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Effect of ultrasound-assisted crystallization in the diastereomeric salt resolution of tetramisole enantiomers in ternary system with *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid

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ABSTRACT

The diastereomeric salt resolution of racemic tetramisole was studied using ultrasound irradiation. We examined the effect of power and duration of ultrasonic irradiation on the properties of the crystalline phase formed by ultrasound-assisted crystallization and the result of the whole optical resolution. The results were compared with reference experiment without using ultrasound. The US time (5–30 min) caused higher enantiomeric excess. Although yield was lower continuously high resolving efficiency could have been reached through ultrasound. We had the best results with 4.3 W ultrasound power when resolvability was even higher than the best of reference. Furthermore, we accomplished a deep and thorough examination of the salts that possibly could form in this resolution. One of the four diastereomeric salts, which have been identified by powder X-ray diffraction, FTIR-spectroscopy, and differential scanning calorimetry (DSC) in the ternary system of the two tetramisole enantiomers and the resolving agent, namely the bis[(*S*)-tetramisole]-dibenzoyl-(*R*,*R*)-tartrate salt have been proven the key compound in the resolution process, and presented the highest melting point of 166 °C (dec.) among the four salts. The originally expected diastereomeric bitartrate salts with 1:1 M base:acid ratio [(*S*)-tetramisole-dibenzoyl-(*R*,*R*)-hydrogen-tartrate salt and (*R*)-tetramisole-dibenzoyl-(*R*,*R*)-hydrogen-tartrate salt] and their ‘racemic’ co-crystal [(*RS*)-tetramisole-dibenzoyl-(*R*,*R*)-hydrogen-tartrate salt] showed somewhat lower melting points (152, 145, and 150 °C, respectively) and their crystallization was also prevented by application of ultrasound. Based on the melting points and enthalpies of fusion measured by DSC, all the binary and ternary phase diagrams have been newly established and calculated in the system with help of classical modelling equations of liquidus curves.

1. Introduction

Molecules which cannot be arranged in a supposable configuration with their mirror image are chiral molecules and these are called enantiomers. The majority of compounds in the human body and the macro-molecules made of them are chiral and this is the reason why enantiomers could have very different biological effects. So, if a new potential drug has more stereoisomers and during synthesis a mixture is produced or they could transform into each other in the body it is compulsory all around the world to isolate enantiomers and study their pharmaceutical activity, toxicity and metabolism separately. Drugs sold today are mainly chiral substances [1,2]. There are many ways enantiomers could be produced including chiral chromatography in the presence of a chiral molecule [3], asymmetric synthesis or enzyme-catalytic reactions [4,5]. However, in the industry the most cost-effective way is the separation of the racemic mixture (a blend with equal amounts of enantiomers).

Nevertheless, the best method is still the diastereomeric salt resolution or “classical resolution” invented by Pasteur [6], when another chiral base (or acid) (***R****) is added to racemic acids (or bases) (***RS***) thus diastereomers form (***RR**** and ***SR****) and during fractionated crystallization enantiomers get enriched in different phases. Decomposing the diastereomers yields enantiomeric mixture therefore various refining methods (recrystallization, partial precipitation, salting out etc.) are needed to obtain the pure enantiomers [7–12].

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In the course of diastereomeric salt resolution we have to take many crystallization parameters in account. Some parameters are already proven to have significant impact on the outcome of the resolution. These are: crystallization time [13–18], temperature [19,20] and cooling profile [21]. Mixing has an important role as well although we haven't found any example for its methodical analysis.

Properties of the crystalline product can be modified by the use of ultrasound through crystallization. During sonocrystallization a sonotrode, which is capable to create ultrasound at a specific frequency (20–200 kHz), is inserted in the solution. Cavitation (made by the ultrasound [22]) and acoustic streaming decrease the induction time and accelerate the primary nucleation, while ultrasound has also a slight effect to the crystal growth mainly via decreasing the aggregation of the crystals [23,24]. Consequently, as a result of the shortened induction time, increased nucleation rate and decreased aggregation rate, sonocrystallization generates smaller and more homogeneous crystal products than crystallization without sonication. In addition, particle size, particle size distribution and structure of the formed crystals could depend principally on frequency and intensity of the ultrasonic treatment and geometry and immersion depth of the sonotrode [25].

Ultrasonic irradiation was applied in producing and separating chiral compounds already as well as asymmetric synthesis [26,27] and enzyme-catalysed kinetic resolutions [28]. Kinetic control was achieved by ultrasound in crystallization of different enantiomeric mixtures [29].

Another application was in diastereomeric salt resolution: in the resolution of an intermediate of silodosin with (*S*)-mandelic acid the yield of the diastereomeric salt was increased from 10% to 34% by 30 min of ultrasonic irradiation [30]. However, ultrasonic power and irradiation time were not mentioned.

One of our aims with present paper was to analyse the effect of intensity and duration of ultrasonic irradiation on the properties of the diastereomeric salt formed by fractionated crystallization and the result of the whole resolution.

Diastereomeric salt resolutions are made in aqueous or alcoholic solvents predominantly (65% of all resolutions [8]) but sometimes an immiscible solvent mix is a better choice [31]. In these cases homogenization of the phases is harder to achieve by mechanical mixing. Hence, we chose a model resolution with a biphasic solvent mixture where we assume the contact between the two phases would be improved by ultrasonic cavitation. The resolution of racemic 2,3,5,6-Tetrahydro-6-phenylimidazo- [2,1-b]-thiazole ((RS)-tetramisole [(*RS*)-**TET**]) with *O,O′*-dibenzoyl-(*R*, *R*)-tartaric acid [(*R*,*R*)-**DBTA**] as resolving agent was carried out successfully in water/dichloromethane non-miscible solvent mix. So we selected this resolution as our model. The (*RS*)-**TET** is an anthelmintic for warm-blooded animals and humans as well. The (*S*)-**TET** is known to be responsible for all of the pharmaceutical activity. On the other hand the systematic toxicities of (*R*)-**TET** and (*S*)-**TET** are approximately on the same order. It follows that administration of pure (*S*)-**TET** gives anthelmintic activity with substantially reduced risk of toxic reactions [32]. The *S*-isomer was given the name Levamisole.

The (*RS*)-**TET** can compose acidic and neutral salts also with (*R*, *R*)-**DBTA** so our other goal was a deep and thorough examination of the salts that possibly could form in this resolution.

2. Materials and methods

2.1. Materials

The racemic 2,3,5,6-Tetrahydro-6-phenylimidazo [2,1-b] thiazole hydrochloride salt [(*RS*)-**TET**·HCl] was acquired from Richter Gedeon Plc. which was dissolved in 5 M NaOH then an extraction with dichloromethane (DCM) followed by evaporation resulted in the free base form (NMR spectra in Section 2.5). The pure (*S*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole hydrochloride salt [(*S*)-**TET**·HCl] was purchased from Richter Gedeon Plc. as well. The pure (*R*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole [(*R*)-**TET**] was made by recrystallization and decomposition of the diastereomeric salt from the resolution of racemic (*RS*)-**TET** with *O,O′*-dibenzoyl-(S,S)-tartaric acid [(S,S)-**DBTA**] as resolving agent. The resolving agent O,O′-dibenzoyl-(R, R)-tartaric acid [(R,R)-**DBTA**] anhydride was purchased from Fluka Chemicals, (*S*,*S*)-**DBTA** anhydride from Sigma–Aldrich and dichloromethane (DCM), HPLC-grade water and acetonitrile from Merck.

2.2. Reference experiments without ultrasound

We have used equal amounts for each experiment. 4.08 g (20 mmol) (*RS*)-tetramisole [(*RS*)-**TET**] was dissolved in 10 ml dichloromethane (DCM) and 8 ml water at 40 °C and 2.365 g (6.6 mmol) (*R*,*R*)-**DBTA** in 14 ml dichloromethane (DCM) at 40 °C as well. The two solutions was mixed and cooled to 5 °C with ice (Fig. 1). Without ultrasound the homogenization was made by magnetic stirrer at 500 rpm. After the precipitation of the first crystal we let the diastereomeric salt to crystallize for different time periods (1, 10, 20 and 30 min). Then we filtered and washed the crystals with 1 ml distiled water. The diastereomeric salt was analysed by chiral reverse-phase HPLC. The salt was decomposed by 50 ml 5 M NaOH solution then extracted with dichloromethane (3 times 50 ml). The organic phase was further extracted with 30 ml brine and dried on $MgSO_4$ then evaporated. The yield of the enantiomeric mixture was calculated on the basis of half the initial (*RS*)-**TET**. The efficiency of resolution was described by the value of resolvability – or Fogassy-parameter (F), which is the product of the enantiomeric excess (*ee*) and yield (Y) of the enantiomeric mixture made from the diastereomeric salt; thus a value between 0 and 1. For each parameter setting we carried out 3 parallel experiments and we averaged the results.

2.3. Experiments with ultrasound

We have used equal amounts for these experiments as well. 4.08 g (20 mmol) (*RS*)-**TET** was dissolved in 10 ml dichloromethane and 8 ml water at 40 °C and 2.365 g (6.6 mmol) (*R*,*R*)-**DBTA** in 14 ml dichloromethane at 40 °C as well. When the solutions were added together, ultrasonic irradiation and cooling (5 °C) was started straightaway. We used a Bandelin Sonopuls HD 2200 ultrasonic homogenizer equipped with MS 72 booster horn probe (diameter 2 mm, length 191 mm; shape: exponential taper; resonance frequency of the equipment is 20 kHz). The sonotrode was placed at the same location during the runs: in a vertical position with its tip on the water–dichloromethane phase interface. The temperature was controlled throughout the whole experiment to avoid the warming effect of ultrasound. The duration of sonication was varied between 1, 5, 10, 20 and 30 min. Then we filtered the diastereomeric salt and washed with 1 ml distiled water (Fig. 2). The salt was analysed with chiral reverse-phase HPLC. We used different ultrasonic power and the real power was measured by the calorimetric method.

The calorimetric ultrasonic power measurement was made in water which gives a different value for our water/dichloromethane biphasic solvent. Therefore, the ultrasonic power determined with water is a nominal value but the value should be closely correlated with the actual one. In the present study all of the experiments were executed at a condition of constant volumetric ratio of water and dichloromethane solution. Thus, we used the nominal ultrasonic power as a guide to express the change of ultrasonic powers