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(71) **Applicant** *(for all designated States except US):* **MATREGEN CORP.** [CA/CA]; 200 Front Street West, Suite 3004, P.O. Box 31, Toronto, Ontario M5V 3K2 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only):* **BRYSON, Nathan** [US/CA]; 99 Glen Road, Apt 1, Toronto, Ontario M4W 2V8 (CA). **KATAYAMA, Yusuke** [JP/CA]; 55 Bloor Street East, Apt 2001, Toronto, Ontario M4W 3W6 (CA). **SHOICHET, Molly, S.** [CA/CA]; 15 Austin Crescent, Toronto, Ontario M5R 3E4 (CA). **YONG, Kintoo** [CA/CA]; 3004 - 200 Front Street West, Toronto, Ontario M5V 3K2 (CA).

(74) Agent: RIDOUT & **MAYBEE LLP;** One Queen Street East, Suite 2400, Toronto, Ontario M5C 3Bl (CA).

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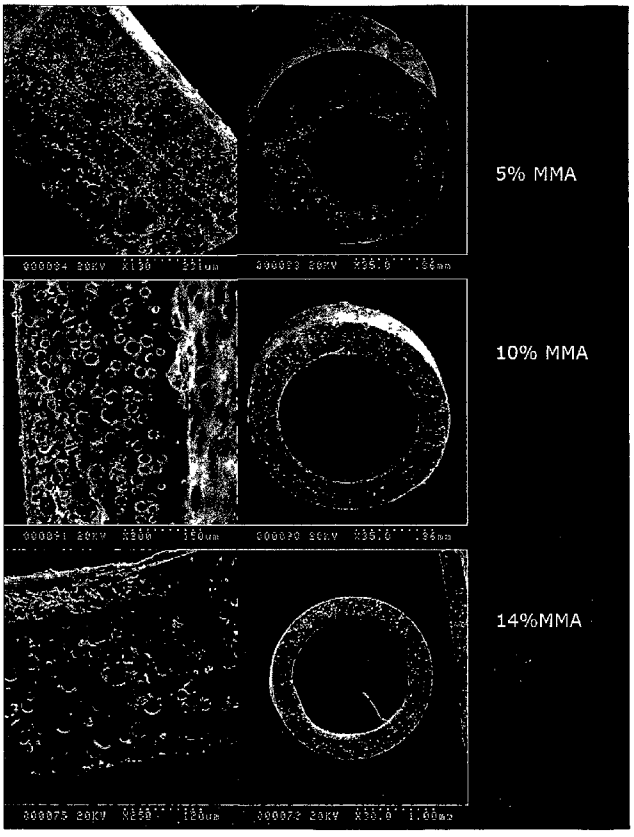

(57) Abstract: An implantable hydrogel device for the administration of GLP-I or an analog of GLP-I for sustained release over extended periods of time; methods of manufacture and uses thereof.

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Title of Invention

GLP-I DEPOT SYSTEMS, AND METHODS OF MANUFACTURE AND USES THEREOF.

RELATED APPLICATIONS

This patent claims priority to US provisional patent application No. 60/867,156, filed November 24, 2006, and US provisional patent application No. 60/912,466, filed April 18, 2007, which are incorporated herein by reference.

Background Of Invention

GLP-I

GLP-I (1-36 and 1-37), or "glucagon-like peptide-1", was first identified in the early 1980's, as a 36, or 37 amino acid peptide generally devoid of biological activity. In 1987, three independent research groups demonstrated that the removal of the first 6 amino acids resulted in a GLP-I molecule with substantially enhanced biological activity, known as GLP-l(7-36) or GLP-1(7-37) (hereinafter collectively referred to as "GLP-I").

GLP-I is secreted from gut endocrine cells in response to nutrient ingestion, and plays multiple roles in metabolic homeostasis following nutrient absorption. The biological roles of GLP-I include stimulation of glucose-dependent insulin secretion and insulin biosynthesis, inhibition of glucagon secretion and gastric emptying, and inhibition of food intake. GLP-I appears to have a number of additional effects in the gastrointestinal tract, in the nervous system, and elsewhere. (Diabetes, 1998 47(2) :159-69; Endocrinology, 2001 Feb: 142(2) :521-7; Curr Pharm Des. 2001 Sep: 7(14) :1399-1412; Gastroenterology 2002 Feb: 122(2):531-544.)

GLP-I has been found to lower blood glucose in patients with diabetes. It has also been suggested that GLP-I may restore b-cell sensitivity to exogenous secretagogues, and regulates islet proliferation and islet

neogenesis. GLP-I appears to also have a role in the control of satiety and food intake, suggesting that administration of GLP-I can reduce food intake in both acute and chronic studies. GLP-I has been shown to dose dependently inhibits food intake (Nature 1996:4:379(6560) :69-72; Am J Physiol 1999 May 276(5Pt2): R1541-4; J. Clin Endocrinol Metab 2001 86(9) :4382-9). GLP-I also appears to increase insulin sensitivity, with no change in hepatic glucose uptake (Metabolism, 1997 Jul 46:7:745-9). GLP-I also improves cardiovascular risk factors, such as HDL/LDL ratios, serum cholesterol and weight (Diabetologia. 2006 Mar;49(3) :452-8; Diab Vase Dis Res. 2004 May; l(l) :40-3). As diabetes also has demonstrated links to Alzheimer's Disease, GLP-I therapy may equally have potential as a therapeutic agent (Curr Drug Targets. 2004 Aug;5(6) :565-71; J Alzheimers Dis. 2002 Dec;4(6) :487-96).

Studies administering GLP-I via IV in humans with type 2 diabetes have shown modest weight loss and an increase in insulin sensitivity (Lancet, 2002 Mar 9; 359(9309):824-30). Other studies suggest a role for GLP-I in the enhancement of glucose disposal in elderly subjects (Diabetes Care, 2003 Oct. 26(10) :2835-41; Diabetes Care 2001 Nov: 24(ll) :1951-6).

GLP-I has also been found to lower blood glucose in both patients with Type 2 and Type 1 diabetes (N Engl J Med 1992 May 14; 326(20) :1316-22; Diabetes 2001 Mar; 50(3) :565-72; Diabetes Care 1996 Jun 19(6) :580-6; Diabetes 1995 Jun 44(6) :626-30). GLP-I has also been suggested to promote insulin or glucagon-independent glucose clearance and/or suppression of glucose production (Am J Physiol Endocrinol Metab 2003 May 28).

GLP-I is not highly efficacious when administered as a therapeutic agent, mainly because it suffers enzymatic degradation, most prominently by the dipeptidyl-peptidase enzyme (DPP4). Thee pharmacokinetic half-life of the GLP-I peptide is on the order of a few minutes (2-5min), and therefore, the peptide must be administered systemically in rather large quantities in order

to produce any therapeutic effect. Many have therefore turned to either blocking the DPP4 enzyme as an alternative strategy to help sustain native GLP-I at their highest endogenous levels, while others have sought modified peptide agonists, with better bioavailability and half-life, as well as better potency.

GLP-I Analogs

Several GLP-I analogs and agonists are known.

One such GLP-I agonist is Exendin-4, also known as exenatide. Exenatide exhibits approximately 53% identity to the GLP-I peptide, and is currently used as a treatment for type 2 diabetes. Early studies using exenatide demonstrated that chronic treatment of diabetic rats with this peptide was associated with both weight loss and increased insulin sensitivity (Diabetes, 1999 May 48:5: 1026-1034, Endocrinology, 2005 Apr: 146(4) :2069-2076). Exenatide displays similar functional properties to native GLP-I, and regulates gastric emptying, insulin secretion, food intake, and glucagon secretion. It has also been shown to lower blood glucose in normal rats and in both mice and rats with diabetes (Regul Pept 1996 Jan 16;61(1) :1-18). Exenatide has been administered acutely or for several weeks to mice and rats with experimental diabetes, and has resulted in improved glucose control, reduced hemoglobin AlC, increased insulin, weight loss, decreased adiposity, reduced food intake, and stimulation of islet neogenesis and islet proliferation (Diabetes 1999 May 48(5) :1026-34; Diabetes 1999 Dec 48(12):2270-6; Diabetes 49:741-748, 2000; Endocrinology 2000 Jun; 141(6) :1936-41; Metabolism, 2001 May 50(5) :583-9; Diabetes 2001 Jul 50(7) :1562-70; Int J Mol Med 2001 Sep; 8(3)269-71; Diabetes 2002 May; 51(5)1443-52; Diabetologia 2002 Sep 45(9): 1263-73; J Biol Chem 2003 Jan 3 278(l):471-8; Diabetes 2003 Feb 52(2)365-371; Diabetes 2003 Mar 52(3): 734-740) Exenatide differs from GLP-I in that the structure is highly resistant to enzymatic degradation. GLPl has a half-life on the order of a few minutes, while that of Exenatide is approx. 40 min.

A longer acting form of exenatide, designated exenatide-LAR, has been studied in single dose studies in rats. This form of exenatide is an injectable poly-lactide-glycolide microsphere suspension of exenatide. Exenatide-LAR has had some early positive results (Diabetologia 2005 May 25).

Exendin agonist compounds are equally agonists of the GLP-·I receptor. Exendin-4 potently binds at GLP-I receptors on insulin-secreting beta cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide is also said to stimulate somatostatin release and inhibit gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268: 19650 55, 1993; Schepp, et al., Eur. J. Pharmacol., 69: 183 91, 1994; Eissele, et al., Life Sci., 55:629 34, 1994). Exendin-3 and exendin-4 were reported to stimulate cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149 56, 1992; Raufman, et al., J. Biol. Chem. 267:21432 37, 1992; Singh, et al., Regul. Pept. 53:47 59, 1994). The use of exendin-3 and exendin-4 as insulinotrophic agents for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Pat. No. 5,424,286). Exendin and exendin analogs are described in US6,989,366 and 7,115,569.

Liraglutide is a GLP-I derivative nearly identical structure to the native GLP-I peptide, but has an additional N-alkyl functionality attached to a Lys residue within the sequence. Peripheral administration of liraglutide, to diabetic rodents, has been found to reduce food intake and achieves weight loss (Diabetes 2001 Nov; 50(ll) :2530-2539).

Liraglutide has also been assessed, with or without metformin, and was found to improve glycemic control and lower body weight in subjects with type 2 diabetes when administered by injection (Exp Clin Endocrinol Diabetes, 2006 Sep; 114(8) :417-23). Daily administration of liraglutide to obese diabetic patients for 8 weeks reduced HbAIc, decreased plasma glucose, prevented weight gain, and provided no change in energy expenditure (Diabetes Care 2004 Aug; 27(8) :1915-21). A 12 week study comparing

liraglutide to metformin found that liraglutide produced comparable HbAIc reduction with prevention of weight gain (Diabet Med 2005 Aug; 22(8) :1016).

Liraglutide administration is plagued with side effects characteristic of therapeutic use of GLP-I and analogs, including headaches, nausea, dizziness, and vomiting, with nausea and vomiting most common, and reported more frequently in high dosage treatment. (Diabetes care, 2002 Aug; 25(8) :1398-404; Diabetes Care 2004 Jun; 27(6); 1335-42; Diabetes 2004 May 53(5) :1187-94).

Other long-acting GLP-I analogs and derivatives are described as in numerous patents including US5,545,618, WO9808871, EP1306092, WO9830231, WO03011892, US2003124669, US2004106547, and WO2005/066207, which are incorporated herein by reference. Chemical and sequence modifications modify properties such as receptor binding capacity, half-live, solubility, degradation resistance, etc, making each of these analogs and derivatives potentially useful candidates for GLP-1-type therapy, as in diabetes, obesity, and other metabolic disorders and conditions affected by metabolic imbalances in glucose homeostasis, dyslipidemia, high free fatty acids and cholesterol, high LDL/HDL ratios, etc, as described in these exemplary patents, WO9819698, WO9830231, US6,583,111, WO9820895, US6,894,024, US6,884,579, US6,998,387, and US6,998,366, which are incorporated herein by reference. A selection of these GLP-I analogs and derivatives is shown in sequence listing form in Figure 1.

Therapeutic delivery of GLP-I and analogs

Therapeutic delivery of GLP-I and analogs, namely balancing maximum efficacy with tolerability over a broad spectrum of patients, continues to be a challenge (Diabetes 2002 Feb; 51(2) 424-429), since GLP-I and analogs have several known side effects, such as nausea and emesis, described further below.

GLP-I and agonists of GLP-I have, to date, primarily been administered through injection. There is considerable debate as to whether intermittent or continuous administration provides better effect on body weight and food intake (Br. J. Nutr. 2004 Mar; 91(3) :439-46). Also unclear is whether a decrease in energy expenditure is linked to GLP-I administration (Gastroenterology 2004 Aug; 127(2) :546-58; Diabetes 2001 Nov 50(ll) :2530-9; Int J Obes Relat Metab Disord. 2000 Mar; 24(3) :288-98).

GLP-I and its analogues are highly biologically active following intravenous or subcutaneous injection. However, a non-injectable alternative for activating GLP-I receptor signaling would clearly be desirable.

GLP-I formulated in buccal tablets has been found to be absorbed into the circulation and lowers blood glucose in human subjects. (Diabetes Care, 1996 Aug; 19(8):843-8).

Oral formulations of GLP-I analogues have also been taught, including a microsphere formulation of D-Ala2-GLP-1, a DPP-4 resistant analogue encapsulated in poly(lactide-co-glycolide)-COOH in olive oil. However, the effectiveness of such an oral, encapsulated GLP-I analogue is not clear, as levels of insulin, glucagon or rate of gastric emptying were not reported with its administration (Diabetologia 2000 43: 1319-1328).

"Gene therapy" approaches, for sustained therapeutic delivery of GLP-I analogues, have also been explored. However, such approaches have known and significant disadvantages (Gene Ther 2006 Aug 24)

Intramuscular injection of a hybrid cDNA encoding a GLP-l/Fc peptide has also been attempted, and has been shown to normalize glucose tolerance by enhancing insulin secretion and suppressing glucagon release in db/db mice (Gene Ther 2006 Aug 31).

Pegylation has also been used to produce stable GLP-I molecules with longer-acting pharmacokinetic profiles (Biochem Pharmacol. 2006 Sep 17).

Hydrogel microencapsulation of GLP-I for injection has also been hypothesized in US 6,770,620, though the viability of such a system in terms of release rate, degradation rate, tolerability, and other variables, and the specific composition of such a system, have not been considered or enabled.

GLP-I analogs have been consistently shown to have side effects, such as dizziness, emesis, and nausea, which make continued use of GLP-I analogues for appetite control and weight loss undesirable, and often unsustainable (Endocrin 2000,141,1936). Unsuccessful attempts to mitigate these side effects were described in the controlled release of GLP-I and analogs through the injection of microparticle suspensions (Diabetologia 2005, 48, 1380) or through sustained release from a "true" zero-order delivery device, such as a minipump or osmotic pump (Int J Obesity, 2006, 1-9). Nausea in rat models is characterized by a sudden severe weight loss, and has been attributed to an emetic reaction or associated learned-distaste due to the drug. Nausea can be reduced in number of incidents by lowering the initial injected dose (for non-sustained delivery applications) for a period of 2 weeks and then adjusting to the desired therapeutic dose (Diabetes/Metabol Research Rev 2004, 20, 411).

A wide variety of GLP-I analogs are known, including those found in US patent application 60/896,584, incorporated herein by reference.

Hydrogel Delivery Systems

Hydrogel delivery systems known in the art can loosely be divided into two groups: hydrogel systems for injection as an extended release solution or semi-solution, and hydrogel casings/depots.

An aqueous based homogeneous hydrogel system can be made by emulsion based polymerizion of acrylate-modified dextrans in the presence of proteins. Microspheres are produced which contain encapsulated protein, such as hGH. Various methods are described to stabilize the protein during the emulsification stage of the process, such that denaturation and 'good' loading are achieved. Encapsulation efficiency was on the order of 50-60%, while loading was 3%.

Similar drug delivery systems, manufactured by emulsion polymerization, resulting in microsphere particles have also been described in US6,770,620, US 6,818,229, US 6,03037, and US60153,211, among others. In a general manner, each of these equally discloses without exemplification a variety of protein encapsulation methods. Molecules encapsulated include GLP-I, the object of the present invention.

The most obvious problems associated with microsphere systems include low loading and processing of protein and polymer system in an emulsion system where denaturation can occur and where only a fraction of the protein is actually encapsulated. When loading is increased typically a significant portion of the drug is found near or on the surface of the microspheres, from where it is released immediately as the spheres are administered. When the drug has a disfavorable side-effect, the rapid release of drug into the system can be a significant deterrent to its development and use.

Hydrogel casings, and other forms of depot delivery of drugs, are known in the art. These can be differentiated from hydrogel suspensions of drug for injection, described above.

Polymers are widely used in drug-delivery in order to control release and optimize therapeutic treatment with drugs (Expert Opinion in Drug Delivery, 2005, 2, 1039). Polymer membranes have been used to control the release of an encapsulated drug by acting as a diffusion barrier controlling the

rate of efflux of drug from the device (Hydrogeis in Medicine and Pharmacy, Boca Raton: CRC Press 1986). However, there have been very few examples of depot delivery of proteins. Such examples are generally limited to the specific protein or protein class, since the individual characteristics of the protein (such as size, charge, glycosylation pattern, etc.) affects the ability of the specific casing to deliver the specific protein, or the dissolution rate of that protein in vivo. Depot delivery of proteins, especially larger proteins, such as proteins greater than 25 kDa in size, have not been routinely shown, and tend to be specific to the particular protein. Certain factors that render establishment of a protein depot system difficult to invent for a particular protein include the appropriate dissolution rates should be for a protein for administration, and the characteristics of the hydrogel casing that can provide this dissolution rate for the particular protein being administered.

An example of delivery of a small molecule in a polymer gel depot is described in US patent 5,756,115. This patent discloses a silicone device to encapsulate an estrogen and slow release of that estrogen via diffusion, both in-vitro and in-vivo. The patent teaches that this device could theoretically be useful as a contraceptive device with extended action. The hydrophobic nature of the polymer membrane used restricts the specific silicone device to the release of small organic molecules, such as estrogen.

Hydrogel tubes are a form of hydrogel depot taught for use as a rate limiting barriers. Empty tubes are produced and are manually filled with powdered, compacted or extruded formulations, eventually containing excipient to adjust solubility and release from the tube. The tubes are sealed in such a manner that drug is contained within the tube. High loadings on the order of 5-90% and therefore, very long sustained delivery durations on the order of 3 to >12 months, are possible with such a design.

An aqueous-based homogeneous hydrogel copolymer system prepared from a mixture of acrylate monomers in a rotating cylinder is described in US patent 5,226,325. The patent discloses that the water-content of the hydrogel

is a determinant of the release properties of moderately water-soluble drugs contained within. The patent also discloses that by adjusting the monomer mixture, the water-content of the hydrogel (and therefore the release rate of a given drug compound) can be controlled. The patent teaches the use of this drug delivery device for sustained continuous release of leuprolide over a period of 250 days.

A water-swellable, hydrophobic system, its method of manufacture, and its use as a drug delivery device is disclosed in US patent 5,292,515. The device has smooth inner and outer walls and is obtained by a photopolymerization method in a spinning glass mold. The patent teaches in vitro release of an LHRH analog into a buffer solution, and discloses that the system may be suitable for delivery of peptides generally, up to a molecular weight of 25 kDa. The same system is disclosed by the same authors for the release of small molecules such as disulfiram, haloperidol, estradiol, naproxen, tamoxifen, nifedipine, and an LHRH analog (Macromol Symp 1996, 109, 15).

The technology taught in the above two patent disclosures have lead to a commercial device that is furnished in a primed/hydrated form, theoretically leading to immediate release of the drug upon implantation. The wetted, primed device, however, has been shown to deliver a high-level "burst" of drug upon implantation that may lead to adverse effect.

A water-swellable device modified by inclusion of a permeation enhancer in order to allow the theoretic release of large molecules upwards to 100 kDa is disclosed in US patent 6,361,797. Release rates, and effectiveness of the device are only demonstrated, however, for in vitro release of lysozyme for a duration of a little over 10 weeks. An undesired variable, 2-order release rate was observed. This drawback was possibly due to the requirement of a permeation enhancer for obtaining release of lysozyme. This may have led to instability of the release rate kinetics due to gradual leaching of the enhancer from the device over time.

A porous hydrogel matrix for drug delivery produced by a method of phase-separation polymerization during rotational casting is disclosed in PCT patent publication WO2004/071736. The porous hydrogel tubes are taught to have inherent porosity, and can theoretically be useful as a reservoir for the delivery of a wide variety of agents, including peptides. The method taught produces a tube that leaves a non-uniform internal surface with low mechanical properties, and an asymmetric membrane structure. The asymmetry of the membrane is purported to allow for rapid exchange and hydration, and the matrix is taught to have a short onset of action from the xerogel state.

Common problems with current depot delivery systems include difficulty of using these delivery systems with proteins, especially proteins of greater than a certain size, as well as difficulty providing consistent delivery of the material at a constant rate for an extended period of time, for example, 100 days. One other problem with the current depot delivery systems results from the hydration rate of the xerogel, which contributes to the "ramp up" time for delivery of the drug.

Methods for producing structures that are able of being used as depots for the delivery of drugs, and the structures themselves, are described in US patent applications 10/169,948, 10/903,384, 11/206,019, and US patent 6,969,480, which are incorporated herein by reference. Polyurethane based polymer depots for the delivery of biologically active compounds at a constant rate for an extended period of time are described in US patent publication number 20050037078.

US Patent 5,266,325 describes LHRH release from hydrogel tubes. The patent describes release from the hydrogel tubes regardless of whether the tubes are irradiated with a gamma source. Gamma irradiation was noted to increase rate of release in certain cases, for a small peptide (LHRH, a 9-mer).

Hydrogel tubes which are treated with gamma irradiation are known to have polymer damage and claim cleavage due to the irradiation, often resulting in a modification of the chemical properties of the tube. US 5,266,325 teaches that the irradiation of the tubes should be considered in optimizing the product to a particular release rate. However, nothing in the prior art suggests that irradiation of a hydrogel tube can enable release of a peptide from a hydrogel tube which would otherwise not release the peptide, nor does anything in the prior art suggest that irradiation of a hydrogel tube would effect the release rate of anything larger than a small, 9-mer peptide such as LHRH.

It would therefore be desirable to provide a depot delivery system for the delivery of GLP-I and GLP-I analogues or derivatives, that provides a consistent delivery of the GLP-I, analogue, or derivative at a relatively constant rate. It would also be desirable to determine a rate and/or method of delivery that decreases the side effects of the GLP-I, analogue or derivative. Finally, it would be desirable to provide such a system for the delivery over an extended period of time.

Summary of the Invention

One embodiment of the present invention is an implantable device for the administration of a compound selected from a group consisting of GLP-I, an analog of GLP-I and a derivative of GLP-I, comprising (1) a hydrogel or xerogel reservoir and (2) the compound, wherein the reservoir encases the compound. The hydrogel or xerogel reservoir may comprise a wide variety of monomers or polymers, for example, a MMA/HEMA polymer. In one embodiment of the present invention, the MMA/HEMA polymer comprises 2 - 40% MMA (w/w), for example, 5 - 15% MMA (w/w), or about 10% MMA (w/w). In another embodiment, the hydrogel or xerogel reservoir comprises a HPMA/HEMA polymer, for example, wherein the HPMA/HEMA polymer comprises 10-60% HPMA, 20-40% HPMA, or about 30% HPMA.

According to one aspect of the present invention, the device is prepared such that, when implanted in an animal, provides an therapeutic serum concentration effective for a desired effect selected from the group consisting of treatment of diabetes, lowering of blood glucose levels, and weight loss, reduced food intake, improved cardiovascular risk factors, improved HDL/LDL ratios, lower cholesterol, for a therapeutic time frame starting between 0 and 20 days post-implantation and comprising between 10 and 365 days.

According to one aspect of the present invention, the compound is exenatide (SEQ ID 3). In one embodiment, the exenatide has a therapeutic serum concentration is between 0.01 and 10 ng/ml. In one embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of exenatide, for example, a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 mg of exenatide, or about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of exenatide.

According to another aspect of the present invention, the compound is liraglutide. In one embodiment, the liraglutide has a therapeutic serum concentration is between 0.01 and 10 ng/ml. In one embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of liraglutide, for example, a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 mg of liraglutide, or about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of liraglutide.

According to another aspect of the present invention, the compound is a peptide of SEQ ID NO. 4. In one embodiment, the peptide has a therapeutic serum concentration is between 0.01 and 10 ng/ml. In one embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of peptide, for example, a tube of about 2 cm in length, about 2 mm in diameter, and containing about

10 mg of peptide, or about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of peptide.

According to another aspect of the present invention, the compound is a peptide of SEQ ID NO. 1. In one embodiment, the peptide has a therapeutic serum concentration is between 0.01 and 10 ng/ml. In one embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of peptide, for example, a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 mg of peptide, or about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of peptide.

According to another aspect of the present invention, the compound is a peptide of SEQ ID NO. 5. In one embodiment, the peptide has a therapeutic serum concentration is between 0.01 and 10 ng/ml. In one embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of peptide, for example, a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 mg of peptide, or about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of peptide.

According to another aspect of the present invention, the compound is a peptide of SEQ ID NO. 2. In one embodiment, the peptide has a therapeutic serum concentration is between 0.01 and 10 ng/ml. In one embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of peptide, for example, a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 mg of peptide, or about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of peptide.

According to one embodiment, the implantable device is prepared such that, when implanted in an animal, provides an effective therapeutic serum concentration of between 0.01 and 10 ng/ml of the compound, for a

therapeutic time frame comprising of from 10 days post-implantation to 100 days post-implantation.

According to another embodiment, the implantable device is prepared such that, when implanted in an animal, provides a ramp-up serum concentration of between 20% and 90% of the therapeutic serum concentration, for a time frame comprising the first 1 to 20 days post-implantation. In one embodiment, the ramp-up serum concentration is variable and generally increasing over time.

According to a further embodiment of the present invention, an instant serum concentration, measured at any point in time over the therapeutic time frame, is within 20% of an average therapeutic serum concentration calculated over the therapeutic time frame.

According to a further embodiment, said device is prepared such that, when implanted in an animal, provides a therapeutic release rate effective for a desired effect selected from the group consisting of treatment of diabetes, lowering of blood glucose levels, and weight loss, reduced food intake, improved cardiovascular risk factors, improved HDL/LDL ratios, lower cholesterol, for a therapeutic time frame starting between 0 and 20 days post-implantation and comprising between 10 and 365 days.

In one embodiment, the compound is exenatide In a further embodiment, the therapeutic release rate is obtained between 0.01 and 500 ug/d of the exenatide.

In a further embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of exenatide.

In yet a further embodiment, the device is a tube of about *2* cm in length, about 2 mm in diameter, and containing about 10 mg of exenatide,

preferably about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of exenatide.

In a further embodiment, the compound is liraglutide and the therapeutic release rate is between 0.01 and 500 ug/d of liraglutide.

In a further embodiment, the compound is a peptide of SEQ ID NO. 4. In a further embodiment, the therapeutic release rate is between 0.01 and 500 ug/day of the peptide of SEQ ID NO. 4. In yet a further embodiment, the device is a tube of between 00.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of the peptide of SEQ ID NO. 4.

In a further embodiment, the compound is a peptide of SEQ ID NO. 5. In yet a further embodiment, the therapeutic release rate is between 0.01 and 10 ng/ml of the peptide of SEQ ID NO. 5. In yet a further embodiment, the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of the peptide of SEQ ID NO. 5.

In a further embodiment, the implantable device is prepared such that, when implanted in an animal, provides an effective therapeutic release rate of between 0.1 and 10 ng/ml of the compound, for a therapeutic time frame comprising of from 10 days post-implantation to 100 days post-implantation.

In yet a further embodiment, the device is prepared such that, when implanted in an animal, provides a ramp-up serum concentration of between 20% and 90% of the therapeutic release rate, for a time frame comprising the first 1 to 20 days post-implantation. In one aspect, the ramp-up serum concentration is variable and generally increasing over time.

In a further embodiment, the device has an instant release rate, measured at any point in time over the therapeutic time frame, within 20% of

an average therapeutic release rate calculated over the therapeutic time frame.

In a further embodiment, the device is prepared such that, when implanted in an animal, provides a therapeutic release rate effective for a desired effect selected from the group consisting of treatment of diabetes, lowering of blood glucose levels, and weight loss, reduced food intake, improved cardiovascular risk factors, improved HDL/LDL ratios, lower cholesterol, for a therapeutic time frame starting between 0 and 20 days post-implantation and comprising between 10 and 365 days. In one embodiment, the compound is exenatide. In a further embodiment, the therapeutic release rate is obtained between 0.01 and 500 ug/d of the exenatide.

A further embodiment, is a method of manufacturing an implantable device as herein described, comprising formation of a tube through a technique selected from the group consisting of extrusion, molding and rotational casting. In one embodiment, the technique is rotational casting and the tube is formed through polymerization of one or more monomer or macromer. In one aspect, the polymerization occurs in a phase separation step. In a further embodiment, the method of manufacturing further comprises irradiation of the tube. In one embodiment, the irradiation dose is from 0.1 to 10 MRad and is sufficient to permit the release of the compound encased at a therapeutically relevant dose. In a further embodiment, the irradiation is at about 2.5 MRad. In another embodiment, the irradiation is at about 5.0 MRad.

A further embodiment of the present invention is method of preparing an implantable device as herein described, comprising: a) filling an interior of a mold with a solution so that substantially all gas is displaced therefrom, the solution comprising at least two components which can be phase separated by a phase separation agent into at least two phases; b) rotating said mold containing said solution at an effective rotational velocity in the presence of said phase separation agent to induce phase separation between said at least

two components into at least two phases so that under rotation at least one of the phases deposits onto an inner surface of the mold; c) forming said device by stabilizing said at least one of the phases deposited onto the inner surface of the mold; d) removing the device from the mold; e) washing the device; f) filling the device with the compound; g) sealing the ends of the device to enclose the compound in the interior.

In a further embodiment, the method further comprises an additional step (h) irradiating the device. In one embodiment, the additional step (h) occurs after step (g). In another embodiment, the additional stem (h) occurs after step (e).

In one embodiment, the irradiation is at about 2.5 MRad. In another embodiment, the irradiation is at about 5.0 MRad.

In an alternative embodiment, steps (d) and (e) can be performed in any order.

In a further embodiment, the device may be dried prior to step (g). In a further embodiment, the device may be dried prior to step (f). In one embodiment, the drying of the device ambient air drying, forced air drying, heated drying, or reduced pressure drying.

In a further embodiment, said at least two components includes at least one monomer and at least one solvent, and wherein said solution is a substantially homogenous solution, wherein said at least one of the phases that deposits onto the inner surface includes at least the monomer, and wherein the step of stabilizing said deposited phase includes gelation of the monomer by polymerization thereof.

In yet a further embodiment, said phase separation agent is light, pH, initiation agents, change in temperature, creation of a chemical product within

the mold, changes in cationic and/or anionic concentrations, or an electric or magnetic field.

In yet a further embodiment, the method further comprises use of an initiation agent. In one embodiment, the initiation agent is a free radical initiator, a thermal and photo initiator, and/or a redox initiator.

In a further embodiment, initiation is achieved by exposure to light, change in pH, change in temperature, creation of a chemical product within the mold, changes in cationic and/or anionic concentrations, or electric or magnetic fields.

In one aspect, the hollow mold is a cylindrical tube so that said product is a polymeric tube.

In one aspect, the solution includes a cross-linking agent, for example, multifunctional methacrylate or acrylate, acrylamide or methacrylamide and preferably one of ethylene glycol dimethacrylate(EDMA), hexamethylene dimethacrylate (HDMA), poly(ethylene glycol) dimethacrylate, 1,5-hexadiene-3,4-diol (DVG), 2,3-dihydroxybutanediol 1,4-dimethacrylate (BHDMA), 1,4-butanediol dimethacrylate (BDMA), l,5hexadiene (HD), or multi-functional star polymers of poly(ethylene oxide) with terminal methacrylate groups.

In one aspect, the solution includes at least one monomer selected from acrylates, methacrylates, and derivatives thereof such as, but not limited to, 2-hydroxyethyl methacrylate, methyl methacrylate, polyethylene glycol ethyl methacrylate, ethyl acrylate, 2-hydroxyethyl acrylate, acrylic acid, methacrylic acid, 2-chloroethyl methacrylate, butyl methacrylate, glycidyl methacrylate, hydroxypropyl methacrylate, dextran-methacrylate; acrylamides and derivatives thereof such as, but not limited to, methacrylamide, hydroxypropyl methacrylamide, N,N-diethyl acrylamide, N,N-dimethyl acrylamide, 2-chloroethyl acrylamide, 2-nitrobutyl acrylamide, ; N-vinyl pyrrolidone, acenaphthalene, acrilonitrile, N-vinyl acetamide, phenyl-

acetylene, acrolein, methyl acrolein, N-vinyl pyridine, vinyl acetate, vinyl chloride, vinyl fluoride, vinyl methyl ketone, vinylidene chloride, styrene and derivatives thereof, propene, acrylonitrile, methacrylonitrile, acryloyl chloride, allyl acetate, allyl chloride, allylbenzene, butadiene and derivatives thereof, N-vinyl caprolactam, N-vinyl carbazole, cinnamates and derivatives thereof, citraconimide and derivatives thereof, crotonic acid, diallyl phthalate, ethylene and derivatives thereof such as, but not limited to 1,1 diphenyl-ethylene, chlorotrifluoro-ethylene, dichloroethylene, tetrachloro-ethylene; fumarates and derivatives thereof, hexene and derivatives thereof, isoprene and derivatives thereof such as, but not limited to isopropenyl acetate, isopropenyl methyl ketone, isopropenylisocyanate; itaconate and derivatives thereof; itaconamide and derivatives thereof; diethyl maleate, 2(acryloyloxy)ethyl diethyl phosphate, vinyl phosphonates and derivatives thereof, maleic anhydride, maleimide, silicone monomers, and derivatives thereof; and combinations thereof.

In a further aspect, the solvent is selected from a neucleophilic or electrophilic molecule selected from the group of water, alcohols, ethylene glycol, ethanol, acetone, poly(ethylene glycol), dimethyl sulfoxide, dimethyl formamide, alkanes and derivatives thereof, acetonitrile, acetic acid, benzene, acetic anhydride, benzyl acetate, carbon tetrachloride, chlorobenzene, n-butanol, 2-chloroethanol, chloroform, cyclohexane, cyclohexanol, dichloromethane, diethyl ether, di(ethylene glycol), di(ethylene glycol) monomethyl ether, 1,4 dioxane, N,N, dimethyl acetamide, N,N, dimethyl formamide, ethyl acetate, formaldehyde, nheptane, hexachloroethane, hexane, isobutanol, isopropanol, methanol, methyl ethyl ketone, nitrobenzene, n-octane, n-pentanol, propyl acetate, propylene glycol, pyridene, tetrahydrofuran, toluene, trichloroethylene, o-xylene and pxylene, a monomer, a liquid crosslinking agent, or mixtures thereof.

In one embodiment, the solvent solubilizes said monomer mixture but not a polymer or crosslinked polymer formed from said monomer mixture.

In one embodiment, said at least one monomer is present in a range from about 0.001% by weight to about 60% by weight.

In one embodiment, the polymer is a polyacrylates, polysulfone, peptide sequences, proteins, oligopeptides, collagen, fibronectin, laminin, polymethacrylates such as but not limited to poly(methyl methacrylate), poly(ethoxyethyl methacrylate), poly(hydroxyethylmethacrylate), polyvinyl acetates polyacetates, polyesters, polyamides, polycarbonates, polyanhydrides, polyamino acids, such as but not limited to poly(N-vinyl pyrrolidinone), polyvinyl actetate), polyvinyl alcohol, poly(hydroxypropyl methacrylamide), poly(caprolactone), poly(dioxanone) polyglycolic acid, polylactic acid, copolymers of lactic and glycolic acids, and polytrimethylene carbonates, poly(butadiene), polystyrene, polyacrylonitrile, poly(chloroprene), neoprene, poly(isobutene), poly(isoprene), polypropylene, polytetrafluoroethylene, poly(vinylidene fluoride), poly(chlorotrifluoroethylene), poly(vinyl chloride), poly(oxymethylene), poly(ethylene terephthalate), poly(oxyethylene) poly(oxyterephthaloyl), polyamides such as but not limited to, poly[imino(l-oxohexamethylene)], poly(iminoadipoyl-iminohexamethalene), poly(iminohexamethylene-iminosebacoyl), poly[imino(l-oxododecamethylene)], cellulose, polysulfones, hyalonic acid, sodium hyaluronate, alginate, agarose, chitosan, chitin, or a mixture thereof.

According to a further embodiment of the present invention, the method includes physically or chemically modifying the inner surface of a mold upon which preselected morphologies are induced into the wall of the said product by inducing beading or spreading of the separated liquid phase.

According to one aspect, the mold can be glass, plastic, or metal. For example, the plastic mold may be PTFE, PP, HDPE, or PE. A glass mold may be treated with an agent to modify surface tension. Such treatment may occur before step (a). In one embodiment, such agent to modify surface tension is selected from the group consisting of surfactant compounds,

polymer surfactants, and silinating agents. Examples of silinating agents according to the invention include (organo)x-Si-Yz, where 'organo' is a substituent of silicon = Cl-18, linear, cyclic or branched chain, aliphatic or aromatic, eventually substituted; x=l-3; Y=alcoxy, chloro, imidazole, labile amino group, isoprenoxy; z=l-3; and x+z = 4, such as trimethyl chlorosilane, triethylchlorosilane, dimethyldichlorosilane, dimethyl-dimethoxysilane, trimethylmethoxysilane, and trimethylethoxysilane. In another embodiment, the mold surface is pretreated with Teflon or an other fluorinated polymer surface. In a further embodiment, this polymer treatment is attached to the mold surface, such as a plastic sleeve of PTFE, PP or PE which is placed in the interior of the mold, into which the polymerization mixture is added for making the device.

In a further aspect of the present invention, the method includes the step of removing the solvent and including repeating steps a), b) and c), at least once to produce a multi-layered product.

In yet a further aspect of the present invention, the polymer is a copolymer composed of hydroxyethyl-methacrylate and methyl-methacrylate, with a multiacrylate crosslinker, examples include ethyleneglycol dimethylacrylate, propylene glycol dimethacrylate, trimethylopropane trimethacrylate.

In one aspect, the polymer is a copolymer composed of hydroxyethyl-methacrylate and hydroxypropyl-methacrylate, with a multiacrylate crosslinker.

In one embodiment of the present invention, the device is between 10% and 90% compound, for example, between 20% and 80% compound, or more than 5% compound.

In a further embodiment, the polymer is a copolymer composed of hydroxymethacrylate and methylmethacrylate, with a multiacrylate

crosslinker, examples include ethyleneglycol dimethylacrylate, propylene glycol dimethacrylate, trimethylopropane trimethacrylate.

In yet a further embodiment, the polymer is a copolymer composed of hydroxymethacrylate and hydroxypropylmethacrylate, with a multiacrylate crosslinker.

In yet a further embodiment, the device is between 10% and 60% HPMA (w/w).

In yet a further embodiment, the device is between 2% and 40% MMA (w/w).

In yet a further embodiment, the product is greater than 5% (w/w) compound.

Yet a further aspect of the present invention is the use of the implantable device described herein, or made as described herein, for weight loss, reduced food intake, improving cardiovascular risk factors (lipids, free fatty acids, cholesterol), reduction of blood glucose levels, or treatment of diabetes.

In yet a further aspect of the present invention, the implantable device described herein, or made as described herein, can be used for the mitigation of a side effect resulting from treatment with a therapeutic selected from the group consisting of GLP-I, an analog of GLP-I, and a derivative of GLP-I. The side effect, in certain embodiments, may be emesis, sudden weight loss, or nausea.

In yet a further aspect of the present invention is a method of treatment of obesity, high blood sugar, or diabetes, comprising implantation of an implantable device as described herein or made as described herein in an animal (such as a human) suffering from said disease state.

In one embodiment, the implantation is a subcutaneous implantation.

In a different embodiment, the implantation is a subdermal implantation.

The device may be explantable, or biodegradable.

In one embodiment, the device has a hydrogel or xerogel reservoir with an equilibrium water content of between 10 and 60 %, for example, between 20 and 40%, or about 30%.

Brief description of the figures

Figure 1 describes the peptide sequences of 5 GLP-I analogs.

Figure 2 shows Scanning Electron Microscope images of a HEMA-MMA hydrogel tube made according to the method of Example 3.

Figure 3 shows Scanning Electron Microscope images of HEMA-HPMA Hydrogel tubes made according to the method of Example 2.

Detailed Description

It has been surprisingly found that a xerogel-hydrogel depot: delivery system can be used to deliver GLP-I, GLP-I analogs and GLP-I derivatives, at therapeutic dosages, over extended periods of time. From this, it can be shown that xerogel-hydrogel depot systems can surprisingly be used to deliver GLP-I, GLP-I analogs and GLP-I derivatives, in a manner that diverges significantly and advantageously from the known, attempted, and utilized methods of delivery of these peptides.

It has also surprisingly been found that controlled delivery of GLP-I, GLP-I analogs and GLP-I derivatives, in a subcutaneous implant depot can effectively provide the beneficial effects of the GLP-I, GLP-I analog, or GLP-I derivative, over an extended period of time, for example, more than 20 days. Such beneficial effects include weight loss (or reduced weight gain), and appetite control, and likely also include the other beneficial effects of delivery of these peptides, such as increased insulin sensitivity and diabetes control.

It has also been surprisingly found that delivery of GLP-I, GLP-I analogs, GLP-I agonists and GLP-I derivatives delivered in a continuous stream (through a drug delivery system like a xerogel-hydrogel depot), at a specific plasma concentration, provides additional advantages of a significant decrease in the side effects normally found when administering GLP-I or its analogs or derivatives.

"GLP-I" means, alternatively, a GLP-I (7-36) having the sequence of SEQ ID NO: 1 or GLP-I (7-35) having the sequence of SEQ ID NO: 2.

A "GLP-I analog" means a compound having biological activity of and structure similar to GLP-I. The term GLP-I analog includes GLP-I receptor agonists. Numerous GLP-I analogs are known in the art. These analogs include, for example, GLP-I (7-36), GLP-I (7-37)01-1, GLP-I (7-36)NG2, Gln9-GLP-l(7-37), D-Gln9-GLP-l(7-37), acetyl-Lys9-GLP-l(7-37), Thrl6-Lysl8-GLP-l(7-37), Lysl8-GLP-l(7-37), the peptide sequence of SEQ ID NO. 4, and the peptide sequence of SEQ ID NO. 5 (Fig. 1). GLP-I analogs may also include derivatives (vida infra for definition of derivatives). GLP-I analogs can be obtained via chemical synthesis, through biochemical synthesis (or molecular biological methods using microorganisms) methods known in the art. GLP-I analogs include GLP-I receptor agonist peptides with as little as 49% of sequence identity relative to native GLP-I, with a variety of substitutions of individual amino acids within the sequence, using either alternative natural amino acids, D-amino acids, non-natural (synthetic) amino acids. The agonists can be natural molecules, such as Exendin, or chemical

analogs made either by chemical synthesis or biosynthesis using molecular biology techniques

"GLP-I agonist" is a compound that binds to GLP-I receptor. Exendin (described in SEQ ID No. 3, Fig. 1) is a GLP-I agonist.

A "GLP-I derivative" is a peptide sequence that has been derived from GLP-I or a GLP-I analog, but has been modified in some way. GLP-I derivatives include, for example, peptides based on GLP-I but having amino acid substitutions, additions or deletions, made with the intention of improving solubility (for example, replacing hydrophobic amino acids with hydrophilic amino acids, or PEGylation of terminal carboxyl groups or the E-amino group of lysine), conferring resistance to oxidation (for example, substitution of Met, Trp, GIn, or Asn), increasing biological potency (for example, one or more amino acid substitutions at positions 11, 12, 16, 22, 23, 24, 25, 27, 30, 33, 34, 35, 36 or 37), increasing half-life in circulation (acyl (cl2-C18) modifications of the E-amino group of lysine), or for some other desired effect. GLP-I derivatives also include acid addition salts, base addition salts, carboxylate salts, lower alkyl esters, and amides of GLP-I and analogs, as well as GLP-I and analogs that have been modified at the N-terminal histidine residue, for example, by alkyl or acyl (C1-C20) groups, substituted and unsubstituted C5-C6 ring structures, etc. Salt forms of GLP-I and analogs are also contemplated as GLP-I derivatives, which may be sufficiently acidic or sufficiently basic to react with any number of organic and inorganic bases, and organic and inorganic acids, to form a salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate,

caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, ethansulfonic, benzenesulfonic, quinic, propanesulfonate, naphthalene-1-sulfonate, naphtalene-2-sulfonate, mandelate, cycohexylsulfamic, and the like. Preferred acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, or simple organic acids, such as acetic. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases, useful in preparing the salts with ions such as sodium, potassium, ammonium, substituted organo-ammonium ions, such as tetramethylammonium, trimethylammonium, trimethylbenzylammonium, and the like. Salt forms of GLP-I analogs are particularly preferred. The salt used must be a pharmaceutically acceptable salt. In addition, the compounds are useful in free acid or free base forms. In practice, acetic acid addition salts are preferred, but not limited, due to favorable stability and solubility.

The active ingredient of the present invention may be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Various excipients may be homogeneously mixed with peptide of the present invention as would be known to those skilled in the art. For example, the peptide may be mixed or combined with excipients such as but not limited to microcrystalline cellulose, colloidal silicon dioxide, lactose, starch, sorbitol, cyclodextrin and combinations of these. The excipient, which may be a solid, semi-solid *or* liquid material which acts as a vehicle, carrier, or medium for the active ingredient. The active ingredient can equally be compressed, compacted or extruded with various excipients, designated below as non-limitative examples, prior to inserting it into the hydrogel tube. These

different formulation aspects constitute a pharmaceutical composition with properties that give desirable release properties, improved stability or facilitate manufacturing of the combination device (tube ÷active ingredient), or otherwise confer desirable properties to the system.

The pharmaceutical composition of the present invention can include also auxiliary agents or excipients, for example, glidants, dissolution agents, surfactants, diluents, binders including low temperature melting binders, disintegrants and/or lubricants. Dissolution agents increase the dissolution rate of the GLP-I, analog or derivative from the dosage formulation and can function by increasing the solubility of the GLP-I, analog or derivative. Suitable dissolution agents include, for example, organic acids such as citric acid, fumaric acid, tartaric acid, succinic acid, ascorbic acid, acetic acid, malic acid, glutaric acid and adipic acid, and may be used alone or in combination. These agents may also be combined with salts of the acids, e.g. sodium citrate with citric acid, in order to produce a buffer system.

Examples of suitable excipients include synthetic, semi-synthetic, modified and natural polymers. Excipients useful in the present invention include but are not limited to, lactose, dextrose, sucrose, trehalose, sorbitol, mannitol, starches, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, PEG, cyclodextrin, alkoxy-modified cyclodextrins, hydroxyethylcellulose, hydroxypropylcellulose, microcrystalline cellulose, albumin, dextran, malitol, xylitol, kaolin, and methyl cellulose. The active ingredient can also be mixed with lubricating agents, such as talc, magnesium stearate, stearic acid and mineral oil; wetting agents, emulsifying and suspending agents, or preserving agents such as methyl and propylhydroxybenzoates.

Other agents can be added to the pharmaceutical composition that may alter the pH of the microenvironment on dissolution and establishment of a therapeutically effective plasma concentration profile of peptide include salts of inorganic acids and magnesium hydroxide. Other agents that may be used

are surfactants and other solubilizing materials. Surfactants that are suitable for use in the pharmaceutical composition of the present invention include, for example, sodium lauryl sulphate, polyethylene stearates, polyethylene sorbitan fatty acid esters, polyoxyethylene castor oil derivatives, polyoxyethylene alkyl ethers, benzyl benzoate, cetrimide, cetyl alcohol, docusate sodium, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, lecithin, medium chain triglycerides, monoethanolamine, oleic acid, poloxamers, polyvinyl alcohol and sorbitan fatty acid esters.

Diluents that are suitable for use in the pharmaceutical composition of the present invention include, for example, pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, sucrose, fructose, glucose dextrose, or other sugars, dibasic calcium phosphate, calcium sulfate, cellulose, ethylcellulose, cellulose derivatives, kaolin, mannitol, lactitol, maltitol, xylitol, sorbitol, or other sugar alcohols, dry starch, saccharides, dextrin, maltodextrin or other polysaccharides, inositol or mixtures thereof. The diluent is preferably a water-soluble diluent. Examples of preferred diluents include, for example: microcrystalline cellulose such as Avicel PH112, Avicel PHlOl and Avicel PH102 available from FMC Corporation; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose DCL 21; dibasic calcium phosphate such as Emcompress available from Penwest Pharmaceuticals; mannitol; starch; sorbitol; sucrose; and glucose. Diluents are carefully selected to match the specific composition with attention paid to the compression properties. The diluent is preferably used in an amount of about 2% to about 80% by weight, preferably about 20% to about 50% by weight, of the controlled release composition.

Glidants are used to improve the flow and compressibility of ingredients during processing. Suitable glidants include, for example, colloidal silicon dioxide, a sub-micron fumed silica that can be prepared by, for example, vapor-phase hydrolysis of a silicon compound such as silicon tetrachloride. Colloidal silicon dioxide is a sub-micron amorphous powder which is commercially available from a number of sources, including Cabot Corporation

(under the tradename Cab-O-Sil); Degussa, Inc. (under the tradename Aerosil); and E.I. DuPont & Co. Colloidal silicon dioxide is also known as colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, and silicon dioxide fumed, among others. In one embodiment, the glidant comprises Aerosil 200.

Another agent that may be used is a surfactant, dissolution agent and other solubilizing material. Surfactants that are suitable for use in the pharmaceutical composition of the present invention include, for example, sodium lauryl sulphate, polyethylene stearates, polyethylene sorbitan fatty acid esters, polyoxyethylene castor oil derivatives, polyoxyethylene alkyl ethers, benzyl benzoate, cetrimide, cetyl alcohol, docusate sodium,, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, lecithin, medium chain triglycerides, monoethanolamine, oleic acid, poloxarners, polyvinyl alcohol and sorbitan fatty acid esters. Dissolution agents increase the dissolution rate of the GLP-I, analog or derivative and function by increasing the solubility of the GLP-I, analog or derivative. Suitable dissolution agents include, for example, organic acids such as citric acid, fumaric acid, tartaric acid, succinic acid, ascorbic acid, acetic acid, malic acid, glutaric acid and adipic acid, which may be used alone or in combination. These agents may also be combined with salts of the acids, e.g. sodium citrate with citric acid, in order to produce a buffer system. Other agents that may be used to alter the pH of the microenvironment on dissolution include salts of inorganic acids and magnesium hydroxide.

Disintegrants that are suitable for use in the pharmaceutical composition of the present invention include, for example, starches, sodium starch glycolate, crospovidone, croscarmellose, microcrystalline cellulose, low substituted hydroxypropyl cellulose, pectins, potassium methacrylate-divinylbenzene copolymer, polyvinyl alcohol), thylamide, sodium bicarbonate, sodium carbonate, starch derivatives, dextrin, beta cyclodextrin, dextrin derivatives, magnesium oxide, clays, bentonite and mixtures thereof.

Lubricants that are suitable for use in the pharmaceutical composition of the present invention include agents that act on the flowability of the powder to be compressed include but are not limited to silicon dioxide such as Aerosil 200, talc; stearic acid, magnesium stearate, calcium stearate, hydrogenated vegetable oils, sodium benzoate, sodium chloride, leucine carbowax, magnesium lauryl sulfate, and glyceryl monostearate.

The delivery device according to one embodiment of the invention is a xerogel-hydrogel system which can release peptides in a continuous sustained manner over extended periods of time, as described in US 5,226,325, CA 2515919 and WO2004/071736. One embodiment of the device uses the system described in WO 2004/071736.

Liquid polymerizable material useful in the preparation of the hydrogel tube include a wide variety of polymerizable hydrophilic, ethylenically unsaturated compounds, in particular, hydrophilic monomers such as the monoester of an acrylic acid or methacrylic acid with a polyhydroxy compound having an esterifiable hydroxyl group and at least one additional hydroxyl group such as the monoalkylene and polyalkylene polyols of methacrylic acid and acrylic acid, e.g., 2-hydroxyethyl methacrylate and acrylate, diethylene glycol methacrylate and acrylate, propylene glycol methacrylate and acrylate, dipropylene glycol methacrylate and acrylate, glycidyl methacrylate and acrylate, glyceryl methacrylate and acrylate, and the like; the 2-alkenamides, e.g., acrylamide, methacrylamide, and the like; the N-alkyl and N,N-dialkyl substituted acrylamides and methacrylamides such as N-methylmethacrylamide, N,N-dimethylmethacrylamide, and the like; N-vinylpyrrolidone; the alkyl-substituted N-vinylpyrrolidones, e.g., methyl substituted N-vinylpyrrolidone; N-vinylcaprolactam; the alkyl-substituted N-vinylcaprolactam, e.g., N-vinyl-2-methylcaprolactam, N-vinyl-3,5-dimethylcaprolactam, and the like. Acrylic and methacrylic acid can also be useful in these formulations.

Mixtures of hydrophilic monomers are employed in the polymerization reaction. The type and proportion of monomers are selected to yield a polymer, preferably a crosslinked homogeneous polymer, which on hydration possesses the desired EWC value, pore size, or characteristicsfor the contemplated application or use. This EWC value can be predetermined by preparing a series of copolymers using different monomer ratios, e.g., mixtures of HEMA and HPMA of varying ratios, ascertaining the EWC values of the copolymers, and plotting the relationship of % HPMA (or % HEMA) units in the HPMA/HEMA copolymers versus weight percent EWC of the copolymers.

In some instances the polymerization of certain hydrophilic monomeric mixtures may result in homogeneous hydrophilic copolymers which dissolve, to a varying extent, in an aqueous medium. In such cases, a small amount, e.g., up to 3 percent, of a copolymerizable polyethylenically unsaturated crosslinking agent can be included in the monomeric mixture to obtain homogeneous crosslinked copolymers which are water-insoluble as well as water-swellable. Slightly crosslinked homopolymer of HEMA has a EWC value of about 38%. Crosslinked copolymers of HEMA and HPMA have EWC values below 38%. On the other hand, crosslinked copolymers of HEMA and acrylamide exhibit EWC values above 38 w/v %, e.g., upwards to approximately 75 weight %, and higher. Therefore, depending on the useful or effective elution rate of the active compound, e.g., drug, that is required of a hydrogel delivery system for a particular application, one skilled in the art, by following the teachings disclosed herein, can tailor-make copolymer hydrogel membranes which will elute the drug at the required rate. Preferred copolymers contain about 15% to about 70 weight % of HEMA units and from about 85 to 30 weight % of units of a second ethylenic monomer and possess predetermined EWC values in the range of from about 20% to about 75%, preferably about 25%. Highly preferred homogenous copolymers are those made from hydrophilic monomeric mixtures containing from about: 80 weight % HPMA, and from about 20 weight % HEMA. In further embodiments, the mixture may further contain a small amount of a polyethylenically

unsaturated crosslinking agent, e.g., ethyleneglycol dimethacrylate ("EDMA") or trimethylolpropane trimethacrylate ("TMPTMA").

Various aspects of the invention include hydrophilic copolymers whose homogeneous polymer structure is formed via the polymerization of a mixture of hydrophilic monomers described previously; and the drug delivery device which utilize the homogeneous polymer cartridges in the delivery system. The polymerization of a mixture of hydrophilic monomers and hydrophobic monomers yields heterogeneous polymers. When hydrophobic segments are present in the polymer, the interfacial free energy increases, thus enhancing protein adsorption and mineralization after implantation in an animal. Hydrogels of polyHEMA were measured to have interfacial free energy close to zero. According to the interfacial free energy interpretation, hydrogels of strictly hydrophilic components would strongly appear to be biocompatible with body tissue. Slightly crosslinked polyHEMA is a homogeneous, hydrophilic "homopolymer" (disregarding the relatively small quantities of polymerized crosslinking agent therein) of relatively fixed characteristics or values. Techniques of altering the "homopolymer" polyHEMA to impart to it additional characteristics or properties are difficult, time-consuming, and oftentimes result in erratic property behavior. On the other hand, mixtures of HEMA with varying quantities of other polymerizable hydrophilic comonomer(s) can be polymerized to give predictable homogeneous hydrophilic copolymers having (predetermined) tailor-made properties.

Useful crosslinking agents which can be included in the polymerizable reaction medium include, for example, the polyethylenically unsaturated compounds having at least two polymerizable ethylenic sites, such as the di-, tri- and tetra-ethylenically unsaturated compounds, in particular, the tri-unsaturated crosslinking agents with/without the di-unsaturated crosslinking compounds, for example, divinylbenzene, ethylene glycol dimethacrylate and diacrylate, propylene glycol dimethacrylate and diacrylate; and the di-, tri- and tetra-acrylate or methacrylate esters of the following polyols:

triethanolamine, glycerol, pentaerythritol, 1,1,1-trimethylolpropane and others.

The polymerization reaction can be carried out in bulk or with an inert solvent. Suitable solvents include water; organic solvents such as water-soluble lower aliphatic monohydric alcohols as well as polyhydric alcohols, e.g., glycol, glycerine, dioxane, etc.; and mixtures thereof.

Compounds useful in the catalysis of the polymerizable ethylenically unsaturated compounds include the free-radical compounds and/or initiators of the type commonly used in vinyl polymerization such as the organic peroxides, percarbonates, hydrogen peroxides, and alkali metal sulfates. Illustrative examples include cumene hydroperoxide, t-butyl hydroperoxide, benzoyl peroxide, bis(4-t-butylcyclohexyl) peroxydicarbonate, hydrogen peroxide, 2,4-dichlorobenzoyl peroxide, acetyl peroxide, di-n-propyl peroxydicarbonate, di-t-butyl peroxide, di-sec-butyl peroxydicarbonate, ammonium sulfate, potassium sulfate, and sodium sulfate. A preferred catalyst is one which is effective at moderately low temperature such as at about 2O0-8O0C, such as tert-butyl peroctoate, benzoyl peroxide, and di(secbutyl) peroxydicarbonate. A conventional redox polymerization catalyst can also be employed. Preferably, polymerization of the ethylenic compounds can be effected using radiation, e.g., U.V., X-Ray, gamma radiation, microwave, or other well-know forms of radiation. A preferred catalyst for U.V. cure is benzoin methyl ether. Catalysts and/or initiators and/or radiation are employed in a catalytically effective amount to optimize the polymerization reaction.

One of the objectives of the device described herein is to reduce the time of hydration and onset of release from a xerogel to < 10days. The ability to use a xerogel in a surgical procedure is an advantage in that the xerogel is a form which is stiff and therefore more easily manipulated and implanted during the procedure. Shortly after implantation, the rapidly hydrating gel,

softens and becomes comfortable and then in only a couple of days begins release of the therapeutic.

Obtaining controlled release over a duration of >20 days and, outward to 3month or more may require a significant loading of peptide. High loading is achieved in the present invention by using sealed-tube geometry wherein powdered, compacted or otherwise formulated drug and eventual excipients are contained. This reservoir type system is particularly attractive since large loadings, > 10% and more, can be obtained. High loading is achieved without having significant fraction of the drug, peptide or protein found on the surface of the device where it can act immediately upon implantation. Furthermore, as processing of the tube is performed independently of drug incorporation, the peptide or protein load is not subjected to chemical stress caused by surfactants, emulsifying agents, heat, monomers, radical initiators, or other potentially denaturing conditions that can lead to chemical or structural modifications of the peptide or protein to be incorporated.

In one embodiment, the hydrophilic implant as a xerogel, readily absorbs water. In a hydrated state it is referred to as a hydrogel. In either form, it is biocompatible and non-toxic to the host and non-biodegradable. It is, of course, water-swellable and water-insoluble. When the hydrogel attains its maximum level of hydration, the water content of the hydrogel is referred to as "equilibrium water content".

Attaining a more desirable release profile can be obtained by using a xerogel implant device that attains near zero-order release only after an initial period of hydration. Therapeutic levels are achieved by solubilization and diffusion of the drug through the rate-limiting membrane which serves as tailorable diffusion barrier, and this occurs only over a period of days, allowing the organism to adjust to the dose and minimizing adverse events and side-effects. This invention seeks to obtain a PK profile that allows a slower onset of action than was previously practiced in prior art.

Surprisingly, we have found that gamma irradiation of the hydrogel provides changes in the hydrogel dynamics (likely to the three dimensional structure of the hydrogel itself) that are advantageous for release of GLP-I. Specifically, we have found that, for certain hydrogel formulations, gamma irradiation of the hydrogel creates structural changes in the hydrogel that allow release of the GLP-I from the hydrogel where the GLP-I would not otherwise be released in substantial quantities.

Examples

Example 1. Preparation of 10% MMA-HEMA depot

A xerogel-hydrogel tube was prepared according to a method based on that described in PCT publication WO2004/071736, which is incorporated herein by reference. Briefly, a solution of 0.21ml methylmethacrylate (MMA), 1.69ml hydroexyethylmethacrylate (HEMA), 0.002ml ethyleneglycol-dimethacrylate, 0.38ml ethyleneglycol, 3.52 water, 8mg metabisulFite and llmg persulfate was poured into a 9 cm section of hollow glass tube pretreated with aminoethyldimethyl-chloro-silane, having an internal diameter of 2.3mm and capped with septa. The solution was loaded to fill the tube completely. The tube, containing the solution, was placed in the chuck of a drill and spun along the major axis at a speed of 5000 cycles per second, as polymerization took place (approximately 180 minutes). After polymerization was complete, the drill was stopped, the septa removed and the newly formed polymer tube was removed from the glass tube. The polymer tube was placed in water for 24h, then dried.

Example 2. Preparation of 30% HPMA-HEMA depot

A xerogel-hydrogel tube was prepared according to the method based on that described in PCT publication WO2004/071736, which is incorporated herein by reference. Briefly, a monomer solution composed of 0.57ml hydroxypropylmethacrylate, 1.35ml hydroexyethylmethacrylate, 0.0027ml

ethyleneglycoldimethacrylate, 3.7ml water, and O.llmg metabisulfite and 8mg persulfate was poured into a 9cm section of hollow glass tube pretreated with aminoethyldimethyl-chloro-silane, having an internal diameter of 2.3mm and capped with septa. The solution was loaded to fill the glass tube completely. The tube, containing the solution, was placed in the chuck of a drill, and spun along the major axis at a speed of 5000 cycles per second, as polymerization took place (approximately 180 minutes). After polymerization was complete, the drill was stopped, the septa removed and the newly formed polymer tube was removed from the glass tube. The polymer tube was placed in water for 24h, then dried.

Example 3. Preparation of MMA-HEMA and HPMA-HEMA depots of varied polymer ratios

Xerogel-hydrogel tubes were prepared according to the methods described in Examples 1 and 2, but with varied MMA/HEMA and HPMA/HEMA ratios. Tubes were constructed with 5, 7, 10, 14, 18% MMA, and 20, 25, 30, 34, 37, 40, 60% HPMA, using the table of reagents given below (Tables 1 and 2). SEM images of samples from MMA series 5, 10 and 14% MMA tubes were shown in Figure 2. SEM images of cross sections of the HPMA tubes were shown in Figure 3.

Table 1: Table of Reagents: MMA/HEMA tubes

	Amounts of reagents						
%MMA	HEMA ul	MMA ul	EDMA ul	EG ul	Water ul	APS* ul	SMBS* ul
5	1792.7	107.4	1.9	0.0	3895.0	95.0	76.0
7	1749.9	150.1	1.9	0.0	3895.0	95.0	76.0
10	1691.0	213.8	1.9	380.0	3515.0	95.0	76.0
14	1615.0	304.0	1.9	570.0	3325.0	95.0	76.0
18	1520.0	380.0	1.9	1045.0	2850.0	95.0	76.0

*10 wt% solution

Table 2: Table of reagents: HPMA/HEMA tubes

	Amounts of reagents						
%HPMA	HEMA	HPMA	EDMA	EG	Water	APS*	SMBS*
16	1463.0	275.5	1.0	0.0	4075.5	95.0	76.0
30	1349.0	570.0	2.7	190.0	3705.0	95.0	76.0
40	1154.3	764.8	2.7	380.0	3515.0	95.0	76.0
50	961.4	957.6	2.7	380.0	3515.0	95.0	76.0
60	769.5	1149.5	2.7	380.0	3515.0	95.0	76.0

*10 wt% solution

Example 4 - Preparation of GLP-I analog-filled depot

Tubes were prepared utilizing the methods of Examples 1 and 2. The tubes were filled with a powder or lightly compressed powder form of exenatide acetate, a GLP-I analog. The filled tubes, were sealed by injecting RTV 2-component silicone into the two open ends, followed by hardening for 2 h then curing for 24h. The filled, sealed tubes resembled a rod shaped pellet.

Example 5. Release of exenatide from xerogel depot

Tubes from Example 1 were loaded with exenatide acetate according to the method of Example 4. The drug-loaded tubes were shaken in 1 ml of PBS buffer (approximating physiological conditions) heated to and maintained at 40^{0}C. Weekly, the sample device was removed from the buffer solution, which was kept for analysis of peptide concentration, and the device was placed in fresh buffer for continuation of the release. The release buffer was analyzed for peptide content using a microBCA peptide/protein assay kit (Pierce) From the peptide content measurements, daily release rate data was determined and this value was divided by the length of active tube surface. These release values of exenatide from the depot are tabulated in Table 3, below.

Days	ug/cm/day released
0	0
4	0.9
8	1.1
12	0.7
15	0.5
18	1.3
21	1.4
25	1.4
28	1.5
32	2.5
35	1.6
39	0.6
42	1.9
46	0.2
50	1.3
54	0.2
57	0.6
60	0.5

63	0.9
67	0.6
70	0.8
74	1.0
77	1.4
81	0.6
84	0.7
90	0.4
95	0.5

TABLE 3: RELEASE OF EXENATIDE FROM DEPOT AT APPROXIMATELY PHYSIOLOGICAL CONDITIONS

Example 6. Release rates of various GLP-I analogs from xerogel depots of varying compositions

Tubes were made using the methods of Example 2 and 3.

The tubes were filled with a GLP-I analog and sealed utilizing the methods described in Example 4. The release rates for the drug loaded depots were measured utilizing the method of Example 5. Average daily release rates, after the initial ramp up period, averaged over a period of 90 days, were tabulated in Table 4, shown below. Release rates obtained were typically between 0.lug/day and 200ug/day. Onset to release from the hydrogel also varied based on the tube composition and the peptide loaded, and was due to the physical characteristics of the hydration of the depots of varying composition, and/or a range of other possible factors.

Peptide	**Tube composition** % HPMA or MMA	**Onset** d	**Average daily release rate** As a function of active tube length (tube diameter 2.3mm) ug/d/cm tube
Exenatide	10% MMA 90% HEMA	7	1
Exenatide	30% HPMA 70% HEMA	<7	20
SEQ ID NO 4	30% HPMA 70% HEMA	10	2
SEQ ID NO 5	30% HPMA 70% HEMA	14	1

TABLE 4 - AVERAGE DAILY RELEASE RATES OVER 90 DAYS FOR GLP-I ANALOG LOADED DEPOTS

Example 7. Release rate of a GLP-I analog from xerogel depots of varying compositions

Tubes are made using the methods of Example 2 and 3.

The tubes are filled with a GLP-I analog and sealed utilizing the methods described in Example 4. The release rates for the drug loaded depots are measured utilizing the method of Example 5. Average daily release rates, over a period of 90 days, are tabulated in Table 5, shown below. Release rates are typically between 0.lug/day and 200ug/day. Onset to release from the hydrogel varies based on the tube composition and the peptide loaded, and is due to the physical characteristics of the hydration of the depots of varying composition, and/or a range of other possible factors.

Peptide	**Tube composition** % HPMA or MMA	**Onset** d	**Average daily release rate** As a function of active tube length (tube diameter 2.3mm) ug/d/cm tube
Liraglutide	10% MMA 90% HEMA	7	0.4
Liraglutide	30% HPMA 70% HEMA	<7	8
SEQ ID NO 6	30% HPMA 70% HEMA	4	2
SEQ ID NO 7	30% HPMA 70% HEMA	4	4

TABLE 5 - AVERAGE DAILY RELEASE RATES OVER 90 DAYS FOR GLP-I ANALOG LOADED DEPOTS

Example 8 - Effect of irradiation on release of GLP-I from hydrogel tubes

Dried tubes of varying compositions were prepared according to Examples 2 and 3. A GLP-I analog filled depot was prepared according to Example 4 into dry tubes, which were packed with peptide powder and sealed with silicone sealant at both ends. The GLP-I analog-filled dry xerogel depot was placed in an Eppendorf, degassed with argon and closed. The eppendorf package, containinf the peptide-loaded depot was irradiated with inside a Cobalt-sourced gamma irradiation chamber to a dose of 2.5 MRad or 5.0 MRad gamma radiation (see table for details).

Release of the GLP-I analog was affected by utilizing the method of Example 5. Steady-state daily release rate values were obtained by averaging Day 14-Day 30. The average release value does not include rate values obtained during the initial ramp-in period (typically Day 0 to Day 14).

Release rates were tabulated in Table 6, below.

Table 6

Irradiation Dose (MRad)	Release Rate (ug/d/cm)	
	30% HPMA	40% HPMA
0	0-0.2	0-0.2
2.5	7	13
5.0	15	20

Irradiation enabled release of GLP-I analog from the hydrogel tube.

Example 9 - Demonstration of speed to hydration rate from xerogel utilizing thermogravimetric analysis

In order to determine the speed to hydration for the xerogel tube, 1-2mm sections of tubes prepared according to Example 1 were placed in PBS buffer, then removed at designated times and measured for water content utilizing thermogravimetric analysis, using a heating program up to 120oC over a period of 15min. To calculate percent water content (%WC), weight loss was divided by final weight.

Percentage of water content was shown in Table 7, below.

hours	%WC
0	4
0.5	6
1	8
1.5	12
2	16
3	18
4	21
6	24
12	26
24	28
After 1 week EWC	30

TABLE 7 - SPEED TO HYDRATION FROM XEROGEL

It was therefore determined that the tubes were >90% hydrated in 24 hours, and that the 10% MMA-HEMA tubes had an EWC of about 30%.

Example 10 - In-vivo release of Exenatide from tubes, weight loss and glucose measurements.

Tubes of 2 cm in length were prepared according to the method of Example 2. The tubes were loaded with a lyophilized powder of exenatide, a GLP-I analog, to lOmg of exenatide powder per 2cm length of tube. The tubes were sealed with Silicone RTV utilizing the method of Example 4 and sterilized by 2.5 MRad gamma irradiation.

Ninety day old Sprague-Dawley rats, fed ad libitum were used to determine whether the depots could affect appetite suppression, manifested by decreased rate of weight gain relative to controls.

The treated group was implanted with the exenatide depots (2 tubes per animal, for a total of 4 cm of tube, or 20 mg of exenatide), and weight gain was compared to control (age-matched, sham implanted male Sprague-Dawley Rat).

Animal was recorded by periodic weighing over a period of 5 months. Serum levels of exenatide were also measured by Enzyme Immuno Assay for the treated group. The treated group achieved steady-state plasma concentration of nearly 0.6-0.8 ng/ml of exenatide by Day 8. The plasma concentration was maintained at that level for a period of 148 days. Deviation in weight gain (as compared to control) was noticeable from week 6 onward, and a lean weight mass (as defined by 10-20% below controls) was attained by day 54 (approximately). Results are summarized in Table 8 shown below.

Days	Serum Exenatide ng/ml	Treated Animal weight g	Control Animal weight g
10	0.7227	435	454
25	0.6206	465	509
37	0.6747	501	540
53	0.6427	535	582
67	0.6576	544	606
81	0.7145	577	634
95	0.7046	595	663
102	0.5694	613	674
109	0.59	613	683
116	nd	615	718
123	nd	619	732
130	nd	634	764
144	nd	635	771

Table 8 - SERUM EXENATIDE AND WEIGHT GAIN OVER TIME (nd=not determined)

To complement weight change data, glucose measurements were made using a standard glucose meter on treated and control animals At 110 days post implantation, control SD rats have an average fasting glucose level of 8.3mM (n=8), while the treated group's level is 7.OmM (N=4). Repeated at 150days post-implantation, the levels are 8.0 and 6.9, respectively, for the same set of control and treated animals, thus demonstrating the continued glucose-lowering effects of the GLP-I analog 150 days after implantation.

The preceding examples are meant to exemplify the preferred embodiments of the present invention, and are not meant to limit the scope of the invention. All references cited herein are hereby incorporated by reference.

I claim :

1. An implantable device for the administration of a compound selected from a group consisting of GLP-I, an analog of GLP-I and a derivative of GLP-I, comprising (1) a hydrogel or xerogel reservoir and (2) the compound, wherein the reservoir encases the compound.

2. The implantable device of claim 1 wherein the hydrogel or xerogel reservoir comprises a MMA/HEMA polymer.

3. The implantable device of claim 2 wherein the MMA/HEMA polymer comprises 2 - 40% MMA (w/w).

4. The implantable device of claim 2 wherein the MMA/HEMA polymer comprises 5 - 15% MMA (w/w).

5. The implantable device of claim 2 wherein the MMA/HEMA polymer comprises about 10% MMA (w/w).

6. The implantable device of claim 1 wherein the hydrogel or xerogel reservoir comprises a HPMA/HEMA polymer.

7. The implantable device of claim 6 wherein the HPMA/HEMA polymer comprises 10-60% HPMA.

8. The implantable device of claim 7 wherein the HPMA/HEMA polymer comprises 20-40% HPMA.

9. The implantable device of claim 6 wherein the HPMA/HEMA polymer comprises about 30% HPMA.

10. The implantable device of any one of claims 1-9, wherein said device is prepared such that, when implanted in an animal, provides an therapeutic

serum concentration effective for a desired effect selected from the group consisting of treatment of diabetes, lowering of blood glucose levels, and weight loss, reduced food intake, improved cardiovascular risk factors, improved HDL/LDL ratios, lower cholesterol, for a therapeutic time frame starting between 0 and 20 days post-implantation and comprising between 10 and 365 days.

11. The implantable device of claim 10 wherein the compound is exenatide (SEQ ID 3).

12. The implantable device of claim 11 wherein therapeutic serum concentration is between 0.01 and 10 ng/ml of exenatide.

13. The implantable device of any one of claims 11 and 12 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of exenatide.

14. The implantable device of claim 13 wherein the device is a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 rng of exenatide, preferably about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of exenatide.

15. The implantable device of claim 10 wherein the compound is liraglutide.

16. The implantable device of claim 15 wherein the therapeutic serum concentration is between 0.01 and 10 ng/ml of the liraglutide.

17. The implantable device of any one of claims 15 and 16 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of liraglutide.

18. The implantable device of claim 10 wherein the compound is the peptide of SEQ ID NO. 4.

19. The implantable device of claim 18 wherein the therapeutic serum concentration is between 0.01 and lOng/ml of the peptide of SEQ ID NO. 4.

20. The implantable device of any one of claims 18 and 19 wherein the device is a tube of between 00.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of the peptide of SEQ ID NO. 4.

21. The implantable device of claim 10 wherein the compound is the peptide of SEQ ID NO. 5.

22. The implantable device of claim 21 wherein the therapeutic serum concentration is between 0.01 and 10 ng/ml of the peptide of SEQ ID NO. 5.

23. The implantable device of any one of claims 21 and 22 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of the peptide of SEQ ID NO. 5.

24. The implantable device of any one of claims 1-23 wherein said device is prepared such that, when implanted in an animal, provides an effective therapeutic serum concentration of between 0.01 and 10 ng/ml of the compound, for a therapeutic time frame comprising of from 10 days post-implantation to 100 days post-implantation.

25. The implantable device of any one of claim 1-23 wherein said device is prepared such that, when implanted in an animal, provides a ramp-up serum concentration of between 20% and 90% of the therapeutic serum concentration, for a time frame comprising the first 1 to 20 days post-implantation.

26. The implantable device of claim 25 wherein the ramp-up serum concentration is variable and generally increasing over time.

27. The implantable device of any one of claims 1-26 wherein an instant serum concentration, measured at any point in time over the therapeutic time frame, is within 20% of an average therapeutic serum concentration calculated over the therapeutic time frame.

28. The implantable device of any one of claims 1-27 wherein said device is prepared such that, when implanted in an animal, provides a therapeutic release rate effective for a desired effect selected from the group consisting of treatment of diabetes, lowering of blood glucose levels, and weight loss, reduced food intake, improved cardiovascular risk factors, improved HDL/LDL ratios, lower cholesterol, for a therapeutic time frame starting between 0 and 20 days post-implantation and comprising between 10 and 365 days.

29. The implantable device of claim 28 wherein the compound is exenatide.

30. The implantable device of claim 29 wherein a therapeutic release rate is obtained between 0.01 and 500 ug/d of the exenatide.

31. The implantable device of any one of claims 29 and 30 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of exenatide.

32. The implantable device of claim 31 wherein the device is a tube of about 2 cm in length, about 2 mm in diameter, and containing about 10 mg of exenatide, preferably about 1 cm in length, about 1 mm in diameter, and containing about 2 mg of exenatide.

33. The implantable device of claim 28 wherein the compound is liraglutide.

34. The implantable device of claim 33 wherein the therapeutic release rate is between 0.01 and 500 ug/d of liraglutide from the device.

35. The implantable device of any one of claims 33 and 34 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of liraglutide.

36. The implantable device of claim 28 wherein the compound is the peptide of SEQ ID NO. 4.

37. The implantable device of claim 36 wherein the therapeutic release rate is between 0.01 and 500 ug/day of the peptide of SEQ ID NO. 4 from the device.

39. The implantable device of any one of claims 36 and 37 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of the peptide of SEQ ID NO. 4.

40. The implantable device of claim 10 wherein the compound is the peptide of SEQ ID NO. 5.

41. The implantable device of claim 21 wherein the therapeutic release rate is between 0.01 and 500 ug/day of the peptide of SEQ ID NO. 5 from the device.

42. The implantable device of any one of claims 40 and 41 wherein the device is a tube of between 0.1 and 5 cm in length, between 0.1 and 5 mm in diameter, and containing between 0.1 and 50 mg of the peptide of SEQ ID NO. 5.

43. The implantable device of any one of claims 1-42 wherein said device is prepared such that, when implanted in an animal, provides an effective

therapeutic release rate of between 0.1 and 500 ng/d/cm of the compound, for a therapeutic time frame comprising of from 3 days post-implantation to 95 days post-implantation.

44. The implantable device of any one of claim 1-43 wherein said device is prepared such that, when implanted in an animal, provides a ramp-up release rate of between 20% and 90% of the therapeutic release rate, for a time frame comprising the first 1 to 20 days post-implantation.

45. The implantable device of claim 44 wherein the ramp-up release rate is variable and generally increasing over time.

46. The implantable device of any one of claims 1-45 wherein an instant release rate, measured at any point in time over the therapeutic time frame, is within 20% of an average therapeutic release rate calculated over the therapeutic time frame.

47. A method of manufacturing an implantable device of any one of claims 1-46, comprising formation of a tube through a technique selected from the group consisting of extrusion, molding and rotational casting.

48. The method of claim 47 wherein the technique is rotational casting and the tube is formed through polymerization of one or more monomer or macromer.

49. The method of claim 48 wherein the polymerization occurs in a phase separation step.

50. The method of any one of claims 47-50 wherein the method of manufacturing further comprises irradiation of the tube.

51. The method of claim 50 wherein the irradiation dose is from 0.1 to 10 MRad and is sufficient to permit the release of the compound encased at a therapeutically relevant dose.

52. The method of claim 50 wherein the irradiation is at about 2.5 MRad.

53. The method of claim 50 wherein the irradiation is at about 5.0 MRad.

54. A method of preparing the implantable device of any one of claims 1-46, comprising:

a) filling an interior of a mold with a solution so that substantially all gas is displaced therefrom, the solution comprising at least two components which can be phase separated by a phase separation agent into at least two phases;
b) rotating said mold containing said solution at an effective rotational velocity in the presence of said phase separation agent to induce phase separation between said at least two components into at least two phases so that under rotation at least one of the phases deposits onto an inner surface of the mold;
c) forming said device by stabilizing said at least one of the phases deposited onto the inner surface of the mold;
d) removing the device from the mold;
e) washing the device;
f) filling the device with the compound; and
g) sealing the ends of the device to enclose the compound in the interior.

55. The method of claim 54 further comprising an additional step (h) irradiating the device.

56. The method of claim 55 wherein the additional step (h) occurs after step (g).

57. The method of claim 55 wherein the additional step (h) occurs after step (e).

58. The method of claim 55 wherein the irradiation dose is from 0,1 to 10 MRad and is sufficient to permit the release of the compound encased at a therapeutically relevant dose.

59. The method of claim 55 wherein step (h) is irradiation at about 2.5 MRad.

60. The method of claim 55 wherein step (h) is irradiation at about 5.0 MRad.

61. The method of any one of claims 54-60 wherein steps (d) and (e) can be performed in any order.

62. The method of any one of claims 54-61 further comprising the step of drying the device prior to step (g).

63. The method of any one of claims 54-61 further comprising the step of drying the device prior to step (f).

64. The method of claim 62 or 63 wherein the drying of the device is performed in one or more procedure selected from the group consisting of ambient air drying, forced air drying, heated drying, and reduced pressure drying.

65. The method of any one of claims 54-64 wherein said at least two components includes at least one monomer and at least one solvent, and wherein said solution is a substantially homogenous solution, wherein said at least one of the phases that deposits onto the inner surface includes at least the monomer, and wherein the step of stabilizing said deposited phase

includes gelation of the monomer by polymerization thereof.

66. The method of claim 54 wherein said phase separation agent is selected from the group consisting of light, pH, initiation agents, change in temperature, creation of a chemical product within the mold, changes in cationic and/or anionic concentrations, electric and magnetic fields.

67. The method according to claim 66 further comprising an initiation agent.

68. The method according to claim 67 wherein the initiation agent is selected from the group consisting of free radical initiators, thermal and photo initiators and redox initiators.

69. The method according to claim 67 wherein initiation is achieved by exposure to an agent selected from the group consisting of light, change in pH, change in temperature, creation of a chemical product within the mold, changes in cationic and/or anionic concentrations, electric and magnetic fields.

70. The method according to claim 54 wherein said solution includes a cross-linking agent.

71. The method according to claim 70 wherein the crosslinking agent is selected from the group consisting of multifunctional methacrylate or acrylate, acrylamide or methacrylamide and preferably one of ethylene glycol dimethacrylate(EDMA), hexamethylene dimethacrylate (HDMA), poly(ethylene glycol) dimethacrylate, l,5-hexadiene-3,4-diol (DVG), 2,3-dihydroxybutanediol 1,4-dimethacrylate (BHDMA), 1,4-butanediol dimethacrylate (BDMA), l,5hexadiene (HD), multi-functional star polymers of poly(ethylene oxide) with terminal methacrylate groups.

72. The method according to claim 54 wherein said solution includes at least one monomer selected from the group consisting of acrylates, methacrylates, and derivatives thereof such as, but not limited to, 2-hydroxyethyl

methacrylate, methyl methacrylate, polyethylene glycol ethyl methacrylate, ethyl acrylate, 2-hydroxyethyl acrylate, acrylic acid, methacrylic acid, 2-chloroethyl methacrylate, butyl methacrylate, glycidyl methacrylate, hydroxypropyl methacrylate, dextran-methacrylate; acrylamides and derivatives thereof such as, but not limited to, methacrylamide, hydroxypropyl methacrylamide, N,N-diethyl acrylamide, N,N-dimethyl acrylamide, 2-chloroethyl acrylamide, 2-nitrobutyl acrylamide, ; N-vinyl pyrrolidone, acenaphthalene, acrilonitrile, N-vinyl acetamide, phen/l-acetylene, acrolein, methyl acrolein, N-vinyl pyridine, vinyl acetate, vinyl chloride, vinyl fluoride, vinyl methyl ketone, vinylidene chloride, st/rene and derivatives thereof, propene, acrylonitrile, methacrylonitrile, acryloyl chloride, allyl acetate, allyl chloride, allylbenzene, butadiene and derivatives thereof, N-vinyl caprolactam, N-vinyl carbazole, cinnamates and derivatives thereof, citraconimide and derivatives thereof, crotonic acid, diallyl phthalate, ethylene and derivatives thereof such as, but not limited to 1,1 diphenyl-ethylene, chlorotrifluoro-ethylene, dichloroethylene, tetrachloro-ethylene; fumarates and derivatives thereof, hexene and derivatives thereof, isoprene and derivatives thereof such as, but not limited to isopropenyl acetate, isopropenyl methyl ketone, isopropenylisocyanate; itaconate and derivatives thereof; itaconamide and derivatives thereof; diethyl maleate, 2(acryloyloxy)ethyl diethyl phosphate, vinyl phosphonates and derivatives thereof, maleic anhydride, maleimide, silicone monomers, and derivatives thereof; and combinations thereof.

73. The method according to claim 54 wherein said solvent is selected from the group consisting of a neucleophilic or electrophilic molecule selected from the group of water, alcohols, ethylene glycol, ethanol, acetone, poly(ethylene glycol), dimethyl sulfoxide, dimethyl formamide, alkanes and derivatives thereof, acetonitrile, acetic acid, benzene, acetic anhydride, benzyl acetate, carbon tetrachloride, chlorobenzene, n-butanol, 2-chloroethanol, chloroform, cyclohexane, cyclohexanol, dichloromethane, diethyl ether, di(ethylene glycol), di(ethylene glycol) monomethyl ether, 1,4 dioxane, N,N, dimethyl acetamide, N,N, dimethyl formamide, ethyl acetate, formaldehyde, nheptane,

hexachloroethane, hexane, isobutanol, isopropanol, methanol, methyl ethyl ketone, nitrobenzene, n-octane, n-pentanol, propyl acetate, propylene glycol, pyridene, tetrahydrofuran, toluene, trichloroethylene, o-xylene and pxylene, a monomer, a liquid crosslinking agent, or mixtures thereof.

74. The method according to claim 54 wherein said solvent solubilizes said monomer mixture but not a polymer or crosslinked polymer formed from said monomer mixture.

75. The method according to claim 54 wherein said at least one monomer is present in a range from about 0.001% by weight to about 60% by weight.

76. The method according to claim 54 wherein said polymer is selected from the group consisting of polyacrylates, polysulfone, peptide sequences, proteins, oligopeptides, collagen, fibronectin, laminin, polymethacrylates such as but not limited to poly(methyl methacrylate), poly(ethoxyethyl methacrylate), poly(hydroxyethylmethacrylate), polyvinyl acetates polyacetates, polyesters, polyamides, polycarbonates, polyanhydrides, polyamino acids, such as but not limited to poly(N-vinyl pyrrolidinone), polyvinyl actetate), polyvinyl alcohol, poly(hydroxypropyl methacrylamide), poly(caprolactone), poly(dioxanone) polyglycolic acid, polylactic acid, copolymers of lactic and glycolic acids, and polytrimethylene carbonates, poly(butadiene), polystyrene, polyacrylonitrile, poly(chloroprene), neoprene, poly(isobutene), poly(isoprene), polypropylene, polytetrafluoroeth/lene, poly(vinylidene fluoride), poly(chlorotrifluoroethylene), poly(vinyl chloride), poly(oxymethylene), poly(ethylene terephthalate), poly(oxyethylene) poly(oxyterephthaloyl), polyamides such as but not limited to, poly[imino(l-oxohexamethylene)], poly(iminoadipoyl-iminohexamethalene), poly(iminohexamethylene-iminosebacoyl), poly[imino(l-oxododecamethylene)], cellulose, polysulfones, hyalonic acid, sodium hyaluronate, alginate, agarose, chitosan, chitin, and mixtures thereof.

77. The method according to claim 54 including physically or chemically modifying the inner surface of a mold upon which preselected morphologies are induced into the wall of the said product by inducing beading or spreading of the separated liquid phase.

78. The method according to claim 77 where the mold is glass, plastic, or metal.

79. The method according to claim 78 wherein the mold is plastic and the plastic is selected from the group consisting of PTFE, PP, HDPE, and PE.

80. The method according to claim 78 wherein the mold is glass, and the glass mold is treated prior to step (a) with an agent to modify surface tension.

81. The method according to claim 80 wherein the agent to modify surface tension is selected from the group consisting of surfactant compounds, polymer surfactants, and silinating agents.

82. The method according to claim 81 wherein the silinating agents are selected from the group consisting of (organo)x-Si-Yz, where 'organo' is a substituent of silicon = Cl-18, linear, cyclic or branched chain, aliphatic or aromatic, eventually substituted; x=l-3; Y=alcoxy, chloro, imidazole, labile amino group, isoprenoxy; z=l-3; and x+z = 4, such as trimethyl chlorosilane, triethylchlorosilane, dimethyldichlorosilane, dimethyldimethoxysilane, trimethylmethoxysilane, and trimethylethoxysilane.

83. The method according to claim 81 wherein the silanating agents are selected from the group consisting of aminopropyl-dimethyl-chlorosilane, aminopropyl-dimethyl-methoxysilane, aminopropyl-methyl-dimethoxysilane, aminopropyl-trimethoxysilane, dimethylaminopropyl-dimethyl-methoxysilane, dimethylaminopropyl-methyl-dimethoxysilane, and dimethylaminopropyl-trimethoxysilane.

84. The method according to claim 81 wherein the silanating agent is dimethylaminopropyl-dimethyl-methoxysilane.

85. The method according to claim 76 where the mold surface is pretreated with Teflon or an other fluorinated polymer surface.

86. The method according to claim 85 wherein the polymer treatment is attached to the mold surface.

87. The method according to claim 86 wherein the polymer treatment is a plastic sleeve of PTFE, PP or PE which is placed in the interior of the mold, into which the polymerization mixture is added for making the device.

88. The method according to claim 54 including the step of removing the solvent and including repeating steps a), b) and c), at least once to produce a multi-layered product.

89. The implantable device of any one of claims 1-46 wherein the polymer is a copolymer composed of hydroxyethyl-methacrylate and methyl-methacrylate, with a multiacrylate crosslinker, examples include ethyleneglycol dimethylacrylate, propylene glycol dimethacrylate, trimethylopropane trimethacrylate,

90. The implantable device of any one of claims 1-46 wherein the polymer is a copolymer composed of hydroxyethyl-methacrylate and hydroxypropyl-methacrylate, with a multiacrylate crosslinker.

91. The implantable device of claim 1 wherein the device is between 10% and 90% compound.

92. The implantable device of claim 1 wherein the device is between 20% and 80% compound.

93. The implantable device of claim 33 wherein the product is more than 5% compound.

94. The method of any one of claims 47-88 wherein the polymer is a copolymer composed of hydroxymethacrylate and methylmethacrylate, with a multiacrylate crosslinker, examples include ethyleneglycol dimethylacrylate, propylene glycol dimethacrylate, trimethylopropane trimethacrylate,

95. The method of any one of claims 47-88 wherein the polymer is a copolymer composed of hydroxymethacrylate and hydroxypropylmethacrylate, with a multiacrylate crosslinker.

96. The method of claim 54 wherein the device is between 10% and 60% HPMA (w/w).

97. The method of claim 54 wherein the product is between 2% and 40% MMA (w/w).

98. The method of claim 54 wherein the product is >5% (w/w) active compound.

99. Use of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 for weight loss.

100. Use of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 for reduced food intake.

101. Use of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 for improving cardiovascular risk factors (levels of lipids, free fatty acids, and/or cholesterol).

102. Use of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 for reduction of blood glucose levels.

103. Use of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 for treatment of diabetes.

104. Use of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 for the mitigation of a side effect resulting from treatment with a therapeutic selected from the group consisting of GLP-I, an analog of GLP-I, and a derivative of GLP-I.

105. The use according to claim 99 wherein the side effect is selected from the group consisting of emesis, sudden weight loss, and nausea.

106. A method of treatment of a disease state selected from the group consisting of obesity, high blood sugar, and diabetes, said method comprising implantation of an implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98 in an animal suffering from said disease state.

107. The method according to claim 106 wherein the implantation is a subcutaneous implantation.

108. The method according to claim 106 wherein the implantation is a subdermal implantation.

109. The implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98, wherein the device is explantable.

110. The implantable device of any one of claims 1-46 or 89-93 or an implantable device made by the method of any one of claims 47-88 or 94-98, wherein the hydrogel or xerogel reservoir has an equilibrium water content of between 10 and 60%.

111. The implantable device of claim 110 wherein the hydrogel or xerogel reservoir has an equilibrium water content of between 20 and 40% .

112. The implantable device of claim 111 wherein the hydrogel or xerogel reservoir has an equilibrium water content of about 30%.

Figure 1

SEQ ID NO: 1: GLP-1 (7-36)
HAEG-TFTSD-VSSYL - EGQAA-KEFIA-WLVKG-R

SEQ ID NO: 2: GLP-1 (7-35)
HAEG-TFTSD-VSSYL - EGQAA-KEFIA-WLVKG

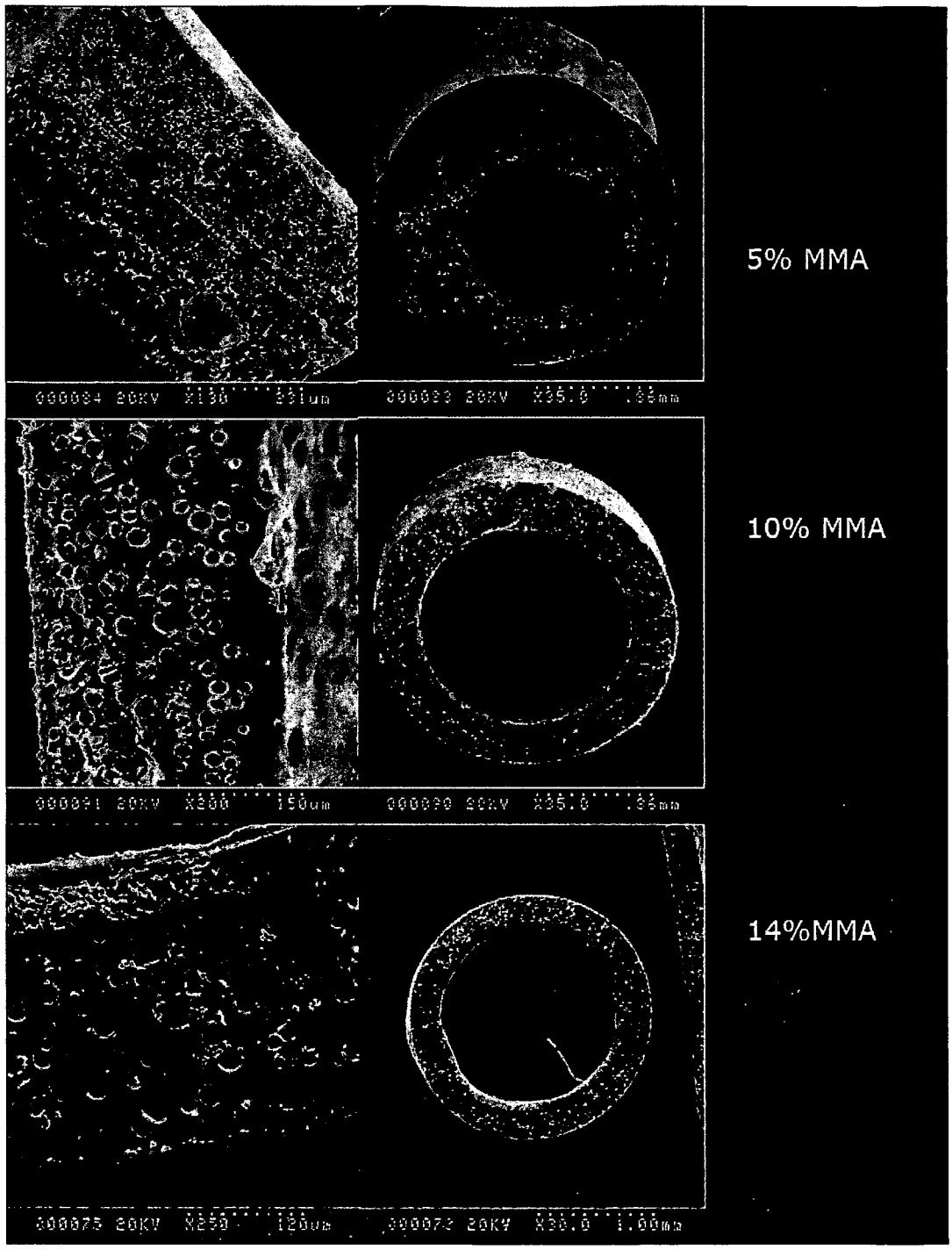
SEQ ID NO: 3: Exenatide
HGEG-TFTSD-LSKQM-EEEAV-RLFIE-WLKNG-GPSSGAPPPS-NH2

SEQ ID NO: 4:
Sal-HAEG-TFTSD-VSSYL – EGQAA-KEFIA-WLVKG-R
Where Sal= salicylyl group = ortho-HO-Ph-CO

SEQ ID NO: 5:
T3h-HAEG-TFTSD-VSSYZ-EGQAA-KAFIE-WLVKN
Where T3h=trans-3-hexenoyl- = trans-CH3-CH2-CH=CH-CH2-CO-
And Z = (S)octyl-glycine

SEQ ID NO: 6:
T3h-H-A-E-G-T-F-T-S-D-V-S-S-Y-Z-E-G-Q-A-A-K-A-F-I-E-W-L-V-K-N-K-K-K-K-NH2
Where T3h= trans-3-hexenoyl- = trans-CH3-CH2-CH=CH-CH2-CO-

SEQ ID NO: 7:
H-G-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-Q-A-A-K-A-F-I-E-W-L-K-N-NH2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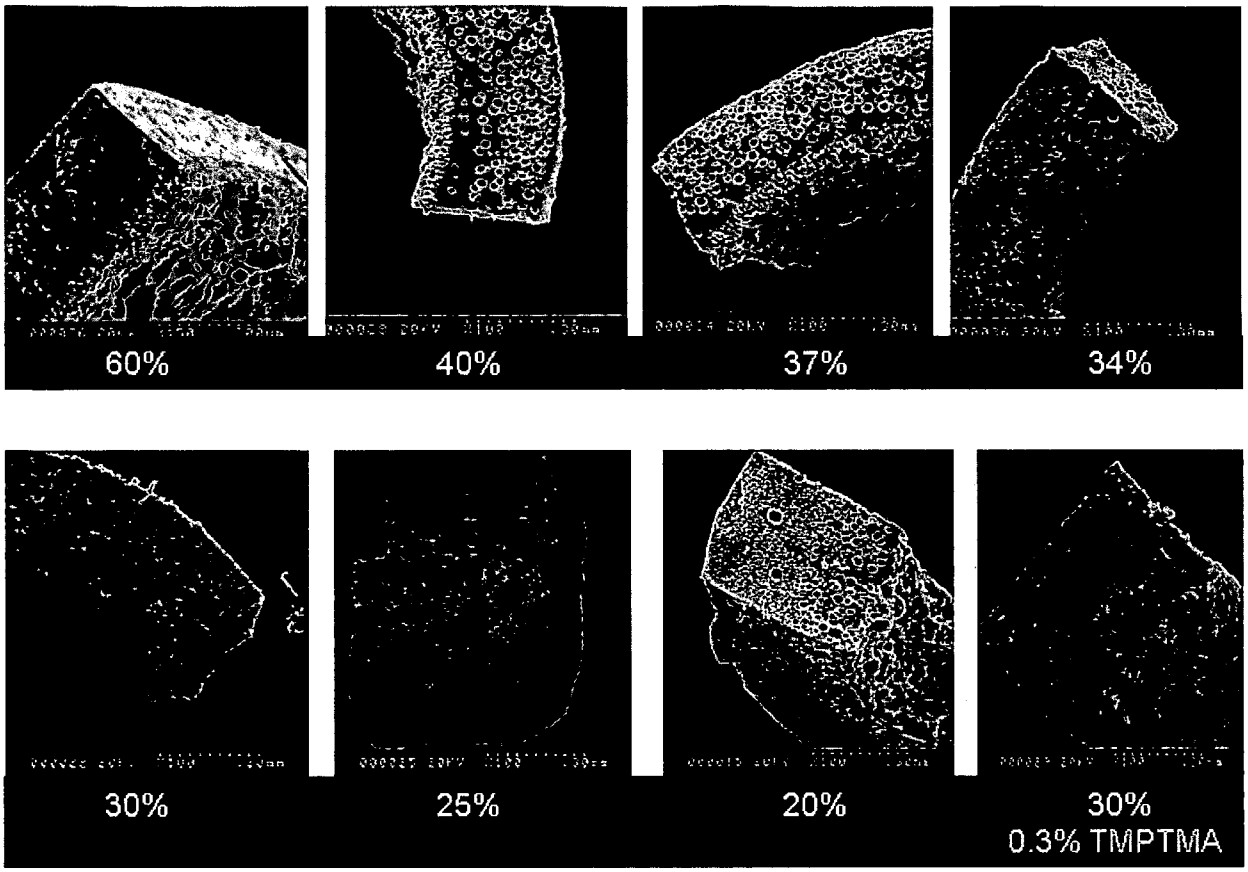
10% MMA
14%MMA


60%
40%
37%
34%
30%
25%
20%
30%
0.3% TMPTMA

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/002090

A. CLASSIFICATION OF SUBJECT MATTER
EPC: *A61K 38/26* (2006.01) , *A61K 47/32* (2006.01) , *A61K9/00* (2006.01) , *A61K 9/107* (2006.01) , *A61P 3/04* (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
E?C: *A61K 38/26* (2006.01) , *A61K 47/32* (2006.01) , *A61K9/00* (2006.01) , *A61K 9/107* (2006.01) , *A61P 3/04* (2006.01)

Documentation searched other than minimum documentation to the extent (hat such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
databases: Delphion, PubMed, SCOPUS search terms: GLP-I, exenatide, extendin, liraglutide, incretin, incretin mimetics, hydrogel, xerogel, depot, sustained release, controlled release, drug delivery, delivery device, implantable device, delivery system

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/071736 A2 (MATREGEN CORP.) 26 August 2004 see whole document	1 to 112
Y	CHOI, et al. Control of Blood Glucose by Novel GLP-I Delivery Using Biodegradable Triblock Copolymer of PLGA-PEG-PLGA in Type 2 Diabetic Rats. PHARM RES. May 2004, Vol. 21, No. 5, pages 827-831 see whole document	H o 112
Y	WO 2005/041873 A2 (AZOPAX THERAPEUTICS LLC) 12 May 2005 see whole document	1 to 112
A, P	KIM D et al. Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight in Subjects With Type 2 Diabetes. DIABETES CARE. June 2007, Volume 30, Number 6, pages 1487-1493. see whole document	

[XJ Further documents are listed in the continuation of Box [X] See patent family annex.

*	Special categories of cited documents	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve *an* inventive step when the document is taken alone
"E"	earlier application or patent but published on *or* after the international filing date	"Y"	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such document!,, such combination being obvious to a person skilled m the art
"L"	document which may throw doubts on priority ctaimQi) or which is cited to establish the publication date of another citation or other fapecial reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior Io the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2008 (13-03-2008)	17 April 2008 (17-04-2008)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, Cl 14 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec KlA 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Cynthia Bruce-Payne 819-997-492 1

C (Continuation), DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant	Relevant to claim No.
A	GEDULIN BR. et al. Dose-response for glycaemic and metabolic changes 28 days after single injection of long-acting release exenatide in diabetic fatty Zucker rats. DIABETOLOGIA. M y 2005, Vol. 48, No. 7, pages 1380-1385.	
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A	WO 2005/102293 A1 (AMYLIN PHARMACEUTICALS, INC.) 3 November 2005	
A	DRUCKER DJ. Enhancing Incretin Action for the Treatment of Type 2 Diabetes. DIABETES CARE. October 2003, Volume 26, Number 10, pages 2929-2940.	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/002090

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item l.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material

[X] a sequence listing

[ ] table(s) related to the sequence listing

b. format of material

[ ] on paper

[X] in electronic form

c. time of filing/furnishing

[ ] contained in the international application as filed.

[X] filed together with the international application in electronic form

[ ] furnished subsequently to this Authority for the purposes of search.

2. [ ] hi addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments :

No paper copy of the sequence listing has been received for the application and has been requested in form ISA225 on Dec. 13, 2007.

As for the present electronic version of the sequence listing, the following non-compliances are noted:

In the submitted sequence listing, SEQ ID NO: 3, 4, 5, 6 and 7 include improper use of the variable symbol "Xaa" which then makes the stated lengths incorrect.

As cited in paragraph 18 of Annex C of the Administrative Instructions under the PCT, the symbol "Xaa" shall represent a modified or unusual amino acid and therefore can not represent a chemical group.

As cited in paragraph 32 of the above staled instructions, when features of sequences are presented, they shall be described by the "feature keys" set out in Appendix 2, table 6. Whenever the "feature keys" are not enough to describe the modifications, "free text" should be used to describe the modification as cited in paragraph 33 of the same instructions.

In SEQ ID NO: 3 (position 40), SEQ ID NO: 6 (position 35) and SEQ ID NO:7 (position 29) "Xaa" represents an "NH2" group in which case it is the last amino acid of the sequence that is amidated. To comply with the rules, referring to Appendix 2, table 6 of the above stated instructions, the feature section for this modification should look like the following (example for SEQ ID NO: 3) :

<220>
<221> MOD_RES
<222> 39
<223> amidation

continued: see extra sheet

continuation of: Box No. I

As for SEQ ID NO: 4 (position 1), SEQ ID NO: 5 (position 1) and SEQ ID NO: 6 (position 1), shall use "free text" under numeric identifier <223> to describe the chemical group that is attached to the known amino acid of the sequence (example for SEQ ID NO: 4):

<220>
<221>MOS_RES
<222> 1
<223> salicylyl group (ortho-HO-Ph-CO) attached

It is important to note that since the "Xaa" will be taken out of the sequences for the above cases, the length of the sequences will be shorter.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/002090

Box No. π Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] ClaimNos. : 106-108
because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 106 to 108 encompass a method of treatment of the human/animal body which this Authority is not obliged to search under Rule 39.1(iv) of the PCT, the search has been carried out based on the alleged effects of the device referred to therein.

2. [ ] Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] ClaimNos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. **m** Observations where unity of **invention** is lacking **(Continuation** of item 3 of **first** sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on **Protest**
[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invention.
[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT7CA2007/002090

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