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RESEARCH PAPER

Different Dissolution Media Lead to Different Crystal Structures of Talinolol with Impact on Its Dissolution and Solubility

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ABSTRACT

During the performance of dissolution tests with immediate and controlled-release talinolol tablets it was detected that the type of the buffer used as dissolution medium had a strong influence on the solubility and the dissolution behavior of the drug. It was proven that talinolol appeared in different crystal structures with strongly differing solubilities when pure water, acetate, or phosphate buffers were employed as dissolution media. The resulting crystal structures were characterized by means of light microscopy, differential scanning calorimetry, and X-ray powder diffraction. All methods were adjuvant to detect changes in talinolol crystal structures. The different solubility and dissolution properties of the talinolol salts or modifications may be viewed as a source for its incomplete and variable bioavailability. Furthermore, the food effect, described in the literature, that leads to a decrease in talinolol absorption, could be due to changes in the composition of gastrointestinal fluids leading to different talinolol crystal structures. Furthermore, it was detected that the addition of sodium chloride increases talinolol solubility and accelerates its dissolution from controlled-release tablets at concentrations between 0% and 1.25%, while an addition of sodium dodecylsulfate (SDS) as surfactant only had a solubility-improving effect at concentrations $>0.75\%$. At lower concentrations SDS decreased the solubility of talinolol and notably decelerated its release from controlled-release tablets.

Key Words: Dissolution; Solubility; Absorption; Polymorph; Ionic strength.

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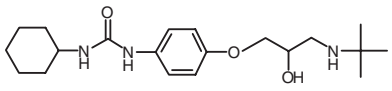
INTRODUCTION

The beta-adrenoceptor antagonist talinolol (Sch. 1) reaches an absolute mean bioavailability of 55% following administration of 50 mg immediate-release tablets in the fasted state. The width of the 95% confidence interval from 36% to 69% indicates considerable pharmacokinetic variability.[1] In addition, plasma concentration time curves frequently display ''double-peak phenomena'' rather than one single C_{max} value, indicating discontinuities in drug absorption profiles.[2] Food diminishes the bioavailability of talinolol even further. The area under the curve (AUC) values decrease to 43.5%[3] and 21.8%[4] in the fed and fasted states, respectively.

Biotransformation does not contribute to the peculiarities of the drug input process, since it is lower than 1% for talinolol.[5,6] One reason that has been discussed quite extensively in the past is that talinolol is a substrate to the efflux pump P-glycoprotein (P-gp) in the intestine.[7–9] As such, the drug molecules are secreted back into the intestinal lumen before reaching the basolateral membrane of the enterocytes and hence the blood circulation.[10,11] Furthermore, intestinal secretion is to a smaller extent a clearance pathway for talinolol from the systemic circulation.[12] Since it is known that the expression of carriers varies among individuals and among different regions of the gastrointestinal tract,[13–15] it is not surprising that the bioavailability of talinolol is also variable.

Physicochemical properties as a source of variability in the absorption of talinolol have not been addressed thus far. In particular, solubility and dissolution issues have not been reported. For the weak base talinolol (pK_a 9.4) the solubility is high in acidic media, but quite poor at pH values above four. Thus it can be assumed that the drug, when administered as immediate-release dosage form, will dissolve completely in the stomach but may precipitate again when entering the intestine. Since the intestinal pH values are subject to considerable inter- and intra-individual fluctuations in particular after ingestion of a meal,[16] the rate and extent of dissolution may also be expected to fluctuate, resulting in diminished bioavailability with high variability. The aim of this work was to elucidate the aqueous solubility of talinolol and its in vitro dissolution behavior and to interpret the results with respect to the in vivo relevance of the in vitro data.

The dissolution of immediate and controlled-release talinolol tablets was tested in several media, such as 0.1 N hydrochloric acid, acetate buffers (pH 4.5 and 6.0), phosphate buffers (pH 3.2, 5.5, 6.0, 6.8) citrate buffer (pH 6.8), TRIS buffer (pH 6.8), and buffers supplemented with sodium dodecylsulfate, cholic acid, Tween 80, Cremophor RH 40, or cetylpyridinium chloride as surfactants. The salt effect was investigated by adding sodium chloride to the dissolution medium to reach final concentrations of 0.4% to 1.25%. It was found that pH, ionic strength, and surface tension of the dissolution medium had an influence on the dissolution profile of the drug. However, there were conspicuities that could not be explained by these parameters alone: the dissolution profiles differed completely when the type of buffer was changed although the other parameters were maintained constant. The underlying mechanism was detected in the formation of different talinolol crystal structures when different buffers were used. Attempts were made to characterize the modifications with the aid of light microscopy, differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD). In addition, solubility tests were performed to demonstrate differences in the physicochemical properties of the different talinolol crystal forms.



Scheme 1. Chemical structure of talinolol.

EXPERIMENTAL

Chemicals and Other Materials

Talinolol pure substance and Cordanum® tablets containing 100 mg talinolol were generous gifts from AWD Pharma, Dresden, Germany. Eudragit® polymers were received in powder form as samples from Roehm (Darmstadt, Germany). The buffer salts and other chemicals were purchased from Merck (Darmstadt, Germany), Grüssing (Filsum, Germany), and Caelo (Hilden, Germany) and had at least p.a. (pro analysi) or Ph. Eur. (European Pharmacopeia) quality.

Solubility Studies

Two hundred milligrams talinolol was weighed in 30 mL glass vessels with screw caps and, depending

on the expected solubility, 10 to 20 mL of the test solvent were added. The samples were shaken vigorously by hand and then by a thermostatically controlled shaker (GFL 3032, Gesellschaft für Labortechnik, Burgwedel, Germany) at 185 rpm at a temperature of 37°C for 30 h until an equilibrium was reached. The samples were filtered through a 0.45 μm filter, diluted with the particular test solvent so that the UV absorbance was in the range between 0.2 and 0.8, and analyzed at 240 nm with a UV–Vis Spectrophotometer Perkin Elmer Lamda 20 (Perkin Elmer GmbH, Überlingen, Germany). When buffers were used as solvents the final pHs were measured after saturation with talinolol. Since the buffer capacities were in most cases exceeded by the high concentrations of the basic talinolol, the measured pHs were in most cases higher than the initial buffer pHs. Comparisons among the solubilities in different buffers were performed on the basis of the final pHs. Adjustment of ionic strengths was performed by diluting with demineralized water the solutions showing the higher ionic strengths. The common method of achieving higher ionic strengths by adding sodium chloride was desisted since it was found that an addition of sodium chloride by itself influenced the solubility.

Preparation of Controlled-Release Dosage Forms

The drug release was controlled by addition of a 1:2 methacrylic acid–methyl methacrylate copolymer (Eudragit S 100) and an ethyl acrylate–methyl methacrylate–trimethyl ammonioethyl methacrylate chlorid copolymer (Eudragit RS PO), both in powder form suitable for direct compression. The mixtures were vigorously ground with the drug substance talinolol. Then controlled-release matrix tablets containing 100 or 200 mg of talinolol were compressed on a PW 20 GS tablet press (Paul Weber, Remshalden-Grumbach, Germany) in a 13 mm die with a compression force of 40 kN.

Dissolution Studies

The dissolution of talinolol tablets was tested on a Pharma Test PTWS III (Pharma Test Apparatebau, Hainburg, Germany) and an Erweka DT7R (Erweka GmbH, Heusenstamm, Germany) dissolution tester complying with United States pharmacopeia (USP) standards (Apparatus II, paddles) and equipped with Hanson Research Dissoette II automatic samplers. The water bath temperature was $37^\circ \pm 0.5^\circ$C, rotational speed 50 min^{-1}, volume of dissolution media 1000 mL. The final pHs in the dissolution vessels after 24 h were measured in order to detect an overload of the buffer capacities. Contrary to the solubility studies, changes in the pH of the buffer after the tests were not detected on any occasion, due to the fact that the talinolol concentrations reached in these studies were much lower than in the solubility studies.

The amount of drug released after specific times was analyzed by means of UV spectroscopy with a Lamda 20 UV-VIS Spectrophotometer (Perkin Elmer, Überlingen, Germany) at a wavelength of 240 nm.

Preparation of Talinolol Crystal Forms

Talinolol (1.3 g) was mixed with 50 mL of the different dissolution media (water and miscellaneous buffer solutions) in 100 mL tubes with screw caps. The suspensions were shaken at 37°C in a thermostatically controlled shaker (GFL 3032, Gesellschaft für Labortechnik, Burgwedel, Germany). Thereafter the samples were centrifuged at 5000 min^{-1} for 5 min and the supernatant was removed. The powders were dried in an oven (B28, BTW Binder, Tuttlingen, Germany) for 72 h at 40°C. Then these samples were observed under a light microscope and analyzed by DSC and XRPD.

Light Microscopy

The crystal structures of the different talinolol salts and modifications were observed under a Hund Wilovert S (Hund, Wetzlar, Germany) light microscope equipped with a Kodak Digital Science DC 120 Zoom Digital Camera. Digital photographs of the crystals were taken with a magnification factor of 1:500.

Differential Scanning Calorimetry (DSC)

Thermograms were measured with a differential scanning calorimeter Mettler DSC 30 connected to a TC 11 TA Processor (Mettler, Greifensee,

Switzerland). The instrument was calibrated with 6.55 mg indium in a temperature range between 20°and 600°C at a heating rate of 10°C/min (Onset temperature: 155.8°C, peak temperature: 156.6°C). Between 1.2 and 1.8 mg of the powdered samples were exactly weighed and their thermal behavior was studied in sealed pans with a pinhole under nitrogen purge. Thermograms were taken between 40° and 300°C at a heating rate of 10°C/min.

X-ray Powder Diffraction (XRPD)

X-ray powder diffractograms were recorded on a Siemens D8 X-ray diffractometer working in the reflection mode using CuK_α radiation with a wavelength of 1.54 nm. The measurements were carried out using 40 kV voltage and 20 mA current. One gram of the finely ground sample powders were packed into standard sample holders and measured at room temperature under the following conditions: start angle 3° 2θ, end angle 40° 2θ, step 0.02° 2θ, and step time 5.0 s.

RESULTS

Solubility in Aqueous Media

The general dependence of the solubility of a monobasic drug such as talinolol on the pH of the medium is[17]:

$$S = S_0(1 + 10^{(pKa-pH)}) \quad (1)$$

where S is the solubility at a certain pH and S_0 is the intrinsic solubility, i.e., the theoretical solubility of the uncharged substance. The theoretical solubility–pH profile for talinolol in accordance with this equation is shown as a bold black line in Fig. 1, taking 9.4 as pK_a and 200 mg/L as solubility at pH 7.0. However, this profile could not be observed in practice since the influence of the pH was superimposed by other factors with a more pronounced impact on talinolol solubility. Variation of the ionic strength of a certain buffer system, for example, led to distinct changes (Table 1). It was remarkable that the solubility in the acetate buffer increased with higher acetate concentrations while it decreased with higher phosphate concentrations. Table 1 already indicates that a change of the buffer system strongly influenced the talinolol solubility. Independent of all other factors, the solubility in acetate buffers was always higher than in phosphate buffers. Figure 1 compares

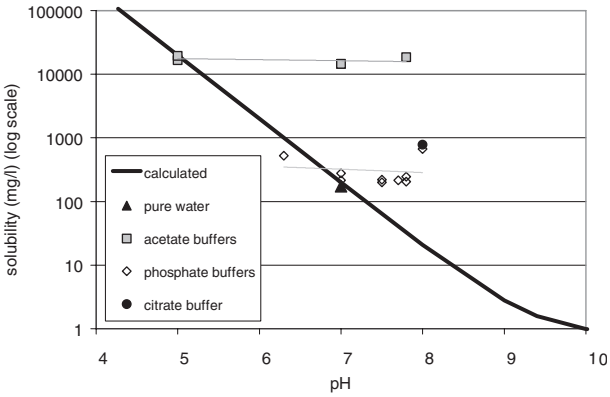


Figure 1. Calculated solubilities of talinolol in the pH range from 4 to 10 compared with experimentally determined solubilities in different dissolution media. *Key:* (◇), phosphate buffers; (■), acetate buffers; (●), a citrate buffer; (▲), pure water (means ± SD; $n = 3$).

Table 1. Impact of the buffer concentration and ionic strength on talinolol solubility at different pH values (mean of $n = 3$).

Medium	Molarity (mol/L)	Ionic strength	Final pH	Solubility (mg/L)
Pure water	—	0	10.0	143
Acetate buffer pH 4.5	0.132	0.132	10.0	[a]
	0.265	0.265	7.5	5,478
	0.529	0.529	6.5	44,994
	1.058	1.058	5.0	66,700
Phosphate buffer pH 6.8	0.044	0.105	9.0	532
	0.087	0.211	8.5	446
	0.175	0.422	8.0	343
	0.349	0.843	7.5	199

[a]No clear solution after centrifugation.

talinolol solubilities in different dissolution media based on acetate, phosphate, or citrate buffers with the calculated theoretical solubility. The media differ in their ionic strengths, their final pHs, and also their surface tensions since sodium dodecylsulfate and cholic acid as surfactants have been added to some of them. The chart shows that all the solubilities in phosphate buffers as well as all those in acetate buffers are located within similar regions, independent of the pH, the ionic strength, and the addition of the surfactants. This demonstrates the predominant impact of the choice of the buffer type on the solubility. For example, talinolol solubility in a phosphate buffer at a final pH of 7.0 was about five

times lower than in an acetate buffer of the same pH and ionic strength. The impact of the addition of different concentrations of sodium dodecylsulfate and cholic acid as surfactants to the diverse buffers was not as distinct as the choice of buffer type. Depending on the concentration of the surfactant, the talinolol solubility did not always increase as would be expected. For sodium dodecylsulfate (SDS), the talinolol solubility decreased when less than 0.75% SDS was added; only with SDS concentrations above 1%, i.e., about four times higher than the critical micelle concentration (CMC) of 0.23%, a pronounced improvement of the solubility could be achieved (Fig. 2a). Within the physiological concentration range the addition of sodium chloride (NaCl) leads to an increase of the talinolol solubility, e.g., in a 0.9% NaCl solution the solubility is nearly 40% higher than in pure water (Fig. 2b).

Dissolution

To detect the impact of the buffer type on the dissolution of talinolol tablets, dissolution tests with Cordanum 100 mg were performed at pH 6.0 in acetate buffer and phosphate buffer of the same ionic strength, and at pH 6.8 in citrate buffer and phosphate buffer of the same ionic strength. Figure 3 shows that the dissolution in acetate buffer is faster at pH 6.0 (Fig. 3a) and at pH 6.8 it is faster in citrate buffer (Fig. 3b), as compared with the phosphate buffers at the respective pH values.

For controlled-release matrix tablets consisting of 40% talinolol, 40% Eudragit S 100, and 20% Eudragit RSPO, the results of the dissolution experiments in several different media with and without addition of surfactants are outlined in Table 2. Like for the immediate-release tablets,

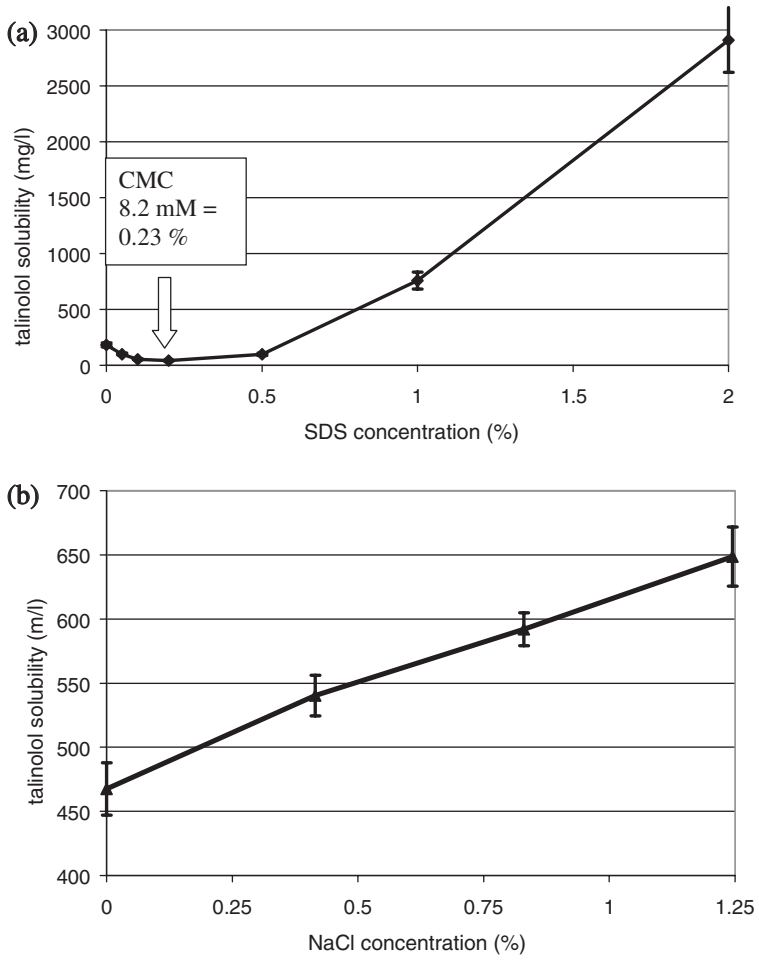


Figure 2. Influence of the addition of (a) sodium dodecyl sulfate (SDS) and (b) sodium chloride (NaCl) on the talinolol solubility in a phosphate buffer pH 6.8 (means ± SD; $n = 3$).

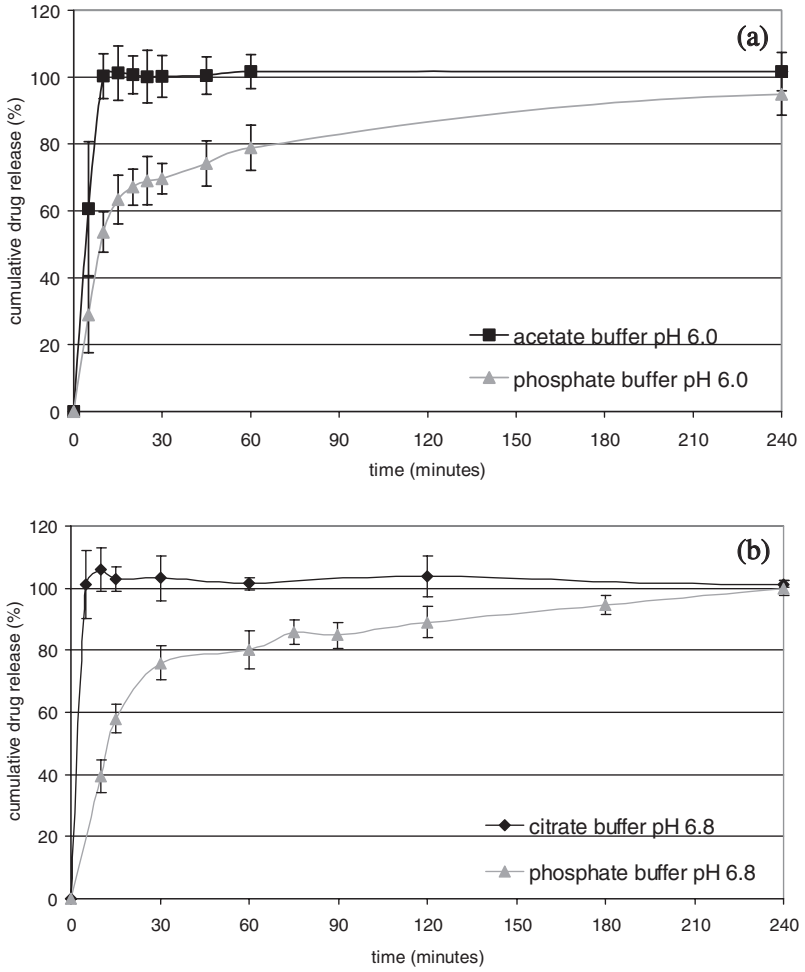


Figure 3. Dissolution profiles of talinolol immediate release tablets (Cordanum 100 mg) in (a) acetate vs. phosphate buffer at pH 6.0 and (b) citrate vs. phosphate buffer at pH 6.8 (Paddle Apparatus, 50 rpm, 37°C, 1000 mL, means ± SD; $n = 3$).

the influence of the buffer type on dissolution exceeds the pH influence: talinolol dissolution in an acetate buffer pH 4.5, for example, is nearly as fast as in 0.1 N hydrochloric acid in spite of a pH difference of 3.5, and dissolution at pH 6.8 differs among phosphate, citrate, and TRIS buffers despite the same pH. In addition to buffer effects, the addition of sodium chloride (NaCl) to phosphate buffer at pH 6.8 led to an increase in rate and extent of talinolol dissolution within the investigated concentration range (0% to 1.25%). This is depicted in Fig. 4. Surfactants modified the dissolution of talinolol in different ways. Cholic acid at concentrations of 0.43% and 1.0 % led to an increased dissolution in the first hours, thereafter the dissolution rate decreased so that the amount of drug released after 24 h was significantly lower as compared with the condition without added surfactant. Cremophor RH 40 and Tween 80 each at concentrations of 1.0% and sodium dodecylsulfate at a concentration of 0.1% decreased both the rate and extent of drug release from the matrix tablets. Only cetylpyridinium chloride (0.5%) accelerated the dissolution and increased the amount of drug released after 24 h.

Crystal Structures

After crystallization from pure water and phosphate buffers pH 6.0 and 6.8, shape and mean size of the crystals obtained appeared similar under the light microscope. Opposite to these clearly cubic structures, precipitation in acetate buffers pH 4.6 and 6.0 generated crystals considerably smaller in size with a longish shape (Fig. 5).

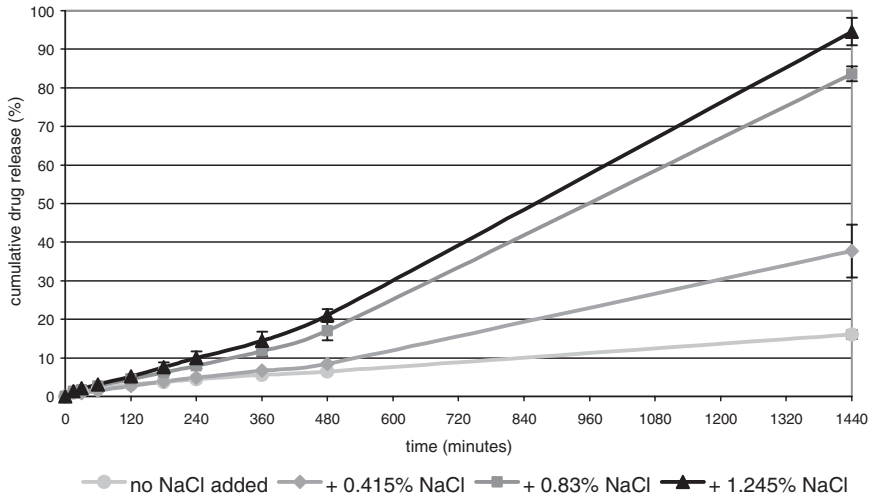


Figure 4. Dissolution profiles of talinolol controlled-release tablets in a phosphate buffer at pH 6.8 and the effect of increase in ionic strength due to addition of sodium chloride (Paddle Apparatus, 50 rpm, 37°C, 1000 mL, means ± SD; $n = 3$). The formulation was composed of talinolol (40%), Eudragit S 100 (40%), and Eudragit RSPO (20%).

Table 2. Dissolution of talinolol controlled-release matrix tablets in different media.

Medium	Dissolution after 1 hr % (S.D.)	Dissolution after 2 hr % (S.D.)	Dissolution after 4 hr % (S.D.)	Dissolution after 8 hr % (S.D.)	Dissolution after 24 hr % (S.D.)
pH 1.0, 0.1 N HCl	25.4 (1.3)	33.7 (1.3)	56.0 (1.8)	85.6 (2.0)	95.6 (1.9)
pH 3.2, phosphate buffer[a]	5.4 (0.6)	7.4 (0.8)	10.5 (1.0)	15.2 (0.9)	27.8 (1.3)
pH 4.5 acetate buffer[b]	26.5 (3.2)	40.1 (3.9)	49.8 (4.1)	71.6 (4.9)	97.7 (3.0)
pH 5.5 phosphate buffer[c]	3.7 (0.4)	4.2 (0.5)	5.1 (0.5)	7.0 (0.7)	13.6 (2.5)
pH 6.8 phosphate buffer[d]	7.7 (0.8)	15.6 (1.2)	30.0 (2.4)	59.4 (6.3)	84.4 (4.4)
pH 6.8 citrate buffer[e]	3.6 (0.2)	6.1 (0.4)	7.5 (0.4)	10.7 (0.4)	20.3 (1.2)
pH 6.8 TRIS buffer[f]	5.3 (0.2)	8.6 (0.5)	13.5 (1.6)	19.4 (1.8)	32.2 (2.0)
pH 6.8 phosphate buffer[d] + 0.1% sodium dodecylsulfate	10.4 (0.6)	13.2 (0.8)	15.3 (0.9)	17.8 (2.1)	17.6 (1.8)
pH 6.8 phosphate buffer[d] + 0.43% cholic acid	24.4 (0.4)	26.1 (0.4)	27.4 (0.7)	35.4 (0.8)	57.3 (8.6)
pH 6.8 phosphate buffer[d] + 1.0% cholic acid	24.4 (0.7)	26.7 (0.7)	27.0 (1.7)	36.4 (0.3)	40.9 (0.9)
pH 6.8 phosphate buffer[d] + 1.0% tween 80	10.9 (1.0)	11.2 (2.6)	12.3 (0.4)	14.3 (0.5)	22.5 (4.7)
pH 6.8 phosphate buffer[d] + 1.0% cremophor RH 40	4.3 (0.1)	5.4 (0.2)	6.3 (0.3)	19.0 (4.6)	76.7 (4.8)
pH 6.8 phosphate buffer[d] + 0.5% cetylpyridinium chloride	5.7 (1.9)	14.1 (2.1)	20.7 (2.7)	33.9 (4.7)	90.4 (3.0)

Mean values of $n = 3$, standard deviations in brackets.
Formulation: Talinolol 40%, Eudragit S 100 40%, Eudragit RSPO 20%.
Composition of buffers:
[a]Phosphate buffer pH 3.2: 4 g/L sodium dihydrogen phosphate, 2.5 g/L phosphoric acid.
[b]Acetate buffer pH 4.5: 2.99 g/L sodium acetate $\cdot 3H_2O$, 1.66 g/L acetic acid.
[c]Phosphate buffer pH 5.5: 13.1 g/L potassium dihydrogen phosphate, 1.29 g/L sodium monohydrogen phosphate.
[d]Phosphate buffer pH 6.8: 6.8 g/L potassium dihydrogen phosphate, 0.90 g/L sodium hydroxide.
[e]Citrate buffer pH 6.8: 1.09 g/L citric acid, 0.60 g/L sodium hydroxide.
[f]TRIS buffer pH 6.8: 6.0 g/L tris (hydroxymethyl) aminomethane, 47.5 mL/L 1 N hydrochloric acid.

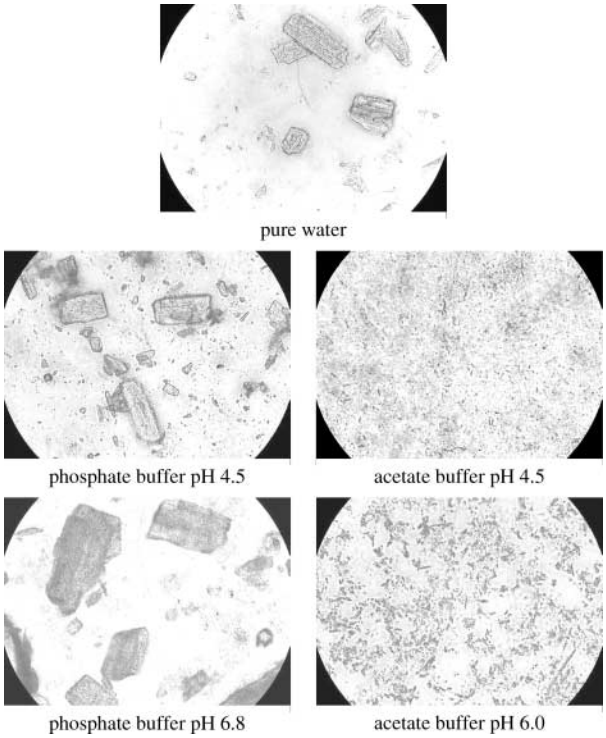


Figure 5. Crystal shapes of talinolol modifications or salts obtained by precipitation in different dissolution media under a light microscope (Magnification 1:500).

Differential Scanning Calorimetry

The DSC spectra showed significant differences for the test samples: Pure talinolol and the powder which was crystallized from water had nearly identical spectra showing a pair of two peaks, the first one between 126° and 131°C and the second one between 139° and 152°C. The latter lies in the range of the melting point of talinolol at 143°C. The samples obtained following crystallization from acetate and phosphate buffers showed only one peak. This single peak was in the range between 156° and 163°C for acetate buffer and between 200° and 204°C for phosphate buffer (Fig. 6).

X-ray Powder Diffraction

The x-ray diffractograms of untreated talinolol and talinolol powder crystallized from purified water were almost identical, while crystallization from phosphate and acetate buffer led to specific changes in the talinolol diffractograms (Fig. 7), proving differences in the crystal structures of talinolol precipitated in the different dissolution media.

DISCUSSION AND CONCLUSIONS

The results reemphasize that media used for dissolution tests have to be chosen with care. The effect discovered in this study—that different media may lead to different crystal structures of solutes with varying physicochemical properties—may not be restricted to the studied compound talinolol but likewise may play an important role for the dissolution of other drugs as well.

For various immediate-release formulations, drug dissolution tests in media simulating the gastric fluid are appropriate, since many drugs completely dissolve before leaving the stomach and show little tendencies towards precipitation in the intestine. For such drug products, 0.1 molar hydrochloric acid or simulated gastric fluid (USP), a solution of 0.2% sodium chloride and 0.32% pepsin in hydrochloric acid, can be used. If dissolution in the middle and lower parts of the gastrointestinal tract needs to be simulated, e.g., for the characterization of controlled-release products, acetate buffers with a pH of 4.5 are commonly used to simulate the pH of the upper small intestine in the fasted state. Phosphate buffers of pH 6.8 and 7.4 as well as the simulated intestinal fluid of the USP, based on a phosphate buffer pH 7.5 to which 1% pancreatin is added, are common for the lower intestinal regions. To simulate the physiological appearance of surfactants in the gastrointestinal fluids and particularly for dissolution tests with formulations containing low-solubility drugs, either 0.1% to 2% sodium dodecylsulfate or the more physiological cholic acid or sodium cholate can be added to the buffer solutions at concentrations of 0.1% to 1%.

To improve the in vivo relevance of dissolution tests, two simulated intestinal fluids have been proposed that mimic the presence of surfactants and enzymes in the intestine[18,19]: One for the simulation of the fasted state (FaSSIF, Fasted-State Simulated Intestinal fluid) and one for the simulation of the fed state (FeSSIF, Fed-State Simulated Intestinal fluid). The FaSSIF is based on a phosphate buffer of pH 6.5, whereas FeSSIF basically consists of an acetate buffer with a pH of 5.0. This switch from phosphate to acetate has no in vivo counterpart and might lead to misinterpretations for drugs that, like talinolol, form different salts or modifications with different physicochemical properties: When

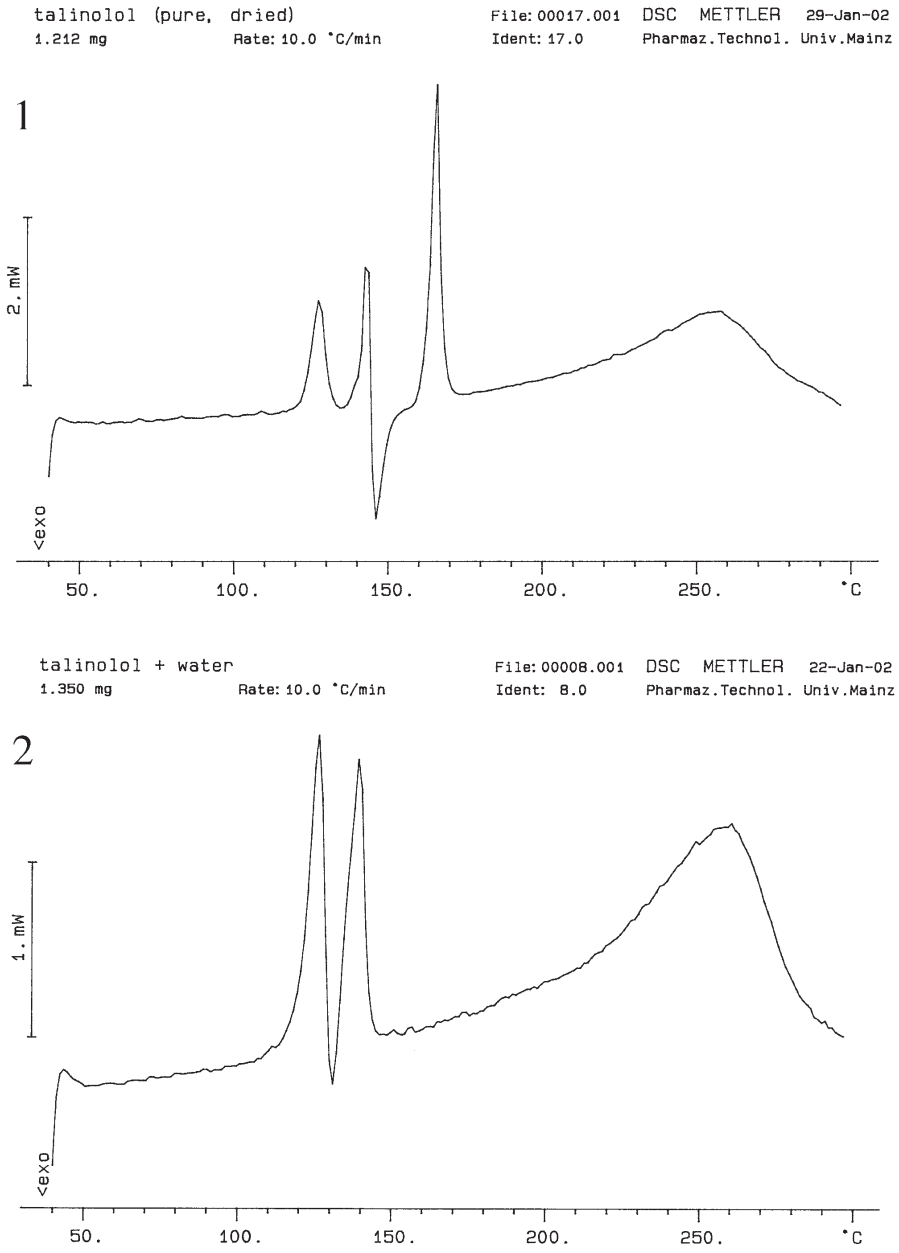


Figure 6. DSC spectra of talinolol modifications or salts obtained by precipitation in different dissolution media in the following order: 1) original powder, 2) pure water, 3) acetate buffer pH 4.5, 4) phosphate buffer pH 6.8.

(continued)

dissolution tests are performed in FaSSIF and FeSSIF to investigate the influence of the ingestion of food on the drug release, changes in the dissolution profiles may hence not only be due to the differences in lecithin and cholate concentrations and different pHs, which shall imitate the fasted and fed states, but can also be caused by the change of the buffer type from phosphate to acetate.

With respect to the type of buffer used, none of the media discussed above accurately reflects the actual composition of the intestinal fluids in vivo. Carbonate buffers, that physiologically regulate the pH in the intestine are inapplicable for in vitro tests because of the evaporation of carbon dioxide and the resulting changes in the pH of the dissolution media.

Apart from the buffer type, the effect of sodium chloride on the solubility and dissolution

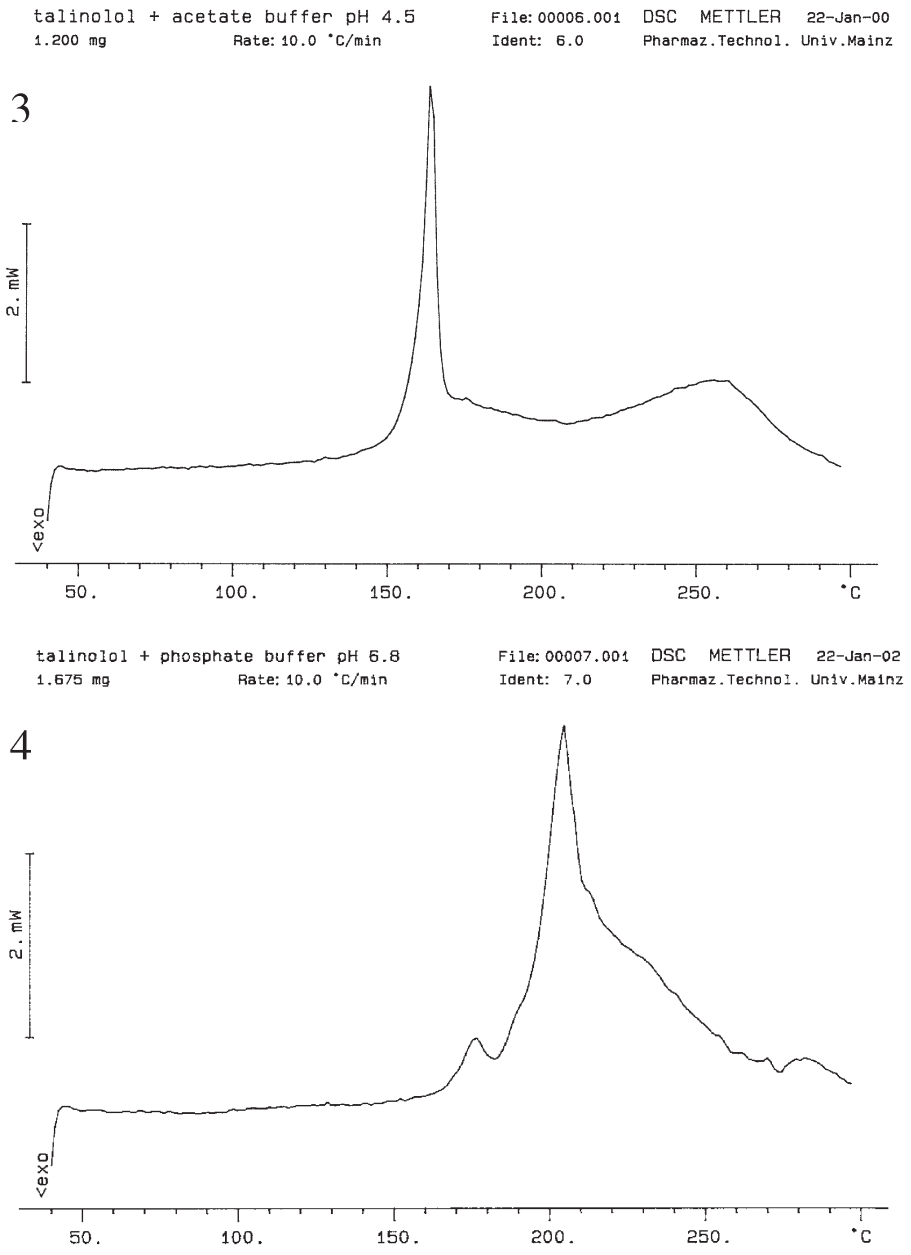


Figure 6. Continued.

rate shows that the concentrations of other ionic constituents that appear physiologically in the gastrointestinal fluids such as sodium, potassium, or calcium chloride may also influence both the solubility of drugs and the dissolution of drug products, which could, at least partly, be caused by changes in the crystal structures of the drugs as well.

With respect to the in vivo relevance, the investigations on talinolol dissolution show that, in addition to P-gp mediated intestinal secretion,[20] differences in the composition of gastrointestinal fluids may also contribute to the relatively poor and variable bioavailability of talinolol. It can be assumed that the decrease in bioavailability after ingestion of a meal may also be due to changes in the composition of the gastrointestinal fluids. Since the in vitro dissolution tests showed that up to a specific level the addition of surfactants can diminish or at least decelerate talinolol dissolution, it may well be

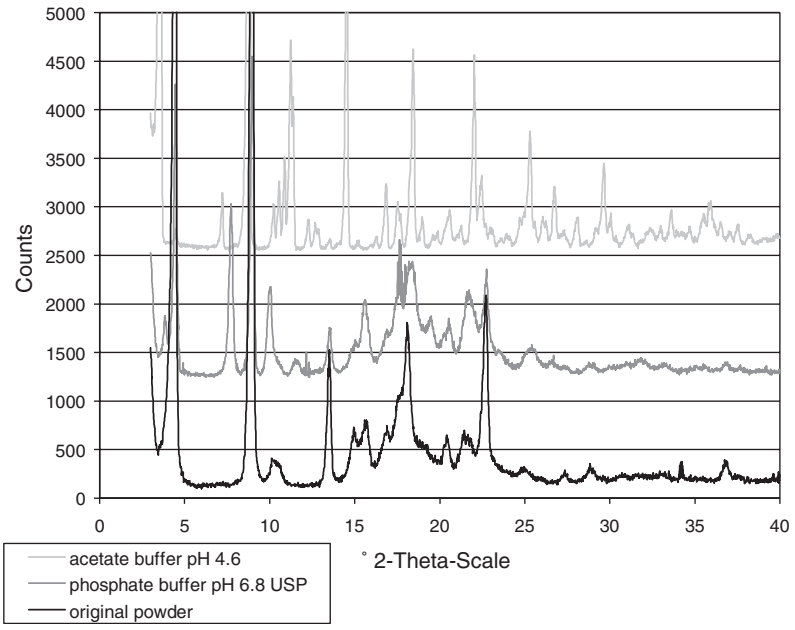


Figure 7. XRPD spectra of talinolol modifications or salts obtained by precipitation in different dissolution media. *Key:* black line, original powder; dark grey line, phosphate buffer pH 6.8; light grey line, acetate buffer pH 4.5.

possible that the physiological surfactants such as bile salts that are secreted after ingestion of food could be held responsible for the decrease in bioavailability as well. An explanation for both the in vitro and the in vivo phenomena could be a complexation between talinolol and the surfactants as it is reported for pafenolol, another beta-adrenoceptor antagonist with a similar chemical structure.[21]

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