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Reaction between drug substances and pharmaceutical excipients: Formation of citric acid esters and amides of carvedilol in the solid state

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ABSTRACT

The reactivity of citric acid towards drug substances in the solid state was examined using the β-blocker carvedilol as a model compound. The reaction mixtures were analysed by LC–MS, the reaction products were isolated by preparative HPLC, and the structures were elucidated by microprobe NMR spectroscopy. Heating a mixture of solid carvedilol and solid citric acid monohydrate for 96 h at 50 °C resulted in the formation of about 3% of a symmetrical ester as well as of a number of other reaction products in smaller amounts. Formation of the symmetrical ester was also observed at room temperature. At 70 °C, the amounts of three isomeric esters formed reached 6–8%. The minor reaction products were citric acid amides, *O*-acetylcarvedilol, and esters of itaconic acid.

1. Introduction

In drug formulation it is important to consider possible interactions and chemical reactions between the ingredients in order to avoid formation of impurities in the final product. This has become even more important with the advent of new technologies like hot melt granulation, where part of the process takes place in a liquid phase and at elevated temperatures. However, the traditional formulation processes may also involve conditions that facilitate chemical reactions. It is therefore important to be aware of the chemistry of all compounds included in a formulation and to assess the possibilities of reactions occurring in the formulation. The occurrence of impurities due to unforeseen reactions occurring during manufacture or storage may alter the quality of the formulation and cause adverse physiological reactions.

Citric acid is widely used in pharmaceutical formulations as an acidifier, complexing agent or buffer substance. Since citric acid is used in many formulations, its reactivity towards other excipients and drug compounds is particularly important. The reactivity of citric acid towards alcohols in the solid state has previously been described [1]. Di- and polycarboxylic acids are able to form intramolecular anhydrides in a rate determining step, which greatly increases the reactivity of the acid [2]. Citric acid is an example of an acid that is able to react via anhydride intermediates. The anhydrides of citric acid have also been synthesised [3]. Degradation of citric acid is known to proceed via aconitic acid (1-propene-1,2,3-tricarboxylic acid) to citraconic acid (2-methyl-2-butenedioic acid) and itaconic acid (methylenebutanedioic acid) [4]. All the three aconitic, citraconic and itaconic acids are able to form intramolecular anhydrides similar to those proposed for other di- or tricarboxylic acids, which would increase the reactivity of the acids substantially [2].

Recently, a reaction between 5-aminosalicylic acid (5-ASA) and citric acid in the solid state has been reported [5]. The reaction is of the same type as that examined more than 100 years ago, when formation of amides from aromatic amines was observed [6]. In another recent example involving a growth hormone secretagogue, an aliphatic amide has been formed from an amine present in the raw material as a synthetic impurity and citric acid used to adjust pH of the formulation [7].

In the present paper, a β-blocker (carvedilol) with a secondary hydroxy group and a secondary amino group was used as a model compound to further evaluate the reactivity of citric acid towards drug substances, in particular to assess the relative reactivity of amines and alcohols.

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2. Experimental

2.1. Chemicals

Citric acid monohydrate, anhydrous citric acid, formic acid, glacial acetic acid, acetic anhydride and tetrahydrofuran (THF) were purchased from Sigma–Aldrich Chemie (Steinhem, Germany). Phosphoric acid, triflouroactetic acid (TFA), methanol, acetonitrile and acetone were purchased from VWR (Leicester, England). Racemic carvedilol (crystalline, free base) was obtained from GEA Pharmaceutical A/S (Hvidovre, Denmark). Methanol-d_4 was obtained from Lab Science (Copenhagen, Denmark).

2.2. Liquid chromatography–mass spectrometry (LC–MS)

LC–MS measurements were performed on an Agilent 1100 series HPLC/MSD system (Agilent Technologies, Palo Alto, CA, USA). The chromatographic system consisted of a Phenomenex Luna 2 mm × 100 mm, 3 μm C_{18} column, kept at 40 °C and eluted at a rate of 0.3 ml/min. UV trace was recorded at 240 nm. The mobile phases were: A, 10% MeOH in water, added 0.1% HCOOH; B, 90% MeOH in water, added 0.1% HCOOH. Gradient elution profile: 20% B at 0 min, 100% B at 33 min, 100% B at 35 min, 20% B at 35.1 min, and end at 42 min. The MSD was used in positive electrospray mode, drying gas flow 8 l/min, nebuliser pressure 40 psi, drying gas temperature 350 °C, capillary voltage 4 kV, and fragmentor 80 V. The MSD was programmed to scan from 100 to 1200 a.m.u. with a cycle time of 1.08 s. Samples were diluted appropriately with the mobile phase; the concentrations were typically in the low μg/ml range and injection volume was 5 μl.

Variations of the separation system were achieved by using a different column (Phenomenex Luna 2 mm × 150 mm, 5 μm Phenyl–Hexyl) as well as using MeOH, MeCN or THF as organic modifier. In addition, formic acid (pH ~2) was exchanged for TFA (pH ~1–2) or 0.1 M phosphate buffer (pH 3.5, pH 5, or pH 8).

2.3. Preparative HPLC

Preparative HPLC was performed on an Agilent 1100 series HPLC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a fraction collector. The chromatographic system consisted of a Phenomenex Luna 10 mm × 150 mm, 3 μm C_{18} column, kept at 40 °C and eluted at a rate of 2.5 ml/min. UV trace was recorded at 240 nm. The mobile phases were: A, 10% MeOH in water, added 0.12% HCOOH; B, 90% MeOH in water, added 0.12% HCOOH. Gradient elution profile: 20% B at 0 min, 100% B at 20 min, 100% B at 25 min, 20% B at 28 min, and end at 35 min.

2.4. Microprobe NMR

Bruker Avance 400 WB spectrometer (Bruker GmbH, Rheinstetten, Germany), equipped with a 1 mm TXI (^{1}H, ^{13}C, ^{77}Se) probe was used for acquisition of all ^{1}H NMR spectra and heteronuclear multiple bond correlation (HMBC) experiments. The temperature was set to 298 K. Methanol-d_4 was used as the solvent and the residual solvent signal (δ 3.31) and the solvent resonance (δ 49.15) were used as chemical shift references for ^{1}H and ^{13}C, respectively. Typically, two HMBC spectra were acquired, optimized for a coupling constant of 9 or 12 Hz.

2.5. Studies of reactions in the solid state

For the solid-state reaction studies, samples of citric acid monohydrate (50 mg) and carvedilol (5 mg, 0.05 eq.) were placed in glass vials. The blend was mixed by manual agitation, the vial was sealed with a Teflon-lined screw cap, and the sample was placed in a heating block, equilibrated at either 50 or 70 °C. Several samples were prepared in order to follow the time course of the reaction. Two samples were removed from the heating block for each time point, the content dissolved in 1 ml of 50% THF, and the solutions were analysed in duplicate by LC–MS after appropriate dilution. The resulting four measurements were used to calculate means and standard errors.

An identical reaction was run at ambient temperature (~20 °C) for 1 month. This sample was injected into the LC–MS system at a concentration of about 10 mg/ml.

2.6. Synthesis of reaction products

In order to generate more of the products for NMR experiments, a mixture of carvedilol (80 mg) and citric acid monohydrate (560 mg) was heated for 2 weeks at 70 °C in a heating block. The

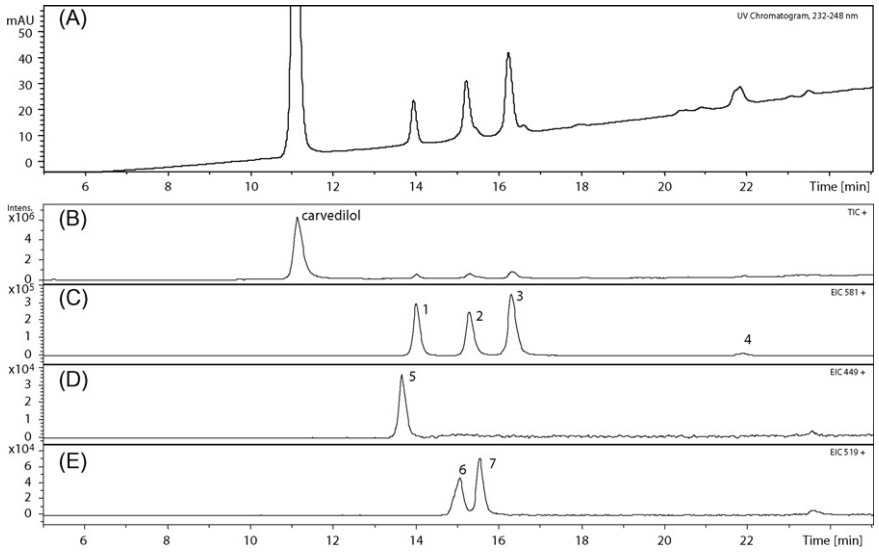

Fig. 1. LC–UV–MS traces of a temperature-stressed (70 °C, 2 weeks) mixture of solid carvedilol and citric acid monohydrate. (A) UV, 232–248 nm. (B) Total ion current. (C) Extracted ion chromatogram, *m*/*z* 581. (D) Extracted ion chromatogram, *m*/*z* 449. (E) Extracted ion chromatogram, *m*/*z* 519. Assignment of peaks: see Fig. 2.

reaction mixture was dissolved in 50% of THF (5 ml), the products were subjected to LC–UV–MS analysis, and subsequently purified by preparative HPLC (20 × 60 μl injections). The solvent of each pooled fraction was removed by nitrogen flow with subsequent freeze-drying to give the reaction products **1**–**7**. Each fraction was re-dissolved in 10 μl of methanol-d_4 for NMR analysis.

In another procedure, citric acid monohydrate (250 mg) and carvedilol (50 mg) were placed in a glass vial and water (250 μl) was added. The vial was sealed with a Teflon-lined screw cap and placed in a 650 W microwave oven, model MDS-81D (CEM Corporation, USA). The sample was irradiated at 50% of maximal power for 5 min and allowed to cool for a few minutes, before being dissolved in 500 μl of THF and 250 μl of water. Purification of **1**–**3** was performed by preparative HPLC injecting 40 μl of the solution per run.

2.7. Synthesis of the reaction product *5*

Carvedilol (10 mg) was dissolved in glacial acetic acid (500 μl), and acetic anhydride (2.4 μl, 1 eq.) was added. The mixture was heated for 2 h at 70 °C. A 10 μl sample was taken for LC–MS analysis. The solvents were removed under reduced pressure, the sample was re-dissolved in 1 ml of mobile phase B, and 500 μl of mobile phase A was added. Purification of **5** was performed by preparative HPLC injecting 100 μl of the solution per run.

2.8. Studies of intramolecular rearrangements

Compound **1** (0.3 mg) was dissolved in THF (1 ml), and 10 μl of the solution was transferred to a glass vial and diluted to 1 ml with either acetonitrile or acetone. Compounds **2** and **3** were treated in the same way. Each vial was closed and placed in a heating block at 70 °C for 2 h, and samples were taken to follow the reaction at suitable time intervals. The same experiment was performed with a mixture of carvedilol and citric acid for comparison. Thus, carvedilol (10 mg) was dissolved in THF (1 ml) and 10 μl of the solution was transferred to a glass vial and diluted to 1 ml with either acetonitrile or acetone. Citric acid was added (50 mg) and the solution was heated as above.

3. Results and discussion

3.1. Identification of reaction products

LC–UV–MS traces of a mixture of products formed in a solid-state reaction between citric acid monohydrate and carvedilol are shown in Fig. 1. UV and total ion chromatograms show the presence of excess of unreacted carvedilol. The extracted ion chromatograms correspond to the identified degradation products and the peaks are numbered accordingly. The structures of the main products (**1**–**7**), elucidated by ^{1}H NMR spectroscopy after isolation of **1**–**7** by preparative HPLC, are shown in Fig. 2. The structures of the individual products are discussed in the following sections.

3.1.1. Citric acid esters

Carvedilol used in this study was a racemate. Therefore, three different racemic citric acid esters can theoretically be formed: R*, i.e., the racemate formed by esterification of the central carboxy group (**1**), and two diastereomeric pairs, R*R* and R*S* (**2** and **3**), formed by esterification of either of the terminal carboxy groups, which results in the conversion of the prochiral citric acid centre to a chiral centre. Accordingly, three peaks of isobaric products with m/z 581 were observed in the chromatograms (Fig. 1). The mass increase by 174 a.m.u. as compared to carvedilol demonstrated that the products are acylated by an intact citric acid residue.

Table 1
^{1}H NMR spectroscopic data (δ values with intensities, multiplicities and coupling constants in Hz in parentheses) for carvedilol and main products of its solid-state reactions with citric acid.

Compound	Aromatic	H-10	H-15	H-16	H-18	H-20	H-21	OCH_3	Citric acid A–CH_2	Citric acid B–CH_2
Carvedilol	6.67–7.43 (10H; m)	8.29 (1H; d; 7.8)	4.26 (2H; m)	4.34 (1H; m)	A: 2.99 (dd; 12.2, 8.1) B: 3.14 (dd; 12.2, 3.8)	3.07 (2H; m)	4.15 (2H; m)	3.77 (3H; s)	–	–
1	5.73–7.41 (10H; m)	8.31 (1H; d; 7.8)	A: 4.45 (dd; 10.5, 5.7) B: 4.56 (dd; 10.5, 4.0)	5.87 (1H; m)	3.73–3.88 (2H; m)	3.54 (2H; m)	4.31 (2H; m)	3.67 (3H; s)	A: 2.64 (d; 14.9) B: 2.91 (d; 14.9)	A: 2.65 (d; 15.5) B: 2.88 (d; 15.5)
2	5.69–7.41 (10H; m)	8.20 (1H; d; 7.8)	A: 4.43 (dd; 10.5, 4.7) B: 4.47 (dd; 10.5, 4.7)	5.77 (1H; m)	3.72–3.77 (2H; m)	3.57 (2H; m)	4.33 (2H; m)	3.71 (3H; s)	A: 2.78 (d; 16.0) B: 2.95 (d; 16.0)	A: 2.83 (d; 13.3) B: 2.91 (d; 13.3)
3	5.69–7.41 (10H; m)	8.19 (1H; d; 7.8)	A: 4.40 (dd; 10.5, 4.7) B: 4.48 (dd; 10.5, 4.8)	5.74 (1H; m)	3.70–3.76 (2H; m)	3.56 (2H; m)	4.36 (2H; m)	3.73 (3H; s)	A: 2.76 (d; 13.5) B: 3.13 (d; 13.5)	A: 2.71 (d; 16.0) B: 2.87 (d; 16.0)

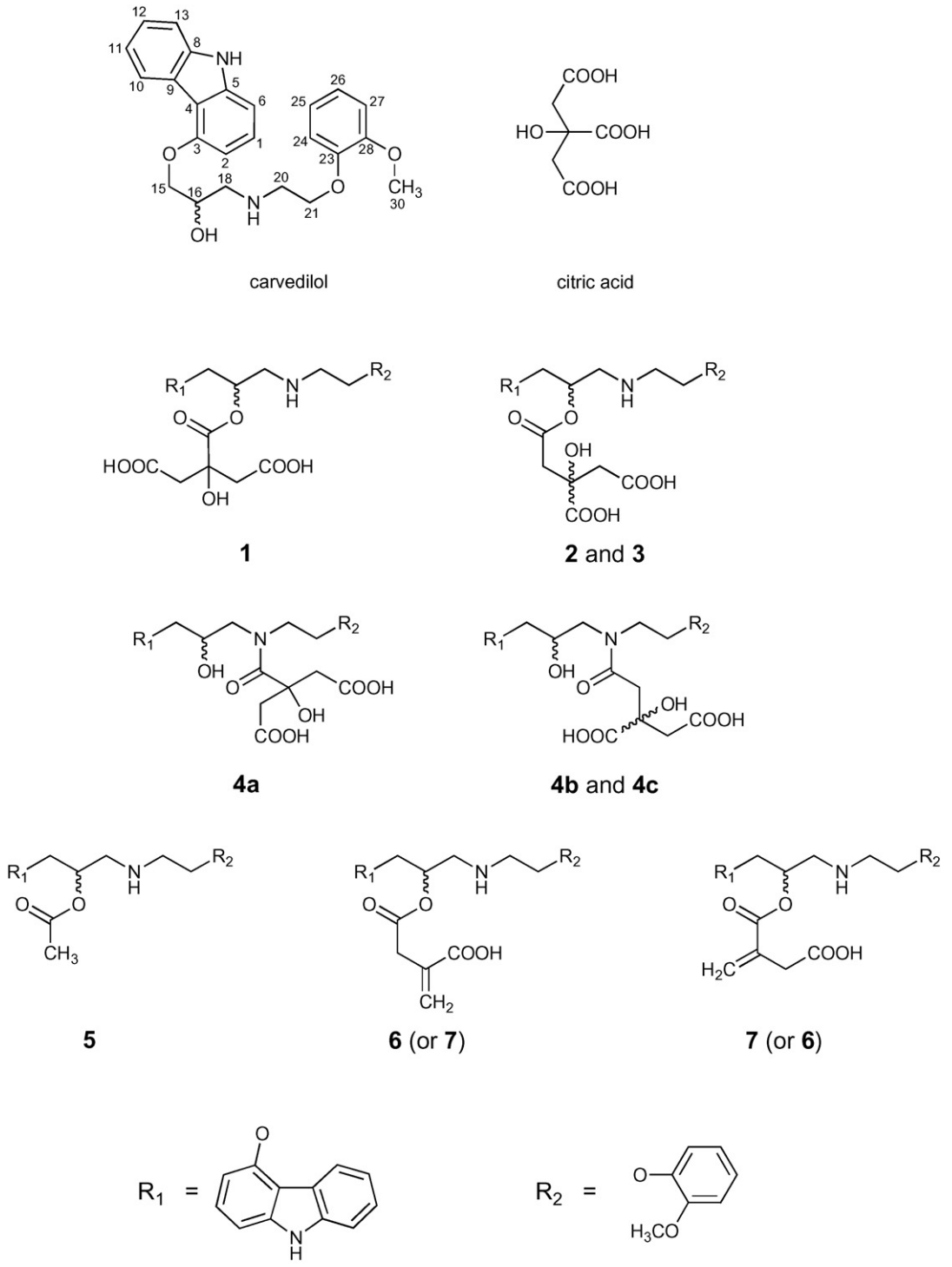

Fig. 2. Structures of reaction products formed in the solid-state reaction between carvedilol and citric acid monohydrate.

All three compounds were isolated by preparative-scale HPLC, and their NMR spectra (1D ^{1}H and HMBC) were recorded. The compounds were characterised by a large acylation shift of H-16 relative to carvedilol (about 1.5 ppm) (Table 1). This feature in the spectrum characterise the compounds as esters rather than amides.

The ^{1}H NMR signals of the methylene protons of the citric acid moiety in all three esters appear as two pairs of doublets (Table 1). In **1**, the citric acid methylene carbons are diastereotopic, as are the two attached proton pairs. In **2** and **3**, the methylene carbons are heterotopic and the two methylene proton pairs are diastereotopic. The anisochrony (dispersion) of the diastereotopic proton resonances in **1** is almost equal ($\Delta\delta$ 0.23 and 0.27) and the coupling constants in each diastereotopic pair almost identical (J_{gem} 14.9 and 15.5 Hz). This corresponds well to the structure **1** with local symmetry in the vicinity of the central carbon atom of the citric acid residue. By contrast, in the more slowly eluting esters **2** and **3** the chemical shift difference within one diastereotopic proton pair is more than twice of the difference within the other pair ($\Delta\delta$ 0.08 and 0.17 in **2** and $\Delta\delta$ 0.17 and 0.37 in **3**). Moreover, the coupling constants within one proton pair (J_{gem} 16.0 Hz) are sig-

nificantly different from those within the other pair (J_{gem} 13.3 or 13.5 Hz), as expected for the non-symmetrically substituted esters **2** and **3**. HMBC spectra showed correlations between the citrate methylene groups (δ_C 44.8), and from the latter to the carboxylic acid groups (δ_C 174.5) and to the quaternary carbon of the citrate moiety (δ_C 73.6). However, distinction between the diastereomers **2** and **3** could not be made.

3.1.2. Citric acid amides

Citric acid amides of carvedilol are isobaric with the esters. Similarly to the esters, three different amides (one racemate and two diastereomeric pairs) are possible. However, only one additional, rather weak peak with *m*/*z* 581 was observed in the solid-state reaction product. Varying pH of the mobile phase and other variations of the chromatographic system (see Section 2) did not result in a separation of this peak into additional peaks. This could suggest that only one amide was formed in appreciable amount in the reaction. ^{1}H NMR spectra of the compound isolated by preparative HPLC revealed the presence of a non-shifted resonance of H-16 (δ 4.28, cf. Table 1), confirming that it is an amide. However, the spectrum was complex, presumably due to the presence of amide bond rotamers, well-known to occur for *N*,*N*-disubstituted amides, and possibly also to the presence of co-eluting isomers. Therefore, the data were insufficient to distinguish between the symmetric amide **4a** and the amides **4b** and **4c**. Nevertheless, it can be concluded that the reactivity of the amino group is apparently much lower than that of the secondary alcohol group under the examined conditions, as evidenced by the formation of much larger amounts of the esters **1**–**3**. Protonation of the amino group with citric acid is a likely explanation for decreased nucleophilicity of the amino group of carvedilol.

3.1.3. Acetic acid ester

The compound designated as **5** has *m*/*z* 449, which indicates acetylated carvedilol. ^{1}H NMR analysis of the isolated product revealed a shifted (δ 5.62) resonance of H-16 relative to carvedilol. The magnitude of this acylation shift ($\Delta\delta$ 1.26) is similar to that observed for **1**–**3** (Table 1). Moreover, a signal attributable to an acetyl group was observed at δ 2.16.

To further confirm the identity of the compound, carvedilol was acetylated with acetic anhydride in acetic acid and the reaction mixture analysed by LC–MS. The reaction product displayed a peak with the same retention time and mass as the compound formed in the solid-state reaction (Fig. 1). ^{1}H NMR spectrum of the isolated synthetic compound unequivocally confirmed its structure. The formation of an acetate ester **5** can be explained by a retro-Claisen-type cleavage reaction [8] of an ester such as **2** or **3** (Fig. 3).

3.1.4. Itaconic acid esters

Two compounds with *m*/*z* of 519 were present in the reaction mixture. The compounds were minor reaction products, as shown by HPLC–UV chromatogram of the reaction mixture (Fig. 1). The mass corresponds to citric acid esters that have lost a water molecule plus CO_2, i.e., either citraconic or itaconic acid derivatives. Both acids are known to be degradation products of citric acid [4].

^{1}H NMR spectrum of the isolated product **6** displayed characteristic signals of geminal vinylic protons at δ 5.63 and δ 6.04, demonstrating the compound to be a derivative of itaconic acid. Similarly, compound **7** displayed signals at δ 5.61 and δ 6.08. This is compatible with two isomers of carvedilol acylated with either of the two carboxylic acid group of itaconic acid. The compounds were esters and not amides, as shown by the presence of a resonance of H-15 at δ 5.46 and δ 5.41, respectively. However, because of the very small amount of material formed and its instability (cf. rearrangement reactions of citric acid esters, Section 3.3), the distinction between the isomeric esters **6** and **7** could not be made.

3.2. Kinetics of the solid-state reactions

Kinetics of the solid-state reaction at 50 and 70 °C was examined by HPLC (Fig. 4). At 50 °C, the ester **1** was formed much faster than the two diastereomers **2** and **3**, which were formed at very similar rates. At 70 °C, the rate of formation of **1** was initially much faster, but the amounts of **1**–**3** formed after 60 h reached a similar level of 6–8% of the initial amount of carvedilol. It appears therefore that **1** is the kinetic reaction product and that a thermodynamic equilibrium involving **1**–**3** is established after prolonged reaction time. The formation of minor reaction products (**5**–**7**) was not detectable by LC–MS at 50 °C after 96 h. However, their formation could be monitored at 70 °C (Fig. 5). The amount of the citrate esters **1**–**3** formed after 96 h was 5–9% of the initial amount of carvedilol at 70 °C. At 50 °C, the final amount of **1** corresponded to 3% of the initial amount of carvedilol.

Over the course of the experimental work, a mixture of citric acid monohydrate and carvedilol was stored at ambient temperature. After 1 month, traces of **1** (ppm range) and barely detectable amounts of **2** and **3** were observed. Thus, the formation of **1** takes place slowly in the solid state at room temperature.

Even though these experiments do not address the question of reaction kinetics in actual pharmaceutical formulations of carvedilol, they strongly suggest that formation of citric acid esters may constitute a significant problem upon long-term storage of preparations containing these two compounds.

3.3. Intramolecular rearrangements

The structure of carvedilol may facilitate intramolecular rearrangement of the citrate esters to amides (*O*-acyl to *N*-acyl shift via five-membered cyclic transition state). To test this possibility, the three esters (**1**–**3**) were subjected to kinetic studies in solution in acetone and acetonitrile. Acetone and acetonitrile were chosen as organic solvents capable of dissolving the compounds and in order to avoid solvents which may react with the esters. For each of the two solvents examined, a control experiment with citric acid monohydrate and carvedilol was performed. Citric acid was used in large

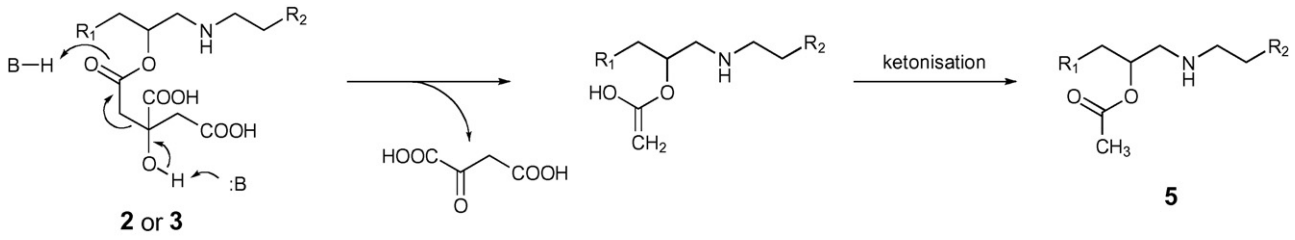

Fig. 3. Plausible mechanism of the postulated retro-Claisen-type fragmentation of the β-hydroxyester system of **2** or **3** to give the acetate **5**.

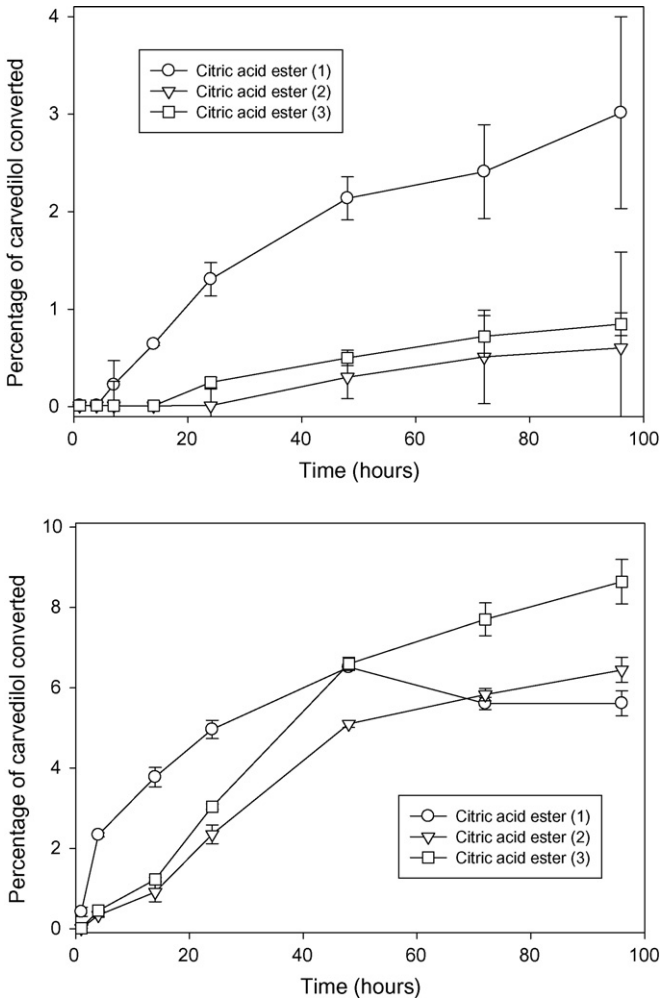

Fig. 4. Kinetics of formation of esters **1**–**3** in the solid-state reaction between carvedilol and citric acid monohydrate at 50 °C (top) and 70 °C (bottom). The content of **1**–**3** is calculated from areas of UV peaks relative to carvedilol.

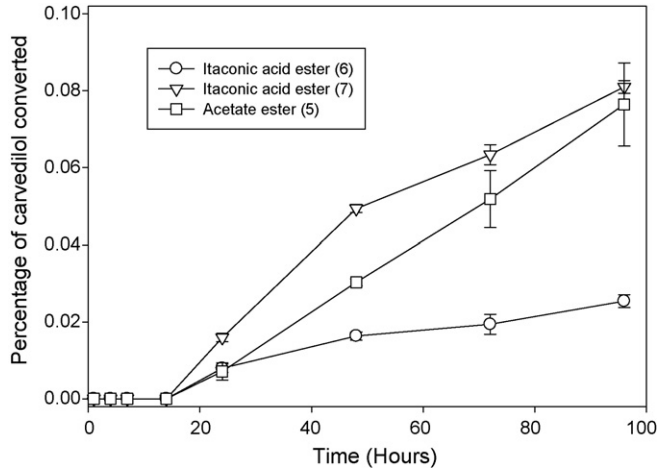

Fig. 5. Kinetics of formation of minor products (**5**–**7**) in the solid-state reaction between carvedilol and citric acid monohydrate at 70 °C. The content of **5**–**7** was estimated from the areas of TIC peaks relative to carvedilol.

excess of carvedilol for the control experiment in order to facilitate ester formation.

Examination of the reaction product did not show any interconversion of the esters. Instead, rapid conversion of the esters into amides took place. Thus, dissolving **1** in either acetone or acetonitrile converted about one-fourth of the ester into amide **4** immediately. On heating the solution, both the ester **1** and the amide degraded. For the two other esters, the reaction gave higher yields of a compound co-eluting with **4**, but required 30 min at 70 °C to reach completion. The control experiment with carvedilol and citric acid in solution under the same conditions did not yield any amide in either of the solvents tested. However, when the reaction time was extended to 2 weeks at 70 °C (acetonitrile solution), it yielded **4** in amounts comparable to the yield of **1** in the solid-state reaction.

3.4. Influence of water on solid-state reaction

When citric acid monohydrate was replaced with anhydrous citric acid, the amount of **1**–**3** formed after 2 weeks at 70 °C was reduced approximately 8-fold. This shows that the presence of small amounts of water significantly speeds up the solid-state reaction. There are several possible explanations for this. Water can act as a solvent for the reaction but in small amounts it might also act as an initiator for the reaction of the solid compounds by re-crystallising small amounts of compound on the surface of the reactant particles, increasing the chance of nucleation [9].

4. Conclusions

The solid-state reaction between citric acid and a model active ingredient compound (carvedilol), possessing both a secondary hydroxy group and a secondary aliphatic amine function, has been examined in a physical mixture of the two compounds at 50 and 70 °C. Citric acid (pK_1 3.12, pK_2 4.8, pK_3 6.4) is expected to efficiently protonate the amino group of carvedilol (pK 8.0 [10]) and the rate of formation of esters is by far greater than that of the formation of amides. The ester of the central carboxy group of citric acid (**1**) appears to be the kinetic reaction product. This parallels the outcome of the reaction between citric acid and codeine in solid state [1], and also between citric acid anhydride and aniline in solution [3], which may be regarded as an indication of the anhydride involvement in the solid-state reactions of citric acid with nucleophiles.

Comparable amounts of the diastereomeric esters **2** and **3** were formed as the reaction progressed. The formation of the esters was also observed after prolonged time at room temperature. Upon dissolution of esters **1**–**3**, rearrangements to amides were observed. The amides formed in the solid-state reactions of carvedilol are therefore believed to be at least in part the product of the rearrangement of esters. In addition, formation of carvedilol esters with degraded citric acid moiety, i.e., **5**–**7**, was observed but not fully elucidated. The identities of minor peaks close to the peak of compound **4** were not elucidated. In conclusion, this work demonstrated the complexity of reactions between citric acid and amino alcohols in solid state and formation of a variety of impurities, which may compromise the quality of solid as well as of liquid formulations.

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