

# Cephalosporin C purification using SepTor technology

Cephalosporin C (CPC) belongs to the largest class of antibiotics, the beta-lactam antibiotics. The overall world market for beta-lactam antibiotics is estimated over \$ 9 billion (in 2001).

CPC is a bulk intermediate for many semi-synthetic antibiotics. After fermentation and purification,



CPC is converted to 7-ACA, which serves as the beta-lactam nucleus for the majority of semi-synthetic antibiotics available today.

CPC is produced by specific high yield strains of *Cephalosporium Acremonium*, a filamentous strictly aerobic fungus. Originally, the commercial recovery processes were based on solvent extraction. Nowadays, most processes are based on the more selective capabilities of polymeric media. This results in a better recovery and higher purity of CPC.

In this application note, we will outline the recovery of CPC by using continuous chromatography on a non-functionalized polymeric adsorbent. The continuous chromatography process involves multiple steps, which makes the SepTor chromatography system the system of choice.

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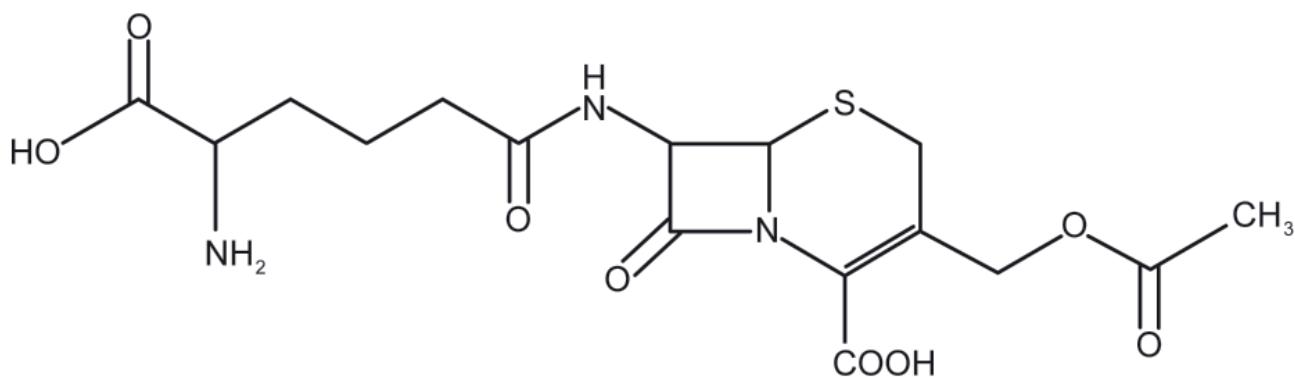


Figure 1. Molecular structure of Cephalosporin.

### Design considerations

CPC is adsorbed on non-functionalized polystyrene adsorbents, such as Amberlite XAD-16 or equivalent resins. The adsorption is carried out near the iso-electric point of CPC, typically at pH 2.

Key issue in the purification of CPC is the removal of desacetyl cephalosporin (DCPC) and desacetyloxy cephalosporin (DOCPC). Typical breakthrough and elution profiles of the three main components in the separation (CPC, DCPC and DOCPC) are shown in figure 2. The graph clearly shows that DCPC is displaced by CPC and that DOCPC binds stronger than CPC.

Depending on the final form of the Cephalosporin that is produced (either its Na or its Zn salt), the elution is done with a water miscible solvent, such as

IPA, or with a sodium acetate buffer.

After the elution, the resin needs to be regenerated with caustic, which is sometimes combined with a solvent. After the regeneration, some sulphuric acid is applied in order to bring the pH down to conditions compatible with the adsorption.

### Pilot test results

During pilot tests, the influence of various parameters on the separation performance has been investigated and process conditions have been optimized. This includes optimization of the settings to accommodate variations in the feed composition.

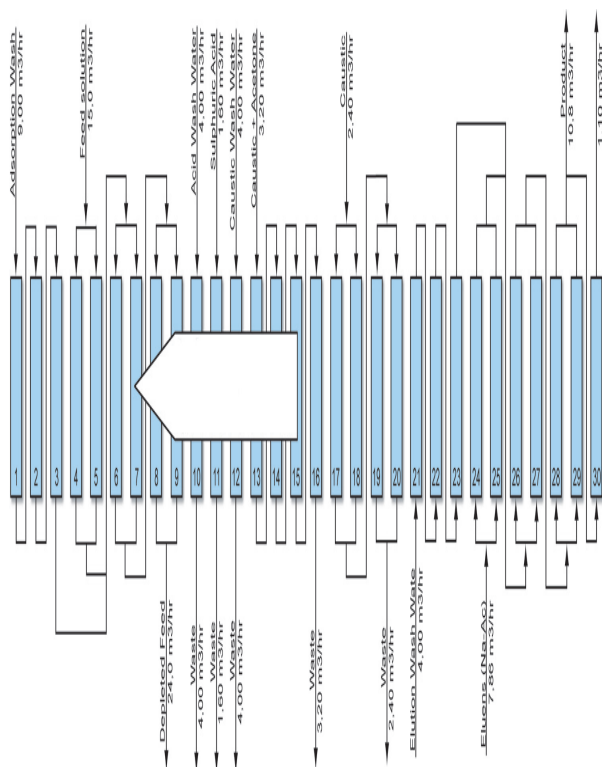
The recovery of CPC is 93 – 95% and the reduction in DCPC and DOCPC are 28 and 3-fold. The colour removal depends on the nature of the fermentation broth. Even in case of very turbid fermentation broths (with a light transmission at 420 nm  $T_{420} < 75\%$  after 50 times dilution), the colour reduced with a factor 50 – 60.

### Commercial process flow diagram

A typical process flow diagram for the purification of CPC from clarified fermentation broth is shown in figure above. The PFD shows a process with a production capacity of 850 tpa CPC.

Most relevant system dimensions of the PFD shown in figure 3 are: Resin volume: 33 m<sup>3</sup> in 30 columns e.g. 1,1 m<sup>3</sup> resin/column.

The process shown in figure 2 would operate at a specific productivity of 26 tpa/m<sup>3</sup>. The performance of large-scale systems is slightly better than for pilot-scale processes. Recoveries of 95% are normally obtained and the reduction of DCPC and DOCPC is very similar or slightly better than in pilot trials. The colour removal is normally in the same range as in the pilot



## Process economy

A typical fixed process for the purification of CPC has a specific productivity in the range of 8 to 15 tpa/m<sup>3</sup>. The overall resin volume for a production capacity equal to the system shown in figure 3 then requires approximately 100m<sup>3</sup> resin and twice as much water and chemicals. A comparison between a typical Fixed Bed process and the SepTor System are shown in the table right.

Generally, the recovery in a continuous system is 2% higher than in a fixed bed process. Based on this, the overall economic benefits for a process as shown in figure 3 are approximately \$ 1 million per year.

The majority of large-scale antibiotics manufacturing processes are nowadays being installed in China. This includes a few installations for CPC purification. Typically, the productivity of these systems ranges from 20 to 30 tpa/m<sup>3</sup>. Due to improvements in the fermentation process, some European companies have been able to obtain significant higher productivities.

	Fixed bed operation	SepTor system
Productivity	8 – 15 tpa/m <sup>3</sup>	25 – 30 tpa/m <sup>3</sup>
Yield	91 – 93%	93 – 95%
Resin volume	60 – 100 m <sup>3</sup>	33 m <sup>3</sup>
Resin consumption	30 – 50 m <sup>3</sup> /yr	20 – 35 m <sup>3</sup> /yr
Water consumption	350 – 450 liter/kg	180 – 225 liter/kg
Solvent consumption	15 – 35 liter/kg	10 – 20 liter/kg
Caustic consumption	60 – 80 liter/kg	25 – 35 liter/kg

Table 1. Comparison between Fixed bed operation and the SepTor System for the purification of CPC.

## Conclusions

The purification of CPC can be efficiently done in a continuous SepTor system. Various commercial applications, both in Europe and in China, have been successfully installed over the past decade.

The versatility of the SepTor system also allows applications for other antibiotics. The latter includes the purification various antibiotics, such as Neomycin, Clindamycin and Erythromycin have been demonstrated.

More information on SepTor Technologies can be found on the web site.

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