



What are the Applications of Continuous Processing?

The Pall portfolio of Continuous Processing Technologies based around Acoustic Wave Separation, BioSMB multicolumn chromatography and Single-Pass Tangential Flow Filtration (TFF) can be used for purification of specific solute molecules in a variety of applications. These organic and inorganic solute molecules include but are not limited to synthetic moieties created through chemical or polymer synthesis or could be biopolymers including peptides, proteins, nucleic acids, oligonucleotides, polysaccharides, lipids, cofactors or combinations thereof, as well as larger molecular entities and cells or sub-cellular fractions including but not limited to virus, exosomes, organelles, inclusion bodies, vesicles etc. The solute molecules or larger molecular entities including cells can be derived from a variety of natural sources such as tissues or biological fluids from various hosts of mammalian, microbial, fungal, reptilian, avian, amphibian, insect, plant or fish origin. Alternatively, the solute molecules or larger molecular entities including cells may be produced using authentic cell types or by recombinant expression in various eukaryotic or prokaryotic hosts of mammalian, microbial, insect, algal or plant origin. These could be either expressed within the host organism and isolated from that source or produced in cell culture based around perfusion and batch or fed batch techniques using adherent or suspension culture.

The solute molecules or larger molecular entities including cells (product) must initially be removed in a continuous or semi-continuous manner from the source material described above either directly or following a disruption, lysing or, homogenisation process using either a filtration process or an alternate clarification technique such as centrifugation, settling, precipitation, flocculation or acoustic wave separation, or a combination thereof.

The clarified feed containing the product is then purified using a series of chromatographic techniques to remove both product related impurities, such as aggregates, and non-product related impurities, such as host cell proteins. Purification may be conducted in a continuous mode using BioSMB multicolumn chromatography and typically uses a sequence of orthogonal techniques to remove the aforementioned impurities from the product. Techniques used can involve either bind-elute, or flow through chromatography using established chromatographic modalities using sorbents, membrane adsorbers, expanded beds or monoliths and can exploit affinity, pseudo-affinity, ion-exchange, hydrophobic interaction, mixed mode, thiophilic, chiral, normal phase, reversed phase or size exclusion techniques. At least 2 chromatography devices would be used for each orthogonal chromatographic step. Throughout the purification process the feed for each chromatographic operation may be optionally continuously concentrated using single-pass TFF or the mobile phase composition adjusted using inline diafiltration to enable optimal performance of the subsequent chromatographic step. Additionally, TFF techniques will enhance purification of the product by removal of smaller molecular weight contaminants (including small proteins, peptides and amino acids). TFF can be used for separation of charged species using charged membranes and also removal of endotoxin from parenteral pharmaceutical ingredients and drug substance, including buffers, excipients, water, etc.

Dependent on the therapeutic dose and the mode of administration, the purified product, often referred to as drug substance, is then optionally concentrated and/or conditioned into an alternate solution phase so it can be formulated and administered in the preferred form. This process can be carried out continuously using a sequence of unit operations using single-pass TFF using inline concentration and/or inline diafiltration to give the final product, often referred to as bulk drug substance. This will then be further processed by for example vial filling or tableting etc.

The aforementioned purification process to generate bulk drug substance from the source material may be carried out continuously or semi-continuously using the techniques outlined above. Dependent on the requirements for bioburden control or sterile operation, the flow path used to purify the product through the processing system may be single-use using aseptic connections between components or containing reusable components that require a cleaning and sanitization cycle. Within, or between, specific unit operations there can be optionally placed filters for additional clarification and/or bioburden control or viral filters for removal of virus. In addition a continuous virus inactivation process using for example a low pH hold can be introduced into the process sequence at a position optimal for the product in question. Additionally, intermediate surge bags or biocontainers as well as sampling ports can be included at any place within the continuous flow path to introduce additional control of the process.

Process monitoring and control can be achieved by use of the various sensors included within the flow path and the feedback control supported via the process control system within the instruments themselves or controlled through a broader facility or SCADA network.



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