

# Evaluation of novel particles as an inhalation system for GLP-1

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**Aim:** The feasibility of administering native glucagon-like peptide 1 (GLP-1) as GLP-1 Technosphere® Inhalation Powder for diabetes therapy has been demonstrated in a rat model.

**Methods:** GLP-1 Technosphere Inhalation Powders containing 5, 10 and 15% GLP-1 were prepared and administered to healthy female Sprague–Dawley rats and to male Zucker diabetic obese rats. Rats received a single dose of GLP-1 Technosphere Powder by pulmonary insufflation. GLP-1 pharmacokinetic and pharmacodynamic responses were measured.

**Results:** Maximum circulating GLP-1 concentrations were achieved at ~10 min after dosing with detectable levels at 40 min. In a food consumption study, Sprague–Dawley rats receiving GLP-1 Technosphere Powder once-daily consumed less food than control rats for up to 24 h after dosing. Cumulative food consumption was decreased approximately 10% after 78 h. In an intraperitoneal glucose tolerance test, Zucker diabetic fatty rats receiving 2 mg GLP-1 Technosphere Powder (0.3 mg GLP-1) by pulmonary insufflation exhibited lower glucose concentrations and higher insulin concentrations than control rats. Pancreatic evaluations showed no differences in apoptotic index or cell proliferation of  $\beta$ -cells. In addition, a dose-related increase in insulin expression within the pancreas was observed.

**Conclusions:** These data demonstrate the feasibility of administering native GLP-1 as GLP-1 Technosphere Inhalation Powder for diabetes therapy.

**Keywords:** animal study, diabetes therapy, GLP-1 Technosphere Inhalation Powder, glucagon-like peptide 1, incretin, insulin secretion, pharmacodynamic, pharmacokinetic, pulmonary administration

**Received 23 March 2009; returned for revision 11 June 2009; revised version accepted 12 June 2009**

## Introduction

Peptide hormones are important modulators of biological function and can be used to manage disease by replacing absent endogenous hormones. Unfortunately, peptide hormones are generally administered by injection; this means of delivery is inconvenient and can be a source of non-compliance. To mitigate this risk, the development of peptide hormone therapeutics has become focused on long-acting analogues of the natural peptides for once-daily or once-weekly injections. Unfortunately, the pharmacokinetic profiles for injected long-acting

peptide hormones can be radically different from those of endogenously secreted hormones [1,2].

Glucagon-like peptide 1 (GLP-1) is an endogenous incretin hormone produced in the gastrointestinal tract for prandial secretion [3–5]. It enhances insulin secretion from pancreatic  $\beta$ -cells, regulates glucagon release and gastrointestinal motility and acts as a neurotransmitter. Studies in rodents showed that GLP-1 and its analogues directly stimulate  $\beta$ -cell growth and replication. If GLP-1 increases  $\beta$ -cell mass in patients with diabetes, then GLP-1 therapy offers the potential to alter the progression of type 2 diabetes [6].

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Clinically, GLP-1 reduces blood glucose, postprandial glucose excursions and food intake, and increases satiety [6]. Together, these actions define the unique and highly desirable profile of an antidiabetic agent with the potential to promote weight loss. Patients receiving GLP-1 by continuous subcutaneous (SC) infusion over 6 weeks reported reduced appetite and significant reductions in body weight [7].

Despite these advantages, the utility of GLP-1 in diabetes treatment is hindered because it requires administration by injection and has a very short circulating half-life (~2 min) [8]. To address the limited half-life of GLP-1, several long-acting GLP-1 analogues, including exenatide (exendin-4, Byetta), exenatide LAR and liraglutide (Victoza), are either approved or in development [6]. Although the circulating half-life of exendin-4 is longer than that of GLP-1, it still requires twice-daily injection. Exendin-4 therapy is further complicated by a poor side-effect profile, including significant nausea. Alternative approaches to prolonging the circulating half-life of GLP-1 involve the development of dipeptidyl peptidase IV (DPP-IV) inhibitors. DPP-IV metabolizes GLP-1 and DPP-IV inhibition increases the half-life of endogenous GLP-1 [9]. Sitagliptin, an oral DPP-IV inhibitor, is approved in the United States for the treatment of type 2 diabetes. The DPP-IV approach makes use of endogenous GLP-1 by inhibiting its deactivation by DPP-IV; however, all other strategies for GLP-1 therapies are based on GLP-1 analogues.

Although long-acting GLP-1 analogues and DPP-IV inhibitors are currently used in diabetes treatment, these products do not mimic natural physiology. In healthy individuals, endogenous GLP-1 secretion is elevated only at mealtime and occurs in short bursts [10]. By contrast, long-acting GLP-1 analogues and DPP-IV inhibitors provide drug exposure for time periods exceeding the postprandial phase. Thus, the ideal GLP-1 therapy might be one in which the drug is administered at mealtime with exposure limited to the postprandial period. The pulmonary route has the potential to provide such a treatment.

The lung is an excellent portal for systemic drug delivery because it provides a very large, absorptive surface area with direct access to the cardiovascular system. Drugs absorbed through the lung avoid first pass metabolism, a potentially critical feature for protein and peptide therapeutics. In addition, agents delivered through the lung enter the arterial circulation directly and reach target organs before returning through the venous stem to pulmonary capillary beds, where endopeptidases are extensively expressed. This may paradoxically result in a higher target organ exposure

to active peptides than would result from a comparable administration via a parenteral route. Indeed, a GLP-1 receptor agonist was absorbed more quickly when administered to rats by the pulmonary route compared with SC injection [11]. Pulmonary delivery of a long-acting pegylated GLP-1 is also under investigation [12].

Technosphere® technology is a drug delivery platform designed for the pulmonary administration of protein and peptide therapeutics [13–17]. It is based on the novel excipient, fumaryl diketopiperazine (FDKP; figure 1), which has the ability to self-assemble into discrete particles upon precipitation from solution [18–23]. These particles are uniform in size, optimized for inhalation into the deep lung (2–5 µm in diameter) and dissolve rapidly at physiological pH [24]. Protein or peptide drugs can be adsorbed onto these particles and inhaled to effect systemic delivery of the drug. Drugs administered as Technosphere powder demonstrate rapid absorption profiles comparable with intravenous injection [25]. Insulin administered as Technosphere® Insulin is an ultra rapid-acting insulin with the potential to provide clinical benefits for diabetes treatment [16,25–30]. Using this technology platform, GLP-1 Technosphere formulations were prepared by adsorbing GLP-1 onto preformed Technosphere particles.

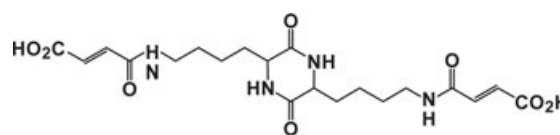
## Methods

### Preparation of Technosphere Particles

FDKP and polysorbate 80 were dissolved in dilute aqueous ammonia to obtain a solution containing 2.5 wt% FDKP and 0.05 wt% polysorbate 80. This solution was mixed with an acetic acid solution containing polysorbate 80 to form Technosphere particles that were washed and concentrated by tangential flow filtration.

### Preparation of GLP-1 Stock Solution

A 10 wt% GLP-1 stock solution was prepared in deionized water by combining 60 mg GLP-1 solids (86.6% peptide) with 451 mg deionized water. About 8 µl glacial acetic acid was added to dissolve the peptide.



**Fig. 1** The chemical structure of fumaryl diketopiperazine (FDKP).

### Preparation of GLP-1 Technosphere Powder

A 1-g portion of the stock Technosphere suspension (108 mg particles) was transferred to a 2 ml polypropylene tube. The GLP-1 was adsorbed (loaded) onto the Technosphere particles in a pH-controlled process by mixing the aqueous Technosphere particle suspension with an aqueous solution of GLP-1 and adjusting the suspension to pH 4.5. The GLP-1 Technosphere suspension was flash-frozen in liquid nitrogen and lyophilized to remove water and produce a dry powder. The target GLP-1 content for the dry powders was 5, 10 and 15% by weight. A high performance liquid chromatography (HPLC) assay confirmed that the GLP-1 content of the powders was within  $\pm 10\%$  of the target value.

Particle morphology was studied by scanning electron microscopy (figure 2). These images demonstrate that GLP-1 Technosphere particles comprise a unique assembly of FDKP microcrystals.

### Aerodynamic Characterization

The powder particles were characterized for aerodynamic performance by discharging the powder into an Andersen cascade impactor at 30 l/min. Inhalation powders for systemic drug delivery must be appropriately sized for deposition in the deep lung. The required particle size distribution is defined as the respirable fraction and includes all particles having aerodynamic diameters in the 0.5–5.8  $\mu\text{m}$  range. Particles  $< 0.5 \mu\text{m}$  are exhaled immediately after inhalation, and particles  $> 5.8 \mu\text{m}$  remain trapped in the upper airways and do

not travel down into the alveoli. The data are generally reported as the percentage of particles in the respirable fraction, or %RF.

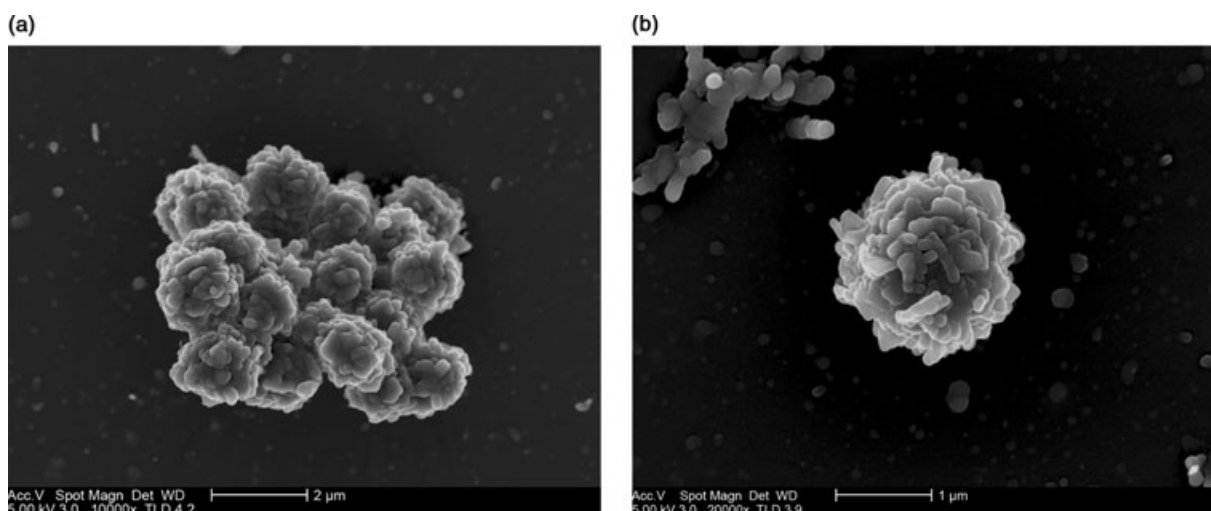
### Animal Studies

All animal protocols adhered to the Principles of Laboratory Animal Care and were approved by the Animal Care and Use Committee of MannKind Corporation. Serum GLP-1 concentrations were measured by a sensitive and specific enzyme-linked immunosorbent assay for human GLP-1 (Linco, St Charles, MO, USA). Serum FDKP concentrations were measured by a sensitive and specific HPLC assay developed by MannKind Corporation (Danbury, CT, USA).

### Pulmonary Administration of Test Articles

Pulmonary administration of dosing solutions was done by liquid instillation. In this procedure, rats were lightly anaesthetized and an intratracheal tube was inserted to the bifurcation of the lungs. The plunger of a syringe filled with the appropriate volume of dose solution was depressed, discharging the solution of test article into the lungs. The volume of solution instilled was typically 0.1 ml.

Test powders were administered by pulmonary insufflation, which is the dry powder equivalent of liquid instillation. In this procedure, rats were lightly anaesthetized and the insufflation device was inserted into the trachea to the bifurcation of the bronchi where the powder was released. The insufflator resembles a syringe



**Fig. 2** Scanning electron micrographs of GLP-1 Technosphere particles: (a) 10 000 $\times$  and (b) 20 000 $\times$ .

**Table 1** Design of pharmacokinetic study in Sprague–Dawley rats

Group	Dose		Delivered as
	(mg GLP-1)	Method	
1	0.125	Liquid instillation	0.1 ml of 1.25 mg/ml solution
2	0.12	Powder insufflation	2.42 mg of 4.8wt% GLP-1 Technosphere® Powder
3	0.17	Powder insufflation	1.85 mg of 9.3wt% GLP-1 Technosphere® Powder
4	0.36	Powder insufflation	2.46 mg of 14.6 wt% GLP-1 Technosphere® Powder

with a chamber for holding the dry powder; the powder is discharged by depressing a plunger. The target dose was controlled by filling the chamber of the insufflator (Penn-Century) with an appropriate amount of powder. The actual powder dose was determined from the difference in the weight of the insufflator before and after dosing. The amount of powder dosed was typically 1–3 mg.

#### Pharmacokinetic Assessment of GLP-1 Technosphere Powder in Rats

Female Sprague–Dawley rats (five per group) weighing 194–211 g were assigned to one of four test groups (table 1). Before dosing, the rats were anaesthetized with isoflurane (inhaled) and then administered a dosing solution or a test powder. Dosing solutions (0.125 mg GLP-1 in 0.1 ml phosphate buffer) were administered by pulmonary liquid instillation. Test powders (2 mg of 5, 10 and 15% GLP-1 by weight) were administered by pulmonary insufflation. Blood samples (100 µl) were collected from the tail vein before dosing and at 2, 5, 10, 20, 30, 40 and 60 min after dosing. Plasma was collected and the samples assayed for GLP-1 and FDKP concentrations.

**Table 2** Pharmacokinetic profile of GLP-1 insufflated as GLP-1 Technosphere® Powders

Test article	N	GLP-1			
		Half-life (min)	T <sub>max</sub> (min)	C <sub>max</sub> (pM)	AUC <sub>all</sub> (pM·min)
GLP-1 (pulmonary instillation)	5	50	20	281 ± 101	10 600 ± 3840
5% GLP-1 Technosphere® Powder	5	14.9	2	2660 ± 1840	57 100 ± 47 600
10% GLP-1 Technosphere® Powder	5	9.5	10	4990 ± 2400	92 600 ± 50 700
15% GLP-1 Technosphere® Powder	5	10	10	11 700 ± 729	228 000 ± 52 500

T<sub>max</sub>, time to maximum mean peak circulating GLP-1 concentrations; C<sub>max</sub>, mean peak circulating GLP-1 concentrations; AUC<sub>all</sub>, area under the GLP-1 concentration vs. time curve

#### Pharmacodynamic Assessment of GLP-1 Technosphere Powder in Rats

##### Food Consumption

Female Sprague–Dawley rats weighing 178–192 g were assigned to one of two test groups and acclimated to a reverse light/dark cycle for 5 days that was continued throughout the study. Animals (five per group) in the control group received air by pulmonary insufflation and animals (10 per group) in the test group received 0.3 mg GLP-1 (as 2 mg 15% wt% GLP-1 Technosphere Powder) once-daily for four consecutive days. Food consumption was measured at 1, 2, 4, 6 and 24 h after dosing on days 1, 2 and 3 and at 1, 2, 4 and 6 h after dosing on day 4. Body weights were recorded on each dosing day.

##### Intraperitoneal Glucose Tolerance Test

Male obese Zucker diabetic fatty rats (eight per group) weighing 289–457 g were assigned to one of two test groups. Animals in the control group received air by pulmonary insufflation and animals in the test group received 0.3 mg GLP-1 (as 2 mg 15% by weight GLP-1 Technosphere Powder) once-daily for four consecutive days. On dosing day 4, rats were administered an intraperitoneal glucose tolerance test. In this procedure, a syringe filled with a precalculated volume of glucose solution was administered into the peritoneal cavity. Blood samples (100 µl) were collected from the tail vein before dosing and at 15, 30, 45, 60 and 90 min after dosing. Blood was collected for serum and plasma evaluation. Blood glucose, plasma GLP-1 and serum insulin concentrations were determined.

Additionally, β-cell proliferation, apoptosis and insulin expression were evaluated in β-islet cells after administration of test article or control article for four consecutive days. Slides were prepared for insulin immunostaining and microscopic evaluation of insulin expression. Apoptotic evaluation was conducted by terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) assay. The TUNEL assay also may

label cells undergoing necrosis or cells that have suffered severe DNA damage. Microscopic evaluation of cell proliferation was conducted in insulin-positive islets and the exocrine pancreas by immunohistochemistry analysis using co-localization of insulin and Ki67. An indirect staining procedure was used to detect insulin in  $\beta$ -cells in islets of Langerhans. The number of insulin-positive cells (expressed as a percentage of the number of nuclei in islets) in a total of five islets were counted per section. For each section, the sum of all five islets and the mean of the five islets were determined.

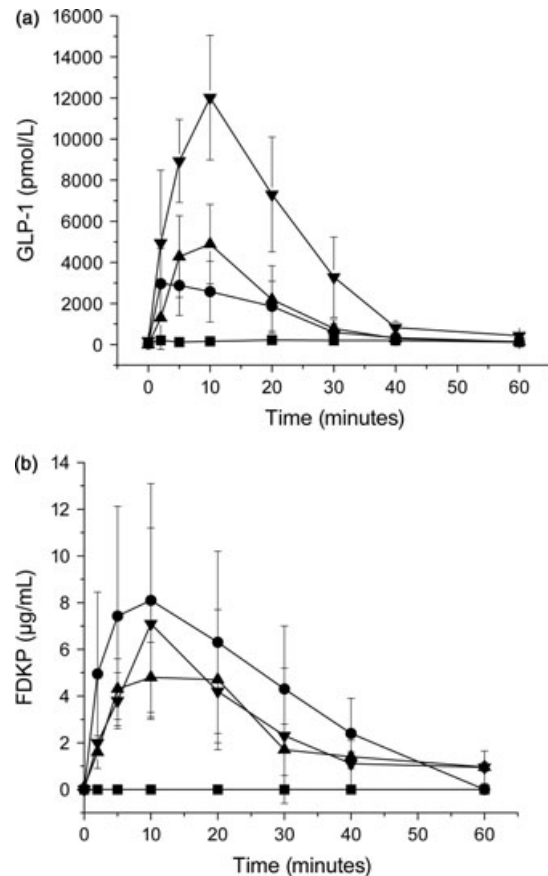
## Results

The %RF for the three GLP-1 Technosphere formulations were 48.8, 57.0 and 32.3% for the 5, 10 and 15% GLP-1 Technosphere Powder respectively. These data demonstrate that >30% of the particles in each of these formulations are in the respirable range. The GLP-1 Technosphere formulations were next evaluated for their ability to deliver GLP-1 by the pulmonary route in rats.

In the rat pharmacokinetic study, maximum plasma GLP-1 concentrations ( $C_{max}$ ) were observed 5–10 min after dosing. Rats receiving 5, 10 and 15% GLP-1 Technosphere Powder reached an average  $C_{max}$  of 2660, 4990 and 11 700 pM GLP-1, respectively (figure 3a), with a circulating half-life of 10–15 min and a time to mean peak maximum systemic GLP-1 concentration ( $T_{max}$ ) of 2–10 min. Both peak GLP-1 concentrations ( $C_{max}$ ) and areas under the concentration vs. time curves were dose-dependent (table 2).

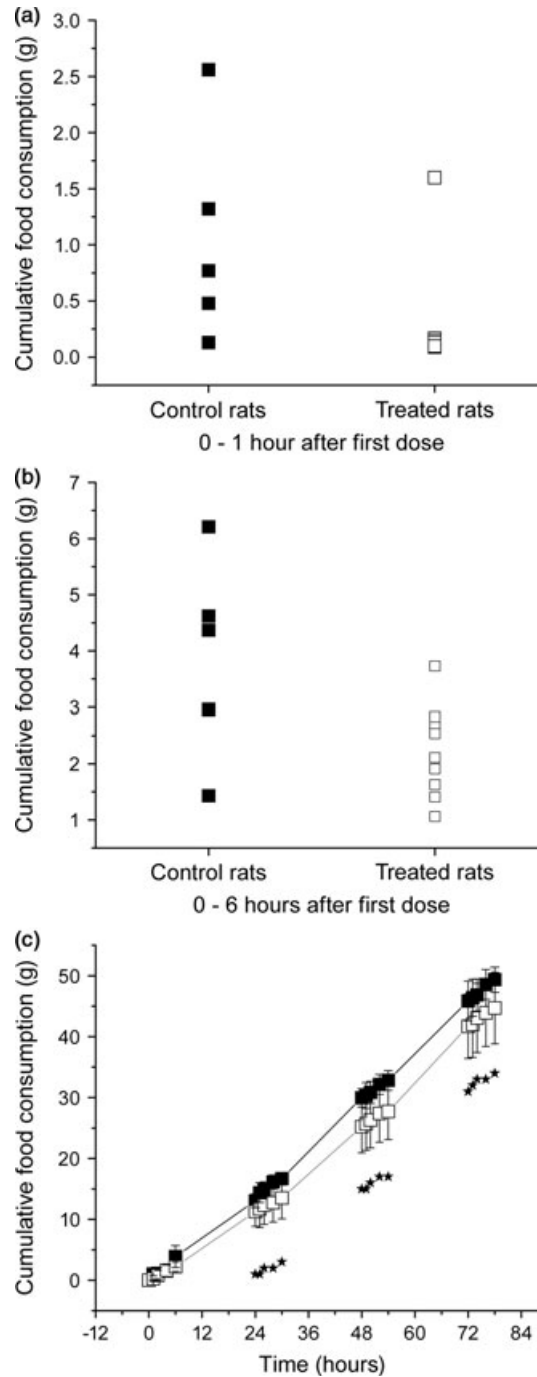
Technosphere particles dissolve rapidly at the physiological pH of the lung and the FDKP molecules are absorbed [17–22]; hence, the dissolution of Technosphere particles was tracked by FDKP absorption (figure 3b). Maximum FDKP concentrations were observed 10 min after dosing. Average  $C_{max}$  was 8.1, 4.8 and 7.1  $\mu$ g/ml following administration of the 5, 10 and 15% GLP-1 Technosphere formulations respectively. This experiment demonstrates that GLP-1 is absorbed following pulmonary insufflation of GLP-1 Technosphere Powder in rats. In addition, a dose–response was observed.

A preliminary pharmacodynamic evaluation was conducted in normal rats. In this study, female Sprague–Dawley rats received air control or 2 mg of 15 wt% GLP-1 Technosphere Powder (0.3 mg GLP-1) by single daily pulmonary insufflation for four consecutive days. The control group contained five rats and the GLP-1 Technosphere Powder group contained 10 rats. Food consumption was measured daily before dosing

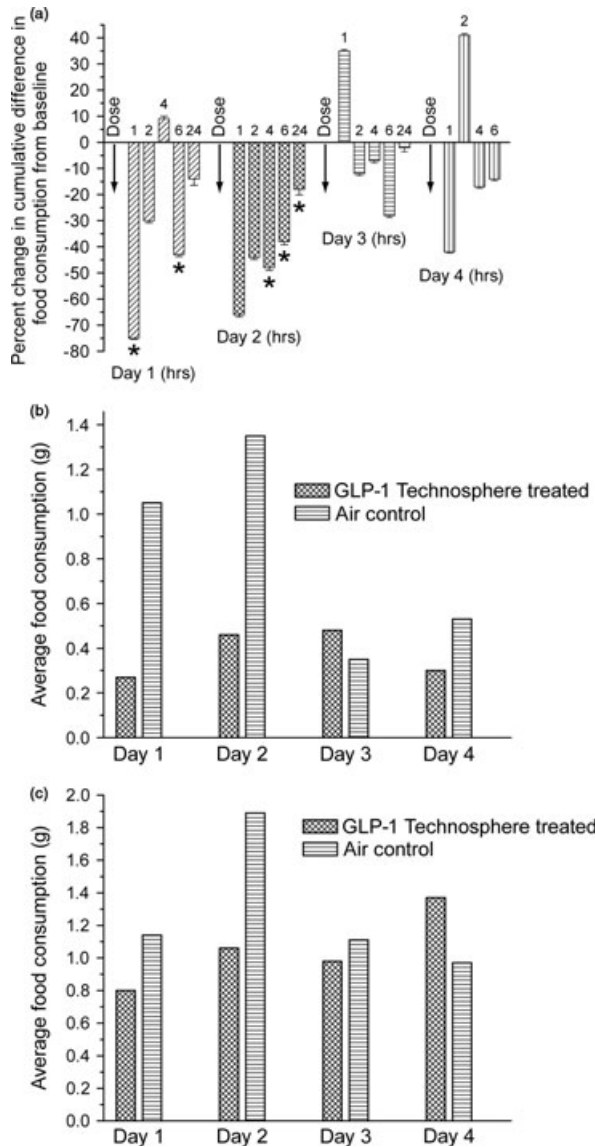


**Fig. 3** Mean plasma concentrations of (a) GLP-1 and (b) FDKP in female rats receiving GLP-1 Technosphere Powder (2 mg/rat) by pulmonary insufflation. GLP-1 alone was administered by pulmonary liquid instillation to three rats. GLP-1 Technosphere Powders were administered by pulmonary insufflation to three groups containing five rats each. The squares (■) represent the response following administration of GLP-1 alone. The circles (●) represent the response following administration of 5% GLP-1 Technosphere Powder. The up triangles (▲) represent the response following administration of 10% GLP-1 Technosphere Powder. The down triangles (▼) represent the response following administration of 15% GLP-1 Technosphere Powder. Data are plotted as group mean  $\pm$  s.d.

and at 1, 2, 4, 6 and 24 h after dosing. One hour after receiving the first dose of GLP-1 Technosphere Powder, 9 of 10 treated rats had consumed <0.2 g of food, compared with only one of five control animals (figure 4a); appetite suppression was still evident up to 6 h after dosing (figure 4b). On average, food consumption was reduced by 75% at 1 h and 43% after 6 h. The reduction in food consumption persisted through successive doses (figure 4c). Nine of the 10 lowest consumers of food were



**Fig. 4** (a) Comparison of food consumption in Sprague-Dawley rats 1 h after the first dose of GLP-1 Technosphere Powder was administered by pulmonary insufflation. Results for individuals are plotted. (b) Comparison of food consumption in Sprague-Dawley rats 6 h after the first dose of GLP-1 Technosphere Powder was administered by pulmonary insufflation. Results for individuals are plotted. (c) Cumulative food consumption following a single daily dose of either air or GLP-1 Technosphere Powder. The black squares (■) represent the control rats. The white squares (□) represent the treated rats. Results are plotted for individuals and group means  $\pm$  s.d. Statistically significant differences in sample means are marked with an asterisk ( $p < 0.05$ , one-tailed  $t$ -test).



**Fig. 5** (a) Average relative difference in food consumption on days 1–4 at 1, 2, 4, 6 and 24 h after administration of GLP-1 Technosphere Powder compared with control. Data are plotted as  $\pm$  s.d. The 24-h data include only study days 1–3. Statistically significant differences in sample means are marked with an asterisk ( $p < 0.05$ , one-tailed  $t$ -test). Mean food consumption over the intervals (b) 0–1 h and (c) 0–2 h on each day of the pharmacodynamic study in Sprague–Dawley rats.

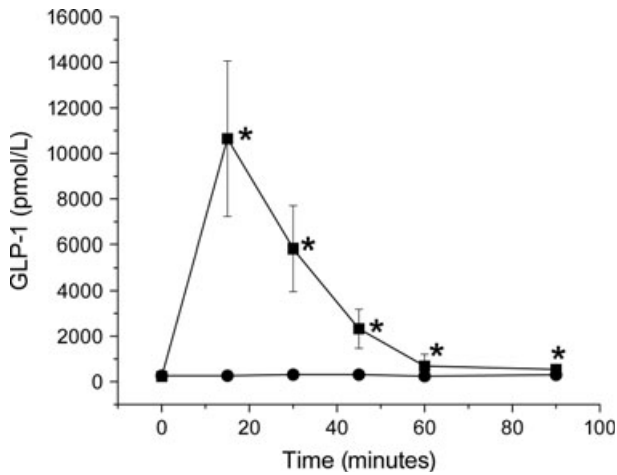
in the treated group. One treated animal ate more food than any other animal.

Analysis of food consumption at each dosing intervals normalized by the average food consumption of the control animals (figure 5a) shows that the greatest relative effect occurs shortly after dosing, but the animals do not fully compensate before the next dose is given. Even 24 h after a single dose of GLP-1 Technosphere Powder, treated animals tended to eat less food than control animals. Body weights were measured daily and were not different between groups at 24 h after each dose.

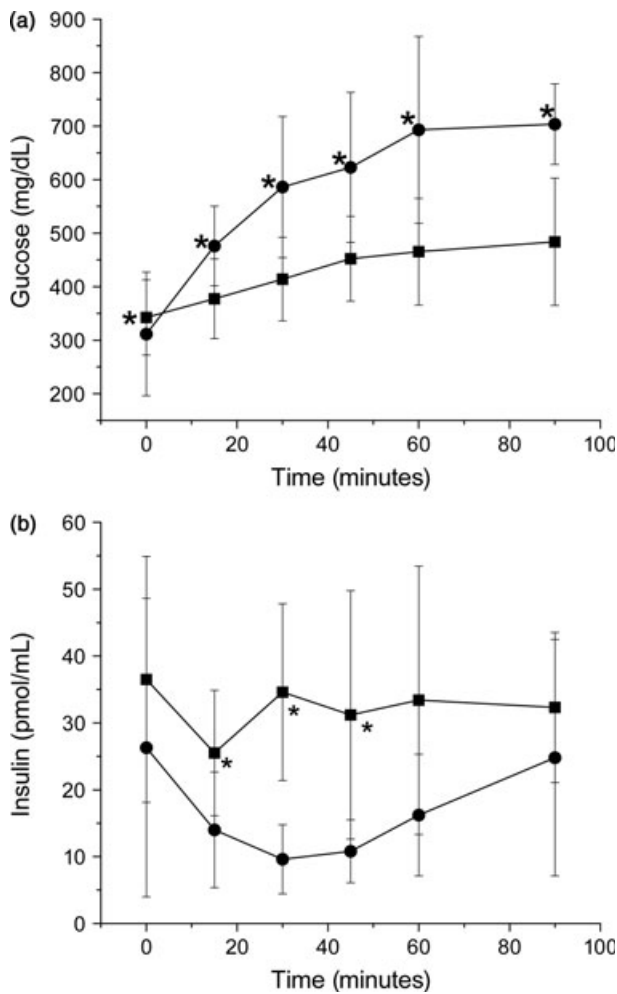
A second pharmacodynamic study was conducted in male Zucker diabetic obese rats to assess the general pharmacokinetic and pharmacodynamic properties of

GLP-1 administered as GLP-1 Technosphere Powder in a recognized animal model of type 2 diabetes [31]. In this study, rats (eight per group) received air control or 2 mg 15 wt% GLP-1 Technosphere Powder (0.3 mg GLP-1) daily for four consecutive days. On day 4 of dosing, an intraperitoneal glucose tolerance test was conducted and blood samples were collected for plasma GLP-1 and glucose analysis. Pancreatic tissues were collected for insulin secretion,  $\beta$ -cell mass and apoptosis analysis by immunohistochemistry.

Pharmacokinetic measurements showed that maximum GLP-1 concentrations of 10 600 pM were reached 15 min after dosing in the treated group (figure 6). In the glucose challenge, this circulating GLP-1 resulted



**Fig. 6** Mean plasma GLP-1 concentrations in male Zucker diabetic obese rats receiving GLP-1 Technosphere Powder by pulmonary insufflation vs. control. The circles (●) represent the response following administration of air control. The squares (■) represent the response following administration of GLP-1 Technosphere Powder. Statistically significant time points ( $p < 0.05$ ,  $t$ -test) are denoted by an asterisk. Data are plotted as  $\pm$  s.d.



**Fig. 7** (a) Glucose concentrations following glucose tolerance test after dosing on day 4 in male Zucker diabetic obese rats receiving GLP-1 Technosphere Powder by pulmonary insufflation vs. control. The circles (●) represent the response following administration of air control. The squares (■) represent the response following administration of GLP-1 Technosphere Powder. Statistically significant time points ( $p < 0.05$ ,  $t$ -test) are denoted by an asterisk. Data are plotted as group mean  $\pm$  s.d. (b) Insulin concentrations following glucose tolerance testing in male Zucker diabetic obese rats receiving GLP-1 Technosphere Powder by pulmonary insufflation vs. control. The circles represent the response following administration of air control. The squares represent the response following administration of GLP-1 Technosphere Powder. Statistically significant time points ( $p < 0.05$ ,  $t$ -test) are denoted by an asterisk. Data are plotted as group mean  $\pm$  s.d.

in blood glucose concentrations that were statistically lower at all time points after dosing in the treated group than in the untreated animals (figure 7a;  $p < 0.05$ ,  $t$ -test). At 90 min after glucose administration, maximum blood

glucose concentrations in the GLP-1 Technosphere Powder group were  $484 \pm 119$  mg/dl compared with  $704 \pm 75$  mg/dl in the control group. Insulin concentrations in control rats decreased significantly during the glucose

challenge, whereas the average insulin concentration in the group receiving GLP-1 Technosphere Powder was stable (figure 7b).

Effects of GLP-1 on insulin levels in pancreatic cells were also evaluated. A dose-related increase in insulin production in the pancreas of obese male rats was observed, as measured by the percentage of  $\beta$ -islet cells expressing insulin. An increase in the insulin-secreting cells per islet ( $51.5 \pm 10.1\%$  vs.  $42.1 \pm 8.4\%$ ) was associated with GLP-1 Technosphere Powder. Neither  $\beta$ -cell mass nor apoptosis were different between groups. These data suggest that the reduced circulating glucose concentrations observed after glucose challenge result from insulin induction rather than an alteration in proliferation or apoptosis.

## Discussion

For these studies, pulmonary insufflation was selected as the dosing route over traditional inhalation chamber techniques. Standard inhalation chambers expose animals to a continuous aerosol cloud of test powder over a period lasting from minutes to hours. Although this technique is useful for toxicology studies in which the goal is to attain a certain exposure, it does not mimic the delivery of drug by a dry powder inhaler in which the drug enters the lungs over a period on the order of 100–500 ms. In contrast, pulmonary insufflation is a close approximation to the ‘delta function’ that is the idealized dry powder inhaler profile [32]. In addition, the technique delivers the powdered test article in a single ‘puff’ placed directly into the trachea of the animal so that the amount of powder reaching the lungs is highly correlated with the amount discharged from the insufflator.

Administration of GLP-1 Technosphere Powder to healthy female Sprague–Dawley rats produced an average reduction in cumulative food consumption of ~10% over the course of the study with a much greater relative reduction shortly after dosing. Over the course of days 3 and 4, treated rats actually ate more food than the control animals immediately following dosing, but consumed less food than the control group overall (figure 5a). These effects do not reflect increased food consumption by the treated animals but are the result of a significant decrease in food consumption by the control group. Food consumption by the treated group is stable or only slightly increased (figure 5b, c).

A pharmacokinetic/pharmacodynamic study in Zucker diabetic obese rats demonstrated GLP-1 exposure comparable with that observed in healthy rats. After 4 days of once-daily dosing, insulin expression in  $\beta$ -islet cells was increased. When subjected to an intraperitoneal glucose

challenge, the treated animals exhibited lower glucose excursions and more stable insulin concentrations than the control animals, and these effects were sustained out to 90 min after dosing. Although the relative contributions of increased insulin induction and GLP-1–driven insulin secretion cannot be determined from the current experiment, the improved pharmacodynamic response is associated with GLP-1 treatment.

Taken together, these studies demonstrate that pulmonary formulations of GLP-1 can be prepared by adsorbing the peptide onto Technosphere particles. Administration of the resulting GLP-1 Technosphere Powder to rats by the pulmonary route results in rapid absorption of pharmacologically active GLP-1 that promotes insulin secretion and controls postprandial glucose hyperglycaemia in a rat model of type 2 diabetes. The high circulating GLP-1 concentrations following pulmonary administration of GLP-1 Technosphere Powder suggest that GLP-1 degradation by DPP-IV in the lung does not preclude this route of administration. These data support the concept of administering native GLP-1 as a diabetes therapy that mimics the natural physiology of healthy individuals.

## Acknowledgements

This study was sponsored by MannKind Corporation. Technical editorial support for this article was provided by MannKind Corporation.

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