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Membrane Filtration

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1. INTRODUCTION

The filtration of protein solutions, especially in the manufacture of biologically derived proteins, is a large and increasingly important step in the production of protein pharmaceuticals. The focus of this chapter is on the use of membrane filters for purification and sterilization of protein pharmaceuticals. However, we also review other important uses of membranes and nonmembrane filters in the production of protein pharmaceuticals. The reader is directed to several useful reference books that describe in more detail both the theory and the practice of filtration in the biopharmaceutical industry (Cheryan, 1986; Ho and Sirkar, 1992; Johnston, 1992a; Meltzer, 1987; Meltzer and Jornitz, 1998). Additional discussion of interactions between filters and protein formulations can be found in Chapters 2 and 3. The appendix to this chapter contains definitions of terms for those readers unfamiliar with terminology of membrane filtration.
1.1. Applications of Membrane Filters in the Production of Protein Pharmaceuticals

Protein biopharmaceuticals are typically produced by fermentation, cell culture, or extraction from tissue.Regardless of the origin of the biopharmaceutical protein, many steps are involved in purification of the protein before it is ready for pharmaceutical sale and use. The physical processes used to purify biopharmaceutical proteins may include filtration, adsorption, centrifugation, and chromatography. These processing methods are typically used to take a protein through the following sequence of steps in the purification scheme:

- Clarification: removal of cell mass from supernatant liquid
- Fractionation: isolation of desired protein from other solutes
- Concentration: concentration of desired protein in solution
- Diafiltration: removal or exchange of small solutes by sequential dilution and concentration steps
- Sterilization: removal of bacterial cells

Microfiltration (MF) and ultrafiltration (UF) membrane processes can be used to perform the above processing steps. Microporous filtration is sometimes used for clarification; UF is used for fractionation, concentration, and diafiltration; and MF is used for sterilization. In the sterilization of protein pharmaceuticals, MF is the method of choice, because proteins are denatured by thermal sterilization processes.

Membrane filtration processes can be divided into two distinct modes of operation. The first is a single-pass dead-end or static mode and the second is a multiple-pass crossflow or tangential-flow mode. Crossflow filtration is distinguished from dead-end filtration in that the flow path of the fluid being filtered is parallel to the membrane surface rather than perpendicular to the membrane surface, as shown in Fig. 1. In crossflow filtration, the flow parallel to the membrane surface generates shear, which limits the thickness of the filter cake or gel layer. In dead-end filtration, the filter-cake thickness increases with time, resulting in the eventual cessation of flow.

1.1.1. DEAD-END FILTRATION

Dead-end filtration is used primarily in microfiltration applications where the goal of the filtration is to remove particles greater than 0.1 μm, where the feed solution is relatively “clean,” and where the filtrate (or solute