

Application note SCT  
**How to use the different  
inserts for antisolvent  
crystallization**





## 1 The Use of the T-cross insert

This insert uses a T-mixer with a small inner diameter. Both flow streams are added from the side, the exit out of the mixer is in the perpendicular direction, see Figure 1. This results in turbulent mixing at the point of impact. Mixing occurs here at the Kolmogorov and Batchelor scale, in which eddies are therefore created. At the mesoscale, vortex shedding occurs, whilst inside these vortices, the momentum and molecular diffusion occurs in between the solute in solution and antisolvent. A paper of Johnson and Prud'homme from 2004 describes nicely these differences at different scales as depicted in Figure 2.

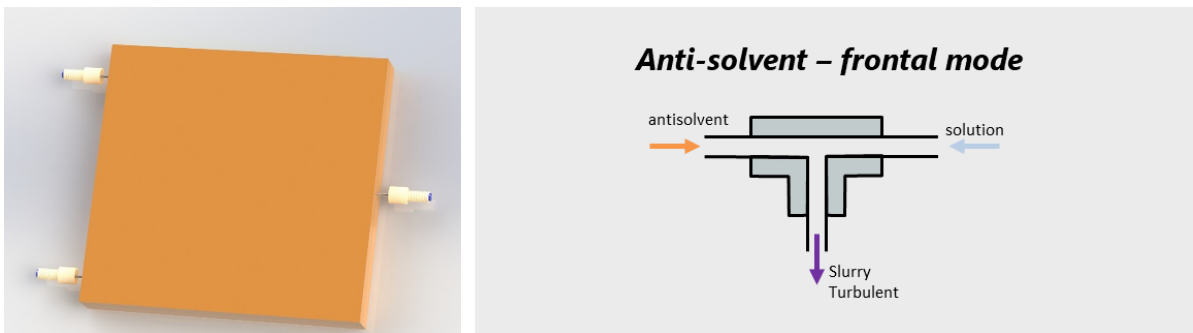


Figure 1: T-cross mixer image with schematics of the inside.

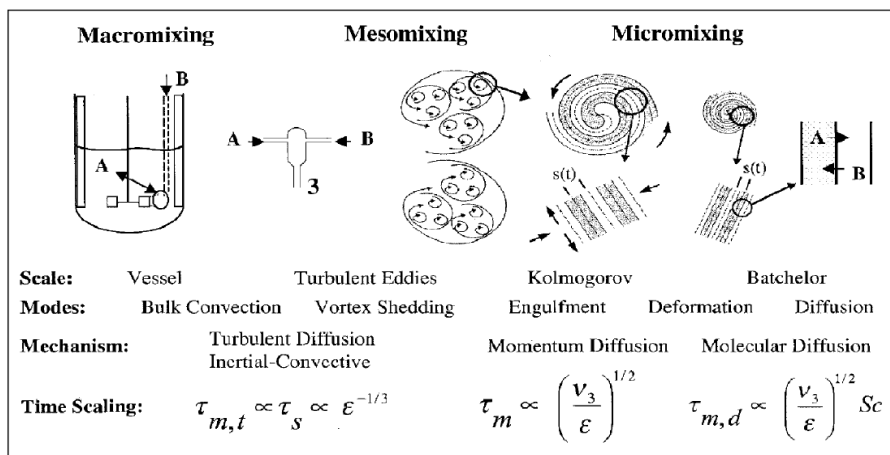


Figure 2: evolution of mixing from macromixing - mesomixing - micromixing, taken from Johnson and Prud'homme, AIChE, 2004

There are clearly some advantages in using different flow rates for both solute in solution and antisolvent. The impact of both streams joined together is larger at higher flow velocities and hence the Kolmogorov scale decreases. Smaller zones indicate smaller interaction areas and therefore smaller particle size as outcome for a product that does nucleate and grows very fast. A very simple but clear example is the crystallization of benzoic acid dissolved in ethanol at a concentration of 250



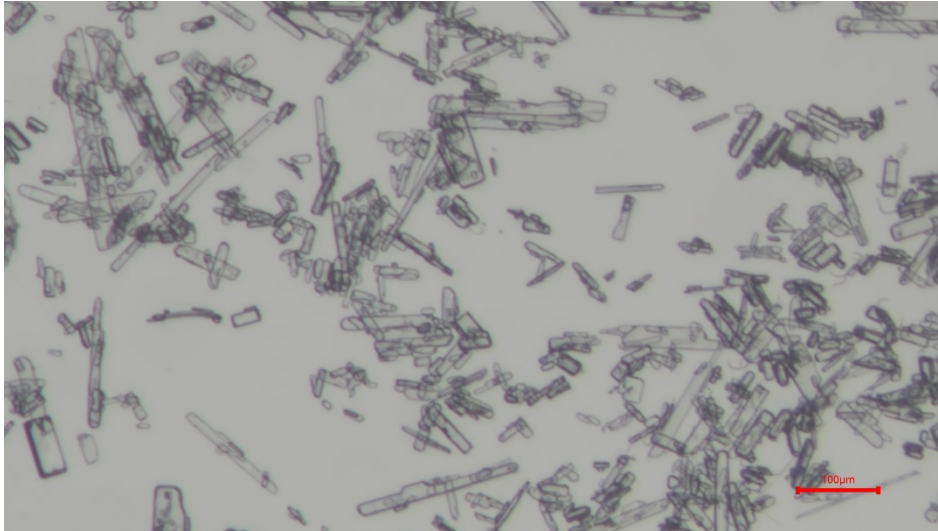
mg/mL at 25°C and water used as antisolvent. The sample details and results are shown in Table 1. As a mixer, the T-Cross mixing insert is used, coupled to a short 1 mL reactor. The crystal sizes at flow rates of 10 mL/min for both solution and antisolvent side result in average particle size of  $60 \pm 42 \mu\text{m}$ . Rather elongated crystals can be observed, see Figure 3. When increasing both flow rates to 20 mL/min, the impact is much higher and therefore smaller crystals are obtained, with a much more uniform particle size distribution as well as an average size of  $29 \pm 10 \mu\text{m}$ . Remark that for both tests, thermodynamics are completely alike, only the kinetics, more specifically the kinetic energy of mixing, is changed. What can be observed from the microscopic data is that not only the size of the crystals can be altered, also the crystal form is changed. Obviously, benzoic acid has only one crystal morphology but the rate of nucleation also has an impact on the crystal growth, resulting in a different aspect ratio length/width.

Table 1: Crystallization of benzoic acid using the T-cross mixer

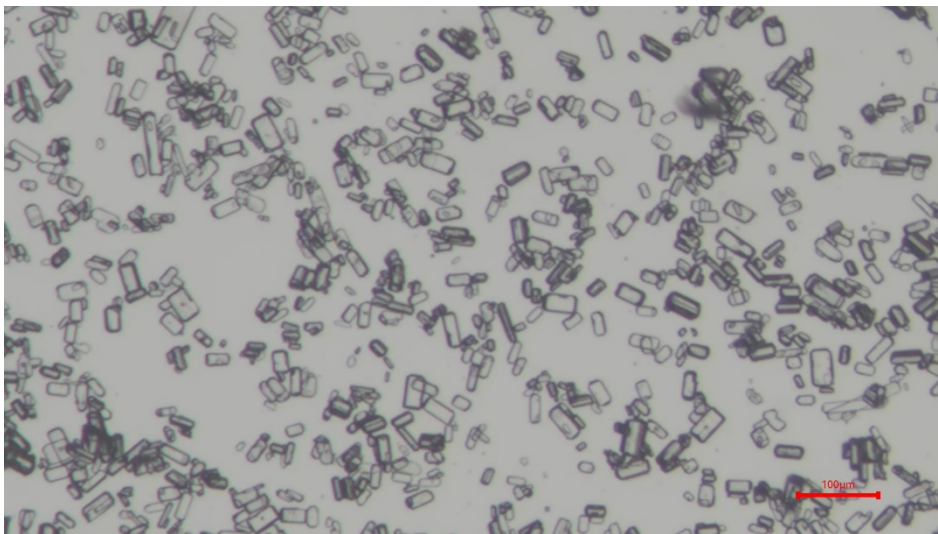
test details	test1	test 2	
product	benzoic acid		
solvent	ethanol		
concentration	250		mg/mL
antisolvent	water		
starting temperature	25		°C
insert	T cross		
reactor	1mL		
collection	25		°C
filtration	funnel P4		
Flow rate solution	10	20	mL/min
Flow rate antisolvent	10	20	mL/min
Analysis result			
average	60	29	$\mu\text{m}$
stdev	42	10	$\mu\text{m}$
d10	28	19	$\mu\text{m}$
d50	45	27	$\mu\text{m}$
d90	110	40	$\mu\text{m}$
span	1.84	0.79	$\mu\text{m}$



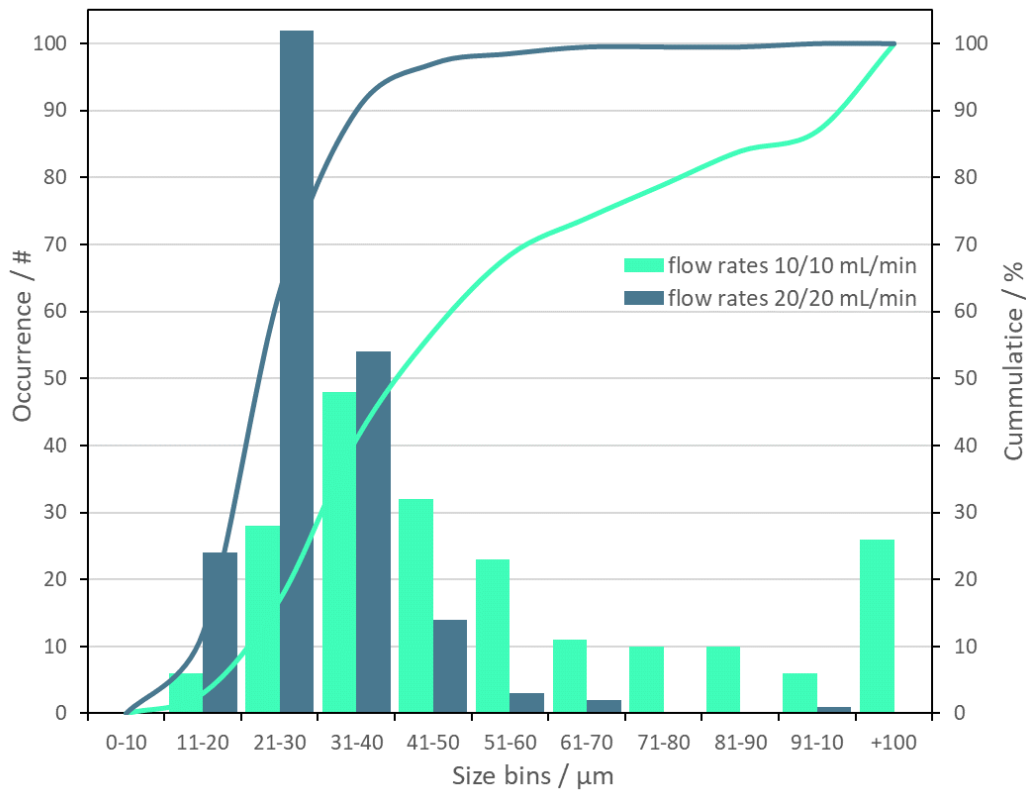
Test 1: flow rates of 10 and 10 mL/min



Test 2: flow rates of 20 and 20 mL/min



*Figure 3: microscopic images of benzoic acid crystallization using different flow rates.*



**Figure 4: Particle size distribution of both benzoic acid crystallization tests**

As a consequence, the particle size distribution shows a slight shift towards smaller size bins for the 20/20 mL/min flow rate tests, but more importantly a more narrow particle size distribution, also expressed by a drop span value from 1.81 to 0.78  $\mu\text{m}$ , is obtained, see Figure 4.

Using the T-cross mixer, one may also use different flow rates for both solution and antisolvent side. It depends on the user to select a flow rate for the solution higher or lower than the flow rate of the antisolvent, depending on the executed tests. However, some care has to be taken into account when having too large differences in flow rates due to less complete mixing in this setup. In Figure 5, two simulations are shown for flow rates from both ends at 20 and 20 mL/min, the second at 20 and 40 mL/min. The homogeneity of the mixing itself is perturbed with 20-40 mL/min flow rates, with the highest flow velocities of the mixing not occurring anymore in the middle of the tubing as is the case for the 20-20 mL/min mixing. Moreover, some backmixing at the outlet of the T-cross mixer cannot be excluded. Therefore, we advise the use of the T-cross mixer when the mixing ratio between solution and antisolvent is not high, and that control of particle size can be simply achieved by changes in kinetics and not thermodynamics.

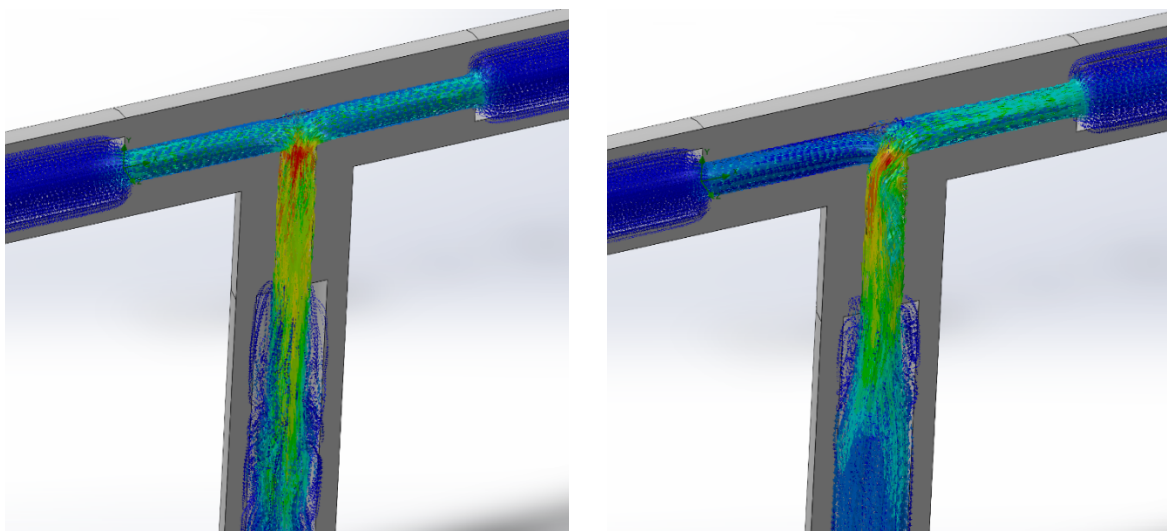


Figure 5: Flow simulation inside a T-mixer as used in the T-cross insert with equal flow rates (left hand side) and a 1/2 flow rate ratio (right hand side).

## 2 The use of the co-flow insert

When more increased differences in flow rate ratio are expected or thermodynamically wanted, we would advise to test the black co-flow mixer. Inside the co-flow mixer, mixing occurs purely diffusive. Inside the co-flow mixer, the solution is injected inside a capillary tubing positioned straight into a wider tubing. Thanks to the use of a T-piece, antisolvent is added and flows around the inner capillary. As the capillary tubing is sufficiently long, both flows are developed into laminar flow regimes at the moment the inner capillary tubing stops to ensure pure diffusive mixing in between both liquids. As there is no change in laminar flow behavior, when particles are formed rapidly at the interface between the solution and the antisolvent, they will be evacuated using the flow inside the tubing towards the outlet. It then depends on the difference in flow velocity whether the formed solids will remain long in contact with other solute and on total concentration inside the fully mixed slurry.

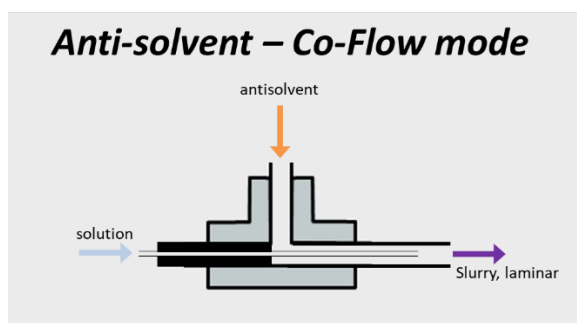


Figure 6: Co-flow insert with schematics of the inside



When looking at the theoretical migration behavior of solid particles in flow conditions inside narrow tubular systems, solid particles take up an excentric position, pushed outward, as published by Rivero and Scheid in 2018. In Figure 7a, the position of a bubble depends on the particle size: small particles tend to remain around  $0.35 \epsilon$ , with  $\epsilon$  the position from the tube center, exactly the point where the mean flow velocity is the highest (Figure 7b). Therefore this migration will decide on the particle size of the product as well. In Table 2, a series of different flow rates and flow velocities are given.

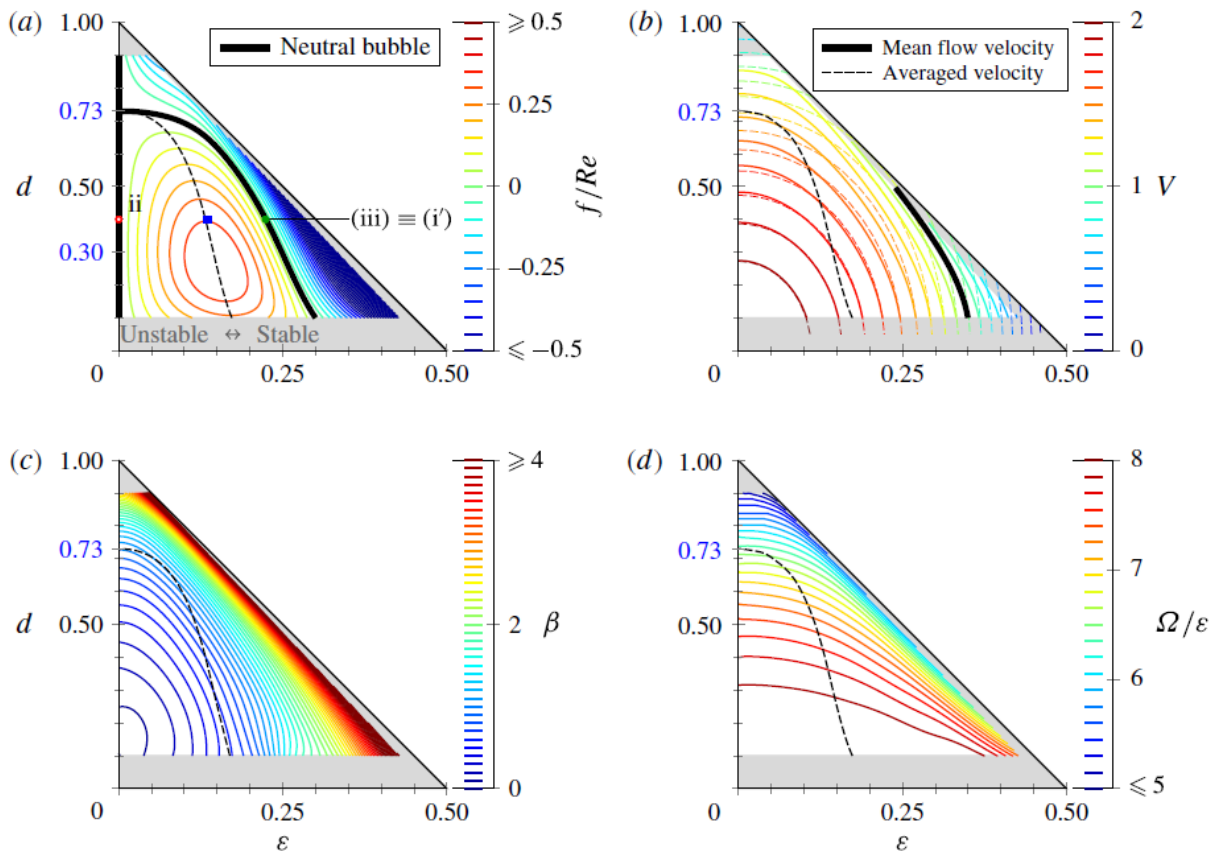
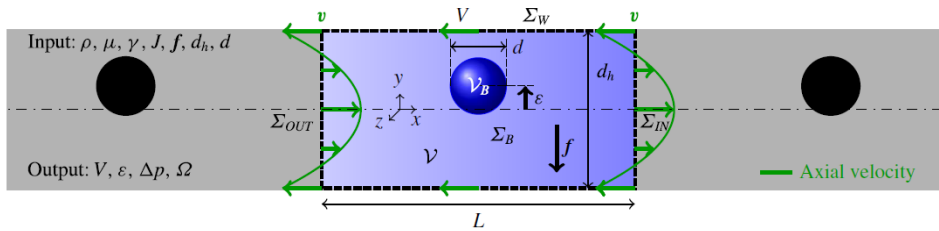


Figure 7: Theoretical considerations concerning the migration of solid particles inside a tubular reactor at ruling flow rates, taken from Rivero and Scheid, *J. Fluid Mechanics* 2018.



*Table 2: Typical flow rates and calculated flow velocities inside the co-flow insert. Please note that mixing ratios may be obtained using different flow rates*

<b>flow rate solution mL/min</b>	<b>flow rate antisolvent mL/min</b>	<b>Mixing ratio</b>	<b>velocity solution cm/s</b>	<b>velocity antisolvent cm/s</b>
10	10	1/1	164	24
10	20	1/2	164	49
10	30	1/3	164	73
10	40	1/4	164	98
10	50	1/5	164	122
10	60	1/6	164	146
10	70	1/7	164	171
10	80	1/8	164	195
10	90	1/9	164	219
10	100	1/10	164	244

Clearly, both liquids have the same velocity flowing out of the capillary tubing between flow rate ratios of 1/6 and 1/7. This means that at flow rate ratios lower than these values, the inner liquid - the solution - will expand its volume while mixing diffusively. At flow rate ratios of 1/7 to 1/10 the outer liquid - the antisolvent - takes up more place, as depicted in Figure 8 below. Now, when a particle is formed at the interface between solution and antisolvent, we know that the particle will migrate directly to its equilibrium position inside the tubing (thick blackline in figure a). Therefore, whenever the flow rate ratio determines that a particle migrates towards the antisolvent rich phase rapidly, the particle itself will be mostly surrounded by antisolvent, resulting in fast arrest of crystal growth due to depletion of the solute around it. Whereas at flow rate ratios of 1/1 up to 1/4 to 1/5, the particle migration does not necessarily mean that you exit the solute rich phase and therefore crystal growth may continue for some time and hence larger crystals will be retrieved. At the transition between both conditions - where both fluid streams have nearly identical velocities - particle migration towards the antisolvent rich phase becomes more and more dominant.

Also, at mixing ratios with higher solute content, higher overall concentration in solute will be present and therefore larger particles will occur whilst growing. This depends as well of course on the potency of the antisolvent itself, causing demixing of the solute in the mixed slurry. The faster this demixing, the more impact the particle migration will have, the smaller the possible size obtained. As such, a combination of solute/solvent/antisolvent will have an underlimit in size depending on the demixing capacities. Hence, it is expected that a threshold value in flow rate ratio might occur, a ratio upon which adding more antisolvent will not have an impact anymore on the particle size you may obtain.



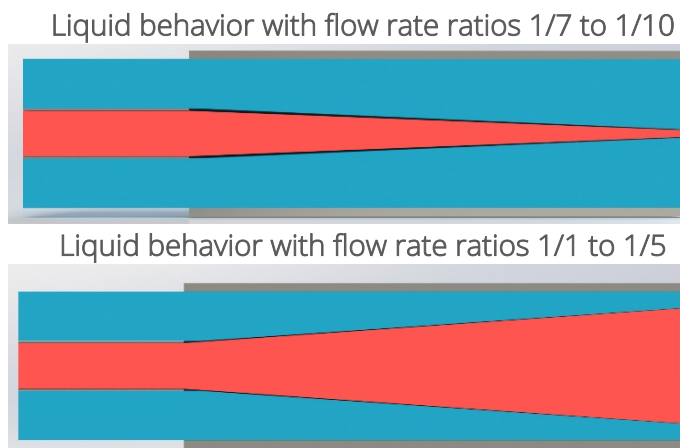


Figure 8: behavior of liquids inside the co-flow mixer with the inner liquid (solution) in red and outer liquid (antisolvent) in blue.

In the following example, Figure 9, this evolution in particle size is shown for a customer's example (a steroid), dissolved in ethanol at a concentration of 20 mg/mL and water added as antisolvent. Whereas with a flow rate ratio of 1/2 the sample variability in between tests is rather high due to variations in mixing, this variability becomes lower and lower towards mixing ratios of 1/5, 1/6 and 1/7. Together with these mixing ratios, the size of the obtained particles drop. Please note that in this case, no surfactant was added to the mixture. In order to avoid particle coagulation, surfactants are typically used to stabilize these particles after production. Usually, the surfactant is added to the antisolvent.

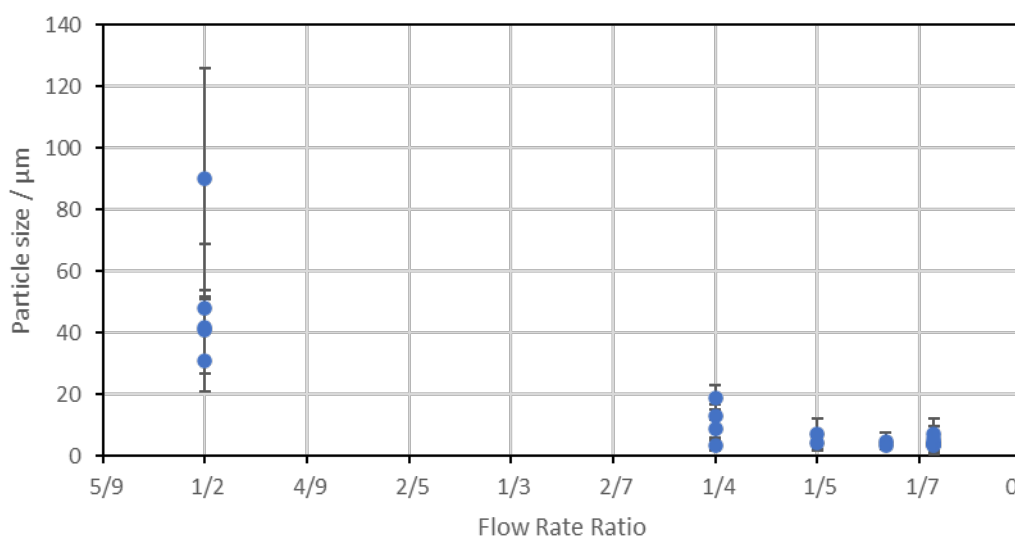


Figure 9: Average crystal sizes of a steroid compound using different flow rates inside the co-flow mixer using ethanol as a solvent and water as antisolvent.