ABSTRACT

Abaloparatide (formerly known as BA058), a novel synthetic analogue of human parathyroid hormone, is currently undergoing a Phase 3 clinical trial as an injectable product to treat osteoporosis. A transdermal patch is also being developed in which abaloparatide is coated onto 3M’s solid microstructured transdermal system (sMTS), a microneedle-based delivery technology.

The purpose of this study was to enhance the stability of the abaloparatide-sMTS drug product by optimizing the formulation used to coat the microneedles, as well as optimizing the final packaging of the drug product. Different levels of histidine, a stabilizing excipient for abaloparatide, were evaluated in the coating formulations, and different methods of controlling moisture in the drug product packaging were investigated. The appearance of the coating, the abaloparatide purity, and the sMTS component moisture level, as well as the in vivo release of abaloparatide from the sMTS arrays, were assayed to characterize the effects of histidine content and packaging conditions on the stability of the abaloparatide-sMTS drug product.

The results indicated that there was an optimal histidine content and preferred packaging conditions, wherein the best stability and product performance of abaloparatide-sMTS were obtained.

EXPERIMENTAL METHODS

The sMTS arrays were injection molded from a medical grade polymer and were composed of approximately 316 microneedles with needle heights of ~500µm and tip-to-tip spacing of ~550µm.

Four formulations containing different levels of abaloparatide and histidine were prepared using phosphate buffered saline (PBS) as solvent, and were coated onto the microneedle arrays using a precision dip-coating process. The coating morphology on the coated arrays was examined microscopically and assayed for array content.

Arrays coated with each formulation were placed into 5 chambers with relative humidity levels of approximately 11%RH, 25%RH, 33%RH, 44%RH and 54%RH, which were controlled with saturated salt solutions at ambient temperature. Coated arrays were also placed into a sixth chamber containing desiccant. Separately, arrays coated with abaloparatide were also packaged into sealed foil pouches containing desiccant or humectant.

Four different types of desiccant/humectant were investigated: Minipax® 1.5G molecular sieve (desiccated), Intellisorb® MR-15 (designed to maintain 10-20%RH), StabilOx® DF-100-H31 (maintains 25-35%RH), and...
Analyses of abaloparatide content and purity levels were conducted using an Agilent 1200 HPLC. Naïve young adult female mixed breed agricultural swine were used to characterize the in vivo release of abaloparatide-sMTS, as previously described.1

RESULTS AND DISCUSSION

The coatings from all four formulations were acceptable and no precipitates appeared to have formed after drying. All the coatings were uniform and located on the upper half of the needles. Examples are shown in Figure 1.

The purity results, presented in Figure 2, indicate that the arrays coated with formulations which included histidine maintained higher abaloparatide purity compared to the histidine-free formulation. The formulation containing 5% histidine provided the best stability over a range of humidity conditions. Also, for all formulations, when the storage humidity was between 11-44%RH, the abaloparatide purity was higher than for storage humidity conditions outside of this range.

An in vivo release study conducted on swine showed that the inclusion of histidine in the formulation did not affect the amount of drug delivered into the skin.

Figure 3 shows that Intellisorb® MR-15 and StabilOx® H31 maintained an optimal storage environment for the drug product; in combination with 5% histidine, packaging with these humectants provided the best product stability.

CONCLUSION

Four formulations of abaloparatide containing different levels of histidine were prepared and coated onto microneedles. The coated arrays were evaluated for coating morphology, stability and in vivo release. The main conclusions are a) the addition of histidine improved product stability without significantly impacting the release performance of abaloparatide-sMTS; b) there is an optimal storage environment for the abaloparatide-sMTS product to maintain stability; c) use of either Intellisorb® MR-15 or StabilOx® H31 in the packaging system provided the best stability for the arrays coated with formulations containing histidine.

REFERENCES