Considerations on the Controlled Release of Injectable Insulin Using Scissor (Subcutaneous Injection Site Simulator)

Kohsaku Kawakami, Ph.D. Group Leader / Chief Researcher, National Institute for Materials Science International Center for Materials Nanoarchitectonics, Medical Soft Matter Group / Professor, Graduate School of Pure and Applied Sciences, University of Tsukuba

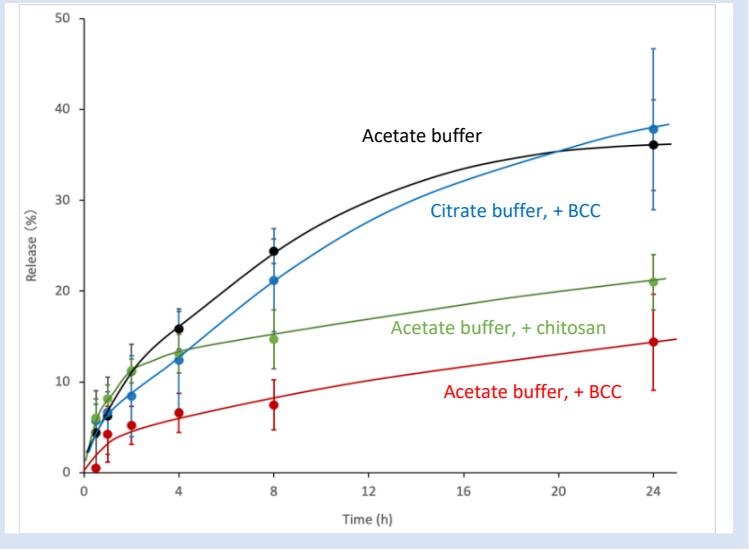
Objective

It is known that our newly developed excipient, β-cyclodextrin-grafted chitosan (BCC), binds strongly with peptides. In addition, morphology of the complex changes depending on the buffer type [1]. When mixed with insulin in an acetate buffer, BCC is conjugated in a molecular dissolved state. However, when it is mixed with insulin in a citrate buffer solution, the chitosan main chain is ionically crosslinked via citric acid, which forms nanoparticulate complexes. It was discovered that when these complexes were administered into the gastrointestinal tract, both complexes increased insulin absorption significantly, and that the former complex led to rapid absorption, whereas the latter complex delayed and sustained absorption [2]. In other words, when BCC was used, the absorption profile of insulin was able to be controlled only by changing the buffer type with the same formulation. An assessment was performed using Scissor with the aim of controlling the absorption profile of the subcutaneous formulation using the same formulation.

Experiment

The following four samples were injected into the Scissor cartridge in 1-mL dosages, and the release of the samples for up to 24 hours was evaluated with a 50-mL chamber. A standard carbonate buffer to which 0.05% methyl cellulose was added was used as a flow buffer. Quantification of insulin was performed using the bicinchoninic acid method.

1. acetic buffer with insulin 2.5 mg/mL (pH 3.6)
2. acetic buffer with insulin 2.5 mg/mL + chitosan 7.2 mg/mL (pH 3.6)
3. acetic buffer with insulin 2.5 mg/mL + BCC 11.2 mg/mL (pH 3.6)
4. citrate buffer with insulin 2.5 mg/mL + BCC 11.2 mg/mL (pH 3.6)



Results

Both chitosan and BCC form complexes with insulin; however, since both chitosan and cyclodextrin sites interact with insulin, the binding capacity of BCC is stronger than that of chitosan. As shown in the above figure, when chitosan and BCC were mixed with insulin in acetic acid media and administered, their releasability was significantly controlled. This is interpreted as that since the binding strength of BCC was stronger than that of chitosan, the diffusion rate of insulin was decreased by the interaction with these polymeric carriers. When citric acid was used as a buffer, the complex becomes nanosized particles, and the release rate of insulin in this case was comparable to that of insulin alone. However, since the initial release of the complex was suppressed a little more than that of insulin alone, the diffusion mechanism was assumed to be changed by nanoparticulation.

Conclusion

Our findings suggest that the absorption rate of insulin after a subcutaneous injection of insulin could be controlled by the addition of BCC. Since BCC similarly combines with other peptides and proteins, it can be expected that BCC would exert a similar effect on them.

References

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Nihon Validation Technologies Corporation
contact@validation.co.jp