Oral Insulin Delivery Using Novel Mucoadhesive Intestinal Patches
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Purpose
We have recently developed a novel intestinal patch for needle-free oral delivery of insulin. These patches are made of mucoadhesive polymers and can be loaded with insulin and placed in enteric-coated capsules for site-specific delivery of the drug to the intestine. Here, we present patch characterization as well as in vivo efficacy studies in diabetic rats.

Methods
Patches were prepared by mixing three different polymers including Eudragit® EPO, pectin and sodium carboxy methylcellulose. To the mixture, a pre-determined quantity of insulin was added and the mixture was pressed into 13 mm discs. The discs were coated on two sides with a water impermeable backing layer made of ethyl cellulose and cut into smaller disks (5 mm sized for in vitro studies and 2 mm sized for in vivo studies). Release of insulin and permeation enhancer, dimethyl palmitoyl ammonio propanesulfonate (PPS) from the patches were studied by placing FITC-insulin or PPS loaded patches in pH 7.4 phosphate buffered saline (PBS) at 37°C with constant shaking. Insulin/PPS content were measured from small amounts of samples withdrawn at various time intervals for up to 5 h. FITC-insulin concentration in the withdrawn samples was determined using fluorescence analysis while PPS was measured using LC-MS. The mucoadhesive strength of the patches was determined by placing patches on porcine intestine and incubating them for 30 minutes in pH 7.4 PBS. Following this, the patches were gradually pulled away from the intestine and the strength required to completely detach the patches from the intestine was quantified using a microbalance. For in vivo efficacy studies, 250 – 350 g male wistar rats were injected with 55 mg/kg streptozotocin to induce the development of diabetes. After diabetes development, the rats were fasted overnight and orally fed with enteric coated capsules containing either 100 U/kg insulin patches, 100 U/kg insulin+10% w/w PPS patches or 100 U/kg insulin patch + 5 mg PPS in capsules (n = 6). Blood glucose levels were thereafter determined at different time points for up to 8 h using a commercial blood glucose meter and the percent drop in glucose levels was calculated.

Results
The patches released 100% of its insulin and PPS content within 5 hours of study and demonstrated good mucoadhesive strength of 24.22 ± 2.85 mN, which corresponds to greater than 100 times the individual patch weight. In vivo efficacy studies revealed that insulin patches containing 10% w/w PPS were the most effective formulation, where the blood glucose levels dropped significantly to 69 ± 2.41 % of initial levels. In comparison, the no treatment control group showed no decrease in blood glucose levels over time.

Conclusion
EPO patches showed a complete drug release profile and demonstrated excellent strength of mucoadhesion. An in vivo efficacy study in diabetic animals demonstrated that the patches were effective in decreasing blood glucose levels significantly and therefore indicates that this unique drug delivery approach could be successfully used to deliver insulin orally in a continuous time-dependent manner. To this end, these patches should be further developed for oral delivery of protein/peptide drugs such as insulin, exenatide and calcitonin, amongst others, that will improve the quality of life of millions of people suffering from diabetes and osteoporosis worldwide.

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