Continuous Purifications in Multistep Continuous Flow Synthesis of Pharmaceutical Compounds

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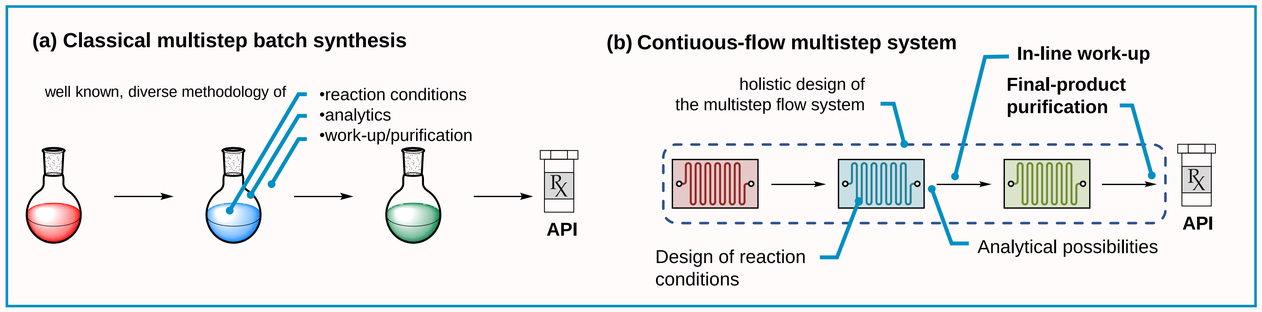
1. Introduction – Continuous flow purifications

Flow synthesis is usually followed by discontinuous purification, because of the fact, that the number of available continuous solutions is limited.[1–3] The existing methods[4,5] can be classified as in-line work-up or final product purification techniques, according to the position in a multistep sequence, where they are preferably used. Most of the in-line work-up steps aim to remove the co-products, which are formed from the reagent in the course of the planned process.[6] These impurities should not be mixed up by the by-products, which are structurally related to the desired product, but their formation is the consequence of undesired side reactions. In-line work-up can be achieved by filtration of solid co-products, liquid-liquid phase separation, gas-liquid phase separation or through the use of solid phase supported scavengers. After the final synthetic step, the API has to be purified to meet the standards of regulatory agencies. The enumerated separation techniques, which could be used between intermediate steps, are not adequate by themselves for this goal.

High purity can be achieved by using multicolumn chromatography,[6] simulated moving bed (SMB) chromatography,[6,7] crystallization[8–10] or recrystallization,[10,11] although the latter two usually require semi-batch processing. Purification of final product could also be aided by catch and release chromatographic methods[12–14] or salt formation – neutralization sequence using multiple-extraction steps.[10]

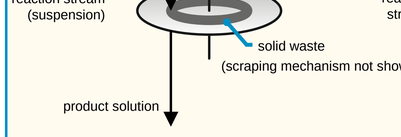
A + B → **P** + C (Co-product) A + B → **P** + P' + P" + … + P^n (By-product)



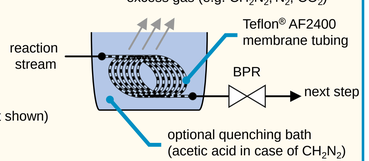
2. Known continuous purification techniques

	In-line workup	Final-product purification
'Co-' product Type	**1.** Side-product **filtration** **2. Liquid-liduid** phase separation **3. Gas-Liquid** phase separation **4.** Use of solid phase supported **scavengers**	**1. Catch and release** chromatography (with semi-batch processing)
'By-' product type	Not common	**1. Simulated Moving Bed** (SMB) Chromatography **2. Crystallization** or recrystallization (with semi-batch processing) **3. CPC** (Centrifugal Partition Chromatography)

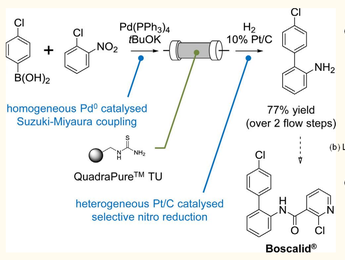
Filtration



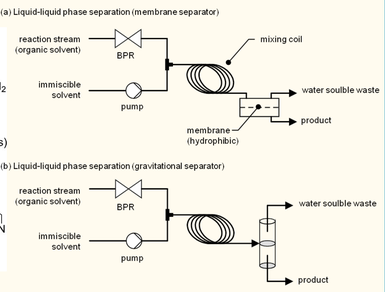
Gas-Liquid phase separation



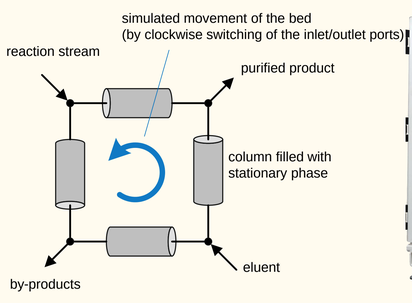
Solid phase supported scavengers



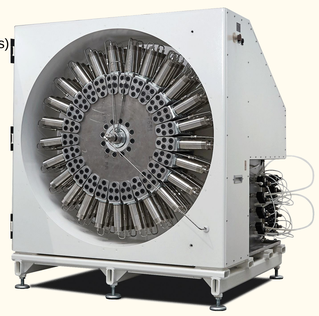
Liquid-liquid phase separation



SMB Chromatography

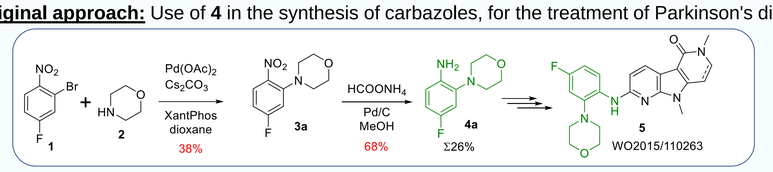


Centrifugal partition chromatography (CPC)

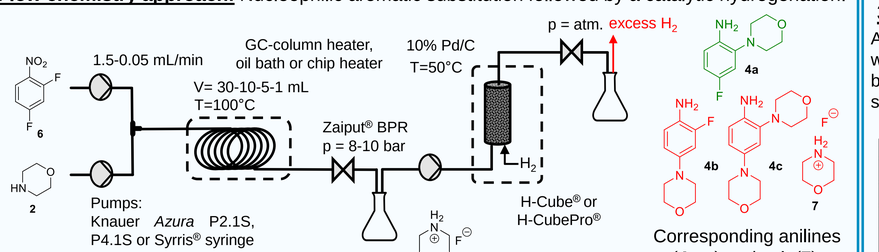


3. The model reaction – Batch *versus* flow approach

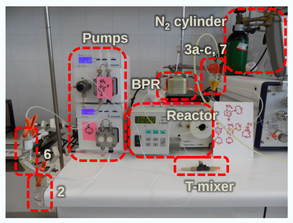
Original approach: Use of **4** in the synthesis of carbazoles, for the treatment of Parkinson's disease.



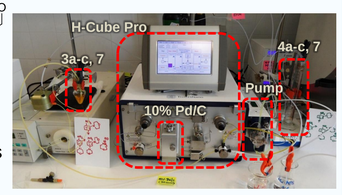
Flow chemistry approach: Nucleophilic aromatic substitution followed by a catalytic hydrogenation.



Corresponding anilines (**4a-c**) and salt (**7**).



Orto- (**4a**) , *para*- (**4b**) and di- (**4c**) substituted isomers and salt were formed.



S_N-Ar reaction using purpose built reactor

Entry [Ref.]	Solv.	T (°C)	V_{loop} (mL)	t_{res} (min)	p_{BPR} (bar)	Select. (%) 3a:3b:3c	Yield (%)	Reactor tubing
1[6]	EtOH	100	Vapor-tech (R2/R4)	10	8	74:13:13[a]	96[a]	N.A.
2[6]	THF	165		10	8	92:5:3[a]	98[a]	
3	EtOH	100	30	10	10	84:7:9[b]	94[c]	1/8"
4			5	10		90:7:3[d]	-	1/16"
5			1	10		92:4:3[d]	-	1/16"
6			1	10	8	89:6:5[d]	-	chip[e]

[a] Calculated from the crude product ^{1}H-NMR spectrum; [b] Calculated from the isolated yield; [c] Sum isolated yield of the *orto*-, *para*- and di-substituted compounds; [d] GC-MS (%); [e] white precipitate (morpholine-hydrofluoride).

Crude reaction mixture's composition

	GC-MS (%) [a]				
	4a	**4b**	**4c**	**by-prod.**	**Conv.**
Av. [b]	**81.5**	**5.4**	**12.3**	**0.8**	**100.0**
Dev.	1.8	0.3	1.4	0.8	0.0

[a] Using 30 mm 10% Pd/C CatCart® with flow rate of 0.1 mL/min; [b] Avarage, mean of 12 (over 30 hours period).

The crude reaction mixture contains **~81% 4a** after the two-step synthesis.

4. Purification with MDM-CPC

Choosing the appropriate **solvent system** in CPC is like choosing the convinient column and eluent for HPLC chromatography. *K* can be determined by the ratio of the analyte's upper and lower phase concentration, which is in a directly proportional relationship with their corresponding peak areas of the GC-MS measurements.

By rule of thumb:

- partition coefficient ($K_{U/L}$=c_U/c_L) → **0.5<K<1.5;**
- the settling time → **20 sec** (no more than 35 sec); and the phase ratio around → **~ 1:1.**

***n*-Hex:MTBE:EtOH:H_2O = 1:1:1:1**

	4a	**4b**	**4c**
pK_a [a]	3.51	3.93	5.42
pK_a [b]	4.08±0.015	4.06±0.029	4.76±0.023
FW (Da)	196.22	196.22	263.34
clogP[a]	1.32	1.32	1.11
PSA[a,c]	38.49	38.49	50.96
$K_{U/L}$ [d]	**1.86**	**0.49**	**0.24**

[a] predicted with MarvinSketch (V3); [b] determined by UV-spectrophotometric titrations at 25.0±0.5°C, based on 6 parallel measurements; [c] Polar surface area; [d] in *n*-Hex:MTBE:EtOH:H_2O =1:1:1:1 two-phase system, determined by GC-MS measurements.

5. Purification with MDM-CPC

1. Ascending mode

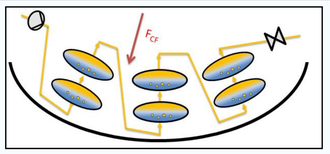
- **Upper** is the **mobile** phase,
- **Lower** is the **stationary** phase.

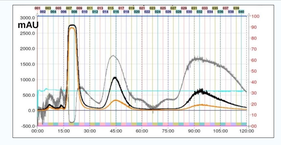
2. Descending mode

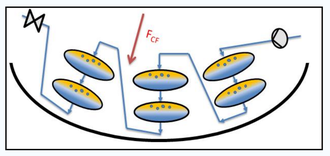
- **Upper** is the **stationary** phase,
- **Lower** is the **mobile** phase.

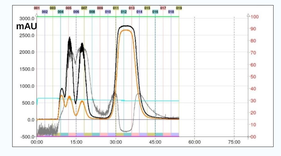
3. Multiple dual-mode:

Alternating asc. and desc. mode with sample injection in between. 'Regenerating the stationary phase.'

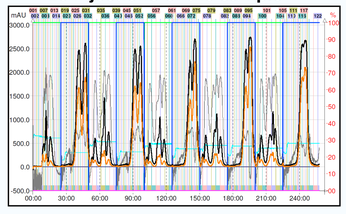




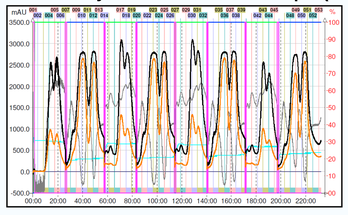




10 injections of the sample



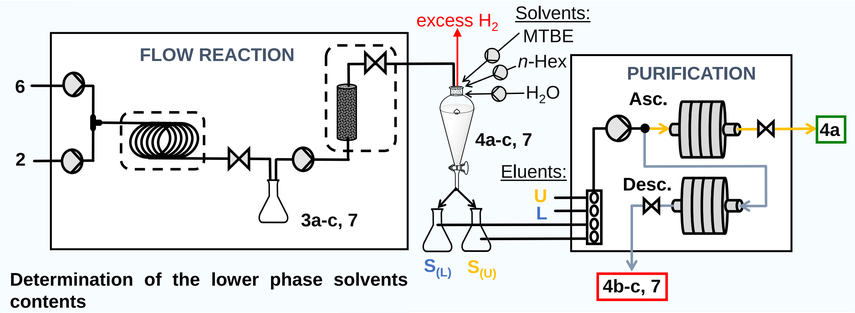
Automated system for intake the sample (in two phases)



Using Armen CPC (100 mL) in MDM. After the equilibration and the first sample injection, the separation started with desc. Mode by 5 mL/min, 2000 rpm. 25-30 min frequency. Detecting on 240 nm and 300 nm wavelength and SCAN (200-600nm).

GC-MS purity is over 99.9%.

6. Connection the flow reactors with the CPC device



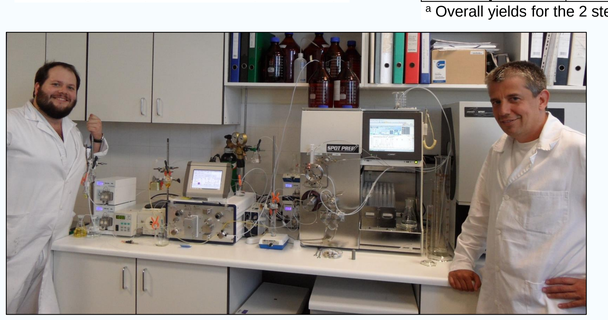
Determination of the lower phase solvents contents

Analitics	H_2O	MTBE	EtOH	*n*-Hex
NMR+KF	54.6	5.0	40.6	~0.0
GC-FID+KF	53.7	8.3	39.0	~0.1
Avarage:	**53.0**	**7.0**	**40.0**	**0**

Determining the composition the lower phase (V/V%).

Sample intake	Yield[a] (%)	Purity[b] (%)	Productivity (g/h/L^{-1})
Two-phase	**57.2**	**>99.9**	**1.44**
One-phase	**62.1**	**>99.9**	**2.27**

[a] Overall yields for the 2 steps; [b] Determined by GC-MS.



Productivity can be **increased** by

- using continuous injection of the feed at an intermediate point of the series of extraction cells (e.g. between two columns → **True Moving Bed**) or
- making the sample solution more concentrated by diluting it into **one phase** only.

7. Summary

We present for the first time, that centrifugal partition chromatography in multiple dual-mode is an effective method for the final product purification of continuous flow reactions. Continuous purification could be achieved by using continuous injection of the feed at an intermediate point of the series of extraction cells → True Moving Bed. In the absence of two CPC columns, only semi-continuous purification is available by synchronizing the flow reactor production with the MDM sequence sample intake. In this case productivity can be increased by using one-phase sample 'injection'. One of the main benefits of this method is that it can be easily scaled up.[19]

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