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RESEARCH PAPER

Direct Compression Tablets Containing a Series of Four β-Cyclodextrin Complexes Formed by Neutralizing an Acidic Drug

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ABSTRACT

A series of four β-cyclodextrin complexes (called products*) was formed by neutralizing an acidic drug to study the effect of drug solubility on complex formation and the dissolution performance from direct compression tablets. Four solid products were prepared by neutralizing the drug in 0.05, 0.10, 0.20, and 0.30 M tromethamine solutions with a constant 0.09 M β-cyclodextrin concentration, filtering the solutions, and removing the water through evaporation with heat and vacuum. The four products contained drug and water in a distinct relationship, thus suggesting a complex formation that was dependent on the tromethamine concentration. Infrared, powder X-ray diffraction, differential scanning calorimetry (DSC), phase solubility, and scanning electron microscopy (SEM) techniques revealed distinct differences among the four products, suggesting three of the four products were complexes, and one product was either a weak complex or a physical mixture. Ultraviolet (UV) analysis showed no evidence of complex formation. Phase solubility results showed one product had a slight increase in drug solubility, and three products had no increase in drug solubility with increasing β-cyclodextrin concentration. The lack of a solubility increase suggests insoluble complex formation. Drug dissolution in water was improved significantly in all tablets containing either a product or a physical mixture when compared to the pure drug. The products prepared with the two highest concentrations of tromethamine showed a dissolution performance that was superior to all other formulations. Enthalpy measurements by DSC were a good indicator of dissolution performance for tablets containing the four products. Drug*

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dissolution through salt formation in the absence of β-cyclodextrin showed the drug-salt dissolution varied from better to worse when compared to the dissolution profiles of the four products. The varying dissolution performance was attributed to the formation of distinct β-cyclodextrin complexes with varying solubilities.
Key Words: *Complex formation; β-Cyclodextrin; Differential scanning calorimetry; Direct compression tablets; Dissolution; Infrared; Phase solubility; Scanning electron microscopy; Spectroscopy; Thermogravimetric; Tromethamine; Ultraviolet; X-ray diffraction*

INTRODUCTION

Forming drug complexes with β-cyclodextrin can be difficult when using a weak acid because low water solubility may slow the equilibrium of complex formation. This study investigated (*a*) increasing the complex formation equilibrium through acid-base neutralization and (*b*) the complex characteristics in the solid state and in a pharmaceutical tablet.

Complexes were prepared by dissolving a water-insoluble acidic drug in 0.05, 0.10, 0.20, and 0.30 M tromethamine solutions containing 0.09 M β-cyclodextrin, filtering the solutions, and evaporating the water to yield a precipitate (called *product*). The acidic drug was a lipophilic molecule with one end able to form a polar salt. Three possible complexes or complex mixtures could be predicted: (*a*) a 1:1 complex with the polar function included within the β-cyclodextrin cavity, (*b*) a 1:1 complex with the nonpolar function included within the β-cyclodextrin cavity, or (*c*) a 2:1 β-cyclodextrin–drug complex with the polar and nonpolar functions included within a β-cyclodextrin cavity.

Drug content was determined by ultraviolet (UV) spectroscopy, and water content was determined by thermogravimetric analysis (TGA). Each product and a physical mixture were characterized by UV and infrared spectroscopy, powder X-ray diffraction, differential scanning calorimetry (DSC), phase solubility, and scanning electron microscopy (SEM) techniques. Association relationships between the drug and β-cyclodextrin were studied by phase solubility analysis. Tablets were prepared by compressing each product and a physical mixture with hydroxypropylmethylcellulose, magnesium stearate, and fumed silicon dioxide. Tablet dissolution was measured for each product, a physical mixture, and the pure drug. The physical mixture contained the same ingredient quantities as the product recovered from the 0.10 M tromethamine solution.

This study was designed considering the findings of other investigators as follows: Zerrouk et al. (1) reported that complex formation with β-cyclodextrin was pH dependent, and that weaker complexes were formed with increasing ionization. Okimoto et al. (2) reported that a neutral drug will form more stable complexes when compared to the anion, and complex formation was related to the intrinsic drug solubility. Johnson et al. (3) reported that pH control could be used to prepare complexes with an acidic tripeptide. Moyano et al. (4) reported that salt formation provided a superior dissolving product of gliclazide. Zornoza et al. (5) reported that the ionization state of glisentide controlled the stability constant and theorized that the ionization state controlled the ability of glisentide to displace water molecules within the β-cyclodextrin cavity. Loftsson and Petersen (6) reported that a zwitterionic drug had little tendency to form strong complexes with a variety of modified β-cyclodextrins, although solubility enhancement was achieved using uncharged β-cyclodextrin derivatives at high pH. Loftsson and Brewster (7) reported that charge can influence complexation, and complex stability is larger for the un-ionized form than for the ionized form. Lin et al. (8) reported that salt formation with indomethacin provided a more complete inclusion. Bergeron et al. (9,10) reported that anion hydration would affect substrate inclusion within the β-cyclodextrin cavity.

EXPERIMENTAL

Materials

β-Cyclodextrin hydrate (99%) and tromethamine base (>99.9%) (tris[hydroxymethyl]aminomethane) were obtained from Sigma Chemical Company (St. Louis, MO). Pharmaceutical-grade drug was manufactured by Zeneca Pharmaceuticals (Wilmington, DE). Hydroxypropylmethylcellulose, magnesium stearate, and fumed silicon dioxide were all USP/NF grade.

Complex Preparation

The drug–β-cyclodextrin complexes were prepared as follows: 10 g β-cyclodextrin (0.09 M) were dissolved in

100 ml of 0.05, 0.10, 0.20, or 0.30 M tromethamine solution. Each solution was heated to 60°C ± 1°C to dissolve the β-cyclodextrin. Once β-cyclodextrin was dissolved completely, excess drug was added to the solution; the dispersion was rotated for 2 hr, filtered, and concentrated to a viscous precipitate using rotary evaporation. The precipitate was transferred to a beaker and dried overnight to a solid at 60°C ± 1°C under vacuum. Each product recovered from a tromethamine solution was powdered with a mortar and pestle and stored at ambient conditions in light-resistant containers.

Analytical Methods

Ultraviolet Analysis and Drug Content

Ultraviolet spectra were examined for either a bathochromic shift or band broadening caused by complex formation with β-cyclodextrin. The study was conducted by dissolving samples of either drug or drug and β-cyclodextrin in 0.20 M tromethamine solution and scanning the samples for absorbance from 400 to 200 nm.

The drug content of each product was determined by UV analysis at a lambda maximum of 295 nm. The calibration plot was constructed by plotting absorbance against concentration. The UV absorbance spectra were obtained using a Perkin Elmer lambda 5 spectrophotometer.

Water Content

The water content of each product was determined by TGA with the Perkin Elmer TGA7. Water content was calculated from the total weight loss from the thermal transition ranging from 30°C to 150°C. Samples were equilibrated for at least 2 hr at 52% relative humidity (ambient) before placing a 10–12 mg sample into a platinum dish for analysis. The nitrogen flow rate was 65 ml/min, and the heating rate was 10°C/min.

Physicochemical Characterization

Scanning electron images were taken using an Amray 1910 field-emission SEM. The instrument settings were as follows: 4-kV acceleration potential, 7–8 mm working distance, and condenser lens setting of −5. The samples were coated with about 10 nm of gold/palladium alloy using a Hummer 6.2 sputter coater. The magnification factor was adjusted so a selected particle was the full-field length as follows: The physical mixture was magnified to 400×, β-cyclodextrin and the 0.30 M product were magnified to 600×, and the 0.05, 0.10, and 0.20 M products were magnified to 1000×.

The Fourier transform infrared spectra were obtained using a Nicolet Magna-IR 550 Series II spectrometer. Samples were prepared by the potassium bromide disk method and scanned for absorbance from 4000 to 400 cm^{-1}.

X-ray diffraction spectra were obtained with a Scintag XDS2000 diffractometer. Samples were prepared for analysis by placing about 30 mg of the powder fraction that passed through a 180-μ sieve on the center of a quartz plate. The quartz plate was designed to give no spectral background. Instrumental parameters were as follows: Nickel-filtered copper K_α radiation was used at 45 kV and 40 mA; step size was 0.02° 2θ; the counting rate was 1°/min; and the analysis range was 2° to 50° 2θ.

DSC analysis was performed with a Perkin Elmer DSC7. Samples were prepared by placing 1–2 mg of sample into an aluminum pan, which was covered and crimped for analysis. Samples were equilibrated for at least 2 hr at 52% relative humidity (ambient) before analysis. Thermograms were analyzed qualitatively by examining the peak temperature and transition contour and quantitatively by calculating the enthalpy associated with the cyclodextrin-cavity dehydration from about 10°C to 150°C. The heating rate was 10°C/min; the analysis range was from 10°C to 150°C; and the nitrogen flow rate was 50 ml/min.

Phase Solubility Analysis

The phase solubility experiment was performed by the method reported by Higuchi and Connors (11) and Connors (12). Each experiment was conducted in duplicate by adding drug and β-cyclodextrin to a tromethamine solution identical in molarity to the solution used to prepare each product to study the specific interaction among drug, tromethamine, and β-cyclodextrin.

Samples were prepared by adding 20 ml of tromethamine solution to a series of 100-ml tubes each containing successively increasing quantities of β-cyclodextrin as follows: 0, 3, 6, 9, 12, and 15 mM. Excess drug was added to each tube to maintain saturated conditions. Each tube was capped and rotated at 30 rpm for 2 hr in a constant temperature water bath at 25°C ± 1°C. A 2-hr equilibrium time was considered sufficient to form a complex since the physicochemical characterization techniques studied in this report failed to show the presence of the pure drug. Following equilibrium, the supernatant phase was removed, filtered, diluted, and assayed for the total dissolved drug content by UV analysis. The phase solubility plot was constructed by plotting dissolved drug against β-cyclodextrin concentration.

Table 1

β-Cyclodextrin Tablet Formulations

	Product Formulation				
Ingredient (%)	0.05 M	0.10 M	0.20 M	0.30 M	Physical Mixture
Product (complex)	97.0	95.9	94.4	95.0	—
Microcrystalline cellulose	1.9	3.0	4.5	3.9	2.7
Magnesium stearate	1.0	1.0	1.0	1.0	0.5
Fumed-silicon dioxide	0.1	0.1	0.1	0.1	0.1
β-Cyclodextrin	—	—	—	—	79.3
Drug	—	—	—	—	7.9
Tromethamine base	—	—	—	—	9.6

Tablet Formulations

All products and a physical mixture of drug, tromethamine, and β-cyclodextrin were mixed with the excipients listed in Table 1 using a powder fraction that had been passed through a 180-μ sieve. The formulation for the pure drug is not provided to maintain business confidentiality. Tablets were compressed directly on a Stokes F-press, model 900.519.2.

Dissolution Studies

Dissolution studies were performed in triplicate using USP apparatus 2 in 900 ml of water with a paddle speed of 50 rpm for tablets containing either a product, a physical mixture, or the pure drug. Dissolution samples were collected at 10-, 15-, 30-, 45-, and 60-min intervals and filtered; UV absorbance measurements were taken. The dissolution profiles were constructed by plotting the cumulative percentage drug released against time.

Additional dissolution studies were performed singularly using tablets containing pure drug in tromethamine solution. Dissolution studies were performed using USP apparatus 2 with a paddle speed of 50 rpm in 900 ml of water containing 1.5, 2.1, 2.8, or 4.3×10^{-4} moles of tromethamine. The tromethamine quantities added to the dissolution medium represented the equivalent mass of tromethamine present in each product (w/w); thus, the investigators could study drug dissolution through salt formation in the absence of β-cyclodextrin.

RESULTS AND DISCUSSION

Ultraviolet Spectroscopy

The drug spectrum was not altered by complex formation with β-cyclodextrin, as supported by the absence of a bathochromic shift and band broadening at the lambda maximum. Although UV analysis failed to show evidence of complex formation, it was considered suitable for drug assay because the drug spectrum was not affected by β-cyclodextrin.

Drug and Water Contents

The drug and water contents of the four products are reported in Table 2. The drug content increased from

Table 2

Drug and Water Contents of the Four Products and β-Cyclodextrin

Sample	Drug Content (%)	Water Content (%)
β-Cyclodextrin hydrate	Not tested	13.4
0.05 M product	6.0	12.4
0.10 M poduct	7.9	8.1
0.20 M product	10.3	6.9
0.30 M product	9.3	6.1

about 6% to 10%, and the water content decreased from about 12% to 6% with increasing tromethamine concentration. The relationships among tromethamine concentration, drug content, and water content are shown in Fig. 1.

We postulated that the 0.05 M product had formed either an enlarged cavity or a channel that was solvated as highly as β-cyclodextrin because only about 1% of the 13% water (Table 2) within the hydrated β-cyclodextrin cavity had been replaced by drug and tromethamine. The other three products were less solvated since some of the water within the β-cyclodextrin cavity had been replaced. Crystallographic studies of other β-cyclodextrin complexes (13) have shown β-cyclodextrin prefers to form a dimeric structure that enlarges the ring cavity and may form channels in the solid state. The dimers are formed in solution either through hydrogen bonds involving the hydroxyl groups or directly through an intermolecular-water network.

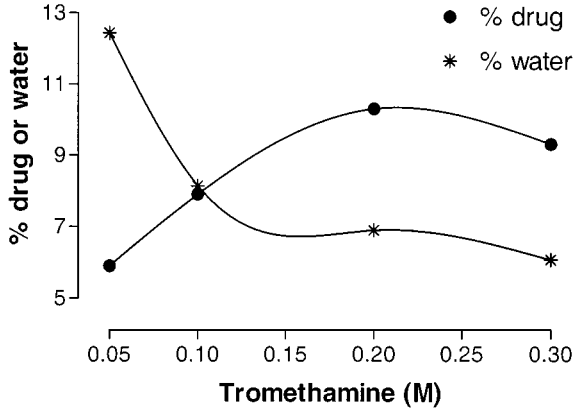

Figure 1. The dependence of drug and water content on tromethamine concentration.

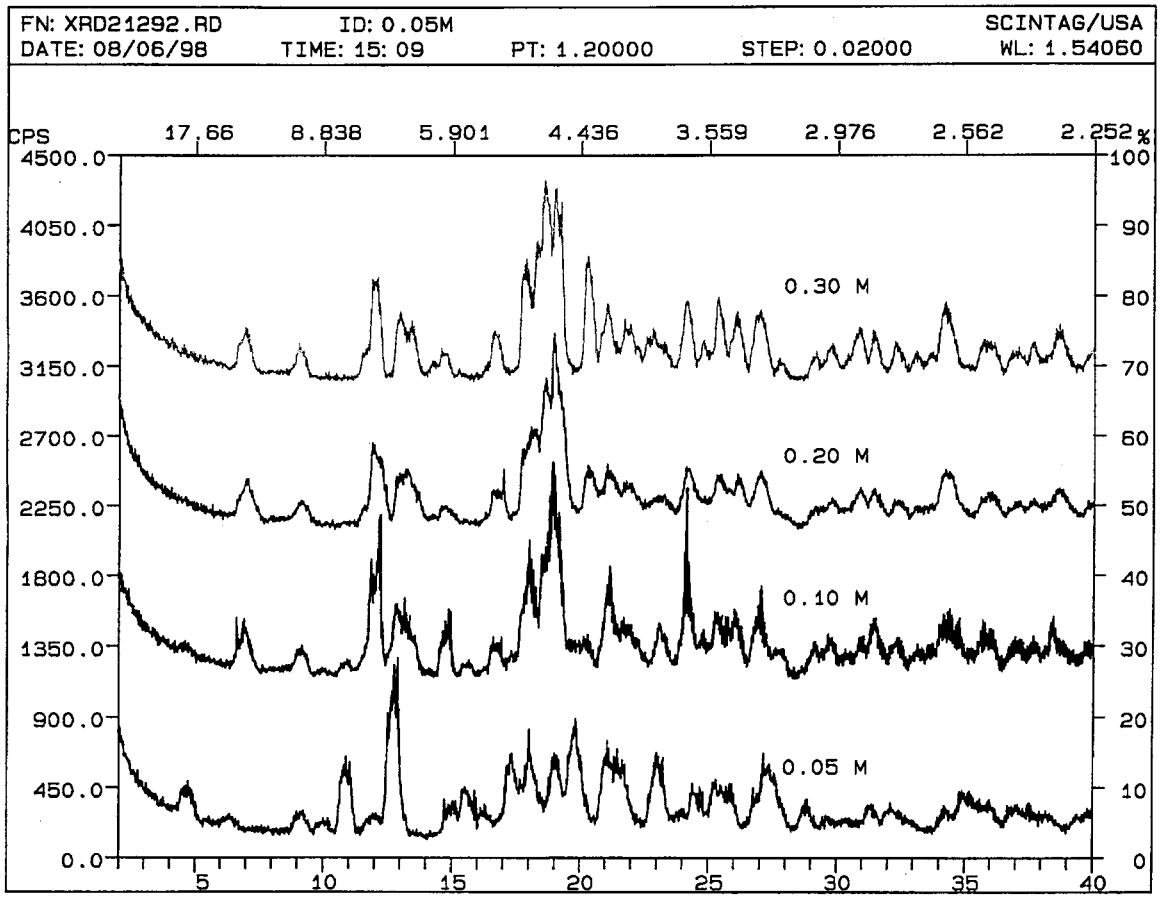

Figure 2. X-ray diffraction spectra.

Physicochemical Characterization

X-Ray Diffraction Analysis

The 0.10, 0.20, and 0.30 M products were alike, but distinctly different from the physical mixture, as shown in the diffraction spectra in Figs. 2 and 3, thus supporting complex formation. The 0.05 M product was similar to the physical mixture, although this product lacked a strong peak for tromethamine at about 31° 2θ, as shown in Fig. 3. The absent tromethamine peak in the 0.05 M product suggests tromethamine had complexed with β-cyclodextrin. The spectra show all four products were essentially crystalline.

Infrared Spectroscopy

The infrared spectra of the 0.05, 0.10, 0.20, and 0.30 M products are shown in Fig. 4. The 0.10, 0.20 (shown as an example), and 0.30 M products show a progressive diminishing of the 1625-cm^{-1} band with increasing tromethamine concentration. The diminishing absorbance of the 1625-cm^{-1} absorption band was attributed to changes in the bound water content of β-cyclodextrin and was considered evidence of complex formation. The 0.05 M product and physical mixture spectra were found to be similar. An absorption band of tromethamine was seen at 1590 cm^{-1} in the 0.30 M product and was attributed to the high tromethamine concentration.

Differential Scanning Calorimetry Analysis

The 0.10, 0.20, and 0.30 M products were different from the physical mixture (Fig. 5). The 0.05 M product was similar to the physical mixture, although it lacked a 135°C endotherm for tromethamine.

All four products show one meaningful endothermal transition: A large transition with a peak temperature in the range 63°C–92°C was observed and attributed to the dehydration of the water within the β-cyclodextrin cavity,

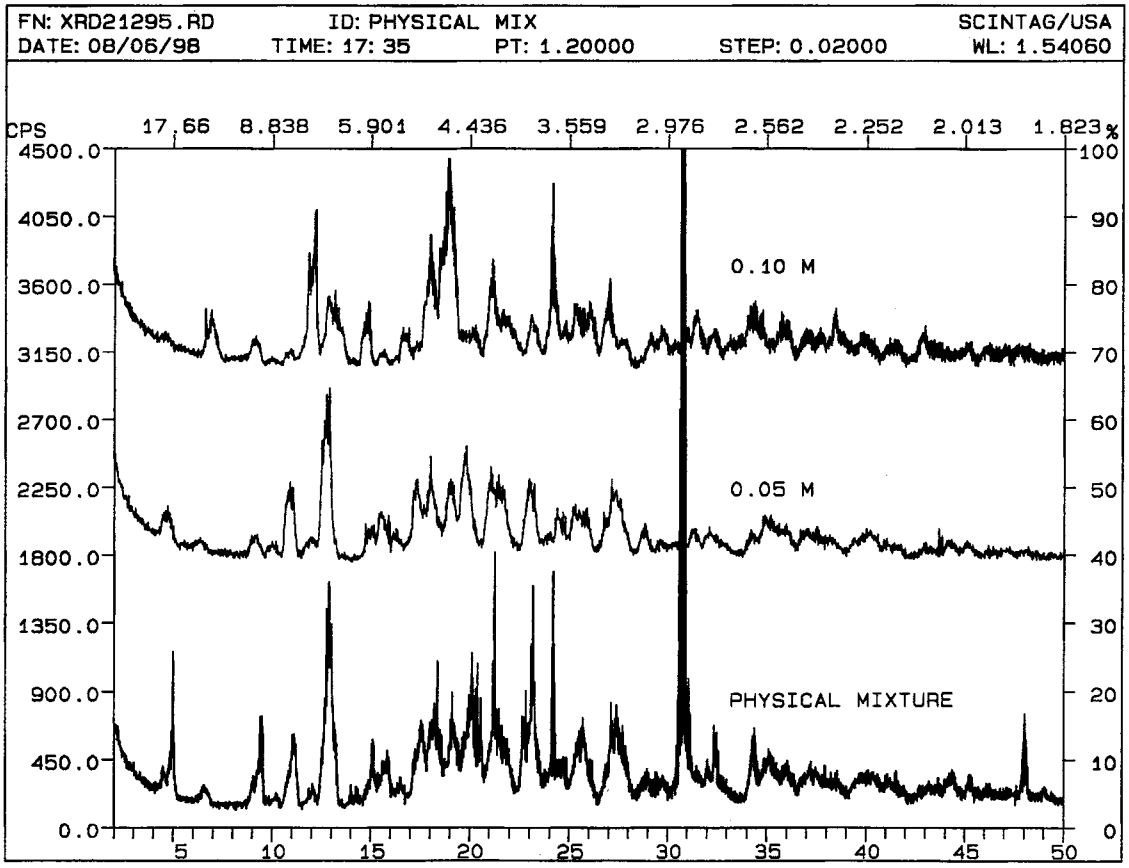

Figure 3. X-ray diffraction spectra.

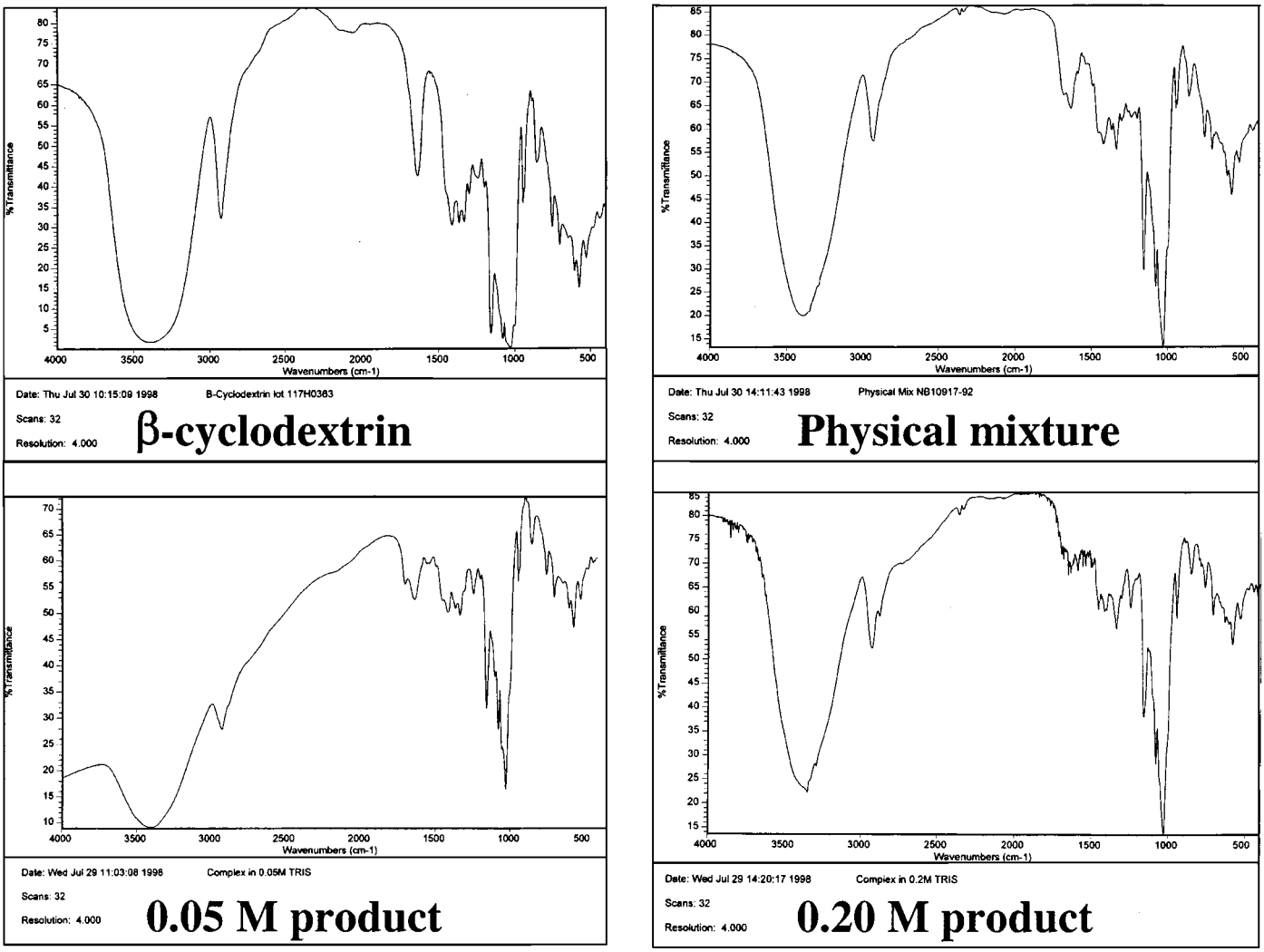

Figure 4. Infrared spectra.

as confirmed by TGA (thermograms not shown). The peaks for the 0.10, 0.20, and 0.30 M complexes were small and broad and do not appear clearly in Fig. 5 because of the large scale needed to show β-cyclodextrin and the 0.05 M complex.

Complex formation was suggested by a negative shift in peak temperature and a change in enthalpy when compared to the physical mixture (Table 3). The peak at about 135°C in the 0.20 and 0.30 M products was attributed to tromethamine. The 0.05, 0.10, and 0.20 M products show an absent or diminished tromethamine peak when compared to the physical mixture. We expected to observe a more intense tromethamine peak considering the physical mixture contained the same tromethamine concentration as the 0.10 M product. The absent or diminished tromethamine peak was considered evidence that tromethamine had complexed with β-cyclodextrin.

The 0.10, 0.20, and 0.30 M products showed a linear relationship between enthalpy and water content (Fig. 6). The 0.05 M product was excluded from this relationship possibly because this product was more similar to a physical mixture than a complex, as suggested by the other physicochemical characterization data.

Scanning Electron Microscopy

The crystal structure of the four products improved with increasing tromethamine concentration (Figs. 7–

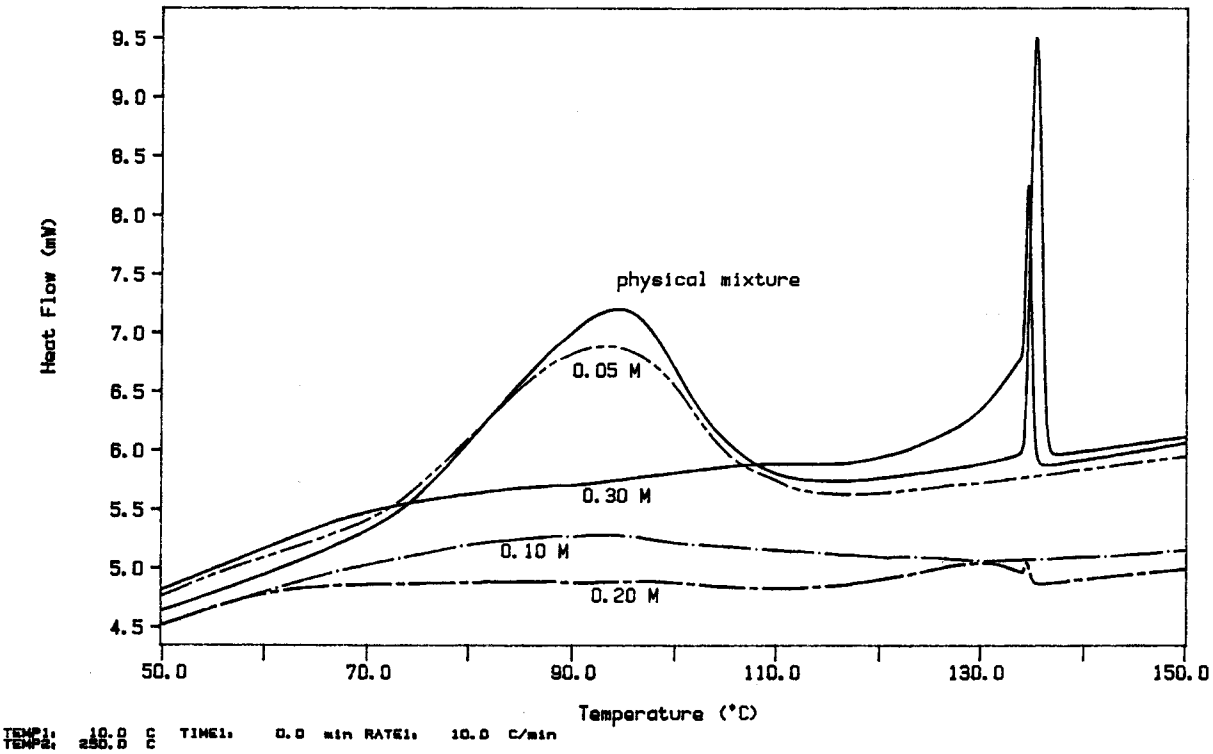

Figure 5. DSC thermograms.

10). The 0.05 M product was of a poor crystal structure since it lacked distinct crystal faces and had numerous large cracks and fissures. The 0.10 M product had small cracks, and some crystal faces were evident. The 0.20 and 0.30 M products had distinct crystal faces with solid surfaces. Figures 11 and 12 show the physical mixture and β-cyclodextrin SEM photographs, respectively, as a reference.

Phase Solubility Analysis

The 0.05, 0.10, and 0.20 M tromethamine solutions gave no increase in drug solubility with increasing β-cyclodextrin concentration (termed class B diagrams) (Fig. 13). The absence of a linear-rising segment (termed a type A segment) suggests either no complex or an insoluble complex had formed; thus, one would expect no dissolution enhancement. No stability constant was calculated due to the absence of a type A segment.

The 0.30 M product showed a small, nonlinear increase in drug solubility with increasing β-cyclodextrin concentration, thus supporting complex formation. The difference between the intrinsic drug solubility (labeled S_0 in Fig. 13), and the solubility increase achieved at 9 mM β-cyclodextrin suggests that complex formation should enhance dissolution.

Table 3

Peak Temperature and Enthalpy for the Four Products and a Physical Mixture

Sample	Peak Temperature (°C)	Enthalpy (J/g)
Physical mixture	93.7	264.34
0.05 M product	91.8	307.99
0.10 M product	82.1	338.86
0.20 M product	63.0	188.79
0.30 M product	68.7	90.07

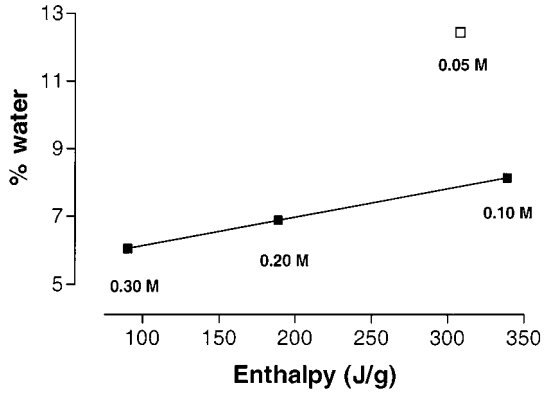

Figure 6. Relationship between water content and enthalpy.

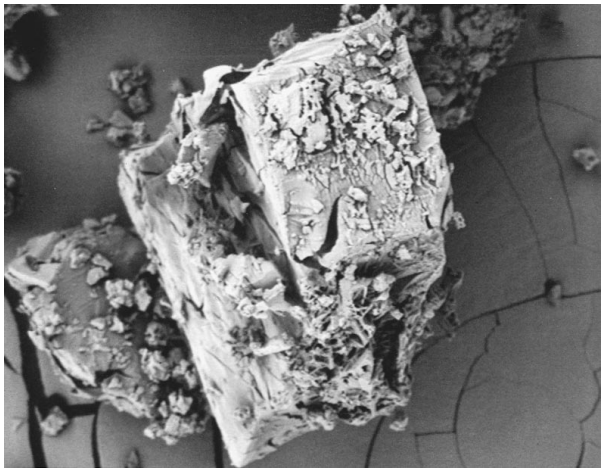

Figure 7. SEM photograph of the 0.05 M product.

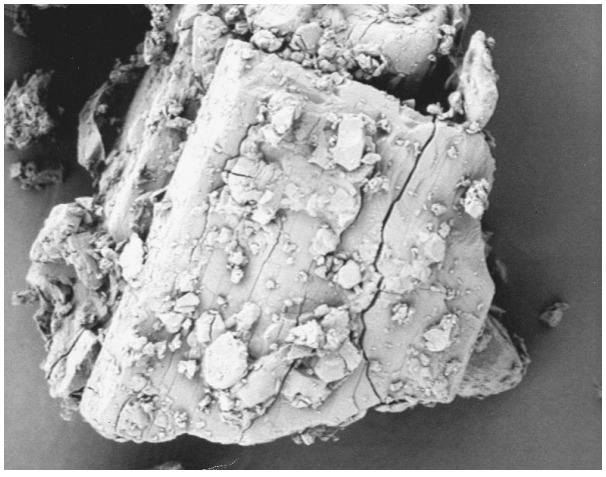

Figure 8. SEM photograph of the 0.10 M product.

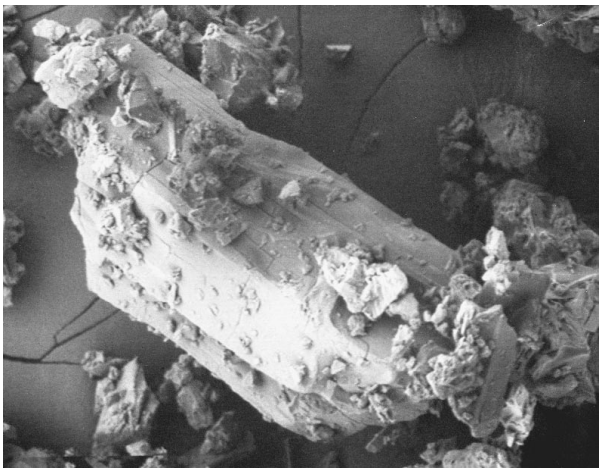

Figure 9. SEM photograph of the 0.20 M product.

Dissolution Studies

Dissolution profiles in water show the drug dissolved better from tablets made with either the products or a physical mixture when compared to tablets containing the pure drug (Fig. 14). Tablets containing the 0.20 and 0.30 M products dissolved rapidly in water within 10 min and performed better than the physical mixture. The small difference (about 5–10% dissolved) between the 0.20 and 0.30 M products was attributed to the loss of a sink condition for the 0.20 M product. The 0.05 M product performed similar to the physical mixture, thus supporting the conclusion that a weak complex had formed.

Tablets prepared with the 0.10 M product dissolved poorly in water when compared to the 0.05, 0.20, and

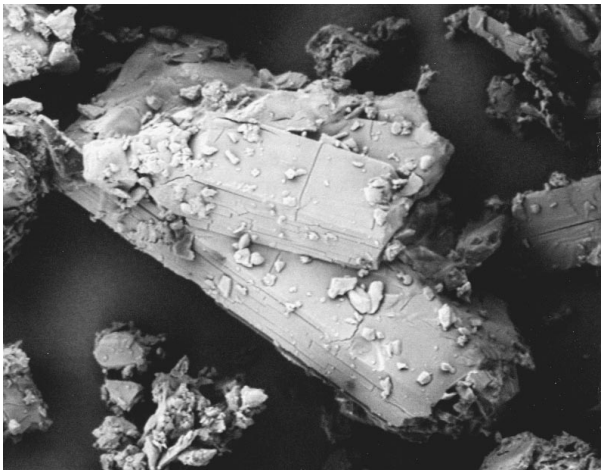

Figure 10. SEM photograph of the 0.30 M product.

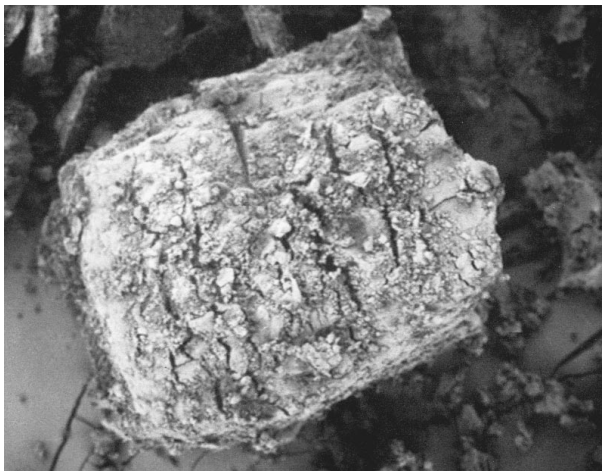

Figure 11. SEM photograph of the physical mixture.

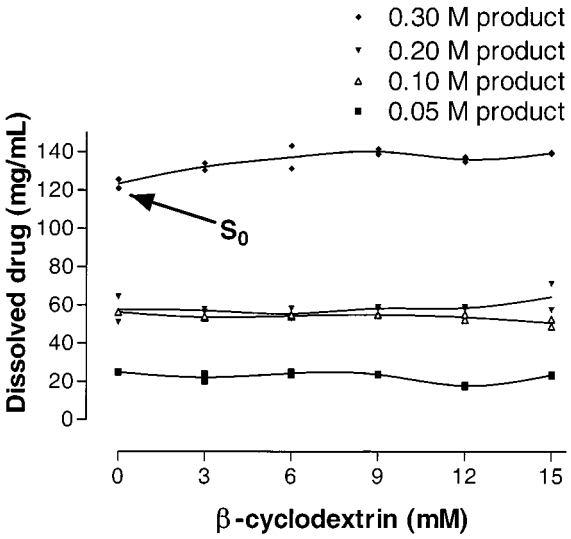

Figure 13. Phase solubility analysis.

0.30 M products and the physical mixture. Tablets containing the physical mixture were prepared with the same ingredient quantities as tablets containing the 0.10 M product; thus, both tablet formulations should have shown similar dissolution profiles. The poor dissolution of the 0.10 M product was attributed to the formation of the least soluble complex in the series.

Dissolution profiles were found to be most discriminating among the four products at the 10-min interval. The dependence of percentage drug dissolved at 10 min and enthalpy is shown in Fig. 15. Dissolution performance was found to be dependent on the enthalpy and suggests that the energy needed to desolvate these complexes was similar to the energy needed to dissolve the complexes in water. Casella et al. (14) showed that enthalpy measurements could be used to predict dissolution performance from indomethacin–β-cyclodextrin complexes.

Dissolution studies in a medium that would form the drug-tromethamine salt (in the absence of β-cyclodextrin) show the salt had faster, similar, or slower dissolution performance than the corresponding product containing β-cyclodextrin (Fig. 16). Dissolution profiles

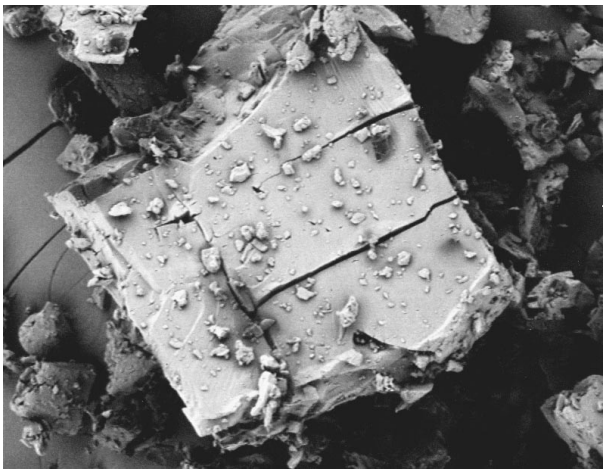

Figure 12. SEM photograph of β-cyclodextrin.

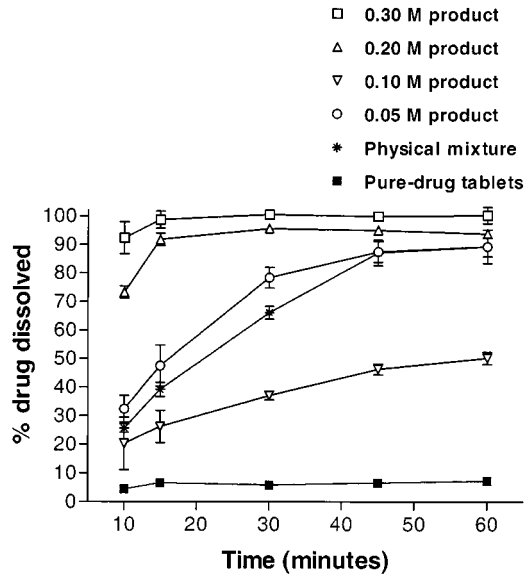

Figure 14. Drug dissolution profiles in water.

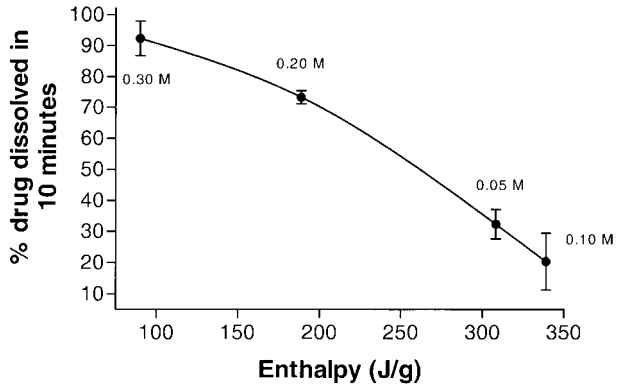

Figure 15. Relationship between dissolution and enthalpy.

show β-cyclodextrin increased drug dissolution in the 0.30 M product, had no effect on dissolution in the 0.20 M product, and lowered dissolution in the 0.10 and 0.05 M products. The variable dissolution performance confirmed the formation of a relatively insoluble complex from the 0.30 M tromethamine solution and the formation of less-soluble complexes from the 0.05, 0.10, and 0.20 M tromethamine solutions, as predicted by phase-solubility analysis.

CONCLUSIONS

A series of β-cyclodextrin complexes was prepared successfully with an acidic drug using tromethamine base as an ionizing agent. Unique complexes were formed rap-

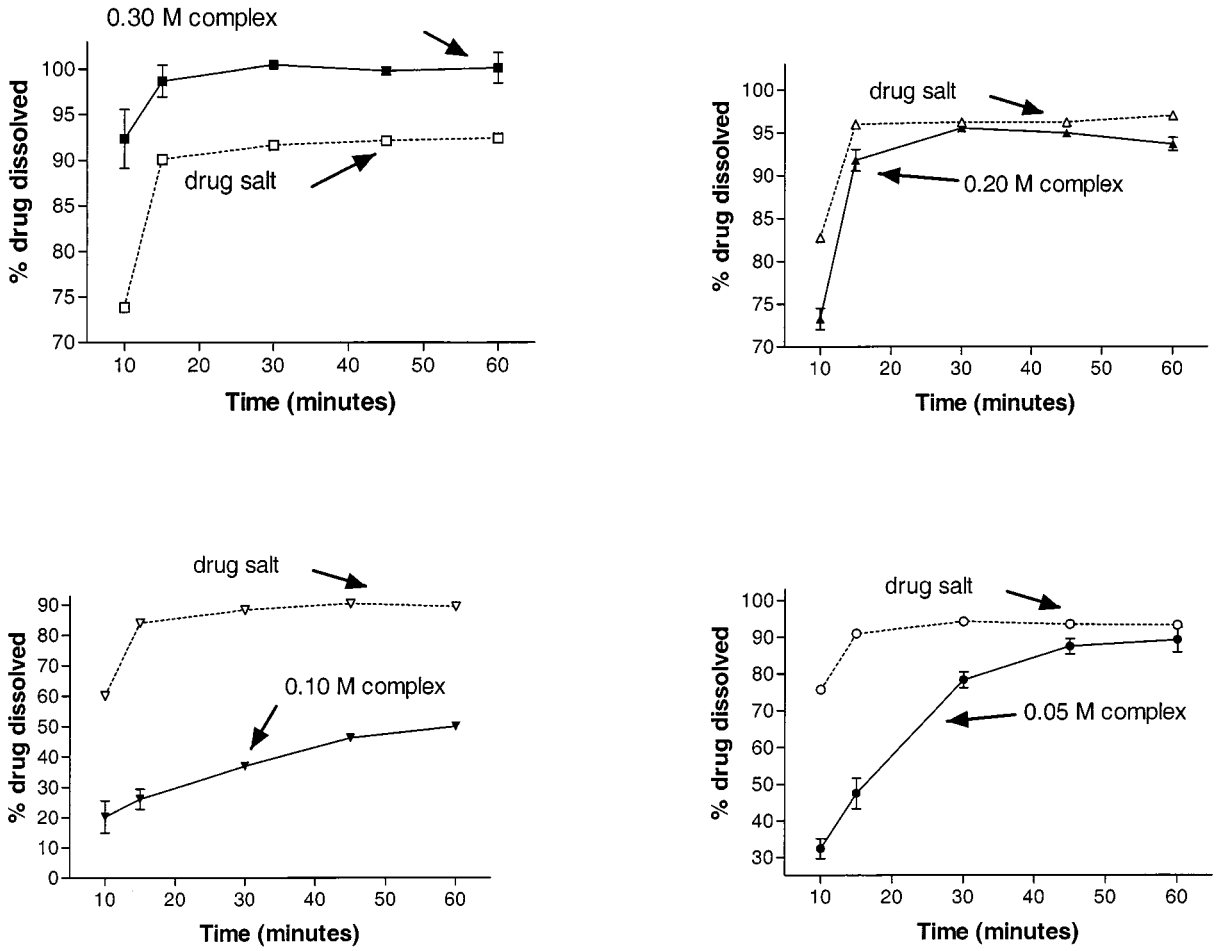

Figure 16. Dissolution profiles of drug in either the salt or complexed form.

idly with β-cyclodextrin, tromethamine base, drug, and water.

The tromethamine base concentration controlled the drug and water contents of the four complexes.

Complex formation was verified by X-ray diffraction, infrared, SEM, and DSC techniques. These methods identified distinct differences among one weak (0.05 M product) and three stronger complexes (0.10, 0.20, and 0.30 M products). The 0.05 M product was considered a weak complex or a physical mixture.

Phase solubility analysis showed an insoluble complex was formed from the 0.30 M tromethamine solution, and less-soluble complexes were formed from the 0.05, 0.10, and 0.20 M tromethamine solutions. Dissolution performance of the drug in the salt and complexed forms was in agreement with the findings from phase solubility analysis.

The 0.10 and 0.20 M products were similar when studied by phase solubility analysis, but behaved differently when dissolving from the solid form. SEM showed these products had a dissimilar crystal morphology.

All tablets containing drug, tromethamine, and β-cyclodextrin showed enhanced dissolution when compared to the pure drug.

Dissolution studies showed the four complexes dissolved faster than, similar to, or slower than a physical mixture of drug, tromethamine, and β-cyclodextrin.

The dissolution performance of tablets containing the complexes was related to the complex enthalpy measured by DSC.

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