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3,4,5-Tri-Dodecyloxybenzoic Acid: Combining Reaction Engineering and Chemistry in the Development of an Attractive Tool To Assist Scaling Up Solid−Liquid Reactions

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Abstract:

The synthesis of tris-*O*-dodecyl-gallic acid (3,4,5-tri-dodecyloxybenzoic acid) was selected as a model system in our program to define design tools and a methodology for fine-chemical scale-up. The just-suspended conditions of potassium carbonate in MIBK have been studied to find a scale-up rule for this system from 1 dm^3 lab-scale to an industrial scale of 6000 dm^3. By adjusting the relation of Zwietering to the values obtained by visual observations of the lowest stirrer speed at which the solid particles are just-suspended on a 1- and a 10-dm^3 scale with different particle sizes and two stirrer types, a scale-up rule was developed which was verified under just-suspended conditions on a 50-dm^3 scale. In addition, a prediction was made using this rule as a minimum criterion for a 6000-dm^3 reactor where no problems regarding off-bottom criteria are expected. The focused beam rotating measurement (FBRM) and photo video measurement (PVM) Lasentec techniques have been used successfully to determine just-suspended stirrer rates and to gain more insight into the dynamic (de)agglomeration behaviour of potassium carbonate during the tri-alkylation of methyl gallate. These techniques proved to be powerful tools in accelerating process development of heterogeneous reaction systems.

Introduction

Fine chemicals are usually produced in multipurpose (semi)batchwise-operated equipment, whereas bulk chemicals are produced in dedicated continuously operated reactors. Consequently, process research and development for the production of fine chemicals asks for a different approach due to short time-to-market and a relatively short lifetime in the market as compared to bulk chemicals. This makes batch-process design quite challenging in view of the lack of appropriate design tools and generic methodologies for scale-up.

The synthesis of tris-*O*-dodecyl-gallic acid (3,4,5-tri-dodecyloxybenzoic acid) was selected as a model system to define design tools and a methodology for fine-chemical scale-up. Tris-*O*-dodecyl-gallic acid (TDGA) is a versatile building block for the flexible part of discotic liquid crystalline materials.[1−4] In an earlier study[5] the synthesis has been optimised and successfully performed on a 1-kg scale in a 10-dm^3 fully automated (semi)batchwise operated reactor (Scheme 1).

In the first reaction step of the synthesis, the tri-alkylation of methyl 3,4,5-trihydroxybenzoate (methyl gallate) (**1**) to methyl 3,4,5-tri-dodecyloxybenzoate (**2**), reaction times appeared to be a function of particle size distribution of the base, potassium carbonate.[5] To deduce a scale-up rule for this challenging type of solid−liquid systems[19,20] from 1-dm^3 lab-scale to a 6000-dm^3 industrial scale the agglomeration behaviour as well as the just-suspended conditions of potassium carbonate in methyl isobutyl ketone (MIBK) were studied on different scales and with different particle sizes.

Also the dynamic behaviour of potassium carbonate during the tri-alkylation reaction was elucidated by monitoring with on-line techniques[6] such as FBRM (focused beam rotating measurement)[7] and PVM (photo video measurement).[8]

Off-Bottom Criteria

Mass transfer of solid reactants may limit reaction rates.[9,17,19,20] To illustrate this limitation, several experiments were carried out on lab-scale (100 mL) using fractions of potassium carbonate with varying particle size limits.

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(1) Discovered in the nineteenth century by Lehman and Reinitzer,[2] liquid crystals constitute a class of molecules sharing mobility and orientational order. Molecular anisotropy or a dichotomy of the structure may provide this ordering. The dichotomy relates to different structural properties (e.g., rigid and flexible)[3] or different chemical properties (e.g., hydrophobic or hydrophilic).[4] Liquid crystalline materials consist of two domains: the rigid part of the molecule, tending to aggregate into large stacks, and the flexible part, which can be derived from TDGA. Liquid crystals exhibit both fluid and solid properties over a certain temperature range. Liquid crystal display (LCD) technology has found new applications in a diverse range of consumer goods.

(2) (a) Reinitzer, F. *Monatsh. Chem*. **1888**, *9*, 421. (b) Collins, P. J. *Liquid Crystals*; IOP publishing Ltd., Princeton University Press: New Jersey, 1990; pp 24−34.

(3) Palmans, A. R. A.; Vekemans, J. A. J. M.; Fischer, H.; Hikmet, R. A.; Meijer, E. W. *Chem. Eur. J*. **1997**, *3*, 300.

(4) Schenning, A. P. H. J.; Elissen-Román, C.; Weener, J.-W.; Baars, M. W. P. L.; van der Gaast, S. J.; Meijer, E. W. *J. Am. Chem. Soc*. **1998**, *120*, 8199.

(5) Hersmis, M. C.; Spiering, A. J. H.; Waterval, R. J. M.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process. Res. Dev*. **2001**, *5*, 54−60.

(6) Lasentec website: http://www.Lasentec.com.

(7) The FBRM (focused beam rotating measurement) probe contains a laser beam that is rotating continuously with high speed, while the reflection of light by the particles is being measured. This online in situ measurement technique provides relevant data regarding the dynamic behaviour of the particles used in the process.

(8) The PVM (photo video measurement) technique consists of a probe that can be placed into the reactor. The probe continuously provides video images of the reaction mixture (even with quite dense slurries), which can be used, for example, to observe changes in particle structure.

(9) Thoenes, D. *Chemical Reactor Development: From Laboratory Synthesis to Industrial Production*; Kluwer: Dordrecht, 1994.

10.1021/op020007w CCC: $22.00

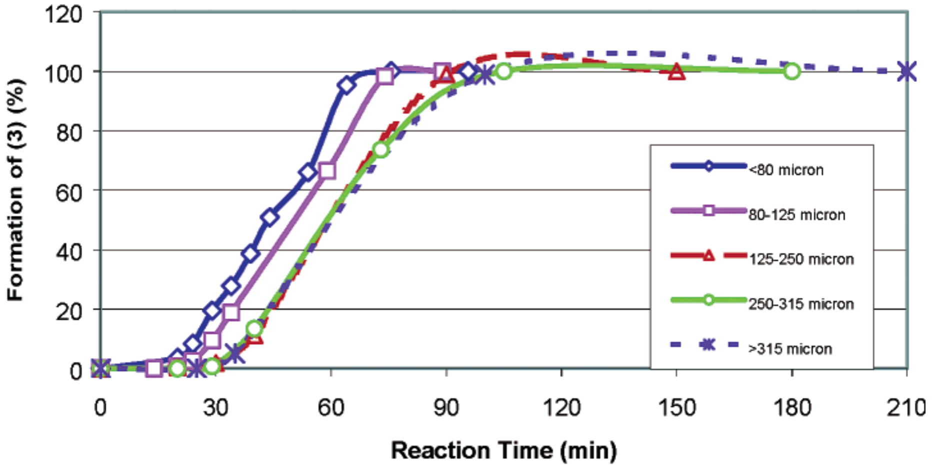

Figure 1. **Rate of tri-alkylation and particle size.**

Scheme 1

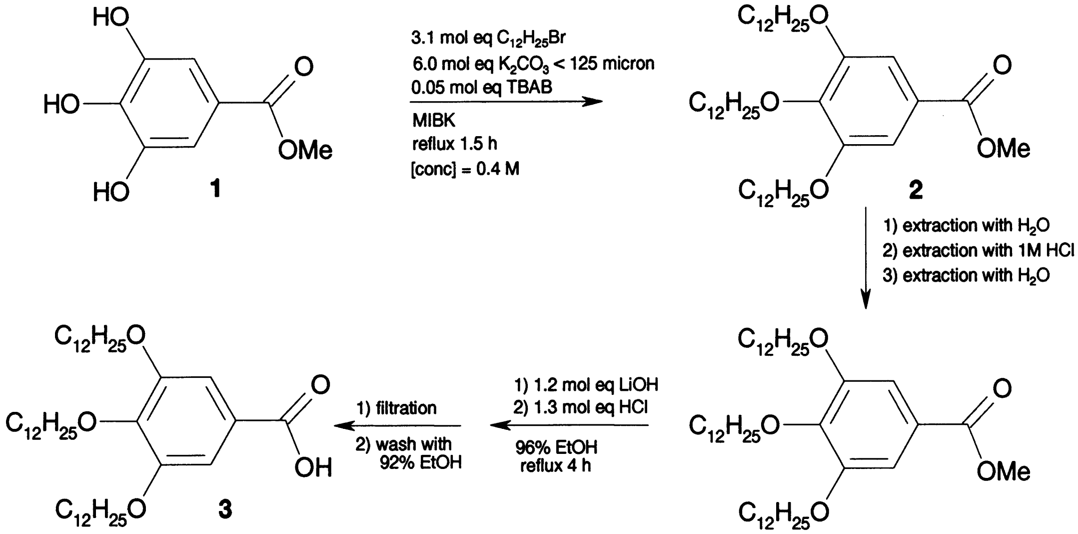

Table 1. **Assignment of fractions**

fraction (μm)	$\overline{d_p}$ (μm)	weight %	
>315	476	14.8	average d_{NV} = 54.4 μm
315−250	273	20.6	
250−125	188	17.3	
125−80	116	5.0	
<80	41	42.3	

An amount of potassium carbonate was ground during a short time and sieved to obtain five fractions. The obtained fractions are displayed in Table 1 together with the mean particle size and the weight fraction, which is a measure of the particle size distribution.

Each of these fractions was used in the synthesis of methyl 3,4,5-tridodecyloxybenzoate (**2**). The conversion of the reactions was monitored by ^{1}H NMR. The formation of the tri-alkylated product is plotted against the reaction time in Figure 1. The results in Figure 1 clearly illustrate that the use of smaller particles can make a huge difference in reaction time as a result of the larger surface area per unit volume of the reaction mixture. Figure 1 also shows that with a particle size greater than or equal to 250 μm an increase in particle size no longer increases reaction times. Therefore, the use of potassium carbonate particles with diameters less than 125 μm will be preferred. However, a calculated surface averaged particle diameter of 45.3 μm in the ground K_2CO_3 batch clearly demonstrates that sieving is not necessary to produce accelerating effects. Grinding of K_2CO_3 is sufficient for generating particles having sufficient solid/liquid surface area per unit volume of the reaction mixture to obtain the required reaction rates.

In the synthesis of **2** the system MIBK/potassium carbonate has a solid mass percentage of 29%, which is reasonably high. This heavy solid mass of the base is a concern for a smooth scale-up without undesired and unexpected effects on the production rate and product purity. A minimum stirrer rate is required to prevent the largest particles from remaining at the bottom of the reactor, the just-suspended stirrer rate. As a consequence, a positive effect of the impeller speed on the reaction rate can be obtained. Higher rates than the just-suspended stirring rates only lead to a small increase in mass transfer coefficient and often incur as prohibitive penalty on power consumption[16] since $P = N_p \rho_m N^3 D^5$, where N_p is the power number. The minimum stirrer rate to suspend all particles mainly depends on the size, geometry of the particles, density, the type and size of the stirrer, and the

Table 2. **Boundary conditions of the Zwietering equation**

parameter	range
solid mass percentage	0.5−20.0%
particle size	125−850 μm
volume reactor	3−170 dm^3
diameter reactor	15−60 cm
diameter stirrer	6−23 cm
viscosity liquid	0.3−9.3 cP

geometry of the reactor. Knowing that the dimensions of the particles will determine the minimum impeller speed provides a second reason to prefer the use of small particles above that of larger ones.

To scale up slurry systems a proper generic scale-up rule has to be found. A lot of work in this field has been done.[10] Zwietering has derived a (semi)empirical correlation that is used to calculate the just-suspended stirrer rate in various geometrically similar reactor systems, see eq 1. This correlation has been considered as the best in relating small with larger scales.[15,18]

$$N_{\mathrm{JS}} = S\left(\frac{\eta_{\mathrm{m}}}{\rho_{\mathrm{m}}}\right)^{0,1} d_{\mathrm{p}}^{\;0,2}\left(g\left(\frac{\rho_{\mathrm{s}} - \rho_{\mathrm{l}}}{\rho_{\mathrm{l}}}\right)\right)^{0,45}(100X)^{0,13}D^{-0,85} \qquad (1)$$

here S stands for a geometry parameter,[15,18,22] η_{m} for the viscosity of the mixture, ρ_{m} for the density of the mixture, $\Delta\rho/\rho$ for the relative density, d_{p} for the particle diameter, X for the solid/liquid ratio, g for the acceleration of gravity, and D for the stirrer diameter.

In eq 1 the just-suspended stirrer rate (N_{JS}) is defined as the rate at which the system obeys the so-called “off-bottom” criterion. This criterion is met if all particles will remain at the bottom of the reactor for no longer than two seconds before they will mix up into the bulk. The boundary conditions belonging to the Zwietering correlation are displayed in Table 2. Sand and sodium chloride were used as solid particles that were suspended in liquids such as water, acetone, and carbon tetrachloride. In addition, Zwietering used various types of impellers in his experiments such as propellers, vaned disks, flat blade turbines, and paddles.

In applying the equation to the MIBK/potassium carbonate system some striking differences were encountered. Most multipurpose batch reactors in the fine-chemical industry are in many cases equipped with Pfaudler retracted curved impellers (RCI) and six-bladed 45° pitched-blade down-pumping impellers. However, both stirrer types have not been covered by the boundary conditions of the experiments where the Zwietering equation is relied upon. Also the 1-dm^3 reactor is outside the range of reactor volumes used by Zwietering (3−170 dm^3). Despite these handicaps the equation would be a good starting point to develop a proper scale-up rule.

The Zwietering correlation in case of the MIBK/potassium carbonate system was verified by comparison of the experimental with the calculated values.

The experiments were performed on three different scales, that is, 1, 10, and 50 dm^3. The reactor configurations are presented in Table 3. The two impellers types used are depicted in Figure 2.

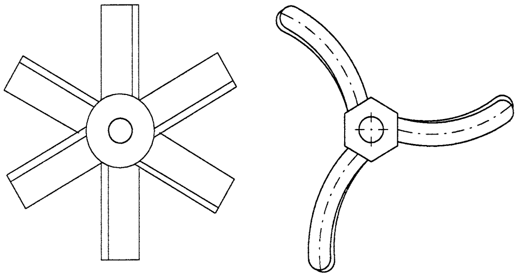

Figure 2. **Six-bladed 45° pitched-blade impeller (left) and Pfaudler RCI (right).**

The results are collected in Tables 4 and 7. The just-suspended stirrer rates of the performed experiments have also been calculated using the Zwietering equation.[11] The results of the calculations are shown in Table 4.

From the data in the tables it can be concluded that the difference between the experimental and calculated values is much larger on 1-dm^3 scale than it is on 10-dm^3 scale, and in both cases the experimental values are lower than the calculated ones. As mentioned earlier Zwietering did not use a Pfaudler and a pitched-blade impeller, and he did not perform experiments on a 1-dm^3 scale. Especially at reactor volumes of 1 dm^3 and less the inner wall may have a considerable effect on the flow pattern of the suspension and therefore on the minimum stirrer rate. The latter is probably the main reason for the difference in deviation between the 1- and 10-dm^3 systems. The difference between both impellers revealed in the experimental values is indicating a large effect of the stirrer-type chosen. On the other hand potassium carbonate particles have a porous structure that easily contains an amount of solvent that may influence the behaviour of the particles in the flow. The effective density of those particles becomes lower in comparison with that of hard spheres used by Zwietering, thus decreasing the just-suspended stirrer rate.[11] Simultaneously, viscous effects become more important when particles get smaller, because the friction factor decreases with increasing particle diameter according to Stokes’s law, and this will introduce some error.[16,21]

From the above results it can be concluded that the MIBK/K_2CO_3 system used has too many differences in boundary conditions to meet the Zwietering equation exactly.

Scale-Up

To determine an appropriate scale-up rule the measured data on 1- and 10-dm^3 scale were taken to predict and validate the just-suspended stirrer rate on 50 dm^3. The just-suspended stirrer rate was measured for different particle size

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(10) Zwietering, T. N. *Chem. Eng. Sci.* **1958**, *8*, 244−253.

(11) For this purpose the viscosity of the suspension was determined using the relation of Batchelor[12] that results in a value of 0.86×10^{-3} Pa·s. The density of the potassium carbonate was corrected due to the porosity ($\epsilon = 0.42$) resulting in a value of 1660 kg/m^3. Other than that a liquid density of 801 kg/m^3, a mixture density of 1055 kg/m^3 and a solid/liquid ratio of 0.41 were used. The geometry factor S mainly depends on the reactor diameter/impeller diameter ratio and reactor diameter/clearance ratio and in this case a value of 4 is chosen according to Zwietering.[10,15,18] Because of the geometric similarity of the reactors S remains 4 at all scales, and so only the stirrer diameter and the average particle diameter are variables.

Table 3. **Dimensions of the reactors**

reactor volume	$50\ dm^3$	$10\ dm^3$	$1\ dm^3$
reaction volume	±30 dm^3	±6 dm^3	±600 mL
diameter reactor (T)	30 cm	20 cm	10 cm
diameter stirrer (D)	15 cm	10 cm	5 cm
clearance	3 cm	2 cm	1 cm
liquid level	33.8 cm	19.3 cm	7.73 cm
diameter shaft	10 mm	10 mm	10 mm
position of baffles (if 2)	1/8T (0° and 180°)	1/8T (0° and 180°)	1/8T (0° and 180°)
position of baffles (if 3)	1/8T (0°, 90°, 180°)	1/8T (0°, 90°, 180°)	1/8T (0°, 90°, 180°)
vessel base shape	flat	flat	flat

Table 4. **Experimental and calculated just-suspended stirrer rates on 1 and 10 dm^3**

impeller →	45° pitched-blade		Pfaudler RCI		calculated		FBRM-measurements 45° pitched-blade	
	by visual inspection							
	N_{JS} (rpm)		N_{JS} (rpm)		N_{JS} (rpm)		particle size (μm)	N_{JS} (rpm)
fraction (μm) ↓	1 dm^3	10 dm^3	1 dm^3	10 dm^3	1 dm^3	10 dm^3		10 dm^3
>315	725	440	671	450	762	422	–	–
315−200	593	355	520	400	681	378	316	350
200−125	424	285	389	325	633	351	–	–
125−80	285	–	281	–	574	–	–	–
<80	216	200	217	185	467	259	86	200

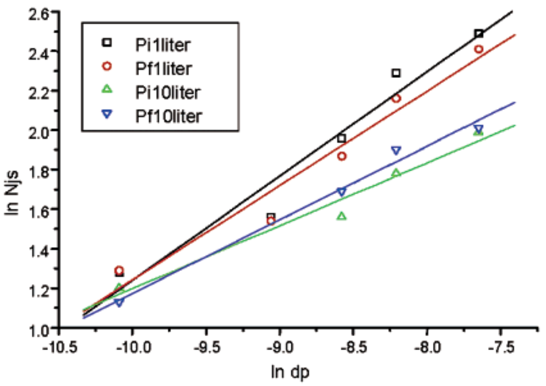

Figure 3. **Linear regression analysis (Pi = pitched-blade, Pf = Pfaudler).**

distributions allowing determination of the particle size effects. Equation 2 can be used to plot the experimental values and to determine the exponent of the particle size:

$$N_{JS} = bd_p^{\ a} \Longrightarrow \ln(N_{JS}) = \ln(b) + a\ln(d_p) \qquad (2)$$

where a is the exponent of the particle size and b is a constant that equals:[10]

$$S\left(\frac{\eta_m}{\rho_m}\right)^{0,1}\left(g\left(\frac{\rho_s - \rho_l}{\rho_l}\right)\right)^{0,45}(100X)^{0,13}D^{-0,85}$$

The data were fitted to eq 2 with the help of linear regression. Figure 3 clearly illustrates that the slope of the 1-dm^3 system is steeper than that of the 10-dm^3 system, which implies a higher exponent of the particle size at 1 dm^3 as a consequence of the wall effects mentioned earlier. The values[13] of ln(b) and a are collected in Table 5.

To come up with a scale-up rule holding for several scales, the corresponding differences in response of a system are to be defined rather than to adapt that system to obey the Zwietering correlation. If the Zwietering equation holds to scale-up a defined system, only the stirrer diameter should not be a constant parameter in geometric scale-up and eq 3 would arise:

Table 5. **Coefficients of particle size**

system	ln(b)	a	R^2
pitch 1L 2b	6.517	0.528	0.949
pitch 10L 2b	4.378	0.318	0.967
Pfaud 1L 2b	6.001	0.476	0.951
Pfaud 10L 2b	4.901	0.373	0.988

$$\left(\frac{N_{JS}}{D^{-0,85}}\right)_{small} = \left(\frac{N_{JS}}{D^{-0,85}}\right)_{large} \qquad (3)$$

In the MIBK/K_2CO_3 system the results showed that the wall effects and others such as the particle size and structure and also the stirrer-type account for the deviations. For this reason a constant Q has been introduced that will include the geometry factor and all deviations. Equations 4 and 5 display the adjusted Zwietering equation and scale-up rule.

$$N_{JS} = Q\left(\frac{\eta_m}{\rho_m}\right)^{0,1} d_p^{\ 0,2}\left(g\left(\frac{\rho_s - \rho_l}{\rho_l}\right)\right)^{0,45}\left(100\frac{M_s}{M_l}\right)^{0,13} D^{-0,85} \qquad (4)$$

$$\left(\frac{N_{JS}}{D^{-0,85}}\right)_{small} = \frac{Q_{large}}{Q_{small}}\left(\frac{N_{JS}}{D^{-0,85}}\right)_{large} \qquad (5)$$

The parameter Q can be calculated by comparing the experimental with the calculated values and by adjusting the geometry factor S of 4 (used in the calculations) to the correct

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(12) Larson, R. G. *The Structure and Rheology of Complex Fluids*; Oxford University Press: New York, 1999; pp 265−267.

(13) In theory the geometry factor S can be calculated from b, provided that there is a small inaccuracy. Here the inaccuracy is too high in the linear fit to obtain a reliable geometry factor.

Table 6. **Adjusted "geometry factor" Q**

fraction (μm)	pitched-blade			Pfaudler RCI		
	1 dm^3	10 dm^3	$Q_{10\mathrm{dm}^3}/Q_{1\mathrm{dm}^3}$	1 dm^3	10 dm^3	$Q_{10\mathrm{dm}^3}/Q_{1\mathrm{dm}^3}$
>315	3.81	4.17	1.09	3.52	4.27	1.21
200−315	3.48	3.76	1.08	3.05	4.23	1.39
125−200	2.68	3.25	1.21	2.46	3.70	1.50
80−125	1.99	–	–	1.96	–	–
<80	1.85	3.09	1.67	1.86	2.86	1.54

Table 7. **Predicted[a] and Experimental N_{JS} on 50 dm^3-scale**

particle size (μm)	pitched-blade impeller	
	predicted	experimental
>315	311	306
<80	141	136

[a] Predicted from N_{JS} a 10-dm^3 scale and eq 5 with $Q_{\mathrm{large}} = Q_{50\mathrm{dm}^3}$, $Q_{\mathrm{small}} = Q_{10\mathrm{dm}^3}$, and $Q_{50\mathrm{dm}^3} = Q_{10\mathrm{dm}^3}$.

Table 8. **Predicted just-suspended stirrer rates on 6000-dm^3 scale**

	$V = 6.3$ m^3, $D = 1.1$ m	
particle size (μm)	pitched-blade N_{JS} (rpm)	Pfaudler RCI N_{JS} (rpm)
>315	57	59
315−200	46	52
200−125	37	42
<80	26	24

value of Q to obey the experimental values. The results are depicted in Table 6 for two impellers. It is clearly illustrated that the largest difference turns up at small scale with small particles. As expected, in this case this configuration does not obey the boundary conditions of Zwietering.

A scale-up rule, see eq 5, from 1 dm^3 to 10 dm^3 for the MIBK/K$_2$CO$_3$ system with $Q_{10\mathrm{dm}^3}/Q_{1\mathrm{dm}^3}$ as a correction factor to deal with wall effects on 1 dm^3 has now been derived. The following step was to verify the predicted just-suspended stirrer rate on 50-dm^3 scale. No significant wall effects were expected on a 10-dm^3 scale; thus, for scaling up from 10 dm^3 to 50 dm^3 eq 6 holds, see also Table 7:

$$\frac{Q_{50\mathrm{dm}^3}}{Q_{10\mathrm{dm}^3}} = 1 \qquad (6)$$

This makes $Q_{Vr>10\mathrm{dm}^3}/Q_{Vr=1\mathrm{dm}^3}$ equal to $Q_{10\mathrm{dm}^3}/Q_{1\mathrm{dm}^3}$ with its values collected in Table 6.

The predicted and experimental minimum stirrer rates for the pitched-blade impeller and two fractions of different particle size are given in Table 7, which demonstrates a good agreement between calculations and experimental observations.

In fine-chemical operations 6000-dm^3 reactors are often used for solid/liquid systems. For practical reasons (motor power limitation and forces exerted on the impeller shaft) the stirrer rate for these reactors is limited to a value of 120 rpm. Verifying that the lab-scale 1-dm^3 reactor is geometrically similar to the large-scale batch reactor, eq 5 may be used to establish whether there is power input limitation or not. For the heavy particles that are the most critical ones to obtain off-bottom conditions, no power input limitation was found as is demonstrated by the results for a 6000-dm^3 scale collected in Table 8.

In brief, an off-bottom criterion tool for slurries with relatively high-density particles has been developed relating 1-dm^3 scale to larger scales. As a consequence, no difficulties regarding off-bottom will be expected in the scale-up of the tri-alkylation process of **1**.

Lasentec

An earlier attempt to get insight into the global reaction kinetics of the tri-alkylation has failed probably because of unpredictable dynamic behaviour of potassium carbonate in the solid/liquid system for three consecutive reaction steps of the alkylation. Therefore, the alkylation reaction and for comparison reasons some experiments with a MIBK/K$_2$CO$_3$ system were performed on 10-dm^3 scale, monitoring the conversion and the dynamic behaviour of the solids using the Lasentec[6] techniques FBRM[7] and PVM.[8] The principle of the FBRM technique is illustrated in Figure 4. As a result a distribution of chord lengths is obtained that provides information about number and size of the particles in suspension.

In the first Lasentec FBRM experiment the behaviour of potassium carbonate particles in MIBK on a 10-dm^3 scale was investigated. In Figure 5 the time history of four different chord length ranges is displayed during the experiment without reaction.[14] Note that all four lines have a different y-axis scale and they can therefore not be compared but only give qualitative insights or trends.

In the experiment potassium carbonate was used as such consisting of a huge number of particles with a diameter above 315 μm and relatively few smaller ones. The experiment was started at room temperature and a stirring rate of 400 rpm. Subsequently, after a period of 150 min the suspension was allowed to heat up. At this point the number of small particles has increased in contrast to the slight decrease in the number of large particles. Pulverisation by the high shear rates will most probably be responsible for this effect. Between 150 and 200 min all fractions show an increase in the number of particles, even the larger ones. Thus, higher temperatures cause the large particles (above 250 μm) to fall apart into smaller ones. Although in the

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(14) One remark about a chord length has to be made. It is not the same as a particle diameter, but in the case of sphere-like shapes it will be a tolerable approximation.

(15) Armenante, P. M.; Nagamine, E. U. *Chem. Eng. Sci.* **1998**, *53* (9), 1757−1775.

(16) Harnby, N., Edwards, M. F., Nienow, A. W., Eds. *Mixing in the Process Industries*, 2nd ed.; Butterworth-Heinemann: Oxford, 1992; pp 365−411.

(17) Doraiswamy, L. K.; Sharma, M. M. *Heterogeneous Reactions*; Wiley: New York, 1984; Vol. 2.

(18) Chapman, C. M.; Nienow, A. W.; Cooke, M.; Middleton, J. C. *Chem. Eng. Res. Des.* **1983**, *61*, 71−81.

(19) Atherton, J. H. *Trans. 1 ChemE, part A* **1993**, *71*, 111−118.

(20) Atherton, J. H.; Carpenter, K. J. *Process Development: Physicochemical Concepts*; Oxford Chemistry, Primers No. 79; Oxford University Press: New York, 1999.

(21) Einenkel, W. D.; Mersmann, A. *Verfahrenstechnik* **1977**, *11* (2).

(22) Wu, J.; Zhu, Y.; Pullum, L. *Chem. Eng. Res. Des.* **2001**, *79* (A8), 989−997.

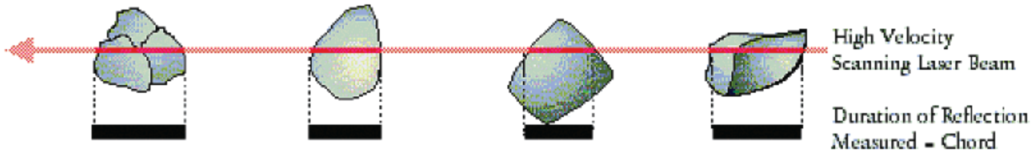

Figure 4. **Principle of the FBRM technique.**

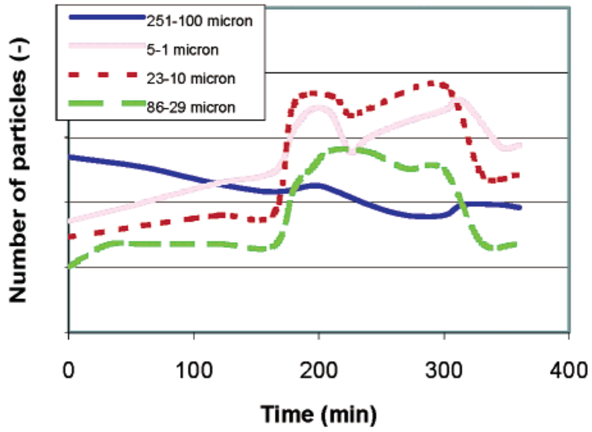

Figure 5. **K_2CO_3 behaviour in MIBK.**

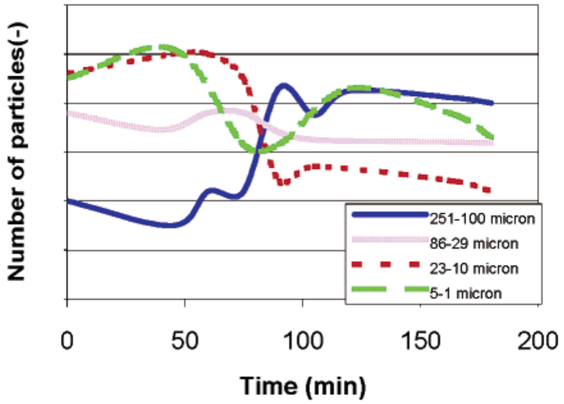

Figure 6. **K_2CO_3 behaviour during tri-alkylation.**

interval between 200 and 300 min the stirrer rate is reduced to 300 rpm (210 min), pulverisation again takes place. In the following cooling period to 25 °C starting at 300 min agglomeration of fine particles occurs. The temperature plays an important role in the agglomeration/deagglomeration of the potassium carbonate particles during the overall process. The results were reproducible in a duplo experiment.

In a second Lasentec FBRM experiment the synthesis of **2** was performed on 10-dm^3 scale. In this case not only the stirring rate and temperature have influence on the amount and size of the particles but also various reaction parameters. During the tri-alkylation 3 of 6 mol equiv of the initially present K_2CO_3 are consumed: KBr and $KHCO_3$ are formed, having a major influence on the particle size distribution. The results of the measurements with the FBRM-probe are depicted in Figure 6.

In the first 45 min the reaction mixture was heated to 80 °C. Analogous results were obtained as in the MIBK/K_2CO_3 experiment without reaction. Large particles fell apart into smaller ones. At a temperature of 80 °C the tri-alkylation reaction initiated, and this resulted in a decrease of the number of small particles of potassium carbonate that react first. In the meantime very large particles (above 250 μm) are still disintegrating into parts of about 250−100 μm as a consequence of a combination of heating and shear. When the reflux temperature (115 °C) is reached after 75 min, the number of smallest particles increases probably due to interference with exploding bubbles in the porous structure of K_2CO_3 and the formation of other salts (1 mol K_2CO_3 gives 1 mol KBr and 1 mol $KHCO_3$). After a period of 90 min the reaction was complete, and the reaction mixture was stirred for several hours. In the subsequent time interval of 90−170 min the temperature dropped to 82 °C, having obviously only a major effect on the smallest particles. All results obtained with the FBRM technique were confirmed by PVM video images. The isolated yield of the reaction was 96% with a 99% purity.

Another range of application of the FBRM probe is the determination of just-suspended stirrer rates to meet the off-bottom criterion. A good approximation could be achieved by measuring the chord length distribution. While reducing the stirrer rate, reflections of large particles would no longer be measured at a certain value as a result of the deposit of those particles on the bottom of the reactor. At that particular point the just-suspended stirrer rate could be determined.

In conclusion, the Lasentec FBRM and PVM probes were demonstrated to be powerful tools to improve understanding the heterogeneous reaction systems in a short time.

Conclusions

In this report the dynamic behaviour of potassium carbonate in MIBK has been studied in detail to define new design tools to increase the development speed of this type of solid/liquid systems, particularly in heterogeneous catalysis. An off-bottom criterion tool has been developed, relating 1-dm^3 scale to larger scales. On the basis of experiments at 1- and 10-dm^3 scale this scale-up rule was verified on a 50-dm^3 scale and used to predict the just-suspended stirrer rate on an industrial scale of 6000 dm^3. As a result no driving motor power limitation was expected on this scale.

The Lasentec FBRM and PVM probes were demonstrated to be powerful tools to improve a quick understanding of heterogeneous reaction systems. The following conclusions can be drawn from the results obtained with these techniques: (i) potassium carbonate particles pulverise under stirring, (ii) deagglomeration of particles occurs when the temperature is increasing, while agglomeration takes place when the temperature is decreasing, and (iii) the FBRM technique allows determination of off-bottom criteria.

Experimental Section

All reagents and solvents were used without further purification. The water content in the solvent MIBK (4-methyl-2-pentanone, Aldrich) was analysed by a Karl-Fisher titration and was within specification. All proton NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer with TMS as internal standard. Large-scale reaction was carried out in a 10-dm^3 fully automated (semi)-batch-wise operated reactor. This Belatec reactor is able to perform under a variety of conditions: a temperature range from −50 to 200 °C, solvent distillation, different agitator types, a pressure range from 0.03 to 1.1 bar. The reactor is controlled by a PLC, a special computer, which monitors physical data (batch history), and secures optimal process and safety conditions.

Determination of Particle Sizes of Potassium Carbonate. Potassium carbonate was ground for 1 min and was separated into fractions by sieving. Four different sieves were used in the separation, which took 0.5 h: 315, 250, 125, and 80 μm. SEM photomicrographs were taken from all of the five fractions, which were used to determine the average particle diameter. Each photo presented a representative amount of particles of a fraction. The boundaries of the fractions were checked by visual inspection of the SEM-photos and turned out to be in good agreement with the particle range shown. The average particle size was calculated by determining the projected area of the particles on the SEM-photo and treating them like spheres.

Procedure for Just-Suspended Stirrer-Rate Measurements. The experiments were performed on three different scales. Geometrically similar glass reactors were built having volumes of 1, 10, and 50 dm^3, respectively. The reactor configurations are presented in Table 3. On 1-dm^3 scale in each experiment 500 mL of MIBK and 166 g of K_2CO_3 were used. A similar ratio was used on 10-dm^3 scale, where on 50-dm^3 scale 20 dm^3 of MIBK and 6.005 kg of K_2CO_3 were used. In the synthesis of **2** at the onset of the reaction the same ratio is used as in the 1- and 10-dm^3 configurations, but when bromododecane has been added to the mixture, the solid/liquid ratio will decrease, and this has a positive influence on the just-suspended stirrer rate. Ten experiments were performed on 1- and 10-dm^3 scale. In these experiments the stirrer type and the particle size were varied (see five fractions of potassium carbonate as given in Table 1). On 10-dm^3 scale no experiments were performed with particle sizes of 80−125 μm for practical reasons. Also the number of baffles was varied during the experiments. No major distinction in the final results was observed. Consequently, only the two-baffled system was considered. Just the pitched-blade impeller and the fractions with the smallest and largest particle sizes were used in two experiments on 50-dm^3 scale. In all experiments the bottom of the reactor was illuminated by a light bulb, and observations were made by visual inspection. For this reason all observed values of the just-suspended stirrer rate are the mean values of five to ten observations starting alternatively from high or low stirrer speed which then had been decreased and increased respectively until the off-bottom condition was met.

Procedure for the Synthesis of Methyl 3,4,5-tri-dodecyloxybenzoate (2). Methyl gallate (**1**) (Fluka, 2.95 g, 16 mmol), K_2CO_3 (13.27 g, 96 mmol), tetrabutylammonium bromide (TBAB, Fluka, 0.26 g, 0.8 mmol), MIBK (40 mL), and 1-bromododecane (Acros, 12.37 g, 50 mmol) were added to a 100-mL three-necked flask. Subsequently, the reaction mixture was heated to reflux and stirred for 2 h. The conversion of the reaction was monitored by TLC (eluent hexane//ethyl acetate 24:1) and ^{1}H NMR. Upon completion the brown mixture was cooled below 100 °C, and water (40 mL) was added. The aqueous layer was separated and the organic layer was washed with water (40 mL), diluted HCl solution (40 mL 1.0 M), and water (40 mL) again. Solvent evaporation from the resulting organic layer gave a yellow oil (11.7 g), which crystallises at approximately 40 °C to afford a light brown solid (**2**). Purification by column chromatography (flash SiO_2; eluent hexane//ethyl acetate 96:4) yielded a white powder (10.2 g): mp 43.2−43.8 °C. ^{1}H NMR (acetone-d_6, 300 MHz): $\delta = 7.27$ (s, 2H, *o*-H), 4.11−3.98 (m, 6H, OCH_2), 3.85 (s, 3H, OCH_3), 1.90−1.70 (m, 6H, $OCH_2\underline{CH_2}$), 1.55−1.20 (m, 54H, $(CH_2)_8$), 0.86 (t, 9H, CH_3). Anal. Calcd for $C_{44}H_{80}O_5$ (MW 689.12): C 76.69, H 11.70. Found: C 77.3, H 11.8.

Alternative Purification of Methyl 3,4,5-tri-dodecyloxybenzoate (2). Crude yellow **2** (27.4 g) was heated above its melting point and poured gently into 1 L of methanol (tech) under stirring. The initial yellow clusters were dispersed, and a white precipitate was formed within 1 h. Filtration yielded 97% pure (based on NMR analysis) material, yield: 25.1 $g = 91\%$.

Master Recipe to Synthesise 3,4,5-Tri-dodecyloxybenzoic Acid (3). The recipe on 10-dm^3 scale has been described previously.[5]

Analysis of FBRM Data. The FBRM probe gives a chord length distribution in graphical form. The maximum value of the distribution, which is an indication of the particle size, can easily been read from the data. We measured all fractions of K_2CO_3 with the FBRM probe to determine whether the obtained distributions were comparable with sphere-like particles. We have concluded that in our case the FBRM data can be used to give an approximation of the real particle size distribution.

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