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Preparation of solid drug/cyclodextrin complexes of acidic and basic drugs

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One of the main obstacles in pharmaceutical applications of cyclodextrins is their increase of the formulation bulk. Even at maximum incorporation 500 mg of a solid drug/cyclodextrin complex will only contain between 50 and 125 mg of the drug, assuming a low molecular weight drug (MW 200 to 400 Dalton) and an average molecular weight cyclodextrin (MW about 1500 Dalton). In general, the complexation efficiency is low and consequently the complex powder contains a significant amount of empty cyclodextrin molecules. In the present study the complexation efficiency is increased by ionization of the drug molecule through addition of volatile acid (i.e. acetic acid) or base (i.e. ammonia) to the aqueous complexation media of basic or acidic drugs, respectively. The volatile acid or base was then removed during lyophilization and heating in a vacuum oven resulting in formation of solid cyclodextrin complexes of the unionized drug. Thus, the complexation efficiency was temporary increased by the ionization but then again decreased leading to formation of the thermodynamically unstable solid drug/cyclodextrin complexes. When dissolved the energy of the system was lowered by expelling the drug molecules from the cyclodextrin cavities resulting in formation of supersaturated drug solutions and ultimately precipitation of the drug.

1. Introduction

For a variety of reasons including production cost, formulation bulk and toxicological considerations, only limited amounts of cyclodextrin can be included in drug formulations (Loftsson and Brewster 1996; Loftsson 1998; Loftsson et al. 1999; Redenti et al. 2000; Mura et al. 2001). For example, the ideal weight of solid oral dosage forms, such as tablets, is between 100 and 500 mg. Even at high drug incorporation rates, 500 mg of a solid drug/cyclodextrin complex would only contain between 50 and 125 mg of drug, assuming a drug with a molecular weight between 200 and 400 Dalton and a cyclodextrin with a molecular weight of between 1200 and 1500 Dalton. Thus, even under ideal conditions, where every drug and cyclodextrin molecule is in a complex, cyclodextrin complexation will result in a 4- to 10-fold increase in the formulation bulk. In general only some fraction of the cyclodextrin molecules forms a complex and, thus, the complex powder produced contains a mixture of drug/cyclodextrin complexes and free cyclodextrin molecules. The increase in formulation bulk limits the use of cyclodextrins in solid oral dosage forms to relatively potent drugs that possess good complexing properties.

Several techniques have been used in an effort to enhance cyclodextrin complexation of drugs (Hirayama and Uekama 1987; Loftsson and Brewster 1997; Hedges 1998). For example, addition of organic solvents, such as ethanol, to the aqueous complexation media increases the apparent intrinsic solubility (S_0) of the drug. Enhanced S_0 shifts the complexation equilibrium towards complexation resulting in enhanced complexation efficiency (Loftsson et al. 1999). However, organic solvent molecules can compete with drug molecules for a space in an the cyclodextrin cavity with subsequent decrease in apparent stability constant (K_C) of the drug/cyclodextrin complex (Pitha and Hoshino 1992). Thus, addition of organic solvents can result in an overall decrease in efficiency. It has been shown that for neutral cyclodextrin such as 2-hydroxypropyl-β-cyclodextrin (HPβCD) the stability constant of the drug/cyclodextrin complex decreased from 2- to 30-fold upon ionization of the drug molecule (Zia et al. 2001). However, it is sometimes possible to enhance cyclodextrin solubilization of ionizable drugs by appropriate pH adjustments (Menard et al. 1988; Loftsson and Bodor 1989; Abdi et al. 1993; Helm et al. 1995; Krishnamoorthy and Mitra 1996; Loftsson et al. 1996). Ionization of an ionizable drug molecule increases S_0 and although some decrease in K_C is generally observed (due to decreased affinity of the drug molecule for the lipophilic cyclodextrin cavity), the increase in S_0 is frequently more than enough to compensate for the decrease, resulting in overall enhanced complexation efficiency. Frequently, increase in aqueous solubility by a factor of 10 to 100 (e.g. a change of pH by 1 to 2 units) can result in a notable increase in the complexation efficiency.

Addition of certain low molecular weight acids, such as acetic, citric, malic, or tartaric acid, to aqueous complexation media can enhance cyclodextrin solubilization of basic drugs through increase in both S_0 and K_C or through salt formation (Agharkar et al. 1976; Loftsson and Bodor 1989; Redenti et al. 2000). Comparable results have been obtained with acidic drugs (Torres-Labandeira et al. 1990). Various pharmaceutical polymers, such as water-soluble

cellulose derivatives and other rheological agents, can form complexes with cyclodextrins (Valero et al. 2003). It has been shown that such multi-component complexes possess physicochemical properties distinct from those of individual cyclodextrin molecules. Not only do the polymers increase K_C but also the aqueous solubility of the drug/cyclodextrin complex resulting in increased drug availability of the complexation media (Loftsson et al. 1994; Ganzerli et al. 1996; Loftsson 1998; Mura et al. 2001). Finally, it is possible to increase S_0 of drug through derivatization (i.e. through formation of water-soluble prodrugs). For example, benzodiazepines are known to undergo a reversible ring-opening reaction in aqueous solutions (i.e. ring-opening of the 1,4-benzodiazepine ring). The ring-open form is somewhat more water-soluble than the ring-closed form and, thus, the apparent S_O increases upon the ring-opening resulting in enhanced cyclodextrin complexation (Loftsson et al. 2001).

The objective of this present study is to enhance the complexation efficiency during preparation of solid drug/cyclodextrin complexes. The complexation efficiency of water-insoluble basic or acidic drugs was temporarily increased through ionization of the drug in an aqueous medium by addition of volatile acid or volatile base, respectively. The acid or base was then removed from the complex during a drying process, resulting in formation of unionized drug/cyclodextrin complexes.

2. Investigations, results and discussion

Many low-molecular acids and bases are volatile in their unionized form and, thus, evaporate from solid surfaces at relatively low temperature (Table). The hypothesis was that addition of volatile weak acids to the aqueous complexation medium of weakly basic drugs, or volatile weak bases to the aqueous complexation medium of weakly acidic drugs, would increase the apparent intrinsic solubility (S_0) of the drug through ionization and, consequently, shift the complexation equilibrium towards complex formation:

$$D + CD = D/CD \quad (1)$$

or

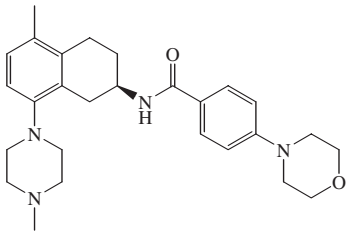
$$K_C = \frac{[D/CD]}{[D] \cdot [CD]} \quad (2)$$

Table: Some volatile weak acids and bases

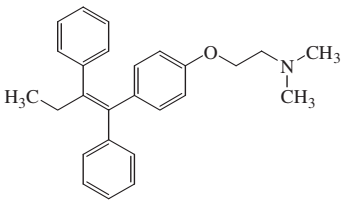
	pKa*	Boiling point at 760 Torr (°C)	Vapor pressure (Torr)	
			at 25 °C	at 88 °C
Acids				
Hydrogen sulfide	7.0	60	16,000	66,000
Formic acid	3.8	101	34	620
Acetic acid	4.7	118	16	250
Propionic acid	4.9	141	3.3	130
Isobutyric acid	4.8	153	2.3	61
n-Butyric acid	4.8	164	1.2	38
Chloroacetic acid	2.9	189	0.3	14
Bases				
Ammonia	9.3	−33	7,400	44,000
Trimethylamine	11.0	3	~2,000	
Diethylamine	11.1	7	1,300	9,200
Ethylamine	10.7	17	900	6,800
n-Propylamine	10.7	49	270	2,400
Pyridine	5.3	115	19	320

* At room temperature. For the bases the pKa value given is the pKa of the corresponding acid. Data obtained from Weast (1971).

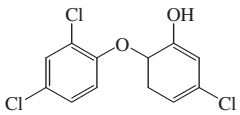
where concentration of free drug ([D]) is equal to S_0 (i.e. when the complexation medium is saturated with the drug), [CD] is the concentration of free cyclodextrin and [D/CD] is the concentration of the complex (assuming 1 : 1 molar ratio of drug and cyclodextrin in the complex). Since the corresponding acids of weakly basic drugs have the tendency to release a proton it was assumed that volatile acids could be removed from solid basic drug/cyclodextrin complexes by heating the complex powder under reduced pressure. By the same analogy it was assumed that volatile weak bases could be removed from solid complexes of acidic drugs and cyclodextrins by heating under reduced pressure. Two basic drugs, AR-A000002 and tamoxifen, and one acidic antibacterial agent, triclosan, were selected to test this hypothesis.



AR-A000002 pKa 8.3



Tamoxifen pKa about 11



Triclosan pKa 7.9

AR-A000002 was added to an equimolar solution of HPβCD in water or an equimolar suspension of βCD in water and up to 20 equivalents of acetic acid were added to this complexation media. After heating and equilibration at room temperature (about 23 °C) the aqueous complexation media was lyophilized and sieved through a

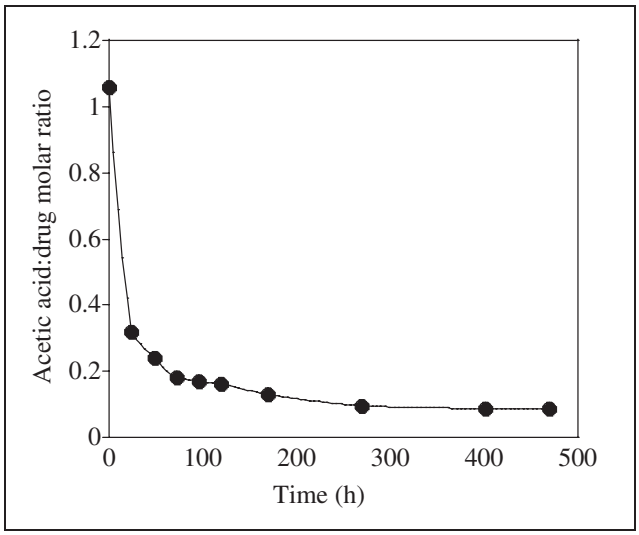


Fig. 1: The rate of acetic acid evaporation from the AR-A000002/HPβCD complex powder in a vacuum oven at 88 °C and 0.1 Torr. The complex was prepared using 20 equivalents of acetic acid but after lyophilization and before heating in vacuum oven the molar ratio of drug, cyclodextrin and acetic acid was 1 : 1 : 1

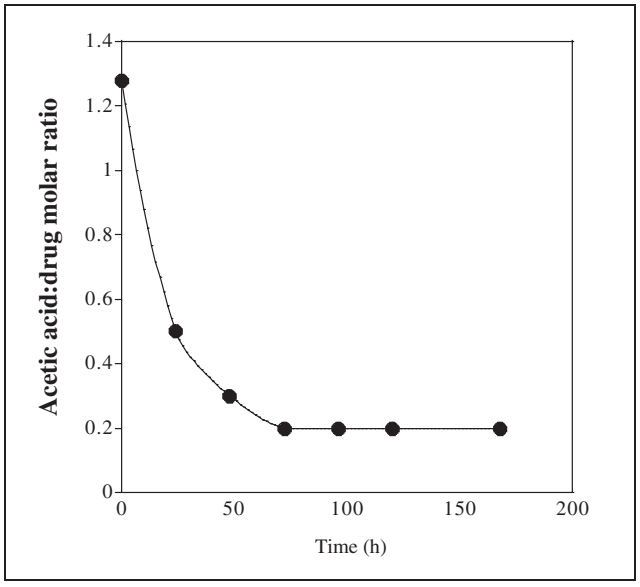


Fig. 2: The rate of acetic acid evaporation from the AR-A000002/βCD complex powder in a vacuum oven at 88 °C and 0.1 Torr. The complex was prepared using 5 equivalents of acetic acid but after lyophilization and before heating in vacuum oven the molar ratio of drug, cyclodextrin and acetic acid was 1 : 1 : 1.3

300 μm sieve. Then, the complex powder was heated at 88 °C under vacuum (0.1 Torr) for up to 8 days. The amount of acetic acid in the complex powder was analyzed at various time points. Figs. 1 and 2 are representative Figures which show the removal of acetic acid from the AR-A000002 complexes. Acetic acid is a weak acid with relatively high vapor pressure (Table). The AR-A000002/HPβCD complex (Fig. 1) was prepared using 20 equivalents of acetic acid (i.e. the initial molar ratio was 1 : 1 : 20). During the lyophilization all unbound acetic acid was removed from the complex powder and thus the molar ratio of drug, cyclodextrin and acetic acid after lyophilization was approximately 1 : 1 : 1. After heating in a vacuum oven for 7 h at 88 °C and 0.1 Torr the amount of acetic acid dropped down to about 0.1 equivalents. The residual acetic acid was then very slowly removed up on further heating dropping down to 0.08 equivalents after heating for 20 days. The AR-A000002/βCD complex (Fig. 2) was prepared using 5 equivalents of acetic acid. After lyophilization the complex the molar ratio of drug, cyclodextrin and acetic acid was 1 : 1 : 1.3. Heating in a vacuum oven for 72 h at 88 °C and 0.1 Torr lowered the ratio to 1 : 1 : 0.2. The differences in the removal rate of acetic acid could be due to the porosity of the complex powder. Evaporation of the acid is a surface phenomenon and the rate is proportional to the effective surface area of the complex particles. Tamoxifen was added to an equimolar suspension of βCD in water and, independent of the initial amount of acetic acid, the molar ratio of drug, cyclodextrin and acetic acid was approximately 1 : 1 : 1 after lyophilization. The tamoxifen/βCD complex shown in Fig. 3 was prepared using 5 equivalents of acetic acid (i.e. the initial molar ratio was 1 : 1 : 5). After lyophilization the drug, cyclodextrin acetic acid molar ratio was 1 : 1 : 1.3 but heating for 48 hours at 88 °C and 0.1 Torr lowered the ratio to 1 : 1:0.2. Further heating resulted in a very slow evaporation of acetic acid (Fig. 3).

Ammonia has a much higher vapor pressure than acetic acid (Table) and, thus, it was completely removed from the triclosan/βCD complex up on lyophilization, independent of the initial amount of ammonia used during the complexation process. Triclosan is a very weak acid (pKa 7.9) and, thus, the corresponding base has a strong tendency to remove a proton from the ammonium ion. About 0.5 equivalent of ammonia was found in the lyophilized βCD complexes of somewhat stronger acids, such as of ibuprofen (pKa 5.2) and naproxen (pKa 4.2). Heating in a vacuum oven removed ammonia from these complexes (data not shown).

The complexes formed through this ionization complexation method consist mainly of cyclodextrin complexes of the unionized drugs. The complexation efficiency was increased temporarily by increasing S_0 but decreased again after the drug was converted to the unionized form. However, the drug molecule is unable to leave the cyclodextrin cavity while the complex is in a solid state. In other words, the drug/cyclodextrin complexes are thermodynamically unstable. When dissolved the energy of the sys-

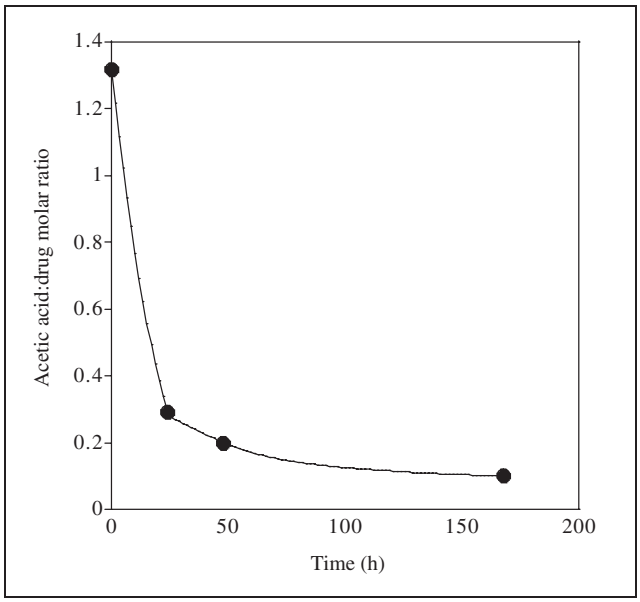


Fig. 3: The rate of acetic acid evaporation from the tamoxifen/βCD complex powder in a vacuum oven at 70 °C and 0.1 Torr. The complex was prepared using 5 equivalents of acetic acid but after lyophilization and before heating in vacuum oven the molar ratio of drug, cyclodextrin and acetic acid was 1 : 1 : 1.3

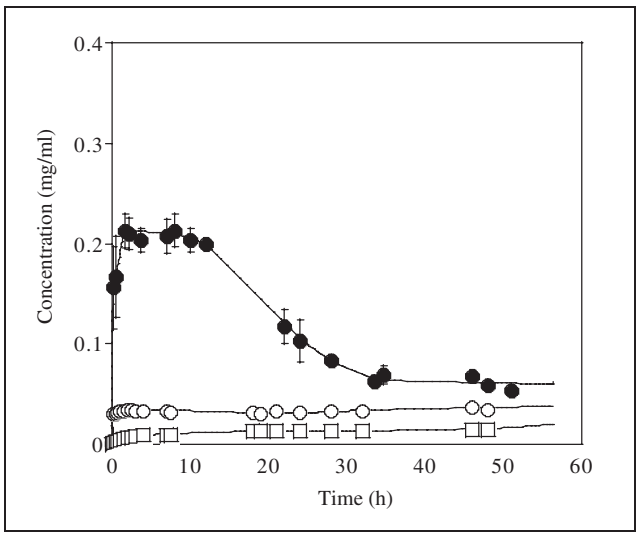


Fig. 4: Dissolution profile of AR-A000002/HPβCD complex prepared with acetic acid (molar ratio 1 : 1 : 0.3) (●), AR-A000002/HPβCD complex prepared without acetic acid (○) and pure AR-A000002 (non-lyophilized) (□) at room temperature. Mean ± SD (n = 3)

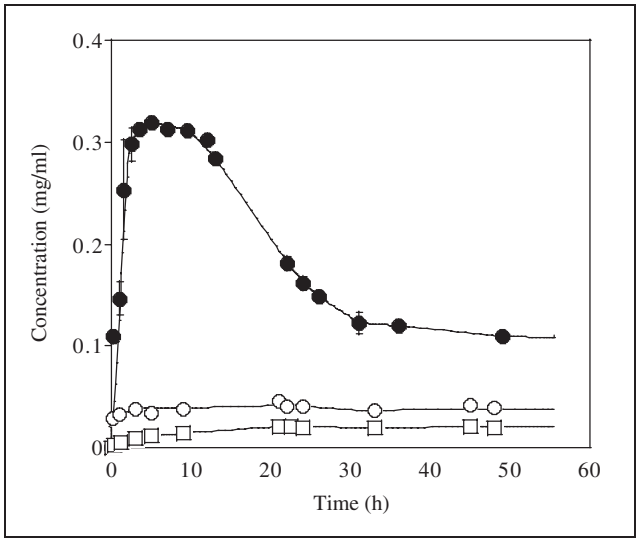


Fig. 5: Dissolution profile of AR-A000002/βCD complex prepared with acetic acid (molar ratio 1 : 1 : 0.7) (●), AR-A000002/βCD complex prepared without acetic acid (○) and pure AR-A000002 (non-lyophilized) (□) at room temperature. Mean ± SD (n = 3)

tem will be lowered by expelling drug molecules from the cyclodextrin cavities, formation of a supersaturated drug solution and eventually precipitation of the drug. It has been shown that drug delivery through biological membranes can be enhanced by formation of supersaturated drug solutions (Smith and Surber 1999; Iervolino et al. 2001).

The dissolution of the AR-A000002/HPβCD complex is shown in Fig. 4. The complex was prepared as previously described and the drug, cyclodextrin and acetic acid molar ratio in the dry complex was 1 : 1 : 0.03. This complex did dissolve very rapidly forming a supersaturated AR-A000002 solution (releasing about 45% of the drug) that was stable for about 10 h before precipitating. The AR-A000002/HPβCD complex prepared without acetic acid did not form supersaturated AR-A000002 solution under these experimental conditions and pure AR-A000002 dissolved very slowly. The solubility of AR-A000002 in the aqueous buffer solution at room temperature was determined to be 0.03 mg/ml when no HPβCD was present but

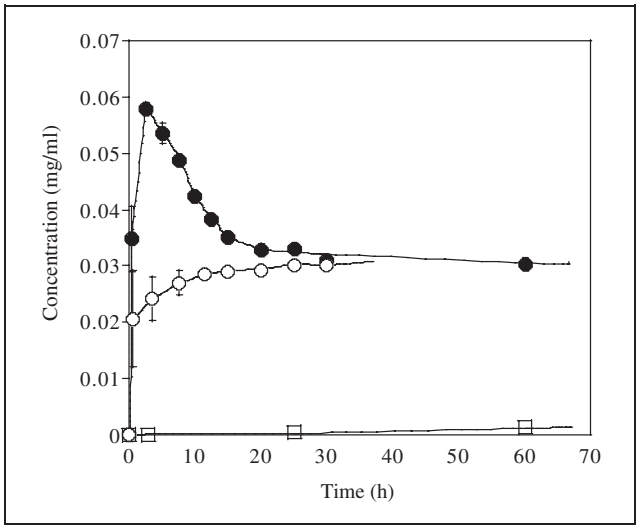


Fig. 6: Dissolution profile of triclosan/βCD complex prepared with ammonia (●), triclosan/βCD complex prepared without ammonia (○) and pure triclosan (non-lyophilized) (□) at room temperature. Mean ± SD (n = 3)

0.05 mg/ml when equimolar HPβCD was present. Comparable results were obtained when HPβCD was replaced by the parent βCD (Fig. 5). A supersaturated AR-A000002 solution was initially formed when the AR-A000002/βCD complex (releasing about 60% of the drug), which had been prepared in the presence of acetic acid, was dissolved. The complex that was prepared by an identical method but without acetic acid, did not form a supersaturated AR-A000002 solution. The acidic antibacterial agent triclosan did also form supersaturated solution when the triclosan/βCD complex, prepared with ammonia, was dissolved (Fig. 6). All triclosan in the complex was dissolved forming a supersaturated triclosan solution which then precipitated. The triclosan/βCD complex prepared by the same method but without ammonia did not form supersaturated triclosan solution under these experimental conditions and free triclosan was dissolved very slowly.

The dissolution studies show that high-energy drug/cyclodextrin complexes are formed when the complexation efficiency is temporary increased by increasing S_0 with the aid of volatile acid or base. When dissolved the drug molecules are more efficiently released from these high-energy drug/cyclodextrin complexes forming thermodynamically unstable supersaturated drug solutions. This property of the high-energy complexes could result in enhanced drug delivery through biological membranes, and consequently enhanced drug bioavailability, compared to conventional drug/cyclodextrin complexes.

3. Experimental

3.1. Materials

AR-A000002 (*N*-[(2*R*)-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-morpholin-4-ylbenzamide) was from AstraZeneca R&D (Södertälje, Sweden), tamoxifen and triclosan were purchased from Sigma (St. Louis, Mo), 2-hydroxypropyl-β-cyclodextrin of molar substitution 0.6 (Encapsin™; HPβCD) from Janssen Pharmaceutica N.V. (Beerse, Belgium), β-cyclodextrin (βCD) from Wacker-Chemie (Burghausen, Germany), ibuprofen and naproxen from Icelandic pharmaceuticals (Reykjavik, Iceland), and glacial acetic acid (analytical grade) and 32% aqueous ammonia solution (extra pure) from Merck (Darmstadt, Germany). All other chemicals used were of pharmaceutical or special analytical grade.

3.2. Preparation of the solid complexes

HPβCD or βCD was dissolved or suspended in distilled water and an equal molar amount of the drug to be tested was added to the solution. Then 0, 1, 5 or 10 mol equivalents of glacial acetic acid or 32% aqueous ammonia solution was pipetted into the solution, for the basic (i.e. AR-A000002 and tamoxifen) or acidic drug (triclosan) respectively. The solutions were subsequently heated in an autoclave for 20 min at 121 °C to dissolve the drug (the heating was not necessary if the drug and/or βCD already dissolved by the volatile acid or base). The solutions were then placed in a shaker for 1 h, during cooling, and subsequently lyophilized for 20–28 h (Snijders Scientific 2040 Lyophilizer, Tilburg, Holland). The solid powder was sieved through a 300 μm sieve and 30–50 mg were reserved for analysis. The remaining powder was heated in vacuum oven (Gallenkamp, UK) at 88 °C at 0.1 Torr for up to 8 days. Samples were removed from the vacuum oven at various time points and analyzed.

3.3. Quantitative determinations

The amount of drug in the solid complex powder was determined HPLC by consisting of a ConstaMetric 3200 solvent delivery system operated at 1.5 ml/min, a SpectroMonitor 3200 UV/VIS variable-wavelength detector, a Merck-Hitachi AS-2000A autosampler, Merck Hitachi D-2500 Chromato-Integrator and a Phenomex ODS 5 μm (150 × 4.6 mm) column. The mobile phase for AR-A000002 consisted of acetonitrile and 0.05 M aqueous pH 3 phosphate buffer (35 : 65), the wavelength was 287 nm and the retention time 2.3 min. For tamoxifen the mobile phase consisted of methanol, acetonitrile, water and glacial acetic acid (18 : 55 : 27 : 0.1), the wavelength was 254 nm and the retention time 2.7 min. For triclosan the mobile phase consisted of acetonitrile and water (74 : 26), the wavelength was 283 nm and the retention time 2.9 min.

Indirect measurement of acetic acid was performed by measuring the increase in light absorbance (Perkin-Elmer Lambda 3A UV/VIS spectrophotometer) due to NADH formation. A special analytical kit for the quantitative determination of acetic acid (Boehringer Mannheim, Cat. No. 148 261) was used for these purposes. The detection limit was less than 0.05 equivalents (or 0.03 μmol).

Quantitative determination of ammonia was performed as follows. Five mg of each complex without ammonia were dissolved in 3 ml of distilled water and the solution titrated with ammonia in 0.1 equivalent intervals while the pH of the solution was monitored. The unknown sample was then dissolved in the same amount of water and the exact pH was determined. The amount of ammonia in the unknown sample was then determined from the titration curves. The detection limit was about 0.05 equivalents (or 0.12 μmol).

3.4. Drug dissolution rate studies

The dissolution apparatus consisted of 50 ml beakers, each containing 5 mm stirrer bar (60 rpm), which were placed on a Variomag multi-position electromagnetic stirrer (Germany). The dissolution medium (25 ml) consisted of 0.1 M aqueous pH 7.4 phosphate buffer (AR-A000002 and tamoxifen) or 0.01 M aqueous pH 4.5 acetate buffer (triclosan). Samples (50 mg) of the complex powder, or of the pure drug (10 mg), were pored into the beaker at time zero. Small samples (0.1 ml) were removed from the dissolution medium at various time points up to 50 h and analyzed by HPLC. Each experiment was performed three times and the results shown are the mean values ± standard deviation (SD).

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