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Evaluation of Dry Connections - A Quantitative Approach

The Tevadaptor® CSTD (Closed System Transfer Device) prevents the release of drug in vapor, aerosol or liquid form during drug preparation and administration. The release of liquid medication in the form of droplets on elastomeric septa was the focus of numerous investigations. These investigations were focused on visual assessment of liquid droplets or residues on the septa following multiple activations, and used various colorful liquids such as methylene blue solutions, green food dye, fluorescein solutions, etc. Needless to say, these liquids are not related to hazardous drug composition, thus results of these studies are not helpful for assessing dry disconnections with real drugs.
Moreover, the analysis in all these studies was qualitative only, based on visual evaluation. Visual evaluation is a subjective method, limited by the capabilities of the human eyes.

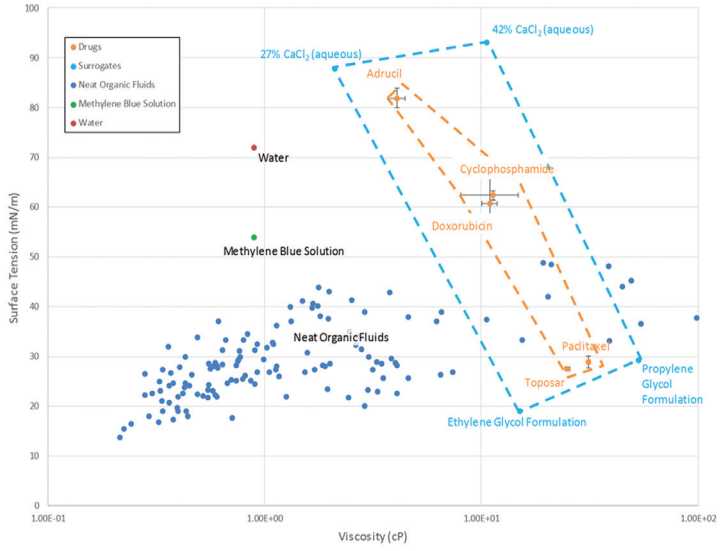
Simplivia™ aimed to:

1. Identify the drug solution properties that affect the interaction between elastomer and solutions, thus determine the formation of droplets on elastomeric septa.
2. Develop a drug surrogate solution that mimics hazardous drugs in these solution properties.
3. Develop a quantitative method to evaluate residues of a liquid drug surrogate on elastomers, based on a solution that resembles hazardous drugs.

Approach

- A quantitative method was developed by an independent research institute (Battelle, Ohio, US)
- Surface tension and shear viscosity were identified as the relevant rheological properties that affect the interaction between the solution and elastomers [1,2].
- Five widely used chemotherapy drugs were chosen for the analysis: Etoposide, 5-fluorouracyl (5-FU), doxorubicin, paclitaxel, cyclophosphamide. Their surface tension and viscosity were compared to water, methylene blue solution and various organic fluids (fig. 1). This analysis proved that water and aqueous methylene blue solution do not have rheological properties as those of hazardous drugs.
- A solution of 27% calcium chloride ($CaCl_2$) was developed as a relevant drug surrogate solution for the quantification of solution residues on the septa (Fig. 1).

Figure 1: Surface tension and viscosity of chemotherapy drugs and potential test liquids



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Method - Quantification of liquid residues on septa based on electrical conductivity

The quantification of the solution residues on the septa involves:

- Extraction of the liquid residues on each septum using an accurate volume (1 mL) of distilled water (Fig. 2)
- Evaluation of conductivity using a conductivity meter (Fig. 3)
- Based on the pre-prepared calibration curve (Fig. 4), calculate the quantity of concentrated $CaCl_2$ solution that was left on the septum
- Twenty five pairs of Vial adaptors (VAs) and Syringe adaptors (SAs) were tested. 4 mL of the drug surrogate soution were transfered from the vial to syringe, and then 2 mL were transfer back to the vial.
- The septa of the VA and SA were extracted with distilled water, and conductivity was determined. This process was repeated 12 times (12 activations).

Results[3]

The level of quantitation of the method (LOQ) was calculated to be 15 nL - a level that cannot at all be seen by human eye. This points to the high sensitivity of the method.
No drug surrogate residues above the LOQ was measured up to the 7th connections/disconnections for all the 25 pairs of VAs/SAs tested (Fig. 5). Only one pair of VA/SA out of the 25 pairs showed any drug solution residue for each connection above the 8th connection. The higher solution residue measured was in the volume of 27 nL.

Conclusion

Practically no drug leakage is detected on Tevadaptor® elastomer following twelve connections/disconnections.

The study was performed using Tevadaptor® products. Since Chemfort™ elastomeric septa are identical to those in the Tevadaptor® products, the results and conclusion of this study are relevant for Chemfort™ products as well.
Therefore, it can be concluded that no drug leakage is expected from the Chemfort™ elastomer following twelve connections and disconnections.

Figure 2: Septa extraction using distilled water in a designated recovery fixture

Figure 3: Example of conductivity measurement using microprobe and a recovery fixture

Figure 4: Calibration curve

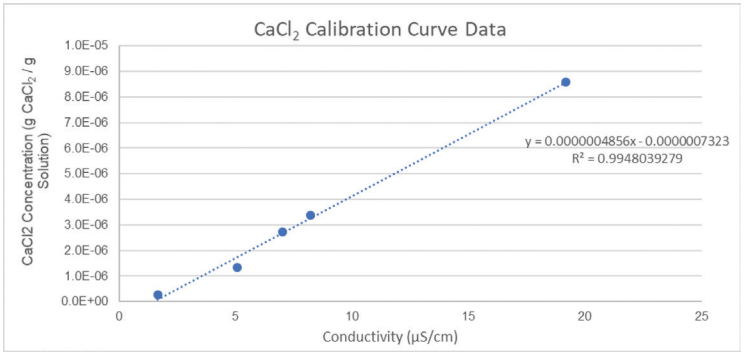
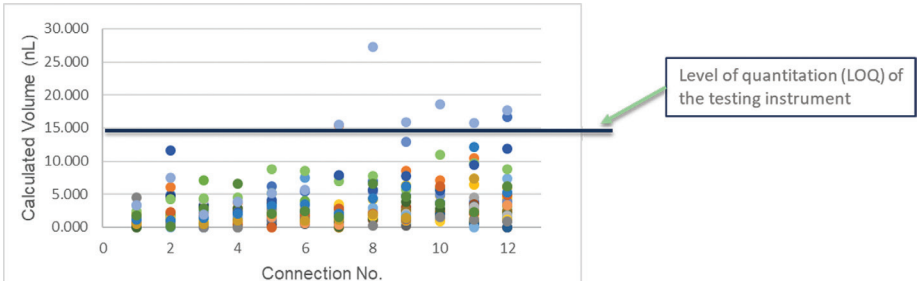


Figure 5: Leak volume distribution for 25 VA/SA pairs for twelve activations



References

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