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Three significant highlights of controlled drug delivery over the past 55 years: PEGylation, ADCs, and EPR

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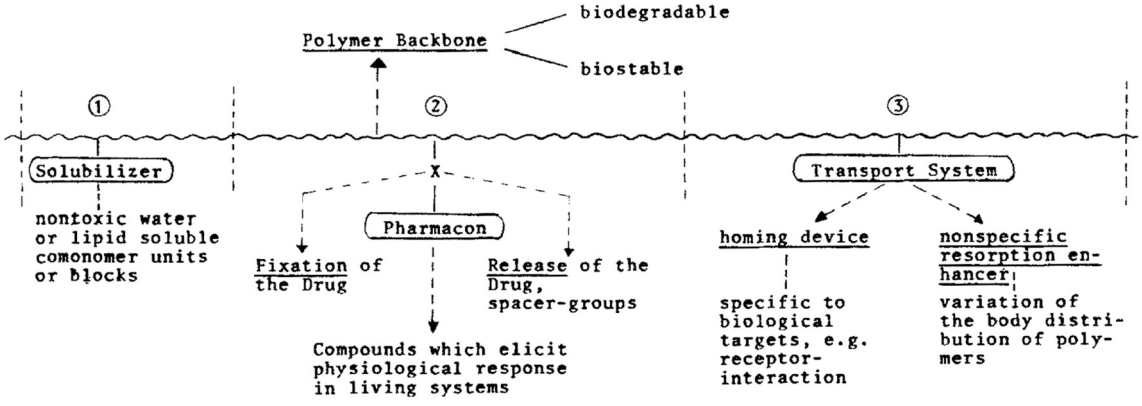
Contents

The three most significant developments in Controlled Drug Delivery (CDD) over the past 55 years are: (1) the conception and commercial development of PEGylation of drugs and their carriers, (2) the discovery and application of monoclonal antibodies (MAbs) and their conjugates with drugs (Antibody-Drug Conjugates, or ADC), and (3) the discovery and application of the "Enhanced Permeation and Retention" Effect (EPR). PEGylation provided protection of biologic drugs from enzymes and thus longer circulation times in vivo. The last two provided the ability to directly target drugs to cells and tissues. The drugs could be either synthetic organic molecules or natural, biologic molecules, and could be of all sizes.

Professor Frank Davis at Rutgers University conceived of the concept of PEGylation [4], and he co-authored the first journal article on PEGylation and PEGylated drugs with his student, Abraham Abuchowski, in 1977 [1]. A few years later, in 1981, Abuchowski founded the first company that offered to develop PEGylated drugs for interested drug companies. He named the company Enzon. Davis was included as a co-founder.

Another PEGylation expert, J. Milton Harris, a professor of polymer chemistry at the University of Alabama in Huntsville, AL was an expert in the polymer chemistry of hydrogels [12]. He founded a second PEGylation company in 1991 along with his colleague, Dr. Michael Bentley. They named their company "Shearwater", after the name of an ocean shore bird. (Milton Harris was also an avid bird-watcher). The two companies used different chemistries to achieve their PEGylations (tresyl vs active ester).

Professor Helmut Ringsdorf, a professor of synthetic organic polymer chemistry at the University of Mainz in Germany, authored an important article back in 1975 on the use of synthetic polymers as drug carriers [9]. The all-inclusive and prescient figure that he prepared for that article is shown here: (Note: the Greek word "Pharmacon" refers to the drug).



Thus, by the late 1990s, PEGylation of drugs and drug carriers had been established as both a valuable discovery and a viable commercial concept.

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There are two other very important developments in the CDD field over the past 55 years. The first was the discovery of Monoclonal Antibodies (MAbs) [7] and the synthesis of their conjugates with drugs, which are referred to as Antibody-Drug Conjugates (ADC)*.

The second was the discovery and description of the Enhanced Permeation and Retention Effect (EPR) in 1986 by Matsumura and Maeda [8]. These significant developments led to the successful targeting of tumor cells and diseased tissues with drugs.

In addition to these CDD developments, much work has been carried out on the use of Temperature-Responsive ("Smart") hydrogels as drug carriers by Hoffman et al., [5, 6, 10, 11] and also by Bae, et al. [2] Work on swelling-deswelling drug delivery using pH-responsive acrylic acid gels has been pursued by Peppas, et al. [3]

> "Antibody-drug conjugates (ADCs) [13] are a class of biopharmaceutical drugs designed as a targeted therapy for treating cancer. Unlike chemotherapy, ADCs are intended to target and kill tumor cells while sparing healthy cells. **As of 2019, some 56 pharmaceutical companies were developing ADCs**." (Wikipedia; authors' bolding).

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