Water Activity Applications in the Pharmaceutical Industry

Edited by

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I dedicate this book to the late John N. Smith, Professor of Biochemistry, Victoria University of Wellington, New Zealand, and A.P. Mulcock, Professor of Agricultural Microbiology, Lincoln College, Canterbury, New Zealand, who were responsible for my graduate education and growth as a scientist. They were outstanding mentors.

Professor John Smith, who had been a RAF bomber pilot in World War II and immigrated to New Zealand to take a chair in Biochemistry, was well known internationally for research in the metabolism of foreign organic compounds in animals and invertebrates. He had the distinction of having a fume hood built in his office so he could synthesize metabolic conjugates while attending to his paperwork. I worked on the metabolism of the insecticide DDT in the common housefly *Musa domestica*. Professor Smith taught me that research required persistence and the need to tell a good story when you write up your findings.

Professor Paul Mulcock, an outstanding applied microbiologist with broad interests in plant diseases, the microbiology of the fleece of sheep, the role of bacteria in the production of insect pheromones, and the production of ethanol as an alternative fuel, was a mentor who gave direction to a youthful and impetuous graduate student. My Ph.D. dissertation was on the biodegradation of vulcanized rubber. This research was the result of the failure of rubber o-rings in water and sewage mains in New Zealand and was supported by the Christchurch Regional Drainage Board, the Pottery and Ceramics Research Association, and the Natural Rubber Research Institute. Professor Mulcock encouraged me to collaborate with others and be willing to tackle microbiological research broadly. Paul remains a mentor and friend to this day.

Also, I would like to thank my present employer Schering-Plough Research Institute, and especially my supervisor Steve Farrand, for giving me the opportunity to work as a microbiologist collaborating with colleagues in Product Development Teams to bring safe and effective new drug products to the market.

Anthony. M. Cundell
May 2009

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FOREWORD

By definition, food is nutritious. The problem for mankind has always been that what is nutritious to humans is equally nutritious to microorganisms. The earliest humans must have quickly realized that seeds which had become dry retained a good appearance longer than seeds which were moist – the first use of drying for preserving food commodities is lost in antiquity. The use of salt, added especially to much sought after and very perishable commodities like meat and fish, probably also dates from a few thousand years ago. The use of sugar as a means of preserving foods is a newer concept, as it clearly had to wait until the time when men began to extract sugar from cane or beets. So the concept of removing or binding water with sugar or salts as a means of preserving foods has been around for a long time. However, it is still only 50 years since the mechanisms underlying these methods have become the subject of scientific enlightenment.

A few papers published before the end of World War II described the influence of reduced atmospheric humidity on the growth of microorganisms, for example L.D. Galloway (*J Text Inst,* Vol 26:, pp T123-129, 1935) and D. Snow (*Ann Appl Biol,* Vol 32, pp 40-45, 1945), and the influence of high concentrations of salts or sugars on their growth (M. Ingram *In* Microbial Ecology, Cambridge University Press, 1957, pp 90-133). However, the modern science underlying our understanding of the influence of reduced water availability on microbial growth came with the seminal paper of W.J. Scott (*Adv Food Res,* Vol 7, pp 83-127, 1957), where he first put forward the principle that a chemical concept, water activity (written a_w), controls the growth or life on Earth, including that of microorganisms. Scott applied this chemical concept to provide the understanding that drying, concentration, the reduction of atmospheric humidity and the addition of solutes were all one and the same thing – means of reducing water availability.

Bill Scott was a tall, well built man, with piercing eyes. His demeanor could best be described as "formidable" – especially to the young novice I was when I first met him. He was not easy with small talk, perhaps he was rather shy. However, he was a meticulous scientist. He was able to show that the ability of certain bacteria to grow in saturated salt was not fundamentally different from the ability of certain fungi to grow in dried commodities or from the ability of some yeasts to grow in concentrated foods. This was a giant leap in our understanding of the fundamentals governing the growth of microorganisms.

He understood that specific solute effects also exist, in particular that bacteria often thrive in salty environments, while fungi prefer to grow in the presence of low molecular weight carbohydrates.

Everyone is familiar with the influence of temperature and nutrition on life, but the overriding influence of water activity is much less well appreciated. The fact is that temperatures are conducive to life over much of the earth's surface and the nutrients necessary for the growth of all types of organisms are also abundant. The significance of water activity in controlling the occurrence of life on earth cannot be overestimated.

Indeed, growth of almost all life on Earth is constrained to water activities greater than 0.95. Life originated in water and a high proportion of life even now exists only in water. Seawater has a water activity in excess of 0.99. The permanent wilt point of most plants is around 0.98 a_w. Animal life universally carries its water with it, and few animals appear to be able to survive with internal water activities lower than that. Only microorganisms appear to have broken through the water activity barrier, and have evolved the capability of growing and reproducing at < 0.95 a_w, in a few cases below 0.70 a_w.

Scott was co-author on just a few more papers on this topic (e.g., Scott, *Aust J Biol Sci,* Vol 6, pp 549-564, 1953; B.J. Marshall and Scott, *ibid* Vol 11, pp 171-176, 1958), but his colleagues at the Commonwealth Scientific and Industrial Research Organization's

Division of Food Science in North Ryde, NSW, Australia carried on his work for a number of years. Preeminent amongst these was J.H.B. Christian, who undertook his Ph.D. with Ingram on bacterial water relations and subsequently published several papers (e.g., Christian and Waltho, *J Gen Microbiol,* Vol 25, pp 97-102, 1961; *ibid* Vol 35, pp 205-213, 1964).

I started work in this area with an MSc degree entitled to "Microbiological problems in prune preservation" (University of New South Wales, 1965). During that work, I was able to isolate nearly all of the known xerophilic fungi, and one or two new ones besides. A couple of papers resulted (Pitt and Christian, *Appl Microbiol,* Vol 16, pp 1853-1858, 1966; *ibid* Vol 20, pp 682-686, 1970) and in due course, a review (Pitt, *in* Water Activity and Foods, Academic Press, London, pp 273-307, 1975). About that time, my colleague Ailsa Hocking and I commenced a program to understand more clearly the influence of water activity on the growth of the common fungi which cause food spoilage (Pitt and A.D. Hocking, *J Gen Microbiol,* Vol 101, pp 35-40, 1977; Hocking and Pitt, *Trans Br Mycol Soc,* Vol 73, pp 141-145, 1979; S. Andrews and Pitt, *J Gen Microbiol,* Vol 133, pp 233-238, 1987; K. Wheeler *et al.*, *Trans Br Mycol Soc,* Vol 90, pp 365-368, 1988; Vol 91, pp 631-638, 1988). To our surprise, we encountered two species of fungi which really prefer to grow in salty environments (Wheeler *et al., J Gen Microbiol,* Vol 134, pp 2255-2260, 1988). We coined the term "halophilic xerophiles" for these fungi to distinguish them from halophilic bacteria, which have an obligate requirement for high NaCl concentrations. Halophilic xerophiles have no requirement for salt, merely a preference. We also dispensed with the term "osmophile" for yeasts, because it is clear that the yeasts which grow at reduced water activity are simply xerophiles like the filamentous fungi.

What has all this to do with pharmaceuticals, you ask? The simple answer is that dehydration is used to provide stability for a very wide variety of pharmaceutical products, and many pharmaceutical products also provide entirely adequate nutrition for a wide range of microorganisms. Pharmaceutical products are just as much subject to the chemical and biological laws governing the growth of microorganisms as are food products. The work carried out at CSIRO in the years from 1950 to about 1990 (and of course also in a number of other laboratories) provided a basis for understanding the potential for the growth of microorganisms in pharmaceutical products.

Dr. Bill Scott died a few years ago, but all of us engaged is in the preservation of foods and pharmaceuticals owe a very large debt of thanks to him.

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PREFACE

After a water activity workshop that the co-editors taught at the 2007 Eastern Analytical Symposium held in Somerset, New Jersey that was poorly attended, we discussed why we did not draw an audience in what could be considered the geographic center of the U.S. pharmaceutical industry. Although we both felt passionately about the role of water activity determination in the development of pharmaceutical drug products, we believe that the technology had not met its potential in the pharmaceutical industry due to a lack of generalized information available to formulators, analytical chemists and microbiologists working in product development. In contrast, water activity is considered a critical development parameter in the processed food industry and is widely applied in product development. However, as the original concept was developed by the food microbiologist William J. Scott over fifty years ago and its application to the food industry is supported by numerous research articles, symposia, books and government regulations, this is not surprising. With the inspiration of the recent book *Water Activity in Foods – Fundamentals and Applications* G.V. Barbosa-Canovas, A.J. Fontana, Jr., S.J. Schmidt and T.P. Labuza (editors) IFT Press/Blackwell Publishing (2007), we decided to edit the current book to advance the knowledge of water activity in the pharmaceutical industry.

The book consists of twelve chapters and a series of appendices written by invited experts in the field of water activity as it is applied to the pharmaceutical industry. The eminent Australian mycologist Dr. John I. Pitt, who was a collaborator with Scott at the Commonwealth Scientific and Industrial Research Organization (CSIRO) in New South Wales, Australia graciously agreed to write a foreword to the book The first two chapters discuss the historic highlights of water activity research and the fundamentals and relationships of water activity (Anthony J. Fontana, Jr.) and the third chapter outlines the role of standard-setting organizations in water activity determination (Anthony M. Cundell). The authors call on their experience of working for a major supplier of water activity testing equipment (Fontana) and as a pharmaceutical microbiologist who is a member of the USP Microbiology and Sterility Assurance Committee of Experts (Cundell) to write these chapters. Chapter 4 discusses the utilization of moisture sorption data in pharmaceutical development (L. Bell). The fifth chapter discusses in detail the measurement of water activity, moisture isotherms and moisture content of pharmaceutical ingredients and drug products (Fontana) and can be seen as the meat and potatoes of the book. The sixth chapter on the role of water activity in formulation development (Roberta Tracy, Michelle Raikes, and Christian Meissner) represents a collaboration between chemists and a microbiologist working in a pharmaceutical company highlighting the potential of the analytical technology. Chapter 7 critically assesses the role of water activity in formation development in the personal care industry (Philip Geis and Steven Schultz) in response to the positions taken in the book *Preservative-free and Self-Preserving Cosmetics and Drugs* (J.J. Kabara and D.S. Orth, editors) Marcel Dekker, New York (1997). The eighth chapter is most timely, with the growing market for probiotics, and discusses the role of low water activity in the survival of live cultures in nutritional supplements (John Coventry and Ross G. Crittenden). The ninth chapter reviews the effects of water activity on the growth and survival of microorganisms of interest to the pharmaceutical industry (Anthony M. Cundell). Chapter 10 assesses the concept of pro-active water activity management in the pharmaceutical industry (Hanns G. Werner) and lastly, the eleventh chapter presents an unique viewpoint on the role of water activity determination in setting up microbial testing in stability testing programs (Linda K. Skowronsky). And lastly, the twelfth chapter, written by a leading FDA microbiologist (David Hussong) brings a regulatory perspective to the role of water activity to the microbial testing and control of pharmaceutical products.

The co-editors congratulate the chapter authors in writing a pioneering book on the application of water activity in the pharmaceutical industry. Any limitations in the scope of the book are the responsibility of the co-editors and their ability to recruit experts to write the chapters. It is our wish that this contribution will greatly encourage the use of the concept of water activity to improve the quality, efficacy and safety of pharmaceutical drug products.

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