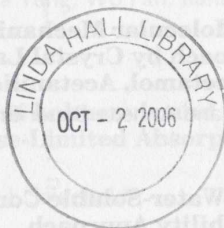


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# Solubilization and Dissolution of Tamoxifen-Hydroxybutenyl Cyclodextrin Complexes

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**ABSTRACT:** The solubility and dissolution of tamoxifen base and tamoxifen citrate with and without hydroxybutenyl- $\beta$ -cyclodextrin (HBenBCD) in aqueous and organic media were examined. The solubility of tamoxifen was greatly enhanced by complexation with HBenBCD; pH of the medium, and choice of buffer significantly impacted the amount of drug that could be solubilized. Different tamoxifen:HBenBCD formulations were prepared, including liquid fill capsule formulations, and their dissolution profiles were obtained. These dissolution studies demonstrated that enhanced solubilization of tamoxifen with HBenBCD was effective across a wide variety of formulation options. By complexation of tamoxifen base with HBenBCD, it was possible to obtain solubility and dissolution profiles for tamoxifen base that were essentially identical to that of tamoxifen citrate. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 95:2246–2255, 2006

**Keywords:** hydroxybutenyl- $\beta$ -cyclodextrin; HBenBCD; tamoxifen; complex; liquid fill; solubility; dissolution

## INTRODUCTION

In designing drug delivery systems for poorly water-soluble drugs, the relationship between drug solubility in a physiological environment, drug absorption across biological barriers, and bioavailability or efficacy is of paramount importance. There are many aspects to this problem; crystallinity, intrinsic aqueous solubility, drug structure, and charge state of the drug molecule are important issues. The ability of a delivery vehicle to solubilize a drug, drug loading, and interaction of the delivery vehicle with membrane transporters (e.g., P-glycoprotein) are also important issues. The medium in which the drug delivery system is contained is a very significant issue.

Tamoxifen (Fig. 1) is a member of a class of compounds known as selective estrogen receptor modulators which have the capability of acting as estrogen receptor agonists in some tissues and as antagonists in other tissues.<sup>1,2</sup> Tamoxifen is an estrogen receptor agonist in bone, the cardiovascular system, and the endometrium, but acts as an antagonist in breast tissue. Tamoxifen is used clinically as a nonsteroidal antiestrogen for first-line endocrine treatment as well as adjuvant therapy in early and metastatic breast cancers in postmenopausal women. Tamoxifen is also approved as a prophylactic agent for women at high risk of developing breast cancer.

Tamoxifen is a weak base ( $pK_a \sim 8.8$ ) with very low aqueous solubility and a melting point of  $100^\circ\text{C}$ .<sup>3</sup> Commercially, tamoxifen base is converted to the citrate salt as a means of increasing the aqueous solubility and efficacy of tamoxifen.<sup>4</sup> However, the increase in tamoxifen solubility via salt formation is limited due to the higher melting point of tamoxifen citrate ( $146^\circ\text{C}$ ) which inhibits

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**Figure 1.** Structure of tamoxifen and the two major metabolites of tamoxifen, 4-hydroxytamoxifen and desmethyltamoxifen.

dissolution.<sup>5</sup> The Z-isomer of tamoxifen is biologically active but the E-isomer has limited biological activity.<sup>6,7</sup> Tamoxifen is a low-dose therapeutic agent typically given to patients for long periods of time.

Cyclodextrins (CD) are cyclic oligomers of glucose, which typically contain 6, 7, or 8 glucose monomers joined by  $\alpha$ -1,4 linkages; these oligomers are commonly called  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD, respectively. Topologically, cyclodextrins form a torus that has a hydrophobic interior and a hydrophilic exterior which allows the CD to be dissolved in water where it acts as a host molecule and forms inclusion complexes with hydrophobic guest molecules. This feature has led to the use of CD in pharmaceutical formulations.<sup>8,9</sup>

Unfortunately, unmodified cyclodextrins, particularly  $\beta$ -CD, are relatively crystalline and have limited aqueous solubility. In parenteral formulations this limited solubility is a very serious issue as renal concentration of the unmodified CD can lead to crystallization of the CD and necrotic damage.<sup>10</sup> Fortunately, the solubility of unmodified cyclodextrins in water can be significantly increased by the addition of a small number of substituents to the hydroxyl groups of the anhydroglucose monomers.<sup>11</sup> It is important to note that cyclodextrin derivatives that are similar in structure can provide significantly different solubilization, dissolution rates, and stabilization of drugs under otherwise similar conditions.

With regard to complexation of tamoxifen with cyclodextrins, Loftsson et al.,<sup>12</sup> have described the solubilization and stabilization of drugs, including tamoxifen, using hydroxypropyl- $\beta$ -CD (HPBCD) and other cyclodextrin derivatives. Loftsson found that the stabilizing effect in aqueous solutions was highly dependent upon the structure of the cyclodextrin derivative. Szejtli has described the use of drug/cyclodextrin/organic acid multicomponent systems in pharmaceutical formulations involving tamoxifen.<sup>13,14</sup> Szejtli found that incor-

poration of hydroxy acids, for example, tartaric acid, in formulations in a specific molar ratio based on cyclodextrin and drug, increased the solubilization of tamoxifen base. Similarly, Loftsson described the increase in complexation efficiency of a basic drug (tamoxifen) by addition of volatile acid (e.g., acetic acid) to an aqueous medium of basic drug and cyclodextrin. The volatile acid was then removed resulting in formation of solid cyclodextrin complexes of the unionized drug.<sup>15</sup> Fischer et al.<sup>16</sup> investigated the utility of HPBCD and sulfobutyl- $\beta$ -cyclodextrin in the solubilization and stabilization of Z-4-hydroxytamoxifen, a metabolite of tamoxifen (Fig. 1). Fischer found that a stable complex of 4-hydroxytamoxifen and cyclodextrin could be obtained in pH 7 saline solution.

Recently we have described the preparation and characterization of highly water-soluble (>50% w/v) hydroxybutenyl- $\beta$ -cyclodextrin (HBenBCD).<sup>17</sup> In this initial account, we reported that HBenBCD was very effective in solubilizing a broad spectrum of drugs including ibuprofen and glibenclamide. In this report, we describe our investigations into the ability of HBenBCD to solubilize tamoxifen base and tamoxifen citrate, the preparation and isolation of solid tamoxifen:HBenBCD complexes, novel formulations of tamoxifen and HBenBCD in organic (PEG 400) liquid formulations, and the dissolution of drugs from different tamoxifen:HBenBCD formulations. Our goals were to demonstrate increased solubility and enhanced dissolution profiles of tamoxifen due to complexation with HBenBCD and the development of suitable formulations for use in preclinical studies.<sup>18</sup>

## EXPERIMENTAL

### General Methods

Hydroxybutenyl- $\beta$ -cyclodextrin (HBenBCD, molar substitution = 4.7) was prepared according to



previously described methods.<sup>17</sup> The HBenBCD was dried at ca. 5 mm Hg at ambient temperature for ca. 14 h prior to use. The water content (Karl Fisher analysis) after drying was typically 2.2%. Tamoxifen base and tamoxifen citrate were obtained from Apin Chemicals and, with one exception, used without further purification or processing. As noted below, we did attempt to obtain amorphous tamoxifen by freeze drying a solution of tamoxifen base dissolved in EtOH. We were unsuccessful as the freeze-dried tamoxifen had virtually the same  $T_m$  and  $\Delta H$  as the native tamoxifen base. Although no attempt was made to characterize differences in morphology between the two physical forms, we did note that freeze dried tamoxifen powder had a much lower bulk density. Water was prefiltered through a Milli-Q<sup>TM</sup> Water System (Millipore Corporation) and had very low total organic and pyrogen content and low-ionic strength. Buffers were prepared using Millipore water.

Modulated differential scanning calorimetry (DSC) curves were obtained using a Q1000 TA spectrometer. First scan DSC heating curves were obtained by heating from 0 to 160°C at 5°/min with a modulation of 2° every 60 s. Prior to collecting the spectra, the instrument was calibrated versus indium-tin-water. Tamoxifen:HBenBCD complexes and physical mixtures were dried at 25°C at ca. 5 mm Hg for 5 days then taken from the vacuum oven and immediately sealed in a hermetic pan.

### Solubility Studies

Solubility measurements were made using a modified version of the traditional shaking flask method.<sup>19–21</sup> To each well of a 2 mL 96-well polypropylene mixing plate was added excess drug (ca. 5–10 mg). To each well of the preloaded 96-well mixing plate was added 300–500  $\mu$ L of water or buffer (blanks with no CD) or the appropriate CD solution. Each determination was made in triplicate. The blanks were used to determine the intrinsic solubility ( $S_o$ ) of drug in that solution, and the wells containing the CD solutions were used to determine the solubility of drug due to CD ( $S_c$ ). After addition of the stock solutions, the plate was sealed using aluminum foil with a nonvolatile adhesive on one surface. The plate was placed on a rotary shaking plate (Heidolph Titramax 1000) and the plate was shaken at 800–1200 rpm at 23  $\pm$  2°C for 48–72 h. Preliminary experiments showed that less

than 24 h was required to reach equilibrium. Longer mixing times were used both for convenience and to insure that we were well above the time required to reach equilibrium. During the mixing period, the plate was inspected to ensure that each well contained undissolved, excess drug. Additional drug was added if necessary.

Following the mixing period, the solutions in each well were transferred to the corresponding wells of a 96-well 2 mL multiscreen filter plate using a multichannel pipette. The bottom of each well was a hydrophilic membrane. The filter plate was placed on top of a vacuum manifold and the solutions were filtered at ca. 20 mm Hg into the corresponding wells of a 2 mL storage plate. The duration of the filtration period was typically no more than 60 s. The storage plate was then sealed with a silicon mat and samples were removed for analysis as appropriate.

The drug content in each well was determined by UV spectroscopy using a SpectraMax Plus 384 Molecular Devices multiwell plate reader. Typically, 10–20  $\mu$ L of drug solution was transferred to the corresponding well of a 96-well measurement plate (UV-STAR plates from Greiner with a spectral range of 190–400 nm) and diluted with 1:1 water:ethanol so that the absorbance was in the linear response range. Absorbance was converted to drug concentration using the appropriate absorptivity for the drug. The drug concentrations were then exported to the appropriate software package for final analysis. Additionally, the final pH of each well was measured to insure that the pH had not drifted significantly due to lack of buffering capacity.

The method described for solubility analysis was developed as a high-throughput method for analyzing many samples on a daily basis. Although HPLC can be used to determine drug concentration, we have found that UV spectroscopy is a much faster and cheaper method of analysis and can be used with >90% of the drugs we have examined. Typically, HPLC is only needed when the drug has both very poor water solubility and low-molar absorptivity or when there are questions about drug stability under the test conditions. In this study, there was no evidence (UV, NMR, LC/MS/MS) of tamoxifen degradation during complex preparation, dissolution studies, or in animal studies.<sup>18</sup> The maximum absorption for HBenBCD is less than 200 nm while the maximum absorption or assay wavelength for many drugs are typically 260–290 nm. In the present case, tamoxifen absorptivity at 280 nm is



32.5 abs/cm/(g/L) versus 0.003 abs/cm/(g/L) for HBenBCD. Hence, at the normal drug concentrations we obtain in these experiments and when the drug has a reasonable molar absorptivity, absorbance contributions by HBenBCD can be neglected. When absorbance contributions by HBenBCD become significant, a correction can be applied by collecting a background spectrum of HBenBCD (no drug) in the measurement solvent.<sup>19-21</sup>

#### Typical Methods for the Preparation of Tamoxifen:HBenBCD Complexes Or Physical Mixtures

The following are example procedures for preparing complexes or mixtures of tamoxifen with HBenBCD. These procedures have not been optimized.

##### Physical Solid Mixtures

Appropriate amounts of tamoxifen base or citrate and HBenBCD were loaded into the holder of a freezer mill (Spex Industries, Inc., Metuchen, NJ). After cooling to liquid nitrogen temperature, the samples were milled for 12 min at maximum mill speed. The samples were then transferred to glass jars and dried at 27 mm Hg for 1 h prior to use.

##### Solid Tamoxifen Base:HBenBCD Complex

A 20 wt% HBenBCD solution was prepared by dissolving 6 g of HBenBCD in phosphate buffer (0.05 M, pH 3). Tamoxifen base (901 mg) was added to this solution. The mixture was briefly vortexed and placed in a preheated (50°C) ultrasonic bath for 30 min. The sample was then placed on a rotary shaker and the temperature of the sample was maintained at 30°C. After ca. 66 h, solids were still present. The sample was removed from the shaker and the pH of the solution was adjusted from 6.5 to 3.1 before returning the sample to the shaker. After an additional 24 h, solids were still evident and the solution pH was 5.6. The sample was filtered through a 0.45 µm filter and the clear solution was freeze dried which provided 6.49 g of a white powder (94% yield). Using UV spectroscopy, the sample was determined to contain 7.2 wt% of tamoxifen base.

##### Solid Tamoxifen Citrate:HBenBCD Complex

A 20 wt% HBenBCD solution was prepared by dissolving 6 g of HBenBCD in phosphate buffer

(0.05 M, pH 3). To this solution was added 900 mg of tamoxifen citrate. The mixture was briefly vortexed and placed in a preheated (50°C) ultrasonic bath for 30 min. The sample was then placed on a rotary shaker and the temperature of the sample was maintained at 30°C. After ca. 66 h, the solution pH was 3.7 and no solids were evident by the naked eye (use of a laser pointer revealed the presence of small particles in the solution). The sample was filtered through a 0.45 µm filter and the clear solution was freeze dried to give 6.8 g of a white powder (>98% yield). Using UV spectroscopy, the sample was determined to contain 11.6 wt% of tamoxifen citrate.

##### Tamoxifen Base:HBenBCD PEG 400/PG Solution

To a 14 g solution of PEG 400 (39.1 wt%), propylene glycol (56.5 wt%), and water (4.4 wt%) was added 6 g of HBenBCD. The sample was vortexed and then mixed until a clear solution was obtained. Tamoxifen base (450 mg) was added and the sample was placed on a rotary shaker for ca. 96 h. Excess drug was removed by filtration at 60°C through a 45 µm filter. The sample was determined to contain 0.62 wt% of tamoxifen base by UV spectroscopy.

##### Tamoxifen Citrate:HBenBCD PEG 400/PG Solution

Tamoxifen citrate (751 mg) was suspended in 14 g of a 42.9 wt% solution of HBenBCD in PEG 400 (39.1 wt%), propylene glycol (56.5 wt%), and water (4.4 wt%). The sample was placed on a rotary shaker for ca. 96 h. Excess drug was removed by filtration at 60°C through a 45 µm filter. The sample was determined to contain 2.46 wt% of tamoxifen citrate by UV spectroscopy.

##### Tamoxifen Base:HBenBCD Prepared by Comixing of Solutions

Thus, 6 g of HBenBCD (6 g) was dissolved in 9 mL of water. In a separate vessel, 422 mg of tamoxifen base (7 wt%) was dissolved in 5 mL of absolute EtOH. The solution of tamoxifen base in EtOH was added slowly to the HBenBCD aqueous solution while stirring. The solution remained clear and nothing was observed to crystallize or precipitate when the solution was stored at ambient temperature overnight. The water/EtOH was removed *in vacuo* providing 6.5 g of a white solid. Thermal analysis of this material by DSC revealed the complete absence of a melting transition for tamoxifen in the first heating scan.



### Dissolution Studies

Dissolution studies were conducted at 37°C according to USP 28-NF 23 711 (United States Pharmacopeia, 2004). For these studies, the solid or PEG 400 liquid fill formulations were filled into hard shell Torpac lock ring gelatin capsules (Size #1 or #0). The apparatus used for the testing was a Varian VK 7000 dissolution tester. The pH values used for the experiments were selected on the basis of the pH normally found in the stomach or upper and lower GI tracts of humans.

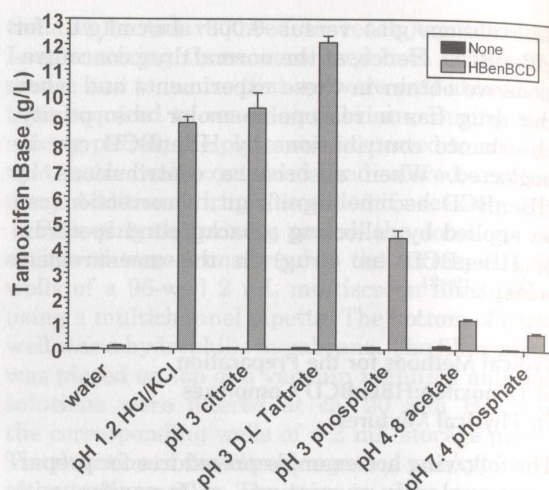
## RESULTS AND DISCUSSION

### Solubility Studies

The first step in our investigation into the ability of HBenBCD to solubilize tamoxifen was to measure the solubility of tamoxifen base and tamoxifen citrate in water and a series of relevant buffers; one set of these media did not contain HBenBCD and a second set contained HBenBCD (10 wt%). We typically conduct this type of initial screening using 5–10 wt% HBenBCD as we have found that increases in drug solubility are usually linear in this range while at higher concentrations, departure from linearity is often observed (*vide infra*).<sup>22</sup> Furthermore, we routinely determine the appropriate buffer strength to be used in this type of screening.

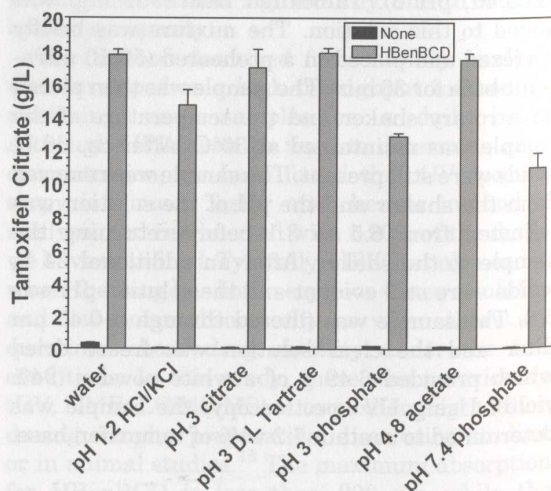
Use of buffers in drug formulations is often a balance between having sufficient buffering capacity and salting out effects due to the ionic strength of the media. In this context, we examined the solubility of tamoxifen base in the presence of 5 wt% HBenBCD in pH 3 phosphate buffers. In 0.025 and 0.05 M phosphate buffer, the amount of tamoxifen base solubilized by HBenBCD was essentially identical (134 mg/g HBenBCD) but in 0.10 M phosphate buffer, the amount of tamoxifen base solubilized was less (117 mg/g HBenBCD). For this reason, 0.05 M buffer was used in all subsequent studies in the report.

Figure 2 shows the results of this investigation for tamoxifen base. The intrinsic solubility ( $S_o$ ) of tamoxifen base in water was quite low (24 µg/mL) and the increase in solubility of tamoxifen base due to complexation with HBenBCD ( $S_i$ ) was only marginal ( $S_i/S_o = 5$ ). At pH 1.2, HBenBCD significantly increased tamoxifen base solubility ( $S_o = 37$  µg/mL,  $S_i/S_o = 241$ ). At pH 3, the solubility of tamoxifen was not only dependent upon the pH of the medium but, was also apparently upon the



**Figure 2.** Tamoxifen base solubility in water and buffers without cyclodextrin and with HBenBCD (10 wt%).

type of buffer. At pH 3, the lowest solubility was observed with the phosphate buffer ( $S_i/S_o = 49$ ) while the highest solubility was observed with the tartrate buffer ( $S_i/S_o = 175$ ). As would be expected, as the pH of the medium (4.9 and 7.4) approached the  $pK_a$  of tamoxifen the solubility of tamoxifen base in the presence of HBenBCD was greatly diminished.<sup>5</sup> Figure 3 shows the equivalent solubility data for tamoxifen citrate. The  $S_o$  ( $S_o = 329$  µg/mL) of the citrate salt of tamoxifen in water was much higher than that of



**Figure 3.** Tamoxifen citrate solubility in water and buffers without cyclodextrin and with HBenBCD (10 wt%).

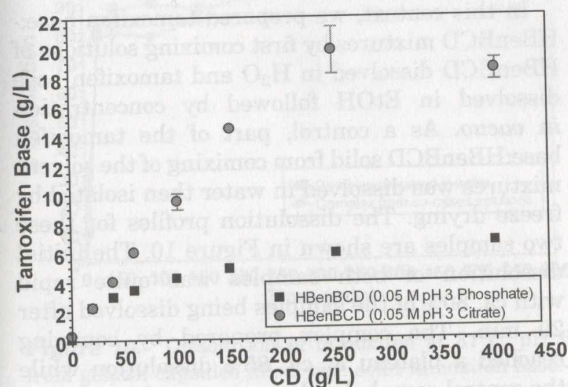


the free base but was somewhat diminished in the buffer solutions due to increased ionic strength of the media.<sup>5</sup> In the presence of HBenBCD, the solubility of tamoxifen citrate was significantly increased in all media;  $S_t/S_o$  ranged from 54 to 293.

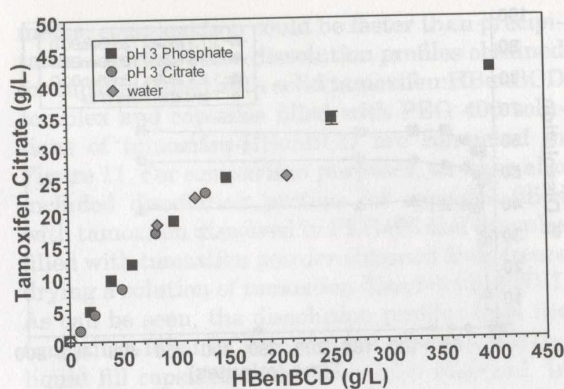
We next examined the solubility of tamoxifen base and tamoxifen citrate in different buffer systems at different concentrations of HBenBCD. Figure 4 shows the results obtained with tamoxifen base:HBenBCD in 0.05 M citrate and phosphate buffers. In the case of the citrate buffer, tamoxifen base solubility increases linearly with HBenBCD concentration until the HBenBCD concentration reaches ca. 25 wt% at which point the apparent drug solubility diminishes slightly. The equilibrium binding constant for the linear part of the curve was 681/M.<sup>23,24</sup> In the case of the pH 3 phosphate buffer, tamoxifen base concentration begins to flatten out much earlier at ca. 5 wt% HBenBCD. This behavior is indicative of formation of tamoxifen base:HBenBCD inclusion complexes with finite solubility ( $B_s$  solubility) which may in part rationalize the differences between the pH 3 buffer systems noted in Figure 2.<sup>22</sup> In contrast, the equilibrium solubility curves for tamoxifen citrate (Fig. 5) in water and 0.05 M citrate and phosphate buffers were essentially identical and were indicative of  $A_n$  phase solubility behavior. In pH 3 phosphate buffer, the equilibrium binding constant for tamoxifen citrate:HBenBCD in the linear part of the curve was 305/M.

#### Dissolution Studies

Figure 6 shows the dissolution of tamoxifen base and tamoxifen citrate (no HBenBCD) at pH 1.2



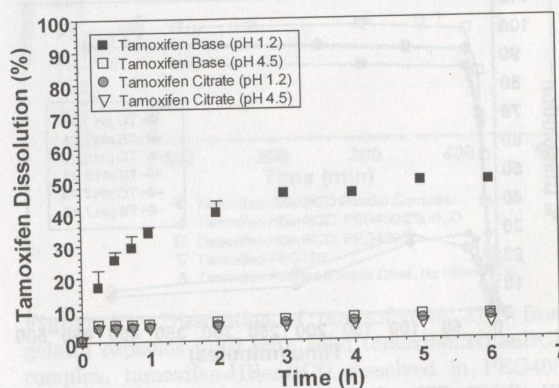
**Figure 4.** Tamoxifen base solubility in HBenBCD buffer solutions with varying HBenBCD concentration.



**Figure 5.** Tamoxifen citrate solubility in HBenBCD buffer solutions with varying HBenBCD concentration.

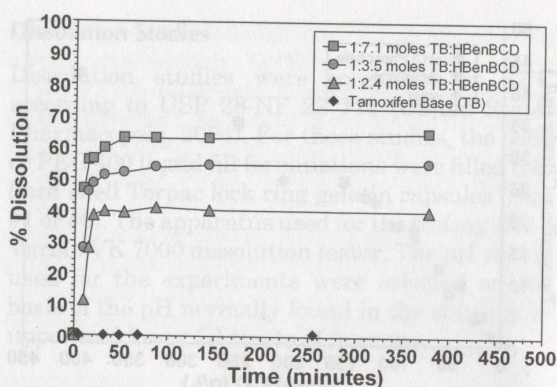
and 4.5. The initial dissolution of tamoxifen base at pH 1.2 was relatively slow (16% at 15 min) and a maximum dissolution of ca. 45% was reached in ca. 3 h. At pH 4.5, the dissolution of tamoxifen base was minimal with only 5 wt% being dissolved after 6 h. The dissolution profiles for tamoxifen citrate were relatively insensitive to pH. At pH 1.2 and 4.5, the dissolution profiles overlapped and the maximum dissolution reached was ca. 5%.

We also studied the dissolution of dry milled physical mixtures of tamoxifen base and HBenBCD in which the molar ratios of tamoxifen base and HBenBCD were varied (Fig. 7). In all cases, the initial dissolution of tamoxifen base was rapid, reaching a plateau after ca. 20–50 min. As can be seen, the total amount of tamoxifen base dissolved increased as the molar HBenBCD:tamoxifen base ratio increased. These observations



**Figure 6.** Dissolution of tamoxifen base (TB) and tamoxifen citrate (TC) at pH 1.2 and 4.5 (no HBenBCD) at 37°C from gelatin capsules.

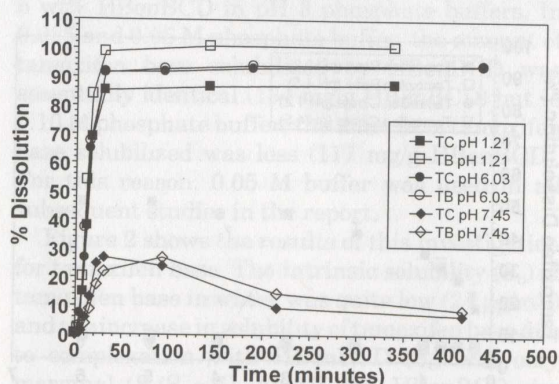




**Figure 7.** Dissolution of tamoxifen at 37°C from gelatin capsules filled with tamoxifen base (TB) and tamoxifen base:HBenBCD physical mixtures (pH 6.0).

indicate that complex formation can be rapid and that it is not necessary to preform a complex with HBenBCD to achieve increased tamoxifen dissolution.

In order to compare the dissolution of tamoxifen base:HBenBCD and tamoxifen citrate:HBenBCD complexes, these complexes were prepared each containing equivalent amounts of tamoxifen on the basis of tamoxifen base (80 mg/mL, 1:3 molar ratio of tamoxifen:HBenBCD). The dissolution of the complexes was then evaluated at pH 1.2, 6.0, and 7.5 (Fig. 8). At pH 1.2, 100% dissolution of tamoxifen base was achieved in ca. 30 min versus 85% for tamoxifen citrate. At pH 6.0, the dissolution profiles of tamoxifen base and citrate were equivalent reaching ca. 92% dissolution within



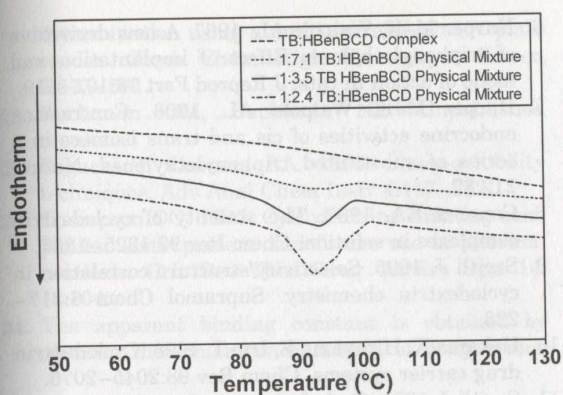
**Figure 8.** Dissolution of tamoxifen at 37°C from gelatin capsules filled with solid tamoxifen base: HBenBCD and tamoxifen citrate:HBenBCD complexes at pH 1.2, 6.0, and 7.45.

30 min. At pH 1.2 and 6.0, precipitation of tamoxifen was not observed during the time scale of the experiment. At pH 7.5, the dissolution profiles for tamoxifen base and citrate were similar. The dissolution rate of tamoxifen citrate was only slightly faster than that of tamoxifen base; the total amount of tamoxifen dissolved was essentially equivalent. In both cases, the percentage of drug dissolved reached a maximum of 26% then decreased as the drugs precipitated. Precipitation of a basic drug can often be expected as the pH of the medium approached its  $pK_a$ . What is noteworthy is that, in the presence of HBenBCD, the dissolution profile of tamoxifen base was equivalent to the salt.

As noted above, acceptable dissolution of tamoxifen can be achieved simply by preparing physical mixtures. However, if one compares the results presented in Figures 7 and 8, it can be seen that the preformed tamoxifen:HBenBCD complexes provided more rapid dissolution rates with increased dissolution of tamoxifen. In the case of the 1:3.5 tamoxifen base:HBenBCD physical mixture, the dissolution of tamoxifen reached a plateau at ca. 52% after 50 min. In the case of the 1:3 tamoxifen base:HBenBCD complex, the dissolution of tamoxifen leveled out at ca. 92% after 30 min. This difference in dissolution profiles may in part be due to the difficulty in achieving a completely amorphous physical mixture of tamoxifen-HBenBCD by milling. Analysis by modulated DSC of the physical mixtures revealed the presence of a melting endotherm corresponding to that of tamoxifen;  $\Delta H$  for the melting endotherm increased as the amount of HBenBCD decreased. In contrast, DSC analysis of the preformed complex revealed the complete absence of a melting endotherm (Fig. 9).

In this context, we prepared tamoxifen base:HBenBCD mixtures by first comixing solutions of HBenBCD dissolved in  $H_2O$  and tamoxifen base dissolved in EtOH followed by concentration *in vacuo*. As a control, part of the tamoxifen base:HBenBCD solid from comixing of the solvent mixtures was dissolved in water then isolated by freeze drying. The dissolution profiles for these two samples are shown in Figure 10. The initial dissolution of both samples was quite rapid with ca. 80% of the samples being dissolved after 20 min. The complex prepared by comixing reached a plateau at ca. 85% dissolution while the control sample leveled out at ca. 90%. Collectively, the results presented in Figures 7–10 indicate that tamoxifen:HBenBCD complexes

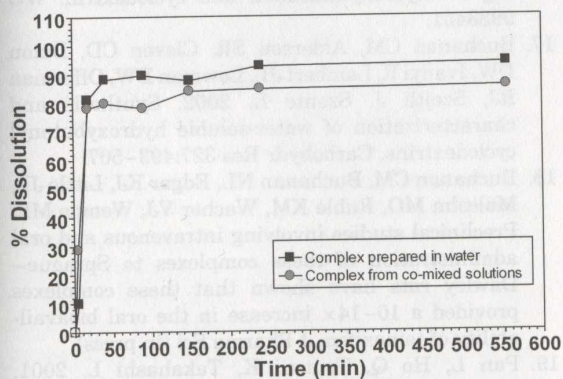




**Figure 9.** DSC spectra for a preformed tamoxifen base:HBenBCD complex and for physical mixtures of tamoxifen base and HBenBCD. The melting point of native tamoxifen base is 100°C.

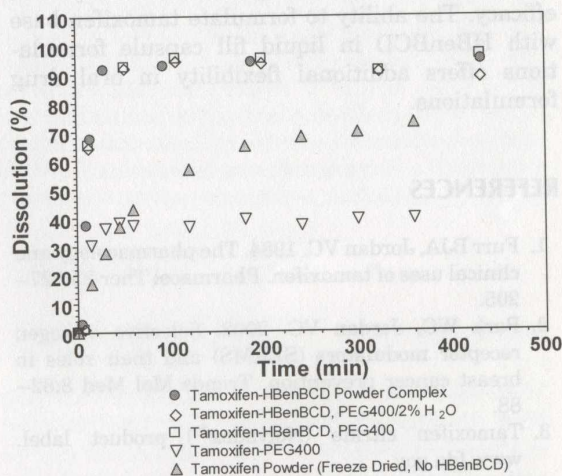
with favorable dissolution profiles can be prepared by different techniques provided that the drug in the final mixture is amorphous.

The observations with comixing of solutions encouraged us to explore the feasibility of preparing drug:HBenBCD mixtures in water-soluble organic solvents that may be suitable for liquid fill capsule formulations. With HBenBCD, this seemed plausible as we had found that HBenBCD was soluble (ca. 50 wt%) in solvents commonly used in liquid fill formulations. We had no expectation that the drug and HBenBCD would form complexes in these solvents but we anticipated that during dissolution or mixing in aqueous



**Figure 10.** Dissolution of tamoxifen at 37°C, pH 6 from gelatin capsules filled with solid tamoxifen base:HBenBCD complexes prepared by (a) comixing of tamoxifen base/ethanol solution with HBenBCD/water solution and (b) prepared by mixing in water.

media, complexation could be faster than precipitation of drug.<sup>25</sup> The dissolution profiles obtained for capsules filled with solid tamoxifen:HBenBCD complex and capsules filled with PEG 400 solutions of tamoxifen-HBenBCD are compared in Figure 11. For comparison purposes, we have also included dissolution profiles for capsules filled with tamoxifen dissolved in PEG400 and capsules filled with tamoxifen powder obtained from freeze drying a solution of tamoxifen dissolved in EtOH. As can be seen, the dissolution profiles from the tamoxifen-HBenBCD solid filled capsules and the liquid fill capsules were essentially identical. In both cases, dissolution was rapid and no precipitation of tamoxifen was observed over the course of the experiment. In the case of the tamoxifen solution (no HBenBCD), upon rupture of the capsule 30%–40% of the drug remained in solution; the remaining drug was observed to precipitate virtually immediately. In the case of capsules filled with freeze-dried tamoxifen (no HBenBCD), the tamoxifen slowly dissolved over time. The rate and extent of tamoxifen dissolution was much less than that observed when HBenBCD was present. However, comparison of the dissolution profile of the freeze-dried tamoxifen to that of the native tamoxifen (Fig. 6) shows that freeze drying of the tamoxifen improved the rate and extent of dissolution relative to the native



**Figure 11.** Dissolution of tamoxifen at 37°C from gelatin capsules filled with solid tamoxifen:HBenBCD complex, tamoxifen-HBenBCD dissolved in PEG400, tamoxifen dissolved in PEG400 (no HBenBCD), or tamoxifen (no HBenBCD) obtained by freeze drying. All experiments were conducted in pH 6 buffer except tamoxifen (no HBenBCD) which was conducted at pH 4.5.



tamoxifen. These findings are significant in that liquid fill formulations could provide additional formulation flexibility for drug:HBenBCD complexes and in some cases will offer a means of higher drug loading relative to solid oral formulations.

## CONCLUSIONS

In this account, we have shown that complexation of tamoxifen base or citrate with HBenBCD was a very effective means for increasing the solubility of tamoxifen in aqueous media. The pH of the medium and the choice of buffer significantly impacted the amount of drug that could be solubilized. Solid and liquid formulations of tamoxifen:HBenBCD inclusion complexes or physical mixtures were prepared by a number of different methods. Dissolution studies using these complexes or physical mixtures revealed that the dissolution profile of tamoxifen could be significantly improved relative to the parent drug.

Collectively, these results indicate that by formulating tamoxifen base with HBenBCD, it is possible to obtain solubility and dissolution profiles essentially identical to that of tamoxifen citrate. These formulations potentially could eliminate the need to convert this basic drug to a salt in order to obtain improved solubility and efficacy. The ability to formulate tamoxifen base with HBenBCD in liquid fill capsule formulations offers additional flexibility in oral drug formulations.

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  24. The apparent binding constant is obtained by plotting the molar concentration of drug versus molar concentration of complexing agent. A fit to the initial linear portion of the curve allows one to calculate the apparent binding constant;  $K = \text{slope} / S_0(1 - \text{slope})$ . Although this equation is commonly used, one should note that the intrinsic solubilities ( $S_0$ ) for poorly water-soluble drugs are typically very small and difficult to measure accurately. Small variations in  $S_0$  will significantly impact the reported binding constant.
  25. The details of cyclodextrin liquid fill formulations exceed the scope of this paper and will be presented elsewhere. Buchanan CM, Buchanan NL, Lambert JL, Ramsey MG. Unpublished results.