Comparing the Blood Glucose Profiles between Rectal and Oral Delivery of Insulin with Our Permeability Promoter A2032

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ABSTRACT SUMMARY
The rectal delivery can be a favorable method to quantify the effectiveness for the screening purpose of permeability promoters, since there are minimal food effects and easy control of dosing amount into the site of delivery. It has been known that the absorption profiles of insulin from rectal delivery might not be equivalent to those from the oral delivery. Understanding of the differences of delivery profiles at the different absorption sites should be important for formulating alternate delivery system for protein and peptide drugs.

The penetration promoter A2032 was adjuvant with insulin solution and administered rectally and orally to the animals. The pharmacodynamics effects were compared with BG profiles and AUC [dec%*min]. The data showed that the pharmacodynamic profiles showed more effective by rectal delivery than by oral delivery.

INTRODUCTION
For many patients diagnosed with Type I diabetes mellitus, the external insulin should be parentally injected since their bodies no longer internally produce the hormone. The most common method of administering insulin is through the injection, which is inconvenient and even threatening.

Numerous methods improving the oral bioavailability of protein and peptide drugs have been published. Based on our preliminary screening study, the permeability promoter A2023 was found to increase the absorption of protein drugs through the rectum. The TEER values were decreased proportionally to concentration, and reversed when the promoter was removed from the CaCO2 monolayer diffusion chamber. The compounds were delivered rectally as solutions, or orally in liquid to the animals. This study should quantitatively show the difference in insulin delivery through the rectal and oral routes with respect to the perturbation of blood glucose.

EXPERIMENTAL METHODS
Sprague Dawley rats were purchased from the Charles River (NY), 225-250 g, and a regular diet was fed with water ad libitum. The study was initiated after a week of acclimation to the facility.

The permeability promoters A2023 was purchased from Anatrace Inc. (OH). The solution was prepared in solution of 5, 15, 25 mg/kg with 0.5 mg/kg insulin in 1 ml/kg dose volume. The blood glucose Monitor was OneTouch UltraMini (LifeScan, Inc.) and the Blood Glucose Test Strips were obtained from Life Scan, Inc. Insulin was obtained from Aldrich-Sigma Inc (St. Louis, MO).

The animals were fasted for 10 hours minimally overnight. The existence of feces in the rectal space was manually checked and removed if detected. The first blood sample was carried out by the tail-clipping method just before administered. The blood glucose was measured with a glucose monitor immediately after sampled at each predetermined time points.

A IM positive study was conducted with insulin to confirm its maximal effects on blood glucose, and to measure the activity of insulin for the rectal delivery, while a negative control study was performed by rectally administering insulin only to confirm its delivery without penetration promoter.

RESULTS AND DISCUSSION
Fig. 1 below represents the blood glucose (BG) decrease followed by the insulin administration...
rectally and intramuscularly. The rectal delivery of insulin without a promoter induced no impact on BG, while the intramuscular administration caused the BG to be significantly decreased (P<0.05). The data confirmed the insulin activity and absence of delivery when insulin was rectally delivered without promoter A2032.

Fig. 2 shows the trend of BG decrease by the rectal delivery of insulin and promoter A2032 combination in a dose response study. The maximal mean decreased BG percentage (%) marked 11.5 % when 5 mg/kg of promoter A, but 27.4 % when 15 mg/kg combined with 0.5 mg/kg insulin, respectively.

Based on the data acquired from the dose response study, an appropriate dose level of insulin and promoter combination was selected to be 15 mg/kg, or higher.

Fig. 3 shows the insulin rectal delivery with the dose of 0.5 mg/kg insulin combined with 25 mg/kg A2032. Pharmacodynamic parameters were evaluated as 21% maximal decrease of blood glucose at 30 minutes post administration. And, mean AUC was calculated as 1548.4 [dec%.min]. Fig. 4 plots the insulin oral delivery with the equivalent dose of rectal delivery as presented. The pharmacodynamic parameters were presented as 13% maximal decrease of blood glucose at 60 minutes post administration. Further, mean AUC was found as 752 [dec%.min]. The AUC ratio showed that pharmacodynamic bioavailability from the rectal delivery was two times higher, compare to that from the oral delivery.

CONCLUSION
The results from the study of in vivo assessment of insulin delivery for comparing the effectiveness of administering sites between rectal and oral insulin indicated the rectal delivery was 2.0 times more effective than oral delivery. The ratio and other data might be applicable to formulating oral delivery of protein and peptide drugs including insulin.

REFERENCES