Solubility and Some Crystallization Properties of Conglomerate Forming Chiral Drug Guaifenesin in Water

ROBERT R. FAYZULLIN,[1] HEIKE LORENZ,[2] ZEMFIRA A. BREDIKHINA,[1] ALEXANDER A. BREDIKHIN,[1] ANDREAS SEIDEL-MORGENSTERN[2]

[1]A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, Kazan 420088, Russian Federation

[2]Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg D-39106, Germany

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ABSTRACT: The solubility of 3-(2-methoxyphenoxy)-propane-1,2-diol, the well-known chiral drug guaifenesin **1**, in water has been investigated by means of polythermal and isothermal approaches. It was found that the solubilities of racemic and enantiomeric diols *rac*- and (*R*)-**1** depend strongly on temperature. The ternary phase diagram of the guaifenesin enantiomers in water in the temperature range between 10°C and 40°C was constructed. Clear evidence was obtained that *rac*-**1** crystallizes as a stable conglomerate. The Meyerhoffer coefficient for the guaifenesin–water system is more than two and strongly depends on temperature. Neither crystalline hydrates nor polymorphs were detected within the range of conditions covered. Metastable zone width data with regard to primary nucleation were also collected for *rac*-**1** and (*R*)-**1**. On the basis of the knowledge acquired, the resolution of racemic guaifenesin by preferential crystallization from solution could be realized successfully. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

Chirality is a fundamental property of an object to be nonsuperposable with its mirror image. Enantiomers are a pair of different stereoisomers related to the mirror symmetry. The need for chiral substances with high degree of enantiomeric enrichment arises because of the difference of the properties of enantiomers in a chiral environment, including the differences in biological activity in living organisms (namely pharmacological, toxicological, pharmacodynamic, and pharmacokinetic properties).[1–5] Stereoselective crystallization is becoming more and more attractive as a method for obtaining scalemic (nonracemic) substances, thanks to freedom from any of chiral auxiliary additives and catalysts, or enantioselective chromatographic phases.[6] However, this method as a sole instrument can be carried out only in the case of spontaneous resolution of racemates, that is, conglomerate formation of the compound under investigation. The spontaneous resolution phenomenon and direct separation techniques and their limitations are the subject of permanent interest and well described in the review works.[6–10]

3-(2-Methoxyphenoxy)-propane-1,2-diol, guaifenesin **1** (see Fig. 1) is a well-known active pharmaceutical ingredient that combines with not only an expectorant, a bronchodilator, a decongestant, an antihistamine, but also a muscle relaxant activity.[11,12] For example, it can be used in treatment of cough,[13–15] rhinitis,[16,17] gout,[18] fibromyalgia,[19] and primary dysmenorrhea.[21,22] Diol **1** is a valuable precursor in the synthesis of the skeletal muscle relaxant and spasmolytic methocarbamol[23] and the muscle relaxant and tranquilizer agent mephenoxalone.[24]

Recently, based on the identity of the IR spectra of the racemic and scalemic crystalline samples, thermochemical studies, and X-ray diffraction analysis, the conglomerate nature of *rac*-**1** has been established.[25–27] Also a separation procedure based on entrainment (i.e., preferential crystallization) of slightly enantiomerically enriched aqueous solution was introduced.[26] Being really readily available in a nonracemic form, enantiomeric guaifenesin, *scal*-**1**, could be considered as a representative of "New Chiral Pool" reagents. So starting from racemic diol *rac*-**1**, passing through the preferential crystallization step, the following important substances have been synthesized: the chiral β-blocker levomoprolol[26] (used in therapy as the single *S*-enantiomer only), the drugs methocarbamol and mephenoxalone in enantiopure forms,[28] and a family of the scalemic crown lariat ethers[29,30] (Fig. 1).

Despite the importance of solubility data for selecting the crystallization strategy and the subsequent optimization of the resolution process, only scattered and nonsystematic data are found in the literature regarding solubility of *rac*-**1** in water (information on solubility of *scal*-**1** was not found at all). For example, Shervington and Shervington[11] reported that "guaifenesin is soluble to the extent of one part in 33 parts of water." In the Merck Index, there is stated that "one gram dissolves in 20 ml water at 25°; much more sol. in hot water".[12] Mani et al.[31] specifies high solubility of *rac*-**1** at elevated temperatures (259.8 mg mL^{-1} at 40°C vs. 40.4 mg mL^{-1} at 25°C). Significant higher values of the solubility of compound *rac*-**1** at increased temperature in water were published by Realdon et al.[31] (446 g L^{-1} at 37°C vs. 37 g L^{-1} at 20°C).

In this work, we systematically investigated the solubility of guaifenesin in racemic and enantiopure form, *rac*-**1** and (*R*)-**1**,

Correspondence to: Robert R. Fayzullin (Telephone: +7-8432319167; Fax: +7-8432731872; E-mail: robert.fayzullin@gmail.com)

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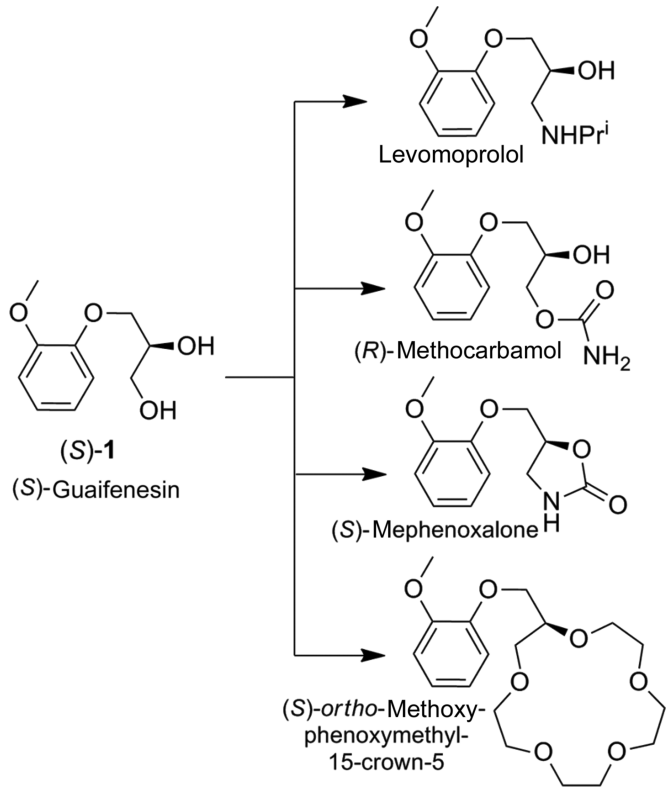

Figure 1. Structure of guaifenesin **1** and its valuable single enantiomer derivatives.

in water via a polythermal method and isothermally through suspension experiments at 10°C, 20°C, 30°C, 38°C, and 40°C. Together with the results of isothermal measurements for intermediate nonracemic mixtures of **1**, the obtained data allowed us to plot the ternary phase diagram within the range of temperature covered. To plan separation experiments, metastable zone width (MZW) data of *rac*-**1** and (*R*)-**1** were determined. Finally, we carried out preliminary attempts to resolve *rac*-**1** by preferential crystallization without any previous enantiomeric enrichment of the starting material, that is, directly from the initial racemate.

EXPERIMENTAL

Chemicals

Racemic guaifenesin *rac*-**1** (guaiacol glycerol ether) was purchased from TCI with purity >98.0%. Enantiopure diol (*R*)-**1** [melting point (mp) 97°C–98°C; $[\alpha]_D^{20} = -9.5$ (*c* 1, MeOH)] was produced by stereoselective crystallization of the racemic material according to our published method.[26]

Analytical Equipment

The enantiomeric excess (ee) of the substances and intermediate samples used was checked by HPLC and was identified as 0% ee for *rac*-**1** and ≥99.9% ee for (*R*)-**1**. HPLC analyses were performed on a Dionex HPLC system (Dionex GmbH, Idstein, Germany), which consists of a P580 pump, an ASI-100 auto-sampler, a TCC-100 column oven, and a UVD340U DAD detector. The UV wavelength selected was 275 nm. The column used was a Chiralcel OD-H (0.46 cm × 25 cm) (Chiral Technologies Europe, Illkirch, France). The HPLC parameters were as follows: column temperature 23°C; eluent: 35:65 (v/v), 2-propanol/hexane; flow rate: 1.0 mL min^{-1}; retention times (t_R): $t_R = 6.4$ min {(*R*)-**1**}, $t_R = 11.6$ min {(*S*)-**1**}.

Solubility Measurement

For solubility measurements, both a classical isothermal (suspension) method and a polythermal method were applied. All experiments were carried out in water purified by a Milli-Q apparatus.

The isothermal experiments were performed according to a known procedure.[33,34] Weighed amounts of *rac*-**1**, (*R*)-**1** or different intermediate mixtures of both were filled in glass vessels of 10 or 20 mL total volume together with a magnetic stir bar. A certain amount of water as solvent, not sufficient to dissolve all solid material, was added and the vessel was hermetically plugged up. The suspension was stirred at 800 rpm at constant temperature using a thermostated double-jacketed glass apparatus. The temperature of the heat-transfer agent was controlled with a Pt-100 resistance thermometer (resolution 0.01°C). A Lauda RC 6 PC thermostat was used for heating of the heat-transfer agent. After 3–4 days of stirring, the saturated solution was isolated by a filter Chromafil PET-45/25 (pore size: 0.45 μm) and samples of 2–3 mL were withdrawn in vials. The stirring time was verified to be sufficient for establishment of solid–liquid equilibrium in a preliminary experimental study. The samples were weighed before and after evaporation to dryness using an analytical balance so as to calculate the weight fraction of compound **1**. Drying of liquid samples was performed for about 40 h at 70°C under reduced pressure. For each sample composition, four or five independent experiments were executed and at least eight to ten samples were checked. The results were subjected to standard statistical analysis to assess the confidence interval of the solubility data ($n = 8$–10, $\alpha = 0.95$).

The polythermal experiments were carried out by analogy with a published method.[35,36] Known amounts of *rac*-**1** or (*R*)-**1** and 0.7 g of water were filled in small vials equipped with a magnetic stirrer. The vials sealed were placed in a Crystal16™ multiple-reactor system (Avantium Pharmatech BV, Amsterdam, The Netherlands). The device consists of four independently thermostated blocks, which are controllably heated and cooled, with four reactors in each block. The turbidity degree was registered for the individual reactor to detect the so-called "clear point" (the temperature where last crystals disappeared taken as saturation temperature). Changes of the turbidity degree were detected by a laser beam. Before determination of the "clear points", the samples were preliminary dissolved and recrystallized. For the experiments, the following conditions were selected: a heating rate of 6 K h^{-1}; stirring rate of 700 rpm.

MZW Measurements

MZW data with regard to primary nucleation were determined for aqueous solutions of *rac*-**1** at concentration of 25 and 40 wt. % and (*R*)-**1** at concentration of 25 wt. %. Experiments were performed in analogy with a published work[35] in the Crystal16™ reactor system by detecting so-called "cloud points" (the temperature where first crystals were detected) in cooling cycles.

Samples of about 1 mL of solution of known composition in plugged vials equipped with a magnetic stirrer were used for