Method for Single-Side Extraction of Transdermal Patches

INTRODUCTION

A transdermal patch is a combination product that falls under the ISO 10993 standard for medical devices. As per the standard, a risk assessment must be performed on these devices. The first step in the risk assessment is chemical characterization. To evaluate potential extractable compounds from the patches, an exaggerated use study was performed which involved only exposing the active side of the patch to the extraction solvents. In this study, three transdermal patches each with a unique chemistry were extracted in a device that has a chamber on both sides of the patch, allowing for testing of each side independently.

METHODOLOGY

The three transdermal patches were extracted with water, simulated sweat, and 20% IPA for 12 hours at 55°C using a permeation testing device (single side extraction). The exposed area of the patch inside the extraction vessel was 20 cm^2 and was extracted with 14 mL of each solution. The patches were also extracted fully submerged in 50% IPA for 48 hours at 55°C.

The resulting extracts were evaluated by several analytical techniques. A Perkin-Elmer Optima 5300 DV ICP-OES was used to evaluate the presence of trace elements. Gradient HPLC paired with an Agilent 6200 series Time of Flight mass spectrometer equipped with a multimode source (electrospray and atmospheric pressure chemical ionization) using positive ionization, negative ionization, and PDA detection (190-500 nm) was employed to monitor for the presence of nonvolatile organic compounds. Finally, an Agilent 7800 GC/MS was used to monitor for semi-volatile compounds, and an Agilent 7800 series GC/MS equipped with an Agilent 7600 series headspace unit was used to monitor for volatile compounds.

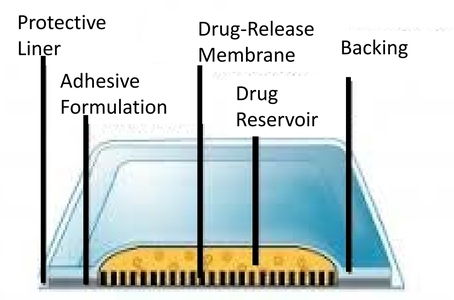

Figure 1. Transdermal Patch Design. To evaluate unique chemistries, the patient-facing side of the patch should be analyzed separate from the exterior of the patch.

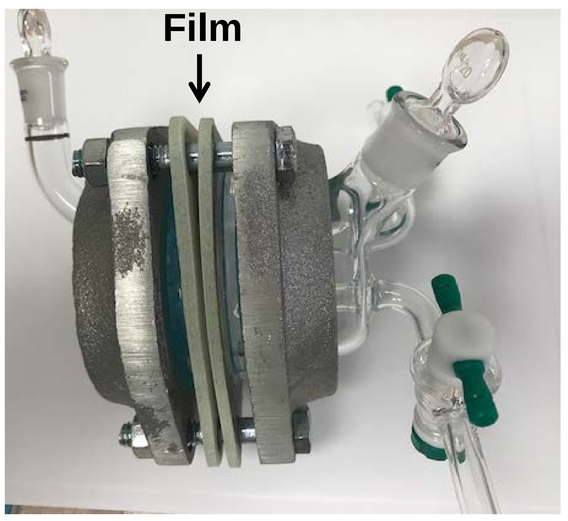

Figure 2. Thin film extraction vessel. The patch or film is held in place between o-rings and a clamp. Extraction chambers can be filled with solvent or solvent can be circulated through the extraction chamber. The device can be incubated at the specified temperature for extraction.

Table 1. Compounds/Elements Detected in 20% and/or 50% IPA Extracts of Transdermal Patch with Three Unique Chemistries

Analysis Type	Acrylic	Polyisobutylene/Mineral Oil (PIB/MO)	Silicone
LC/TOF-MS	Polymer related*, Phthalate*, Ethoxylated glycol	Polymer related*, Phthalate*, Ethoxylated glycol	Polymer related*, Phthalate*
GC/MS Semi-Volatile	ND	Alkanes*	ND
GC/MS Volatile	ND	ND	ND
ICP-OES	ND	ND	ND

*** Only detected in the 50% IPA extract, ND = Not detected, AET = 4.4 μg/g**

DISCUSSION

In the exaggerated use extraction using the single-sided extraction method, no elements or compounds were detected in the extracts from water or simulated sweat. Ethoxylated glycols were detected in the 20% IPA extracts for the acrylic and PIB/MO patches. No extractable elements were reportable by ICP-OES in any of the extracts.

In the worst case scenario extraction performed at 55°C in 50% IPA for 48 hours, ethoxylated glycols, alkanes, phthalates and polymer degradation compounds were detected. Compounds identified in this extract were further evaluated in the water, simulated sweat, and 20% IPA extracts using extracted ion analysis, but none were detected.

CONCLUSION

Transdermal patches are becoming a common means to administer drug product to patients. Currently, patient safety is evaluated largely through biological end points that require animal testing. This study demonstrates that the large majority of the risk assessment for patches can be done through extractables evaluation of the patient contact surface. In this study, compounds detected in extracts from the whole patch were not detected in any of the single-sided extracts suggesting that compounds from the non-patient contacting side of the patch did not migrate through the patch, minimizing the risk to the patient. The extractables data demonstrates that even in a worst case extraction there are no compounds coming from the patches that pose either a carcinogenic or teratogenic risk to patients. This novel approach to testing transdermal patches may be utilized to reduce the need for animal testing.

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