Fluid Phase Equilibria 392 (2015) 56–64

Contents lists available at ScienceDirect

Fluid Phase Equilibria

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

Solubility of pharmaceuticals in water and alcohols

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ARTICLE INFO

Article history:
Received 13 October 2014
Received in revised form 5 February 2015
Accepted 11 February 2015
Available online 14 February 2015

Keywords:
DSC
Solubility
pK_a
Thermodynamic correlation

ABSTRACT

The aim of this study was to examine the phase equilibria in binary systems: {pharmaceutical, Ph (1) + water, or alcohol (2)}. This work was carried out for four pharmaceuticals, Phs: aminophylline and (−) lobeline hydrochloride, perphenazine and indomethacin. Solubility of tested Phs was determined in three solvents. Water, the main component of any living organism. Ethanol, substance corresponding to the transport of the Ph in the body, and 1-octanol, a model compound of human cell and skin membrane. All studied Phs have aromatic structure and functional groups typical for drugs.

The differential scanning microcalorimetry technique, DSC was used to measure basic thermal properties of pure drugs, i.e., temperatures of fusion, enthalpy of fusion, glass-transition temperatures and heat capacity change at the glass-transition temperature. Molar volumes have been calculated with Barton group contribution method. The Bates–Schwarzenbach method enabled us to determinate the pK_a of used Phs. These values are important because it may designate the Phs dosage and the activity at the certain pH. The pK_a experimental values are slightly different than the literature data which was already published as a results of different experimental methods. In this work, altogether 12 binary systems {Ph (1) + solvent (2)} were studied with the use of dynamic and spectrophotometric method. Three G^{Ex} thermodynamic models were used to correlate the experimental data: Wilson equation, NRTL equation and UNIQUAC equation.

1. Introduction

Pharmaceuticals, Phs are substances of a very different structure from the structures of media that occur in the body. Introduced into the body, Phs are involved in the biochemical processes and influence the work of each cell to combat pathologies. Pharmaceutical substances studied in this work were: aminophylline, (−)-lobeline hydrochloride, perphenazine, and indomethacin. These drugs have a variety of different structures and functional groups. Aminophylline is a mixture of a purine alcaloid and theophylline. Operation of aminophylline stimulates the central nervous system, skeletal muscle and cardiac muscle. It affects the relaxation of airway smooth muscle and lowers the bronchial reactivity to histamine, methacholine, adenosine, and allergens. It is used in the treatment of bronchial asthma, chronic bronchitis, pulmonary emphysema [1]. The drug also prevents the occurrence of apnea in infants treated with prostaglandin E1 due to congenital heart defects [2]. Referring to the favorable properties it has been found that aminophylline may be applied in the form of a cream. This property has been used in studies aimed at overcoming the cellulite [3]. The second drug (−)-lobeline hydrochloride causes strong stimulation of the respiratory center, which leads to the acceleration and deepening of breaths. The drug also interacts strongly on the centers of the medulla oblongata, and vascular. It proves the ability to apply it as a substitute for anti-smoking therapies [4], as well as studies on animals gives hope that it may be used in the future as a potential drug for the treatment of alcoholism [5]. Perphenazine is derivative of phenothiazine. Perphenazine is a piperazinyl phenothiazine used to treat psychosis. The drug affects on the central nervous system. It belongs to the first generation neuroleptics. It shows a strong antipsychotic activity. Due to having in their structure piperazine group, the drug has a stronger influence on behavior than other phenothiazines. Inhibitory effect on the nerve cells responsible for psychic phenomena. Mechanism of action this drug is mainly associated with the dopaminergic system and blocking receptors D [6]. Clinical indications for perphenazine include: schizophrenia, psychotic depression, hallucinations and hyperemesis gravidarum.

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http://dx.doi.org/10.1016/j.fluid.2015.02.018
0378-3812/

Nomenclature

a	Activity
$\Delta Cp_{g,1}$	Difference in solute heat capacity at glass transition temperature ($J K^{-1} mol^{-1}$)
D	Absorbance value
g_{ij}	Molar energy of interaction between i and j ($J mol^{-1}$)
G^E	Excess Gibbs free energy ($J mol^{-1}$)
$\Delta_{fus}H$	molar enthalpy of fusion ($kJ mol^{-1}$)
k	Number of parameters
n	Number of experimental points
P_1,P_2	Binary interaction parameters of NRTL equation
R	Universal gas constant ($J K^{-1} mol^{-1}$)
T	Equilibrium temperature (K)
ΔT	Estimated error of temperature (K)
x	Mole fraction
w	Weight of experimental point

Greek letters

γ	Activity coefficient
σ_T	Root-mean-square deviation in temperature

Superscript

A^-	Base value
cal	Calculated value
exp	Experimental value
HA	Acid value

Subscripts

fus	Fusion
i	Component
lit	Literature data
T	Temperature
1,2	Type of component (1-solute)

Perphenazine exhibits greater solubility when present as a complex with β-cyclodextrin [7].

Indomethacin is a nonselective cyclooxygenase inhibitor. It inhibits the production of elkosanoid, reduces joint swelling and improves the function of the locomotor system. It is used in rheumatoid arthritis, inflammation of the veins and slipped disc due to analgesic and anti-inflammatory. In small concentrations, it is also used in cataract surgery [8]. This drug can be classified into a group of drugs acting on the cardiovascular system [9]. Indomethacin is a non-steroidal anti-inflammatory drug used to reduce pain, fever, stiffness and swelling. Clinical indications for indomethacin include: arthritic gout, ankylosing spondylitis, rheumatoid arthritis and for closing the still patent ductus arteriosus Botalli in prematures. Indomethacin, whose mechanism of action is similar to the mode of action of aspirin was tested for the solubility in propylene glycol, PEG400 and Tween 80 [10], and chloroform [11]. In many publications also emphasized that indomethacin is very sparingly soluble in water [12].

In order to specify the medical issue, it should be clarified where the grip point of the drug is located. The interpretation of these properties takes into account the solubility of the drug and the pK_a values. Therefore, the issue carried out by physical chemistry is to show the basic information of Phs [13]. Measurement of drug solubility in various solvents is one of the key elements of compound characterization during the whole discovery and development process [14]. Solubility is thus a very important property of a product designed for Ph because it affects the drug efficacy. It is future development and formulation efforts, and also influences the pharmaco-kinetics, such as the release, transport and the degree of absorption in the organism [15]. The issue of solubility is the most important and the most difficult aspect of drug development. It has a huge impact on the bioavailability of drugs. It is associated with the achievement of a certain concentration of the drug in the bloodstream [16]. It specifies the dosage regimen because poorly soluble drugs require delivery of large doses to achieve therapeutic levels in the plasma [17].

The knowledge of solubility needs the basic thermophysical information: melting point and enthalpy of fusion, determined by differential scanning calorimetry (DSC). These values are necessary to describe the thermodynamic solubility. The solubility is not the ideal solubility but is dependent on the solvent [18]. However, the solubility data of many new drugs are often not available in the literature. Although some thermodynamic models can be used to predict the solubility of the drug, the availability of experimental data is still a basic problem for the proper development and evaluation of the different models. The prediction of the solubility is usually performed under general solubility equation or structure of the molecule. Solubility, as (solid + liquid) phase equilibria, is influenced by the purity of the material, thermophysical properties, by polymorphism, temperature, pressure and the pH of the solution [19]. Most of the therapeutic factors describes the solubility in water. The test is usually at room temperature (298 K) or at the boiling temperature of water [20]. The issue of the solubility of Phs depends on the melting point, the melting enthalpy and the heat capacity at melting temperature as the difference between the heat capacity of liquid and solid phase extrapolated to the melting temperature.

Solubility is based on the highest-dose strength of an immediate release product. The Ph is considered as a highly soluble when the highest dose strength of 250 ml soluble in aqueous medium, when the pH is in the range of 1–7.5 [21]. The solubility of drugs is so dependent on the pH of the environment in which the drug is absorbed. Important values of solubility is also lipophilicity and dissociation rates, namely, the ability for dissolving of fat molecules. This has the reference in the study of the drug solubility as a function of temperature. Mostly used solvents are alcohols and water in buffers. The solubility of the drug substance can be influenced by changing it polarity and pK_a. An example would be masking drug polar functional groups with other groups, which in the body subject to the relevant conversion to the active form [22]. Knowledge of the pK_a values allows to determine which form of the drug is present in higher concentrations in the tissue. It provides clues for dosing Ph substance. The acidity constant is an important parameter determining the degree of ionization of physical and chemical functional groups in the pH range. It plays an important role in optimizing the manufacturing process of drugs. The best example is the study executed for a constant acidity of drugs used in the treatment of osteoporosis [23].

Determination of pK_a is sometimes very problematic, because many drugs are poorly soluble in water. Measurements of pK_a are mostly made with two methods: potentiometric or spectrophotometric. Spectrophotometric method is used more frequently, although it is not universal and cannot be applied in all cases. In this study a pK_a value measurements were performer with the Bates–Schwarzenbach method using UV–vis spectrophotometer. This method is characterized by higher accuracy for a narrow range of solubility [24]. Measurements of the acidity constant are also performed with the following techniques: NMR titration, capillary electrophoresis, liquid chromatography or different methods of calculation [25]. The pK_a is a thermodynamic parameter. It depends on the temperature and functional groups. Important values for the