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INTRODUCTION

Voriconazole is a widely applied antifungal medication. Its synthesis typically results in a racemic mixture of (2*R*,3*S*)- and (2*S*,3*R*)-enantiomers, where the (2*R*,3*S*)-form is the eutomer, while the (2*S*,3*R*)-isomer is the less potent distomer. [1]

Centrifugal partition chromatography (CPC) is a liquid-liquid chromatographic technique where both the stationary and mobile phases are liquids, and the resolution is governed by the partitioning of solutes between these phases. CPC technique for purifying racemic voriconazole via a semi-batch mode (stacked injections) has increased productivity by threefold compared to conventional resolution, while costs are comparable [2]. The dual-mode CPC (MDM-CPC) technique facilitates the simultaneous execution of stationary and mobile phase functions within a single run, thereby offering a streamlined approach for separation.

Continuous CPC implements the unique MDM-CPC approach in which two CPC devices are interconnected. Multiple Dual-Mode (MDM) separation involves the alternation between the stationary phase and the mobile phase multiple times, ensuring uninterrupted operation and continuous production.



Figure 1: Dual rotor pilot-scale Continuous CPC device

MATERIALS & METHODS

Racemic mixture

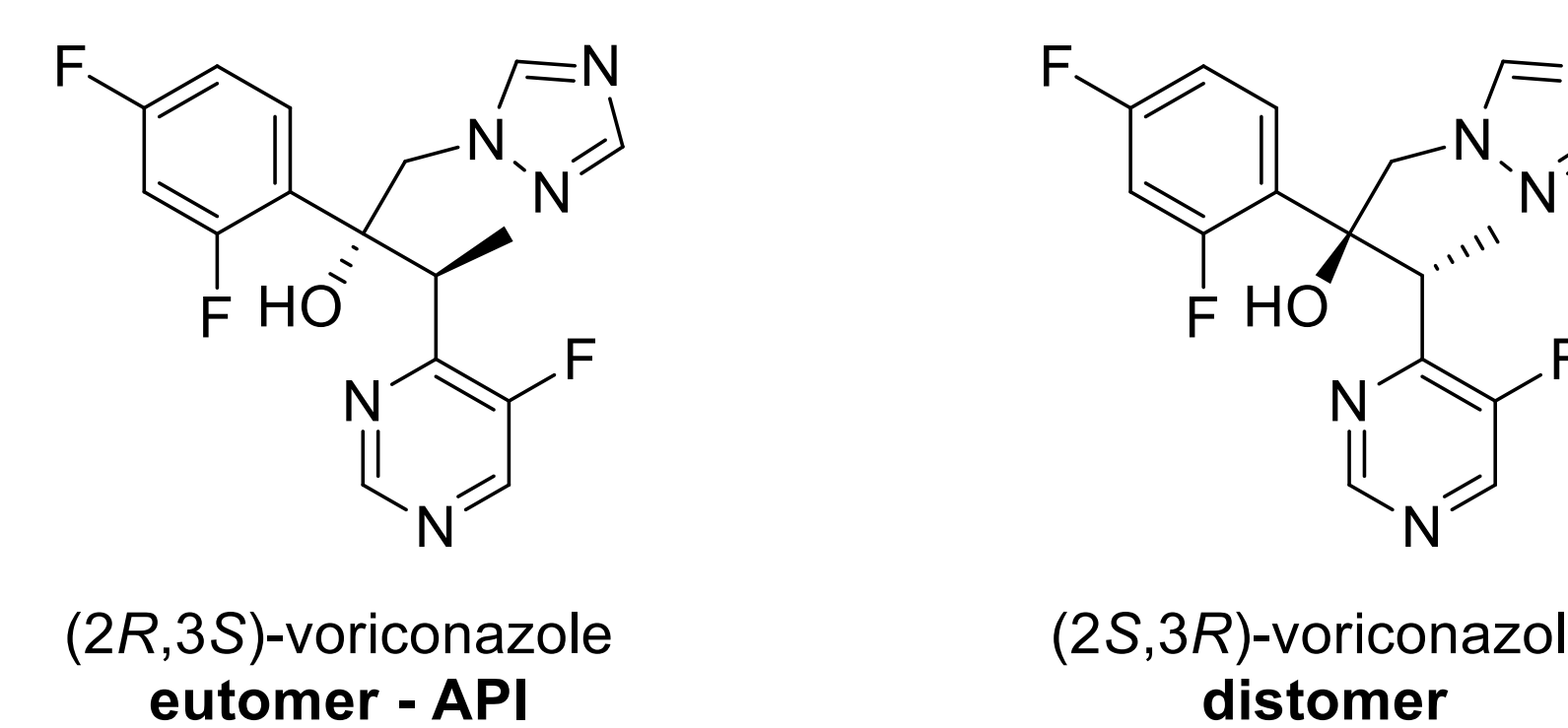


Figure 2: Voriconazole enantiomers

CPC method

- Separation occurs between two **immiscible** liquid phases
- Stationary phase is immobilized inside the rotor by a strong **centrifugal force**
- The mobile phase containing the sample to be purified is fed under pressure into the rotor and pumped through the stationary phase in the form of **tiny droplets**
- The chromatographic column in CPC is the **rotor**: cells interconnected in series by ducts attached to a large rotor
- Simple mechanism: difference in **partition (K_D)**
- Continuous operation – multiple dualmode CPC (MDM-CPC): the flow direction of the liquid phases is altered by switching a valve in the CPC system

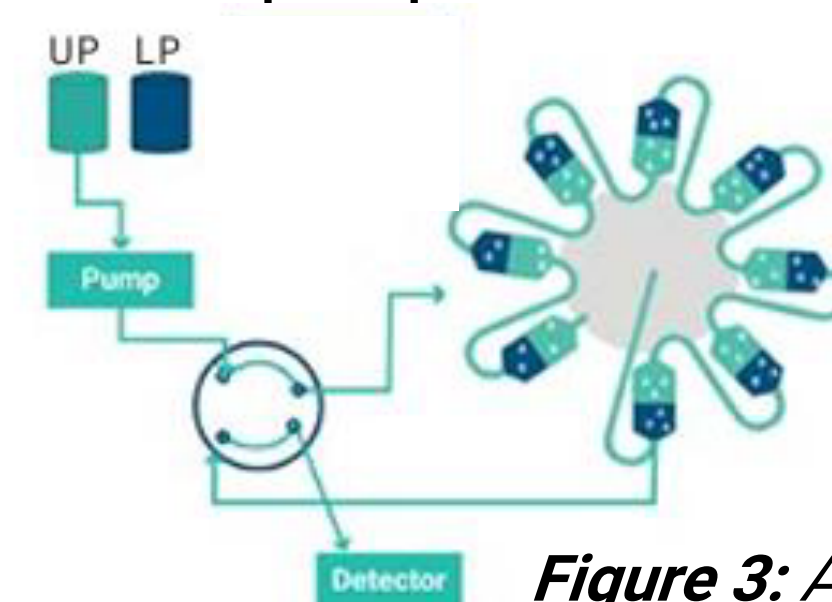


Figure 3: Ascending mode separation

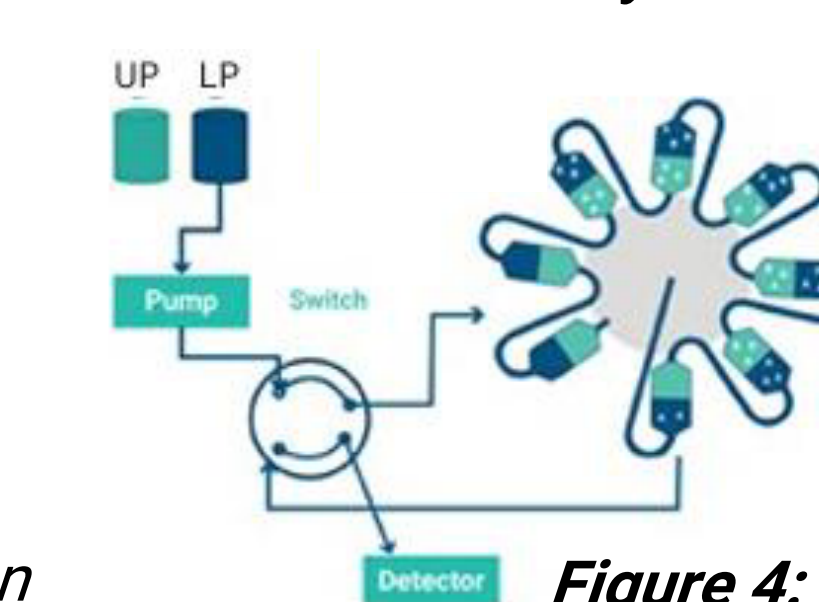
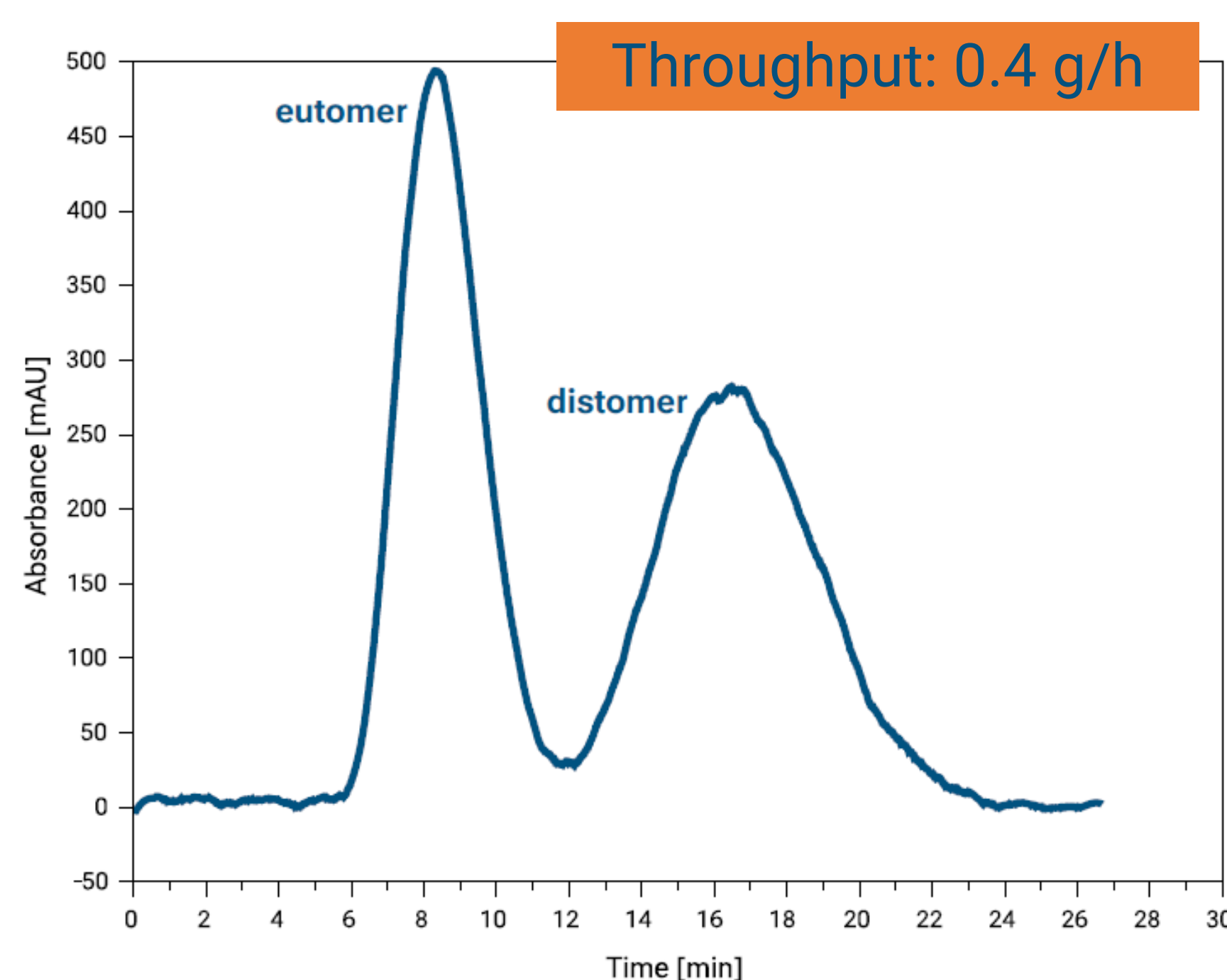


Figure 4: Descending mode separation

RESULTS & DISCUSSION

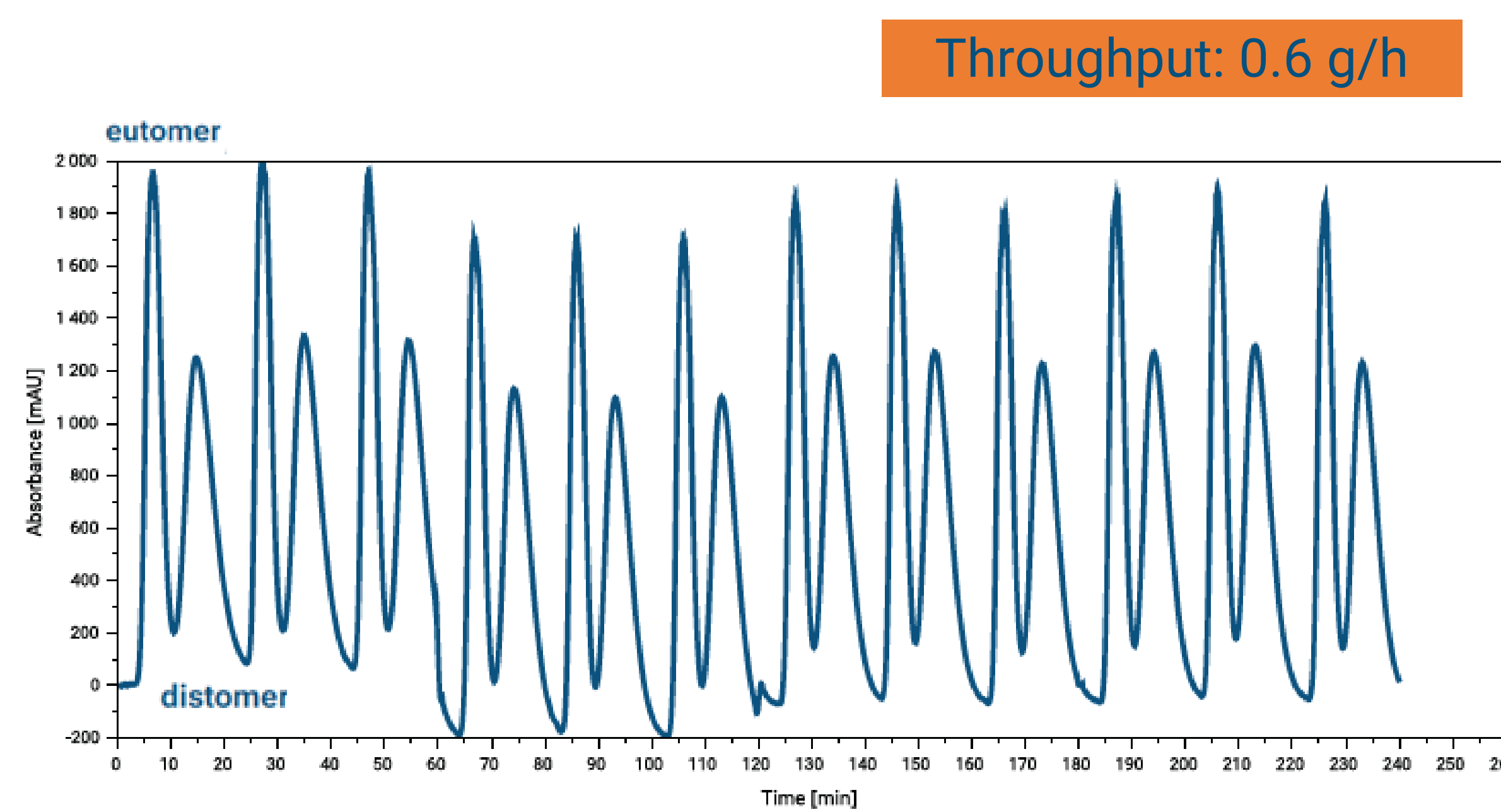
Batch Method



Solvent system	alkane/ester/SBE β CD _(aq)
Sample	200 mg in 20 mL UP
Flow	20 mL/min
Rotational speed	2500 rpm
Mode	asc/elution
Elution	100% UP

Figure 5: Separation by CPC, batch mode

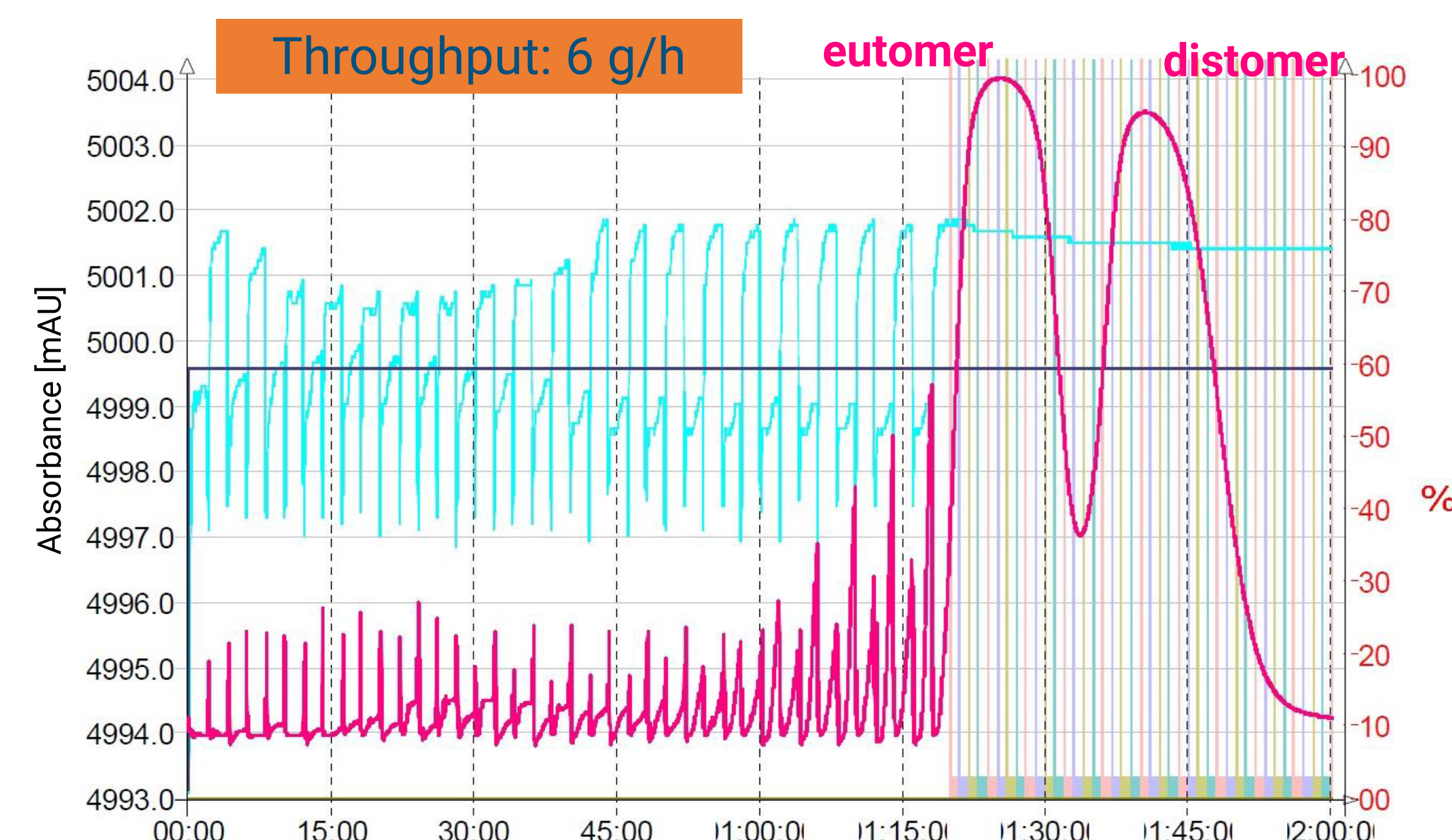
Stacked Injection Method



Total amount of sample	2.4 g/240 mL UP
Amount of sample/injection	200 mg/20mL
Flow	20 mL/min
Rotational speed	2500 rpm
Mode	asc/elution
Purity	99.1%
Yield	95%

Figure 6: Separation by CPC, 12 consecutive stacked injections

Multiple Dual-mode (MDM)



Total amount of sample	3 g/150 mL UP
Solvent system	Alkane/ester/Me β CD _(aq)
Flow	20 mL/min
Rotational speed	1800 rpm
Mode	multiple dual (ASC-DSC-ASC)
Purity	99.5+%
Yield	92%

Figure 7: Separation by CPC, MDM continuous mode

	Resolution	CPC – Stacked Injection	CPC - Multiple Dualmode (MDM)
Yield (%)	37	95	92
Mode	batch	Semi-batch	Continuous
Time of Process	2 days	Semi-batch	Continuous
Productivity (g/L*h)	0.28	0.80	5.0

Figure 8: Comparative table between traditional resolution and continuous CPC methods

CONCLUSIONS

Utilizing continuous CPC methods, we could achieve:

- **High productivity** – results almost in a 15x increase in productivity compared to conventional resolution
- **High valuable component yield**
- **Robust and reproducible** method
- **Cost efficient purification** – no need for expensive solid stationary phase or resolution agent, thereby reducing operational costs
- **Green purification method** – the cyclodextrine phase can be recycled and reused
- **Time efficiency** - CPC runs can be finished in much less time than traditional chromatographic steps
- **No Further Manipulation Needed** – The API will readily be available right after purification

