ANTIBIOTIC BROTH

PCI Membranes specialises in custom-built crossflow membrane filtration systems and membrane technology for liquid separation in water, wastewater treatment, food & beverage, pharmaceutical and industrial applications. With experience developed over fifty years, PCI Membranes provides process solutions for a wide variety of filtration applications using microfiltration, ultrafiltration, nanofiltration and reverse osmosis technologies.

PCI Membranes Tubular Method: Minimal Pre-Screening

The tubular method of filtration tolerates the suspended solids present in extracts from pieces of stems, seeds or leaves. It requires only minimal pre-screening, whereas the other membranes require a substantial solid removal system prior to their use to avoid blockage.

In many cases, initial separation is possible whilst the membranes are clarifying the extract. For example, PCI tubular **Ultrafiltration** (UF) membranes can retain the larger molecular weight compounds as the membrane simultaneously retains the unwanted solids. This reduces the load on other downstream separation and purifying equipment.

In addition to this, PCI Membranes have found that the tubular format has a higher recovery of filtrate than others, making it more cost-effective particularly when the raw material is expensive.

A second phase of tubular membrane **Nanofiltration** or **Reverse Osmosis** can also be utilised to concentrate the desired compounds in the permeate from the first stage of filtration. This further increases the yield from the raw materials and eliminates wastage.

PCI Tubular Membrane: Maintenance

The PCI tubular membrane, with its high crossflows, reduces this fouling tendency and is easy to clean when the filtration cycle is completed.

Another key advantage of this method is that it tolerates higher temperatures than the other alternatives and, therefore, is able to process the delicate materials more quickly and precisely.

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ANTIBIOTIC BROTH

PCI Membranes offers a broad range of tubular membrane rental units for piloting the Antibiotic Broth application. Our units provide MF, UF to NF and RO processes and available in the following platforms: lab scale, pilot scale and semi full scale (multi-stage) pilot plant. Available for all unit types, our engineers facilitate a complete requirement assessment available at our own laboratory or the customer's site. By conducting a series of pilot plant trials, the most effective membrane configuration is attained.

Our Filtration Solutions Are:

Safer

Our products meet common certifications for pharmaceutical and food & beverage contact.

Healthier

We develop products that improve the quality of life for humans and animals.

More Productive

Our solutions allow you to produce more product at a lower cost, improving your bottom line.

Advantages To Working With Us:

- Access to an extensive network of filtration professionals from all over the world who have experience with thousands of unique processes and applications.
- Products designed to maximize your productivity, product quality and bottom line.
- Ability to quickly adjust to your changing needs.
- Technical support from initial conversations to implementation and beyond.
- Shortest lead times and highest value in the industry.

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ANTIBIOTIC BROTH

Through Ultrafiltration

Process Fluid General Description

Broths fall into two categories, whole broth and filtered broth.

Whole broth is a suspension of Mycelia, which may have been homogenised. The continuous phase contains the antibiotic, which is the desired product, as well as dissolved proteins and residual nutrients. The high level of suspended material imparts non-Newtonian rheological behaviour to these broths. In general, these broths are shear thinning.

Filtered broths have much smaller amounts of suspended material than whole broths. Because of this, the rheology tends to be Newtonian until high concentration factors are achieved.

The properties of a broth will be affected by the type of antibiotic being produced and the recipe of the broth, or media. Broths also vary with natural, unquantifiable variations in the media, strain of mycelia or fermentation conditions. These can affect the performance of all downstream processing operations.

"We have one active site in Italy which is using PCI Membranes to process their broth"

Physical Proponents	Whole	Filtered
pH		
Suspended Solids	4% - 8% wt/wt	0.5% wt/wt
Total Solids	8% - 16% wt/wt	
Rhelogy	μa = 30-70 mP a.s $^{-1}$	
Mol. Weight	334	
Pk	2.5 - 3.1	

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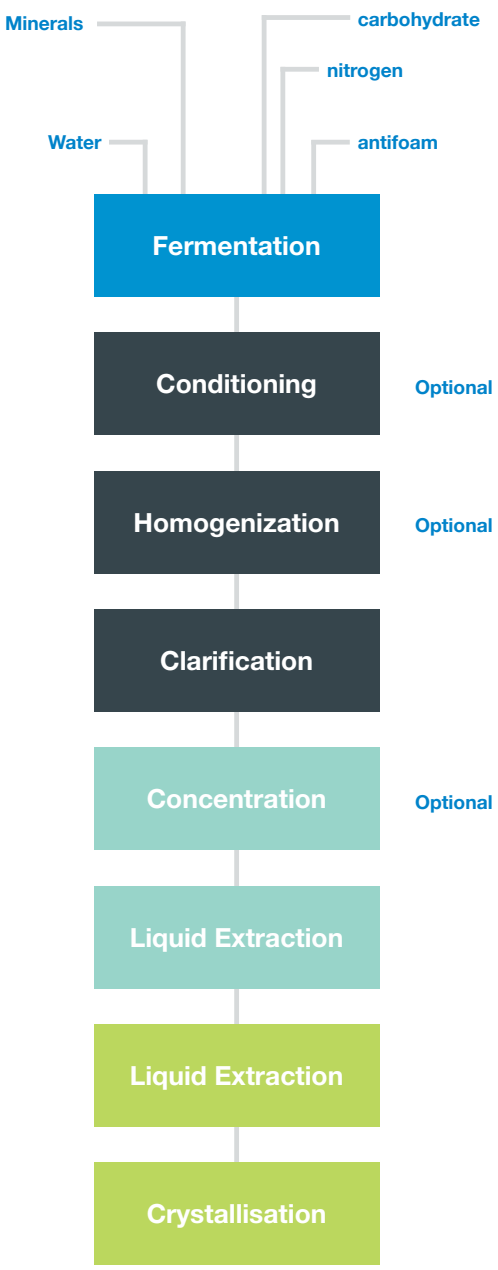
PROCESS DESCRIPTION



Fermentation

This is usually carried out in batch stirred tank fermenters. Batch volumes can be up to 180m^3 and batch times are normally around 5 to 6 days for Penicllin. At the end of the fermentation it is normal to cool the broth to prevent the antibiotic from degrading.

The media used for fermentations can be either “defined media”, or, “undefined media.” In defined media the ingredients are all relatively pure, eg. glucose, so the components are fully known. This type of media is ‘not’ common for bulk antibiotics. Undefined media uses less pure materials such as molasses for carbohydrate and blood as a nitrogen source.

The mycelia require carbohydrate, nitrogen, trace minerals and a suitable pH for growth. In addition, antifoam is commonly used.

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Conditioning

This step is optional and does not apply to all broths. It involves conditioning the broth to make clarification easier. There are four principal options:

1) AGING - In some broths the mycelia will flocculate naturally when the fermentation stops.

2) HEAT TREATMENT - To induce flocculation.

3) pH ADJUSTMENT - To induce flocculation.

4) ADDITION - Flocculents.

If the antibiotic is intracellular, this step is necessary to release the antibiotic from the cells. The process may be carried out using a homogeniser, or by ball mill. The operation is often referred to as cell disruption.

Homogenisation

If the antibiotic is extracellular, this step is optional. However, it does reduce the viscosity of the broth, which may aid processes further downstream.

Clarification

The traditional techniques are filtration using rotary vacuum filter (RVF) and centrifugation. Ultrafiltration can replace both, or it can be used in conjunction with either.

Concentration

In some processes, the clarified broth is concentrated before further processing. Evaporators or RO may be used.

Extraction

This is usually done by liquid/liquid extraction. The antibiotic is extracted from the aqueous phase into an organic phase. It may then be transferred back to an aqueous phase prior to crystallisation.

The extraction stage is hindered by the presence of proteins in the clarified broth and surfactants are added to improve the extraction.

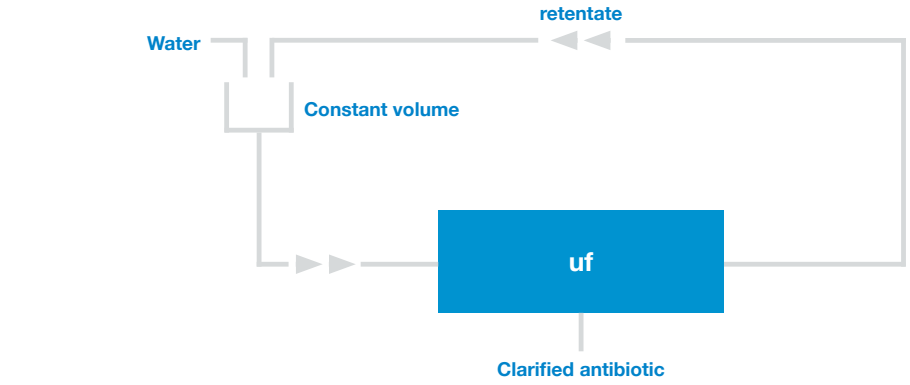
Crystallisation

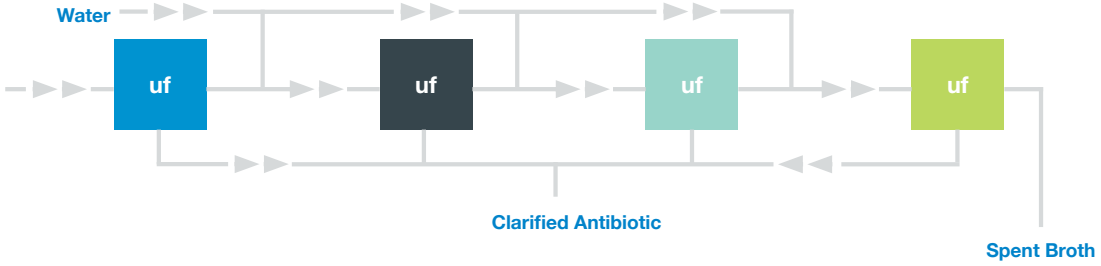
Here the crude antibiotic is crystallised out. In some cases this involves further washing and purification. The crude antibiotic is then either used as a feed stock for the manufacture of “synthetic” antibiotics, or it is formulated into commercial drugs.

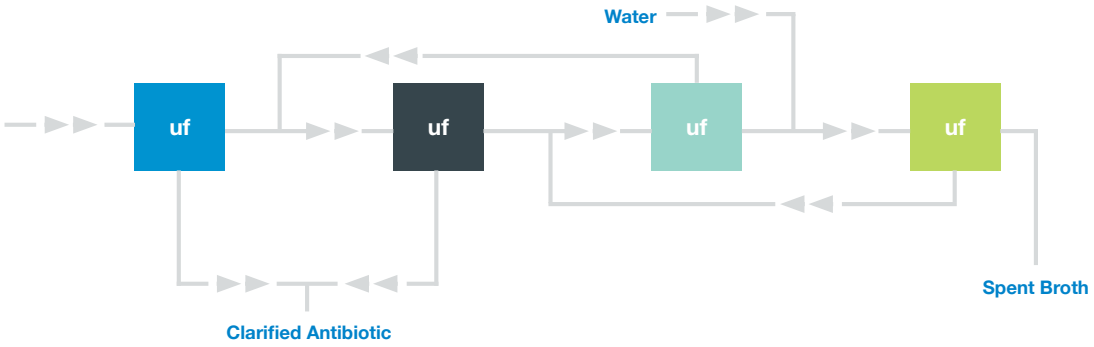
Ultrafiltration

Whole Broth

Due to the high viscosity of the broth the maximum concentration factor achievable is very low, ranging from 1 to 3. Therefore, in order to attain yields of >95% diafiltration must be employed. There are 3 basic ways of doing this:







Note:

In the continuous plants the first stage carries out a concentration of the broth. This concentration is maintained throughout the rest of the plant. The advantage of concentrating the broth is that it reduces the diafiltration requirement and gives higher concentration of antibiotic in the bulk permeate, which is a clear advantage to further downstream processes. The membranes used in this stage are the same as those used in the rest of the plant.

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Filtered Broth

Filtered broth can be concentrated to volumetric concentration factors (VCF) of up to 50 times. This obviously reduces the need for diafiltration, thus a normal plant would either be batch, or co-current diafiltration.

Comparison of Plant Options

	Batch	Co-Current	Counter Current
Residence time	High	Low / Medium	Low / Medium
Operation	Easy	Medium	Difficult
Automation	Easy	Medium	Complex
Control	Easy	Medium	Complex
Water Usage	Low	High	Medium / Low

Process Design

	Flux	Solute Passage
Penicillin G	20 - 30 l/m^2/h	**100%**
Cephalasporin C	12 - 40 l/m^2/h	**No Data**
Clavulanic Acid	25 - 30 l/m^2/h	**No Data**
Penicillin V	100 - 160 l/m^2/h	**100%**
Protein	-	**0-10%**

Due to the high yield requirements, even a small retention of the antibiotic can have a major impact on the plant size and diafiltration requirement.

Note:

Flux is a function of concentration factor. However, the variation from batch to batch of broth makes it impossible to quote a general equation. It is normal to design on an average flux determined during trials.

The above fluxes represent the results of different trials conducted at different sites at different times. Therefore, they are not necessarily the maximum fluxes achievable with current membranes. See membrane types below.

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Pressure

8 - 12 bar module inlet, 2 bar module outlet
Delta P = f (broth, vcf)

Temperature

10 - 25°C

This depends on the customer and the residence time in the plant. At higher temperatures the antibiotic tends to degrade due to the action of enzymes

pH

No adjustment is required

Cross Flow

Nominal ~ 4 m/sec. (=30 L/min)
Range ~ 2.6 - 4 m/sec. (=20 - 30 L/min)

There is no contradictory evidence as to whether or not flux is a function of cross flow velocity. It should be noted that, due to the non-newtonian rheological behaviour of whole broth, reducing cross flow velocity may not always reduce the pressure drop.

Cleaning

This cleaning procedure has proved successful for PU 120 in trials lasting more than one year. See membrane life below.

Membrane Life

6 months to 1 year.

This is based on extensive trials on 100 sets of PU120 membranes, cleaned once per day. After 6 months, the passage of proteins starts to increase.

Application Status - Penicillin G

Large scale trials have been carried out using PU120 membranes. Batch trials, principally on filtered broth, using >100m^2 membrane area and counter current diafiltration on a three stage plant of 26m^2 have been conducted at two different sites.

Trials Required

Due to the nature of the industry and the variability of broths, trials will be required before firm quotes can be given, providing no difficulties are encountered in cleaning. The trials need to be extensive.

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