# Scalable continuous flow technology for the development of pharmaceutical nanoformulations

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## Abstract

In the past decades flow chemistry became an important and rapidly advancing field of organic synthesis. However, it has been only introduced and was translated into the daily practice during the past years to prepare nanostructured particles. Decreasing the particle size down to the submicron range allows us to create nanoparticles with unique and novel material characteristics.

As a non-traditional approach, we have developed a continuous flow method for the production of nanoparticles in order to tailor the physicochemical properties of poorly soluble active pharmaceutical ingredients. The flow technology enabled us to positively impact the following physicochemical properties of the formulated drug: apparent solubility, drug dissolution profile, passive permeability and bioavailability. In this paper we will discuss a flow chemistry-based nanoparticle production approach using Fulvestrant as model drug.

The compound has negligible oral bioavailability due to poor solubility in aqueous media. Therefore, Fulvestrant is administered as a painful oil based intramuscular injection hindered by several adverse effects. We have prepared Fulvestrant nanoparticles using the controlled flow-precipitation method developed. The composition of the nanostructured particles was identified by high throughput screening. Downhill simplex method was used for flow parameter optimization. With the optimal parameter set, the nanoparticles were produced in small scale. The flow production process was scaled up and optimized to laboratory scale to meet the material need of animal studies. *In-vitro* characterization predicted complete absorption from the GI tract. The *in-vitro* results translated to excellent *in-vivo* performance. Rat PK studies showed that Fulvestrant formerly known as non-bioavailable was made bioavailable by creating nanostructured particles.

In the long term, we believe that the flow-technology could provide a suitable solution for the pharmaceutical industry to develop and prepare novel drugs with improved biological performance.

## Fully scalable instrument line

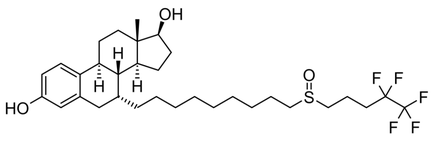
Prediction → HT Screening → NanOpti → NanoActive → NanoPilot

| Primary objective(s) | *In silico* analysis | Preformula identification | Flow optimization (Lab scale production) | Lab scale production (Flow optimization) | Pilot plant scale production |
|---|---|---|---|---|---|
| Solid formulation | n/a | Lyophilization | Lyophilization (Spray drying) | Spray drying (Lyophilization) | Spray drying |
| Capabilities | Prediction of viable formulations | 2000+ formulae / day | Robotized flow optimization | 70+ g / day production capacity | 2+ kg / day production capacity |

## Production process


- ✓ Continuous flow production process in proprietary instrument
- ✓ The produced colloid is forwarded to solid formulation
- ✓ For solid formulation regular freeze-drying or spray-drying can be applied
- ✓ Solid dosage forms (PiB, tablet, capsule, etc…) can be developed

## Optimization and scale-up of the Fulvestrant formula

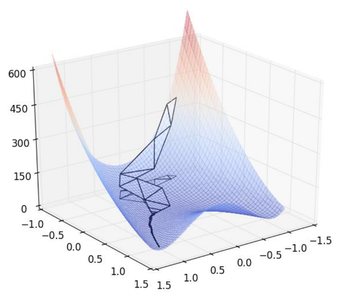


Structure of Fulvestrant

| HT screening identified a composition that wetted and dispersed instantaneously | |
|---|---|
| $d_{mean}$ | 266 nm (polydisperse) |
| $P_{app}$ | 0 (*$10^{-6}$ cm/s) |

*Optimization*

| Parameter set | $P_{app}$ (*$10^{-6}$ cm/s) |
|---|---|
| #1 | 0 |
| #2 | 0.03 |
| #3 | 0.22 |
| #4 | 0.19 |
| #5 | 0.51 |
| #6 | 0 |
| #7 | 0 |
| #8 | 0.14 |
| #9 | 0.27 |



Example downhill simplex optimization

- ✓ Flow optimization based on simplex method
- ✓ Target parameter: PAMPA permeability
- ✓ Parameters had significant effect on the permeability of the formula

| | |
|---|---|
| $d_{mean}$ | 186 nm (monodisperse) |
| $P_{app}$ | 0.52 (*$10^{-6}$ cm/s) |

*Process intensification*

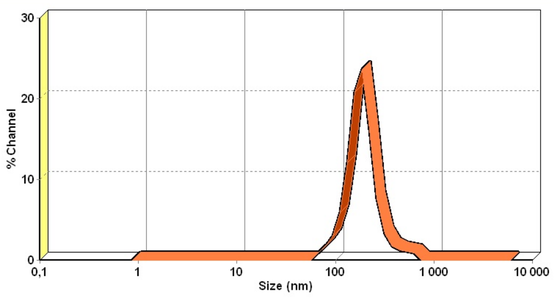
| Solvent flow rate | Antisolvent flow rate | Particle size of the redispersed colloid | |
|---|---|---|---|
| | | $d_{50}$ (nm) | d90 (nm) |
| 1 ml/min | 4 ml/min | 138 | 304 |
| 2 ml/min | 8 ml/min | 171 | 357 |
| 4 ml/min | 16 ml/min | 181 | 294 |
| 8 ml/min | 32 ml/min | 179 | 274 |

| | Particle size of the as-synthetised colloid prepared with 4:16 flow rates | | |
|---|---|---|---|
| | 20°C | 25°C | 30°C |
| $d_{50}$ (nm) | 390 | 426 | 422 |
| $d_{90}$ (nm) | 543 | 937 | 579 |
| PDI | 0.067 | 0.224 | 0.061 |

- ✓ The flow process was scaled-up to laboratory scale
- ✓ NanoActive instrument was used for production

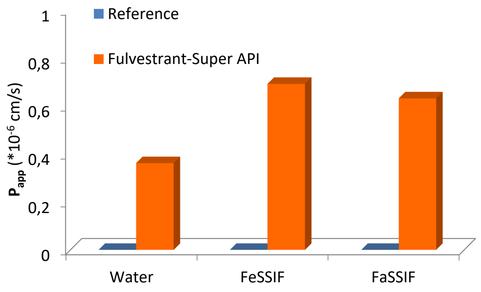
## *In vitro* characterization of the formula

### Particle size measurement




- ✓ Narrow, monodisperse size distribution
- ✓ Mean particle size < 200 nm

### Comparative PAMPA measurement

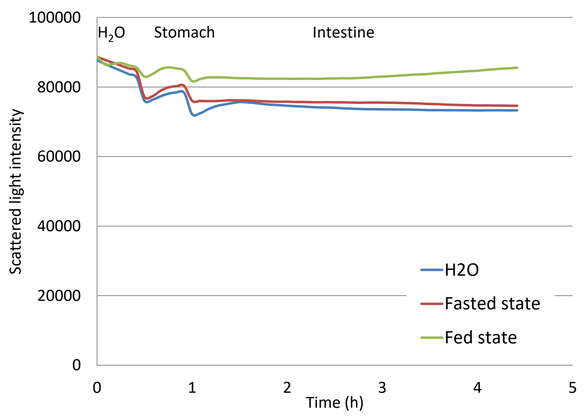



- ✓ Significantly increased apparent permeability

### Apparent solubility measurement

| | Apparent solubility |
|---|---|
| Unformulated | Not detectable |
| Nanoformulated Fulvestrant | 1.43 mg/ml |

### GI tract simulation

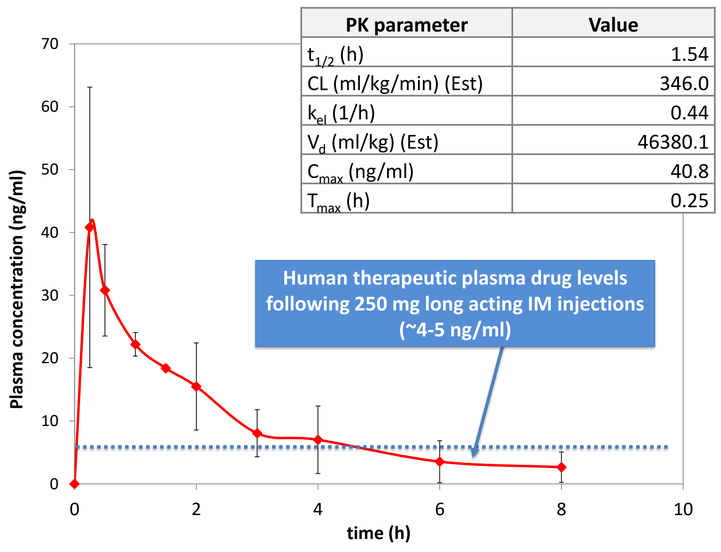



- ✓ The formula was stable throughout the GI tract in both fasted and fed states
- ✓ No issues were expected during PK studies

## *In vivo* characterization of the formula

**Animal PK studies showed that Fulvestrant formerly known as non-bioavailable was made bioavailable by creating a nanoformulation**

| PK parameter | Value |
|---|---|
| $t_{1/2}$ (h) | 1.54 |
| CL (ml/kg/min) (Est) | 346.0 |
| $k_{el}$ (1/h) | 0.44 |
| $V_d$ (ml/kg) (Est) | 46380.1 |
| $C_{max}$ (ng/ml) | 40.8 |
| $T_{max}$ (h) | 0.25 |




*Oral absorption was tested in a rat model at 2.5 mg/kg*

## References

1. Instrument and process for nanoparticles production in continuous flow mode, WO2009/133418
2. Complexes of Fulvestrant and its derivatives, process for the preparation thereof and pharmaceutical compositions containing them, HU P1300646

## Conclusions

With Fulvestrant we have demonstrated the capabilities of the flow technology developed. The production process was optimized and scaled-up and a commercially viable dosage form was prepared. Ultimately, an orally non-bioavailable drug achieved complete absorption from the GI tract in multiple animal studies in different species.