Microfabricated Drug Delivery Systems: Concepts to Improve Clinical Benefit

Frank J. Martin¹,² and Carl Grove³
¹iMEDD, Inc., 1224 Kinneer Road, Suite 130, Columbus, OH 43212
²ALZA Corporation, 1050 Hamilton Court, Menlo Park, CA 94025

Abstract. Important classes of drugs have yet to benefit from advances in drug delivery technology. Strategies to provide reasonable oral bioavailability of peptide and proteins drugs remain elusive, for example. Systemic cancer drugs produce dose-limiting toxicities largely due to their lack of selectivity. Although delivery systems such as immunotoxins and liposomes improve selectivity of a few cancer drugs, current technology is not suitable for the vast majority of such molecules. Systems able to mimic the body’s natural feedback mechanisms for secretion of hormones such as insulin represents yet another unmet medical need. Microfabrication techniques may permit the creation of drug delivery systems that possess a combination of structural, mechanical, and perhaps electronic features which may surmount some of these challenges. In this review, drug delivery concepts are presented which capitalize on the strengths of microfabrication. Possible applications include micromachined silicon membranes to create implantable biocapsules for the immunoisolation of pancreatic islet cells—as a possible treatment for diabetes—and sustained release of injectable drugs needed over long time periods. Asymmetrical, drug-loaded microfabricated particles with specific ligands linked to the surface are proposed for improving oral bioavailability of peptide (and perhaps protein) drugs. Similarly designed particles with sizes in the 2–10 µm range may be safe to administer intravenously and a clinical strategy is suggested for using such microparticles for treating solid tumors. Although hypothetical now, work is in progress to prove the concepts presented here and to validate the intuitive belief that there is an important place for microfabricated systems in drug delivery.

Key Words. microfabrication, bioMEMS, drug delivery, nanopore membranes, microparticles, peptides, proteins

Introduction

Microfabrication technology has been applied to the successful development of a variety of health care-related products including diagnostic (“lab-on-a-chip”) systems and techniques and apparatus for high throughput screening of new drug candidates (Figueys et al., 2000; Wang, 2000). Drug delivery remains an important challenge in medicine (Breimer, 1999) and microfabrication techniques may be used to develop novel drug delivery devices with capabilities not possible with current systems. Two main categories are envisioned: micromachined nanopore membranes and microparticles. It is believed that each may provide a platform from which multiple product concepts will emerge.

Nanopore membrane technology

Nanopore membranes are produced using photolithography, thin film depositions and selective etching to create membranes composed of silicon with highly uniform pores in the nanometer range. Through newer techniques, pores with dimensions 10 to 100 times smaller than the limit of resolution of standard photolithographic techniques are now possible. While membrane technologies such as ion track-etched polycarbonate (e.g., Osmonics, Minnetonka, MN) and porous alumina (e.g., Whatman, Ann Arbor, Michigan) provide alternate means for making nanometer-sized pores, none offer the combination of features provided by microfabricated membranes: pore sizes in the 10–100 nanometer range with highly uniform pore size and thin membrane thickness. Moreover, unlike polymeric membranes, because microfabricated membranes are made from silicon, they are biologically, thermochemically and mechanically stable. The product concepts based on these nanopore membranes combine these features to provide important advantages over conventional technologies.

Microparticle technology

Unlike conventional particulate drug delivery systems such as polymer microspheres, and liposomes, microfabrication techniques may be used to create drug delivery particles which are thin planer structures (such as discs). These particles can be designed with a thickness of 1 to 50 microns and diameters of 1 to 100s of microns. Particles can be asymmetrically designed with single or multiple drug reservoirs and ligands bound to one side to target specific sites (Figure 1).

Two therapeutic product concepts are proposed here. Oral microdelivery particles (Oral-MEDDS) may be in the 100 micron range and are proposed for the delivering peptides and other macromolecules through the

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intestines and into systemic circulation. The Intravenous microdelivery particles (IV-MEDDS) require much smaller particles (e.g., < 5 μm) as an intravenous therapy for treatment of solid tumors.

**Immunosolating Biocapsule**

**Medical need and product concept**

Diabetes mellitus (DM) represents a serious medical problem. In the United States it is the third largest cause of death. While the majority of patients have type 2 diabetes (noninsulin-dependent DM), about 10% of all patients diagnosed with DM are insulin-dependent (type 1). In both cases, disease is caused by decreased circulating concentrations of insulin and decreased response of peripheral tissue to insulin (insulin resistance) (Davies and Granner, 1996). The disease manifests itself as hyperglycemia. Insulin remains the mainstay of virtually all type 1 DM and many type 2 DM patients; in most cases the drug is administered subcutaneously (sc). However, the kinetics of insulin administered by this route does not mimic the normal rapid rise and decline of insulin secretion in response to ingested nutrients.

Efforts to address the short-comings of current sc administration of insulin, including the use of complex multidose regimens, has led to the development of other dosage forms and routes of administration such as “needleless” injectors, constant infusion pumps, and inhaled insulin. These newer approaches still suffer from the same general issue plaguing current sc administration (kinetics dissimilar to those in persons with normally functioning pancreatic islet cells).

A potentially useful approach, which has proven effective in only a handful of cases, is the allotransplantation of islets or whole pancreases from a suitable human donor into a diabetic recipient. Researchers in Canada recently reported successful transplantation of islet cells into seven patients with type 1 DM (Shapiro et al., 2000). Although the potential complications of immunosuppressive therapy were reduced by avoiding the use of glucocorticoids, each transplant required two harvesting of islet cells from organ donors. Moreover recipients are still required to take immune suppressing drugs for the rest of his or her life. These immunosuppressive drugs are toxic and have potential adverse side effects, including cancer. For this reason, an islet or pancreas allotransplant is normally performed only in conjunction with a kidney transplant, for which immunosuppression is required in any case.

Because of the toxicity of immune suppressing drugs, and the shortage of organ donors, islet and pancreas allotransplantation appears to hold limited promise as a cure for diabetes. A method then is required to sequester the islets from the body’s immune system which is able to recognize and reject these xenogeneic cell grafts. For the past twenty years, investigators have focused on a range of microencapsulation methods most commonly involving sodium alginate and another polycationic substance such as polysine. These materials have been used in an attempt to create a semipermeable membrane capable of blocking immune molecules such as IgG, cytokines, and cell-secreted antigens from reaching the encapsulated xenogeneic islet cells while allowing glucose and insulin to freely diffuse through the barrier (Lanza and Kuthreiber, 1999). However, this approach has proven generally unsuccessful due to mechanical rupture of the membrane, biochemical instability, incompatibility with islet cell heterogeneity, and broad pore size distributions (Colton and Avgoustiati, 1991; Lacy et al., 1991; Soon-Shiong et al., 1991; Lanza et al., 1996; Lanza and Kuthreiber, 1999). When the barrier between the xenogeneic cells and the external bioware is compromised, these foreign cells are subject to various endogenous cells and antibodies as well as complement and a host of cytokines such as tumor necrosis factor, all of which can inflict cell damage. As a result, the use of polymeric microcapsules for allotransplantation has been unsuccessful clinically in the absence of immunosuppression (Lacy et al., 1991; Lanza et al., 1996; Lanza and Kuthreiber, 1999).

Microfabrication techniques have been applied to create a biocapsule for effective immunosolization of transplanted islet cells for treatment of diabetes (Desai et al., 1998). These nanopore membranes are designed to allow the permeability of glucose, insulin, and other metabolically active products, while at the same time, preventing the passage of cytotoxie cells, macrophages,