A Review of the Management of Implanted Medical Devices for Diabetes: Trends and Directions

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Abstract

The management of diabetes is progressing rapidly from the use of traditional finger sticks for glucose monitoring and multiple daily injections of insulin to more user-friendly devices and approaches. These advances hold the promise of freeing persons with diabetes from the need for continued daily compliance, thereby improving their quality of life and improving control of their underlying diabetes. An underlying theme to solutions based on percutaneous or fully implanted devices is that the useful lifetime of such devices is often limited by the body's foreign body response. This review briefly outlines general factors associated with point-in-time needle stick approaches to the growing use of short-term percutaneous implants (≤7 days) to the challenges of more extended devices, both technical and regulatory, faced by developers of these devices.

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Introduction

Diabetes mellitus, whether type 1 or type 2, may be described as a disease requiring recurrent measurement of physiological parameters or the delivery of therapeutic agents, admittedly in dramatically different forms and scopes. Treatment regimens are accordingly tailored to the individual to match the form and severity of diabetes. Regardless of the nature of the diabetes and/or treatment path, a widespread solution to meet the need for biofluid sampling and/or for drug delivery has been the employment of intrusive devices such as needles or percutaneous implants. Whatever the shape or form, intrusive devices initiate a reaction termed the foreign body response, which frequently limits the useful lifetimes of these introduced materials and devices.

This review outlines the use of point-in-time needle-based approaches and the growing use of short-term percutaneously implanted devices that, in large measure, avoid the body's foreign body response. The escalating difficulties encountered for the creation of more effective long-term solutions are subsequently presented. It is hoped that this brief review will give the reader a better appreciation of the factors influencing percutaneous or fully implanted devices toward developing truly long-term solutions.

Point-in-Time Solutions

Active management of diabetes mellitus involves the interplay between the measurement of fluctuating glucose levels and the delivery of one or more therapeutics to maintain blood glucose within desired ranges.[1] Historical approaches have been based on multiple daily invasive measurements possibly coupled with insulin injections to

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provide this control over serum glucose levels. However, this approach has limited desirability from both the clinician's and the patient's perspective.

Effective point-in-time glucose measurement or therapy delivery is highly dependent on patient compliance.[2] This compliance is requisite at multiple points throughout the day in order to maintain blood glucose levels within desired baselines or postprandial excursions. Compounding the difficulty of effective patient compliance are complicated treatment regimens based on multiple formulations, activity, diet, injection pain, convenience, and social discomfort.[3] Taken together, these factors lessen the likelihood of effective compliance, even if appropriate therapeutic agents and delivery regimens are available.

That is, although patient compliance is a key component for effective diabetes management, patients are understandably demotivated by the pain and frequency of the required needle sticks and the complexity of treatment schedules. No matter how well-motivated an individual patient may be, understanding and lifestyle may preclude the individual from achieving the desired frequency of glucose measurement and therapy delivery for optimal management of their diabetes. In an ideal world, diabetes management would include a system that would automatically, painlessly, and unobtrusively provide measurement of glucose levels and delivery of therapy, e.g., insulin, such that serum glucose levels might be maintained within desired limits with minimal variation. Such a system offering dynamic responsiveness to fluctuating blood glucose levels with nominal patient involvement would obviate the difficulties and shortcomings associated with patient compliance.

Short-Term Solutions (≤7 Days)

As first steps toward the goal of patient-transparent diabetes management, a variety of implanted or semi-implanted glucose monitoring devices and insulin delivery systems offering reduced patient involvement are becoming more widely known and available. Broadly stated, these devices may be thought of as devices with a structure residing on the outside of the body having a percutaneous access enabling function. These may be considered a short-term implementation strategy or approach, i.e., devices with useful lifetimes measured in days, not weeks. In general, these devices are attached to the skin using adhesives and involve replacement by the user every 3–7 days. A variety of devices for glucose sensing or drug (insulin) delivery

employing microneedles, ultrasonic holes, short tubes, or small, flexible sensors are either in the marketplace or undergoing active development. However, in use, these systems and devices typically require removal/replacement every few days.

To understand why these systems have an abbreviated lifetime, a brief review of the body's foreign body response is in order. Implantation into soft tissue results in the formation of a fibrous capsule at the interface between tissue and the introduced device or structure. This capsule formation may be considered as an outcome of the body's wound-healing process, i.e., introduction of material into the body results in damage to the surrounding tissue and the body's subsequent reaction. The wound-healing response can be described as a sequence of events arbitrarily divided into the following stages: inflammation, proliferation, and remodeling. In inflammation (including hemostasis), platelets, endothelial cells, fibrin, and fibronectin act as a result of the release of growth factors and cytokines, including lymphokines and interleukins. Inflammation occurs through the actions of neutrophils, macrophages, and lymphocytes mediated by growth factors and proteases. Proliferation takes place through the actions of fibroblasts and epithelial and endothelial cells and is largely dependent on growth factors and collagen deposition. Remodeling is facilitated by collagen cross-linking and collagen degradation.[4] A recurrent theme is that introduced materials result in a wound-healing response.[5] More importantly, the capsule composed of densely packed fibroblasts and collagen layers is detrimental to the exchange of fluids between the implanted biomaterials and the surrounding tissues.[6]

Therefore, by exploiting the timeline for initial stages of the body's wound-healing response, a window of opportunity becomes available for glucose sensing and/or drug delivery based on an inserted device. An example of such devices targeting this early temporal window is the FreeStyle Navigator® continuous glucose monitor from Abbott Laboratories[7] or the Guardian® REAL-Time system from Medtronic MiniMed.[8] These systems provide the user with continuous glucose measurements, trends, and graphical displays of glucose levels, as well as alarms over a period of up to 3 or 5 days, respectively, postinsertion. Likewise, the DexCom Seven® continuous glucose monitor has been approved for use up to 7 days.

It should be noted that these continual glucose monitors require periodic device calibrations utilizing traditional finger stick blood glucose measurements, although these sticks are reduced greatly as compared to numbers

required for self-assessment. In particular, these glucose oxidase-based sensors tend to drift over time because of the body's foreign body response and concomitant changes in glucose and oxygen diffusion in the vicinity of the sensor, therefore requiring periodic recalibration to maintain accuracy. Temporal differences may exist between these measures of interstitial glucose as compared to accepted venous glucose measurements; however, these appear unaffected by insulin and are corrected readily through the use of digital filters.[9]

Continuous glucose monitoring through such devices offers the ability to monitor trends,[10] and the data sets provided by continuous glucose monitoring have led to reported improvements in glucose management as compared to traditional, self-administered assays.[11–14] Complementing these multiday continuous glucose monitoring systems are continuous subcutaneous insulin infusion (CSII) systems. Typically employing a pump and an infusion set, these devices offer improved glucose profiles as well as improved acceptance.[15–18] However, it should be recognized that with younger users, the age/development of the user may affect the ability to employ CSII effectively in all situations.[19–21]

Systems coordinating glucose sensing in tandem with insulin delivery, such as the Insulet OmniPod® insulin management system, which combines FreeStyle test strip monitoring with wirelessly controlled OmniPod insulin delivery, offer the user even greater levels of control and glucose management. Clinical improvement resulting from the combination of glucose monitoring with CSII systems[20,22] is not unsurprising nor is the recently announced decision to integrate the OmniPod with DexCom's continuous glucose monitoring system. Systems such as the Medtronic Paradigm® REAL-Time system employing a real-time monitor in wireless communication with the Medtronic pump offer the functionality of continual glucose monitoring with CSII, albeit still requiring twice-a-day finger stick-based glucose monitor calibration. Anticipated to be available in the near future is the coupling of the OneTouch Ping® pump from Animas to the DexCom Seven monitoring system. It is expected that others will offer similar systems in order to take advantage of the strengths of effectively continuous monitoring coordinated with infusion.

Long-Term Strategies (Months/Years)

User compliance with short-term solutions remains a concern, despite improvement in overall blood glucose management as compared to multiple daily needle sticks for measurement and/or injection. As an alternative

strategy, companies are exploring the use of devices intended to be implanted for an extended period of time—weeks, months, or even years—to minimize user involvement and to lay the foundation for a truly closed loop glucose management system. In order for these approaches to provide the desired efficacy, safety, and user comfort over the extended time periods envisaged, the devices must manage or mitigate the human body's efficiency in rejecting these implanted materials as a foreign substance over extended periods of time beyond the initial wound-healing stages.

To accomplish the goal of extended useful device lifetime in body, e.g., months or years, successful minimization of the body's foreign body response and resulting in encapsulation is needed. In 1982, Hench (who is well known in the world of biomaterials and may be considered to be among the thought leaders for biomaterial design and constructions) with Ethridge[23] observed that "implanted biomaterials must be in contact with living tissues, resulting in an interface between living and non living substances. It is the long term stability of this interface that determines the success or failure of a biomaterial and devices fabricated from biomaterials." Based on this broad statement, a variety of materials and structures may be classified as biomaterials. In order to clarify the nature of these materials, Hench and Etheridge[23] classified biomaterials into four categories (**Table 1**).

Table 1. Biomaterial Categorization	
Type	Characteristic
1	Nearly inert, smooth surface
2	Nearly inert, microporous surface
3	Controlled reactive surface
4	Resorbable

Hench and Ethridge[23] noted that the body's response to type 1 materials is a fibrous capsule separating implant from host tissue and that "although this capsule is contiguous to acellular components of the tissue, it is not adherent to the implant. It is this lack of adherence that results in motion of the tissue-implant interface under stress or flow and is responsible for the lifetime limitations of many devices…" They noted that the theory behind type 2 (microporous) implants is that the network of porosity provides for the ingrowth of tissues. In contrast, type 3 implants are designed to elicit a tissue interaction at the surface rather than limit it. Finally, type 4 materials are designed to be ultimately replaced

by regenerating tissues, eliminating the original tissue–implant interface. With this as a framework, they stated that the formation of either a fibrous capsule or a stable adherent bond was the primary determinant in the long-term performance of the device and went on to propose a general theory describing an implant material: "An ideal implant material performs as if it were equivalent to the host tissue."

This theory may broadly be employed to describe the general direction of long-term implant design over the last two decades. In particular, the desire to have surface interfaces approximate normal surface interactions with the surrounding tissues. Thoughts about critical factors for implant surfaces accordingly have evolved from an either/or approach regarding surface topography or surface chemistry, progressing to an understanding that both are important and coupled. In addition, the micromechanical properties (viscoelastic properties) are now also recognized to affect interfacial processes, interacting with both topography and chemistry.[24]

The surface of implanted biomaterials, in short, has a significant effect on the nature of the surrounding tissue that develops in response to these introduced surfaces. The fluid transport and perfusion properties of the surrounding tissues are affected by this developed tissue to lesser or greater degrees. The degree of this dependence is governed by the organization of the newly developed tissue, specifically in its permeability and hydraulic flow resistance, and also on the degree of vascularity, as this promotes greater exchange with the systemic circulation. Accordingly, structures of implanted devices in contact with body tissues incorporate design features involving materials, topology, and/or coatings, including drug release,[25] to improve the device biocompatibility and acceptance by the surrounding implanted environment.

In particular, the surface topography approach as a means of achieving enhanced biocompatibility (and minimized capsule formation) has received significant attention. These efforts have been focused on providing a three-dimensional biomaterial surface such as would be found in the body. A simplified view of this approach is the realization that features on the scale of biological entities (proteins 1–10 nm) or cells (1–100 μm) will induce biological interactions more closely akin to those present in the tissue and are different than those arising from a flat surface.[26]

A variety of features, including ridges, grooves, and random features, on both the micrometer and the submicrometer scale have been shown to be useful for promoting integration and lessening capsule formation. Factors supporting mimicry of the surrounding cell dimensions and organization coupled with mechanical ductility have been particularly encouraging. For example, Sharkawy and colleagues[6,26,27] evaluated membranes of either polyvinyl alcohol (PVA) or polytetrafluoroethylene of various pore sizes, as placed adjacent to implanted sensors. Nonporous membranes with a smooth topography promoted the formation of a classic foreign body capsule, with tightly packed collagen organized parallel to the implant surface. In contrast, porous materials produced a less densely packed structure that was organized more randomly and was also more vascularized.

Another illustrative study of the use of micrometer scale materials has been shown by Ward et al.,[28] who examined the foreign body response to solid or porous subcutaneous long-term (7 week) implants of different compositions. This study illustrated the tendency of solid implants to result in a thick layer (approximately 100 μm) of closely packed collagen and fibroblasts with little intervening space (the foreign body capsule) as compared to a less structured cell organization and decreased amounts of collagen and fibroblasts surrounding implanted porous PVA sponge material with an average pore size of 60 μm. The authors also examined a material having different porosity, expanded polytetrafluoroethylene (ePTFE) with a pore size of 1 μm. This material yielded similar capsule formation as the PVA. Both the PVA and the ePTFE implants had significantly greater numbers of vessels close to the implant as compared to solid polyurethane. In short, thin implants lead to thin capsules, and porous implants result in more angiogenesis than solid implants.

The aforementioned work utilized materials of differing porosities as surfaces to enhance adhesion and lessen capsule formation. Alternatively, pillar-like structures can be employed to the same end. Picha and Drake[29] reported on the use of subcutaneous silicon pillars (100-μm-diameter pillars 500 μm in height spaced 200 μm center to center) significantly reducing subcutaneous capsule diameter and increasing vascularity as compared to smooth surface controls. In a related study, Smahel and co-workers[30] noted that textured silicon, with a feature size of approximately 300 to 500 μm, significantly delayed subcutaneous thin connective tissue capsule formation as compared to smooth silicon controls (>3 months, as compared to <1 month in nontextured controls).

Overall, the impact of surface texture appears to be to disrupt the organization of fibrous tissue from the

elongated morphology typically found in the foreign body response to smooth surfaces. In the presence of a discontinuous porous surface, fibroblasts form multiple focal contacts in adhering to the surface, often independent of surface chemistry.[31,32] A more randomly oriented tissue results, possibly due to the effects of receptor binding and alterations in the cytoskeletal structure that occur within the cells to produce focal adhesion. The extracellular matrix that is subsequently deposited is therefore also less organized, consequently less dense, and more open and less resistant to transport and fluid flow. In contrast, fibroblasts responding to a smooth nonporous surface do not adhere and align parallel to the surface to form a more organized tissue and a more tightly packed collagen matrix.

Likewise, neovascularization of the tissue is increased through the use of surface texture, an effect that greatly enhances perfusion to allow greater exchange of chemical components between the implant and the host plasma. Brauker and colleagues[33] suggested a link between the degree of neovasculature and the microarchitecture of implanted synthetic membranes. Materials with an average pore size comparable to the size of host cells promoted the greatest inducement of new blood vessels. It is hypothesized that an optimal pore size for these materials exists, characterized as large enough to allow the penetration of inflammatory cells, but which prevents flattening of these cells on the structural surfaces that define the pores.[34] Instead, cells assume a rounded morphology, which either allows them to stimulate neovascularization directly or prevents their activation to stimulate fibrous capsule formation and the suppression of endothelialization for the assembly of desired capillary structures.

At a considerably smaller scale (nanometer), the *in vitro* work of Dalby and associates[35] indicated that the height of surface features influences the spreading of endothelial cells upon both hydrophobic and hydrophilic surfaces. An optimal height of 13-nm "islands" induces cytostructural features (stress fibers) more rapidly than either lower or substantially taller (e.g., 95 nm) features. A common morphological feature of these cells on these "nano-islands" is an arcuate or curved cell shape. The authors noted that, *in vivo*, the cells are arranged in a monolayer around a scaffold of collagen and, despite high phenotypic variation, a common feature is the arcuate shape of these cells. At the nanometer scale, both chemistry and topography are intertwined, and the authors speculated that the regular nanometric topography provides cues similar to those given by

collagen, resulting in the more natural phenotype than that observed on flat tissue culture plates. The authors noted that other cell types, e.g., fibroblasts, recognize surface features and react to them, resulting in contact guidance. Focal adhesion formation followed by a cytostructural element (actin and tubulin microtubules) may serve to stabilize the contact. Thus, nanometer-scale features may also provide a means to influence cell adhesion and response in addition to the micrometer-scale features mentioned earlier.

Employing technologies such as those reported previously, Gilligan and co-workers[36] have reported some level of success with glucose sensors having extended lifetimes. In their limited clinical study ($n = 6$), one of the five functional sensors responded with a clinically useful performance to manipulated glucose levels for a period of over 6 months. Periodic recalibration of the sensor was required. This admittedly small study indicates that a long-term glucose sensor may be feasible and might be developed.

In contrast to glucose sensing, issues associated with the possible long-term impact of the delivery of insulin or insulin analogs at fixed subcutaneous sites remain unclear at this time. CSII over extended periods of time may lead to some difficulties in certain patient populations and with certain forms of insulin.[37,38] Of more concern is the possible development of lipoatrophy or lipohypertrophy. Lipoatrophy resultant from immune-mediated inflammatory lesions is becoming less frequent with the advent of human insulin, but is still occasionally observed.[39,40]

However, alternative, nonsubcutaneous implant insulin infusion systems, e.g., peritoneal delivery, have been under development since the mid-1980s.[41–43] Studies such as those reported by the Evaluation dans le Diabete du Traitement par Implants Actifs study group have shown promise in overcoming difficulties associated with insulin aggregation through the use of modified insulin formulations and promoting extended accurate insulin delivery[44,45] and support the use of long-term delivery as a means of effectively controlling glucose levels.[43]

Business Considerations

This discussion has focused primarily on the technology of implanted devices and, to a lesser extent, the need for this technology to match the needs of the patient and clinician. However, this brief review of factors governing the use of long-term implanted devices would not be

complete without mentioning two additional factors critical to the success of any product in the marketplace. To be successful, a product must also meet the needs of the manufacturer for commercialization and the oversight requirements of appropriate regulatory agencies. That is, from the manufacturer's viewpoint, the product must make economic sense. Economic sense may be taken to mean that the product, whether a glucose sensor, an insulin delivery system, or a combination of the two, must be capable of large-scale manufacture, delivery, and sale such that a viable business model is supported.

The business model need not be a classic sales model based on disposables in order to be appropriate to the diabetes market place. In fact, the complexity of diabetes treatment, requiring lifestyle management, as well as appropriate measurement and therapy delivery, may well support more novel business models that include outside follow-up/service delivery in conjunction with device/drug sales. The selection of the business model to be followed is dependent on multiple considerations, such as technologies employed, reimbursement strategies, available resources, market timing, competition, and available strategic alliances, and is accordingly specific to each company.

Regardless of the business model followed, the bottom line remains that a company is governed by the forces of the marketplace in a highly competitive arena. Price and device performance must overcome these forces in order to maintain the viability of the manufacturer. These depend not only on device performance, but also on reimbursement routes available supporting implementation of the technology. If reimbursement is not clearly projectable and supportive, then the business will fail and the technology will not be introduced. Hurdles to the implementation of effective reimbursement often involve catch-22 scenarios wherein reimbursement, whether from government agencies or private sources, will not be implemented without demonstrable efficacy. Demonstrable efficacy in turn often requires extended studies in large populations, imposing a financial burden and barrier to product introduction. These considerations are therefore entered as a part of a comprehensive business model when a company is considering the introduction of a new technology.

Likewise, significant regulatory hurdles must be passed for a device or system to obtain Food and Drug Administration approval. The cost and time of this clearance/approval process may be challenging for smaller entities to successfully support. For example, consider the cost on a company that has potentially developed a long-

term, e.g., >1 year, implanted glucose sensor. Appropriate regulatory agencies would, in all likelihood, insist that clinical studies be performed for at least this time period to demonstrate efficacy over the claimed implant period and that these studies be performed in populations representative of the target market. When the logistics of recruitment and study oversight are factored in, it is clear that clinical studies may represent a significant challenge beyond initial technical efficacy demonstration. Intermediate claims, e.g., implant lifetimes of a month or two, may be attractive to meeting regulatory burdens; however, these may adversely impact selected business models and reimbursement strategies. A solution to the competing needs for regulatory approval as compared to time-to-market/revenue is a hurdle that all companies must resolve when considering entry into this market. In practical terms, regulatory factors are part of the initial determinations of any entity within terms of planning, product introduction, and financing strategies.

Conclusion

As daunting as the aforementioned technical, business, and regulatory challenges may be, the growing need for effective long-term diabetes management and the concomitant opportunities that such need creates continue to generate considerable activity on the part of researchers and developers. Through ever more advanced technologies providing long-term solutions, clinicians and patients alike can look forward to an improved quality of life and effectively pain-free management of their underlying condition.

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