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Determination of pK_a-values and Solubility-pH Profiles of Selected ß-blockers

Schönherr D.[1], Wollatz U.[1,2], Hanke U.[1,4], Haznar-Garbacz D.[1], Box K.[2], Taylor R.[2], Ruiz R.[2], Beato S.[3], Becker D.[3,5], Weitschies W.[1]

[1]University of Greifswald, Center of Drug Absorption and Transport, Institute of Pharmacy, Greifswald, Germany
[2]Sirius Analytical Ltd., East Sussex, UK
[3]Novartis Pharma AG, Technical Research & Development, Basel, Switzerland
[4]present address: LTS Lohmann Therapie-Systeme AG, c/o BioTechnikum GmbH, Greifswald, Germany
[5]present address: Vivo Drug Delivery GmbH, Wollerau, Switzerland

dana.schoenherr@uni-greifswald.de

PURPOSE

The most common route of drug administration is the oral route. When taken orally the drug substance passes through the gastrointestinal tract with varying pH-levels. They range from pH 1 to 3 in the stomach, pH 5.6 to 7.6 in the small intestine and pH 5 to 7 in the colon. At a given pH the ionization constant (pK_a) determines the ionization state of a drug substance and therefore several other properties (e.g. lipophilicity, solubility and permeability). Consequently, these properties can affect the absorption, bioavailability and pharmacokinetics of a drug.
In this study we investigated the physicochemical characteristics of selected ß-blockers by measuring the pK_a and intrinsic solubility of the compounds. The results were compared with calculated values and reported data found in the literature.

METHODS

Measurements were performed on a SiriusT3 (Sirius Analytical, UK), to determine the pK_a and intrinsic solubility of nine weakly basic ß-blocker drugs, using acid-base titration methods. Therefore, the sample was first dissolved at low pH where the secondary amine group of the ß-blocker was fully ionized and the sample was most soluble. Then, the solution was titrated with a concentrated base reagent until the amine became fully unionized. The pK_a was determined as the pH where the ß-blocker was half ionized. To measure solubility, an excessive amount of drug was used to induce precipitation of the free form of the compound. Solution concentrations in the presence of precipitate were determined using the principles of mass and charge balance. The computation of pK_a and solubility values was performed using the prediction program ACD/ChemSketch (Version 11).

RESULTS & DISCUSSION

For the ß-blockers studied here, pK_a-values of approximately 9.5 were measured by Sirius T3 which is as expected for drug substances with a secondary amine, with the exception of carvedilol with a pK_a of 8.0 (Tab. 1). The observed difference is probably due to the more electronegative ether function within the side chain of carvedilol. Furthermore, the experimentally obtained pK_a values were in good accordance to the calculated using the Chem/Sketch software. Calculated pK_a values were found to be 8.2 for carvedilol and approximately 9.2 for further drug substances. However, the published literature pK_a values of the ß-blockers covered a wider range from 7.0 to 9.7. The measured intrinsic solubilities of the ß-blockers ranged from 0.014 to 18.4 mg/mL, whereas the calculated solubilities were found to be between 0.003 mg/mL and 13.7 mg/mL. The solubility-pH profiles determined from these results (Fig. 1), demonstrated for all ß-blockers a high solubility at low pH and a low solubility at high pH, consistent with the expected behavior of weak bases.

Tab. 1: Measured pK_a and intrinsic solubility values of ß-blockers using SiriusT3 titration methods in comparison with calculated and published data; given are means ± SD, n = 3, * n = 4, ** n = 6. References are reported separately.

Name of compound	Measured pK_a by SiriusT3	Calculated pK_a using Chem/Sketch	Published measured pK_a-values	Measured solubility (mM)	Calculated solubility (mM)
Alprenolol	9.57±0.04	9.16±0.38	9.19[1]; 9.34[2]; 9.38[3]; 9.447[4]; 9.5[5]; 9.51[6]; 9.65[7; 8]	2.04±0.11** (≙0.51 mg/mL)	9.12 (≙2.27 mg/mL)
Atenolol	9.57±0.06	9.16±0.38	9.54[4; 6]; 9.6[7; 9; 10; 11; 12; 13; 5; 8; 14]	69.0±7.3* (≙18.4 mg/mL)	51.3 (≙13.7 mg/mL)
Bisoprolol	9.48±0.22	9.15±0.38	9.16[1]; 9.2[2]; 9.57[9]	34.7±5.6 (≙11.3 mg/mL)	21.4 (≙7.0 mg/mL)
Carvedilol	8.01±0.05	8.16±0.19	-	0.035±0.006** (≙0.014 mg/mL)	0.007 (≙0.003 mg/mL)
Metoprolol	9.57±0.47	9.17±0.38	9.18[1; 14]; 9.31[2]; 9.56[4; 6]; 9.68[8]; 9.7[3; 7; 9; 13; 5; 14]	59.8±2.1** (≙16.0 mg/mL)	38.9 (≙10.4 mg/mL)
Nadolol	9.77±0.12	9.17±0.48	9.00[2]; 9.17[1; 15]; 9.67[8]; 9.69[6]; 9.696[4]	20.7±1.2* (≙6.4 mg/mL)	11.2 (≙3.5 mg/mL)
Pindolol	9.52±0.22	9.20±0.38	6.98[2]; 8.8[7; 8]; 9.21[1]; 9.54[4; 6]; 9.7[7]	0.29±0.04** (≙0.07 mg/mL)	15.8 (≙3.9 mg/mL)
Propranolol	9.49±0.09	9.14±0.14	9.03-9.06[10]; 9.15[1]; 9.25[2]; 9.45[7]; 9.5[13; 5]; 9.52[8]; 9.53[4; 6]	0.36±0.03** (≙0.09 mg/mL)	1.55 (≙0.40 mg/mL)
Talinolol	9.71±0.13	9.16±0.48; 13.82±0.20	- -	0.24±0.11** (≙0.09 mg/mL)	0.16 (≙0.06 mg/mL)

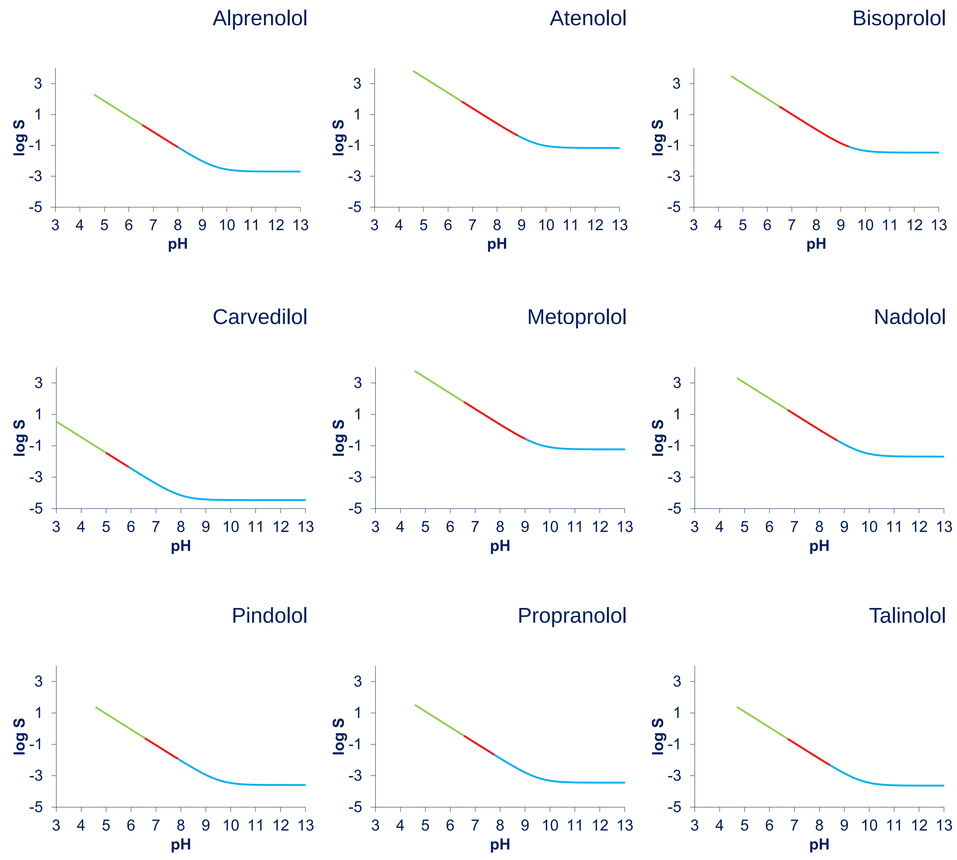

Fig. 1: Solubility-pH profiles of selected ß-blockers (aqueous solubility in blue, solubility beyond the experimental range in red and the solubility beyond experimental range that may be affected by salt-solubility issues in green).

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CONCLUSION

The SiriusT3 allows for the characterization of the physico-chemical behavior of the investigated drug substances by measuring the pK_a and solubility values as well as generating the respective solubility-pH profiles. The experiments demonstrated a good agreement between calculated, measured and published pK_a data. Since the experimentally obtained results closely match the mathematically obtained data the SiriusT3 setup and the used titration method are a reliable analytical technique to determine pK_a values of drug compounds. The ease of measuring and its high reproducibility (as indicated by its markedly low standard deviations of the measured pK_a and solubility values) makes it a very useful technique for drug characterization in an early stage of drug development and formulation of oral dosage forms.