UNDERSTANDING TRANSPORT PHENOMENA IN CONTROLLED RELEASE

Nicholas A. Peppas, ScD
Cockrell Family Regents Chair in Engineering, Department of Biomedical Engineering,
McKetta Department of Chemical Engineering,
Department of Pediatrics, Surgery and Perioperative Care, Dell Medical School, and
Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy
Director, Institute for Biomaterials, Drug Delivery and Regenerative Medicine
The University of Texas at Austin, 107 W Dean Keeton Stop C0800, Austin, TX 78712-1801, USA
Tel : (512)-471-6644, Fax : (512)-471-8227, E-mail : peppas@che.utexas.edu

Introduction: Mathematical and Physical models have been used over the past 45 years to analyze or predict the transport behavior of small drugs or larger therapeutic agents in 3D carriers and other structures controlling the release behavior. We examine three important areas where our lab continues to contribute. *Polymer Structure Affects Transport of Therapeutic Agents*. We present updates to three fundamental theories relating structure and function in hydrogels through the uniting perspective of the swollen polymer network hypothesis. While our new equations include extensive assumptions about swollen polymer networks, they also formalize a deep body of accumulated theoretical and experimental knowledge on polymer network properties. Unlike simulated and machine learning approaches, the formal modeling approach provides clear and specific opportunities for improvement and a logical, fundamental basis for each component. The new equations (N Richbourg and NA Peppas, *Progr. Polym. Sci.,* 105, 101243 (2020)) reveal the extensive parallelism between swelling, mechanical, and diffusive properties in hydrogels. Taken together, these equations indicate that a hydrogel's swelling data could be used to predict the hydrogel's stiffness and the diffusivity of solutes within the hydrogel.

Non-Fickian Solute Transport is Solvent-Dependent and Affects the Therapeutic Agent Release Mechanism. Exhibition of linear and non-linear viscoelastic and relaxational phenomena creates conditions of solute transport that can lead to deviations from the expected Fickian behavior. The result is an unexpected non-Fickian behavior that can lead in certain cases to a desirable zero-order release (NA Peppas and B Narasimhan, *J Controlled Release*, 190, 75-81 (2014)).

Modeling of Real Transport in Intestinal Walls (Diffusion, Endocytosis, Convection, Reaction Models). Scientific advances have led to the development of new biomaterials that can successfully deliver therapeutic proteins to the bloodstream via several physiological routes. The apparent simplicity of delivering a compound via one of these routes is overshadowed by the biological conditions that limit the achievement of sufficient absorption and transport of the therapeutic agent. The oral route is a perfect example of this dichotomy. The complex nature of the organs and conditions in the gastrointestinal tract mandates a robust investigation when developing novel materials for protein delivery. Utilizing cell culture and other laboratory techniques, a significant understanding of the physics of the problem has been achieved in the last few years. A number of successful protein delivery formulations like thiomers and stimuli-sensitive complexation and anionic hydrogels have been designed, tested and shown promising results. The development of models that could accurately predict the protein blood concentration as a function of the structure and characteristics of protein delivery systems greatly enhances our capabilities, potentially ushering in a new class of materials that provide better absorption and transport of protein therapeutic agents. (DA Carr and NA Peppas, *Chem Eng. Sci*, 64, 4553-4565 (2009)).