Chapter 10
The Role of Chemical Engineering in Medicinal Research Including Alzheimer's

Georgios M. Kontogeorgis

Abstract Various disciplines of chemical engineering, especially thermodynamics and kinetics, play an important role in medicinal research and this has been particularly recognized during the last 10–15 years (von Stockar and van der Wielen, J Biotechnol 59:25, 1997; Prausnitz, Fluid Phase Equilib 53:439, 1989; Prausnitz, Pure Appl Chem 79:1435, 2007; Dey and Prausnitz, Ind Eng Chem Res 50:3, 2011; Prausnitz, J Chem Thermodynamics 35:21, 2003; Tsivintzelis et al. AIChE J 55:756, 2009). It is expected that during the twenty-first century chemical engineering and especially thermodynamics can contribute as significantly to the life sciences development as it has been done with the oil and gas and chemical sectors in the twentieth century.

Moreover, it has during the recent years recognized that thermodynamics can help in understanding diseases like human cataract, sickle-cell anemia, Creuzfeldt-Jacob ("mad cow" disease), and Alzheimer's which are connected to "protein aggregation." Several articles in the *Perspectives* section of prominent chemical engineering journals have addressed this issue (Hall, AIChE J 54:1956, 2008; Vekilov, AIChE J 54:2508, 2008).

This work reviews recent applications of thermodynamics (and other areas of chemical engineering) first in drug development and then in the understanding of the mechanism of Alzheimer's and similar diseases.

10.1 Introduction

The significant role of chemical engineering in medicinal research and biotechnology has been intensively recognized, especially during the last 20 or so years, with thermodynamics being one of the disciplines of importance [1–6]. In downstream biotechnology, the main interest is in the design of separation processes such as chromatography and crystallization. In the pharmaceutical industry there is interest

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P. Vlamos, A. Alexiou (eds.), *GeNeDis 2014*, Advances in Experimental Medicine and Biology 821, DOI 10.1007/978-3-319-08939-3_10

in optimizing the selection of solvents, which is of major importance in the manufacturing process of many pharmaceuticals. Thermodynamics is also of importance in the understanding of the mechanisms of several diseases, like cataract, Creutzfeldt-Jakob ("mad cow" disease), and Alzheimer's, which are now believed to be caused by protein aggregation [4, 5, 7, 8]. This understanding may contribute to the discovery of new cure for such diseases.

Complex physicochemical interactions are a common denominator in most of the aforementioned applications due to the presence of the biomolecules and the often aqueous solutions in the presence of salts and polymers. Thermodynamics, e.g., solubility estimations, is often associated with complex phase diagrams which must be known as a function of temperature, charge, solvent type, pH, and ionic strength.

10.2 Medicinal Research and Solvent Selection

Screening for solvents and calculating the solubility of pharmaceuticals in the selected solvents are important tasks in the pharmaceutical industry [9–13]. The thermodynamic properties of pharmaceuticals and other biomolecules are of importance for rational design and optimizing separations such as crystallization, but they are also relevant to understanding the complex phenomena and interactions, e.g., aggregation, associated with certain diseases. Another important application is the controlled release of pharmaceuticals through polymeric capsules. In this case, the permeability of the pharmaceutical and its diffusion rate ultimately depend on the solubility of the pharmaceutical in the polymer [5].

Thermodynamics of pharmaceuticals is complex, because these are multifunctional chemicals, frequent use of mixed solvents and polymorphism. Nevertheless, there is much industrial interest, as shown in several publications from industrial colleagues [9–13]. Several computational thermodynamic models are now used for solvent selection in the pharmaceutical industry including QSAR, local-composition models, variations of solubility parameter concept, and quantum chemical approaches; for a review see Kontogeorgis and Folas [14].

Most of these approaches are essentially empirical in nature, requiring several adjustable parameters which are obtained from experimental solubility data that must be available prior to using the models. Moreover, these models do not explicitly account for complex interactions present in pharmaceutical mixtures, which are due to the strong intermolecular forces especially polarity and hydrogen bonding. We have recently developed [6, 15] for mixtures with pharmaceuticals a theoretically oriented model (called NRHB; non-random hydrogen bonding), based on an advanced theory, which explicitly accounts for hydrogen bonding and other complex interactions. The model is in a form of an equation of state and can thus be used both at low and high pressures, both for single and mixed solvents, wide temperature range and for both pharmaceuticals and polymers. Also, the model is combined with the concept of solubility parameter, which is widely used for the

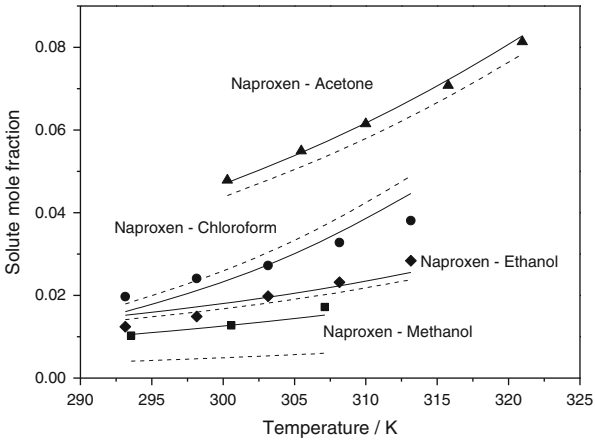

Fig. 10.1 Solubility of naproxen in various solvents. Experimental data (*points*), model predictions (*dashed lines*) and model correlations (*solid lines*) using a single temperature-independent parameter. From Tsivintzelis et al. [15]

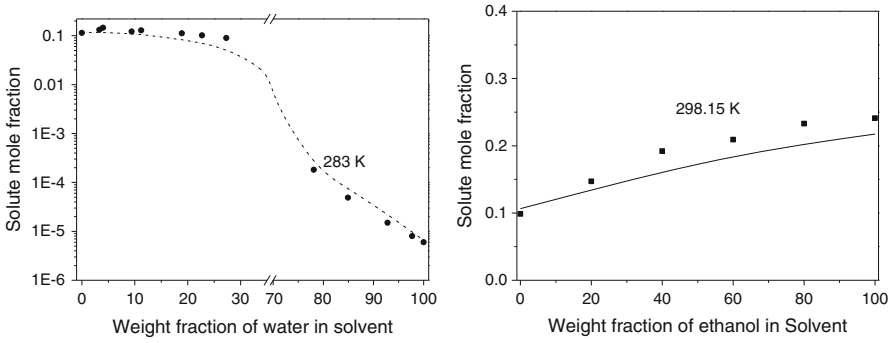

Fig. 10.2 (*Left*) Solubility of ketoprofen in the acetone–water mixture. Experimental data (*points*), and model predictions using binary interaction parameters from the corresponding binary systems. From Tsivintzelis et al. [15]. (*Right*) Solubility of ibuprofen in ethanol–propylene glycol mixture at 298.15 K. Experimental data (*points*), model predictions using binary interaction parameters from the corresponding binary systems (*line*)

screening of solvents in pharmaceutical applications. But the most important characteristic of NRHB is the adoption of a segment-type approach which ensures that all the involved hydrogen bonding interactions are accounted for and moreover that the parameters are obtained from low-molecular-weight compounds.

Thus, the new model (NRHB) has the potential of being an invaluable tool in pharmaceutical industry and related applications. The model is described in recent publications [6, 15] and some typical results are shown in Figs. 10.1 and 10.2. The results for mixed solvents are predictions and no new parameters are used. The method can be readily extended to new pharmaceuticals and solvents but should be of course tested prior to use. So far nine pharmaceuticals and intermediates have been considered, which contain a variety of hydrogen bonding forming groups.

10.3 Chemical Engineering in Alzheimer's Research

Peter Vekilov [8] writes that amyloid diseases will be of increasing importance in the coming years as Alzheimer's effects, in some form, touch about half of the people above 85 years of age and there will be more and more patients as life expectancy increases. Carol Hall states [7] that five million Americans (5–10 % of 65–74-year-olds and 50 % of 85-year-olds) have Alzheimer's, at a cost to society of $148 billion/year.

Alzheimer's in one of the many "amyloid" type diseases, which are now believed to be due to protein deposition or protein conformation change. The causes of amyloid formation are not fully understood. Several of the key proteins, e.g., APP (amyloid precursor protein) are present in both healthy and diseased people. APP is cleaved to form Alzheimer's proteins. In Alzheimer's these proteins aggregate to form fibrils but in healthy people they do not, and it is not clear why.

Actually, beyond Alzheimer's it is suggested that many more diseases are connected to "protein aggregation" or agglomeration, e.g., human cataract and sickle-cell anemia.

This "protein aggregation" can be understood in thermodynamic terms in various contexts; for example, it can be described by a liquid-liquid equilibria diagram. One example is illustrated in Fig. 10.3 showing the importance of thermodynamics (liquid-liquid equilibria in this case) as linked to protein aggregation. This figure shows the separation of g-crystallin in the eye. The broken line represents the body temperature. As the years go by and the eye ages, the protein concentration in the eye changes and one or more proteins may achieve a concentration that exceeds the saturation concentration and we may enter in the liquid-liquid equilibrium region [5]. The second (concentrated) liquid phase, partly crystalline, which is shown on the right remains in the eye as a dispersion and interfere with vision. This second phase may be responsible for cataract symptoms. Precipitation of this second phase may be avoided by adding a small amount of glutathione that forms a soluble complex with crystalline and keeps it in solution over more extended temperature ranges, as shown in Fig. 10.3 [5].

Experimental results such as the ones shown in Fig. 10.3 can provide methods to prevent cataracts in the human eye, a disease that strikes millions of elderly men and women throughout the world. Similar studies have been reported for fibril formation that is considered responsible for Alzheimer's disease [16].

10.4 Outlook

The role of chemical engineers in understanding the challenges in protein structure and contribution to amyloid diseases has been discussed in several recent publications in the *Perspectives* section of *AIChE J* [7, 8, 17].

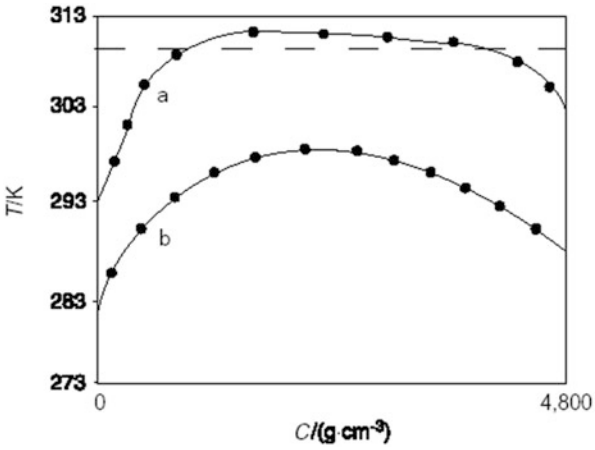

Fig. 10.3 Cataract formation and protein aggregation: Liquid–liquid separation of g-crystallin in the eye shown as temperature plotted against concentration. (*a*) Native g-crystallin; (*b*) g-crystallin/glutathione complex. The *broken line* denotes body temperature 310 K (37 °C). The *x*-axis represents a protein concentration from 0 to 4.8 g/cm^3. From Prausnitz [5]

It has been emphasized that the thermodynamics of the protein systems involved in the amyloid diseases is indeed very complex but understanding of hydrogen bonding phenomena [7] and use of tools such as osmotic second virial coefficients [17] can contribute in a quantitative understanding of Alzheimer's disease. For example, according to molecular-level computer simulations by Hall's group [7] the hydrogen bonding between backbone NH and CO and the hydrophobic interactions between side chains are the key driving forces for fibril formation in Alzheimer's. Hall [7] also reviews several ongoing and future trends in drug research related to Alzheimer's, including several recent drug efforts designed to reduce the amyloids responsible for the disease. Nevertheless, as she also states [7], there are still many unanswered questions about the structure of the amyloid fibrils, the reaction pathway of proteins during aggregation, the role of the environment and toxic steps or species during the aggregation process, and why these proteins behave differently in different people.

Acknowledgement The author acknowledges Dr. Ioannis Tsivintzelis for providing Fig. 10.2 (right) for the ibuprofen system.

References

1. von Stockar U, van der Wielen LAM (1997) Mini-review - thermodynamics in biochemical engineering. J Biotechnol 59:25
2. Prausnitz JM (1989) Biotechnology: a new frontier for molecular thermodynamics. Fluid Phase Equilib 53:439
3. Prausnitz JM, Foose L (2007) Three frontiers in the thermodynamics of protein solutions. Pure Appl Chem 79:1435
4. Dey SS, Prausnitz JM (2011) Opportunities for chemical engineering thermodynamics in biotechnology: some examples. Ind Eng Chem Res 50:3

5. Prausnitz JM (2003) Molecular thermodynamics for some applications in biotechnology. J Chem Thermodyn 35:21
6. Tsivintzelis I, Economou IG, Kontogeorgis GM (2009) Modeling the solid-liquid equilibrium in pharmaceutical-solvent mixtures: systems with complex hydrogen bonding behavior. AIChE J 55:756
7. Hall CK (2008) Thermodynamic and kinetic origins of Alzheimer's and related diseases: a chemical engineer's perspective. AIChE J 54:1956
8. Vekilov PG (2008) Chemical engineers and the fundamental understanding of human disease. AIChE J 54:2508
9. Franck TC, Downey JR, Gupta SK (1999) Quickly screen solvents for organic solids. Chem Eng Progress 95(12):41
10. Chen CC, Mathias PM (2002) Applied thermodynamics for process modeling. AIChE J 48 (2):194
11. Kolar P, Shen J-W, Tsuboi A, Ishikawa T (2002) Solvent selection for pharmaceuticals. Fluid Phase Equilib 194–197:771
12. Crafts P (2007) Chapter 2: The role of solubility modeling and crystallization in the design of active pharmaceutical ingredients. In: Ng NM, Gani R, Dam-Johansen K (eds) Chemical Product Design: toward a perspective through case studies. Elsevier, Amsterdam
13. Mathias PM (2005) Applied thermodynamics in chemical technology: current practice and future challenges. Fluid Phase Equilib 228:49
14. Kontogeorgis GM, Folas G (2010) Thermodynamic models for industrial applications. Wiley, Chichester. ISBN 978-0-470-69726-9
15. Tsivintzelis I, Economou IG, Kontogeorgis GM (2009) Modeling the phase behavior in mixtures of pharmaceuticals with liquid or supercritical solvents. J Phys Chem B 113:6446
16. Booth DR et al (1997) Instability, unfolding and aggregation of human lysozyme variants underlying amyloid fibrillogenesis. Nature 385:787
17. Randolph TW, Carpenter JF (2007) Engineering challenges for protein formulations. AIChE J 53:1902