A quest to find the cause of unknown peaks in cleaning verification chromatography following the manufacture of pharmaceutical preparations.

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INTRODUCTION

Cleaning equipment following the manufacture of pharmaceutical products is of paramount importance to ensure that the following batch of product manufactured is not contaminated with therapeutic levels of the prior manufactured product. The patient must only receive the therapeutic effect expected from the drug they take.

During a number of cleaning verification studies, it was discovered that unknown peaks were present in the chromatography, the source of which was unclear. A study was performed to examine a theory that the gloves used by the operator during the cleaning procedure, in combination with the solvent based cleaning products were responsible for the unknown peaks that were evident in the chromatography. NASA had performed a similar study for the critical parts of the space shuttle in the space shuttle program[1]. The following poster examines the conclusions that were made from the data that was attained for the study. The data will answer the question: 'Are the gloves themselves responsible by way of leachables for the unknown peaks in the cleaning verification chromatography.'

MATERIAL AND METHODS

ThermoFisher Finnegan Surveyor HPLC system; UV detection at 260nm; Phenomenex Synergi MAX-RP 80A; MPA: 0.1% formic acid (aqueous); MPB: HPLC grade methanol; Gradient elution; Flow rate 1.0 mL/min; Column oven 40^{o}C.

Swabs: Alpha swabs long handle (TX761); Klercide 70/30 IMS spray ethanol; Klerwipe IPA wipes; nitrile gloves; latex gloves; stainless steel plates (5cm x 5cm); swabbing solvent / recovery solvent 0.5N hydrochloric acid; IPA, ethanol, water.

Vigorously scrub the surface of the stainless steel plate with a gloved hand in the 5 cm x 5 cm square for approximately 5 minutes using the solvent under investigation (in effect ethanol, IPA or water). Following scrubbing with a glove, the plate may be treated with and without water rinsing. In all cases, the surface of the plate was allowed to dry, then the area was swabbed using the technique in Figure 1.

Swabbing technique:

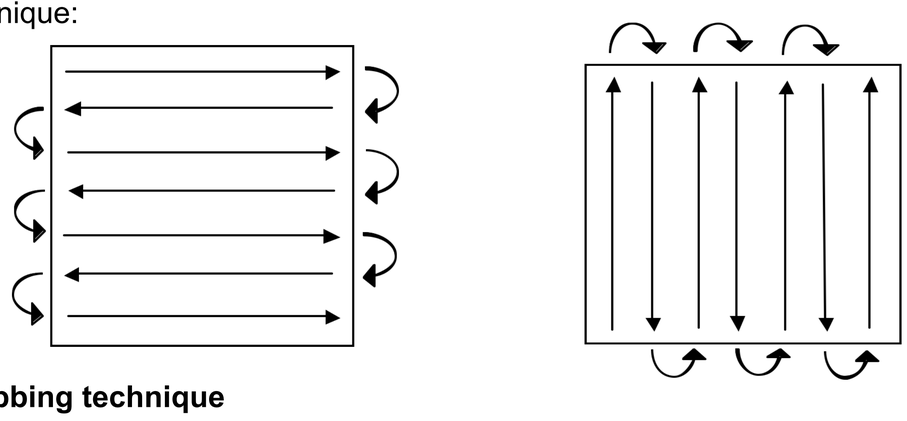

Figure 1: swabbing technique

As indicated in Figure 1, dip the swab in extraction solvent, then swab across plate using one side of the swab, and then up to down on the opposite side of the swab. Snip head off swab, and extract the swab with recovery solvent.

RESULTS AND DISCUSSION

The following samples were prepared:

Sample	No. of injections
Swab blank	Single injection
IPA / nitrile glove	Single injection
IPA / nitrile glove + water rinse	Single injection
IPA / latex glove	Single injection
IPA / latex glove + water rinse	Single injection
IPA / plate only	Single injection
Ethanol / nitrile glove	Single injection
Ethanol / nitrile glove + water rinse	Single injection
Ethanol / latex glove	Single injection
Ethanol / plate only	Single injection
Water / nitrile glove	Single injection
Water / nitrile glove + water rinse	Single injection
Water / latex glove	Single injection
Water/ latex glove + water rinse	Single injection
Water / plate only	Single injection
Ethanol spray / IPA wipe / latex glove	Single injection

Table 1: Table of samples ran for the glove study.

RESULTS AND DISCUSSION (CONTINUED)

The various parameters in Table 1 were designed to ascertain the effects of both the contents of the cleaning fluids used in the GMP manufacturing area and to replicate their major constituents when applied to the stainless steel surface in conjunction with the glove material. One of the tests also mimics how the GMP manufacturing area is routinely cleaned with the actual cleaning products themselves to see the effect of the actual cleaning materials with respect to the leachable / deposition theory.

Table 2 summarises the data achieved from the described study.

Condition	RT (mins) peaks observed
IPA / nitrile glove	3.2, 5.6
IPA / nitrile glove + water rinse	None observed
IPA / latex glove	5.6
IPA / latex glove + water rinse	None observed
IPA plate only	None observed
Ethanol / nitrile glove	5.4
Ethanol / nitrile glove + water rinse	None observed
Ethanol / latex glove	1.9
Ethanol / plate only	Small peaks only
Water / nitrile glove	None observed
Water / nitrile glove + water rinse	None observed
Water / latex glove	None observed
Water / latex glove + water rinse	None observed
Water / plate only	None observed
Ethanol spray / IPA wipe / latex glove	0.9, 2.2, 3.6, 5.5 + multiple small peaks

Table 2: Summary of chromatographic data

Each of the tests in this experiment are designed to replicate a specific condition of the solvent / extractable process in combination. Ultimately, if an extractable is observed on the surface of the stainless steel, it is also imperative that the water wash rids the plate of that deposition so as to clean the surface following the deposition (and thus prevent any further adulteration of the next product with leachables). It can be seen that either glove type in conjunction with solvents used in cleaning fluids will give rise to deposition of leachables from the glove material itself. The data strongly indicates that water flushing or water washing of the stainless steel area is an important part of the described cleaning cycle when gloves are used in cleaning product / glove cleaning procedures themselves.

It is advised that if gloves and solvents are used in conjunction, adequate water washing and rinsing is also applied to the stainless steel surface.

CONCLUSIONS

- Gloves potentially deposit leachable material upon stainless steel manufacturing surfaces;
- Adequate rinsing of the stainless steel with water removes any deposits from the gloves;
- Nitrile gloves deposit surface contaminants on the steel surface. This runs at 5.4minutes in the given chromatography. This contaminant is removed with water;
- Latex gloves are potentially the most prone material for solvent related extractants;
- Water used as a solvent causes no extraction from either type of glove material;
- Thorough washing and rinsing cycles are recommended for stainless steel equipment. This is especially the case for difficult to access areas of the equipment following cleaning using either latex or nitrile gloves with solvent based products;
- It is safe to clean the equipment using water with either type of glove material in terms of the deposition of leachable materials.

Acknowledgements

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References

[1] Contamination of critical surfaces from NVR Glove residues via dry handling and solvent cleaning, NASA/TM-2004-212752, Rpt-2004-212752, M.F.Sovinski, 2004.

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