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SYMPOSIUM

Development and Testing of Solid Dose Formulations Containing Polysialic Acid Insulin Conjugate: Next Generation of Long-Acting Insulin

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Abstract

Background:

The need for lifelong, daily insulin injections can have a dramatic effect on patient compliance, can be painful, and runs the risk of local infections. Furthermore, needle-stick injuries are common, and the issue of needle disposal is troublesome. Injecting a long-acting insulin analog with needle-free administration would be a significant improvement for diabetic subjects, but is not currently feasible. To achieve a constant, reliable delivery of a novel, long-acting insulin analog, Lipoxen's SuliXen® (polysialylated insulin) in a solid dosage form capable of being delivered without a needle has been developed. The aim of this study was to evaluate the feasibility of Lipoxen's SuliXen delivery with the Glide solid dose injector, Glide SDI®.

Materials and Methods:

A formulation containing 14 kDa polysialic acid (PSA)-recombinant human insulin conjugate was manufactured at Lipoxen PLC and transferred to Glide Pharma. The PSA–insulin conjugate solution was incorporated into different excipients at Glide Pharma (excipients 1 and 2), and formulations were manufactured containing implants with doses of 0.3 and 1.0 IU of insulin, respectively. Two different polymeric excipients were investigated for their suitable release profiles. The physicomechanical properties of the formulations were characterized in terms of solid dosage form strength (via three-point bend and compression) and disintegration time at 37°C. A preclinical efficacy study was performed in a nondiabetic rat model (Sprague-Dawley).

Results:

The study demonstrated successful incorporation of PSA–insulin conjugate into formulations compatible for use with the solid dose injector. Physicochemical characterization indicated that each formulation produced was physically robust. For excipient 1, the compressive stress and three-point-bend-test values recorded for the 0.3 IU formulation were 106.99 ± 14.3 MPa and 30.6 ± 1.4 N (force in newtons), respectively.

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Abbreviations: (BCA) bicinchoninic acid, (CA) colominic acid, (CV) coefficient of variation, (EU) endotoxin unit, (N) Newton, (PEG) polyethylene glycol, (PSA) polysialic acid, (SDS-PAGE) Sodium dodecyl sulfate polyacrylamide gel electrophoresis, (SE-HPLC) size-exclusion high-performance liquid chromatography, (WB) Western blotting

Keywords: colominic acid, diabetes, needle-free injection, polysialic acid, polysialic acid insulin, solid dose injector, SuliXen

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Abstract cont.

Corresponding values for the 1.0 IU dose were 53.10 ± 10.2 MPa and 16.66 ± 1.0 N. For excipient 2, the compressive stress and three-point-bend-test values recorded for the 0.3 IU dose were 53.10 ± 10.2 MPa and 7.64 ± 0.9 N, respectively, whereas the corresponding values recorded for the 1.0 IU dose were 41.61 ± 7.4 MPa and 13.18 ± 1.3 N. Each formulation successfully penetrated a laboratory substrate, achieving 100% penetration in each case. *In vivo* analysis demonstrated that PSA–insulin conjugate shows prolongation of activity (at least two-fold more compared to insulin) for more than 5 hours in the rat model.

Conclusion:

Even though additional work may be required, for example, to develop several fixed dose formulations, the preliminary results show that solid dosage forms incorporating PSA–insulin conjugate maintained the prolongation of PSA–insulin conjugate activity in the rat model. Convenient and easy to use, the solid dose injector will not only ensure diabetic patient compliance and trust but also provide cost-effective solutions for safe, reliable, and controlled needle-free injection of PSA–insulin conjugate.

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