EFFECTS OF MIXING IN PHARMACEUTICAL PRODUCT DESIGN

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SUMMARY

The product design procedure is considered in this work in relation to process design and choice of equipment with a goal to match the desired product specification. The procedure is based on inverse analysis and scale up methods; it includes mathematical modeling and experimental investigations. Two problems of pharmaceutical product design are presented in detail, namely manufacturing of pure products at high reaction selectivity by applying clever mixing procedures, and designing mixing strategy to control particle size distribution (PSD).

The problem of reactive mixing is solved in this work using hierarchy of methods, starting from a simple time scale analysis, applying then directly mechanistic models, and finally combining mechanistic models with CFD. Examples of CFD simulations and related experimental data for test reactions are presented to illustrate proposed methodology.

The problem of manufacturing particles characterized by a well defined size distribution (PSD) is discussed and methods of process design are presented. In particular methods for prediction of PSD in the case when precipitation is carried out using supercritical fluids are considered; mathematical modeling is used afterwards to interpret related experimental data, illustrating influence of process parameters on PSD. More traditional processes (reactive precipitation) are briefly considered for comparison as well.
INTRODUCTION

The product design procedure consists of defining needs that the product should fulfil, generating and selecting ideas to meet these needs, defining product properties and finally deciding how the product should be manufactured in commercial quantities (Cussler and Moggridge 2001). In this publication the last problem is considered, namely the process design and choice of equipment are applied to match the desired product specification. Solution of these problems requires application of complex procedures that are based on inverse analysis and scale up methods. The procedure proposed in this work is based on time scale analysis and includes as well detailed mathematical modelling and experimental investigations.

To illustrate proposed method two fundamental product design problems are considered: manufacturing of pure products at high reaction selectivity by applying clever mixing strategy and designing mixing procedures to control particle size distribution (PSD).

In the pharmaceutical industry, many chemical reactions leading to desirable intermediate and end-products are accompanied by side reactions producing undesired by-products. By-products decrease reaction yield and complicate product separation. To improve selectivity, the competition between reactions can be enhanced; one can either add a homogeneous catalyst that increases the rate of desired reaction or an inhibitor that decreases the rate of side reactions. This creates again separation problems; moreover, when the rate constant of desired reaction is increased, its rate becomes controlled by mixing, rather than by the reaction kinetics. Competition is then between the mixing-controlled desired reaction and the slower side-reactions (Baldyga and Bourne 1999). The problem of reactive mixing arises, and it will be solved in this work using hierarchy of methods; reactive mixing will be analyzed using time scales of mixing and chemical reaction and simulated using mechanistic models and CFD. To illustrate proposed methodology examples of CFD simulations and related experimental data for fast test reactions will be presented.

In many pharmaceutical applications particles with strictly defined size distribution (PSD) and morphology are required. For example efficient systemic delivery using inhalation requires aerosol particles to be designed with an aerodynamic diameter between 1 and 5 µm to maximize deposition in the alveolar region, whereas the aerodynamic diameter depends on the geometric particle size and the particle dynamic shape factor. At this point the aim of this work is to show how one can predict PSD when supercritical fluids are used to precipitate particles; more traditional processes (milling, traditional crystallization and precipitation) will be briefly considered for comparison as well.

SELECTIVITY OF CHEMICAL REACTIONS: MATERIALS AND METHODS

Many desirable chemical reactions that are of importance for pharmaceutical industry are accompanied by side reactions and undesired by-products, which waste raw materials and complicate product isolation, its purification and formulation. In previous section enhancing of the competition between reactions by applying catalysis has been mentioned. Here we concentrate on controlling reaction by mixing; this is because controlling the product distribution by reactive mixing can lead to economical and ecological benefits at much smaller costs than applying catalysts. Namely, a clever interplay between mixing and chemistry that can be expressed using equations describing kinetics of chemical reactions and expressions describing mixing rates can lead to significant improvements in selectivity. “Reactive mixing” or “mixing on the molecular scale” has been described and explained in detail in several books and papers, see for example Baldyga and Bourne (1999), Bourne (2003) and Fox (2003).

There are many very complex schemes of multiple reactions that are sensitive to mixing. However, all multiple reaction schemes can be considered to be made up of a combination of two primary reaction types, competing or parallel, and consecutive or series. (Levenspiel 1962). Hence, to study effects of operation mode and process conditions on reaction selectivity one should start from such elementary building blocks that can form “mixed” reaction schemes. That is why in this paper the following schemes of parallel, Equation 1
\[ A + B \xrightarrow{k_1} R, \ A + C \xrightarrow{k_2} S \]  

(1) and competitive-consecutive, Equation 2, second order reactions are considered for \( k_1 >> k_2 \).

\[ A + B \xrightarrow{k_1} R, \ R + B \xrightarrow{k_2} S \]  

(2)

Some useful simple rules for contacting reactants are presented by (Levenspiel 1962). For example in the case of reaction scheme given by Equation 2 adding \( A \) to \( B \) results in creation of the undesired by-product \( S \). On the other hand slow addition of \( B \) to \( A \) results in negligible production of \( S \); of course the number of \( B \) moles must be then smaller than the number of \( A \) moles applied. Similarly to avoid the second, slower reaction in scheme given by Equation 1, one should add slowly \( A \) to premixture of \( B \) and \( C \), and not vice versa. Such simple rules are, however, only valid assuming that there is an ideal mixing down to the molecular scale. Notice that when the first reaction is very fast it can be controlled not by reaction kinetics characterized by the rate constant \( k_1 \) but by the rate of mixing on the molecular scale; and then we have competition between the mixing process controlling the first reaction and the chemical kinetics controlling the second reaction.

The mixing-sensitive reactions are usually classified by comparing time constants or so called characteristic times for mixing and chemical reaction. For example in the case of parallel reactions, Equation 2, we have two time constants characterizing reaction kinetics:

\[ \tau_{R1} = \frac{1}{k_1\langle(c_A) + \langle c_B \rangle \rangle}, \ \ \tau_{R2} = \frac{1}{k_2\langle(c_A) + \langle c_C \rangle \rangle} \]  

(3) where \( \langle c_i \rangle \) represents a local average concentration of reactant \( "i" \). Often as \( \langle c_i \rangle \) the “un-reacted” reactant concentration \( \langle c_{Ri} \rangle \) is applied in Equation 3.

The process of mixing, or contacting reactants, can be represented by several time constants. The largest one represents macromixing or bulk blending. The macromixing process can be well characterized by macroscopic flow pattern. Related time constant reflects the time necessary to distribute the fresh feed over the vessel without, however, reducing concentration fluctuations. As a simple characteristic of macromixing in stirred tank one can use the circulation time, \( \tau_C \), equal to the tank volume, \( V_T \), divided by the circulation capacity.

\[ \tau_C \equiv \frac{V_T}{ND_{imp}^2} \]  

(4)

In Equation 4 \( N \) represents stirrer frequency and \( D_{imp} \) is the impeller diameter.

When reactant \( B \) is fed into the tank with flow rate \( Q_B \), then the time constant for reactant distribution by turbulent diffusion reads:

\[ \tau_D = \frac{Q_B}{\bar{u}D_T} \]  

(5) where \( D_T \) represents turbulent diffusivity and \( \bar{u} \) is the local fluid velocity. The diffusing large eddies or spots rich in fresh reactant are first disintegrated by inertial velocity fluctuations (time constant \( \tau_S \))

\[ \tau_S = \frac{3}{4} \left( \frac{A^2}{\epsilon} \right)^{1/3} \]  

(6) then the lamellar structures are formed in the process of engulfment (time constant \( \tau_E \)),

\[ \tau_E = 17 \left( \frac{\nu}{\epsilon} \right)^{1/2} \]  

(7) and finally the fluids are mixed on the molecular scale by molecular diffusion in deforming laminae; the last process is characterized by

\[ \tau_{DS} = 2 \left( \frac{\nu}{\epsilon} \right)^{1/2} \text{arcsin} h(0.05Sc) \]  

(8) where \( \epsilon \) represents the rate energy dissipation, \( A \) is the integral scale of turbulence (scale of energy containing eddies), \( \nu \) is the kinematic viscosity and \( Sc \) represents the Schmidt number (\( Sc = \nu/D \)), where \( D \) is the molecular diffusivity. The reaction is regarded as instantaneous when the reaction time constant is several orders of magnitude shorter than that for mixing, and then its rate is determined by mixing. For the reaction time constant orders of magnitude longer than that for mixing the reaction is regarded as slow and is not affected by mixing. Many reactions are considered as fast, having time constants for reaction and mixing of similar magnitude; such reactions are affected by mixing but of course less than the instantaneous reactions.

Analysis of time constants is very useful to check which of the sequence of mixing processes
can directly or indirectly affect the course of chemical reactions. For example when the feed time to the semibatch reactor or the mean residence time in the continuous flow reactor are of the order of circulation time, the relevant scale of inhomogeneity is macroscopic over the whole vessel; for sufficiently slow addition one can assume uniform concentration of the bulk and model the region close to the feed. Coming back to the case of reacting systems, Equations 1 and 2, in any applications the first reaction can be regarded as instantaneous or fast, and the second reaction fast or slow.

As an example of parallel reactions we consider in what follows neutralization and simultaneous ester hydrolysis, when concentrated sodium hydroxide solution (A) has been added to a solution containing hydrochloric acid (B) and ethyl chloroacetate (C) with the first reaction instantaneous and the second one fast, and with \( k_1 \) about 8 orders of magnitude higher than \( k_2 \).

\[
\begin{align*}
\text{NaOH} + \text{HCl} & \overset{k_1}{\rightarrow} \text{NaCl} + \text{H}_2\text{O} \\
\text{NaOH} + \text{CH}_2\text{CICOOC}_2\text{H}_5 & \overset{k_2}{\rightarrow} \text{CH}_2\text{CICOONa} + \text{C}_2\text{H}_5\text{OH}
\end{align*}
\]

Experiments illustrating effect of mixing conditions on selectivity of parallel reactions were carried out in the stirred tank reactor operated either in a semibatch or continuous mode as shown in Figure 1.

The limiting reagent A is gradually added to premixture of B and C, which is either added through the second feed port (a continuous-flow stirred-tank reactor) or present in the stirred tank (a semibatch reactor). The product distribution is denoted by \( X_S \) and represents the fraction of the sodium hydroxide A that reacts with the ethyl chloroacetate, C.

\[
X_S = \frac{\overline{c_{C_0}} - \overline{c_C}}{c_{A_0}}
\]

where the overbar means here an average over the whole tank. Notice that for fast enough mixing \( X_S \to 0 \), and for very slow mixing, when both reactions become mixing controlled, and for equivalent amounts of B and C, \( X_S \to 0.5 \).

![Figure 1. Schematic presentation of the stirred tank reactor applied in experiments.](image-url)
Experiments in the case of the continuous-flow system were carried out for two sets of feed concentrations: (1) $c_A = 1 \, \text{mol/dm}^3, \, c_{B0} = c_{C0} = 0.02 \, \text{mol/dm}^3$, and (2) $c_A = 0.45 \, \text{mol/dm}^3, \, c_{B0} = c_{C0} = 0.009 \, \text{mol/dm}^3$. In the case of the semibatch reactor the stirred tank containing initially $V_{BC,0} = 0.02079 \, \text{m}^3$ of the premixture of HCL (B) and CH$_2$CICOOC$_2$H$_5$ (C), each of concentration 40 mol m$^{-3}$, whilst the related volume of NaOH solution added ($c_A = 2000 \, \text{mol m}^{-3}$) was 2% of the tank capacity ($V_{A0} = 4.16 \times 10^{-4} \, \text{m}^3$). The feed point was located in the impeller discharge stream at the impeller disc level, at a distance of 0.09 m from the axis (Fig. 1).

Experiments were carried out for the feed time or residence time between 8 and 20 minutes, for the rotational stirrer speed in the range $106 \, \text{rpm} \leq N \leq 214 \, \text{rpm}$. Simulations of the flow pattern were performed using the CFD code FLUENT, version 6.0, using standard k–ε model and the multiple reference frame approach. Typical results illustrating flow pattern are presented in Figure 2. As shown by (Baldyga et al. 2001) and (Baldyga and Makowski 2004), there is a good enough agreement between LDA experimental data and model predictions for the flow pattern.

To interpret experimental data one can use the time constant analysis based on Equations 3–8, and predict selectivity using either the mechanistic model or the CFD based conditional moment closure.

Let us start from the mechanistic model. Under typical process conditions for mixing of aqueous solutions the process of viscous-convective engulfment controls mixing below the Kolmogorov microscale. The fluid containing considered reagent is not distributed uniformly (because mesomising is not ideal) but rather concentrated in large spots of the size within the inertial-convective subrange of turbulence. Denoting by $X_U$ the local volume fraction of such spots, one gets the micromixing equations for the volume fraction of mixed on the molecular scale fluid in the form

$$
\frac{dX_i}{dt} = EX_i(1-X_i/X_U)
$$

(10)

Where $E=1/\tau_E$ and

$$
\frac{dc_i}{dt} = E(1-X_i/X_U)(\langle c_i \rangle - c_i)+r_i,
$$

(11)

where $\langle c_i \rangle$ refers to the immediate surroundings of the reaction zone outside the micromixed region, but within the reactant spots forming the inertial-convective subrange. Evolution of the volume fraction $X_U$ is described by the mesomixing equation

$$
\frac{dX_U}{dt} = \frac{X_U(1-X_U)}{\tau_S}
$$

(12)

To account for effects of the macroscale distribution of the properties of turbulence on

![Figure 2. The flow pattern in the stirred tank; notice effect of the feed pipe on the flow.](image-url)
mixing two approaches are used. One can use a simple one-dimensional single-circulation-loop plug flow model with the circulation capacity calculated from the circulating number or apply the same model of mixing but instead of the artificial circulation loop a more exact CFD solution can be applied to identify the fluid element trajectory and distributions of the rate of energy dissipation and the integral scale of turbulence (Baldyga et al. 2001).

To model effects of mixing on various scales on the course of chemical reactions using directly CFD, a non-equilibrium multiple-time-scale mixing model and a beta distribution of the mixture fraction are applied in combination with a simple conditional moment closure based on linear interpolation of local instantaneous reactant concentration values (Baldyga and Bourne 1999). The mixing model is linked to CFD (standard \( k-\varepsilon \) model). A set of averaged differential balance equations for reacting species is solved to predict distributions of averaged concentrations of reactants

\[
\frac{\partial \bar{c}_i}{\partial t} + \nabla \cdot (\bar{u} \bar{c}_i) = \frac{\partial}{\partial x_j} \left[ (D_m + D_T) \frac{\partial \bar{c}_i}{\partial x_j} \right] + \bar{r}_i
\]  

with the local average values of the reaction kinetics terms expressed using the mixture fraction distribution \( \Phi(f) \) and stoichiometric relations between the mixture fraction \( f \) and the local, instantaneous values of concentrations, \( c_i(f) \),

\[
r_2 = k_2 \bar{c}_A \bar{c}_B = k_2 \int_0^1 c_A(f)c_C(f)\Phi(f)df
\]  

As a second example of complex reactions that includes both schemes, competitive-consecutive and parallel, a simultaneous diazo-coupling between 1- and 2-naphtols and diazotized sulphanilic acid is considered:

\[
\begin{align*}
A_1 + B & \xrightarrow{k_{1p}} p - R \\
A_1 + B & \xrightarrow{k_{1o}} o - R \\
p - R + B & \xrightarrow{k_{2p}} S \\
o - R + B & \xrightarrow{k_{2o}} S \\
A_2 + B & \xrightarrow{k_3} Q
\end{align*}
\]

where \( A_1 \) denotes 1-naphtol, \( A_2 \) is 2-naphtol, \( B \) represents diazotized sulphanilic acid, \( o-R \) and \( p-R \) are two mono-substituted dyes (ortho and para), \( S \) represents a bisazo dye and \( Q \) is a single monoazo dye. At temperature equal to 298K, pH = 9.9 (with sodium carbonate and bicarbonate employed as buffers), for ionic strength \( I = 444.4 \) mol/m\(^3\) the rate constants take following values:

\[
\begin{align*}
k_{1p} &= 12238 \pm 446 \text{ m}^3/\text{mol s} \\
k_{1o} &= 921 \pm 31 \text{ m}^3/\text{mol s} \\
k_{2p} &= 22.25 \pm 0.25 \text{ m}^3/\text{mol s} \\
k_{2o} &= 1.835 \pm 0.018 \text{ m}^3/\text{mol s} \\
k_3 &= 124.5 \pm 1.0 \text{ m}^3/\text{mol s}
\end{align*}
\]

Extend of mixing is characterized by the product distribution. Two measures of product
distribution can be applied for this scheme, one concentrating on the yield of secondary product $S$ and the other on the yield of the competitive product $Q$.

$$X_S = \frac{2c_S}{(c_{or} + c_{pR} + c_Q + 2c_S)}$$  \hspace{1cm} (15)

$$X_Q = \frac{c_Q}{(c_{or} + c_{pR} + c_Q + 2c_S)}$$  \hspace{1cm} (16)

Both definitions express yields relative to the limiting reagent $B$.

Experiments with these reactions were carried out in the stirred tanks (Baldyga and Bourne 1999), the static mixer (Baldyga et al. 1997), the rotor-stator mixer (Baldyga et al. 2007) and a micro-channel system (Baldyga J, Jasińska M, unpublished observation, 2008).

**Figure 3** shows typical flow pattern in the rotor-stator mixer predicted using CFD for two different values of the rotor speed $N$.

**SELECTIVITY OF CHEMICAL REACTIONS: RESULTS AND DISCUSSION**

We start from presentation of typical results of experimental investigations and comparisons with model predictions. **Figures 4, 5 and 6** illustrate effects of process conditions on the product distribution for parallel reactions between sodium hydroxide solution (A) and either hydrochloric acid (B) or ethyl chloroacetate (C), (Baldyga et al. 2001; Baldyga and Makowski 2004).

Next results, shown in **Figures 7, 8 and 9** are for the complex system of diazo-coupling between 1- and 2-naphthols.

Presented results lead to following conclusions:

1. The results agree with conclusions from the time constant analysis. Decreasing of time constants for mixing always decreases $X_S$ and $X_Q$. This is well shown in **Figures 4 and 5** by effect of increase of the rate of energy dissipation; this decreases the time constants $\tau_S$, $\tau_E$ and $\tau_{DS}$ (**Eqs 6, 7, 8**) and $\tau_D$ (**Eq. 5**) due to increase of turbulent diffusivity, and decreases the product distributions as well. Increase of feed time (**Fig. 6**) is related to

**Figure 4.** Influence of the energy dissipation on $X_S$ in the continuous flow reactor; $c_{B0} = c_{C0} = 0.02$ mol/dm$^3$, $c_{A0} = 1$ mol/dm$^3$; model I – engulfment model with the circulation loop based on correlations, model II – engulfment model with circulation based on CFD, model IV – model based on PDF closure and CFD.
Figure 5. Influence of the energy dissipation, $\varepsilon$, on the selectivity, $X_S$, observed in the continuous-flow stirred tank reactor and the semibatch stirred tank reactor; $\tau = t_f = 20$ min; $c_{B0} = c_{C0} = 20$ mol m$^{-3}$; $c_{A0} = 1000$ mol m$^{-3}$. Application of CFD closure model.

Figure 6. Influence of the feed time, $t_f$, on the selectivity, $X_S$, observed in the semibatch stirred tank reactor; $N = 214$ rpm; $c_{B0} = c_{C0} = 40$ mol m$^{-3}$; $c_{A0} = 2000$ mol m$^{-3}$. Application of CFD closure model (model I) and application of CFD neglecting micromixing effects (model III).

Figure 7. Effect of the rate of energy dissipation and stoichiometric ratio on the product distribution; $c_{B0, sr} = 0.5$ mol/m$^3$, $c_{A10, sr} = 0.6$ mol/m$^3$, $V_A / V_B = 20$.

Figure 8. Yield of dye from 2-naphtol at two viscosities as a function of flow rate in a tubular reactor equipped with static mixer elements (Baldyga et al. 1997); engulfment model applied for diazo-coupling.
decrease of the flow rate $Q_B$, and as a result decrease of $\tau_D$ (Eq. 5), which decreases product distribution.

2. Figure 6 shows also effect of changing of limiting mixing mechanism, namely with decreasing the flow rate only the time constants $\tau_D$ and possibly $\tau_S$ (due to decrease of integral scale) decrease, whereas $\tau_E$ and $\tau_{DS}$ are not affected, and once they control the process, further decrease of the flow rate becomes ineffective. Similar effect is observed on Figure 8; at small flow rate viscosity affects the process through $\tau_E$ and $\tau_{DS}$, but increasing $Q$ increases the rate of energy dissipation and because $\tau_E$ and $\tau_{DS}$ are more sensitive to $\varepsilon$ than $\tau_S$, they become negligible at higher flow rates and the process becomes completely controlled by inertial-convective mixing that competes with chemical reactions.

3. Figure 7 shows that at high power input the first reaction is mixing controlled, the third and fourth reactions in the diazo-coupling scheme become chemistry controlled, which means much slower than mixing and no $S$ is produced, whereas the fifth one that is faster is still affected by mixing. This explain why this reaction scheme can be used as a good indicator of mixing; through $X_S$ at small energy input and through $X_Q$ at high energy.

4. Comparison of model predictions with experimental data shows that the model based on CFD and PDF closure gives best results; however much simpler mechanistic model that is less exact, predicts anyhow all trends observed in experiments, see Figures 4, 8 and 9.

**PRECIPITATION OF PARTICLES: MATERIALS AND METHODS**

The aim of this section is to present the method of particle production using such precipitation processes that employ supercritical fluids and then to present in detail the Solution Enhanced Dispersion by Supercritical Fluids Process (SEDS-Process). The process of crystallization or precipitation involves the nucleation and growth of crystals (particles) from supersaturated solution, and is often followed by agglomeration. Supersaturation is the driving force for precipitation which is defined by the difference between the real, $c$, and equilibrium, $c_{eq}(P,T)$, solute concentrations. The strict definition of supersaturation is linked to the difference of chemical potential, $\Delta \mu$. In practical applications, including precipitation from supercritical fluids (SCF) the simplified definition of supersaturation, $S$, is usually applied:

$$S = \frac{c}{c_{eq}} = S_a = \frac{a}{a_{eq}}$$

(Baldyga et al. 2004).
The particles are created by nucleation events including a primary nucleation with creation of crystals not affected by the presence of the crystallizing material itself, which may be homogeneous when occurs in the absence of any solid phase, and heterogeneous when nucleation is facilitated by the presence of foreign solid particles. In secondary nucleation formation of solid phase is affected by the presence of solid phase of the crystallizing material. In precipitation from SCF, the supersaturation is typically very high and the most important mechanism is the primary homogeneous nucleation with the rate:

\[ R_N = R_{N,\text{homo}} = R_{N,\text{max}} \exp\{-A[\ln(S)]^2\} \]  

(17)

where \( A \) is a constant proportional to the specific surface free energy of nuclei and inversely proportional to \( T^3 \). The nucleation constant is defined as the time required to form a given number of nuclei: \( \tau_N \sim 1/R_N \).

Crystal growth in a supersaturated solution is a complex process that occurs in many stages including transport of solute from the bulk solution through the diffusion and adsorption layers, integration into the crystal lattice, and release and transport of crystallization heat. The simplest description of this complex process is based on the diffusion-reaction theories, with the rate of growth of a crystal being proportional to the driving force.

\[ G = k_G (c_c - c_i) = k_r (c_c - c_{eq})^g \]  

(18)

where \( G = dL/dt \) is the rate of growth of a crystal of size \( L \). For the crystal growth the characteristic time can be expressed in relation to the rate of product concentration decrease resulting from the crystal growth (Baldyga and Bourne 1999).

\[ \tau_{Gcr} = \left( \frac{D_G A_g}{M} \right)^{-1} \langle c_C \rangle \]  

(19)

where \( \langle c_C \rangle \) is the concentration of precipitating substance.

Precipitation results in the formation of a solid-liquid dispersion. Small particles forming this dispersion have a tendency to aggregate, i.e. to form larger entities called agglomerates. The rate of particle agglomeration depends on particle size, shape and number concentration, solution composition and flow structure. On the other hand mechanical stresses generated by the flow can disperse agglomerates; both processes are described by specific kernels; \( \beta \) for agglomeration kernel and \( \Gamma \) for breakage kernel; the adequate time constants \( \tau_a \) and \( \tau_b \) for agglomeration and breakage respectively are inversely proportional to breakage kernels.

There is usually large number of particles in the system and it is more convenient to consider not histories of particles but rather properties of the particle population. A predictive multi-dimensional particle distribution theory is based on the population balance equations. For a single internal coordinate \( L \) (crystal size) the population balance takes the form:

\[ \frac{\partial \Psi}{\partial t} + \frac{\partial}{\partial x_j} \left( u_{\mu j} \Psi \right) + \frac{\partial}{\partial L} \left( G_{\Psi} \right) = B - D \]  

(20)

with

\[ \Psi(L, x, t) = \frac{R_N[S(x, t)]}{G[S(x, t)]} \]  

(21)

where \( L_0 \) is a size of nuclei, \( \dot{u}_{\mu j} = (u_{\mu 1}, u_{\mu 2}, u_{\mu 3}) \) is a vector of particle velocity along external coordinates \( \mathbf{x} = (x_1, x_2, x_3) \) and \( B \) and \( D \) are the birth and death functions representing effects of agglomeration and breakage.

To start crystallization or precipitation process one needs to create supersaturation. This can be done by cooling, evaporation of solvent, carrying out chemical reaction, and adding antisolvent (drawing out precipitation). To produce small particle one can use reactive or drawing-out precipitation method.

To interpret the process of reactive precipitation the models represented by Equations 10–12 and 13–14 that are linked to the population balance equation (Eq. 20) should be used to interpret experimental data from (Podgórská 1993) and (Baldyga and Bourne 1999). Supersaturation was created as a result of chemical reaction between the barium and sulphate ions \( \text{Ba}^{2+} + \text{SO}_4^{2-} \rightleftharpoons \text{BaSO}_4 \). Experiments were carried out in a Rushton type single-feed semibatch stirred-tank reactor of diameter \( T = 0.242 \) m and impeller diameter \( d_{imp} = 0.075 \) m, which was operated in a semibatch manner. The feed position considered in what follows was placed near the impeller (\( r = 0.060 \) m, \( z = 0.080 \) m) and the feed pipe i.d. was equal to
0.0015 m. In experiments the final volume, being the sum of volumes of barium chloride and sodium sulphate solutions, was kept the same in all experiments whilst the volume ratio of the solution of barium chloride present in the vessel initially to the volume of sodium sulphate solution fed to the system, $\alpha$, varied from 20 to 200. Stoichiometrically equivalent amounts of reactants were applied in experiments. The crystal size distributions were measured after the experiment using a Coulter Multisizer II (Coulter Electronics Ltd., Luton Beds, UK). For the system with no agglomeration a good agreement between model predictions and experimental data was observed.

Now we consider the drowning-out or antisolvent crystallization. Idea of this method is presented schematically in Figure 10. The unsaturated solution of the substrate (point A) is mixed with the antisolvent as shown in triangular diagram. The solution composition then varies along a straight line A-B-C-Antisolvent. The solution becomes saturated at point B and further addition of the antisolvent increases supersaturation. The rate of supersaturation creation then depends on the amount of added antisolvent, feeding rate and intensity of mixing. Drowning-out precipitation usually produces crystals that have a smaller size than those produced by cooling or evaporation at the same supersaturation.

An example of application of the supercritical anti-solvent is Solution Enhanced Dispersion by Supercritical Fluids Process (SEDS-Process) that was developed by the Bradford University Group (Hanna and York 1994). The method is presented...
schematically on Figure 11 and enables an intensive mixing of the fresh substrate solution with the supercritical anti-solvent in the coaxial nozzle with two coaxial passages for the solution and the solvent respectively.

Figure 12 shows the phase diagram for ethanol - carbon dioxide system calculated using the Peng-Robinson equation of state. The area within the envelope corresponds to the vapor-liquid system. The broken line in Figure 12 shows that at the same pressure precipitation may be carried out in the two-phase system of two, partly miscible fluids ($T = 363$ K), and in the single-phase system of the completely miscible compounds ($T = 313$ K).

The SEDS experimental apparatus presented schematically in Figure 11 has been employed to crystallize paracetamol and nicotinic acid (interpreted as model compounds) from ethanol solution and using supercritical carbon dioxide as an antisolvent. The main aim of this study was to present mixing effects on particle size in the coaxial mixing jet system. The particle formation vessel equipped with the high pressure optical cell and the two-component coaxial nozzle were placed in the air-heated oven. Temperature was set and controlled, with accuracy equal to 0.1 K, using platinum resistor thermometer connected to a digital controller. Pressure in the vessel was controlled within accuracy equal to 0.2 bar. The CO$_2$ flow rate was set by metering valve and controlled by flow meter. Paracetamol (single phase system) and nicotinic acid (two phase system) were used as materials to be precipitated. Pressures were 9.0 MPa for nicotinic acid and 250 bar (in the vessel) and 300 bar at the inlet to the nozzle for paracetamol. Temperatures were 363 K for nicotinic acid and 308–313 K for paracetamol.

Solution flow rates varied in a range 0.05–3 cm$^3$/min for paracetamol and it was set to $6.67 \times 10^{-9}$ m$^3$/s for nicotinic acid and maintained with 0.1 % accuracy. The used flow rates of CO$_2$ were $1.39 - 3.13 \times 10^{-4}$ Nm$^3$/s for nicotinic acid and 2.5–75 cm$^3$/min for paracetamol. For paracetamol the flow rate ratio was kept constant and equal to 0.01. The concentration of nicotinic acid in ethanol was 0.0039 mole fraction and the concentration of paracetamol in ethanol was 10 kg/m$^3$. The diameter of the nozzle was 0.35 mm for nicotinic acid and 0.2 mm for paracetamol.

After each experiment particles were dried by 20–30 minutes by SC CO$_2$ at the same pressure and temperature as used in experiments. The particles were collected in the vessel and analysed afterwards using scanning electron microscopy (SEM, Hitachi S-520, Tokyo, Japan) and two techniques of particle size measurements: the laser diffraction method (Sympatec, Helos system, Sympatec Ltd, Bury, UK) and based on time of flight measurements (AeroSizer™, TSI Inc.,

![Figure 12. Effect of pressure and temperature on carbon dioxide-ethanol equilibrium.](image-url)
Minneapolis, MN, USA). Results of measurements are shown together with model predictions in next section of this paper.

When the SEDS process is operated in a two phase regime then it is hardly possible to distinguish between droplets and precipitated particles. That is why, to characterize droplet dispersion, the size and velocity distribution of droplets were measured for dispersion of pure ethanol droplets in SC CO\textsubscript{2}. More details describing experimental methods are presented by (Shekunov et al. 2001) and (Kubicki 2006). Modelling details one can find in previous studies (Shekunov et al. 2001; Baldyga et al. 2003; Baldyga et al. 2004; Henczka et al. 2005; Kubicki 2006).

In the first set of experiments for paracetamol precipitation solvent and antisolvent are completely miscible, i.e. remain above the mixture critical point at all solvent-antisolvent proportions (see Fig. 12). Figure 13 shows the flow pattern predicted with CFD for this case.

In computations the $k$-$\varepsilon$ model by Fluent together with in-house mixing models were applied. To account for compressibility of fluids the Favre averaging method together with the Peng-Robinson equation of state were applied. Figure 13 shows that in the particle formation vessel there is an intensive circulation in the region of the jet, which means that in the system there is back-mixing of the fresh fluid from the nozzle with the reservoir fluid. This has significant effect on the process.

In the second case of the two-phase system and precipitation of nicotinic acid the effect of dispersed phase on flow field can be neglected in computations because the volume fraction of the dispersed phase was very small. The droplet size distribution was calculated using the population balance equation for drops with breakage resulting from both initial instabilities and turbulent, breakage kinetics was derived using the multifractal theory of turbulence as described in detail by Baldyga and Podgór ska (1998). Examples of model–experiment comparison (Kubicki 2006) for the drop size distribution are shown in Figure 14.

![Figure 13. Structure of the flow in the SEDS particle formation vessel.](image)

![Figure 14. Comparison of calculated droplet size with experimental data measured in the SEDS system a) CO\textsubscript{2} flow rate=1.39 \times 10^{-4} \text{Nm}^3/\text{s}, b) CO\textsubscript{2} flow rate =2.78 \times 10^{-4} \text{Nm}^3/\text{s}.](image)
PRECIPITATION OF PARTICLES: RESULTS AND DISCUSSION

In the case of paracetamol precipitation in the single phase system experiments were performed at a fixed flow composition (i.e. for the same proportion of mass fluxes of the carbon dioxide and paracetamol solution in ethanol) but at different flow velocities expressed through the jet Reynolds number, $Re$. Experimental and simulation results are presented on Figure 15.

The particle size exhibits a rapid decrease leading to a minimum particle size, whereas at higher $Re$ the particle size increases with $Re$. Creation of supersaturation results from mixing of the solution with the fresh anti-solvent within the nozzle-mixing chamber, and this results from decreasing solubility; there are also effects of decreased temperature (observed and predicted), that in the single-phase system result from the heat of mixing and the Joule-Thomson effect.

A rapid decrease of particle size at $Re < 10000$ is caused by the establishment of supersaturation profile; up to $Re = 10000$ maximum supersaturation increases with increasing $Re$. Afterwards the supersaturated jet fluid that enters the vessel becomes diluted with the reservoir fluid ($CO_2$ and solvent mixture saturated with paracetamol), which reduces supersaturation. Some increase of particle size observed at high $Re$ is related to this phenomenon. After reaching $Re = 10000$ further increase of $Re$ does not enhance mixing of fresh fluid, so the supersaturation cannot be increased by mixing anymore, and just small increase of supersaturation may result from cooling effect. On the other hand increase of $Re$ decreases the residence time of fluid elements in the region of high supersaturation, so decreases the time available for nucleation process in the zone of high supersaturation. As a result a smaller number of larger particles is produced. Simulations with E-model based on equations similar to (10) to (12) (Shekunov et al., 2001) well predict these effects and this is shown in Figure 15. Application of CFD (see Eqs 13 and 14) leads to good results when the closure for kinetics is included. An increase of $Re$ also affects the shape of particles; at $Re < 10000$ the plate-like crystal are produced, whereas at $Re > 10000$ the compact, isometric crystals are formed.

The examples presented here show that modelling, including the application of Computational Fluid Dynamics, can be useful for understanding the process and helpful in process optimization and up-scaling. Examples of comparison of model predictions with

![Figure 15. Effect of the nozzle Reynolds number on the particle size in the single-phase ethanol CO₂ system.](image_url)
experimental data for double-phase system and precipitation of nicotinic acid are presented in Figure 16.

(Baldyga et al. 2004a) pointed out that overall mass transfer coefficient $K$ in the case of SC CO$_2$-ethanol system can be calculated as a sum of mass transfer resistances including the interfacial mass transfer coefficient $k_i$, mass transfer coefficient $k_L$ effective within liquid phase, and the diffusion mass transfer resistance $k_D$ within the vapour phase boundary layer.

This differs this system from typical chemical engineering applications where the interfacial resistance is usually negligible. The time constant for mass transfer can be estimated as $\tau_{mt} = d/(6K)$. The size of particles precipitated within droplets was calculated using 2 methods; the first one is based on the one droplet – one particle concept, the second was employing the moment transformed population balance equation for primary particles with experimentally identified nucleation kinetics (Kubicki 2006). One droplet–one particle model gives almost the same results as method of moments (Fig. 16). The difference is observed at low CO$_2$ flow rates, which corresponds to large droplets and larger amount of nicotinic acid present in the droplet, which means that agglomeration is then more possible.

Presented results lead to following conclusions:

1. The results shown on Figure 15 agree with conclusions from the time constant analysis. Increasing the flow rate (and related Re) increases the rate of energy dissipation and decreases all time constants that depend on $\varepsilon$, as given by Equations 5, 6, 7 and 8. Until they are larger than the time constant for nucleation, $\tau_N$, the supersaturation increases and the number of particles increases as well provided that the time constant for crystal growth is larger than $\tau_N$ and decrease of supersaturation due to crystal growth is negligible. However, when the residence time in the nozzle chamber becomes shorter than $\tau_N$, then there is less time for nucleation and smaller amount of particles is produced. The aggregation time is longer than the residence time in the nozzle-chamber, there is no aggregation in the region of high supersatuation, where the particles can

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**Figure 16. Effect of CO$_2$ flow rate on particle size; comparison of model predictions with experimental data.**
be connected by the crystalline bridges. Because the residence time in the particle formation vessel is much longer than $\tau_G$, almost all paracetamol is used up, and smaller amount of particles is equivalent to larger particle size.

2. Figure 16 shows that the size of particles decreases with increasing the flow rate and increasing energy input. This decreases the size of drops (Fig. 14) and decreases the time constant for mass transfer. When only one particle is produced in the drop the particle of course decreases with decreasing the drop size. When, however, several primary particles are produced, then in smaller drops supersaturation increases faster, $\tau_N$ becomes shorter than $\tau_{mt}$, which means that also primary particles become smaller at higher flow rates.

3. Comparison of model predictions with experimental data shows that the model based on CFD, PDF closure and population balance gives very good results; however much simpler mechanistic model that is less exact, predicts experimental trends as well.

**TIEVISTELMÄ**

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