2015 中技社科技研究獎學金

CTCI Science and Technology Research Scholarship

自我組裝氣泡式奈米載體用於口服蛋白質藥物傳遞的研發

Self-assembled Nanobubbles as a Carrier for Oral Protein Drug Delivery

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研究重點

Successful oral delivery of therapeutic proteins such as insulin can greatly improve the quality of life of patients. This study develops a bubble carrier system by loading diethylene triamine pentaacetic acid (DTPA) dianhydride, a foaming agent (sodium bicarbonate; SBC), a surfactant (sodium dodecyl sulfate; SDS), and a protein drug (insulin) in an enteric-coated gelatin capsule. Following oral administration to diabetic rats, the intestinal fluid that has passed through the gelatin capsule saturates the mixture; concomitantly, DTPA dianhydride produces an acidic environment, while SBC decomposes to form CO_2 bubbles at acidic pH. The pressure of the generated gas disintegrates the capsule, aiding a quick release of its loaded contents. The gas bubbles grow, from nanoscale to microscale, among the surfactant molecules (SDS) owing to the expansion of the generated CO_2. The walls of the CO_2 bubbles consist of a self-assembled film of water that is in nanoscale and may serve as a colloidal carrier to transport insulin and DTPA, sandwiched between two layers of SDS. The grown gas bubbles continue to expand during their transit in the intestinal tract until they bump into the wall and burst, releasing their transported insulin, DTPA, and SDS into the mucosal layer. The released DTPA and SDS function as protease inhibitors to protect the insulin molecules as well as absorption enhancers to augment their epithelial permeability and eventual absorption into systemic circulation, exerting their hypoglycemic effects. These experimental results demonstrate that the developed bubble carrier system is a promising vehicle for oral insulin delivery.

研究成果

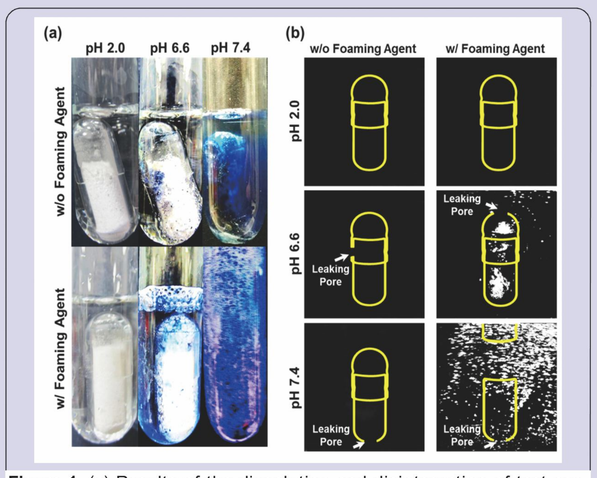

Figure 1. (a) Results of the dissolution and disintegration of test capsules with or without SBC evaluated in vitro under varying pH to simulate the pH environments in the GI tract; (b) ultrasound images showing the gen-

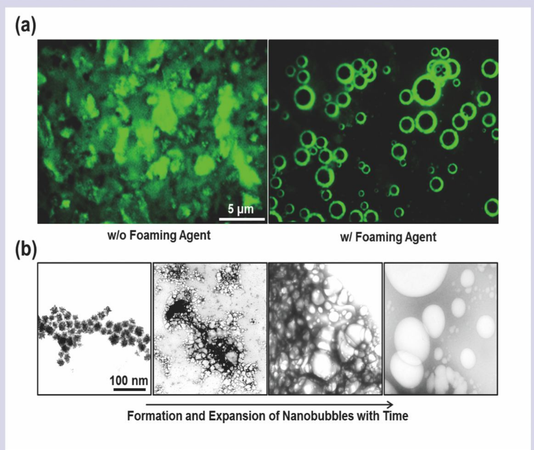

Figure 2. (a) Fluorescence images showing the dispersion of the FITC-labeled insulin released from the capsule with or without the foaming agent (SBC) upon exposure to water; (b) TEM micrographs showing the evolution and expansion of nanobubbles generated by the capsule containing SBC

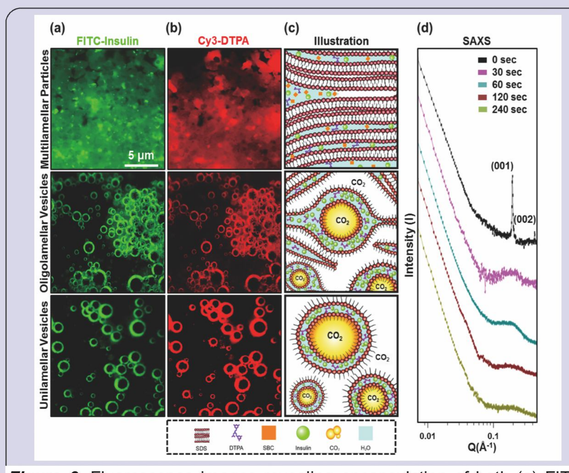

Figure 3. Fluorescence images revealing encapsulation of both (a) FITC-insulin and (b) Cy3-DTPA within the water film of the bubble carriers; (c) corresponding schematic illustrations displaying the bubble carriers produced upon exposure to water; (d) SAXS profiles showing structural changes in

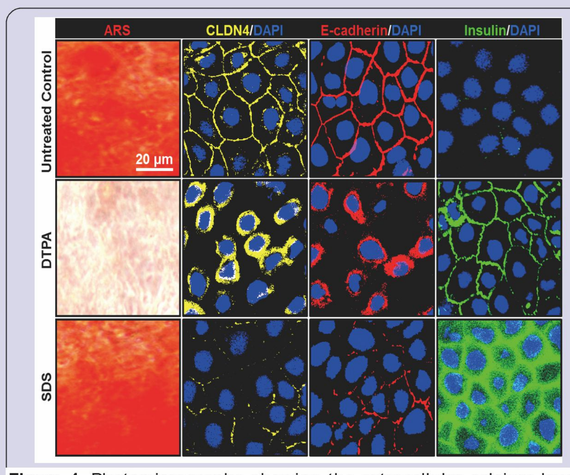

Figure 4. Photomicrographs showing the extracellular calcium levels (red ARS-labeled Ca^{2+}) and immunofluorescence staining results for Caco-2 cell monolayers treated with DTPA or SDS in the presence of FITC-insulin.

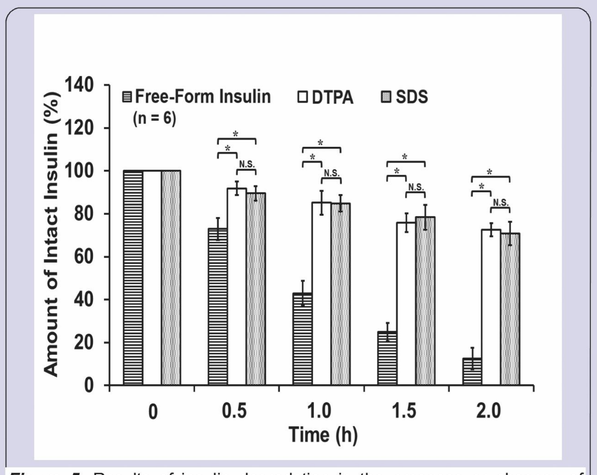

Figure 5. Results of insulin degradation in the presence or absence of DTPA or SDS in proximal intestinal segments freshly isolated from rats. N.S.: not significant; *: statistically significant (P < 0.05).

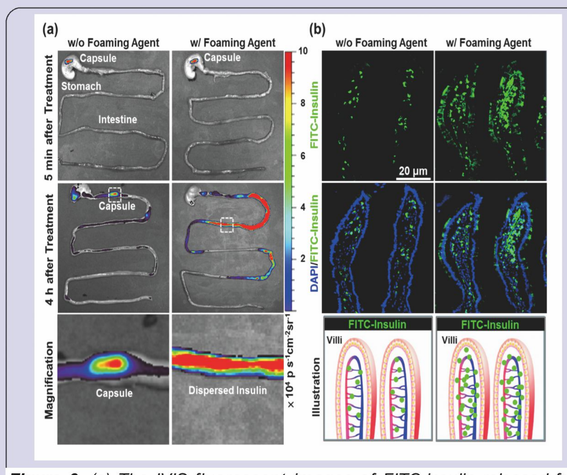

Figure 6. *(a) The IVIS fluorescent images of FITC-insulin released from capsules with or without foaming agent during their transit in the GI tract; (b) CLSM images of frozen intestinal sections with schematic diagram of insulin*

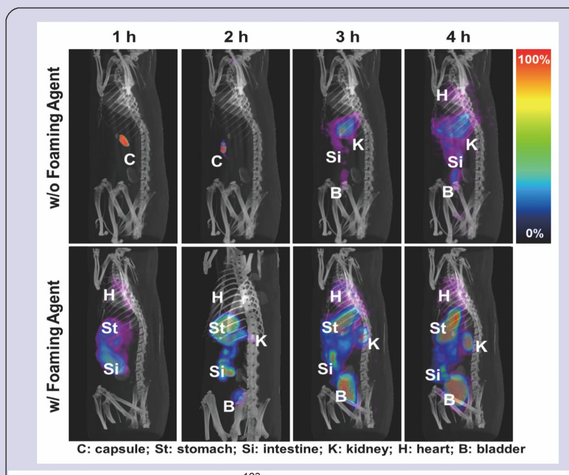

Figure 7. Biodistribution of ^{123}I-insulin illustrated by contrast-enhanced tomographic images. The intensities of ^{123}I-insulin in different organs are shown in rainbow pseudo-color scale.

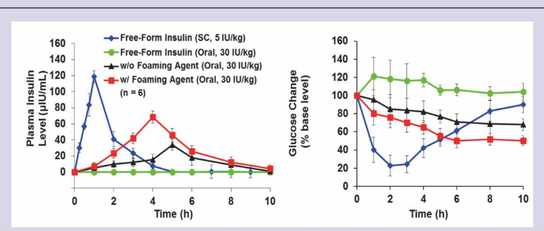

Figure 8. Plasma insulin level vs. time profiles and blood glucose change vs. time profiles of diabetic rats treated with varying insulin formulations. Oral: oral administration of test capsules and SC: subcutaneous injection.

	Free-Form Insulin (SC)	Free-Form Insulin (Oral)	w/o Foaming Agent (Oral)	w/ Foaming Agent (Oral)
Dose [IU/kg]	5.0	30.0	30.0	30.0
C_{max} [μIU/mL]	119.6 ± 3.8	1.8 ± 0.7	34.0 ± 6.4	68.4 ± 6.8
T_{max} [h]	1.0	5.0	5.0	4.0
$AUC_{(0-10\ h)}$ [μIU h / mL]	191.3 ± 30.7	6.5 ± 2.7	123.8 ± 28.4	249.2 ± 34.1
BA_R [%]	100	0.5 ± 0.3	10.8 ± 3.1	21.7 ± 1.7

Table The PK parameters of insulin in diabetic rats given varying insulin formulations (n = 6).

研究生活及心得

邁入研究生的第四個年頭，感謝家人在背後的體諒和支持。讓我得以在研究的路上心無旁騖，也是我往前走最大的動力。這些年面對研究，從力不從心到現在可以知道解決問題的方向，要感謝的是實驗室學長姐的教導還有指導教授的督導。感謝中技社對於我的肯定，讓我對於自己的研究也開始有了些信心，可以更有自信的往下邁進。未來也期許自己可以繼續在研究上面有更多的建樹，並以自己能力對社會產生貢獻。

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