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Preface

In honor of Takeru Higuchi

This year we are celebrating 50 years from the publication date of the most famous and useful mathematical equation for the design and analysis of pharmaceutical formulations and drug delivery systems. This is a very important anniversary for the field of pharmaceutical sciences, as this mathematical equation became the standard of analysis of most simple and advanced pharmaceutical systems.

The model was put forward by Prof. Takeru Higuchi, then Professor of Pharmacy at the University of Wisconsin, in August 1960; it was published in October 1961 (Takeru Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, Journal of Pharmaceutical Sciences 50, 874–875, 1961).

(Photo taken from http://www.hbc.ku.edu/about/history.html, with permission)

Higuchi (1918–1987) was a great pioneer of the field of pharmaceutical sciences. His analysis was based on a relatively simple idea, namely that the presence of a large amount of drug in the polymer would lead to a "front" at saturation concentration that would allow continuous drug transport through a layer containing only dissolved drug. The result of this pioneering effort was that the cumulative amount of drug released from such a device would be proportional to the square root of time. This in turn, would define a behavior where the rate of drug release would be proportional to the reciprocal of the square root of time.

This rather simple idea was not that obvious 50 years ago. A major contribution of Higuchi was that he was able to incorporate in his expression/equation the physical parameters that could be controlled in order to modify the release rates, parameters such as the drug diffusion coefficient and the drug solubility. His equation was based on the assumption of a quasi-steady state approximation and was originally developed for a continuous phase system. Soon thereafter came the equation for drug release from porous systems, where the diffusion coefficient was expressed in terms of the porosity and tortuosity of the pharmaceutical device (Takeru Higuchi, Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices, Journal of Pharmaceutical Sciences 52, 1145–1149, 1963).

The diffusion problem was solved exactly (for transient conditions) by Don Paul and his student S. McSpadden in 1976 (D.R. Paul and S.K. McSpadden, Diffusional release of a solute from a polymer matrix, Journal of Membrane Science 1, 33–48, 1976). The idea of drug release with associated bioerosion or biodegradation was addressed soon thereafter by Harold Hopfenberg in a seminal paper (Harold Hopfenberg, Controlled release from erodible slabs, cylinders, and spheres, in: D.R. Paul and F.W. Harris, Eds., Controlled Release Polymeric Formulations, pp. 26–32, ACS, Washington, 1976), while the idea of drug delivery from polymer carriers that exhibit swelling and are therefore characterized by a relaxational process was introduced by one of us in 1980 (Nicholas A. Peppas, et al., Modelling of drug diffusion through swellable polymeric systems, Journal of Membrane Science 7, 241–253, 1980).

This volume is a tribute to the genius of Professor Takeru Higuchi and his pioneering work in the field. Professor Higuchi was born in Los Altos, California on January 1, 1918. He studied at the University of California at Berkeley (A.B., 1939, chemistry) and received his Ph.D. from the University of Wisconsin in organic chemistry in 1943. He was in the University of Wisconsin Pharmacy faculty from 1947 to 1967. During that period he started developing a number of design equations for pharmaceutical products, while also becoming a much sought after consultant of the pharmaceutical industry. In 1967 he moved to the University of Kansas where he served as a professor and chair of the Pharmacy Department. Higuchi was not only a pioneer on physical pharmacy but also a gifted educator who served as a mentor of numerous Ph.D. students, postdoctoral fellows and visiting scientists from around the world.

This special issue starts with contributions by those who worked with him and followed him in this development. Then it turns to a series of reviews on the use of advanced modeling equations to analyze complex problems, including lipid dosage forms, polymer-coated devices, inert matrices, degradable systems, drug transport through the skin as well as in vitro–in vivo correlations.

At a specialized scientific meeting entitled "Emploi des polymères dans l'élaboration de nouvelles formes médicamenteuses", sponsored by the Vifor company and the University of Geneva, and held in Geneva, Switzerland, on October 2, 1980, one of us (NAP) asked Professor Higuchi if he expected – when he derived his equation – that it would become the standard of design of novel pharmaceutical formulations. Higuchi replied with a

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characteristic modesty that "... *all I did* was to derive an equation my students could use to analyze their dissolution data"... If there is one equation that has revolutionized so much our field, it is the *Higuchi equation*. With this volume we honor a pioneer in the field of pharmaceutical sciences.

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