DYNAMIC CROSS-FLOW FILTRATION FOR ISOLATION OF EXTRACELLULARE BIO-PRODUCTS

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ABSTRACT

Cross-flow technology for separating substances with poor filtration properties are state of the art. With traditional cross-flow filtration the development of the clogging layer is prevented at the surface of the filter membranes by pumping the feed. When handling sensitive or highly viscous products, this method is not efficient or even not applicable. The pumping cross-flow filtration technologies would not be able to concentrate a fermentation broth to an extend were more or less no valuable liquid compound would remain in the retentate. Because the dynamic cross-flow filtration is able to concentrate the biomass of the fermentation broth close to 100% by volume, the efficiency of the separation and the yield of the valuable compound are higher than at any other cross-flow technology.

KEYWORDS

Fermentation broth, Antibiotic, Harvesting, Pharmaceutical Ingredient, Rotating Disc Membrane, Retentate, Transmembrane Pressure, Cross-Flow, Tangential Flow

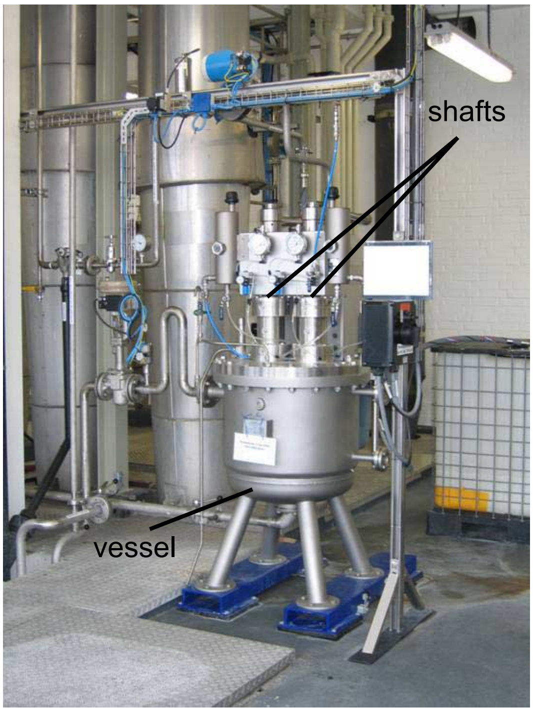

Figure 1: DCF unit installed

1. Introduction

ANDRITZ KMPT GmbH has further developed the process of Dynamic Cross-Flow Filtration (DCF). In this process overlapping rotating disks generate a differential speed between themselves. This set-up generates a cross-flow without using a pump to circulate the slurry.

By applying wall shear stresses which are at least 50% higher than at conventional cross-flow systems, the development of a clogging layer which obstructs the permeate flow can be avoided or at least reduced substantially.

Figure 1 shows a DCF unit with 10 m² installed at a customer site.

2. Advantages of high wall shear stress

The in-stationary principle of cross-flow is causing a zone of discontinuity at the entrance of the overlapping zone as well as at the exit of the overlapping zone. This zone of discontinuity is causing a very efficient local cleaning effect due to turbulent flow. The turbulent flow is directed parallel to the membrane surface but also vertical to the surface. Especially the vertical component is providing high detaching forces even for very adhesive clogging layers.

Figure 2 shows three prints which are the results of fluid modelling simulations. These segments represent horizontal cross-sections at different distances from the overlapping disks that are rotating counter-currently. The colour code represents the absolute velocity of the retentate in m/s. In the centre between the discs, i.e., where symmetry is given, a stagnation point can be seen (see middle print). The circumferential speed at the outer rim of the disks is set by 7.3 m/s for this model simulation. Therefore it is no surprise that the retentate has also an appreciable velocity in the vicinity of the disk surface which is depicted in the two pictures left and right. The spatial difference of velocities, i.e., the velocity gradient is directly proportional to the shear stress which is seemly high, given the disk velocity and the simulated velocity in the vicinity of the disks (left and right print). It is certainly sufficiently high to reduce the tendency of retentate deposits to build up and permanently block the disk surface. But on the other hand the induced shear stress is gentle enough not to destroy the product which is often encountered when using pumps to maintain a circulating flow.

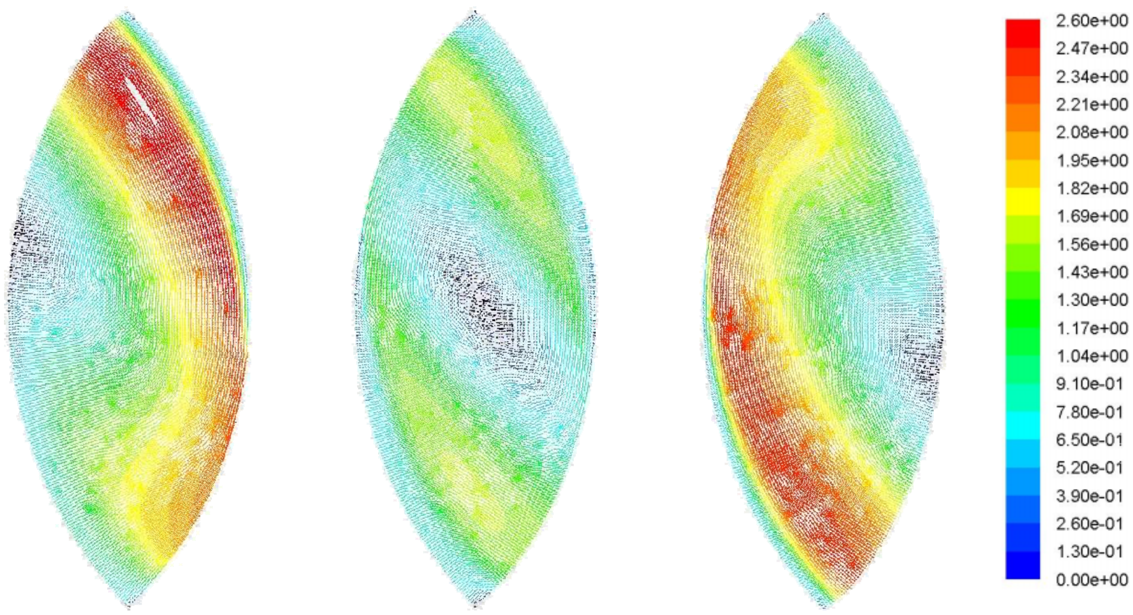

Figure 2: High cross-flow velocities in overlap of discs at different spatial distance from the disks: left – 0.1 mm from the left disk surface, middle – equal spacing between discs, right – 0.1 mm from right disk surface. (Please note that the right and left picture show the same but mirrored velocity pattern.)

For retentates with low viscosity this effect is causing significantly higher permeate flux, approx. 2 times the optimum permeate flux from cross-flow technologies with pumped retentate (traditional systems). This effect is even more important for higher concentrated / higher viscous retentates: The dynamic cross-flow is often providing permeate fluxes which are 2 to 3 times higher than traditional systems. Figure 3 is showing, e.g., the Concentration of protein.

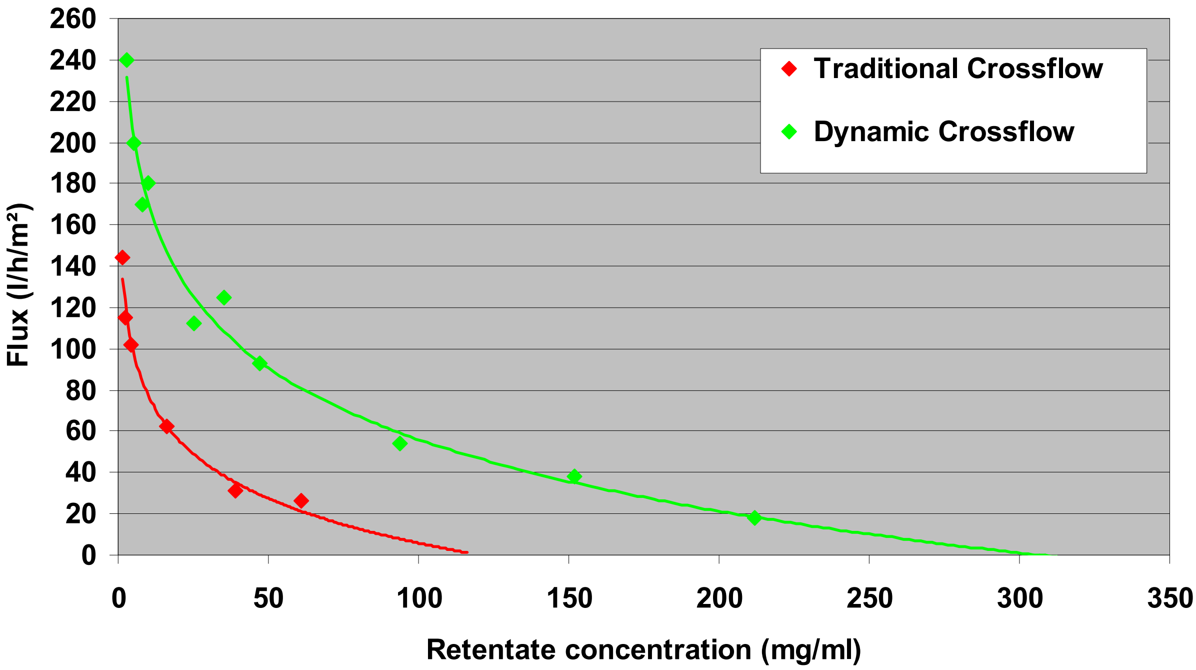

Figure 3: Comparison of permeate flux rates

This leads to the possibility to achieve very high solid concentrations in the retentate. The achievable solid concentration is in the range of 25 % to 50 % higher. In some cases it is even up to 300 % higher. Also this can be seen in Figure 3: The concentration of proteins that could be achieved with traditional filtration is in the range of 70mg/ml. The dynamic cross-flow filtration achieved maximum concentration in this case of about 220 mg/ml, given the same minimum flux rate of termination of 23 l/m2/h

3. Task of harvesting from fermentation broth

The valuable compound (product) of a fermentation process is typically the active pharmaceutical ingredient which either remains within the cells or is released by the cells during the fermentation process. In case the product is produced in extra cellular form, the harvesting process is easier, since no destruction of the cells is necessary and therefore also the filtration is easier.

Typically the fermentation broth is containing just very small quantities of the product, but a lot of other compounds such as salts, cells, foreign organic matters and impurities. The task of the harvesting equipment is to isolate the product as much as possible from the other compounds, i.e. all solid matters need to be removed but without containing any valuable product. Figure 4 is showing on the left side the permeate which is containing the product.

Furthermore it is of importance not to carry too much of additional liquids over into the product stream. This carry-over liquid dilutes the product stream which is of course undesired.

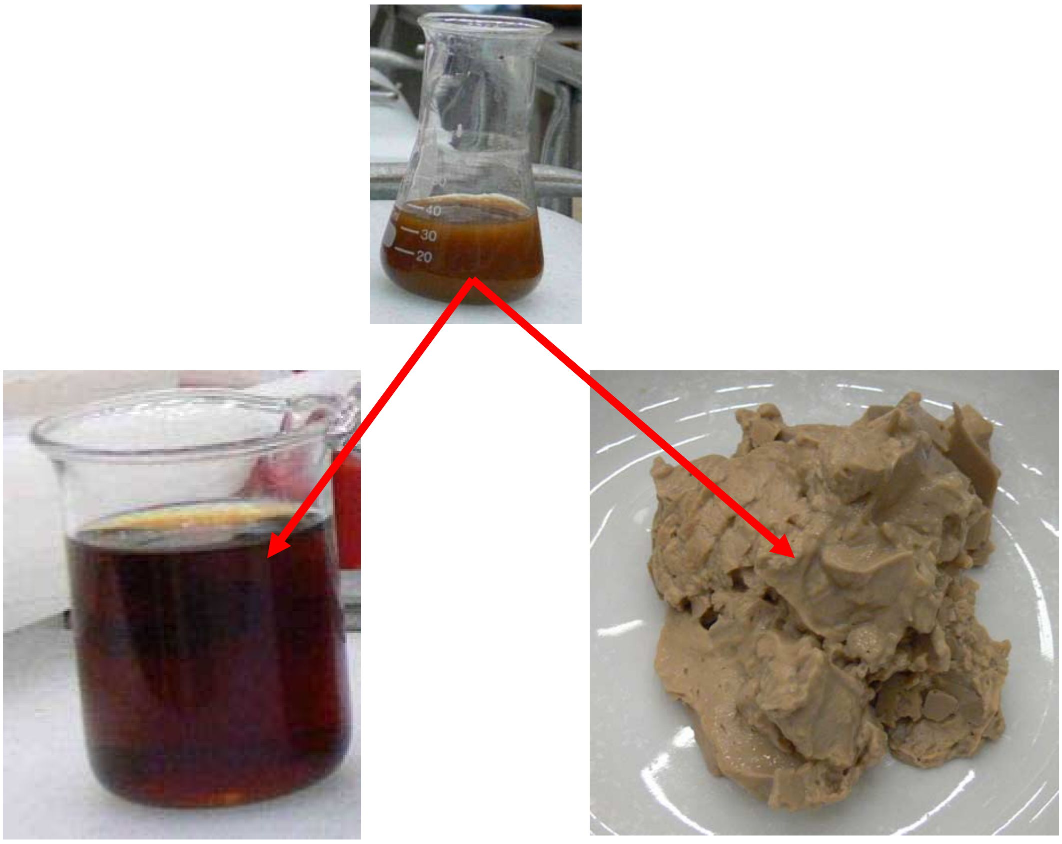

Figure 4: Outlet streams of DCF from fermentation broth

3.1 First step of harvesting

In case the product of the fermentation is an extra cellular compound, this compound can be harvested by dynamic cross-flow filtration directly after the fermentation.

The first step of the harvesting process is the concentration step. The biomass will be concentrated as high as possible. When it comes to yeast based fermentation processes, typically very high concentrations of the biomass can be achieved. Often close to 100% by volume. This can be seen in figure 4 on the right side picture. The retentate is exhibiting a very high viscous.

With increasing concentration of biomaterial in the retentate, the filtration is getting more and more difficult. An example graph for a fermentation broth can be seen in figure 5. The very high flux rates in the range of several hundred kg/m²/h are impressive. The initial concentration of solids is approx. 1% in Volume. At minute 32 a back flush step was done to remove the clogging layer of cells at the membrane. A tremendous increase of flux of about 30% can be seen. At minute 37 the concentration step was stopped.

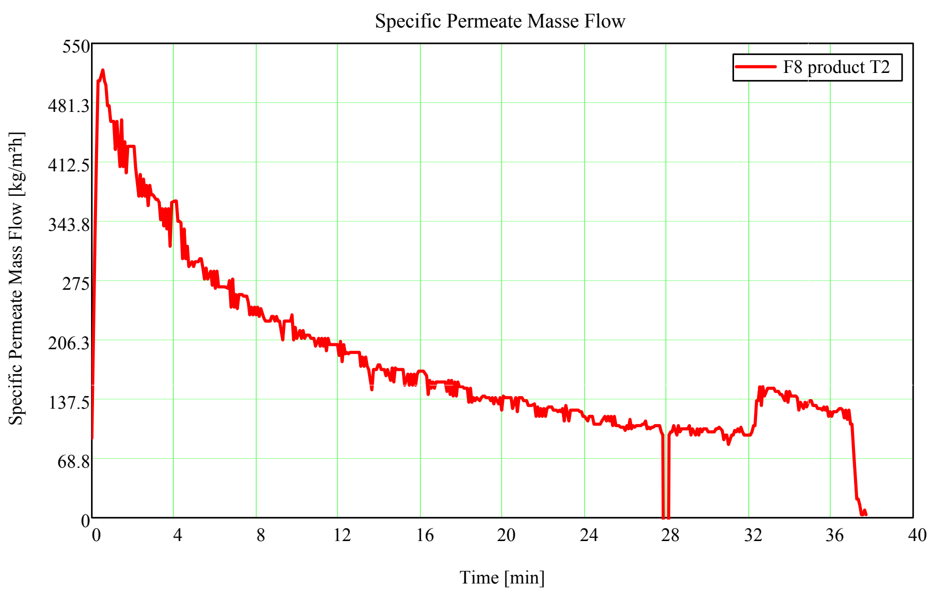

Figure 5: Transient permeate flux of product T2.

Thus the major fraction of the liquid from the fermentation processes is filtered out by this first concentration step. This liquid phase contains most of the product. Nevertheless, there is some free liquid and therefore some remaining product in the retentate. Since the product is typically very expensive and a lot of consecutive process steps are necessary in the downstream process, it is of importance that each step, including the harvesting, aims for very high yields. Therefore a second step of harvesting is necessary.

3.2 Second step of harvesting

The second step of harvesting is called diafiltration. The remaining amount of product containing liquid in the retentate is removed by exchanging it with an additional buffer liquid. By increasing the amount of diafiltration liquid the yield can be increased as far as specified but at the cost of higher product dilution.

Because the remaining amount of liquid within the retentate is already very small after the first concentration step, the amount of diafiltration liquid is only a fraction compared with that of traditional systems.

This results in less diafiltration liquid, increased yield but also a significantly reduced operation time.

4. Comparison to other technologies

The biggest advantage of the DCF technology is that it combines the harvesting task and the task to clean and purify the product stream (polishing step) within one piece of equipment. No additional police filters are necessary, because the resulting permeate from harvesting is absolutely free of particles and clear.

Combining different process steps within one piece of equipment increases the yield significantly. Often 8 % additional amount of product can be obtained compared to other technologies.

On the other hand the product is treated as carefully as possible. This is caused by the effect, that no circulation pump is needed. The shear rates at the membrane surfaces are obviously lower than the shear rates induced through the circulation pump traditionally used. There is no cell destruction at all, the process temperature is kept at a low and constant level, there are no hotspots, and there is no mechanical impact by pumps or by extensive centrifugal forces.

5. Conclusion & outlook

The DCF technology has already shown its vast potential in various applications but the tests revealed that the prediction of the performance is difficult and actual tests are paramount the correctly access its applicability and optimal range of operation.

Therefore ANDRITZ KMPT GmbH has setup a large park of test units. Modules with sizes from 0.03 m² to 10.0 m² of filtration area are available for rent or to perform tests at the ANDRITZ KMPT GmbH test center in Vierkirchen.

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