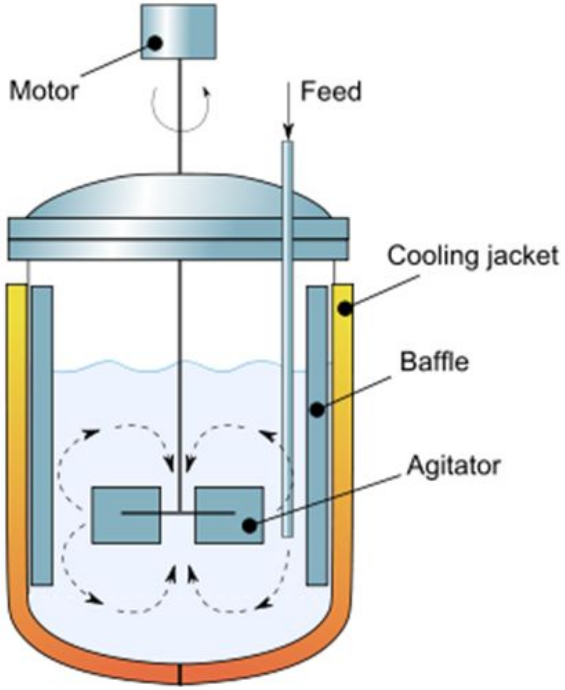


TAPI

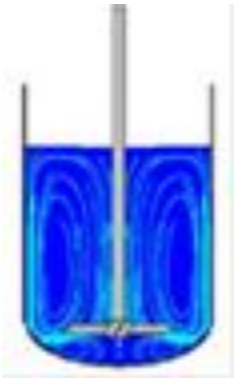
Teva Active Pharmaceutical Ingredients

Using computational tools for effective scale up

Yossi Mendel

Example – Scale Up of competitive reactions

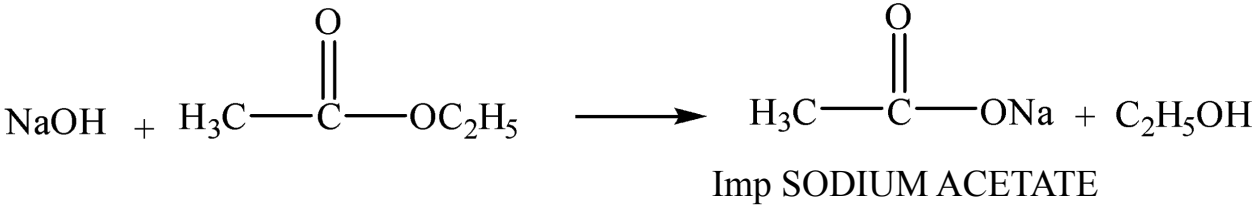
Using visimix for the scale up of competitive reactions at plant 68 teva tech : achieving equivalent mixing at different scales



Case Study – PNT SODIUM

Two reaction compete for NaOH

PNT FREE ACID + NaOH ⟶ PNT SODIUM



Imp SODIUM ACETATE

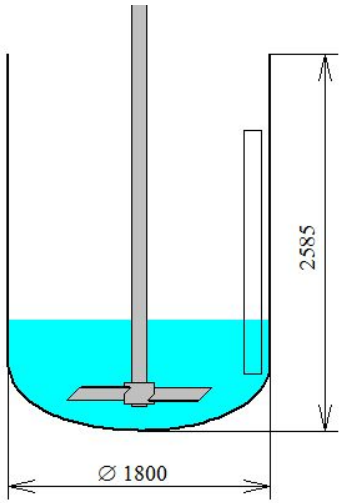
Solid – Liquid interaction

- Solid phase – PNT free acid
- Liquid phase – ethyl acetate + NaOH 47%

PURPOSE , CURRENT SITUATION

PURPOSE – scale up of the process from 125 kg to 240 kg free acid to meet market demand

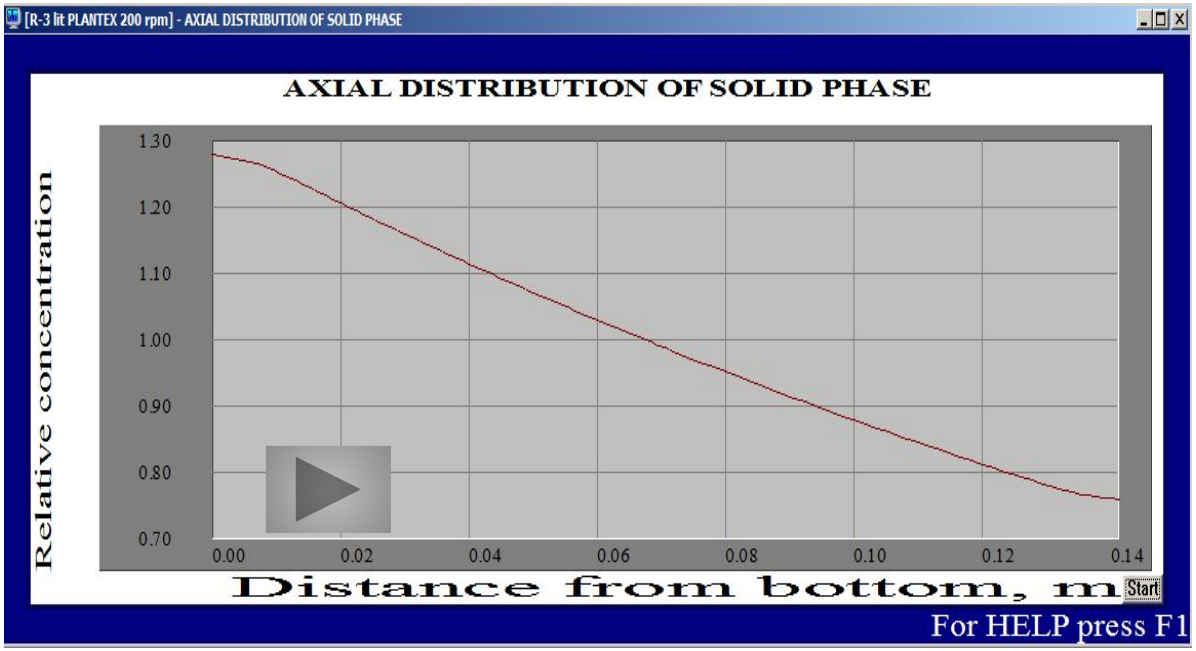
CURRENT SITUATION – working at R-6824 with 125 kg FA , exploiting only 40% of the nominal volume of the reactor .

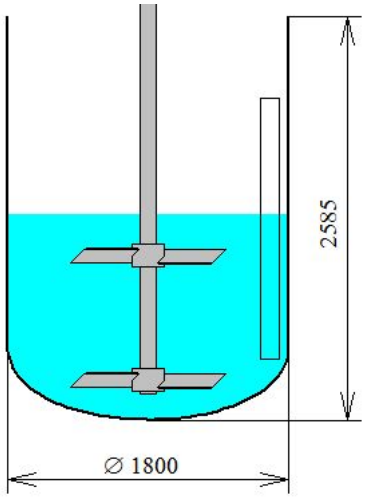


It is necessary to understand what is the impact of mixing on the product quality

VSM model followed by experimental work

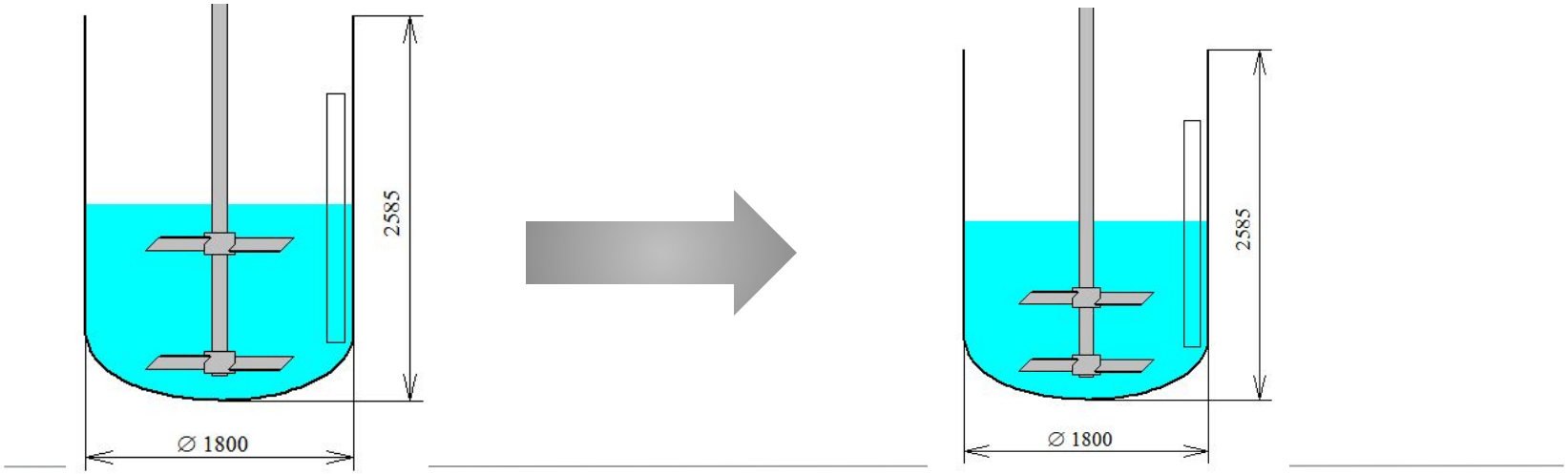
Parameter name	Units	R-3 lit PZ-22013	R-3 lit PZ-22014	R-6824 125 kg FA	R-6824 240 kg FA
baffles		2	2	2	2
rpm		200	500	90	90
batch volume	LIT	2.3	2.3	1,975	2,975
number of impellers		1	1	1	2
imp level	%	%0.42	%0.14	0.2% - %0.1	Should stay 0.2% – 0.1%
% ,Maximum degree of non-uniformity - axial	%	30.5	11.6	5.2	12.9





Modify agitation to improve solid dispersion

Parameter name	Units	R-6824 125 kg FA	R-6824 240 kg FA	R-6824 240 kg FA
Distance between impellers		NR	mm 800	mm 500
rpm		90	90	90
batch volume	LIT	1,975	2,975	2,975
number of impellers		1	2	2
imp level	%	0.2% - %0.1	Should be as before	Should be as before
macromixing time	s	8.80	7.72	8.45
Energy dissipation - maximum value	W/kg	38.6	54.6	54.6
Energy dissipation in the bulk volume	W/kg	0.226	0.337	0.337
% ,Maximum degree of non-uniformity - axial	%	5.2	12.9	3.77



RESULTS

acetic acid	situation
0.1% - 0.2%	125 kg free acid
0.17%	240 kg free acid
NMT 0.5%	specification

- Maintaining the same chemical quality in reference to acetic acid .
  (all other features – appearance , yield , PSD , description stayed the same)

- Capacity – Increase production rate from 770 to 1,050 kg/week

- Robustness – Reducing the amount of failures to less than 0.5% a year

Working Procedure at TAPI IL

- Defining the hydrodynamic parameter to maintain during scale up – SIMULATION PROTOCOL in the PILOT REPORT

PILOT

- Evaluating the suitability of the production reactor to the process – Mixing evaluation is part of the DESIGN QUALIFICATION (DQ)

ENGINEERING

- Production of validation batches

VALIDATION

- Calibrating VISIMIX model according the results of the validation batches

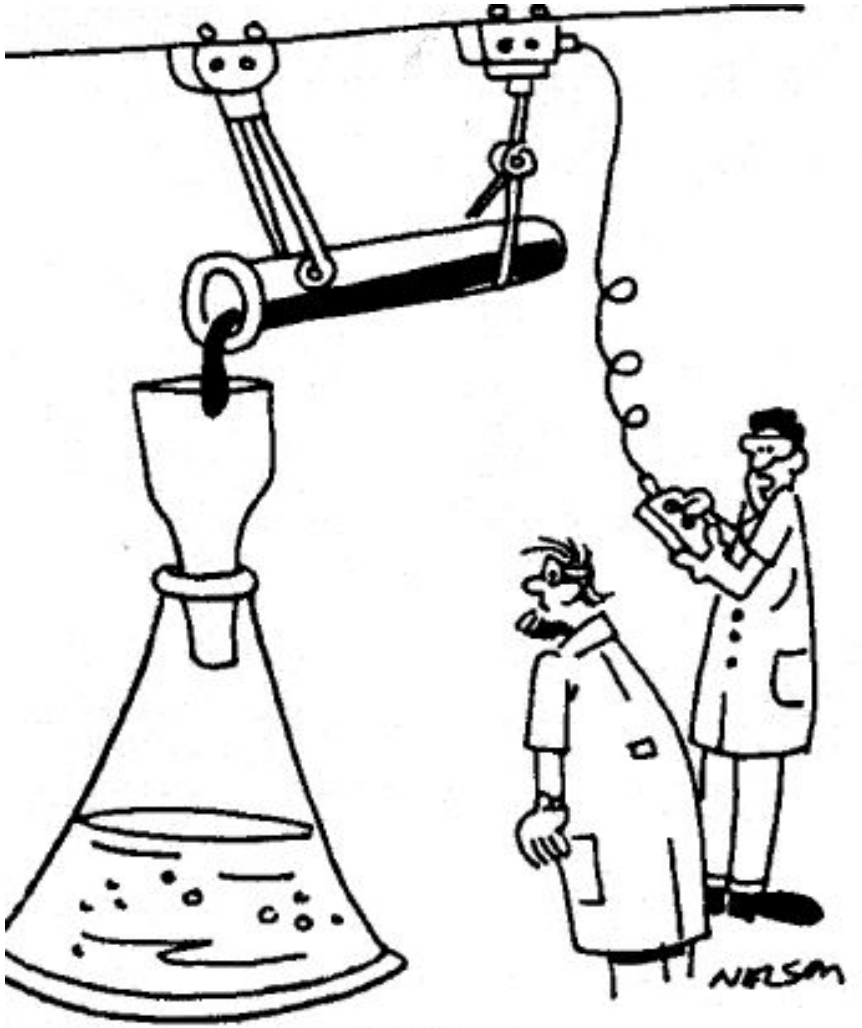
CALIBRATION

- Using the model to anticipate the success during further scale up

SCALE UP

Visimix® provided meaningful and reliable scale up info !

Thanks



"Say when."