Sensitivity Analysis of CPP's* for Solvent Removal Process of an API-Polymer Based Nano-suspension

C. C. Huang, T. Liu, F. Faassen
Generic R&D, Teva Pharmachemie B.V., Haarlem, The Netherlands

❖ Introduction:

A weak API-Polymer bonded nano-particle product is currently under development in Teva Pharmachemie R&D in Haarlem. This product is highly sensitive to temperature, mixing speed and solvent removal rate.

Constraints	Potential Consequences
High temperature	Particle degradation
High mixing speed	Dissociation of API-polymer and foam formation
Slow solvent removal	Precipitation of free API

Table 1. Relationship between constraints and potential consequences

In this work, the process of solvent removal during the manufacturing of API-Polymer based nano-suspension[1] was modeled using COMSOL Multiphysics®. Sensitivity of the CPP's on the solvent removal was evaluated.

Figure 1. illustrated basic steps of solvent removal process of nano-particle fabrication[1].

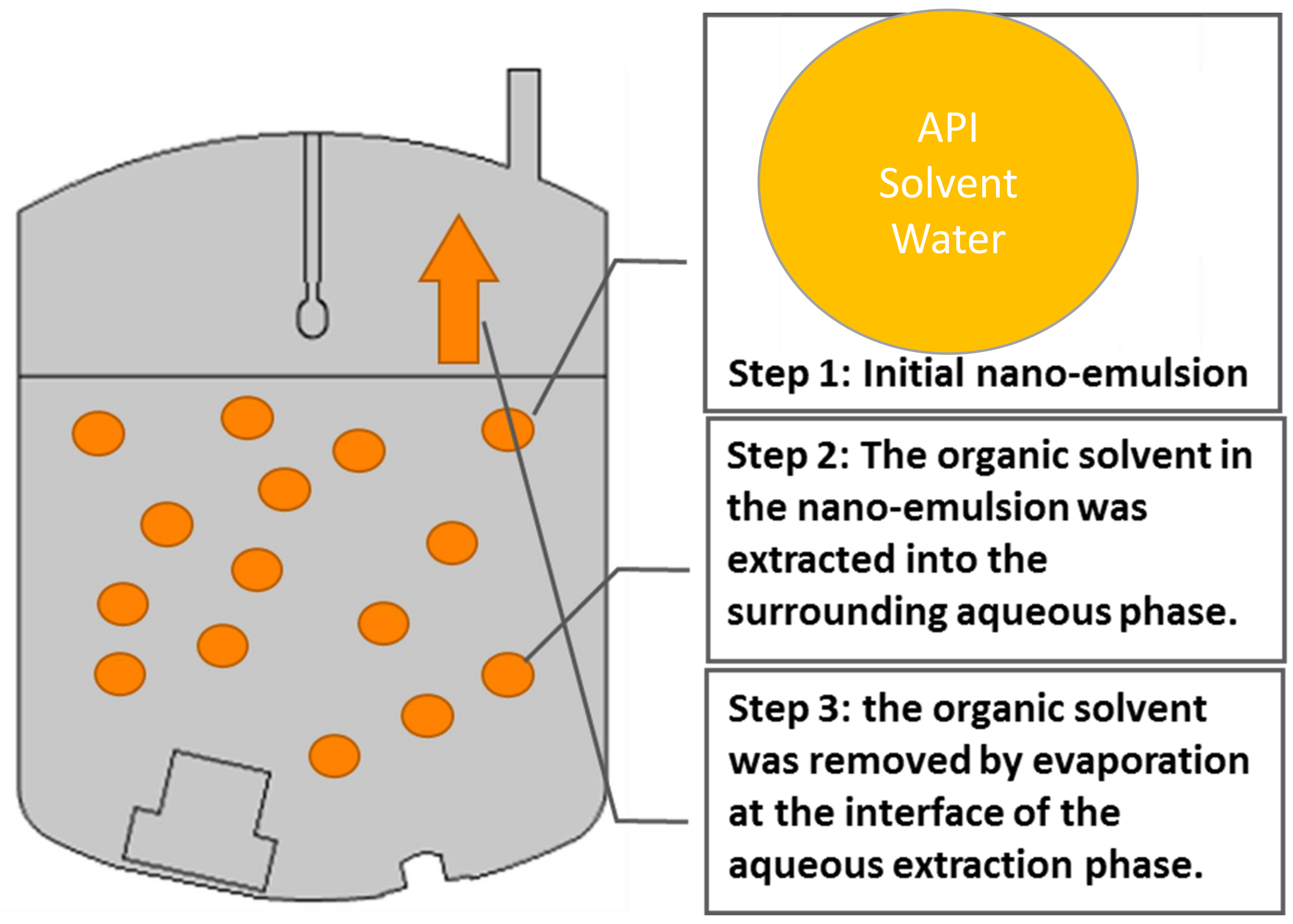

Figure 1. Illustration of solvent removal mechanism[1]

❖ Computational Methods:

2D and 3D models were built using COMSOL Multiphysics®. **Turbulent Flow** and **Rotating Machinery** physics interfaces in the CFD Module were used to determine the stationary velocity profile of the air inlet through an air distributor and the mixing of the nano-suspension in the reactor. The **Transport of Diluted Species** interface was used and coupled with a **Multiphysics** interface to describe the mass transfer of the solvent from the nanoparticles to the liquid solution and solvent evaporation at the air/liquid interface.

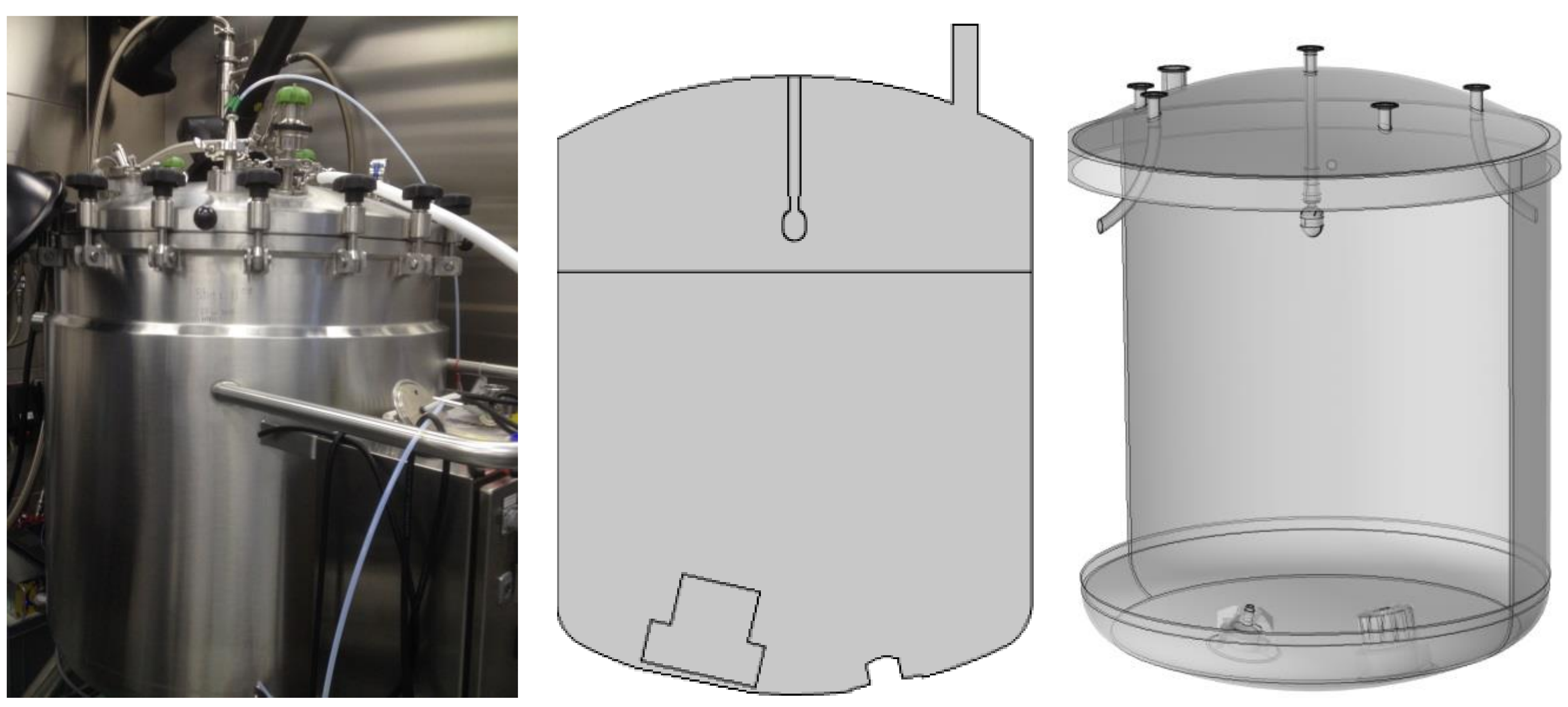

Figure 2. 2D and 3D geometry of 500L reactor

❖ Results:

Figure 3 shows the velocity profile of gas and liquid in the 2D model. The model shows good fit with experimental data (**Figure 4)** using different process conditions.

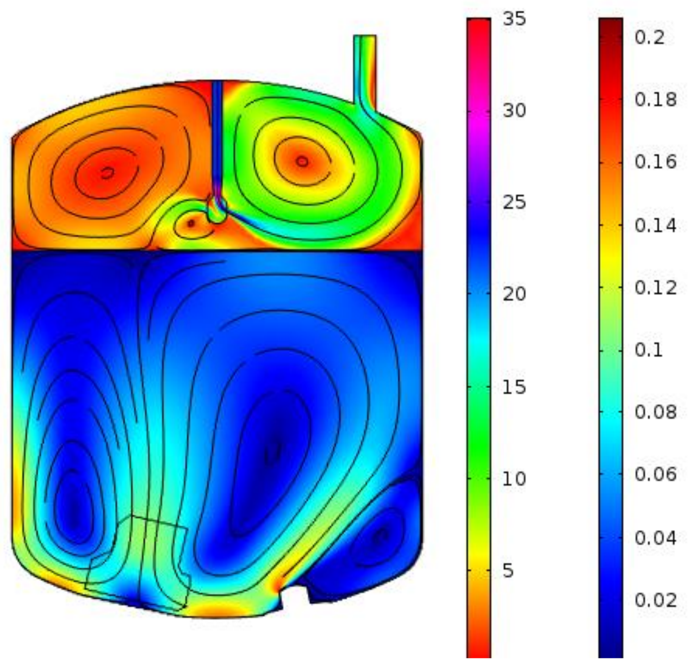

Figure 3.
Velocity streamlines

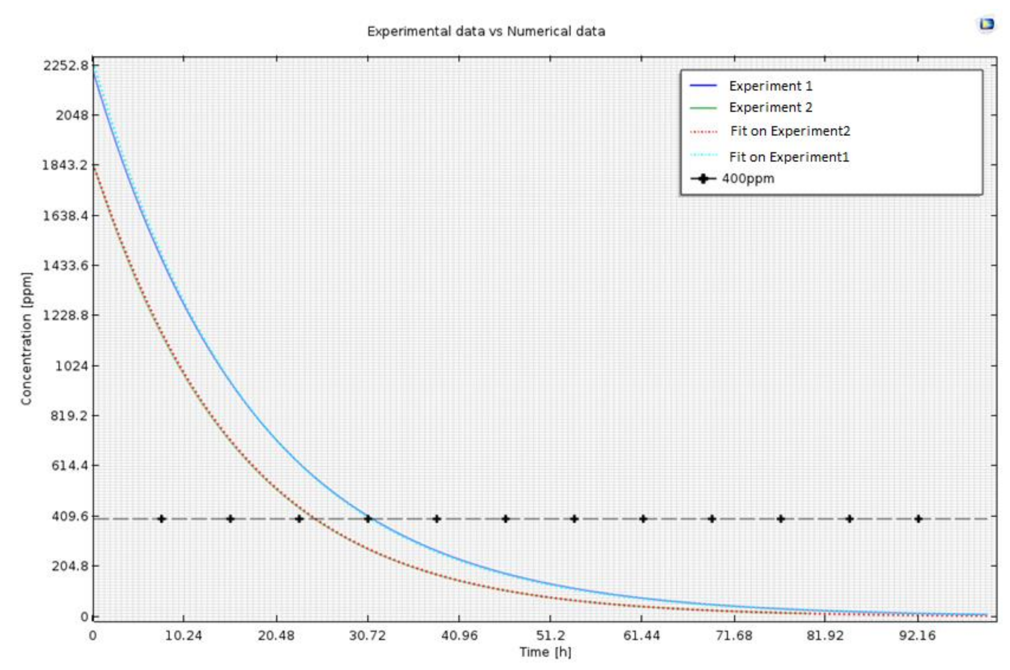

Figure 4.
Solvent concentration profile in liquid

The influence of temperature, surface area, particle size, stirring speed and air flow rate on the solvent removal rate were investigated. **Figure 5** indicates the sensitivity of the variation of CPP's on the solvent removal rate/process time. The CPP's and the consequence of its variation are normalized using the optimal process settings and the experimental data (**Table 2)**.

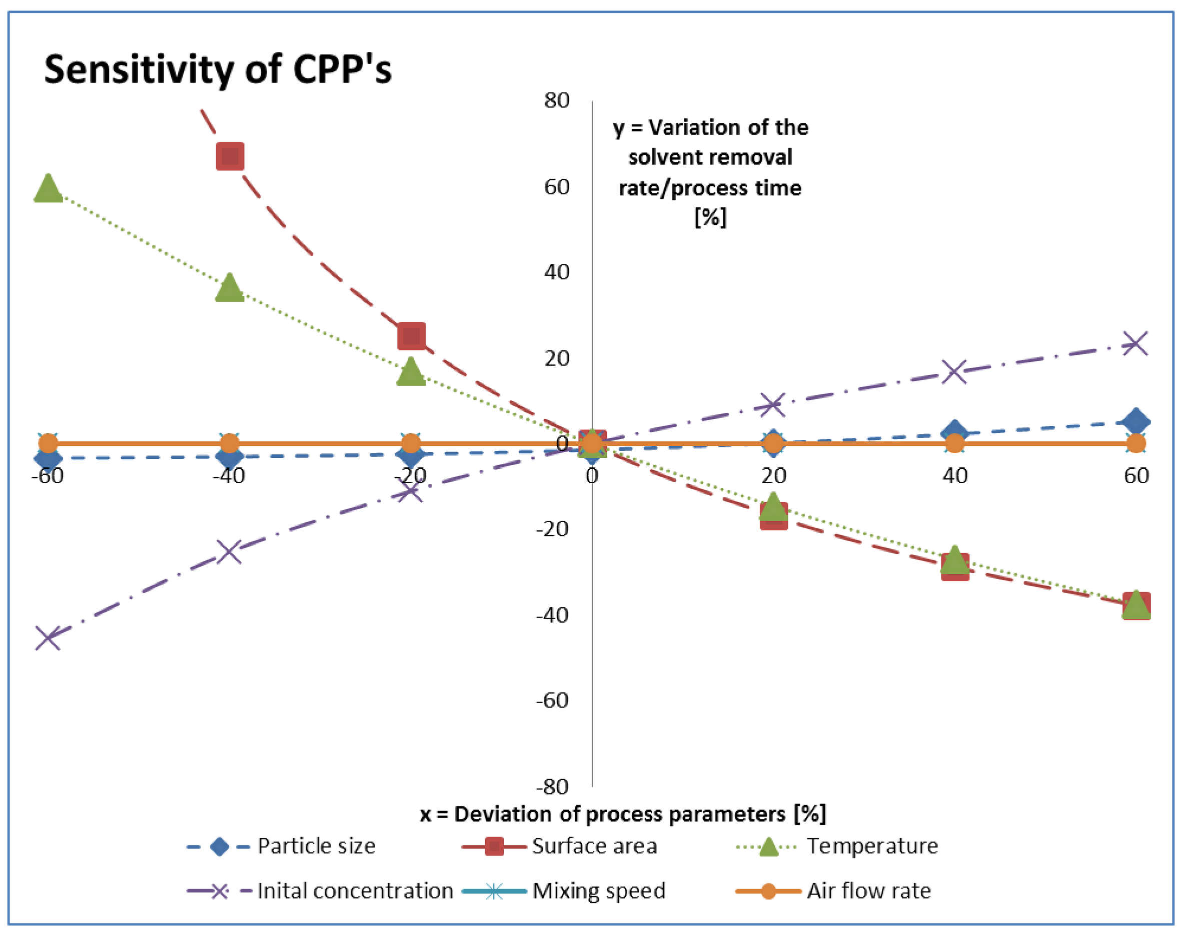

Figure 5. Influence of CPP's on the solvent removal process

CPP	Value	Units
T*	10	[° C]
C(t=0)*	8000	[ppm]
A*	100	[%]
R*	10	[nm]
Mixing speed	300	[rpm]

Table 2. Reference process settings

❖ Conclusions:

- ➢ Temperature and surface area are the most critical factors during the solvent removal process.
- ➢ To prevent API precipitation, the solvent removal rate should be maximized considering the constraints of temperature and vessel surface area **(Table 1)**.
- ➢ The mixing speed should be kept minimal in order to reduce the foam formation.
- ➢ This model and sensitivity graphs are able to provide a critical information for decision making.

References:

1. A lipid-polymer nanoparticle containing wortmannin, http://www.pnas.org/content/109/21/7949/F2.expansion.html PNAS 2012 109: 7949-7950.

*CPP	T	C	A	R
Critical Process Parameter	Temperature	Concentration	Surface area	Radius