of Lot C-3 could not be determined because of its rapid conversion to the dihydrate in solution when excess solid was present, which acts as a nucleus for this conversion process. In the absence of seed crystals solutions as high as 4 mg/ml were prepared in distilled water at 15° C. These were physically stable for several hours at this temperature. All lots showed a decrease in solubility with increase in temperature in the range of 15°-55° C as shown in Figure 10. These observations confirm the findings reported previously for this compound (8). The heat of solution is negative presumably due to so called "iceberg" formation, that is, water molecules surrounding the drug molecules forming frozen patches of ordered structures. Thermodynamically, the negative enthalpy of iceberg formation more than offsets the positive enthalpy of mixing resulting in a net negative enthalpy of solution. The magnitude of the negative heat of solution increases with decrease in temperature (15). The differences in solubility among different lots are therefore most pronounced at the lowest temperature studied, e.g. at 15° C.

## Dissolution Studies

The results of dissolution studies carried out on bulk powders of the various lots of erythromycin base loosely filled into capsules are shown in Figure 11. The dissolution profiles were obtained in 0.2 M phosphate buffer, pH 7.5. This medium was chosen because it provides the necessary sink conditions. The equilibrium solubility of the different lots were found to vary from 2.8 mg/ml for Lot A to 3.4 mg/ml for Lots B, C-1 and C-2. Lots A, B, C-1 and C-2 gave rapid dissolution under the test conditions. Lot C-3,

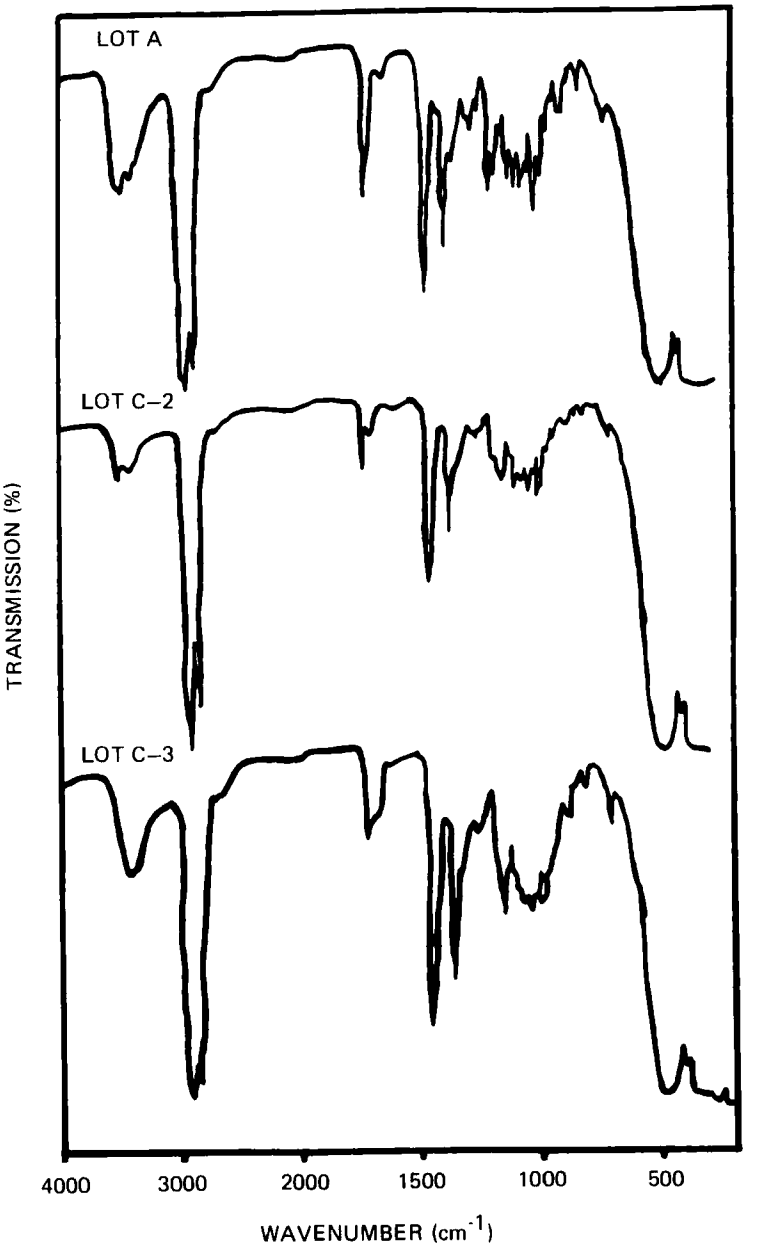


FIGURE 9

IR Spectra of Erythromycin Base of Lots A, C-2 and C-3.

TABLE 1

Solubilities of Different Lots of Erythromycin Base in Distilled Water at 25° C and 37° C.

| Lot | Solubility (mg/ml) | |
|---|---|---|
| | 25° C | 37° C |
| A | 0.74 | 0.50 |
| B | 0.76 | 0.50 |
| C-1 | 0.80 | 0.56 |
| C-2 | 1.11 | 0.63 |
| C-3 | > 4.0 | > 3.0 |

in spite of its high aqueous solubility, was very slow dissolving. In case of Lot C-3, at the end of one hour of test period, the capsule contents were mostly intact after the gelatin shell had dissolved. Examination of the capsule-shaped powder revealed a dry inner core. Presumably, drug release was impaired due to lack of wetting by the solvent and the limited area of contact between the powder mass and the dissolution fluids. Among the dihydrates, Lot C-1 gave a somewhat slower release due to the very cohesive nature of the bulk powder. The amount of drug in solution at one hour was 64.8% for Lot C-1 compared to 91.2% for Lot A and 72.4% for Lot B.

Effect of Buffer Concentration on Dissolution Rate

In order to ascertain if the drug release is dependent on the buffer strength used in the test, the dissolution rates were determined in 0.02 M phosphate buffer, pH 7.5 and compared with corresponding data obtained with 0.2 M phosphate buffer, both solutions were adjusted to a constant ionic strength of 0.5. The results are shown in Figures 12 and 13 and indicate that for both the fast dissolving and slow dissolving lots use of lower buffer strength results in slower dissolution. This effect is attributed to the fact that because of low buffer capacity of 0.02 M phosphate buffer

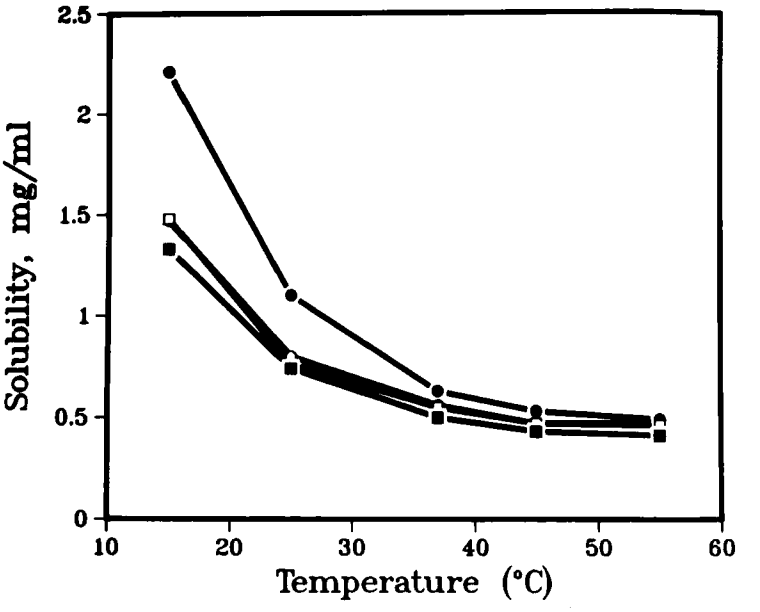


FIGURE 10
Effect of Temperature on the Solubility of Erythromycin Base in Distilled Water.

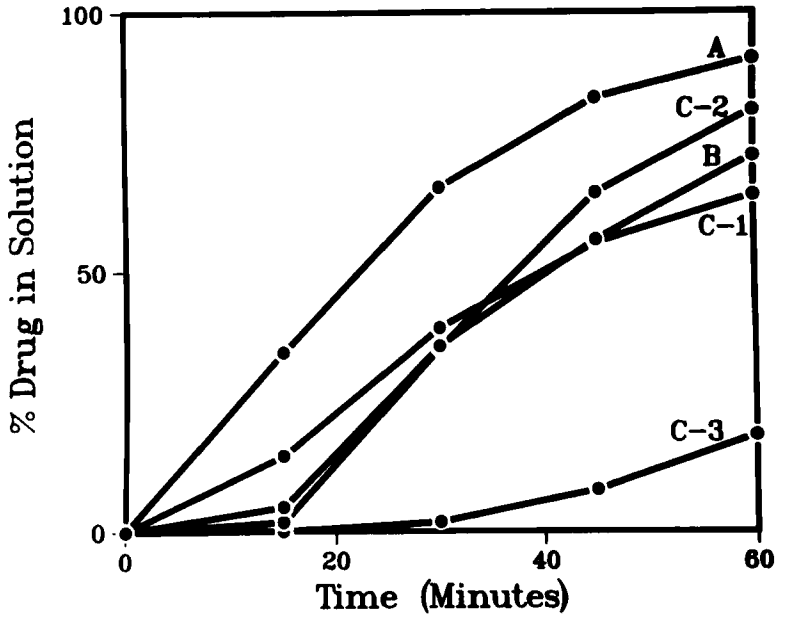


FIGURE 11
Dissolution Profiles of Different Lots of Erythromycin Base in 0.2 M Phosphate Buffer pH. 7.5 at 50 rpm and 37° C.

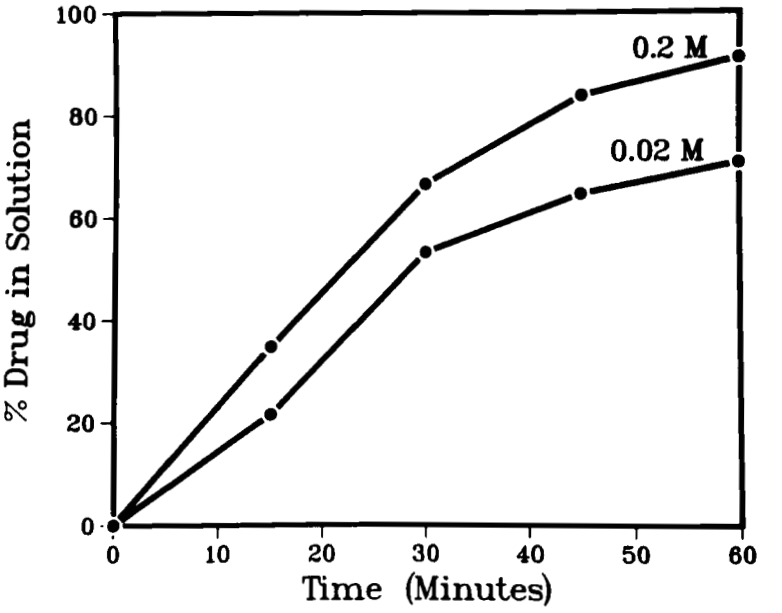


FIGURE 12
Effect of Buffer Concentration on the Dissolution Profile of Erythromycin Base Lot A.



dissolution fluid, the hydrogen ion concentration of the bulk solution is not equal to the hydrogen ion concentration in the diffusion layer. The pH of the diffusion layer is higher than the bulk solution. Accordingly, the true dissolution rate is lower than predicted based on the bulk solution hydrogen ion concentration.

The pH of the diffusion layer was determined by measuring the bulk pH of the buffer solution saturated with the drug. The equilibrium solubilities and the pH of saturated solutions are given in Table II.

## Wetting Studies

In order to assess if the differences in dissolution rates displayed by different lots of erythromycin base are due to differences in their wetting properites, contact angle measurements were made on powder compacts prepared from these materials. After depositing a known volume of test liquid on the compacts the angle formed at the point of contact between the

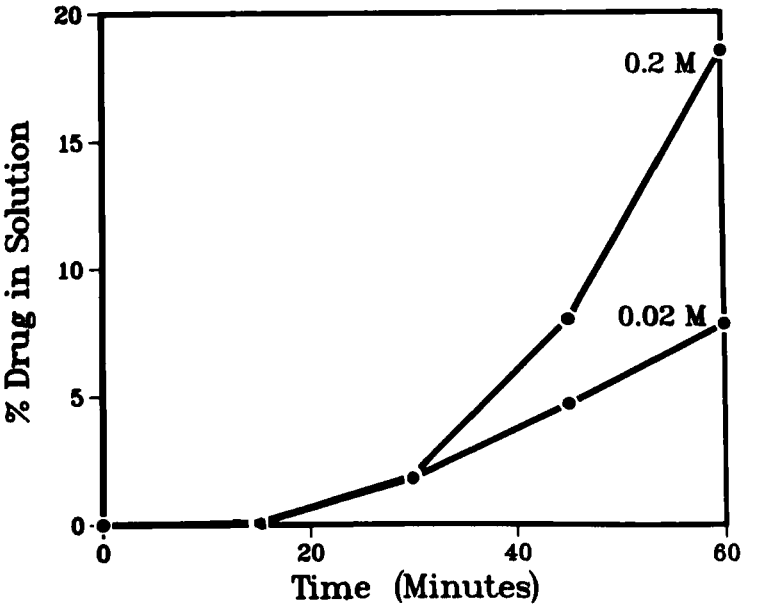


FIGURE 13
Effect of Buffer Concentration on the Dissolution of Erythromycin Base Lot C-3.

TABLE 2

Solubilities of Two Lots of Erythromycin in pH 7.5 Phosphate Buffer at 37° C.

| Lot | 0.2 M Buffer | | 0.02 M Buffer | |
|---|---|---|---|---|
| | Solubility mg/ml | Final pH | Solubility mg/ml | Final pH |
| A | 2.8 | 7.6 | 1.21 | 8.5 |
| C-3 | > 5.0 | 7.6* | 1.40 | 8.6 |

*pH of a 5 mg/ml solution in the medium.

tangent to the liquid droplet and the surface was recorded on both sides of the droplet. These values served as a measure of the wettability of the powder. Higher contact angles signifiy a more hydrophobic surface relative to a material which gives a lower contact angle. In the course of preliminary experimentation, it was observed that contact angle values obtained with hydrophobic powders were relatively stable while with the hydrophilic materials there was a rapid decrease in the angles with time as a result of spreading. This was observed on other materials and by other investigators (16). Therefore, the contact angles were measured as a function of time.

The results of contact angle studies are shown in Figures 14 and 15. With dihydrate materials A, B, and C-1 not only are the intial contact angles low, but rapid spreading and formation of continuous film of liquid over the compact resulted within a short measuring period indicating good wetting behavior. For example, with powder compacts made from Lot A, the experimental contact angle dropped from 36° to 8° in 4 minutes. On the other hand, Lot C-3, not only had a higher initial contact angle, but the angle remained stable for 20 minutes or more, confirming that this lot is hydrophobic. No significant differences were apparent in the data obtained whether distilled water or 0.2 M phosphate buffer pH 7.5 was used as the spreading liquid. Thus, poor wettability of Lot C-3 may partially account for its slow dissolution as was noted for other materials (17).

The apparent high and stable contact angle noted for Lot C-2 is somewhat unexpected in view of the fact that rapid drug release was observed in the dissolution studies. A possible explanation for this anomalous behavior may be that factors other than wettability may be involved in controlling the dissolution rate.

Unlike Lot C-3, no undissolved dry inner core of powder was present at the end of dissolution experiments for Lot C-2. Also, this lot of crystalline anhydrate rapidly converts to the dihydrate in suspension as evidenced by the DSC thermal curves of the undissolved solid.

There was marked enhancement in the dissolution rate of Lot C-3 when the experiments were run in 0.2 M phosphate buffer containing 0.5% polysorbate 80. The percent drug in solution at one hour increased from 9.0

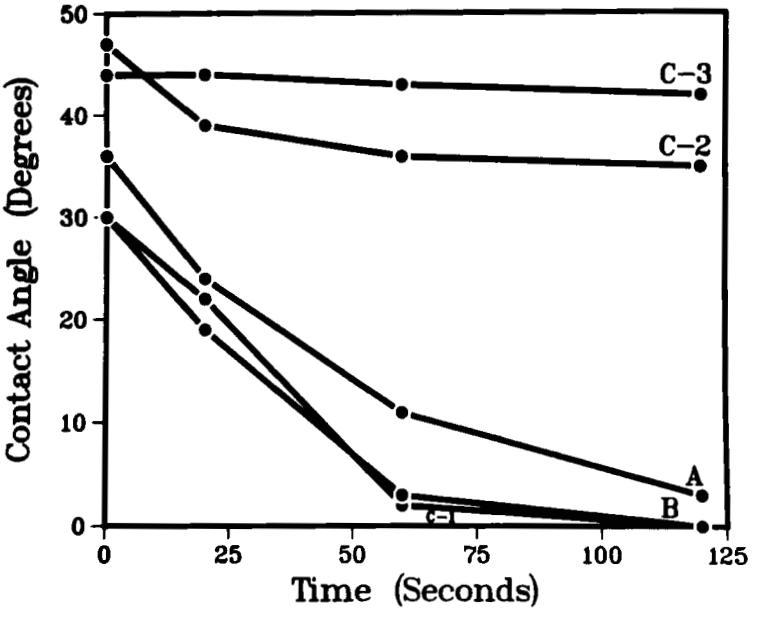


FIGURE 14
Variation of Contact Angles of Erythromycin Base with Time Using Distilled Water as the Test Liquid.

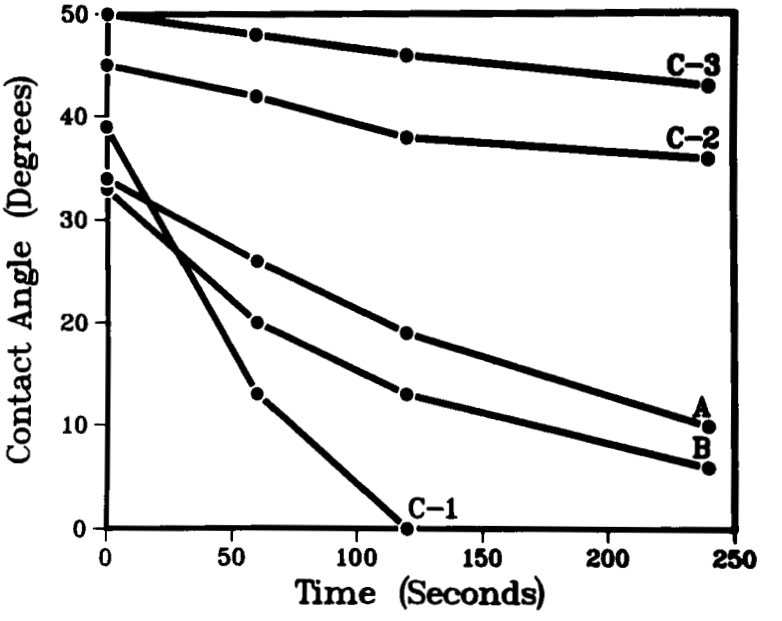


FIGURE 15
Variation of Contact Angles of Erythromycin Base with Time Using 0.2 M Phosphate Buffer pH 7.5 as the Test Liquid.

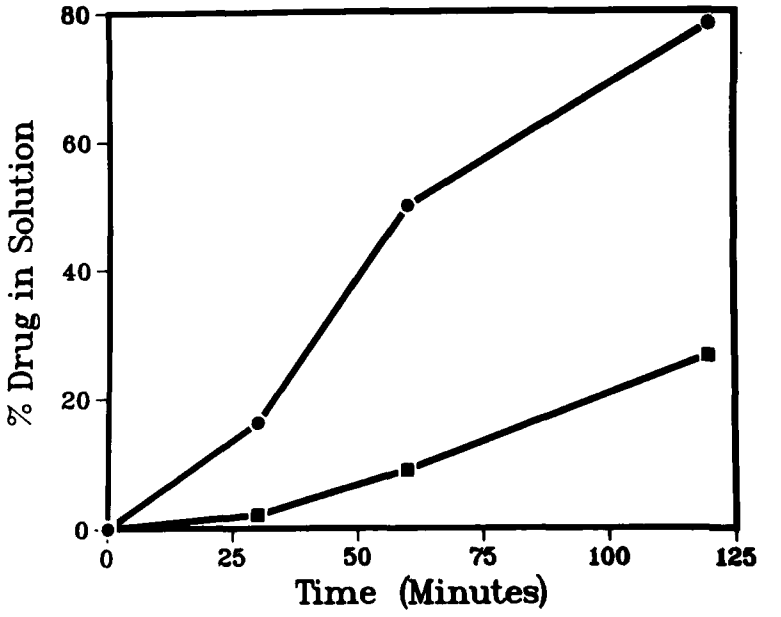


FIGURE 16
Dissolution of Erythromycin Base, Lot C-3 in 0.2 Phosphate Buffer pH 7.5. Solvent: ■ 0% Polysorbate 80 and ● 0.5% Polysorbate 80.



to 50.1 with the inclusion of a surfactant in the medium. The data are shown in Figure 16.

Thermodynamically, because of its higher energy state, the amorphous form of the drug substance should be more soluble than the crystalline dihydrate or anhydrate (18). Consequently, one would expect the amorphous form to dissolve faster than the corresponding crystalline form. However, the benefits of higher energy state for drug release can only be realized when sufficient wetting is achieved.

Efforts to convert the crystalline dihydrates to anhydrate or anhydrate to the dihydrates through storage of samples of bulk powders under low or high humidity environments were unsuccessful in our laboratory, indicating that these forms are stable in the solid state.

Although the amorphous form of erythromycin (Lot C-3) is slow dissolving, it does not follow that dosage forms prepared from this material will necessarily fail to give satisfactory **in vivo** performance. As was

pointed out by Gibaldi (19) a preparation which manifests a wetting problem may dissolve more slowly **in vitro** than in the gastrointestinal tract. The presence of surface active agents in the gastrointestinal tract may overcome the wetting problem observed **in vitro.** Nevertheless, it would be prudent to confirm the performance of amorphous forms of erythromycin in bioavailability trials prior to use in formulation studies.

## SUMMARY

Three basic forms of erythromycin base were distinguished among five commercial lots of the drug characterized. These are: crystalline dihydrate, crystalline anhydrate and amorphous solid.

Erythromycin dihydrate can exist in different crystal forms. These may differ in their thermal behavior while showing no significant variations in equilibrium solubilities in distilled water.

All forms of erythromycin display an inverse temperature-solubility relationship, that is, the solubility decreases with increase in temperature in the range of 15°-55° C.

The amorphous form of erythromycin base has a higher equilibrium solubility but much lower dissolution rate compared to the crystalline form. The dissolution rate of both forms is slower in media with low buffer concentration compared to media with a higher buffer strength.

The slower dissolution of amorphous forms of erythromycin is partly due to its poor wettability as indicated by its high contact angle and absence of spreading by test liquid on a powder compact.

The aqueous suspensions, both crystalline anhydrate and amorphous forms convert to the crystalline dihydrate.

In selecting erythromycin bulk drug for dosage form preparation, it is important to insure that the raw material is crystalline unless **in vivo** testing demonstrates no significant difference in the performance of amorphous and crystalline forms.

## ACKNOWLEDGEMENTS

The authors wish to thank Dr. R. M. Eggerth for her initial observations on this project and Mrs. Ruth Cohnstein for typing the manuscript.

## FOOTNOTES

[1]Lot A: Erythromycin Base Dihydrate, Upjohn Lot 080UC.

[2]Lot B: Erythromycin Base Dihydrate, Pierrel Lot 1132.

[3]Lot C-1: Erythromycin Base Dihydrate, Abbott Lot 58-921-CD.

[4]Lot C-2: Erythromycin Base Monohydrate, Abbott Lot 57-089-CR.

[5]Lot C-3: Erythromycin Base Anhydrous, Abbott 51-151-SA.

[6]Leitz, Wetzler, Ortholux Microscope
Ernst-Leitz (Canada) Ltd., Midland, Ontario

[7]Mettler FP2 hot stage, Mettler Analytical and precision balances, CH-Greifensee, Zurich, Switzerland.

[8]Perkin-Elmer DSC-2C Differential Scanning Calorimeter, Perkin-Elmer Corp.,Norwalk, CN.

[9]Perkin-Elmer TGS-2 Thermogravimetric system, Perkin-Elmer Corp., Norwalk, CN.

[10]Siemens Type F Powder Diffractometer with KIV X-ray generator.
Siemens Inc., Iselin, NJ

[11]Perkin-Elmer Infrared Spectrophotometer Model 283 B, Perkin-Elmer Corp., Elmwood Park, NJ

[12]Lauda RC-20 Brinkman Circulating Bath Model S-1, Brinkman Instruments Co., Westbury, NY.

[13]Labline Multiwrist Action Shaker, Model 3587, Labline Instruments, Inc., Melrose Park, IL.

[14]Millex-HV filter unit, Millipore Corp., Bedford, MA.

[15]Beckman DU7 UV-Visible Spectrophotometer, Beckman Instruments, Inc. Irvine, CA.

[16]NRL Contact Angle Goniometer, Model 100-00, Rame-Hart Inc., Mountain Lakes, NJ.

[17]Carver Press Model B., Fred Carver, Inc., Menomenee Falls, WI.

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