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Evolution of Formulation Practices

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From Empiricism and Art (<'50s); to Physical and Technology ('50s to late '60's); to Technology Assessment (Biopharmaceutics/Pharmacokinetics; '60s to late '70s); to Drug Delivery Systems and Targeting Strategies ('70s to '80s); to Formulation with a View Towards the Molecular Level ('90s)

The role of pharmaceutical research and development groups in industry as well as the education of pharmaceutical scientists at our universities, has changed dramatically since the late 1940s-early '50s. Prior to this period, formulation practice was considered more of an art than a science, although small pockets of good science were practiced at some industrial and academic sites.

In the late 1940s-early '50s, pharmaceutical scientists, academicians such as the late Professor Takeru Higuchi and their proteges, began to influence the way formulation research and practice were performed in industry and how young scientists were trained in universities (Higuchi, 1952, 1955). Various evolutionary phases have occured since that time.

One of the easiest ways to trace these changes is to review the research, publication and patent record of Professor Takeru Higuchi (Riley, 1990). It is most appropriate that this presentation was given at the University of Wisconsin, because Professor Higuchi spent more than 30 years of his professional life there. As one reviews his contributions-as

measured by the number and influence of his papers and patents, and the impact of his students on the pharmaceutical sciences and formulation practices-one notes with envy the breadth of his contributions, his timing, the amount of data presented in his papers and the interface of his work with physical and organic chemistry, and later in his career, the biological sciences.

Physical sciences and technology dominated the 1950s and 60s. This can be seen in Professor Higuchi's publication numbers in the area of analytical chemistry (mainly spectral and non-aqueous titration methods of analysis), thermodynamics (solubility, complexation studies) and his tableting technology papers. The 1950s and '60s can be viewed as a period during which products, and the drugs in them, became better defined. The emphasis was on quality control analytical studies, solubility assessments as they relate to drug and product characterization and methods whereby a particular drug's properties could be manipulated to effect better formulations. Products were generally of the bolus type i.e., the emphasis was on the quality and overall release rates of drug rather than the control of drug release. Again, exceptions did exist and attempts at controlled release products could be found during this period.

In the 1960's, Higuchi began to publish in the area of chemical kinetics. He emphasized that a product should not only meet some standard as it left the production plant, but that the product should maintain its efficacy during long term storage. Higuchi and Professor Ed Garrett were two of the few scientists in pharmacy who began to look at drug degradation kinetics at the molecular level. The level of mechanistic sophistication that both of these scientists showed in their publications and emphasized in their student's training was quite amazing.

The late 1960's was the period during which we began to question whether our formulation practices truly produced a quality product from the perspective of rate and extent of release to systemic circulation. Led by scientists such as Professors' Sid Riegelman, John Wagner, Gary Levy and others, the subdiscipline of pharmacokinetics and biopharmaceutics, an *in vivo* application of kinetics, began to evolve. For a historical perspective see

Wagner, 1981. This was a critical period for formulation practice because we learned not all drug products behaved in the manner that we had projected in the laboratory i.e., the pharmacodynamics or therapeutic efficacy of a drug could not always be predicted from *in vitro* experiments and the interface with the biological system was more complex than predicted by simple concepts such as pH-partition theory, etc. This new emphasis on measuring the *in vivo* behavior of drugs forced a renewed interest in analytical chemistry. Sensitivity and specificity became a major issue. The development of then sophisticated technologies, such as GC, HPLC and mass spectrometry, greatly enhanced our abilities to question old concepts of how and to what extent drugs were delivered systemically to man as well as animals.

Although Higuchi did not embrace the area of pharmacokinetics and biopharmaceutics as an area of research, he realized the importance of temporal patterns in drug delivery and formulation practice. This can be seen in his numerous publications and patents on controlled drug release from matrices and transdermal systems (Higuchi, 1961). In the 1970s, he shifted his publication pattern to the area of drug delivery research. Professor Higuchi attacked the idea of drug delivery research from two major fronts, chemically driven systems, such as prodrugs (Higuchi and Stella, 1975) and physically driven drug delivery systems, such as device oriented drug delivery. This also coincided with Higuchi's movement from Wisconsin to Kansas in 1967, and into what might be called his entrepreneurial period. His relationship with Alex Zaffaroni and the establishment of Alza forever changed the way we think about the delivery of drugs. The systems approach to drug delivery was born.

It was during this period that Higuchi began to express the frustration that those researchers responsible for new drug design, though more rational from the viewpoint of drug receptor interactions etc. forgot that drugs also need to be deliverable. As drug design moved away from whole animal testing to testing at the molecular level of inhibition of a biochemical event or blockage of an aberrant cellular process, drugs became more polar, eg., the ACE inhibitors, peptides and proteins, and drug delivery often became the

rate limiting step to commercialization. In one of his more frustrated moments Higuchi was heard to mutter, "drugs need to be designed with delivery in mind". Perhaps with the advent of sophisticated delivery modalities his plea should be changed to "drugs need to be designed with delivery systems in mind".

It was also during the 1970s that interest in the concept of drug targeting as a means of effecting better therapy was revived. This may have been triggered by the continued growth of pharmacokinetics/pharmacodynamic concepts, as well as improved knowledge at the molecular level of how cells function, signal information and utilize biochemical events. The concept that drugs could be effectively delivered to their site of action while sparing exposure of the rest of the body was first proposed by Erhlich earlier this century with his "magic bullet" concept (Ehrlich, 1908). It is my contention, that the renewed interest in targeting concepts might have been the first step in the evolution of formulation practice where communication breakdown between disciplines began to truly affect the quality of scientific thought. The biochemically-based scientists had their view of what was possible, as did the molecular biologists, the polymer chemists, the biochemists, the peptide/protein chemists, the drug metabolism scientists, and the physical scientists including engineers. What many of these scientists forgot was that the body is a very complex series of chemical reactors and conduits and that what might work in a test tube, in a cell culture system or in the presence of a purified enzyme preparation might not work in an intact animal. That is, many targeting strategies were flawed by the narrowness of thought that any specialist brings to a process of this complexity. The lack of commercial success of liposomes (Poste and Kirch, 1983; Pozansky, Juliano, 1984) and antibodies (Weinstein et al., 1986) as targeting modalities are good examples.

Consider the simple targeting hypothesis, "*I will achieve targeting to a particular site by designing a delivery system that will only release drug at the target site thereby effecting targeting*". This strategy might be representative of either chemically based delivery systems, such as the use of prodrugs, or physically based delivery systems such as liposomes or other

microparticulates, amongst others. Why have delivery concepts that embrace this hypothesis led to limited successes? This question has been answered by those using various hypothesis testing mathematical models (Aarons et al., 1989; Stella and Himmelstein, 1980, 1985; Hunt et al., 1986; Smits and Thijssen, 1986). What these models showed was that, not only were the properties of the delivery strategy important, but the properties of the "to be targeted" agent were critical to the chance that targeting will be effected by a particular targeting strategy. For example, to effect targeting via prodrugs, Stella and Himmelstein (1985) concluded that:

- the prodrug must be readily transported to the target site and uptake at the site must be rapid, essentially perfusion rate limited, or selective
- once at the site, the prodrug must be selectively cleaved to the active drug (relative to its conversion at other sites), but perhaps as important, it must be selectively cleaved relative to more highly perused tissues, such as the liver and kidney
- once the active drug is generated at the target site it must be retained somewhat by that site.

Since most active therapeutic agents must be capable of reaching their target site, these conclusions suggest that targeting will be difficult to achieve with already currently useful therapeutic agents. This point has been recently emphasized by others (Aarons et al., 1989; Hunt et al. 1986; Smits and Thijssen, 1986; and Levy, 1987).

The 1990s and beyond will present a major challenge to the formulation scientist. The need to develop formulation delivery strategies for proteins and peptides, to design pulsatile delivery systems to prevent the build up of tolerance and to develop and incorporate sensors critical to the practical commercialization of a true therapeutic systems, will be monumental tasks. These tasks will be made easier if the formulation scientist is better in tune with the biological interface and understands the molecular basis for various cellular transport and biochemical phenomena. This will present a major challenge to our educational system. How much of the old do we retain versus how much of the new do we add?

Finally, I am reminded that few delivery or targeting strategies will be commercialized if we do not consider the economic ramifications of the strategy i.e., can the health care system afford the products of the strategy?

This presentation has focused on some historical aspects of formulation practice and tried to project some future trends. Please note, however, that the retrospective and prospective views presented are limited by this authors biases and experiences which I hope the reader will forgive.

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