Oral Delivery of Insulin Using pH-Responsive Complexation Gels

A. M. LOWMAN,[†,‡] M. MORISHITA,[§] M. KAJITA,[§] T. NAGAI,[§] AND N. A. PEPPAS*[,‡]

Contribution from *Biomaterials and Drug Delivery Laboratories, School of Chemical Engineering, Purdue University, West Lafayette, Indiana 47907, and Department of Pharmaceutics, Hoshi University, Tokyo 142, Japan.*

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Abstract ☐ The goal of oral insulin delivery devices is to protect the sensitive drug from proteolytic degradation in the stomach and upper portion of the small intestine. In this work, we investigate the use of pH-responsive, poly(methacrylic-*g*-ethylene glycol) hydrogels as oral delivery vehicles for insulin. Insulin was loaded into polymeric microspheres and administered orally to healthy and diabetic Wistar rats. In the acidic environment of the stomach, the gels were unswollen due to the formation of intermolecular polymer complexes. The insulin remained in the gel and was protected from proteolytic degradation. In the basic and neutral environments of the intestine, the complexes dissociated which resulted in rapid gel swelling and insulin release. Within 2 h of administration of the insulin-containing polymers, strong dose-dependent hypoglycemic effects were observed in both healthy and diabetic rats. These effects lasted for up to 8 h following administration.

Introduction

Diabetes mellitus affects 20 million people in the U.S. alone.[1] Approximately, 10% of these diabetics are treated using insulin therapy. The most common form of this therapy is twice-daily subcutaneous injections of insulin. This type of treatment is painful and as a result encourages noncompliance by up to half of the diabetics.[2] One way to significantly improve patient compliance would be by developing oral delivery systems for insulin.[3] Oral delivery is the most popular method for drug delivery. However, two problems exist in developing oral delivery systems for insulin. The major problem is the inactivation of insulin by digestive enzymes in the gastrointestinal (GI) system, mainly in the stomach and the proximal regions of the small intestine.[3−10] This can be overcome by designing carriers which can protect the insulin from the harsh environments of the stomach before releasing the drug into more favorable regions of the GI tract, specifically the colon.[4−13] Additionally, researchers have attempted to incorporate protease inhibitors into oral insulin formulations which serve to prevent insulin degradation by the proteolytic enzymes.[4,7−10,12,14]

The other major barrier is the slow transport of insulin across the lining of the colon into the blood stream. Researchers have attempted to bypass this hurdle with the addition of compounds known as absorption enhancers which can facilitate the transport of macromolecules across the lining of the GI tract.[4,7−10]

Several research groups have attempted to use polymeric carriers as oral delivery systems for insulin. Touitou and Rubinstein[11] designed a system consisting of insulin encapsulated by polyacrylates. The coating was designed to dissolve only in the colon. In this work, weak hypoglycemic effects were observed only with very high insulin doses and the addition of absorption enhancers. Saffran[4] developed a system of insulin dispersed in a terpolymer of styrene and hydroxyethyl methacrylate cross-linked with a difunctional azo-containing compound. The azo bond was cleaved by microflora present in the colon, and the polymer degraded allowing for release of insulin into the colon. In this work, a hypoglycemic effect was obtained only with addition of absorption enhancers and protease inhibitors. However, the hypoglycemic effect obtained was not affected by the initial dosing.

Morishita et al.[12] administered insulin contained within Eudragit 100 gels. We observed strong hypoglycemic effects in healthy and diabetic rats after the addition of absorption enhancers. Platé et al.[7] developed a hydrogel system containing immobilized insulin and protease inhibitors that was effective in lowering the blood glucose levels in rabbits. More recently, Mathiowitz et al.[13] have developed insulin containing poly(anhydride) microspheres. These materials adhered to the walls of the small intestine and released insulin based on degradation of the polymeric carrier. They observed a 30−50% decrease in the blood glucose levels of healthy rats.

In this work, we have used a pH-responsive carrier designed to protect the insulin in the harsh, acidic environment of the stomach before releasing the bioactive agent in the small intestine. The delivery system consists of insulin-containing microparticles of cross-linked copolymers of poly(methacrylic acid) which are grafted by ethylene. These new systems glycol (henceforth designated P(MAA-*g*-EG)) function because the structure of the copolymers exhibits pH sensitive swelling behavior due to the reversible formation of interpolymer complexes stabilized by hydrogen bonding between the carboxylic acid protons and the etheric groups on the grafted chains.[15] The complex formation in the insoluble copolymers is sensitive to the nature and pH of the surrounding fluid as well as the copolymer composition and graft chain length.[15]

In the acidic environment of the stomach, the gels are in the complexed state. Under these conditions insulin cannot readily diffuse through the membrane because of the small mesh size, ζ, and is protected from the harsh environment of the stomach.[16] As the particles pass the stomach into the intestine, the environmental pH increases above the transition pH of the gel. The complexes immediately dissociate and the network pore size rapidly increases leading to the release of insulin.[16] Because of their nature, these materials may be ideal for the delivery of drugs at rates specified by the pH of the environmental fluid.[16,17]

Experimental Section

Hydrogel Synthesis—Microparticles of P(MAA-*g*-EG) were prepared[18] by a free-radical bulk, suspension polymerization of methacrylic acid (MAA, Sigma Chemical Co., St. Louis, MO) and

* To whom correspondence should be addressed.
† Current address: Chemical Engineering Department, Drexel University, Philadelphia, PA 19104.
‡ Purdue University.
§ Hoshi University.

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poly(ethylene glycol) (PEG) monomethacrylate (PEGMA, Polysciences Inc., Warrington, PA) with PEG of molecular weight 1000. The MAA was vacuum-distilled prior to use to remove the inhibitor. The PEGMA was used as received.

For the polymerization reaction, the suspending phase, 250 mL of silicon oil, Dow 200 fluid (Dow Chemical Co., Midland, MI) was added to a three-necked flask and heated to 70 °C while being agitated at 250 rpm using an overhead stirrer. A reflux condenser was attached to the flask. The flask was sealed and purged with nitrogen to ensure an inert atmosphere for the reaction vessel.

The monomers were mixed in appropriate molar ratios to yield a 1:1 ratio of MAA:EG units in the gel. Tetraethylene glycol dimethacrylate (TEGDMA, Polysciences Inc., Warrington, PA) was added as a cross-linking agent in the amount of $X = 0.075$ mol of TEGDMA per mole MAA. Following complete dissolution of the monomers, nitrogen was bubbled through the well-mixed solution for 30 min to remove dissolved oxygen, a free radical scavenger, which would act as an inhibitor. 2,2′-Azobis(isobutyronitrile) (AIBN) was added in the amount of 0.5% of the total monomers as the thermal reaction initiator. Poly(dimethyl siloxane-*b*-ethylene oxide) (P(DMS-*b*-EO), Polysciences Inc., Warrington, PA) containing 25% DMS was added in the amount of 1% of total monomers as a surfactant to prevent microparticle aggregation during and after the reaction.

The monomer mixture was added to the oil phase, agitated at 350 rpm, and allowed to react for 3 h at 70 °C. After 3 h, the temperature was increased to 90 °C and allowed to react for an additional 2 h. Following the higher temperature reaction period, the solution was cooled to 37 °C, and the agitation rate was decreased to 250 rpm. Once the temperature reached 37 °C, 20 mL of deionized water was added to the reaction vessel, and the polymer suspension was mixed for an additional 2 h.

The suspension was allowed to settle and the oil was decanted. The reaction flask was filled with deionized water, and the swollen particles were stirred for 24 h at 100 rpm. After 24 h, the particles were filtered and rinsed with fresh deionized water. This process was continued until all of the silicon oil had been removed (approximately one week). Following the washing, the particles were stored in deionized water with the pH adjusted to 8 by the addition of NaOH.

Drug Loading—Drug loading was accomplished by equilibrium partitioning of insulin into the P(MAA-*g*-EG) microparticles. Crystalline porcine insulin (10 mg, 26.9 IU/mg, Shimizu Pharmaceutical Co., Ltd., Shizuoka, Japan) was dissolved in 100 μL of 0.1 N HCl. The insulin solution was diluted with 19.8 mL of phosphate buffer solution (pH = 7.4) and normalized with 100 μL of 0.1 N NaOH. The final pH of the loading solution was 7.4. Loading was accomplished by soaking 140 mg of dried P(MAA-*g*-EG) microparticles for 24 h in the insulin solution. The concentration of insulin in the solution was monitored over time using HPLC.

The particles were then filtered using filter paper with 1 μm pores and washed with 100 mL of 0.1 N HCl solution to collapse the microparticles and exude the remaining buffer solution. The insulin-loaded microspheres were dried under vacuum and stored at 4 °C. The degree of loading was determined from HPLC analysis of the insulin concentrations of the initial solutions and the filtrate from the washings. Using this loading technique, 94 ± 9% of the insulin in the initial solution was entrapped within the polymer.[19] The activity of the insulin loaded in the gels was verified using an Insulin EIA kit (Abbot Laboratories, Chicago, IL).

In Vivo Studies—For these studies, male Wistar rats (200 g) were used. Diabetes was induced[12] in the rats by intraperitoneal injection of streptozotocin (40 mg/kg body weight once daily for three consecutive days) dissolved in citrate buffer at pH = 4.5. The rats were considered diabetic when the fasted glucose levels exceeded 250 mg/dL at 2 weeks following the streptozotocin treatment. The average blood glucose levels of the healthy animals used in the studies was 80 mg/dL while the diabetic animals had average glucose levels of 345 mg/dL.

Prior to administration of the insulin-loaded polymer, the animals were fasted for 48 h. The rats were restrained in the supine position. The insulin-loaded P(MAA-*g*-EG) microparticles and the control solutions were administered via the mouth using a gelatin capsule. The gelatin capsules dissolved readily in the stomach. During the experiment, a 0.2 mL aliquot of blood was collected from the jugular vein at 0.25, 0.5, 1, 2, 4, 6, and 8 h following dosing. The blood serum was separated by centrifugation at 3000 rpm for 3 min and stored in a freezer until analysis. The serum insulin levels were determined by an enzyme immunoassay using an Insulin EIA kit (Abbot Laboratories, Chicago, IL). Serum glucose levels were determined by the glucose oxidase method using a glucose B-test kit.

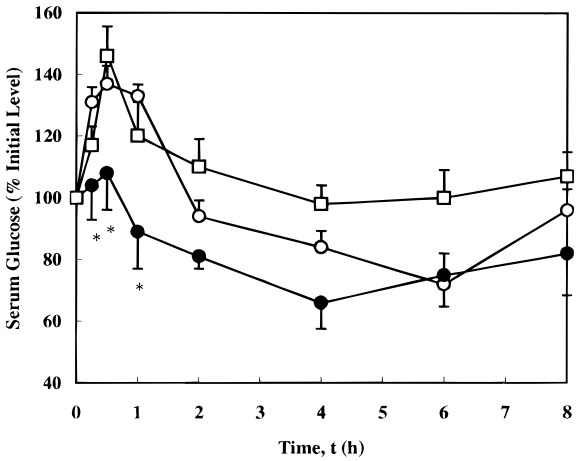

Figure 1—Blood glucose response in healthy male Wistar rats following the oral administration of P(MAA-*g*-EG) microspheres containing insulin doses of (○) 25 IU/kg body weight ($n = 7$) and (●) 50 IU/kg body weight ($n = 5$) and (□) insulin solutions (50 IU/kg body weight, $n = 4$). Comparison calculated between the doses at each point *$p < 0.05$.

To determine the relative efficacy of each formulation, healthy and diabetic rats received sc injections, and the blood glucose levels were monitored over time. Healthy rats received injections of 0.5, 1, and 3 IU/kg, while diabetic rats received injections of 0.25, 0.5, and 1.0 IU/kg. The cumulative area under the curve (AUC) was determined from each dosage, and the following dose dependent AUC relationships were developed for subcutaneous injections:

$$\text{healthy Rats } (n = 4): \quad AUC = 219.29 \log(\text{sc dose}) + 145.96 \tag{1a}$$

$$\text{diabetic Rats } (n = 4): \quad AUC = 512.64 \log(\text{sc dose}) + 319.76 \tag{1b}$$

Results and Discussion

In designing a device for oral delivery of sensitive peptide drugs such as insulin, it was important to protect the drug in the harsh environment of the stomach and upper GI tract and release the drug into the distal portions of the intestine. Therefore, in an effective carrier the release rates must be significantly greater in neutral or basic conditions than acidic conditions. One significant parameter in evaluating the viability of a particular hydrogel for oral delivery of proteins and peptides was the ratio of the diffusion coefficients of the drug in the carrier in the stomach (acid environment) and the intestine (neutral environment). In the P(MAA-*g*-EG) gels, the release rates in neutral or basic conditions were more than 1 order of magnitude greater than the release rates in acidic solutions.[16]

In Vivo Response to Oral Administration of P(MAA-*g*-EG) Microspheres—The blood glucose response of rats following oral administration of insulin doses contained in P(MAA-*g*-EG) microparticles is shown in Figure 1. The rats received insulin doses of 25 IU/kg and 50 IU/kg contained in the polymer microparticles and a control solution (50 IU/kg). Initially, the blood glucose levels rose due to the physical stress on the animals during administration and blood sampling. The initial rise was followed by a decrease back to normal levels due to absorption into the muscle. Because of the nature of these gels, little if any of the insulin was released in the stomach, as the gels were in the collapsed state due to the formation of polymer

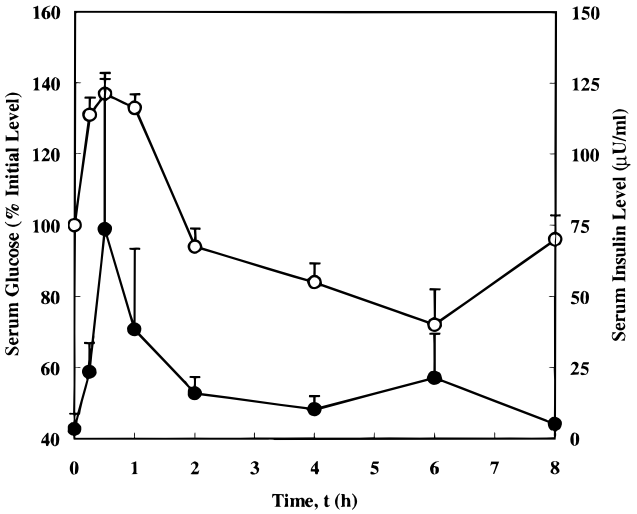

Figure 2—Serum (○) glucose and (●) insulin levels in healthy male Wistar rats following oral administration of insulin-containing P(MAA-g-EG) microspheres (25 IU/kg body weight doses) ($n = 7$).

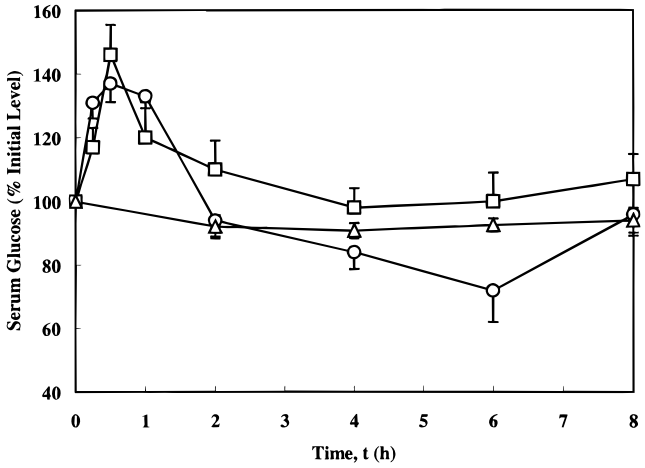

Figure 3—Blood glucose response in healthy male Wistar rats following the oral administration of 25 IU/kg body weight insulin doses contained (○) P(MAA-*g*-EG) microparticles ($n = 5$) and (△) Eudragit microspheres ($n = 10$) and (□) insulin solutions ($n = 4$).

complexes in the acidic environment of the stomach. The insulin was protected inside of the gel from the proteolytic enzymes that were unable to penetrate the gel.

Within 2 h of receiving the polymeric dosage form, a strong hypoglycemic effect or lowering of the blood glucose level was observed in the animals that had received the polymeric dosage forms. This was clear evidence that the insulin was delivered effectively in the biologically active form to the small intestine. Insulin delivery in the small intestine was due to the rapid dissociation of the polymer complexes in the basic environment of the intestine. As the complexes dissociated, the pore size of the gels increased dramatically, and insulin was rapidly released into the intestine. Additionally, the reduction of the blood glucose levels depended strongly on the insulin dose. The reduction in blood sugar was greater in the animals receiving the higher doses of insulin (50 IU/kg). The hypoglycemic effects were present for up to 8 h in these animals.

The serum insulin levels of the rats following oral administration of the dosage forms are shown in Figure 2. Within 1 h of administration, the insulin levels in the rats receiving the insulin containing rose to greater than 20 times their initial levels. The serum insulin levels remained at elevated levels for up to 6 h following administration as the polymer delivered the insulin to the proximal small intestine. As a result, the blood glucose levels were decreased for the period.

One major reason for the effectiveness of this device is the pH-sensitive swelling behavior of the gels. However, such strong effects could not be obtained with the use of another pH-responsive carrier that had been used as oral delivery vehicle for insulin, Eudragit L100. In our previous work,[12] we prepared insulin-containing microspheres of Eudragit L100 to serve as oral insulin delivery systems. A comparison of the hypoglycemic effects following oral administration of 25 IU/kg doses of insulin contained in P(MAA-*g*-EG) and Eudragit L100 microparticles is shown in Figure 3. Clearly, the hypoglycemic effects observed following administration of the complexation gels are much greater than those obtained using the Eudragit carrier.

The P(MAA-*g*-EG) gels are significantly more effective in delivering biologically active insulin than traditional enteric coating-type carriers because of the presence of the PEG-grafts. Such strong hypoglycemic effects were not observed using other oral delivery carriers without the addition of additives such as protease inhibitors or absorption enhancers.[4,7,12,13] The addition of PEG to the gels is critical because the PEG chains participate in the macromolecular complexes, function as a peptide stabilizer, and enhance the mucoadhesive characteristics of the gels. In these gels, the PEG will form interpolymer complexes with the PMAA in acidic media. Not only do the complexes contribute strongly to the pH-dependent changes in the network structure,[15–18] they also serve to stabilize the insulin.[16,20] Additionally, the presence of the PEG grafts helps maintain the biological activity of the insulin by stabilizing the drug and preventing binding to ionizable backbone chain.[16,17,21]

Another important characteristic of these gels is their ability to adhere more strongly to the mucosa of the small intestine than the mucosa of the stomach. This is significant because the major impetus for controlled drug release is to maintain a steady flux of an active agent over an extended period of time. One such means of increasing the residence time would be through the use of a mucoadhesive carrier. The primary goal of such devices is to localize the delivery vehicle within the desired location to enhance the drug absorption process in a site-specific manner.[22–24] Hydrogels of P(MAA-*g*-EG) exhibit excellent mucoadhesive characteristics for delivery of drugs to the small intestine due to the presence of the graft PEG chains which serve as adhesion promoters.[16,17] Adhesion promoters, such as polymer grafts or even linear polymers, function by penetrating the gel/mucosa or gel/gel interface and forming temporary anchors.[25,26]

The mucoadhesive characteristics of P(MAA-*g*-EG) hydrogels are strongly dependent on the pH of the environmental fluid. These gels adhere to the mucosa of the intestine to a much greater extent than the stomach.[16] Therefore, the residence of insulin carriers would be much greater in regions where the insulin could be absorbed, such as the distal regions of the small instestine.

The reduction of blood glucose in healthy animals following oral administration of the insulin-loaded polymers was significant in that it showed the efficacy of P(MAA-*g*-EG) carriers. However, it is more significant if these results can be obtained in diabetic animals. The blood glucose response of diabetic rats following oral administration of insulin containing P(MAA-*g*-EG) microparticles (25 IU/kg doses) is shown in Figure 4. The blood glucose levels of the diabetic rats were lowered by up to 40% for greater than 8 h. The degree to which the glucose levels were suppressed was in fact greater for the diabetic animals

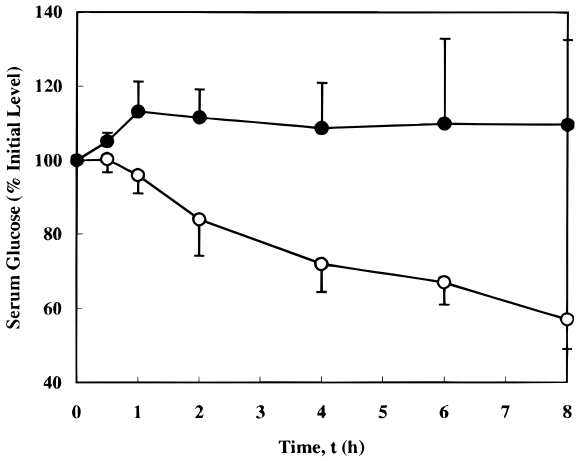

Figure 4—Blood glucose in diabetic, male Wistar rats following oral administration of 25 IU/kg body weight doses contained in (○) P(MAA-*g*-EG) microspheres and (●) insulin solutions ($n = 5$).

Table 1—Efficacy of Oral Administration of Insulin Using Complexation Polymers Relative to iv Injection

dosage form	insulin dose (IU/kg)	bioavailability	
		healthy rats	diabetic rats
P(MAA-g-EG)	25	3.40 ± 1.53	2.44 ± 0.41
	50	4.22 ± 2.09	ND[a]
solution	25	ND	0.88 ± 0.34
	50	0.55 ± 0.08	ND
Eudragit L100[12]	25	0.9 ± 0.3	1.1 ± 0.2

[a] ND: no data collected.

than the healthy animals. Additionally, the strong hypoglycemic effects were observed to last longer in the diabetic animals.

Relative Efficacy of P(MAA-*g*-EG) Carriers to S. C. Injection—The overall efficacy of each of the formulations was determined in comparison to the efficacy of an iv injection. For each dosage form, the AUC was determined. The overall efficacy was determined as the ratio of the AUC for the oral dosage divided by the AUC for a sc injection of the same dose. These data appear in Table 1. When the insulin was administered orally using solutions, the efficacy of the formulation in comparison to sc injection was less than 1%. However, when the insulin was delivered using polymer microparticles, the efficacy was increased significantly. Of all of the samples tested, the greatest efficacy or bioavailibility (4.22%) was observed for the P(MAA-*g*-EG) gels containing 50 IU/kg doses delivered to healthy rats. Significant bioavailibilities were also observed for polymers containing 25 IU/kg doses in both healthy and diabetic animals. All of the P(MAA-*g*-EG) devices were found to be significantly more effective than Eudragit L100 as oral delivery devices for insulin.

Conclusions

Oral insulin delivery systems must be able to protect the sensitive macromolecular drug from the harsh environment of the stomach and deliver biologically active insulin for an extended period of time to more favorable regions for absorption along the GI tract. Because of their nature, complexing P(MAA-*g*-EG) hydrogels are ideal for such an application. P(MAA-*g*-EG) hydrogels were able to effectively deliver biological active insulin via the oral route. Microparticles prepared from these gels were prepared and loaded with insulin. Following administration of insulin-loaded microparticles to healthy and diabetic rats, the blood glucose levels in these animals were decreased significantly for at least 8 h due to the absorption of insulin in the GI tract. The strong hypoglycemic effects were observed without the addition of additives such as absorption enhancers or protease inhibitors and were found to be strongly dependent on the administered dose.

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