hand, the "downregulation" of insulin release seemed to occur much more slowly for the macroencapsulated islets providing a slow release system of insulin that may have advantages over the rapid downregulation seen in microencapsulated islets. This provides the potential advantage of a continuous low level baseline of insulin in vivo.

Thus, it was clear that the decreased porosity expected in case of the AP 3.4 k gel compared to the AP 10 k gel did not affect the diffusion of small molecules such as glucose and insulin through these gels although the diffusion of macromolecules may be affected.

Canine islets in conventional alginate-polylysine microcapsules were also further encapsulated in AP macrocapsules. The results in FIG. 4 clearly show the initial basal level of secreted insulin followed by an insulin secretion response to the stimulatory level of glucose (for the time period between dashed lines) and a slow return to basal insulin secretion levels towards the end of the experiment.

It should be noted once again that the response to stimulus lags by about 10–15 minutes and this is comparable to the microcapsules and macrocapsules above. The downregulation is slower compared to the microcapsules as observed for the macrocapsules above. Nevertheless, the results are once again indicative of healthy functioning islets and the relatively innocuous encapsulation procedure.

Example 12

In Vivo Tests of Function of AP Encapsulated Islets in a Xenotransplant Model Followed by Retrieval of Functioning Implants

Islets were encapsulated in a microcapsule of the AP 10 k solution. The procedure involved suspension of the islets in a AP solution and formation of tiny droplets (300–800 microns) by injection of the suspension through a coaxial flow jethead (with an external air flow) and subsequent photopolymerization by exposure to green light from a Hg lamp. The droplets were rinsed thoroughly in saline and culture media. They were cultured for three days before transplantation into the peritoneal cavities of streptozotocin (STZ) induced diabetic rats. The rats were kept in metabolic cages and their blood glucose, urine volume, and body weight were measured routinely.

FIG. 5 shows the blood glucose, urine volume and body weights of the rats receiving microencapsulated islets (AP 10 k solutions). 10,000 canine islets were transplanted into the peritoneal cavities of these rats. The blood glucose shows an immediate drop to normal levels Normoglycemia is maintained for 34 days at which time these implants are retrieved (although they are functioning normally) for purposes of assessing the state of the implant. Immediately after retrieval the blood glucose and urine volumes are seen to raise back towards diabetic levels. The body weights of these rats were seen to increase at a steady rate of approximately a gram per day during the period of the transplant which is typical in a healthy rat.

The implanted microcapsules were recovered at 34 days and the animals sacrificed. The recovered microcapsules were cultured in vitro, observed for tissue reaction to the material, subject to viability staining, static glucose stimulation (SGS), and perifusion for assessment of islet function. Most of the microcapsules were free from tissue overgrowth and staining of islets with dithizone (stain for insulin) showed the presence of insulin in more than 80% of the recovered islets. SGS gave stimulation ratios to be 1.0:50.8:10.9 indicating extremely healthy islets. The perifusion profile (FIG. 6) of these recovered islets showed a result that essentially matched the SGS in terms of stimulation ratios showing the characteristic profiles of insulin secretion that were observed in in vitro studies prior to implantation.

An intravenous glucose tolerance test (IVGTT) was performed on the transplanted rats prior to retrieval of the implants to determine the kinetics of glucose clearance from the vascular system of these rats when challenged by an injection of glucose. The procedure involved the cannulation of the external jugular vein of these rats with a catheter under general anesthesia. The animals were then allowed to recover for a day or two. Glucose (500 mg/kg body weight) was administered through the catheter and blood was withdrawn periodically after the injection at 1, 5, 10, 20, 30, 60, and 90 minutes. Blood glucose was measured and plotted as a function of time to determine the rapidity of clearance from the vascular system of the rat. FIG. 7 shows these results. The rapidity of clearance is measured in terms of a K value which is computed by determining the slope of a line between the glucose values at 1 minute and 30 minutes plotted on a logarithmic scale. The higher the K value, the faster the clearance of glucose. For a normal rat, the K value is typically greater than 3.0 while for diabetic namilas it is significantly lower. The curves in FIG. 7 show the results for a normal rat, a diabetic rat, and a diabetic rat receiving a xenotransplant of canine islets in AP microcapsules, at 30 days after transplantation. The glucose clearance curve for the transplanted rat very closely approximates that of the normal rat indicating the success of the transplant and alleviation of diabetic symptoms.

Example 13

In Vivo Tests of Islet Function in a Xenotransplant Model with Conventional Alginate/PLL Microcapsules Further Encapsulated in AP Macrocapsules

Canine islets encapsulated in conventional alginate/PLL microcapsules (MIC) were further encapsulated in AP 10 k macrocapsules by suspension of the MICs in the AP mixture and extrusion through a syringe to form droplets (5–7 mm diameter) into a calcium solution followed by photocrosslinking. These were transplanted into the peritoneal cavity of STZ induced diabetic rats and the blood glucose, urine volumes, and body weights monitored over time. FIG. 8 shows the results of these transplants indicating a complete reversal of diabetes in these rats as determined by their normal blood glucose levels (<200 mg/dl), normal urine volumes (15–25 ml/24 hours), and increase in body weights by approximately a gram per day. The status of these implants was ongoing for more than 45 days at the time of this application, totally independent from exogenous insulin requirements.

We claim:

1. A crosslinked biocompatible material comprising:
at least one ionically crosslinked component; and
at least one covalently crosslinked component, wherein the ionically crosslinked component is selected from a polysaccharide, a polyanion, or a polycation.

2. The crosslinked biocompatible material of claim 1, wherein the ionically crosslinked component is alginate.