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Research Paper

Magnetically Responsive Polymeric Microparticles for Oral Delivery of Protein Drugs

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Purpose. Protein drugs cannot be delivered efficiently through oral routes. To address this challenge, we evaluated the effect of prolonged gastrointestinal transit on the bioavailability of insulin carried by magnetically responsive microparticles in the presence of an external magnetic field.
Methods. Magnetite nanocrystals and insulin were coencapsulated into poly(lactide-*co*-glycolide) (PLGA) microparticles and their effects on hypoglycemia were evaluated in mice in the presence of a circumferentially applied external magnetic field.
Results. A single administration of 100 U/kg of insulin–magnetite–PLGA microparticles to fasted mice resulted in a reduction of blood glucose levels of up to 43.8% in the presence of an external magnetic field for 20 h (bioavailability = 2.77 ± 0.46 and 0.87 ± 0.29% based on glucose and ELISA assay, respectively), significantly higher than similarly dosed mice without a magnetic field (bioavailability = 0.66 ± 0.56 and 0.30 ± 0.06%, based on glucose and ELISA assay, respectively).
Conclusions. A substantially improved hypoglycemic effect was observed in mice that were orally administered with insulin–magnetite–PLGA microparticles in the presence of an external magnetic field, suggesting that magnetic force can be used to improve the efficiency of orally delivered protein therapeutics.

KEY WORDS: insulin; magnetic particles; microparticles; oral delivery; protein drugs.

INTRODUCTION

The development of technologies for oral delivery of peptides and protein therapeutics has been an area of extensive investigation for several decades. This route of administration is preferred because oral drug delivery results in improved patient compliance and comfort compared to the parenteral route of administration. Despite this, parenteral routes of drug delivery are used in the majority of FDA-approved protein drugs, demonstrating the need for the development of clinically effective oral delivery systems for protein therapeutics.

Orally administered protein therapeutics encounter many obstacles before being absorbed into the circulatory system. These barriers include acidic and enzymatic degradation in the stomach and low levels of permeability across the intestinal mucosal membranes (1). To alleviate these difficulties, many approaches have been used for protecting proteins, such as insulin, from degradation during administration. These approaches have included encapsulation within pH-sensitive hydrogels (2), liposomes (3–5), polymeric nanoparticles (6, 7), and the use of permeation enhancers (8–10) and enzyme inhibitors (11). Despite many years of research, no clinically feasible approaches exist to deliver protein drugs orally.

Biodegradable polymers, such as FDA-approved poly (lactic acid) (PLA) and poly(lactide-*co*-glycolide acid) (PLGA), may be potentially useful as materials for oral delivery vehicles. Such particles can be easily prepared with high protein encapsulation efficiencies (>50%), as well as with the capability to effectively protect encapsulated proteins from degradation in the gastrointestinal tract (GIT) (1). However, only a small fraction of the particles is absorbed by the intestine, because the residence time of these particles is relatively low (~4–6 h) due to the intestinal fluid flow and peristalsis action of the small intestine (12). To improve the degree of protein absorption, various methods have been used to increase the residence time of delivery vehicles within the small intestine. One such method is the use of mucoadhesive polymers (13).

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Recently, Whitehead *et al.* (14) reported that a mucoadhesive, insulin-containing intestinal patch successfully induced hypoglycemia in rats because of the release of insulin from the patch. This study suggests that insulin that is protected from degradation until it reaches the small intestine can be absorbed into the bloodstream in its biologically active form (14). Therefore, a noninvasive system that releases insulin in the small intestine without being absorbed may be advantageous in comparison to insulin-containing nanoparticles that can be absorbed.

Magnetically modulated particulate systems have recently attracted much attention for *in vivo* imaging and targeted drug delivery (15). In this approach, imaging agents or drugs can be localized to specific sites through the application of an external magnetic field. Building on our previous work using magnetic force to increase the intestinal retention of magnetite containing liposomes (16), we developed a magnetically responsive polymeric delivery system that can safely and effectively enhance the oral delivery of therapeutic proteins. As a proof of concept, we tested the feasibility of the proposed approach for oral delivery of insulin for treatment of a mouse model. We hypothesized that the application of magnetic forces in the intestinal area to localize insulin controlled-release vehicles could improve the drug delivery efficiency. The application of an external magnetic field applied to the intestinal area, as with a magnetic belt, would slow down the transit of magnetite-containing polymeric particles and extend the residence time of the orally delivered microparticles (MP) in the small intestine, which will potentially increase the absorption of protein drugs. We developed PLGA microparticles comprising magnetite nanoparticles coencapsulated with insulin. We demonstrate that insulin delivery from PLGA microparticles is significantly greater in the presence of a magnetic field, resulting in a substantially improved hypoglycemic effect in mice. Therefore, magnetic forces can be potentially used to improve the efficiency of orally delivered protein therapeutics.

MATERIALS AND METHODS

Materials

Human insulin (Humulin R, 500 U/mL) was purchased from Drugstore.com (Bellevue, WA, USA). PLGA (50:50) with acid terminal groups (inherent viscosity 0.18 dL/g) was obtained from Absorbable Polymers International (Pelham, AL, USA). Poly(vinyl alcohol) (PVA, M_W = 30 kDa), iron (III) chloride, and iron (II) chloride were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received. Scanning electron microscopy (SEM) was recorded on a JEOL JSM 6060 system. Fluorescent images were taken on an Axiovert 200 inverted microscope (Zeiss). Magnets (Neodymium iron boron rare earth magnets, 1 × 1 × 0.5 in. (thickness), Grade N40, magnetized through the thickness) were purchased from Amazing Magnets amazingmagnets.com). (3-[^{125}I]Iodotyrosyl^{A14}) insulin (human recombinant) was obtained from Amersham Biosciences (Piscataway, NJ, USA). Radioactivities of ^{125}I insulin or ^{125}I insulin containing MPs were analyzed on a TRI-CARB Liquid Scintillation Analyzer (Model 2200CA; Packard Instrument, Downers Grove, IL, USA). Hionic-Fluor and Scinti-Safe scintillation cocktails and Solvable tissue solubilizer were purchased from Packard. Magnetite nanocrystals were synthesized following the published procedure (17). Balb/c mice (8 weeks old) were purchased from Charles River Laboratories (Wilmington, MA, USA).

Preparation of Insulin–Magnetite–PLGA Microparticles

Insulin and magnetite coencapsulated MPs were prepared using the water-in-oil-in-water solvent evaporation procedure (double emulsion). A portion (50 μL) of the insulin solution (Humulin R, 500 U/mL) was emulsified with 50 mg PLGA in dichloromethane (1 mL) and 1–5 mg of magnetite nanocrystals for 30 s using a probe sonicator at 10 W. The first emulsion was transferred to a 50-mL aqueous PVA solution (1% w/v) and homogenized at 8,000 cycles/min for 1 min. The resulting emulsion was immediately poured into a 150-mL aqueous PVA solution (0.3 % w/v) with gentle stirring. Dichloromethane was removed through slow evaporation at room temperature for 2.5 h. The resulting insulin and magnetite coencapsulated MPs were isolated as a gray to light brown solid by centrifugation at 3,200 × *g* at 10 °C for 10 min, washed twice with double-distilled water and lyophilized.

Preparation of all other MPs (either PLGA or PLA) with encapsulated insulin (either Humulin R or ^{125}I insulin) either with or without magnetite were the same as described above using appropriate materials.

MP Characterization

The sizes of MPs were measured on a Beckman Coulter Multisizer™-3. Electrophoretic mobilities were measured at 25 °C on a ZetaPALS dynamic light scattering system (Brookhaven Instruments Corporation, Holtsville, NY, USA) using BIC PALS zeta potential analysis software. Zeta potentials were calculated using the Smoluchowsky model.

Encapsulation efficiency was determined using MPs encapsulating ^{125}I-labeled insulin. The supernatant after centrifugation was collected and measured along with an aliquot of MPs by liquid scintillation counting. The encapsulation efficiency was calculated by the difference between the total amount of radioactivity in the initial solution and the remaining amount in the supernatant.

In Vitro Magnetic Responsiveness

An apparatus approximating the physiology of the mouse small intestine was constructed. A syringe pump (New Era Pump Systems, model NE-1600) was used to generate a constant flow rate in silicone tubing (inner diameter: 1/16 in.; Fig. 2) through syringe B. The flow rate of the mobile phase (1× PBS, pH = 7.4) was maintained constant at 2.5 mL/min. The tubing diameter was selected to approximate the mouse small intestine (18). PLA–^{125}I insulin–magnetite MPs (~0.5 μCi) was injected into the system through syringe A. MPs containing no magnetite served as the control. The magnets were applied to the model system at the same distance as during *in vivo* studies. The eluted liquid was collected at scheduled time points (20 s to 1 min interval). Scinti-Safe scintillation cocktail (10 mL) was added to the liquid, and radioactivity was measured by liquid scintillation counting.

In Vivo Magnetic Responsiveness

Animals were cared for under the supervision of MIT's Division of Comparative Medicine and in compliance with NIH's *Principles of Laboratory Animal Care*.

For quantitative determination of magnetic responsiveness, Balb/c mice were fasted for 12 h and then orally administered with 1 μCi ^{125}I insulin–magnetite (2 wt.%)–PLGA MPs in 200 μL water. Forty minutes after administration, mice were restrained. A magnet was placed near the abdominal area with magnetization surface facing abdomen. Mice were sacrificed at 6 and 12 h. The small intestine was homogenized, and approximately 100 mg of the homogenized intestine mixture was placed in a 20-mL scintillation vial. Solvable tissue solubilizer (2 mL) was added to the vial and then incubated until the tissue completely dissolved (6–10 h) at 55°C. After the solution was cooled to room temperature, an EDTA–disodium solution (0.05 mL, 0.1 M) was added to the vial, followed by slow addition of 0.2 mL 30% hydrogen peroxide. The solution was agitated gently between additions of hydrogen peroxide to allow reaction and foaming to subside. The solution was then incubated in the oven at 55°C for another hour to result in a colorless solution. Scintillation cocktail (10 mL Hionic-Fluor) was added to the liquid. Samples were acclimated to light and temperature conditions in the counter for 30 min prior to counting, and the radioactivity was measured by liquid scintillation counting.

In Vivo Efficacy

Balb/c mice were fasted for 12 h and then orally administered with Humulin R-PLGA–magnetite (8 wt.%)–PLGA MPs at 100 U/kg. Five mice were assigned to each group such that the mean values of their initial glucose levels were identical. Humulin R-PLGA–magnetite (100 U/kg) in 400 μL water was administrated orally using syringe with gavage needles. Control mice were administered with 200 μL water only. Ninety minutes after administration, mice were restrained in the presence or absence of a magnetic field (similar as above). The glucose level of each mouse was monitored over time by collecting blood from the tail vein and measuring using the One Touch Ultra glucose monitor (Lifescan, Milpitas, CA, USA). As an intravenous standard, 0.5 U/kg of Humulin R was injected into the tail vein, and the glucose level was monitored as described above. To calculate the biological effect, the area under curve (AUC) for the plot of decrease in blood glucose levels (%) over time (h) were calculated using the trapezoidal method. Bioavailability (f) was calculated based on Eq. (1) (7, 19, 20).

$$f = \frac{\dfrac{\mathrm{AUC_{oral}} \times \mathrm{weight_{oral}}}{\mathrm{Dose_{oral}}}}{\dfrac{\mathrm{AUC_{i.v.}} \times \mathrm{weight_{i.v.}}}{\mathrm{Dose_{i.v.}}}} \times 100\% \qquad (1)$$

To measure *in vivo* insulin concentration, the above experiment was performed, blood (~25 μL) samples were collected into Sarstedt serum gel microtubes. Serum (5 μL) was analyzed for insulin content by the Mercodia insulin ELISA kit (ALPCO Diagnostics, Inc., Windham, NH, USA). As an intravenous standard, 2 U/kg Humulin R was injected into the tail vein, and insulin concentration was similarly detected. Bioavailability (f) was also calculated based on Eq. (1) as described above.

Results in the text are expressed as mean ± SD unless otherwise stated. Data were analyzed using ANOVA. For statistical tests, a p value of 0.05 or less was considered significant.

Acute Toxicity Histological Analysis

Mice were gavaged with magnetite–PLGA MPs and restrained in the presence of the magnetic field, as described above in the efficacy study. After 24 h, mice were sacrificed, and tissues were harvested for analysis of acute toxicity.

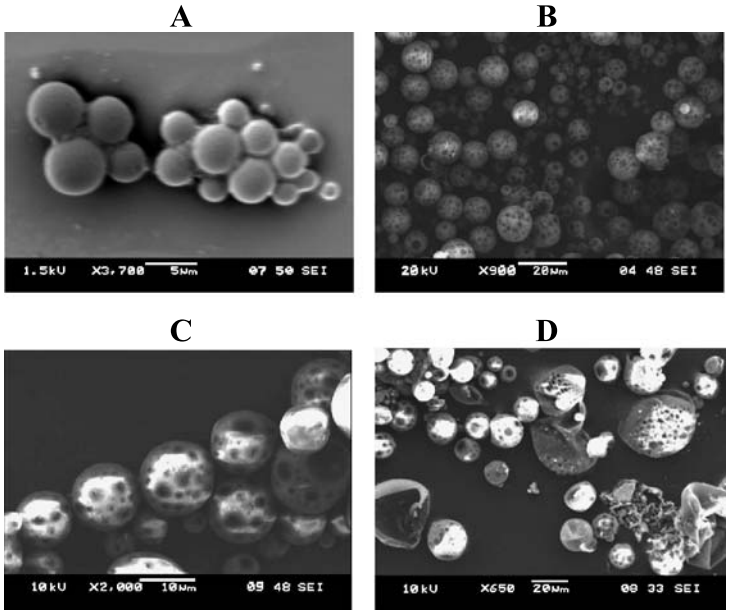

Fig. 1. SEM images of Humulin R-encapsulated, magnetite–PLGA image/MPs. Magnetite content in weight percentage: (A) 0%, (B) 2%, (C) 5%, (D) 10%.

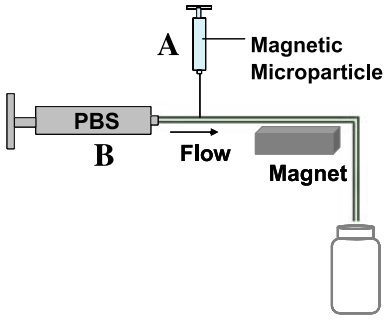

Fig. 2. Schematic representation of the *in vitro* flow apparatus for the study of magnetic responsiveness of the ^{125}I insulin–magnetite–PLGA microparticles. Microparticles containing 0.5 μCi ^{125}I radioactivity were introduced to the flow system through syringe A. Syringe B delivered a mobile phase at 2.5 mL/min (PBS, 1×, pH = 7.4). A magnet was placed under the silicone tubing between the injection site and the collection vials

For comparison, control mice were similarly sacrificed and treated. Tissue sections from the small intestine, spleen, kidney, and liver were fixed in 10% formalin and processed for histology as per standard techniques. Sections were stained with hematoxylin and eosin (H&E) and investigated for acute inflammation and particle toxicity. Sections were stained for colloidal iron using the Mallory method with Prussian Blue to determine magnetite uptake by the body. Magnetite–PLGA MPs were separately embedded and stained as a positive control for the iron staining.

RESULTS AND DISCUSSION

To incorporate magnetic targeting into an oral drug delivery system, we coencapsulated magnetite (10–15 nm in diameter as measured by transmission electron microscopy; data not shown) and insulin into polymer microparticles using the double emulsion method. Phase separation of the hydrophobic PLGA in the organic phase from the aqueous phase results in random distribution of the magnetite nanocrystals in the PLGA matrix and generates magnetically responsive polymeric MPs. The average sizes of MPs containing 0, 2, and 5 wt.% magnetite are 4.6, 6.4, and 7.2 μm with insulin encapsulation efficiencies of 68, 78, and 79%, respectively. MPs containing 2–5% magnetite are 40–56% larger than MPs without magnetite. The spherical structures of MPs containing 0–5% magnetite were very well maintained, and the majority of particles observed under SEM show minimum disruption of their spherical structures (Fig. 1A–C). When the content of magnetite increases to 10%, however, the spherical structures of the resulting MPs become less stable. The lower stability of the MPs may be attributable to the weakening of the polymer matrix connections with increased magnetite nanocrystal content (Fig. 1D).

The retention of MPs in the small intestine was modeled *in vitro* using a flow system as shown in Fig. 2. Silicone tubing with similar internal diameter as the small intestine of the mouse was used as the model system. To measure the retention of magnetite-containing MPs in the presence of an external field, an aliquot of ^{125}I insulin coencapsulated PLA MPs was injected into the flow apparatus. PLA MPs, instead of PLGA MPs, were used in this study to minimize the initial burst release of free ^{125}I insulin, to facilitate the accurate measurement of eluded particles rather than released insulin. The flow rate of mobile phase (1× PBS, pH = 7.4) was maintained at 2.5 mL/min even though the fluid flow rate in the small intestine of mouse is estimated to 0.03 mL/min (18, 21). We purposely chose a flow rate much higher than the actual flow rate in the mouse small intestine to counterbalance intestinal contraction forces that cannot be easily modeled and thus were omitted in this study.

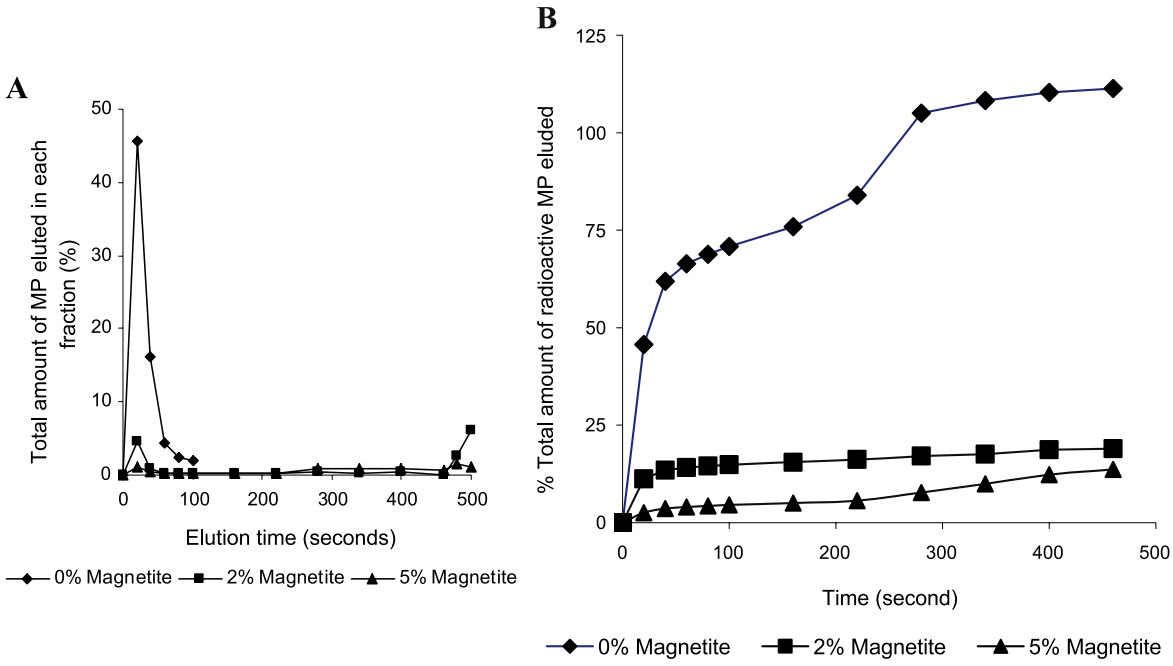

Fig. 3. (A) Elution of ^{125}I insulin–PLA MPs containing 0, 2, and 5% magnetite from the *in vitro* flow apparatus (shown in Fig. 2) in the presence of a magnetic field. (B) Cumulative profile for the elution of ^{125}I insulin–PLA MPs containing 0, 2, and 5% magnetite from the *in vitro* flow apparatus in the presence of a magnetic field.

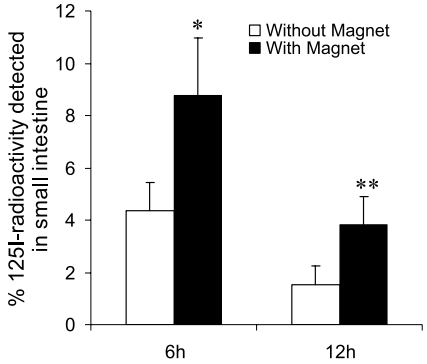

Fig. 4. *In vivo* intestine retention of mice treated with 1 μCi ^{125}I insulin–magnetite (2 wt.%)–PLGA microparticles, restrained in the presence or absence of a magnetic field. Small intestines were collected, solubilized, and analyzed using a scintillation counter at 6 and 12 h. (*p = 0.015; **p = 0.039).

^{125}I activity of each fraction collected from the *in vitro* flow apparatus was analyzed on a scintillation counter and normalized against the total amount of radioactivity in the PLA MPs injected through syringe B. In the presence of an external magnetic field, elution of the majority of the MPs without magnetite occurred in a shorter time compared to the elution of magnetite-containing MPs (Fig. 3A). Cumulatively, 66.4% elution of control MPs was observed during the first minute as compared to 14.1 and 4.0% for the MPs containing 2 and 5% of magnetites, respectively (Fig. 3B). When control MPs were completely eluded at t = 5 min, only 17.1 and 7.7% of MPs containing 2 and 5% of magnetite, respectively, were eluded. This study demonstrated that magnetite encapsulation in PLA MP induced magnetic responsiveness of the particles. The retention of the magnetite-containing MPs under a constant flow rate is inversely proportional to the magnetite content in these MPs.

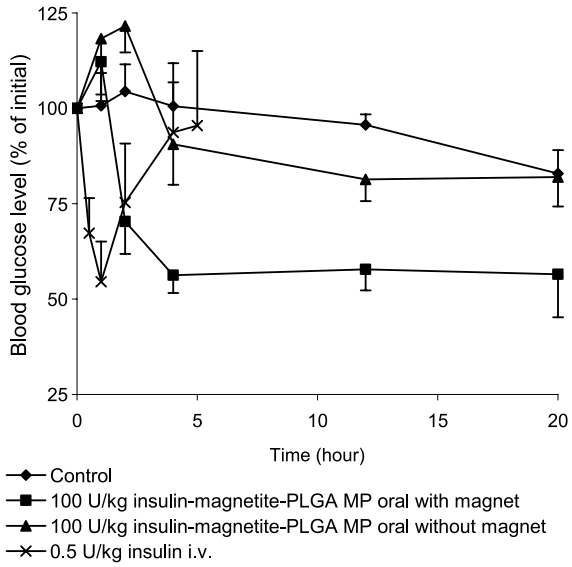

Fig. 5. Glucose reduction by insulin (0.5 U/kg, i.v.) and by insulin–magnetite (8%)–PLGA microparticles (100 U/kg) in mice in the presence or absence of a magnetic field ($p_{w-w/o}$ < 0.01).

The use of an external magnetic field to increase the retention of ^{125}I insulin–magnetite–PLGA MPs *in vivo* was evaluated in mice. After 6 h, the recovered radioactivity in the small intestine, as a percentage of total dose, was 8.75 ± 2.2 and 4.35 ± 1.1% (p = 0.015) for the groups applied with external magnets and the groups in the absence of a magnetic field, respectively. At 12 h, the amount recovered for the respective groups was 3.80 ± 1.1 and 1.55 ± 0.7% (p = 0.039), respectively. Thus, the intestinal retention of ^{125}I insulin–magnetite–PLGA MPs was improved by 101–145% in the presence of a magnetic field 6–12 h after oral administration (Fig. 4). The blood radioactivity was higher in the magnet-applied groups by 143 and 189% at 6 and 12 h, respectively. The serum radioactivity decreased more than 50% from 6 to 12 h in both groups (data not shown). Thus, the greater quantity of ^{125}I insulin recovered in the small

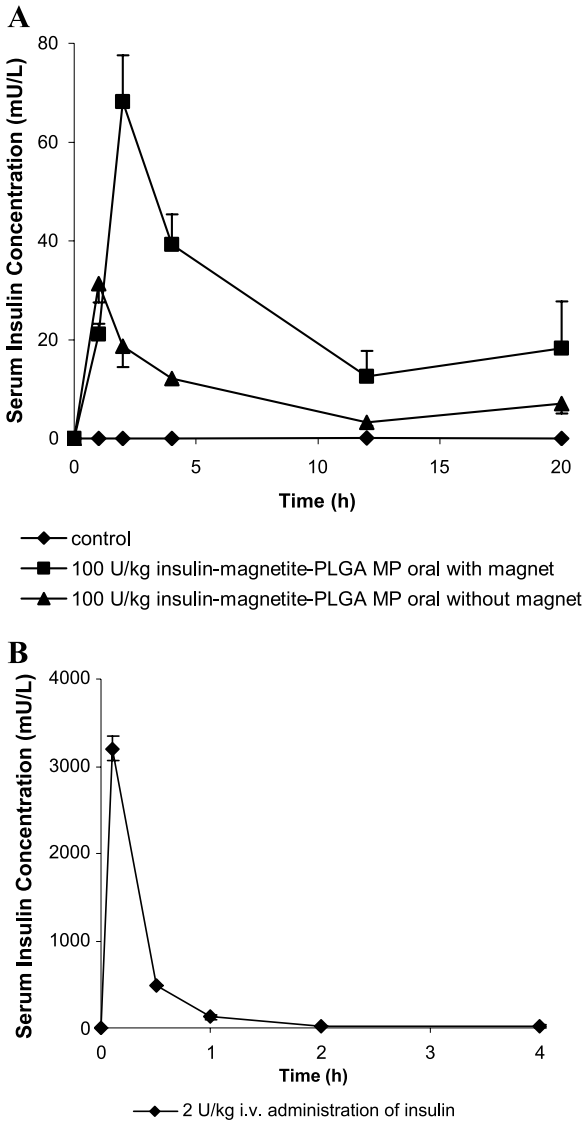

Fig. 6. Serum insulin concentration of oral administration of insulin–magnetite (8%)–PLGA microparticles (100 U/kg) in mice in the presence or absence of a magnetic field ($p_{w-w/o}$ < 0.03) (A). Serum insulin concentration of tail vein i.v. administration of insulin (2 U/kg) in mice (B).

intestine for the magnet-applied group compared to the control group was due to increased residence time and not increased absorption.

We hypothesized that extending the residence time of insulin containing microparticles in the small intestine would improve pharmacological efficacy, as more insulin can be released and then absorbed. This hypothesis was tested by monitoring glucose levels in animals. After an initial increase in blood glucose in response to stress associated with the oral gavage method, the mice became hypoglycemic as a result of the treatment. Our studies indicated that magnetically assisted delivery of insulin containing microparticles decrease glucose levels for at long as 20 h. A single oral administration of 100 U/kg of Humulin R magnetite–PLGA MPs to fasted mice resulted in 43.5% reduction of blood glucose concentration in the presence of an externally applied magnetic field after 4 h. Interestingly, this blood glucose was maintained at this level for at least an additional 16 h (42.8 and 43.2% of reduction of blood glucose concentration at t = 12 and 20 h, respectively). Mice gavaged a single dose of 100 U/kg of Humulin R magnetite–PLGA MPs in the absence of a magnetic field showed a glucose reduction of 18.6% at 12 h (Fig. 5). The average decreased AUCs are 763 ± 112 and 218 ± 127% · h ($p < 0.01$) for the groups restrained in the presence and absence of an external magnetic field, respectively.

Intravenously (i.v.) administered Humulin R, at a dose of 0.5 U/kg, served as a standard for bioavailability. Highest glucose reduction (46 %) was observed 1 h after i.v. dosing,

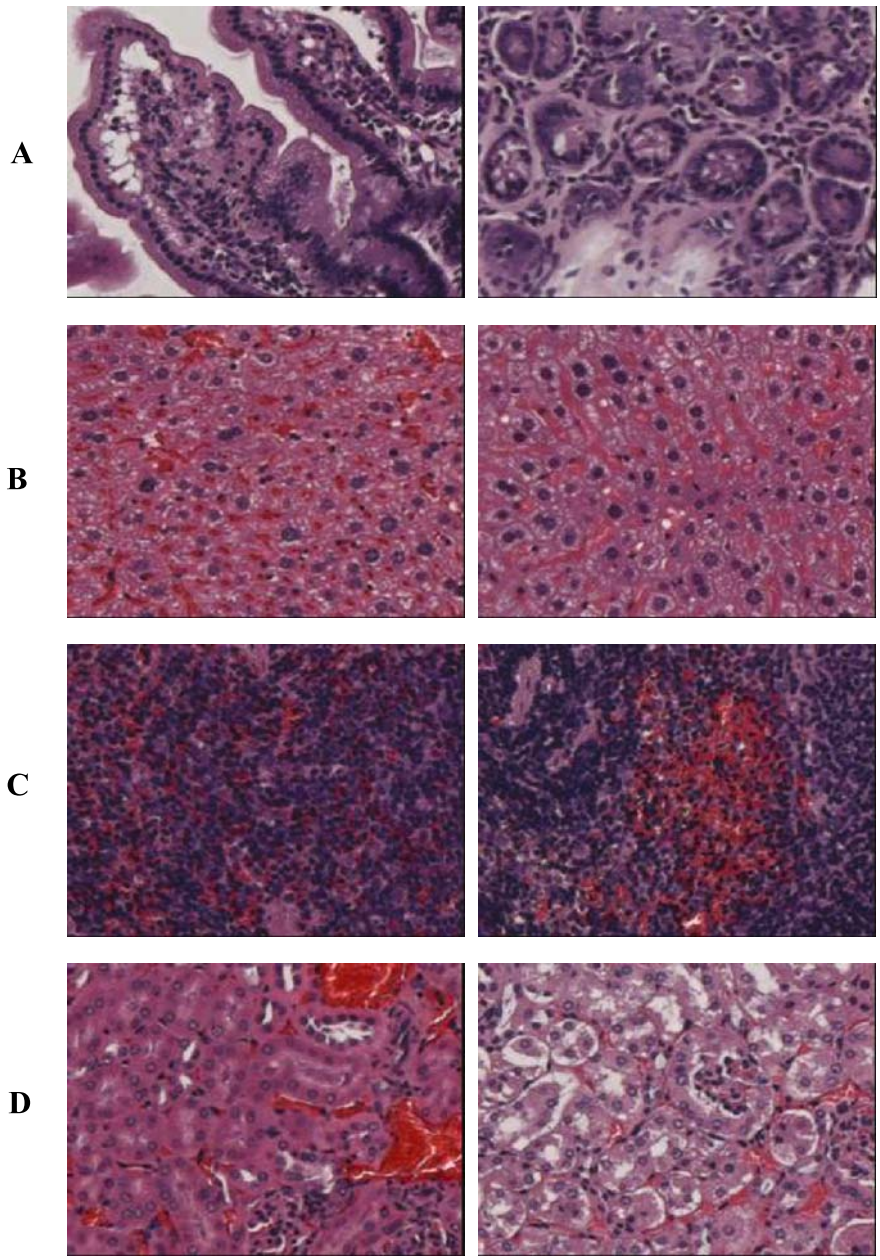

Fig. 7. H&E-stained tissue sections magnified in 50× from the organs: (A) small intestine, (B) liver, (C) spleen, (D) kidney. Images on the left show sections from controls, whereas images on the right were taken from mice administered with magnetite-encapsulated microparticles.

and this period of glucose depression lasted for about 4–5 h (Fig. 5). The average AUC of the i.v. group was 120.9 ± 45.2% · h. Using Eq. (1), bioavailability was calculated to be 2.77 ± 0.46 and 0.66 ± 0.56% ($p < 0.01$) for the groups restrained in the presence and absence of an external magnet, respectively. Application of a magnetic field to the mice orally dosed with magnetically responsive, insulin–PLGA MPs led to an increase in bioavailability by 420%.

The magnetic-induced increment of bioavailability was confirmed by direct analysis of serum insulin levels (Fig. 6). Magnetically assisted delivery of insulin and magnetite co-encapsulated microparticles reached the highest level of insulin concentration of 68 mU/L at $t = 2$ h, and gradually decreased to 18.2 mU/L at $t = 20$ h. As a comparison, the control group without the external magnet reached the highest level of insulin concentration of 31 mU/L at $t = 1$ h, and gradually decreased to 7.1 mU/L at $t = 20$ h (Fig. 6A). Intravenously (i.v.) administered Humulin R, at a dose of 2 U/kg, served as a standard for bioavailability. The highest concentration of insulin (3.2×10^3 mU/L) was observed 6 min after administration, and the insulin level rapidly decreased to 14 mU/L at 2 h (Fig. 6B). Bioavailability calculated based on the AUC derived from insulin concentration measurement are 0.87 ± 0.29 and 0.30 ± 0.06% ($p < 0.03$) for the groups restrained in the presence and absence of an external magnet, respectively.

The bioavailabilities obtained from serum insulin measurement are roughly 30–45% of the bioavailability obtained from blood glucose measurements. This difference is presumably attributable to the different detection techniques used. Previous work indicated that 50% of insulin absorbed from the small intestine will be entrapped or metabolized in the liver and not released back into the blood (first pass effect) (19). However, this insulin can still regulate glucose level to some degree, but is not detectable in serum insulin measurements. Similar comparisons between glucose and insulin bioavailabilites due to the difference in detection techniques was also reported by Hovgaard *et al.* (19).

After demonstrating the efficacy of this approach, we investigated the biocompatibility of the magnetite–PLGA MPs in gastrointestinal tissue as well as toxicity in other organ systems. Microscopic analysis of histological tissue sections reveals no apparent signs of increased acute inflammation, leukocyte infiltration, tissue edema, or necrosis. When comparing tissue sections derived from animals administered with MPs *vs.* controls, small intestine tissue section analysis does not show enhanced migration of macrophages or increased numbers of neutrophils and lymphocytes. In addition, tissue sections from mice administered with the magnetite–PLGA MPs did not exhibit the formation of an inflammatory exudate, which is often observed as a response to an acute tissue insult (Fig. 7A). A similar lack of toxicity is also exhibited in other tissue sections: liver (Fig. 7B), spleen (Fig. 7C), and kidney (Fig. 7D). Examination of tissue sections stained for colloidal iron showed no detectable accumulation of magnetites (positive control slide provided in inset). After 24 h, the magnetites were no longer present in the small intestine (Fig. 8A) and were not observed in the liver (Fig. 8B). Based on this histological analysis of various tissues from the dosed animals and controls, we conclude that administration of the magnetite particles is accompanied by little, if any, acute toxicity in these organ systems. Furthermore, the magnetites do not seem to be absorbed after administration.

Although magnetic forces have been widely used in many biomedical applications including targeted drug delivery and imaging, relatively few examples exist of the use of magnetic forces to improve the efficiency of oral delivery. We have previously studied magnetite-encapsulated liposomes as oral protein delivery vehicles in an external magnetic field, which showed substantially improved retention and absorption of the liposomal particles in the GIT in mice (16). This

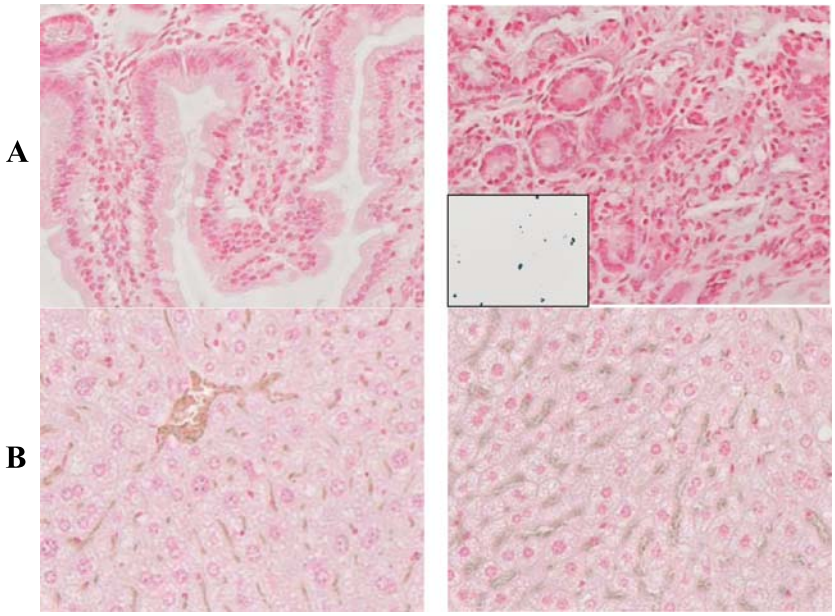

Fig. 8. Colloidal iron (Mallory method) stained sections magnified 50× from the organs: (A) small intestine and (B) liver. Left images are control, and right images are magnetite-treated mice. Inset in (A) is positive control for stained magnetites.

study improves on this concept by demonstrating that the incorporation of magnetite in polymeric microparticulate delivery vehicles in the presence of an external magnetic field can dramatically improve the intestinal retention of these delivery vehicles. In addition, sustained transit of insulin-containing delivery vehicles through the GIT improved and prolonged their hypoglycemic effect in mice.

In conclusion, PLGA-encapsulated magnetite particles exhibit strong potential as externally modulated oral drug-delivery vehicles. Utilization of magnetic force to delay the transit of orally administered drugs may become an attractive strategy for enhancing the efficacy of orally delivered proteins. As compared to other extensively studied intestinal targeting or retention techniques, the proposed magnetic strategy shows clear advantages. For instance, two methods currently used to prolong GIT transit involve the mucoadhesive coating of polymer particles or the surface modification of the polymer particles with lectins to directly target the M cells in Payer's Patches. This magnetic strategy may prove advantageous when compared to these two techniques, because it does not depend on physiological factors such as mucin turnover time or the integrity of Payer's Patches, which vary drastically with age. Initial investigation into any potential acute toxicity was promising; however, further investigation of long-term treatment safety may be necessary. Once this technique is further optimized, for instance, via the regulation of the magnetic field with a magnetic belt or other electromagnetic device, it can be conveniently used to enhance the oral delivery of proteins or other therapeutics in patients.

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