Assessing detergent-mediated virus inactivation, protein stability and impurity clearance in biologics downstream processes

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October 13, 2021

Abstract

Detergent-mediated virus inactivation (VI) provides a valuable orthogonal strategy for viral clearance particularly for next generation continuous manufacturing. Furthermore, there exists an industry-wide need to replace the conventionally employed detergent, Triton X-100, with eco-friendly alternatives. This study provides a systematic approach to screen detergents as VI agents through the study of VI of three different enveloped viruses for monoclonal antibodies and fusion proteins. We investigated three major aspects of VI namely, the impact of VI agent on the therapeutic quality attributes, clearance of the VI agent and other impurities through subsequent chromatographic steps and lastly the efficacy of VI for the said detergent. Several quality attributes such as charge variance, oxidation, deamidation, glycosylation and aggregation were investigated. Aggregation was a key indicator of stability. Experimental and modeling data was used to decipher the mechanism and kinetics of aggregation for pH sensitive molecules by exploring worst case VI conditions. We found product aggregation and its kinetics to be driven by extrinsic factors such as detergent and protein concentration. Aggregation was also impacted by initial aggregation level as well as intrinsic factors such as the protein sequence and detergent hydrophobicity and critical micelle concentration (CMC). VI efficiency was dependent on the virus tested, duration of incubation as well as detergent CMC and concentration. Dodecyl maltopyranoside (DDM) was found to be a promising candidate for potential application in VI. Knowledge gained here on factors driving product stability and VI provides valuable insight to design, standardize and optimize conditions (concentration, duration of inactivation) for screening of detergent-mediated VI.

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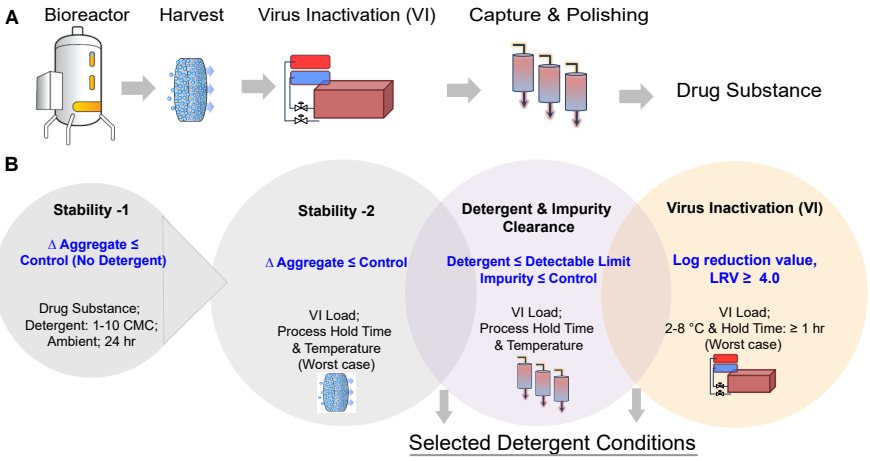

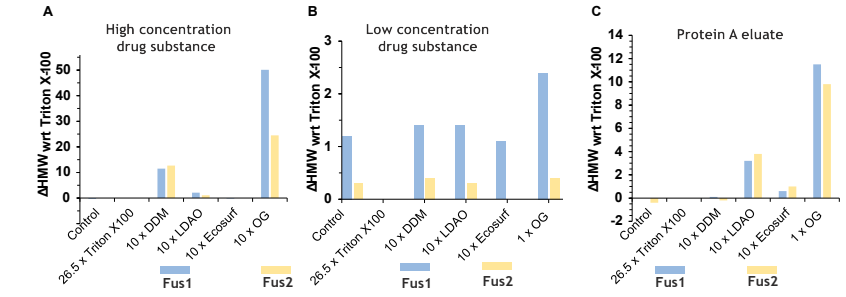

	A		B		C	
	Fus1	Fus2	Fus1	Fus2	Fus1	Fus2
Initial HMW (%)	1.9	1.0	1.3	0.1	25.8	9.8
Protein concentration (g/L)	39.5-45.2	21.2-24.3	3.0	3.0	12.2-14.3	9.7-10.3

Detergent concentration	Control	Triton X-100	DDM	LDAO	Ecosurf	OG	OG
x CMC	No detergent	26.5	10	10	10	10	1
w/v %		0.5	0.061	0.032	1.066	6.8	0.68