

Biological Nanoplexes: Process engineering advancements in production platform development

Michael W. Wolff

Institute of Bioprocess Engineering and Pharmaceutical Technology, University of Applied Sciences Mittelhessen, Wiesenstrasse 14, 35390 Giessen, Germany

Viral epidemics and pandemics pose a substantial challenge to our society. They not only threaten the health of each individual, but also affect our political, social and economic systems. The COVID-19 pandemic showed that our society was and still is not sufficiently prepared to effectively control such infections through prophylactic vaccination. Some of the barriers that need to be overcome to ensure a timely supply of vaccines include political, economic and technical challenges. The latter are particularly evident in the following current limitations in the production process: (1) viral space-time yield in the upstream, (2) specific product performance in the downstream (DSP), and (3) translation of the process from the development scale to the production plant. We are currently addressing some of these shortcomings with platform technologies in the DSP.

We have developed two membrane-based platform technologies for the chromatographic purification of cell culture derived viral particles. The first is based on chemically sulfated cellulose, where the backbone of the stationary phase is the pseudo-affinity ligand, sulfated cellulose. Sulfated polysaccharides are involved in a variety of pathogen-host cell interactions in nature, and sulfated cellulose presumably mimics these natural ligands. Sulfated cellulose based chromatography has been successfully used to purify a variety of viruses.

The second platform technology revolves around membrane steric exclusion chromatography. Its selectivity is primarily based on the size of the target and the nanoplexes are captured without direct chemical interaction by mutual steric exclusion of PEG between the product and the hydrophilic matrix. Results obtained with this method typically indicate very high yields and purities for a broad range of cell culture derived viruses.

We are currently working on a process platform that covers the entire purification process. For this purpose, a combination of tangential flow filtration (TFF) followed by multimodal size exclusion chromatography (mmSEC) is used for clarified, nuclease treated cell culture derived virus particles. The mmSEC is based on a chromatographic stationary phase with porous, restrictive outer surfaces and ligand-activated cores. Small impurities penetrate and adsorb to the core while larger particles pass through unimpeded. Accordingly, the entire DSP (depth filtration, TFF and mmSEC) is largely independent of the highly variable physicochemical properties of the viral outer structure. This, in combination with the high robustness and ease of implementation of the process, is a prerequisite for the broad application of the process platform for locally produced viral vaccines and therapeutics with the potential to support a fast, economical, global vaccine supply in the future.