



API Recovery from Pharmaceutical Waste Streams by High Performance Counter-current Chromatography (HPCCC) and Intermittent Counter-current Extraction (ICcE)

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Introduction

- TSB STEP project – Scalable Technology for the Extraction of Pharmaceuticals
- Technical background to CCC and ICcE
- Development of HPCCC method for isolation of lost material from an in process stream
- Development of ICcE approach
- Further development



Scalable technology for the extraction of pharmaceuticals (STEP)

Intention - Develop a “plug & play” High Performance Counter Current Extraction (HPCCE) processing system

- new *continuous* processing and production techniques for material isolation and purification provide a key commercial *platform technology* for the future

Objective - Step-change in speed & scale-up of isolations

- Generate a *portfolio of practical applications* at various scales
- Demonstrate *reduction* in processing complexity and cost
- Develop and integrate *robust, easy to use* systems

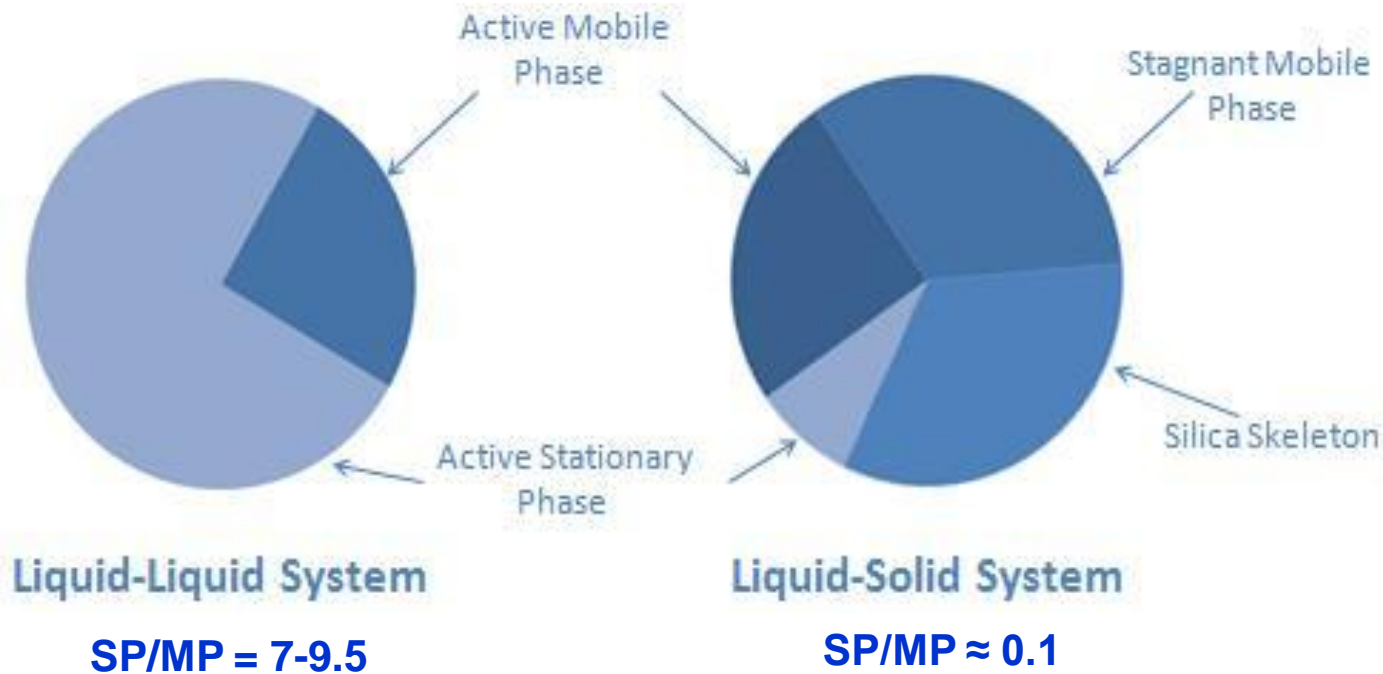
Approach - Align the technology to the pharmaceutical industry

- *End-user driven* development of the technology
- Encourage broader *industry uptake*

Project duration 3 years - started September 2009

Counter Current Chromatography (CCC)

Both Mobile (MP) and Stationary (SP) Phases are liquid



The liquid stationary phase is immobilised within the column by centrifugal forces

What is the difference?

Extraction is commonly used as a first purification step following a reaction

- ✓ Effective but limited selectivity
- ✓ Large difference in distribution coefficient K_d required

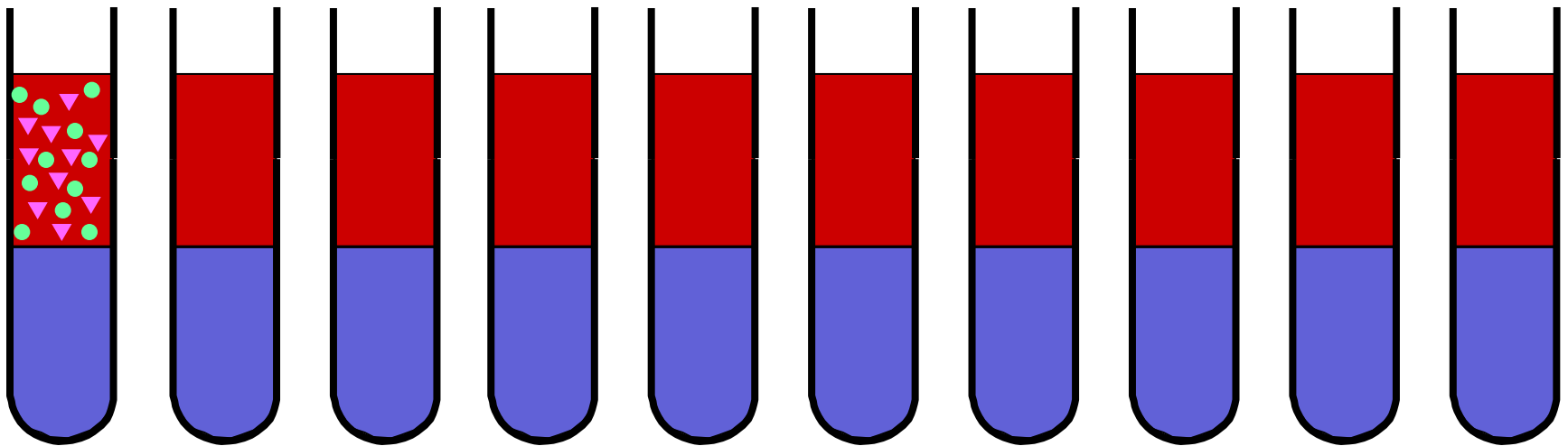
Counter-current Chromatography

- ✓ Uses multistage extraction to selectively isolate the required compound from a mixture
- ✓ Solvent system is selected to give a distribution coefficient K_d of the target in the range 0.5-2

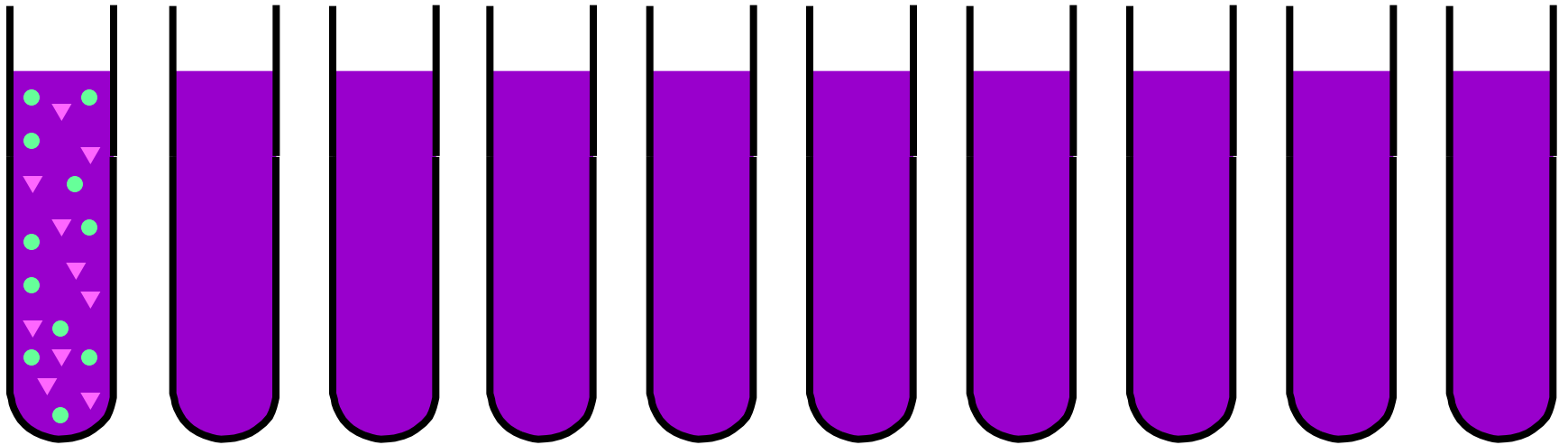
How Does it Work?

● Has a slightly greater distribution in upper (red) phase

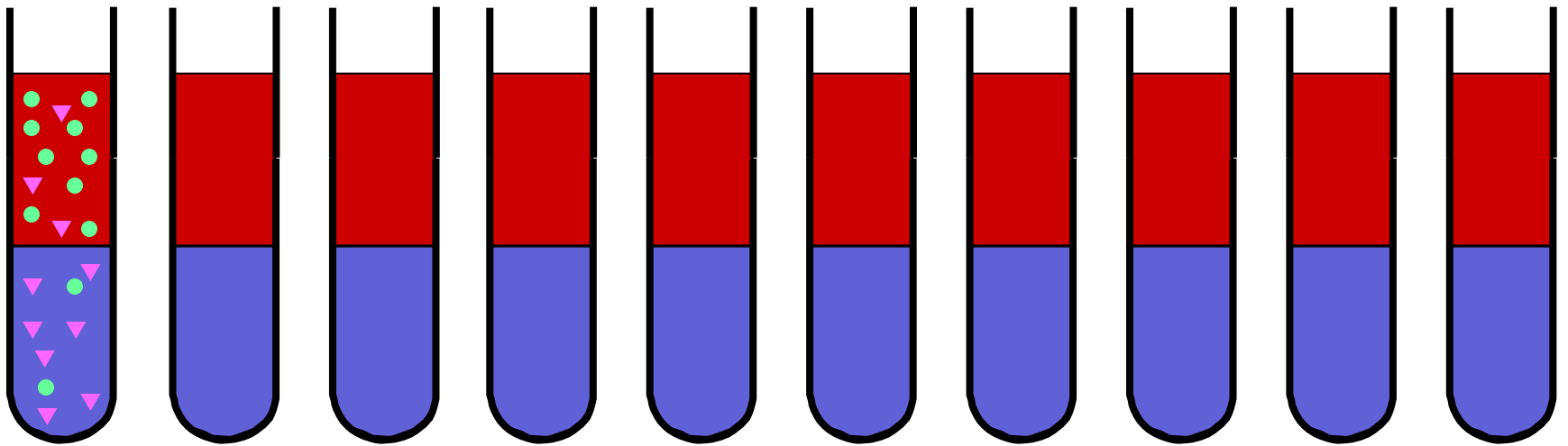
▼ Has a slightly greater distribution in lower (blue) phase



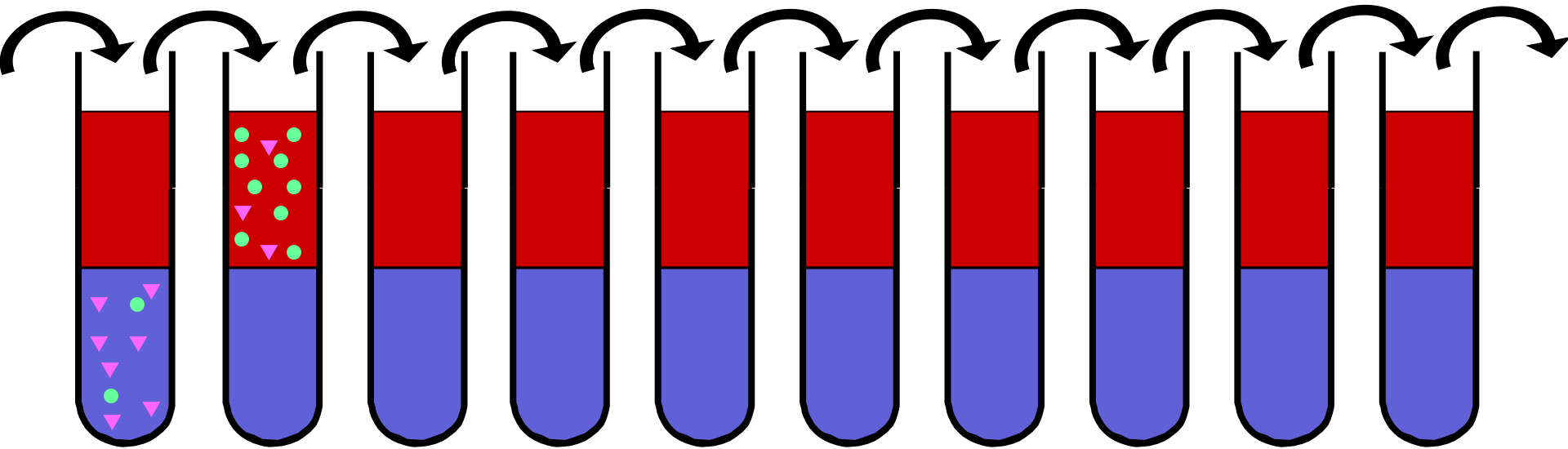
Shake to mix



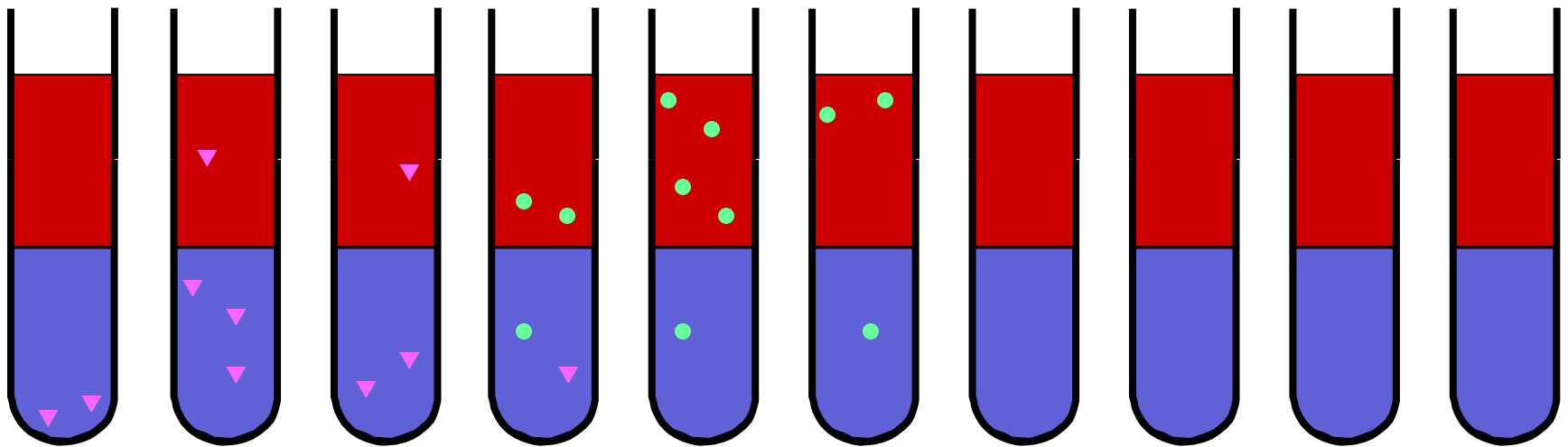
Settle



Move on the top layer

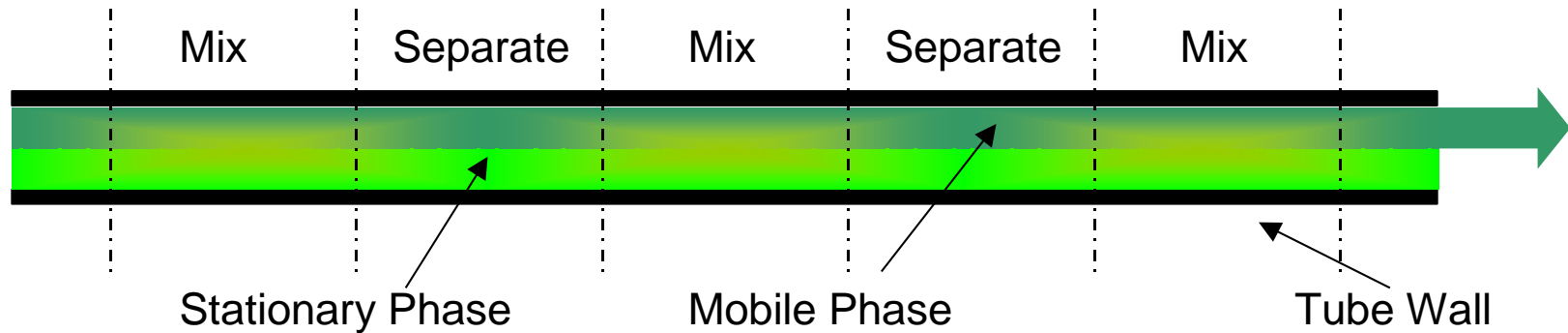


Repeat the cycle until the mix is separated



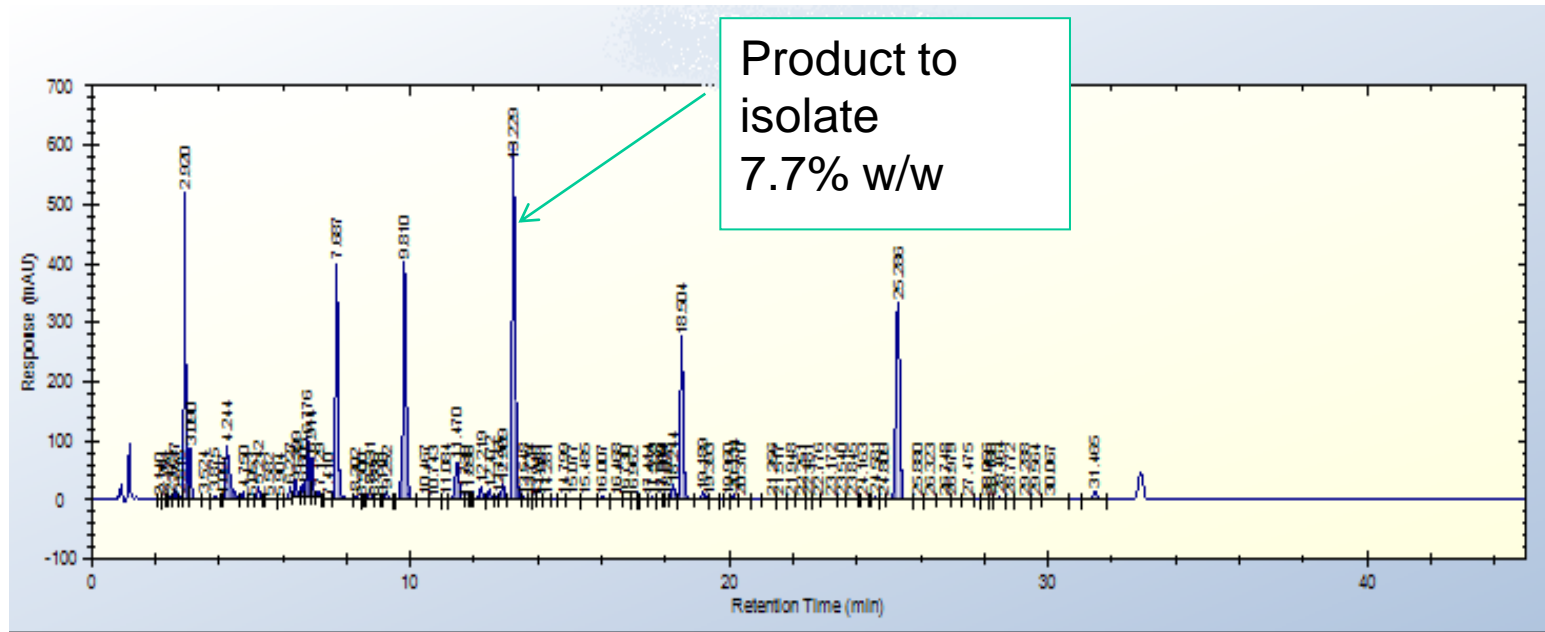
Separation in HPCCC column

Schematic diagram



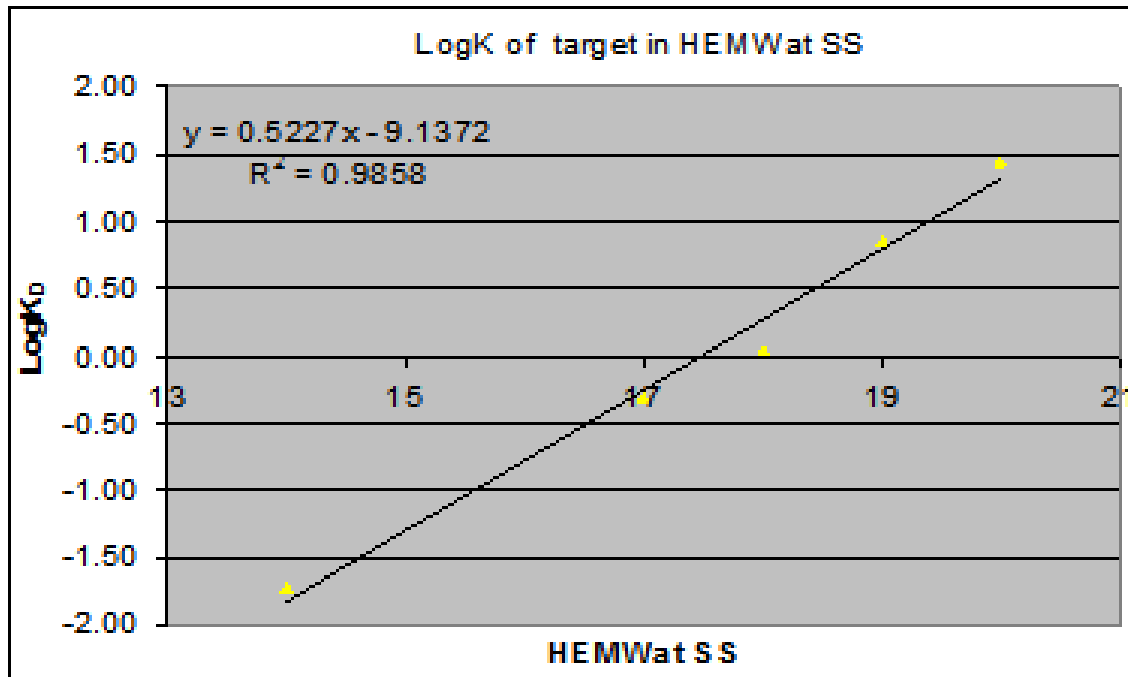
- Separation is based on target compound partition between two phases of the immiscible solvent system
- Use of different solvents mixtures provides high solubility of the complex crude materials
- CCC is very attractive in terms of selectivity, sample loading capacity and scaling-up capability

Sample from late stage API purification step



- Aim :**
1. To recover valuable API which would otherwise be lost.
 2. Recovered API must be of suitable purity to be processed by crystallisation to meet product IG specifications
 3. To make a first assessment of the materials costs of the recovery process

Partition studies



**Heptane-Ethyl Acetate-
Methanol-Water
solvent systems**

(HEMWat SS)

K_d in SS18 = 1

HPCCC solvent systems screening :

Co-elution of product with impurities with SS17 (1:1:1:1) and SS18 (1.5:1:1.5:1)

S17.5 (12:11:12:11) seemed suitable at 50mg/mL loading

Loading studies and Scale up



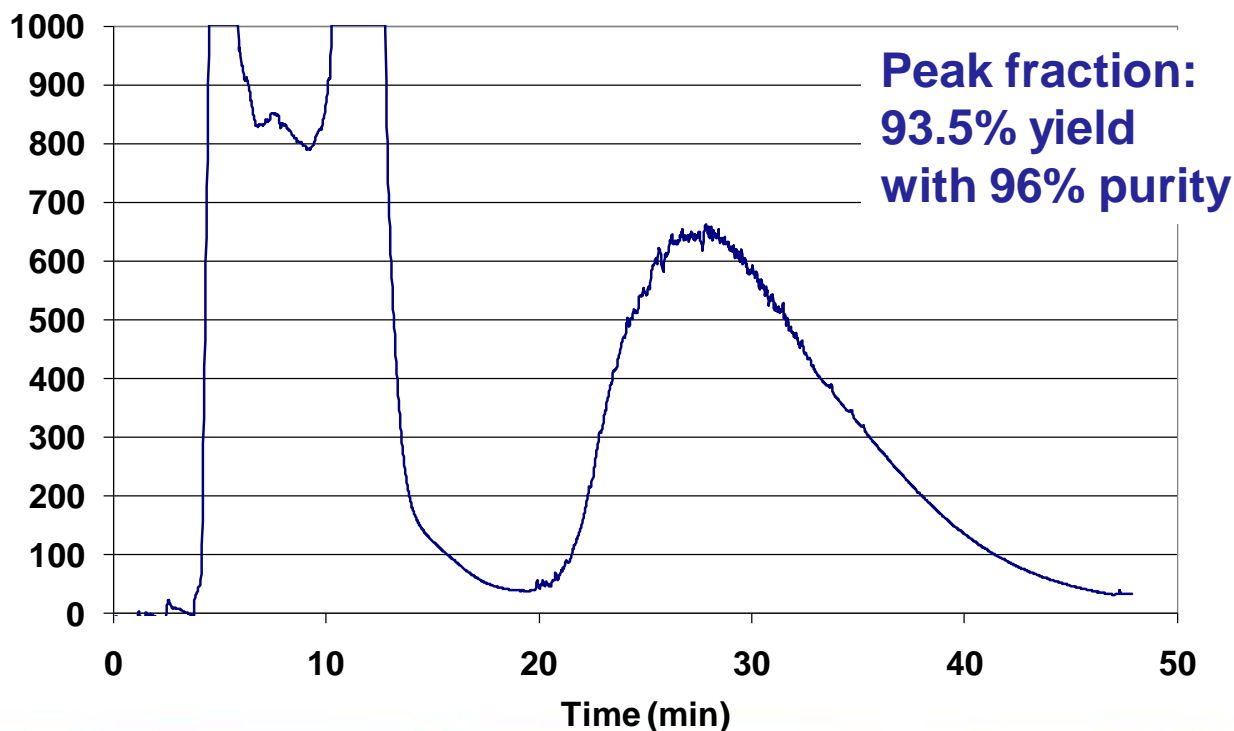
Spectrum

Midi

Coil volume (mL)	22 and 132	1000
Flow rate (mL/min)	0.5 - 12	10-80
Loading (g/run)	Up to 2	5 to 40
Rotational speed @240g (RPM)*	1600	1400
Elution time for D=1 component (min)	20	20

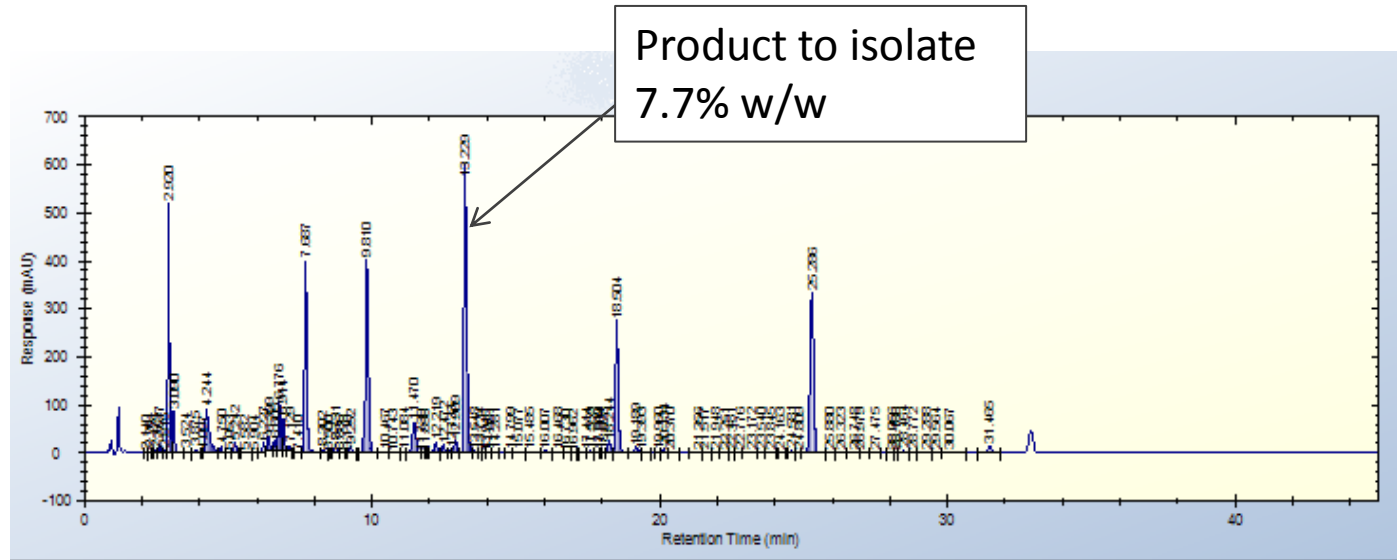
Scale-up run on Midi

Instrument	Dynamic Extractions MIDI HPLCC preparative 999.5mL column
Solvent system	Heptane : Ethyl acetate : Methanol : Water (12:11:12:11) Stationary phase retention : 78%
Operation mode	Normal phase isocratic mode, upper phase as mobile
Flow rate	62mL/min; elution-extrusion
Sample loading	10g in 50mL UP (200mg/mL)

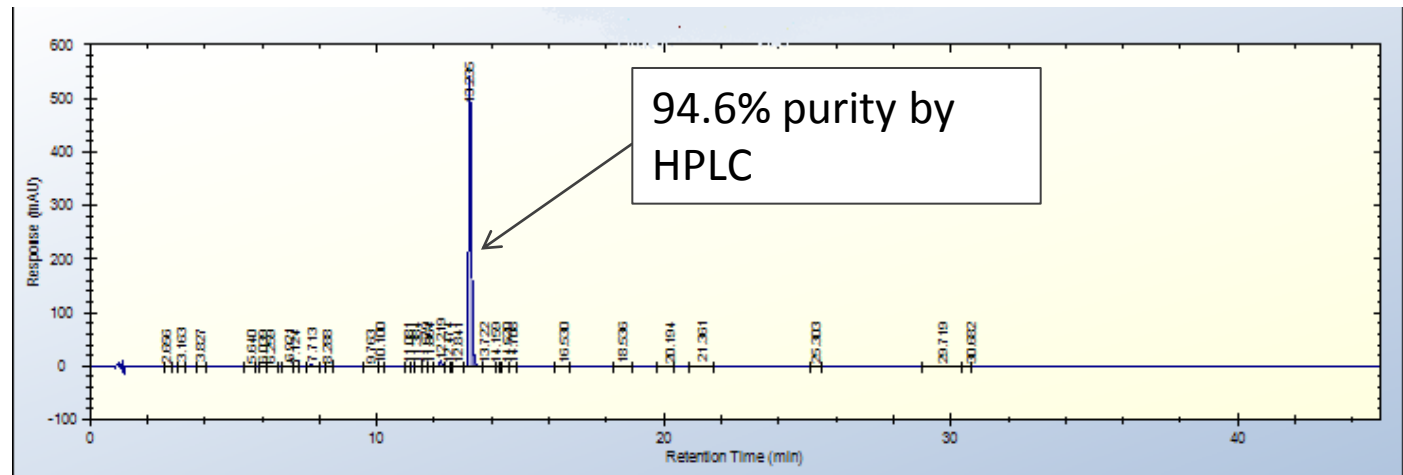


Scale-up run analysis

Input material

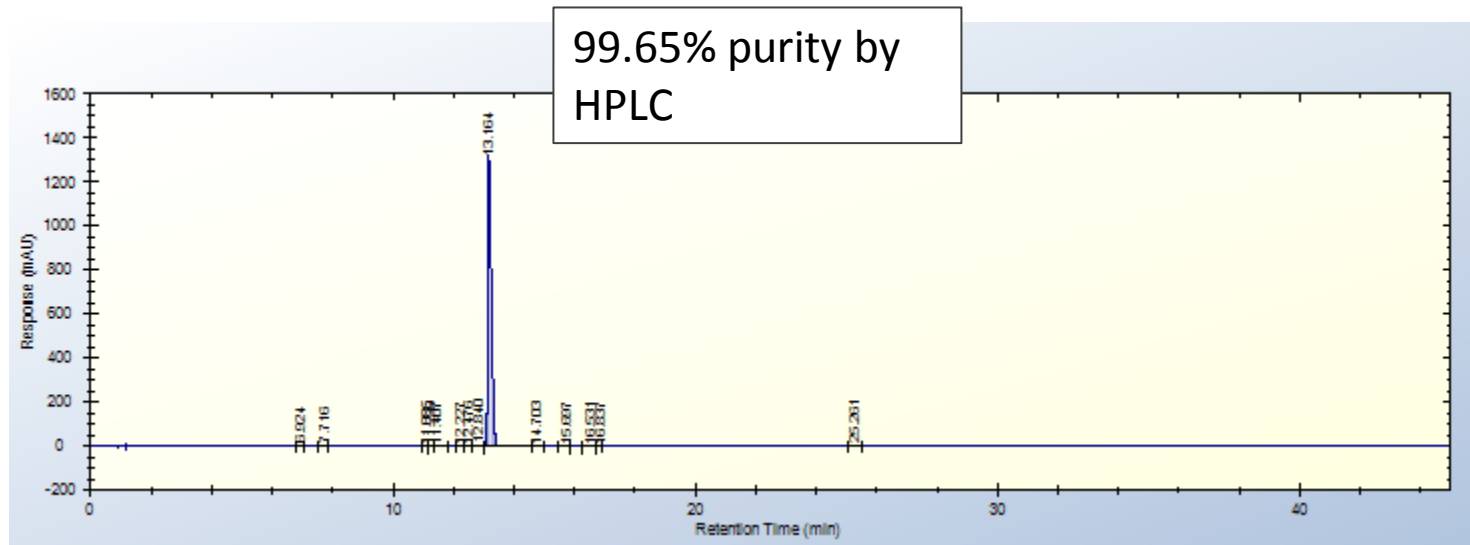


Output material
(combined fractions)



Crystallisation

- Cooling crystallisation
- 87% yield (based on 94% pure input material)



Crystallised product purity matches IG specifications

Loading studies on Midi with column volume 1000ml

Loading	Sample	Throughput	Purity	Purity
	volume		@ >80%	@ >85%
(g)	(ml)	(kg/day)	yield	yield
9.9	50.0	0.26	97.3	97.0
15	75.3	0.39	94.5	94.1
20	100.0	0.52	91.9	91.0
20	75.3	0.52	91.6	91.0
30	75.3	0.79	79.0	79.0

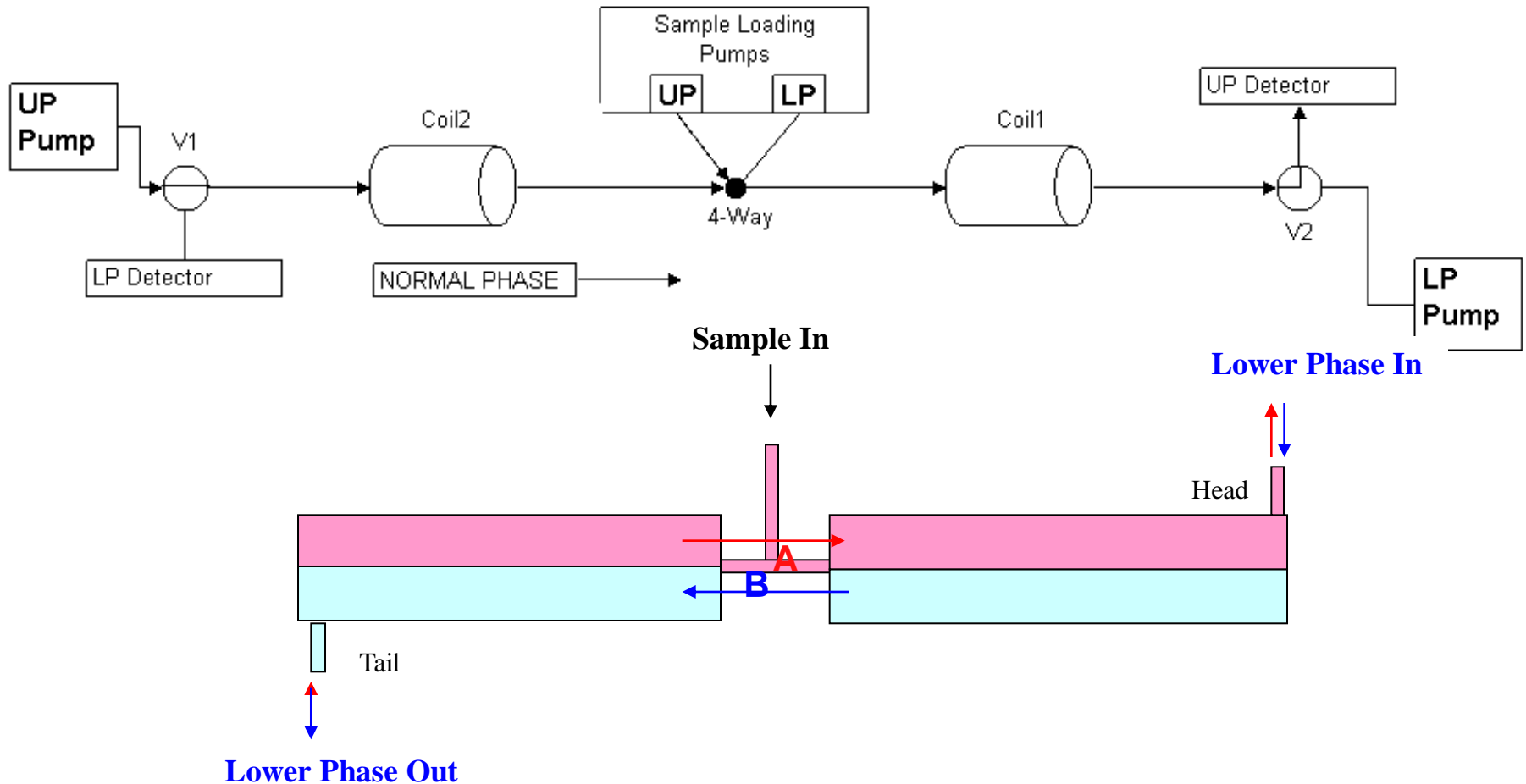
Scale-up from Midi (1000ml) to Maxi (18000ml)

Instrument	Injected Mass (g)	Crude Throughput (kg/day)	Yield (%)	Purity (%)	API Recovered (g/day)
Midi	9.9	0.26	93.5%	96.0%	15.17
Maxi	172.3	1.84	86.8%	96.0%	117.92
Midi	20.0	0.52	89.6%	90.3%	27.58
Maxi	347.6	3.71	84.5%	88.1%	212.54

Solvent usage when scaling-up from Midi (1000ml) to Maxi (18000ml)

Instrument	Injected	Solvent Usage (crude per unit time)		Crude Throughput (kg/day)	Solvent Usage / kg API recovered (L/kg)
	Mass (g)	(L/kg)	(L/hr)		
Midi	9.9	433	4.0	0.22	6018
Maxi	172.3	400	30.7	1.84	5992
Midi	20.0	215	4.0	0.44	3111
Maxi	347.6	199	30.7	3.71	3051

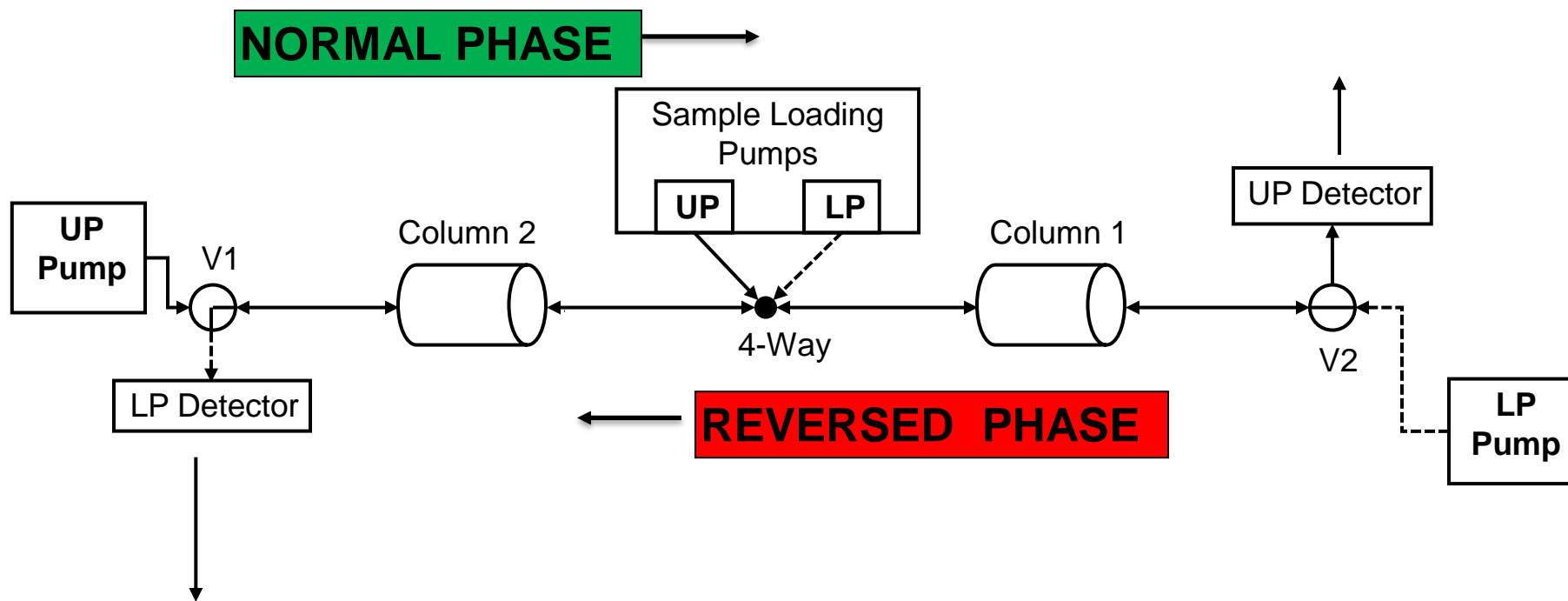
Intermittent Counter-current Extraction (ICcE)



Features of ICcE

- Separating binary or multicomponent mixtures into two streams
- Concentrating component(s) present in the crude at low abundance
- Higher sample loading as upper and lower phases are replenished intermittently
- Increase in separation efficiency due to the “extended” column length

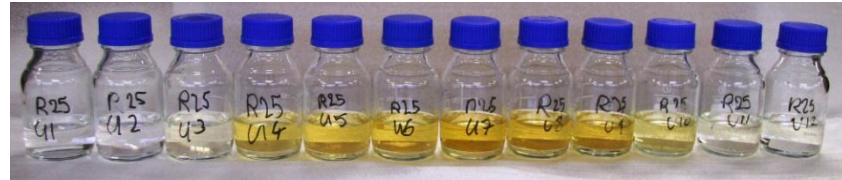
Intermittent Counter-current Extraction (ICcE)



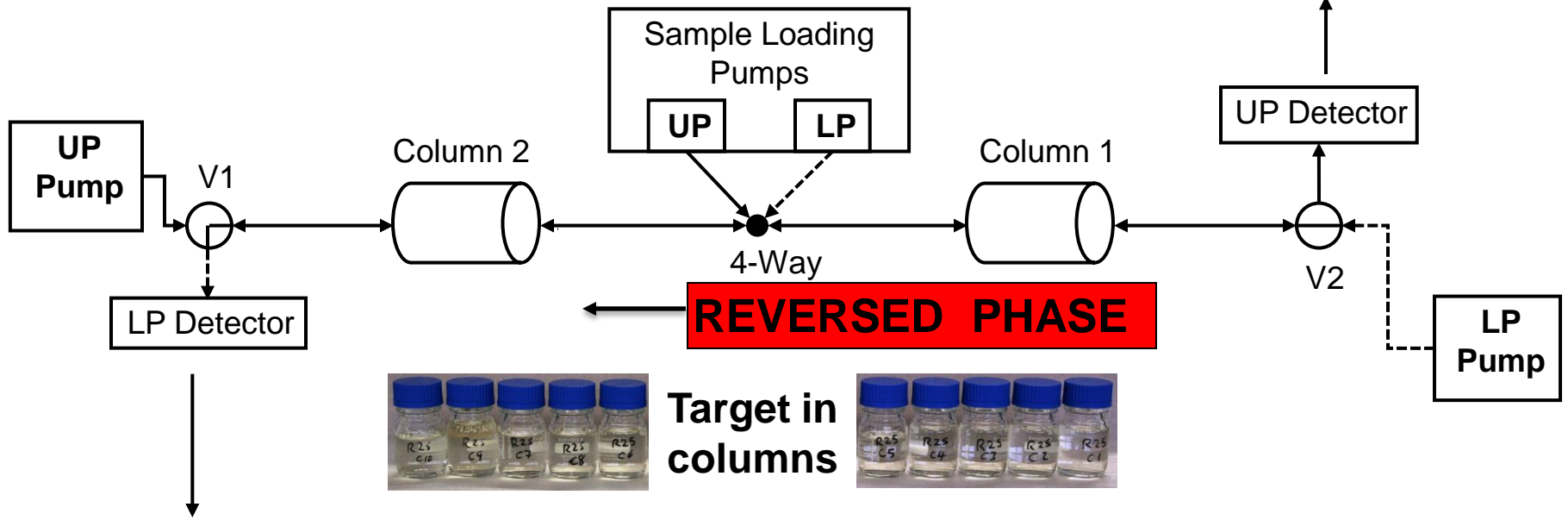
ICcE – Target enriched in column



Non-polar impurities in upper phase (UP) fractions



NORMAL PHASE



Polar impurities in lower phase (LP) fractions

Comparison between isocratic HPCCC and ICcE elution modes on Midi (1000ml)

Parameter	Isocratic HPCCC	ICcE	Factor
Loading (g/inj)	15	30.5	2
RunTime (full cycle) (min)	65	128	-2
Throughput for crude processed(g/h)	13.8	14.3	1
Total Solvent Consumption for API recovered (L/g)	4.09	2.5	1.6
Purity (%)	94.5	95.4	1
Yield (%)	80	82	1

1. Both elution modes provide the same throughput for the crude processed, however, ICcE requires less solvent (only 60% compared to isocratic CCC)
2. For CCC any LC set up can be used while ICcE set up is more complex.

Conclusions

- ✓ HPCCC is capable for recovering of API that otherwise would be lost in waste steams in one process step
- ✓ This process is capable of reducing the environmental impact these waste steams have
- ✓ The scalability of the HPCCC process enables optimization work at laboratory scale to be transferred directly to the Pilot plant scale
- ✓ HPCCC Midi has been used in two elution modes (isocratic HPCCC and ICcE) to demonstrate the flexibility of the platform technology

Future development

- Avoiding solvent swaps and the associated expense – development of process solvent friendly separations enabling injection of mother liquors directly
- Strategies for efficient solvent recycling
- Improve purity/yield/solvent usage via optimisation of operating parameters for ICcE

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