Designed ONE-FLOW System for the Synthesis of Rufinamide

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Abstract

A nano-compartmentalized one-solvent (ONE-FLOW) procedure was developed for the two-step synthesis of Rufinamide, employing a combined simulation and experimental approach. Computer-aided solvent selection was combined with reagent/catalyst compartmentalization in a continuous flow set-up. The synthetic route encompassed azidation of benzyl chloride, followed by a Cu-catalyzed azide alkyne cycloaddition (CuAAC) reaction. A functional solvent was chosen via a COSMO-RS based method, which allowed a one-phase reaction while facilitating a thermally induced final product separation from the reaction mixture. To perform azidation and CuAAC reactions in a microfluidic system, both azidation reagent and Cu(I) catalyst were immobilized, on a packed bed and in the hydrophobic membrane of polymer vesicles, respectively, as this allowed a higher reaction efficiency, facile regeneration of azidation reagent, and recovery of the metal catalyst. This ONE-FLOW process has great benefits for the pharmaceutical industry in their quest to scalable, efficient and safe synthetic processes with minimal waste generation.

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Significance: Herein we describe the first designed nano-compartmentalized micro-flow process for the synthesis of Rufinamide by combining a computer-aided functional solvent selection with catalyst compart-

mentalization in polymeric nanoreactors. Product purification, reactant and catalyst recovery are achieved via spontaneous separation in flow, due to the specific features of the functional solvent and the nanoreactors. This generic concept of integrated reactor and separator units (ONE-FLOW) using micro and nanostructured reaction conditions can greatly simplify multiple-step cascade reactions.

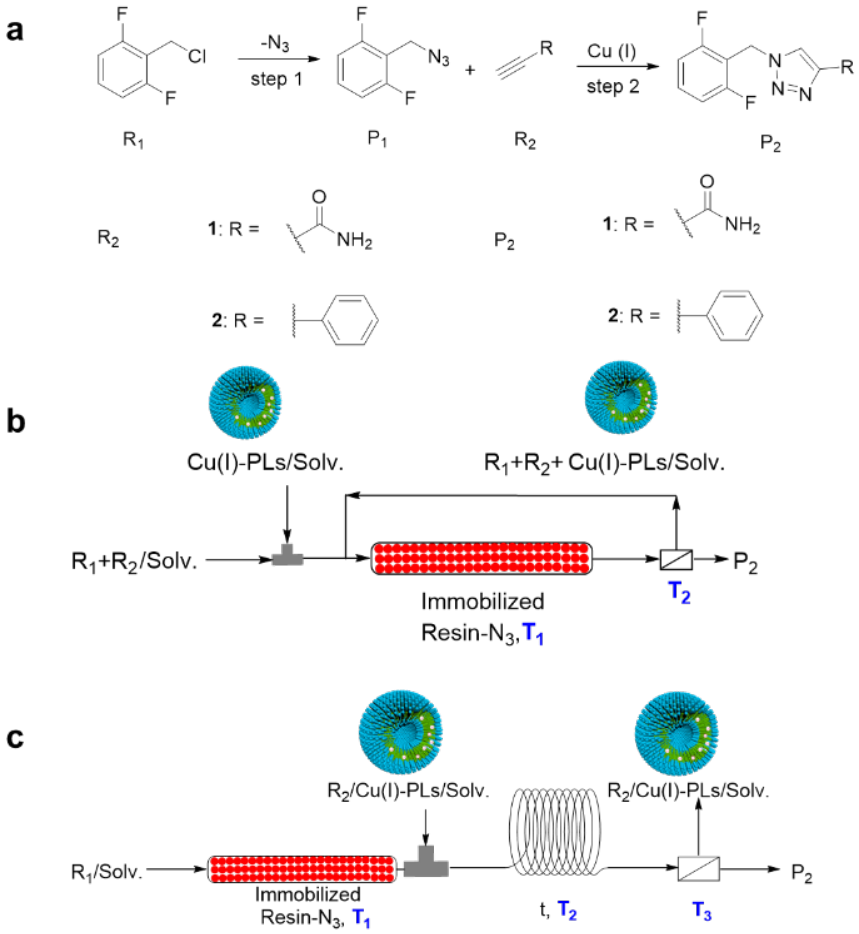
Keywords: microreactors, nanotechnology, self-assembly, solvent effects, sustainable chemistry.

Introduction

The process design of pharmaceutical synthesis has attracted much attention over the years. One of the more intriguing developments has been the end-to-end processing of medicines from raw materials in one run, which even involved the connection with compounding/formulating equipment to deliver ready-to-use pills continuously.[1,2]{Adamo, 2016 #237} Chemists have in the past two decades expanded the concept of continuous micro-flow reactors, initially employed for a plethora of single chemical reactions, to a much broader choice of chemistries involving multi-step reactions in continuous-flow, which has been coined flow chemistry.[3-5]Still, this process chain commonly needs to incorporate work-up steps in between the flow reactors, due to compatibility issues, which leads to a high number of reactor and separator units and complicated controller tasks, i.e. high system complexity.[1,2]

To simplify this complicated and expensive production process, an alternative approach might be to employ an integrated reactor-separator unit which can cope with these issues. For this approach, it is important to think of another way of combining the reaction with separation spaces, which are traditionally not integrated. This separate chain of reactors and separators – one after the other - is what we call the 'vertical' alignment of a series of flow equipment. The inspiration for alternative multistep synthetic processes can be found in nature, in particular in living cells. Nature did not choose for a 'vertical' series of cells, each being unique to one kind of operation. Rather, all is done in one cell which internally is hierarchically compartmentalized (with its membranes and organelles) and which is modular, meaning different cells refer to the same building principle. That approach, of conducting diverse chemistries at the same time and virtually the same place, may be termed 'horizontally' in order to distinguish it from the aforementioned traditional approach.[6-8]

Learning from nature and in order to turn a microfluidic reactor into a soft-matter structured operating unit, an entirely new reactor concept for multi-step organic reactions involving catalytic conversions is presented based on micro-flow continuous processing. This work describes the development of functional solvent and nanoparticle combinations to provide a compartmentalized flow reactor/separator system with 'horizontal hierarchy' – as opposed to the 'vertical hierarchy' of common multi-step flow syntheses (or batches) with their consecutive reactors-separators. The solvent plays a dual role, since it provides a homogeneous solution for the reaction to take place, while it enables a spontaneous separation of the final product from the reaction mixture. Concerning the design of the catalyst, the choice of immobilizing it in nanosized compartments combines the benefits of homogeneous catalysis, i.e. high accessibility, with ease of separation from the product flow. Such flow cascade processing ideally needs just one reactor passage ('ONE-FLOW').[9] The 'ONE-FLOW' process will fluidically open and close interim reaction compartments with the aims to facilitate (a) orthogonality during the reaction, (b) recycling of catalysts and reactants, (c) purification of products, (d) high-c processing, and (e) ensured activity and stability of the catalysts.



This work aims to translate a multi-step and multi-phasic cascade reaction into a one-step and one-phase reaction via a continuous flow process, exemplified by the synthesis of Rufinamide (**1**) and its analogue 1-(2,6-difluorobenzyl)-4-phenyl-1*H* -1,2,3-triazole (**2**) (Scheme 1).

Scheme 1. (a) Reaction scheme for the 2-step synthesis of Rufinamide (**1**) and analogue 1-(2,6-difluorobenzyl)-4-phenyl-1*H* -1,2,3-triazole (**2**). (b), (c) Proposed ONE-FLOW processes for the preparation of product**1** and **2** .

Results and Discussion

As for the current production of **1** and **2** , multiple steps are required to obtain the purified product and most of the published processes are energy intensive and time consuming; meanwhile, sustainability and circularity issues such as reagent and catalyst recovery are in most published papers still not addressed.[10-12] For instance, in previous work from our group, the first step involving the synthesis of the azide, a 40 min residence time at 160 °C and 7 bar (yield 93%) was selected as optimized reaction condition in flow,[10] following the use of the 'novel process windows' (NPW) concept to boost flow chemistry reactions.[13] In this work, we used a packed-bed resin-N_3 microreactor to achieve possibly full conversion under moderate reaction conditions. In the previous study,[10]also a solvent-free three-step Rufinamide flow process was developed, as another NPW variant, based on the use of undiluted reactants (omission of the solvent) with resulting sustainability benefits.[14] Yet the need for three consecutive steps, each one with a long reaction time, requires a start-up time for the whole synthesis of a few hours,[15] while in this work starting up the reaction takes only a

few minutes, in combination with compression of two steps into one and favorable reaction rates. We have designed a system, which is meant to simplify the whole cascade of reactors and separators traditionally used in a ONE-FLOW operation leading directly to the purified solid product. This is achieved by the selection of a designed solvent, screened by COSMO-RS,[16] which enables a selective separation of the product simply by temperature variation; and a designed catalytic nanoreactor based on cross-linked polymer vesicles, or polymersomes,[17] which facilitates catalyst recycling.

For the reaction solvent selection, we used a COSMO-RS based selection to screen out the reaction solvent candidates for the Rufinamide (**1**) synthesis, as shown in Table 1. Firstly, the solubilities of the two reactants (benzyl chloride R_1, propiolamide R_2) and product (rufinamide P_2) at two temperatures (T_1: 25 °C, T_2: 65 °C) in common solvents were calculated separately by an auxiliary batch-processing program in COSMOthermX.$\mathrm{Log}_{10}(x)$ ($\log S$, Equation S1, in supporting information) describes the optimized mole fraction of solute in one solvent and was chosen as the key parameter to characterize solubility. The maximal value of $\log S$ is 0, meaning total dissolution in the solvent; as the values of $\log S$ decrease, the solubility tends to be smaller.[18] At 25 °C, the potential solvent should comprise high values for$\log S_R$, while keeping low $\log S_P$ and$\log S_{P-R}$. The target was to find a candidate solvent which can dissolve reactants R_1, R_2 at 25 °C but in which product P_2 is insoluble. As the key scenario constraint, the cut-off values of the following four parameters were chosen as $\log S_{R1} > -1$ (freely soluble),[19] $\log S_{R2} > -1$, $\log S_{P2} < -1$,$\log S_{P2-R1} < -1$, $\log S_{P2-R2} < -1$. It decreased the total solvent candidates from 11957 to 1833. Next the difference in product solubility at different temperatures was used as the second main constraint. The aim was to find a solvent in which the product dissolves at higher reaction temperature 65 °C to achieve homogeneous conditions and precipitates automatically while cooling down to 25 °C. The chosen values were $\log S_{P2}^{65} > -1.5$ sparingly soluble),[19]$\log S_{P2}^{65} - \log S_{P2}^{25} > -0.5$. With the above screening step, the number of solvents that satisfied this condition was reduced to 356. To improve on the current synthetic processes, three commonly used solvents for this reaction were used as benchmark solvents and only solvents with more favorable characteristics (37 candidates, Table S1, in supporting information) were considered for the next step.[20,21]To narrow the screening space further, other chemical and physical properties and the economic effect of the solvents were considered. Finally, acetonitrile (ACN) was recognized as the top solvent and its suitability was validated with solubility tests.

Table 1. Number of solvents in different screening steps.

Step	Considerations	Constraints	Remaining Solvents
1	COSMO-RS database	-	11957
2	Solubility at 25 °C	$\log S_{R1} > -1$, $\log S_{R2} > -1$, $\log S_{P2} < -1$	2159
3	Solubility selectivity at 25 °C	$\log S_{P2-R1} < -1$, $\log S_{P2-R2} < -1$	1833
4	LogS_{P2} variation with different temperatures (65 °C, 25 °C)	$\log S_{P2}^{65} > -1.5$, , $\log S_{P2}^{65} - \log S_{P2}^{25} > -0.5$	356
5	Benchmark solvents	ethanol, DMSO, water	37
6	Chemical and physical properties, commercial availability	reactivity, melting point & boiling point, low price	1

In good agreement with the COSMO-RS results, ACN proved to be a selective solvent for reactants and product at room temperature (r.t.), as it dissolved both reactants, but not the product. Moreover, the solubility of the product Rufinamide increased with increasing temperature. At r.t., the solubility was <1.5 g/L; when heating up to 65 °C, the product dissolved in ACN at a concentration of 5 g/L, which guaranteed homogeneous reaction conditions. Upon cooling down spontaneous precipitation happened at

this concentration (Figure S1, in supporting information). Notably, the selected solvent ACN also dissolved the benzyl azide, the intermediate product (P_1) synthesized from benzyl chloride (R_1). ACN was also a favorable solvent and showed similar solubility selectivity for the synthesis of Rufinamide analogue**2** . In ACN at r.t. the reagent phenylacetylene R_2 was soluble whereas **2** was not; however at 65 °C analogue **2** totally dissolved (> 10 g/L) in ACN as well.

The synthesis of Rufinamide and **2** consists of two parts. First, the benzyl chloride (R_1) is azidated, followed by a [3+2] Huisgen cycloaddition reaction catalyzed by Cu(I) (CuAAC). For the first part of the reaction, the synthesis of 2,6-difluorobenzyl azide in a continuous flow process, an azide-functional resin (resin-N_3) was prepared using an ion-exchange resin-Cl (Amberlite IRA-400 chloride) in a batch reaction with sodium azide for 6 hours, resulting in an azide loading of 3.9 mmol/g.[22] Then, a designed packed-bed was made of the resin-N_3 in a flow device (Figure 1a), and the synthesis of 2,6-difluorobenzyl azide from 2,6-difluorobenzyl chloride was executed. With flow rates of 6 mL/h, at 80 °C the resin-N_3 reactor reached 97% conversion from R_1 (1 M); and at 65 °C, an average conversion of 87 % was reached. The resin could be recovered easily and regenerated by azidation up to at least 3 times with similar conversions (Figure 1b). Therefore, 6 mL/h (residence time 1 min) and 80 °C were defined as optimal conditions for the azidation step.

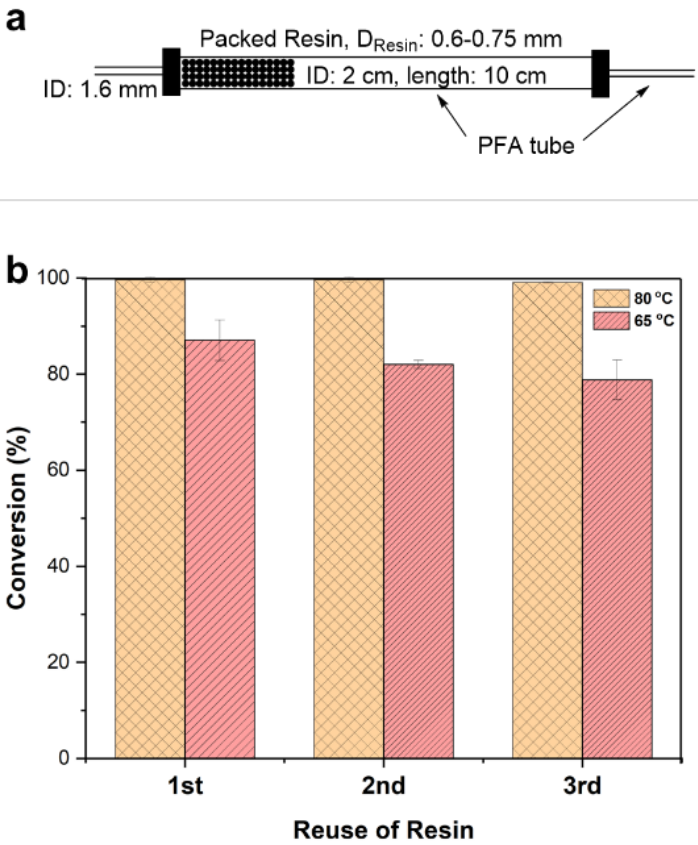
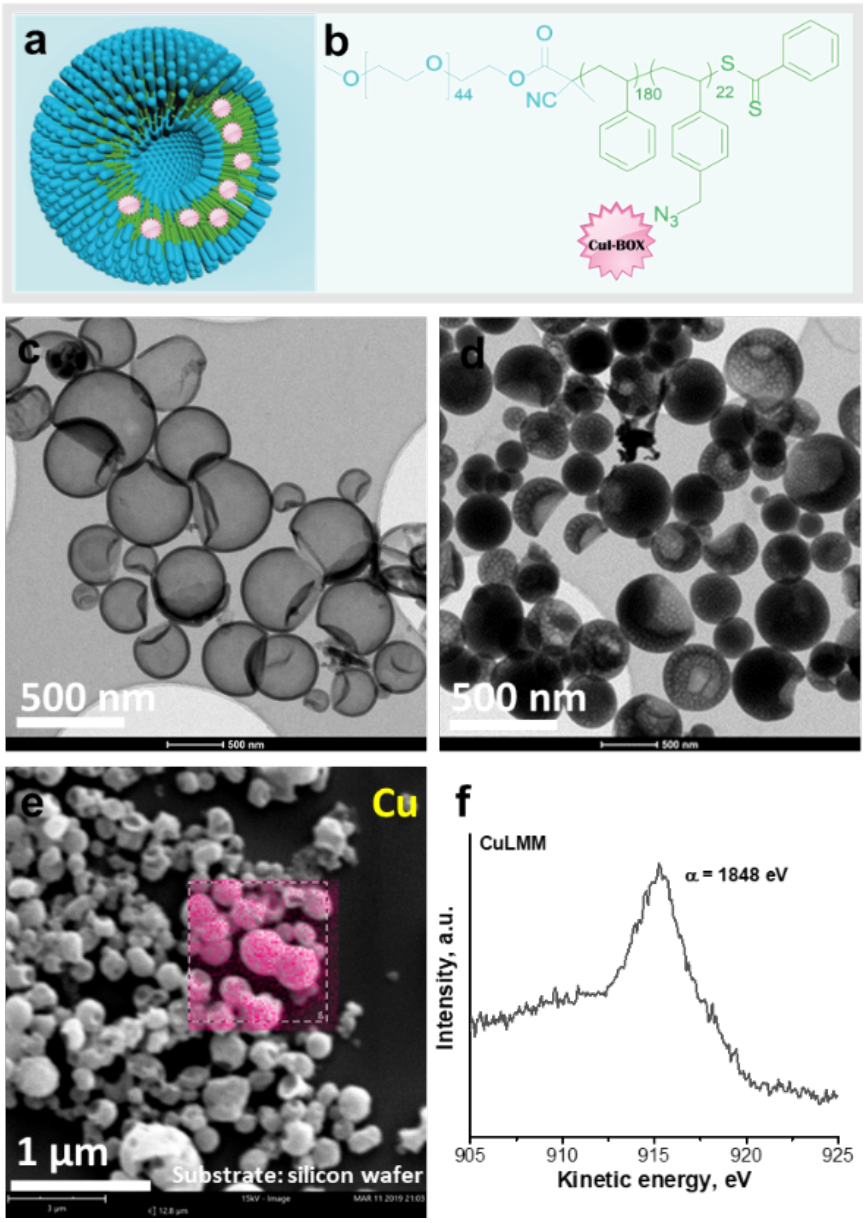


Figure 1. (a) Schematic set-up of the packed-bed resin-N3 flow device. (b) Azidation of benzyl chloride with resin-N_3at different temperatures and different runs, with 0.1 ml/min flow rate. The plot reports the conversion obtained when the resin-N_3 was reused three times, the total volume of benzyl chloride passed through the resin bed at the optimized conditions was 18 mL (6 mL per each use). This resulted in a total production of 2,6-difluorobenzyl azide of 3.0 g at 80°C (average conversion 99.5 ± 0.4%) and 2.5 g at 65°C (average conversion 82.6 ± 3.1%).

For the second reaction, Cu-bis(oxazoline) loaded cross-linked polymersomes were employed as a nanosized reactor and separator. These functionalized polymersomes were successfully applied previously for a Cu (II) catalyzed cyclopropanation reaction at r.t. in a batch reactor,[17] but were never exploited before in a CuAAC reaction toward the synthesis of pharmaceuticals. The objective of introducing polymersomes in this microflow process was to integrate the two-step synthetic procedure into one step, and to protect the Cu (I) catalyst, positioned in the bilayer membrane from undesired interactions with the azide ion.



The polymersomes were prepared using poly(ethylene glycol)-polystyrene (PEG-PS) block copolymers with azide functionality in the side chain, which self-assembled in water in well-defined vesicles. A bisoxazoline ligand [17] with two alkyne moieties was used to stabilize the polymer membrane via a crosslinking reaction and which simultaneously introduced binding sites for the metal catalyst Cu(I) (Figure 2a-2b). In order to achieve a high catalyst loading the cross-linked polymersomes were incubated twice with Cu(I) (Cu(I)-PLs,

detailed synthetic procedure, and characterization are given in the supporting information), leading to a Cu(I) content of 0.035 mol/L. The polymersome morphology (Figure 2c-2d), copper distribution (Figure 2e), and oxidation state were determined (Figure 2f). Due to the presence of Cu(I), the polymersomes were visualized as dark spheres.

Figure 2. (a), (b) Schematic representation of block copolymer structures and cross-linked Cu(I) polymersomes (Cu(I)-PLs). (c) TEM picture of Cu(I)-PLs after first loading with Cu(I); (d) TEM picture of Cu(I)-PLs after second Cu(I) loading. (e) Copper distribution in the membrane of Cu(I)-PLs (indicated in pink), derived by SEM-EDX measurements. (f) XPS analysis on Cu(I)-PLs, to confirm the oxidation state of Cu(I).

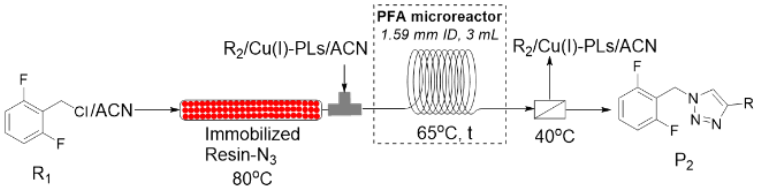
Firstly, after preliminary stability tests of Cu(I)-PLs under different conditions (in the supporting information), the CuAAC reaction was optimized in batch using the Cu(I)-PLs with the synthesized 2,6-difluorobenzyl azide and the 2 alkynes (R_2, 2M) at 65 °C, and compared with CuI powder and the homogeneous CuI-ligand complex (Cu(I): 0.05M, Table 2).

Table 2. Optimization of the batch reaction conditions.

Entry	Solvent	Catalyst	R	t [min]	Yield [%]
1	ACN	CuI powder	phenyl	120	89
2	ACN	CuI ligand	phenyl	120	89
3	ACN:H_2O 1:1	Cu(I)-PLs	phenyl	120	-
4	ACN	Cu(I)-PLs	phenyl	120	86
5	DMSO	Cu(I)-PLs	phenyl	120	90
6	ACN	Cu(I)-PLs	phenyl	60	86
7	ACN	Cu(I)-PLs	phenyl	30	72
8	ACN	CuI powder	amide	30	95
9	ACN	Cu(I)-PLs	amide	30	93
10	ACN	Cu(I)-PLs	amide	15	93
11	ACN	Cu(I)-PLs	amide	5	82

From the results, it is evident that the Cu(I)-PLs performed at least equally well as the CuI powder or the Cu-ligand catalyst. Furthermore, as expected, the reaction toward Rufinamide (employing propiolamide) was considerably faster than the reaction to product **2** with phenylacetylene. Only the Cu(I)-PLs experiment with water as co-solvent was not successful. This may be caused by the increased solvent polarity that makes the bilayer membrane less accessible to reagents. After the reaction was completed, the reaction mixture was cooled down to r.t. (around 10 mins) and gratifyingly, for all reactions performed in pure ACN, the product crystallized out and could be conveniently collected from the bottom of the reaction vials. This demonstrates a good agreement with the COSMO-RS prediction. Furthermore, based on analysis of Entry 6, the polymersomes were effectively retrieved in the ACN layer. In case of Rufinamide, due to the faster reaction time and lower solubility compared to **2** , product precipitation already occurred after 2 minutes during reaction and only 15 mins were needed for full conversion from R_1. However, the Rufinamide crystals were contaminated to some extent with polymersomes. This could be circumvented by addition of ACN after the reaction to wash and filter the polymersomes out. In Entry 10, the isolated Rufinamide yield was 93%, with 4% of product retained in the organic layer. In addition, although the conversions in DMSO were high, no product precipitated at r.t. and Cu(I)-PLs were not observed by TEM after the reaction.

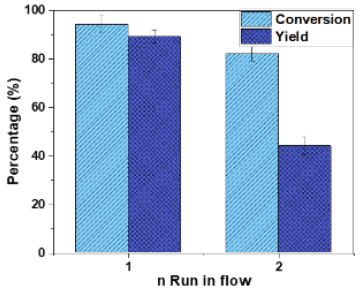
a



b

Entry	R	Flow rate [ml/h]	Yield [%]
1	Phenyl	6	92
2	Phenyl	12	89
3	Phenyl	24	83
4	Amide	96	90
5	Amide	192	87
6	Amide	384	81

c



To integrate both reaction steps in a ONE-FLOW set-up, the polymersomes and reagents were passed over the packed-bed of resin-N_3(Scheme 1b). Initially, the synthesis of **2** was attempted as model reaction system. The conditions used were 65 °C, with a flow rate of 6 mL/h. 1 M 2,6-difluorobenzyl chloride, 2 M phenylacetylene, and 0.05 M Cu(I)-polymersomes were passed through the resin-N_3 reactor (2 M). This process only led to 60% conversion of R_1 and no product **2** was collected as a crystalline product upon cooling down. The reaction solution and resin-N_3 were further characterized. From the SEM characterization (Figure S7, in the supporting information), product**2** was present but Cu(I)-PLs could not be detected; we hypothesized that they were probably adsorbed on the resin-N_3 . Therefore, a second one-flow process (Scheme 1c) was conducted. As depicted in Scheme 2a, the synthesis of azide was conducted at 80 °C and the reaction temperature for cycloaddition was set to 65 °C. The reaction solution after both steps was collected in a vial heated up to 40°C, to avoid uncontrolled product crystallization. Several flow experiments were performed to find the optimal conditions for both synthetic steps (Scheme 2b). Using a flow rate of 12 mL/h, resulting in a residence time of 15 min, yielded the desired triazole**2** in 89% isolated yield. For the synthesis of Rufinamide, the concentrations of the starting compounds had to be lowered by a factor of three in order to achieve a homogeneous phase during the flow reaction. Using a flow rate of 192 mL/h and a residence time of 1 min, Rufinamide was obtained in a satisfactory 87% isolated yield. Although full conversions were not achieved, the ACN layer containing R_1, P_1, and P_2 could be recycled after filtration. This was demonstrated with the outflow of the experiment, as performed under entry 2. The ACN layer containing the polymersome nanoreactors was collected after simple filtration and subsequently diluted twice by mixing it with the reactant solution (0.5 M R_1) before being reintroduced in the flow reactor. 82% conversion could be achieved and 44% isolated yield of product**2** were obtained (Scheme 2c). The possible reason of the decreased yield is the lower concentration of the final product, which makes the spontaneous recrystallization process less effective; however the recycling had no essential impact on the conversion.

Scheme 2. (a) Designed ONE-FLOW process of Rufinamide and product **2** preparations. (b) Optimization of the one-flow reaction conditions. (c) Reuse of the residues of ACN layer in a one-flow process (entry 2), exemplified by product **2** synthesis.

We have successfully introduced an integrated reactor-separator concept combining nano-compartmentalized polymersomes with a functional solvent system. The synthesis of Rufinamide was chosen as the model reaction and the conceptual approach of a 'designed micro-nano ONE-FLOW system' was verified via the selected functional solvent acetonitrile and the application of Cu(I) cross-linked polymersomes. In the future, we aim to extend this approach to other top-list drug syntheses. The final goal is to intensify multiple-step cascade reactions and separations by fully integrating them in an automatic and controllable one-flow process. This will increase the attractiveness of flow chemistry as a synthetic modality for scalable and cost-efficient

pharmaceutical processes.

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Conflicts of interest

There are no conflicts to declare.

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