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Factors to Consider in Filter Validation in Pharmaceutical QC

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INTRODUCTION

Many pharmaceutical QC tests such as dissolution testing, content uniformity, assay, blend uniformity require filtration of sample prior to HPLC / UHPLC analysis. Since quantitation of analytes is critical after these tests, filter validation studies should look at analyte binding to membrane filters. Different membrane filters can cause varying degree of binding of analyte depending on membrane type, analyte type as well as analyte concentration.

OBJECTIVE

Objective of this study was to provide guidance on filter selection and factors to consider during method development & validation. Following factors were evaluated during this study.

- Choice of membranes
- Effect of physico-chemical properties of analyte
- Effect of analyte concentration
- Membrane pore size
- Processing conditions and its effect on analyte recovery.

METHODS

Drug dissolution study was performed using multiple commercially available formulations and methods outlined in respective USP monographs. Samples were filtered using different syringe filters and various filtrate fractions were collected. Filtrate was analyzed by HPLC for quantitation of API. Centrifuged samples were used as controls for 100% analyte recovery to calculate analyte binding to syringe filters.

Similar studies were also conducted on a blend uniformity sample provided by a customer. Sample was dissolved in a solvent blend and filtered through various syringe filters. HPLC analysis of the filtrate was carried out and recovery was calculated using standard prepared in the same way. Finally volumetric sample recovery was determined from different syringe filters.

RESULTS

Figure 1: Table shows effect physico chemical characteristics of analytes and membrane on analyte binding. Neutral caffeine doesn't bind to either of the membranes whereas acidic and basic analytes (Acetyl salicylic acid and Acetaminophen) show strong binding to Nylon membrane. Membrane binding can be significantly reduced by rinsing the syringe filter with sample.

Analyte of Interest	Filtrate (ml)	Syringe Filter Used		
		Hydrophilic PTFE	Nylon	PVDF
Acetaminophen (Log P = 0.49, pKa = - 4.4, Basic, BCS = III)	1st ml	110.4	58.4	109.0
	2nd ml	112.3	109.3	110.6
	3rd ml	112.2	111.3	110.8
	5th ml	112.2	111.5	110.7
Acetyl Salicylic acid (Log P = 1.19, pKa = 3.5, Acidic, BCS = I)	1st ml	119.5	28.2	117.4
	2nd ml	121.4	116.1	119.0
	3rd ml	121.2	121.6	119.1
	5th ml	121.3	122.0	119.2
Caffeine (Log P = -0.07, pKa = 14, neutral, BCS = I)	1st ml	114.2	106.0	112.2
	2nd ml	113.9	112.6	112.6
	3rd ml	113.8	112.9	112.7
	5th ml	113.6	112.9	112.7

Figure 2 shows volumetric recovery when 2 ml sample is filtered through various syringe filters. It can be clearly seen that sample recovery is dependant on filter design rather than membrane pore size. As much as 1.3 -1.4 ml sample is retained by PP syringe filters (vendor E) where as PTFE syringe filters from Vendor A show the lowest amount of sample retention by syringe filter (0.6 ml). This sample hold up can be critical when sample volume is limited.

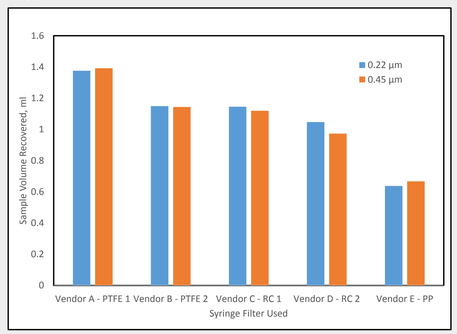
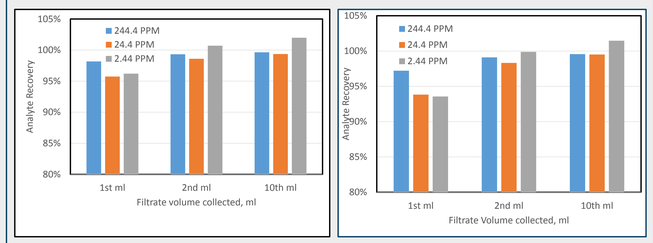
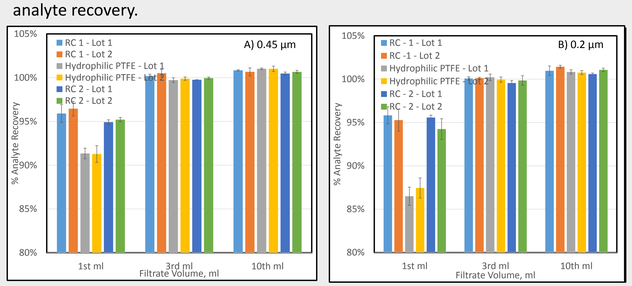


Figure 3 shows impact of analyte concentration on membrane binding and subsequent recovery of analyte for Hydrophilic PTFE membrane. Some analyte binding effect is observed when concentration of reduced from 244 ppm (µg/ml) to 24.4 ppm or 2.44 ppm. This effect is only observed for 1st ml of filtrate, when the membrane is not fully saturated, but with 2nd and 10th ml of filtrate, no concentration effect is observed as the membrane is fully saturated. No significant difference is observed between 0.2 and 0.45 µm membrane filter.



3A) 0.45 µm 3B) 0.2 µm

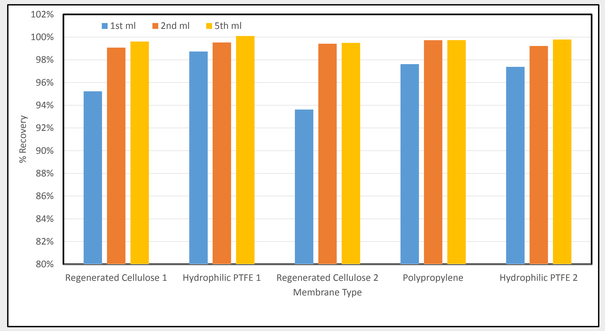
Figure 4 shows lot to lot variability observed with syringe filters for cetirizine quantitation following dissolution testing. Three different membranes were selected, regenerated cellulose membrane from two vendors and hydrophilic PTFE syringe filters from a third vendor. As can be seen from the data, all the membrane filters show very consistent results from lot to lot with very low variability. As observed earlier, 0.2 and 0.45 µm membranes didn't show significant difference in analyte recovery.



Standard Used	% Recovery		
	PVDF 1	PVDF 2	PTFE
Filtered standard	102.1	100.5	102.7
Unfiltered standard	97.0	98.5	100.6
Centrifuged sample	95.9	97.3	99.4

Figure 5 shows that differences in sample and standard processing can affect recovery. When sample and standard undergoes the same procedure, consistent recovery is obtained, whereas when standard is processed differently than sample, higher variability in sample recovery is obtained. This can lead to OOS results.

Figure 6 shows naproxen recovery after sample filtration using various membranes. Both regenerated cellulose membranes show reduced naproxen recovery for 1st ml of filtrate collected. On the other hand, hydrophilic PTFE membranes don't show any loss of analyte even for the 1st ml of filtrate collected. All the membranes show quantitative recovery when 2nd or 5th ml filtrate is collected indicating that sample flushing will help reducing analyte binding to syringe filter.



CONCLUSIONS

- Filter validation is critical part of various pharmaceutical QC tests and various filter parameters need to be taken into consideration during method validation.
- Membrane and analyte physico-chemical properties have largest impact on analyte recovery. Low analyte concentration exacerbated this effect.
- Differences in syringe filter designs led to differences in volumetric recovery. This can be critical for small sample volumes.
- Membrane pore size has limited impact on analyte recovery but pore size selection is dictated by downstream analytical technique.
- Most filters tested in this study showed very good lot to lot consistency.

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