ABSTRACT

Assessment of dermal irritation is an essential component of the safety evaluation of medical devices. Reconstructed human epidermis (RHE) models have replaced rabbit skin irritation testing for neat chemicals (OECD TG 439). However, medical device (MD) extracts are dilute solutions with low irritation potential, therefore the validated RHE-methods needed to be modified to reflect needs of ISO 10993. A protocol employing RHE EpiDerm was optimized in 2013 using known irritants and spiked polymers (Casas et al., TIV, 2013). In 2014 a second laboratory assessed the transferability of the assay. Two additional exposure times were tested along with other medical device materials.

After the successful transfer and standardization of the protocol, nine EU and USA laboratories were trained in the use of the protocol in the preparation for the validation. All laboratories produced data with almost 100% agreement of predictions for the selected references.

Two of the laboratories performed additional tests with heat-pressed PVC sheets spiked with Genapol X-080 (Y-4 polymer), Vicyl suture, and polymers spiked with heptanoic acid and heptanoic acid in sesame oil. All materials were extracted for 24 or 72 hours in both saline and sesame oil at either 37°C or 70°C. Significant irritation responses were detected for Y-4 under all conditions. These results were consistent with those reported by other research groups in the forthcoming validation study. Vicyl suture was negative and spiked polymers were either positive or negative dependent on the extraction solvent. We conclude that a modified RHE skin irritation test has the potential to address the skin irritation potential of the medical devices, however, standardization and focus on the technical issues is essential for accurate prediction.

RESULTS

Figure 1. Representative results for Vicyl suture (viabilities % and IL-1α levels): Regardless the extraction time and the extracting conditions tested (DPBS, Saline, Sesame Oil) or Water – samples were split into 2 pieces and 70 pieces). Vicyl suture did not produce cytotoxicity or elevated release of the IL-1α, an inflammatory marker.

Figure 2. Representative results for Y-4 Polymer (viabilities %): Regardless the extraction time (24 or 72 hours) and the extracting conditions tested (DPBS, Saline, Sesame Oil, Water) – polymer Y-4 produced significant cytotoxicity after 18 and 24 hours of exposure and could therefore be classified as irritating.

Figure 3. Representative results Silicone samples spiked with 15% and 17% of SDS - SS (viabilities %): Silicone samples were extracted for 72 hours in DPBS, Saline and Sesame Oil. While in the washy extracting solutions the samples produced significant cytotoxicity, in sesame oil the effect was less sever. This can be explained by the affinity of the SDS for the polar solvents and limited solubility (and thus extractability) of SDS in non-polar solvents.

Figure 4. Representative results Silicone samples spiked with 20% of Heptanoic Acid – HA (viabilities %): Silicone samples were extracted for 24 and 72 hours in DPBS, Saline and Sesame Oil. While in the sample extracted into the sesame oil produced significant cytotoxicity, the effect in both aqueous solutions was less sever. This can be explained by the affinity of the HA to the non-polar solvents and limited solubility (and thus extractability) of HA into polar solvents.

Figure 5. Results obtained by the nine test laboratories during the training sessions with the shortest exposure time of 4 hours. 1% of SDS in polar and non-polar solvents was used as the positive control and 2 chemicals at low concentrations (Lactic acid at 4% and Heptanoic acid at 2%) were used as benchmarks due to their known irritating properties in rabbits and humans. Training was conducted with 4-hour exposure, since at 18 and 24 hours, all the test materials provided viabilities below 25-30%

SUMMARY & CONCLUSIONS

- We have developed a highly sensitive protocol for testing skin irritation potential of extracts from medical devices.
- The protocol was evaluated for transferability and predictive capacity in several laboratories.
- Initially 4, 18, and 48 exposure times were evaluated (also Casas et al.) and 18 hours exposure was selected as being the optimal in this protocol.
- When validated, this protocol has potential to reduce or even replace the rabbit skin irritation test for the medical devices.

REFERENCES


Table 2. Nine laboratories underwent training in the EpiDerm SIT-MD protocol

Table 3. Extracts from Medical Device samples tested in the EpiDerm SIT-MD protocol