COMSOL CONFERENCE 2017 ROTTERDAM

Sensitivity Analysis of CPP’S for Solvent Removal Process of an API-Polymer Based Nano-suspension

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TEVA

Teva Pharmachemie

What do we do:

World's leading generic medicine maker

Headquarter in Israel

Teva Haarlem:

1946 founded as Pharmachemie

1998 acquired by Teva

Products:

Dry powder inhalation capsules

Cytostatic injectables

Complex sterile products

Basic Process Steps

Basic unit operation	
Emulsification	Solvent removal
Particle size engineering	Filtration
Concentration	Drying
Cristalizatoin	Filling

Problematic

Failure of Engineering Batch

↓

Sterile Filtration Blockage

Product out of specification

↓

Root cause analysis

Slow solvent removal

↓

API precipitation

Filter blockage

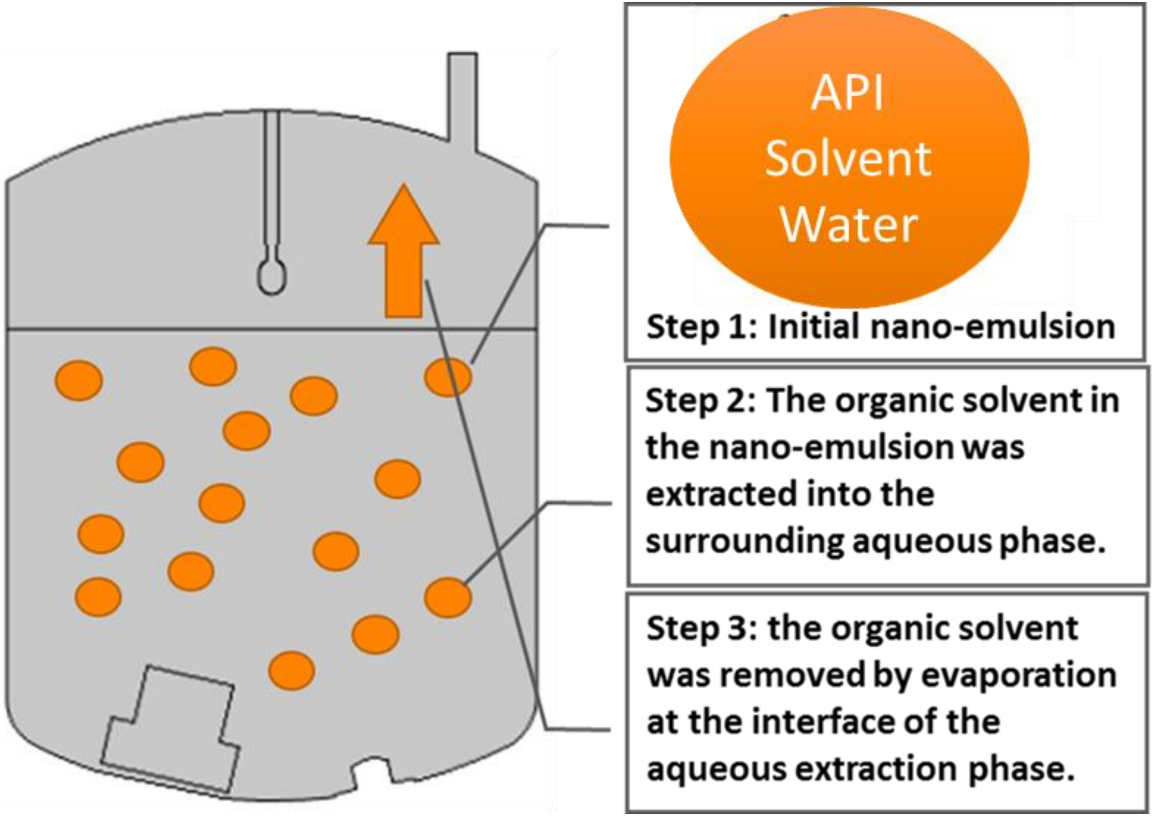
Mechanism of the Process & Difficulties

Criticals Process Parameters

1. Temperature
2. Surface area
3. Agitation
4. Pressure
5. Air flow rate

Constraints:

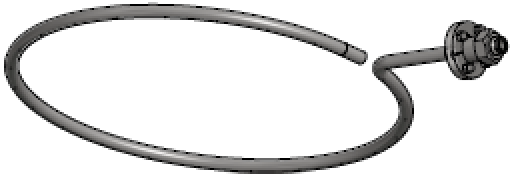
- ❖High temperature-> product degradation
- ❖High mixing speed-> Dissociation API-polymer and foaming
- ❖Low solvent removal rate-> API precipitation



Proposed Solutions

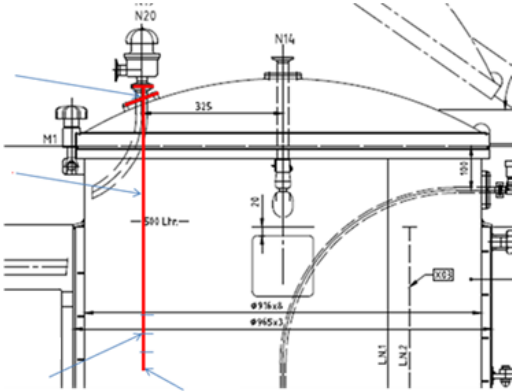
1. Sparging
2. New air distribution system
3. Vacuum
4. Temperature
5. Mixing speed

Ring ventilation?



Temperature increase?

Sparger?



Vacuum?

Process Variation and Its Impact

Process Parameters	Settings	Tolerance
Temperature [°C]	20-25	±2
Agitation speed [rpm]	200-300	±50
Air flow rate [L/min]	300-500	±50
pH	6.5-7.5	±1
Particles size distribution [nm]	95-115	±15
Foam formation on surface		

1. What are the impact of these variations on the solvent removal rate?
2. In a worst case senario, how does it compromize the product quality?

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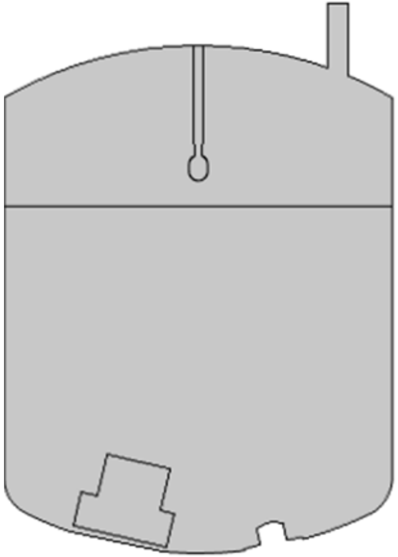
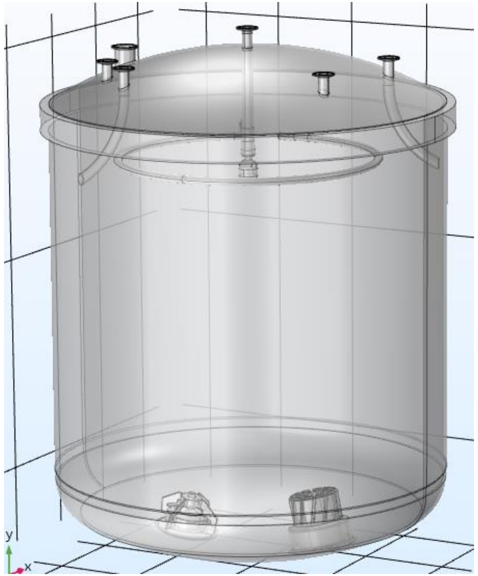
Geometry Design

2D



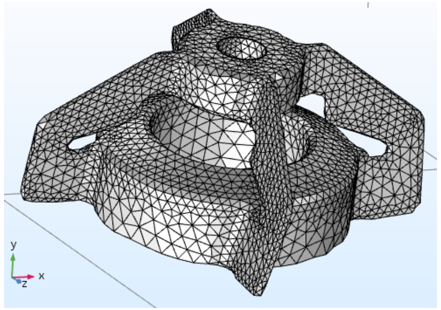
3D

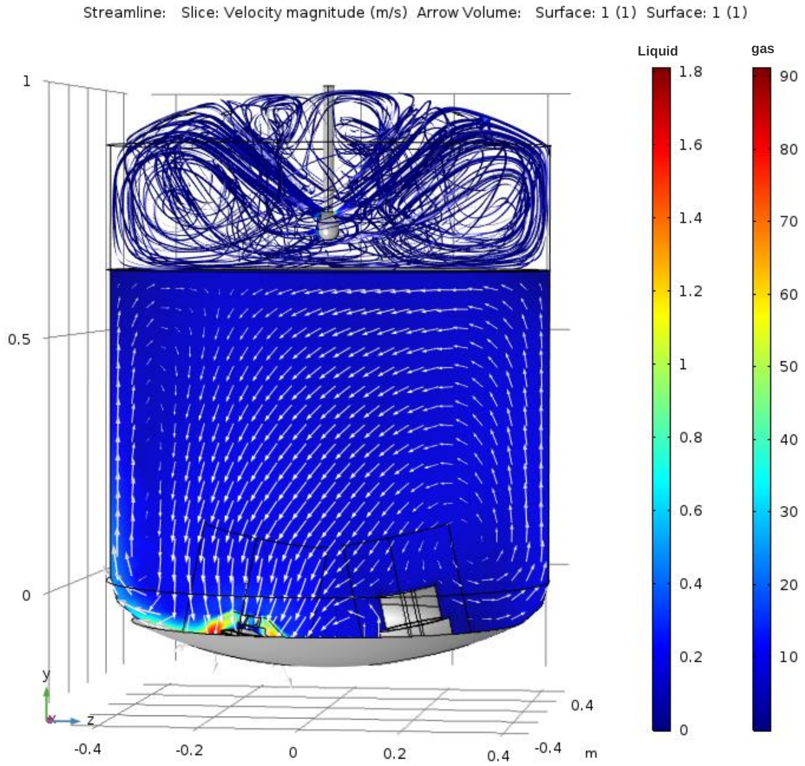


2D and 3D Stationary RANS simulation
Turbulent $k-\varepsilon$ model

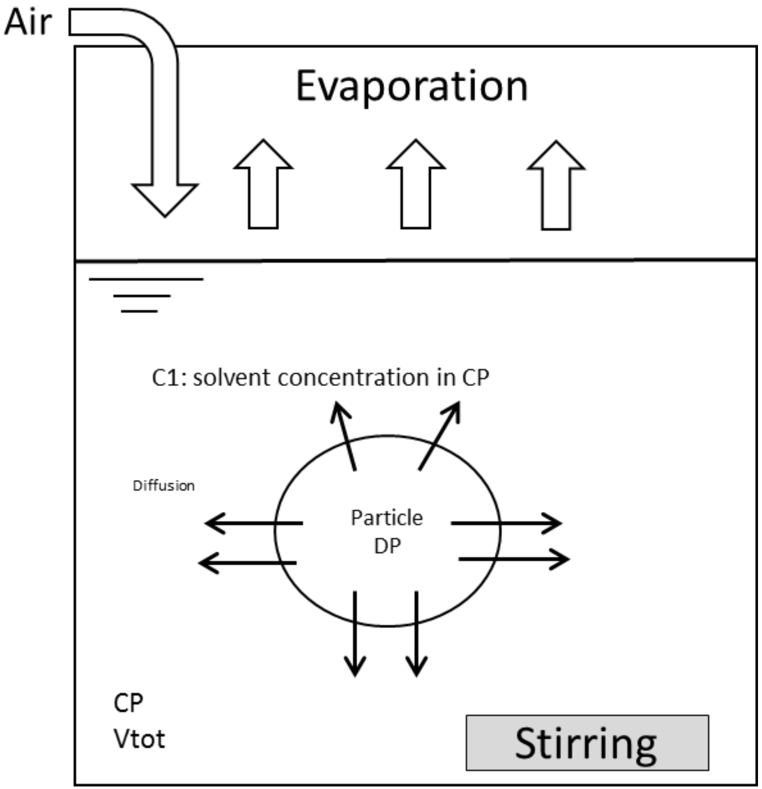
$$\rho\left(\frac{\partial u}{\partial t}+u\nabla u\right)= -\nabla p+\nabla(\mu(\nabla u+(\nabla u^{T}) -\frac{2}{3}\mu(\nabla u)I+F$$

$$\frac{\partial \rho}{\partial t}+\nabla(\rho u)=0$$





Mass Transfer



Diffusion and convection of the solvent in the gas and liquid phase

$$\frac{\partial c_i}{\partial t} + \nabla.(-D_i \nabla c_i + u c_i) = R_i$$

Diffusion of the solvent in the nanoparticle

$$\frac{\partial c_i}{\partial t} + \nabla(-D_{part} * \nabla C_{part}) = 0$$

Flux of the solvent at gas/liquid interface

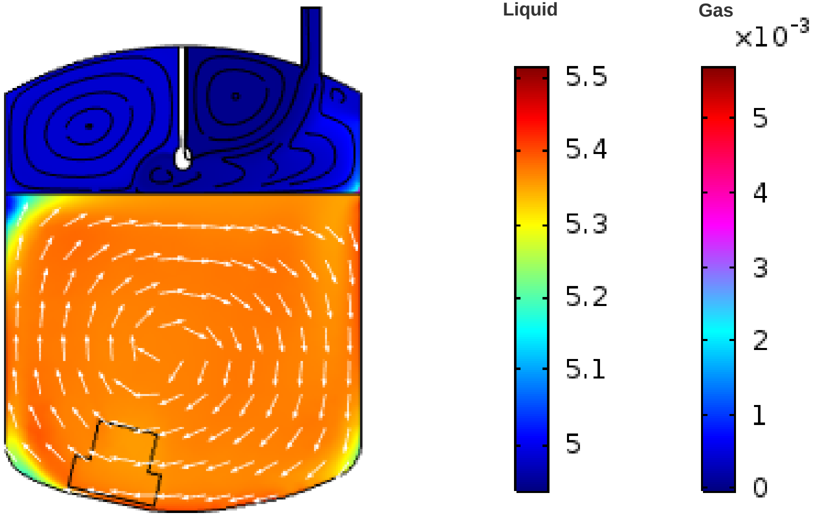
$$m_{evap} = x_{solvent} A_{spec} K_{evap} (\frac{P_{sat}}{RT})$$

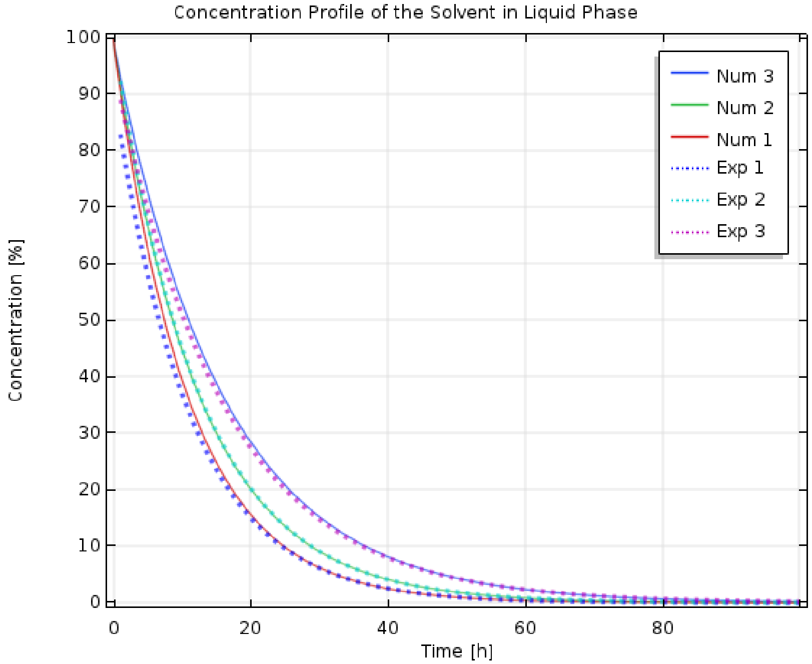
Flux of the solvent through the nanoparticle/liquid interface

$$m_{part} = A_{tot} k_{part} (C_{part}^{e} - C_{liq})$$

Concentration Profiles

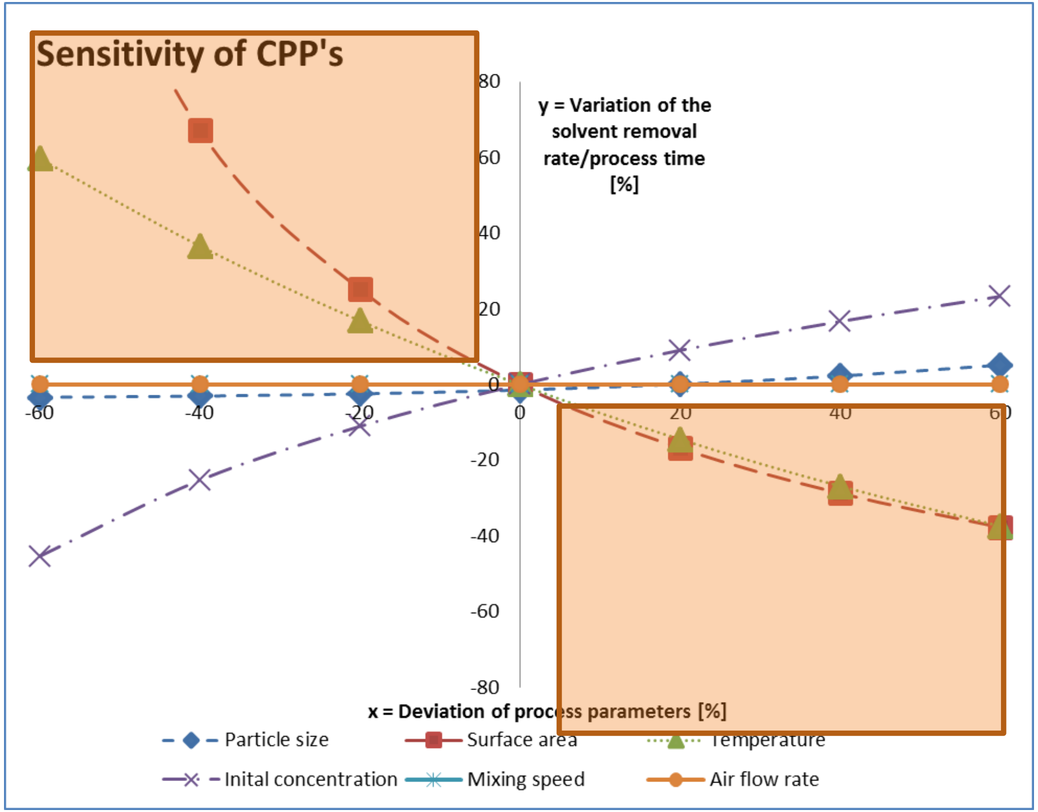
Concentration profile of the solvent in the liquid and in the gas phase





The model shows good fit to the experimental data.

Sensitivity of CPP’s



1. Temperature and the surface area are the most critical process parameters

2. Mixing speed and air flow rate do not have any impact within 60% of the variation.

3. PSD has slightly impact

Conclusion

Improvements

- Identified CPP's and quantified their impacts
- Process understanding and the control strategy
- Reduce the risks for the process change
- Improved decision making and scale up strategy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Q&A