European Journal of Pharmaceutics and Biopharmaceutics 92 (2015) 155–170

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Characterisation of selected active agents regarding pK_a values, solubility concentrations and pH profiles by SiriusT3

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ARTICLE INFO

Article history:
Received 28 October 2014
Revised 18 February 2015
Accepted in revised form 27 February 2015
Available online 7 March 2015

Keywords:
pK_a measurement
Ionisation constant
Potentiometric titration
Intrinsic solubility
Solubility-pH profile
Biopharmaceutical classification system
ACE-inhibitors
β-Blockers
Antidiabetics
Lipid lowering substances

ABSTRACT

The aim of this work was to determine pK_a values and solubility properties of 34 active agents using the SiriusT3 apparatus. The selected drug substances belong to the groups of ACE-inhibitors, β-blockers, antidiabetics and lipid lowering substances. Experimentally obtained pK_a and intrinsic solubility values were compared to calculated values (program ACD/ChemSketch) and pK_a values to published data as well. Solubility-pH profiles were generated to visualise the substance solubility over the gastrointestinal pH range. The relationship between the solubility characteristic of a substance, its bioavailability and categorisation according to the Biopharmaceutics Classification System (BCS) was examined as well. The results showed a good agreement between experimentally obtained, calculated and published pK_a values. The measured and calculated intrinsic solubility values indicated several major deviations. All solubility-pH profiles showed the expected shape and appearance for acids, bases or zwitterionic substances. The obtained results for the pK_a and solubility measurements of the examined active agents may help to predict their physicochemical behaviour in vivo, and to understand the bioavailability of the substances according to their BCS categorisation. The easy and reproducible determination of pK_a and solubility values makes the SiriusT3 apparatus a useful tool in early stages of drug and formulation development.

1. Introduction

After oral application, active agents have a long way from the mouth to the site of absorption in the intestine. On the way they come into contact with a wide range of fluids with various pH values, volumes and compositions. In particular, the alteration of pH from 6.8 to 7.3 in the mouth [1–3], decreasing to pH 1 to 3.5 in the stomach, increasing again to pH 6 to 8 in the small intestine and pH 5.5 to 8 in the colon [4], may have a strong influence on the substance. At a given pH, the ionisation constant (K_a) determines the charge state of an ionisable drug substance and therefore has an impact on other physicochemical properties (e.g. lipophilicity, solubility and permeability). For example, the ionised form of a compound is in general more water soluble than the more lipophilic and permeable neutral form. Consequently, these properties can influence the pharmacokinetics, such as absorption, distribution, metabolism, and excretion (ADME) of a drug substance in vivo.

With the determination of pK_a values, solubility properties and the generation of solubility-pH profiles, estimation of the in vivo behaviour of orally administered drug substances is possible. Furthermore, the development of active agents and oral dosage forms can be improved by including this knowledge to achieve a target-oriented release and absorption of the active agent from the intestine.

Previously published works dealt with the determination of the physicochemical characteristics of active agents. Profiles were obtained using small-scale shake flask [5] or potentiometric titration methods [6–8]. However, often only the pK_a or solubility values of individual drug substances [9–12] or representatives of various medicinal classes [13–16] were determined.

In this work, the physicochemical properties pK_a and solubility of a wide range of compounds from clinically established active

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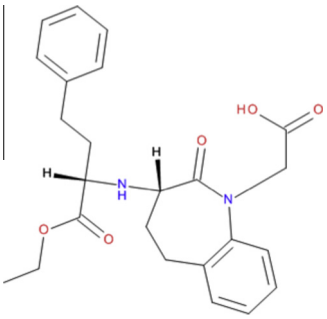
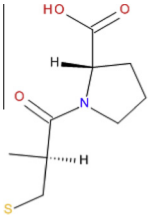
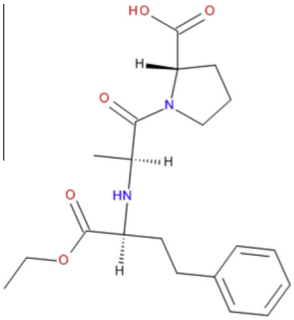
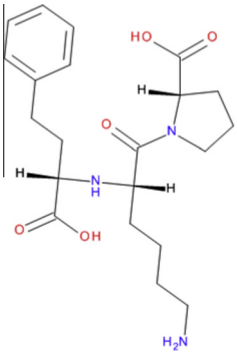
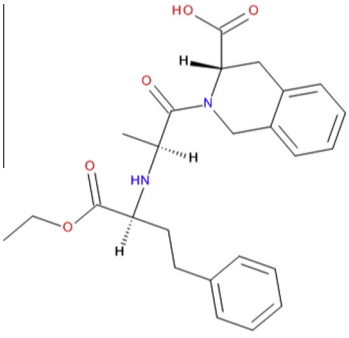
http://dx.doi.org/10.1016/j.ejpb.2015.02.028
0939-6411/

Table 1
BCS class and bioavailability of ACE-inhibitors.

Name of compound	Structure of compound	BCS class	Bioavailability (%)
Benazepril		I [25]	37 [26], >37 [27], 50 [28]
Captopril		I/III [29,30]	65 [28], 75–91 [27]
Enalapril		I/III [25,29]	60 [27,28]
Lisinopril		III [29]	25 [26,28], 6–60 [27]
Quinapril		I [25]	50 [28], 60 [31], >60 [27]