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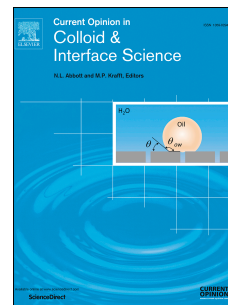
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Reactive crystallization: from mixing to control of kinetics by additives

Sébastien Teychené^{1†*}, *Isaac Rodriguez-Ruiz*^{1†}, *Raj Kumar Ramamoorthy*^{1,2†}

¹Laboratoire de Génie Chimique, Université de Toulouse, CNRS, INP, INSA, UPS Toulouse, France.

²FR FERMAT, Université de Toulouse, CNRS, INP, INSA, UPS, Toulouse France .

The study of the mechanisms laying underneath reactive crystallization is a key subject in a myriad of natural and industrial processes. Here, control on particle nucleation and growth are active topics of research, in which important advances can be highlighted within the last years. While novel mechanisms for crystal nucleation have been recently unveiled, the effects of reagent mixing process and timescales on them, together with the effect of impurities and/or additives present during the reaction, still lack of fundamental comprehension. This work intends to provide a general view on the latest advances made on the critical parameters involved in reactive crystallization processes: nucleation, fast and efficient mixing and use of additives.

1. Introduction

Reactive crystallization is at the core of numerous pharmaceutical, chemical, biological and industrial processes. In this latter case, it is a particularly active research subject for novel hydrometallurgical processes associated to materials recycling in urban mines, such as the recycling of permanent magnets, LED light sources and rechargeable batteries [2], and also to the recycling of catalysts from industry or the recovery of lanthanides and actinides on nuclear waste treatment [2, 3]. Beyond a simple purification and separation step, the main objective of crystallization and precipitation processes is to produce a controlled population of crystals in terms of (among other parameters) crystal structure, crystal habit/aspect ratio (shape), size distribution, physical and chemical quality (purity, composition in case of co-crystals), porosity, etc. This wide range of properties to be controlled are dependent on the coupling between the hydrodynamics of the reactor (from both macroscopic and microscopic point of views), and the complex physico-chemical processes responsible for the formation of crystals, in which other molecules and/or by-products might be involved. In this regard, the control, not only on the previously mentioned product properties, but also on crystal nucleation kinetics, becomes essential for the selective recovery of compounds in complex fluid media [2, 4], avoiding undesired by-product precipitation along with main products, or forming unwanted solid depositions in pipelines, heat exchangers and reactors.

The design, the understanding, and the control of a reactive crystallization process usually rely on phase diagrams. These phase diagrams are used to represent the frontiers between each equilibrium phases, but also, in case of crystals, between metastable phases like polymorphs, solvates, amorphous and liquid phases, etc., as a function of reaction variables (reagent/solvent/additive concentration, pressure, temperature). Though, it is widely known that non-equilibrium (i.e. dynamic) constraints, would determine the crystallization pathway, which critically influences the final crystal properties [5]. Indeed, the recent works of P. Vekilov, J De Yoreo H. Coelfen, and D. Gebauer research groups (discussed in the following sections), have experimentally proved that non-equilibrium intermediate phases play a vital role on determining crystallization routes. However, within the dynamic constraints favouring the formation on non-equilibrium phases, and thus affecting crystallization routes, two critical factors are frequently overlooked: it is of high importance to consider reagent mixing process and their time and length scales, and also the action mechanisms of additives or impurities, which can locally and dynamically modify reagent-reagent and solvent-reagent interactions.

This paper aims to provide a global vision of the most critical parameters or mechanisms that control reactive crystallization processes: nucleation, fast and efficient mixing and additives. The current state of the art on the subject is approached from the basis of the understanding of crystallization mechanisms to the influence of mixing, and of the presence of additives, on the control of both nucleation and crystal growth.

2. Classical and non-classical nucleation

Reactive crystallization is a particular case of first-order phase transition. Even if the basic principles on which first-order phase transitions are founded were laid down almost 150 years ago, they are not yet well understood. These principles and developments are nowadays framed within the so-called Classical Nucleation Theory (CNT) [6]. Despite its well-known limitations on the quantitative description of certain experimental observations, CNT is widely utilized in process engineering as an empirical modelling tool, with an undeniable qualitative predicting value. Indeed, although CNT has been recently challenged by novel experimental observations, all more recent alternative theories and proposed nucleation mechanisms remain on the qualitative, and sometimes merely conceptual, experimental description, and up to date CNT represents the only quantitative theoretical and parameterable nucleation framework.

The possible existence of thermodynamically metastable states is a characteristic feature of the first-order phase transitions, and also the cause of multi-stage systems occurrence, which will be discussed below. Here, a multi-stage system is defined by the formation of transient metastable phases, eventually transforming into more thermodynamically stable ones. Physically, this is due to the threshold character of the nucleation rate dependence on the supersaturation. From a practical and classical point of view, it is found that phase metastability is lost at a certain critical supersaturation, $\Delta\mu_c$ at which the energy barrier is already small enough for nucleation to occur at an observable rate. In fact, the determination of $\Delta\mu_c$ is among the first problems addressed by the CNT, and it can additionally be obtained experimentally [6]. Accordingly, Alimi et al. [7] determined a decreasing activation energy for calcium sulfate dehydrate precipitation (from 71 to 51 kJ.mol⁻¹) as a function of the increase in supersaturation range (from 2.5 to 11). Additionally, precipitation occurring via metastable intermediate phases in multi-stage systems, or in the presence of additives or impurities requires lower activation energies to precipitate than the direct precipitation of more thermodynamically stable ones. In this regard, an illustrative model system for multi-stage precipitation is calcium carbonate. Energies of 69 kJ.mol⁻¹ [8] and 66 ± 2 kJ.mol⁻¹ [9] have been reported for vaterite-mediated systems (46 kJ.mol⁻¹ in presence of additives [10]), while 155 kJ.mol⁻¹ have been reported for pure calcite [11], decreasing to 45 ± 7 kJ.mol⁻¹ for the heterogeneous calcium carbonate nucleation on quartz [12]. However, $\Delta\mu_c$ represents a kinetic limit of metastability, as it is sensitive to the concrete kinetics of nucleation and growth of the new phase, and to the particular experimental technique used to detect the onset of the nucleation process [6].

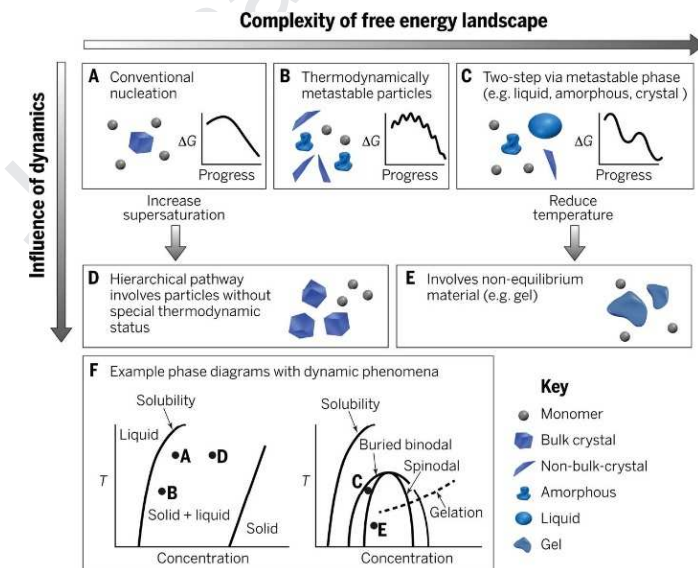
Multi-stage systems are often present in reactive systems located far from thermodynamic equilibrium (i.e. $\Delta\mu \gg \Delta\mu_c$), where the reagents diffusion times are in the same order of magnitude as the phase transition kinetics, and very local supersaturation conditions favours the appearance of different metastable phases. In this context, more and more evidences nowadays indicate alternative routes for nucleation, which cannot be explained with a straightforward classical interpretation. Besides, the observation of pre-nucleation dense liquid clusters formation, leading to a two-step nucleation mechanism has been reported [13, 14]. These two-step (multi-step) mechanisms have to be differentiated from the multi-stage classical mechanisms already described, as long as the molecular densifications taking place would remain as a part of the mother phase, and thus could not be defined as a nucleating phase *per se*. Indeed, CNT states that crystal nucleation from solution occurs when a sufficiently large density fluctuation (that is, a cluster that has reached a critical size) pushes the system over a free-energy barrier. In this sense, the two-step mechanisms described by Vekilov and co-workers can be understood from a classical point of view as nucleation events taking place in metastable local densifications of the molecular populations, which generate a local supersaturation increase, reducing the bulk free energy and thus lowering the barrier for nucleation. These densifications become more stable than the free molecules in solution and thus when occurring, nucleation cannot take place by the single thermodynamic path described by CNT [15]. Analogously to these reported observations for macromolecular systems, the existence of liquid precursors have also been observed in ionic compounds for which reactive crystallization systems lead to the quick onset of high supersaturations, and also for poorly soluble salts. This latter is the case for calcium carbonate [16, 17], and more recently, liquid precursors have been observed for rare earths oxalate reactive precipitation systems [18]. Indeed, the formation of liquid precursors is explained by either a binodal demixing or spinodal decomposition. Figure 1F, depicts two different phase diagrams, with or without a spinodal region, combining the thermodynamic nature of solubility curves and phase equilibrium with the existence of dynamic phenomena [1]. On this graphical example we can observe that the binodal line marks the metastable (thus implicitly considering the existence of an energy barrier) coexistence of the solid and the liquid phase under a given set of conditions, where the spinodal line depicts a region of instability where nucleation proceeds in a barrierless manner. For a more detailed description of liquid-liquid phase separation routes, we invite the readers to address the works of Garcia-Ojalvo et al. [19] and Gebauer et al. [20].

In both previously mentioned ionic systems in which liquid precursors have been observed [16-18], the liquid-liquid separation observations are consistent with a binodal rather than a spinodal route, being this first phase separation an illustrative example of a classical nucleation pathway for phase transition, prior to the appearance of the solid phase. In fact, the existence of a proper spinodal decomposition from the onset of supersaturation to the formation of a crystalline phase has been debated [21, 22], and the observation of liquid-liquid separation on systems in which supersaturation is increased gradually [17], points to a binodal separation. Out of the discussion about liquid-liquid phase separation mechanisms, a subsequent crystallization episode after the formation of a liquid precursor brings a more complex and dynamic multi-stage crystallization route, where two or more phases would temporary coexist in a non-equilibrium system. A good example for that is the case of calcium carbonate system, where the initial formation of a liquid phase gives rise to the formation of different amorphous phases, which eventually transform into more stable calcium carbonate crystalline phases [23]. Actually, often a phase transition may not induce the formation of the most thermodynamically stable phase, when it is also possible that a metastable phase appears in the supersaturated old one. This led to the formulation of the so-called *Ostwald's Rule of Stages*. According to this rule, 'if the supersaturated state has been spontaneously removed then, instead of a solid phase which under the given conditions is thermodynamically stable, a less stable phase will be formed' [24]. Abundant multi-stage systems of very different nature can be found in literature, from metals [25], to ice [26], proteins [27], fatty acids [28] or polymers [29], among many others. When the direct formation of the thermodynamically stable phase is not possible, overall crystallization becomes a two-stage process: the formation of the stable phase (second stage) is preceded by the appearance of the metastable one (first stage). Experimentally, whether these crystallization routes should be considered as a classical multi-stage mechanism in a multi-phase system, or a "less classical" multi-step phase transition, would depend on observers capability to spot if the appearing solid phase is born within the bulk of the first nucleating phase, or independently in the bulk of the mother solution, where the Ostwald's rule would apply. In this regard, it has been proposed that pre-nucleation clusters have little impact on nucleation rates, and that amorphous phases formed prior to or during crystal nucleation are not the stable products of nucleation and are not observed to act as precursors to the crystalline phase [30]. These observations have been attributed to kinetically favoured multistage pathways resulting from extreme driving forces typically used in experiments, and thus not to multi-step nucleation mechanisms. Besides, evidently, the possible nucleation and growth of a stable phase within the metastable one makes the kinetics of formation of the first (apparent formation kinetics in this case)

depend on those of the second. Considering a molecular scale, whereas instantaneous equilibrium is considered by the CNT, there are two rate-limiting phenomena involved in the apparent formation kinetics of the more stable phase: first, any solvent-mediated phase transition would be a diffusion-rate limited process, while at the same time these apparent kinetics would also be affected by the formation and dissolution rate of the precursor phase. Hence, the apparent kinetics will be governed by the slowest mechanism, and the possibility of experimentally spotting the precursor metastable phase (therefore having a sufficiently long lifetime allowing for its observation), would depend on the apparent nucleation and growth kinetics of the more stable phase. As an example of apparent formation kinetics involving two different multi-stage systems, Figure 2 illustrates i) the metastable precipitation of calcium carbonate hexahydrate (crystalline ikaite), firstly detected as a transient precursor for calcite precipitation at normal P and T [31] (Figure 2a to 2h), and ii) the solvent-mediated phase transition, from a liquid precursor to the crystalline product for the cerium oxalate reactive precipitation system in acidic media (Figure 2i – 2j) [18].

Additionally to the previously discussed multi-stage and multi-step routes for crystallization, another mechanism of particle stabilization and growth have also been observed to occur by colloid aggregation in stable pre-nucleation clusters [32-34]. These observations have also been recently reported for ionic systems such as calcium carbonate, and they are being today in the spotlight of hot scientific discussions [20, 35]. These pre-nucleation clusters appear to be thermodynamically stable species, and thus from the CNT point of view they are considered as intermediate metastable phases trapped in a minimum free energy pit [15]. Thus they are not considered as nucleation precursors, however they can be orders of magnitude more abundant than critical nuclei [35]. But besides the discussion around their classical or non-classical nature, pre-nucleation clusters have been reported to be chain-like structures, resembling highly dynamic liquid-like structures, which as a function of supersaturation, can develop higher degrees of coordination [36]. These formations would eventually lead to the formation of a novel phase of highly hydrated liquid nano-droplets approximating a binodal route [20, 37], which barrier associated with condensation toward solid-state phase appears to be based on prior aggregation/coalescence mechanism to form larger droplets and a subsequent dehydration [16].

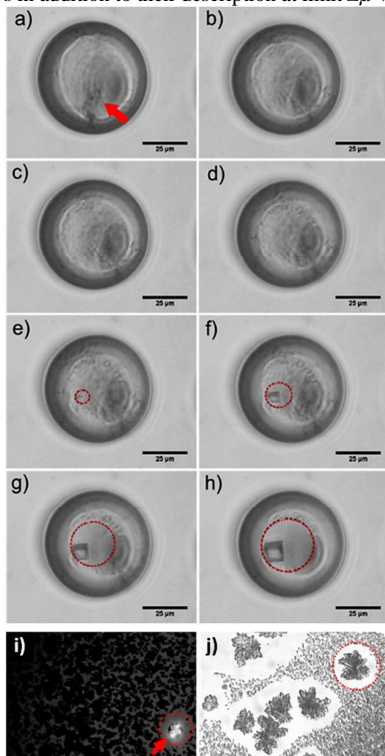
Noticeably, there is more and more evidence of the role of liquid precursors on the precipitation of very different crystallizing systems, either salts [18, 36], drug molecules [38] or macromolecules, where its existence and study were first reported [13, 33, 39]. However, it becomes clear that there is no single pathway to the crystalline state, and the thermodynamically favoured one will strongly depend on the dynamics and the energy landscape of each system (Figure 1 published by De Yoreo and coworkers [1]). While classical mechanisms can be observed in systems close to thermodynamic equilibrium and/or in controlled environments [30, 40], nucleation by stable clusters can be kinetically dominated [16, 20]. Moreover, particle growth can follow non-classical routes, such as by oriented aggregation of clusters or nanocrystalline particles, leading to the formation of mesocrystalline assemblies [41, 42]. There is therefore no single picture, and just as different phase-change mechanisms might occur among different systems, various different mechanisms can be involved in a single system, from the nucleation of a first phase, to subsequent transitions to various solid phases (multi-stage nucleation), as a function of the energy of the system.



• Figure 1. Nucleation pathways for different free energy landscapes from De Yoreo and coworkers 2015[1]. Reprinted with permission from AAAS.

At this point, the observation of possible different cluster formation mechanisms must be framed in a bigger picture, and observed from an energy point of view, in order to bring out the following question: can different cluster formation mechanisms being explained in a single theoretical framework, as a function of the energy of the system? Some conceptual attempts have been made to bridge the gap among the existing classical and non-classical (from the point of view of single monomer attachment to form the new phase) theories [30, 43]. However, and owing to the previously defined unknowns, this question remains unanswered to date, and it is crucial to understand how systems free energy affects the work for cluster formation and thus potentially the nucleation pathways. The difference between Gibbs energy in the initial phase (equilibrium state), G_{old} , and at the formation of the new phase, G_{new} , that is $\Delta G = G_{old} - G_{new}$, can be proposed as a thermodynamic quantity describing if the initial state is close or far from equilibrium. By means of eq. (1) we can easily define this Gibbs

energy differential as a function of $\Delta\mu$, by which we can also define the boundaries within a given phase is considered metastable. These boundaries outline a range of supersaturations enclosed between $\Delta\mu = 0$, at equilibrium, and the thermodynamic limit of metastability, where Gibbs ΔG second derivative is zero. The locus of these points is known as the spinodal curve. For any states within this curve, there is no energy barrier for nucleation, and thus, infinitesimally small density fluctuations will lead to phase separation via spinodal decomposition. Therefore, we can conceive a linear thermodynamic approach in the neighbourhood of the equilibrium, i.e. when $\Delta\mu$ reaches small values, and a completely non-linear situation when $\Delta\mu$ widely overpasses a critical value $\Delta\mu_c$ and gets to its thermodynamic limit. At this point, the boundaries of linearity, and the nucleation pathways in addition to their description at limit $\Delta\mu$ values are still ill-defined.



- Figure 2. a) to h) Time sequence of micrographs showing the course of calcium carbonate reactive precipitation in a 400 pL droplet containing 100 mM CaCl₂ and 100 mM Na₂CO₃: (a) $t = 0$ s, a viscous sol is first formed (arrow); (b) $t = 10$ min; (c) $t = 20$ min; (d) $t = 80$ min; (e) $t = 112$ min; a calcite crystal nucleates; (f) $t = 115$ min, the depletion area surrounding the crystal starts to increase; (g) $t = 118$ min, growth of calcite crystal consumes most of the solute coming from the dissolution of the fine ikaite particles composing the sol; (h) $t = 120$ min, the growth of calcite stops few seconds after complete dissolution of the sol particles. Adapted with permission from [31]. Copyright (2014) American Chemical Society. i),j) Analogous solvent-mediated phase transition observed from a liquid precursor for the cerium oxalate reactive precipitation system in acidic media. Adapted from [18] with permission from the Royal Society of Chemistry

3. Mixing

When two miscible fluids meet, they homogenize their content: this phenomenon is called mixing. This generic term includes a number of processes that involve different spatial and temporal scales. In 1958, Danckwerts [44] was the first to discuss about the influence of mixing on precipitation and reactions. Indeed, for chemical reactions which characteristic times are shorter than the mixing times, or in the same order of magnitude, the latter have a significant role on the path followed by the precipitation reaction and thus consequently on the yield, purity and physical quality of the produced suspension. The mixing time is the time needed to achieve a certain degree of homogeneity of a tracer (typically a fluorescent dye or a colorant) in a vessel. For instance in the case of a binary mixture of two miscible compound A and B, the quality of mixing can be deduced from the intensity of segregation by the following expression [44]:

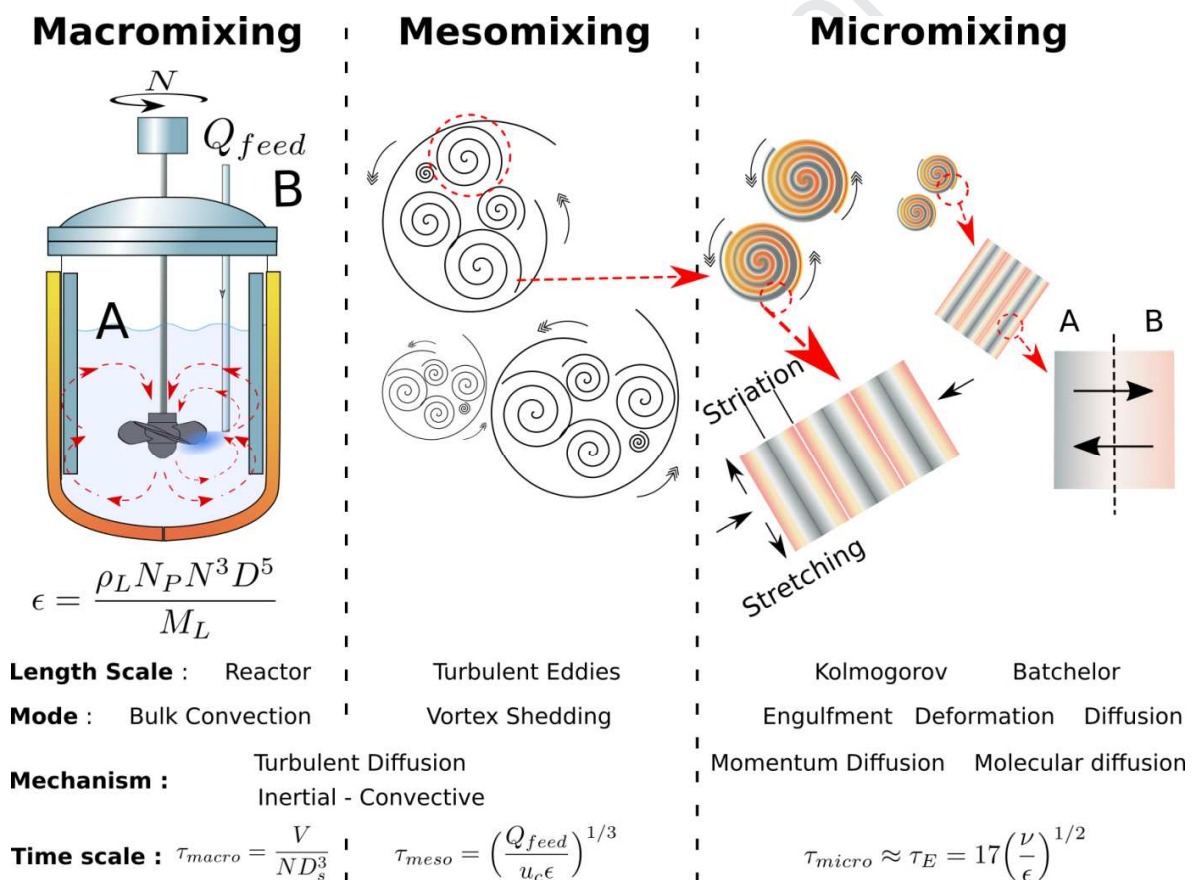
$$I = \frac{\overline{(\phi - \bar{\phi})^2}}{\bar{\phi}(1 - \bar{\phi})} \quad \bullet \text{ Eq.1}$$

Where $\bar{\phi}$ is the average (expected) volume fraction of compound A in B and ϕ is the measured value of the volume fraction at given point and time. The average can be take either over space (in a stirred vessel) or time in a continuous (i.e. tube) crystallizer. The values of I range from 0 for a uniform mixing at molecular scale to 1 when segregation is complete (no mixing). From a macroscopic point of view, the bulk mixing time (macromixing) is the time required to achieve a uniform concentration in the entire vessel. From a microscopic point of view, it is the time to evenly distribute material in a particular region of the vessel. In the case of reactive crystallization, if the reaction occurs before the complete homogenization of reagent concentrations in the reactor (i.e. when the concentration gradient of each reactant in the vessel is non-zero), it will take place in fluid regions more or less rich in certain elements, in which the supersaturation levels may be very different.

This generally results in the formation of crystals of different nature (crystallization of impurities, formation of polymorphs) or with non-homogeneous size distributions (correlated to a distribution of residence time in the reactor).

Turbulent mixing process in stirred vessels is generally divided into two main length-scales (Figure 3): the macro- and micro-mixing. Macro-mixing corresponds to the homogenization of concentrations at the macroscopic scale and reflects the existence of residence time distributions within the reactor. Micro-mixing refers to the homogenization of concentrations at the microscopic or molecular level. At this scale, the mixing is carried out by molecular diffusion and is accelerated by the convective viscous process that creates a sheet structure and thus increases the exchange surface between the fluid layers. The link between these two mixing processes occurring at very different scales is ensured by an intermediate-scale mechanism: the mesomixing (or turbulent dispersion). This phenomenon is, for instance, responsible for the formation of a fluid plume when injecting a reagent into an agitated tank.

J. Baldyga [45] classified reactive-crystallization as instantaneous ($\tau_M \gg \tau_R$), fast ($\tau_M \approx \tau_R$) or slow ($\tau_M \ll \tau_R$) where τ_M is one of the mixing time (macro, meso or micro) and τ_R is the reaction time. For an “instantaneous”, mixing-controlled reaction (i.e. for τ_R much smaller than any mixing time scale) but with $\tau_N > \tau_E$, the influence of molecular diffusion on nucleation can be neglected. However, when $\tau_N \approx \tau_E$, the viscous-convective micromixing (engulfment) affects precipitation. Usually, $\tau_N \ll \tau_G$, thus mixing affects precipitation mainly through the nucleation step.



- Figure 3. Turbulent mixing mechanism across various time and length scales. The macromixing time, can be defined as the time to circulate the tank content once, it depends on the tank volume (V) and on the stirrer geometry (D_s) and its rotational speed D_s . The mesoscale mixing usually occurs at the vicinity of the feed solution, its time scale depends on the feeding rate (Q_{feed}), the mean velocity close to the feed tube (u_c), and the turbulent energy dissipation (ϵ). At small length scale (i.e. length scale smaller than the Kolmogorov length scale, $\lambda_K = \nu^2/\epsilon$) mixing is driven by the mechanism of viscous-convective deformation of fluid elements, followed by molecular diffusion (micromixing). Its time scale depends on the fluid viscosity and the turbulent energy dissipation.

The analysis based on mixing time scale are only used in first approximation, for scale-up purpose for example, precise spatial and time scales of turbulence are extracted from computational fluid dynamics (CFD) simulation results. Vicum et al. [46], Baldyga et al. [47] found satisfactory agreement between the experimental results of a reactive mixing process in a semi-batch stirred-tank reactor and an engulfment model as well as a CFD-based approach. More recently, Bal et al. [48] have developed a coupled CFD – Population Balance equation model that incorporate, mixing, reaction nucleation, growth, coagulation and Ostwald ripening. Their model was able to predict SiO_2 nanoparticle sizes over a wide range of operating conditions (temperature, mixing intensity and solvents). In addition, they found that, in order to predict

(without any adjustable parameter) the nanoparticle size distribution for the syntheses performed at elevated temperature, the solvent evaporation rate becomes a critical factor. Indeed, the solvent evaporation significantly reduces the critical radius of the Oswald ripening process. For more detailed information on coupling CFD and population balance models, we suggest the review of D. Ramkrishna [49] and the references [50-53]. The timescale analysis for fast reactive crystallization processes shows that the limiting phenomenon is micromixing. As in stirred batch crystallizers the mixing time cannot be as low as few hundreds of milliseconds, micromixers have been particularly designed to overcome this issue. In addition, they have been used for the study of fast nucleation kinetics or to achieve a higher control on the continuous production of nano and microparticles.

Within the framework of the discussed timescale analysis, the mixing time scales in turbulent flows are relevant as long as the crystal size is much smaller than the smallest characteristic length scale of the flow structures (the Kolmogorov length scale). As the crystal size becomes of the order of the Kolmogorov scale, mixing time scale should take into account the flow modulation by the presence of the dispersed phase, that depends in a complex way on the size, inertia and concentration of the dispersed phase [54, 55]. The modulation of mixing properties may come into play in the estimation of the crystal growth rate at the latest stage of crystallization, only in case the volume concentration of crystals is larger than 1%. Moreover, the mixing timescales as presented here assume the solvent is Newtonian. Yet, in some conditions, especially if polymer additives are present at high concentration or in case strong electrostatic repulsions takes place between charged surfaces, the solution might behave locally as a visco-elastic medium. Studies considering visco-elastic turbulence have shown that the energy spectrum is changed compared to Newtonian fluids, as the energy of small eddies is reduced while that of large eddies is increased [56]. This suggests an increase of the micromixing time scale, and a decrease of the macromixing one.

A micromixer usually consists of several inlet pipes, a mixing chamber and an outlet pipe. The characteristic dimensions of these mixers are in the order of few tens of microns to few millimetres. As the volume of the mixing chamber is very small, compared to those of conventional reactors, they dissipate a very large amount of energy per unit volume and therefore allow a very good control of the micromixing times. In addition, as the size of the mixing element are usually small, the flow in such devices is mainly laminar.

The energy dissipation per mass unit of fluid at low Reynolds number calculated from a Hagen-Poiseuille flow is proportional to the product of pressure drop by the volumetric flow rate as[57]:

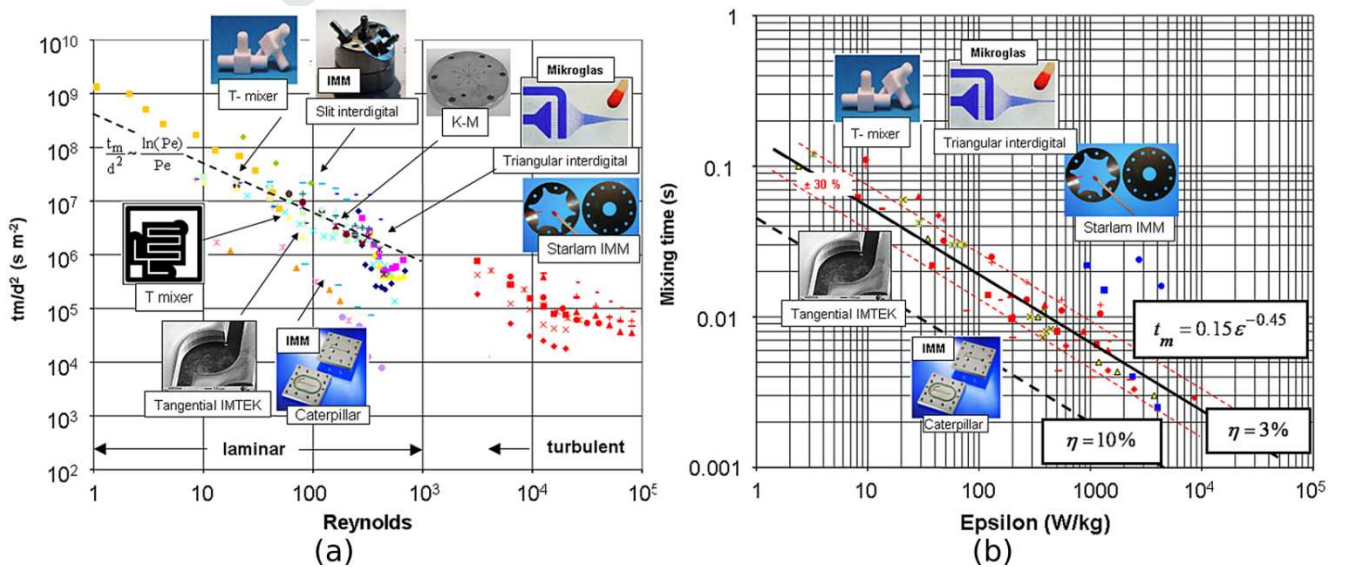
$$\epsilon = \frac{Q\Delta P}{\rho V} = \frac{32\nu u_m^2}{d^2} \quad \bullet \text{ Eq.2}$$

Where u_m is the mean velocity, d the diameter of the channel, Q the volumetric flow rate, and ΔP the pressure drop.

Falk and Commenge [57] propose a theoretical expression for the mixing time in micromixer, t_{mix} , defined as:

$$t_{mix} = \frac{(d/D)}{8Pe} \ln(1.52Pe) \quad \bullet \text{ Eq. 3}$$

In their paper, Falk and Commenge [57] compare the performance of different types of micromixers from two criteria : the ratio between the mixing time, divided by the square of the characteristic flow dimension, vs. the Reynolds number (Figure .a). It can be observed that, at low Reynolds number, mixing is purely diffusive, whereas at higher Reynolds values, no matter the type of mixer, the mixing time is correctly predicted by Eq. 3. The mixing time was also compared to dissipation power for several micromixers. The Figure .b shows that the mixing time is inversely proportional to the square root of the energy dissipation. From this analysis it can be stated that the dissipation energy is the only relevant parameter for designing an efficient mixer.



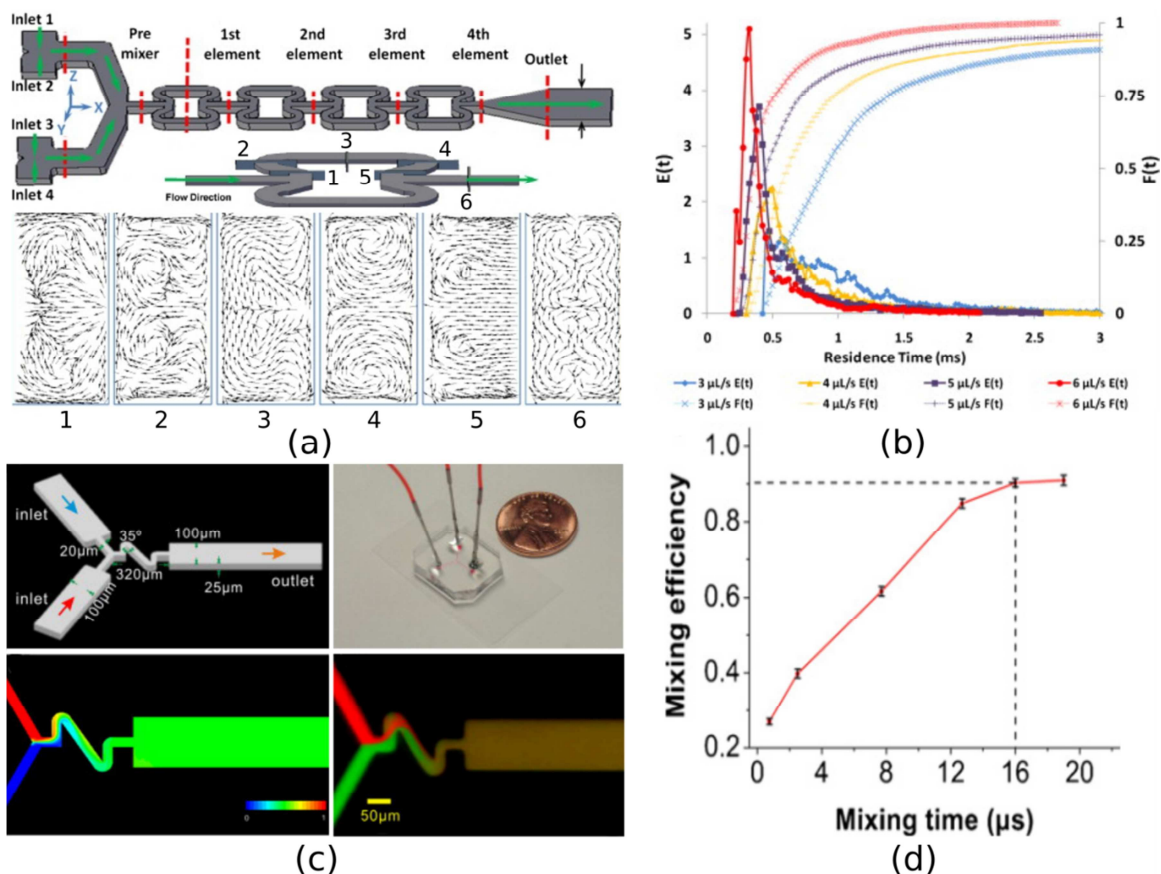
- Figure 4 (a) Comparison of different micromixers: Ratio of the mixing time, divided by the square of the characteristic flow dimension, versus the Reynolds number. (b) Influence of the energetic mixing efficiency: Evolution of the mixing time in different micromixers versus the specific power dissipation. *Reproduced from Falk et al. with permission from Elsevier [57].*

However, this analysis based on dissipation energy gives only a rough estimation of the mixing efficiency in micromixers. The geometry of the mixing chamber also plays a very important role in the optimization of mixing time. Complex geometries create temporal secondary flows in a laminar flow regime, promoting mixing and substantially differing from those observed in stirred tank configurations. This is the case, for instance, for the pair of vortices generated at the junction of a T-mixer [58], and for the Dean vortices created in curved [59] or in sharp [60] microchannels.

Based on these physical concepts of micromixing, a wide range of microfluidic micromixers has been developed during the last ten years [61-71]. The operation principles of the microfluidic mixers are mainly based on fluid stretch, folding, breakup, and molecular diffusion. The reviews of Hessel et al. [61] and of Nguyen [72] give a general overview of the mixers developed for Lab On chip and μ TAS applications. In very few studies, some researchers have used these microfluidic systems for production purposes. The small size of these microreactors ensures that thermal and chemical homogeneity is maintained throughout the entire reactor, leading to well-controlled reaction conditions [73, 74]. Until now, the applications of microfluidic reactors remain dedicated to niche production, or on demand production of high added value chemicals [75-77].

Among all the relevant micromixer designs available in the literature, two types of micromixers are of great interest for studying fast nucleation events. These mixers can achieve controllable homogeneous mixing of reactant in millisecond or sub-millisecond time frames before significant interactions, reactions or phase transition can occur. For instance, these microfluidic mixers (Figure 5) combine a T or Y shaped pre-mixers followed by a butterfly structure [78] or a zigzag channel [79]. Such low mixing times, allows the experimentalist to instantaneously reach specific point in the phase diagram without any influence of the pathway taken to reach it. These mixers are thus promising tools to characterize possible nucleation intermediate states existing in the microsecond to second time scale, which could be characterized by electron paramagnetic resonance, nuclear magnetic resonance, X-ray scattering, infrared and Raman spectroscopy, or cryo-electron microscopy techniques.

However, these microfluidic mixers could hardly be used for mass production mainly due on the one hand, to the lack of scale-up studies based on numbering-up, but also, on the other hand, because they have been originally designed to operate at low flowrates for analytical studies for which valuable reagent quantities are limited. For reactive precipitation, confined impinging jet mixers (T-mixers, Y mixers and vortex mixers) are preferentially used at lab scale but also for industrial production of micro or nanocrystals. Hartridge Roughton or Multi-Inlet Vortex Mixers (MIVM) promotes the rotation and stretch of the fluids in the mixing chamber, whereas T-mixers are essentially based on turbulent mixing. These mixers have been proved to be very efficient in organic [80-83], oxides and mixed oxides [84-86], and salt nanoparticles production [53, 87, 88]. Schwarzer et al. [53, 89] have shown how the supersaturation build-up influences the particle size distribution. They also demonstrated that the particle size distribution become self-similar when the turbulent flow in the mixing channel is fully developed. Similarly, Wei et al. [84] have compared the synthesis of magnetite nanoparticles performed in batch, T-mixers and MIVM. They found that the MIVM appears to be the most efficient way of producing magnetite nanoparticles. Compared to other synthesis methods, MIVM allows for the production of highly monodispersed and pure magnetite nanoparticles. In addition, compared to T or Y-mixers, thanks to its tangential inlet geometry, MIVM allows using different flow rates for each inlet, with a flow rate ratio up to 1 to 5.



- Figure 5 Examples of submillisecond micromixers (a) Design and configuration of the butterfly mixer and Velocity vectors at different planes normal to the flow path of the first butterfly mixing element. The velocity vectors showed the evolution of the secondary flow patterns (vortices) inside the mixer channel. (b) Particle residence time distribution $E(t)$ and $F(t)$ at the mixer outlet. Submillisecond mean residence time was achieved at high flow rates $>5.0\mu\text{L/s}$. (c) Design and configuration of the zigzag mixer. Simulation and fluorescent experiment results of the zigzag mixer at a flow rate of 10 $\mu\text{L/s}$. (b) Mixing efficiency as a function of various total flow rates (the dead time of the mixer was estimated to be 16 μs at a flow rate of 10 $\mu\text{L/s}$). Adapted from [64,65], with permission from Elsevier.

In addition, Fu et al. [90] have developed a sequential nanoprecipitation technique by combining two MIVM. This technique allows continuous production of a micelle-based template, followed by an in-situ formation of mesoporous silica nanoparticles. They have shown that the parameters of the resulting nanoparticles, such as silica shell thickness and inner cavity size, can be easily controlled by tuning the compositions of the reactant streams and that the drug loaded nanoparticles present excellent properties such as high storage stability, prolonged release time and high drug encapsulation efficiency.

3.1. Influence of Mixing on nucleation: beyond classical nucleation framework?

All the studies above presented and the analysis on time and length scale of mixing are mainly focussed on how fast a homogeneous supersaturated solution can be created. All these papers neglect the influence of mixing, and more specifically the influence of the mechanical stress, thus generated, on nucleation. Since the work of Mullin et al. [91], it is well known that the nucleation rate follows a non-monotonic behaviour with the mixing rate, or the turbulent dissipation energy (see fig. 3 in the case of a turbulent flow in a stirred reactor or eq. 3 for a laminar flow in tubes). Based on nucleation experiments performed for a large number of electrolytes solutions for different mixing rates, they demonstrated that the nucleation rate increases with the increase of the agitation speed, reaches a maximum, and decreases again. More recently, this behaviour has also been found for the crystallization of organic molecules in organic solvent in stirred reactors [92-94]. In totally different flow conditions, for instance when the reactants are confined in droplets, some authors have observed the same non-monotonic dependence of the nucleation rate with the agitation rate or the droplet speed in the case of proteins [95] and organic molecules [96] crystallization. Even if their results show that the nucleation kinetics strongly depends on the fluid dynamic conditions in the system, no definitive relation between shear rate and nucleation rate was found. This lack of understanding is mainly due to the complexity of the flow, either in stirred reactors or in flowing droplets. Forsyth et al. [97] have performed nucleation experiments in a Taylor-Couette flow cell, which allows to precisely control and to compute the shear stress imposed to the solution, coupled with turbidimetry measurements and image analysis to detect nucleation. They found that the induction times for nucleation of aqueous glycine solutions are, first, much lower in sheared than those in non-sheared solutions. Secondly, they found that the induction time of a sheared solution scales with the characteristic

time $\dot{\gamma}_{av}A^{-1}$: the higher the shear rate, the lower the induction times are. In previous studies on glycine and vanillin solutions, the authors have shown, by means of dynamic light scattering (DLS) experiments, the existence of liquid-like clusters that are responsible of glycine and vanillin nucleation. Consequently, to explain the relationship between nucleation rates and shear rate, the authors have performed DLS experiments on sheared and non-sheared solutions. They have found that the size of the liquid-like clusters, supposed to be precursors of the glycine crystal nucleation, increases with the increase of the shear rate. The increases in size were thought to be due to the aggregation or coalescence of glycine mesoscale clusters. As in their previous study [98] on glycine nucleation, they reported that glycine-rich mesoscale clusters of around 250 nm diameter with liquid-like properties exist in aqueous glycine solutions. These were not thought to be directly involved in productive crystal nucleation, but could coalesce to larger clusters to give access to a more rapid nucleation pathway. Then the proposed nucleation pathway in this system includes mesoscale clusters, where primary nucleation is more likely to happen within larger cluster. However, even if this proposed mechanism is quite interesting, there is, at the moment, no study that proves the conversion of small nanoscale clusters to larger nanoscale clusters, by measuring the evolution of the size and /or the concentration of the mesoscale clusters in solution while sheared. In addition, no direct observation of the conversion of liquid-like mesoscale clusters into crystals has been reported for these systems, and the real formation mechanism of the crystals is still unknown.

To explain the influence of the shear rate on nucleation, the authors of the study above presented have focussed on non-classical nucleation, in which nucleation proceed via a liquid-liquid phase transition or mediated by mesoscale intermediates. However, the influence of the shear rate on nucleation can also be explained by classical nucleation theory. Allen et al. [99] have performed numerical simulations of a nucleating system under shear rate, using a 2D Ising model. Even if their model is very simple and cannot capture the whole complexity of nucleation, this paper provides a fundamental understanding of the influence of the shear rate on nucleation. They explained the observed decrease in the nucleation rate for large shear rates due to shear-mediated breakup of the growing clusters (mainly due to its elongation), while the increase of the nucleation rate is due to shear-induced clusters coalescence as well as to shear-induced cluster growth by increasing its surface roughness. The authors conclude that the contributions of shear-enhanced cluster coalescence and shear-enhanced cluster growth appear to be of the same order of magnitude. Similarly, Mura and Zaccone [100], proposed a theoretical development, based on the CNT, by coupling the master equations describing the nucleus formation by addition molecules to a subcritical cluster with an analytical solution to the governing Smoluchowski diffusion-advection equation. Their model also takes into account the effect of shear-induced mechanical deformation of the cluster. Using their approach, they found complementary conclusions: at low shear rates, the nucleation rate increases with shear rate, because of the increase in adjective transport rate towards the nucleus. As the shear rate increases further, the increase in the elastic energy of the strained nucleus becomes more and more important, which increases the nucleation energy barrier.

4. Influence of additives in reactive crystallization

In reactive crystallization, additives can be added to either enhance or inhibit a reaction [101-103] and to control the final particle morphology [104-106]. Therefore, investigating the role of additives on a reactive crystallization becomes as essential as the control of other synthesis parameters (e.g.: concentration, temperature, pH) [107]. Here, the word additive stands for any foreign substance added to a reaction in minor quantities to alter a chemical reaction. The incorporation of such foreign substances can modify the precipitation routes in different ways:(a) altering the atomic and molecular structure arrangement of precursors (crystalline polymorphs) [108], (b) modulating crystal shape [105], and (c) guiding and stabilizing the formation of nanoparticles [109, 110], otherwise reaching larger sizes or undergoing aggregation. In this regard, several studies can be found in the literature on the study of additives effects on crystallization [111]. In these cases, both precursor and final crystal have been considered to have the same composition, and growth models have been extensively described on the basis of both theoretical and experimental aspects [111]. However, taking into account the more recent observation of various intermediate precursor phases (as mentioned in the section 2.2) [1], it can be expected that additives would interact with them, potentially modifying the crystallization routes. Consequently, it can be argued that additives will alter, not only crystal growth mechanisms [112, 113], but also the thermodynamic and kinetic aspects associated to the structure and composition of the nucleation precursors during reactive crystallization.

In order to facilitate the comprehension of the analysis of additive effects on nucleation and crystal growth made here below, table 1 intends to summarize the main works discussed along this section. Understanding additives role during reactive crystallization, would not only provide a better knowledge on crystallization mechanisms, but it will enable us to unravel various questions of very different nature, which still remain unanswered, such as (i) how crystallization happens under geological conditions [114], (ii) which are the dissolution-precipitation mechanisms for cements [115], (iii)how rare and unstable polymorphs emerge along a crystallization process [116],and (iv)how to control the final morphology of nanoparticles for diverse applications of interest [117].

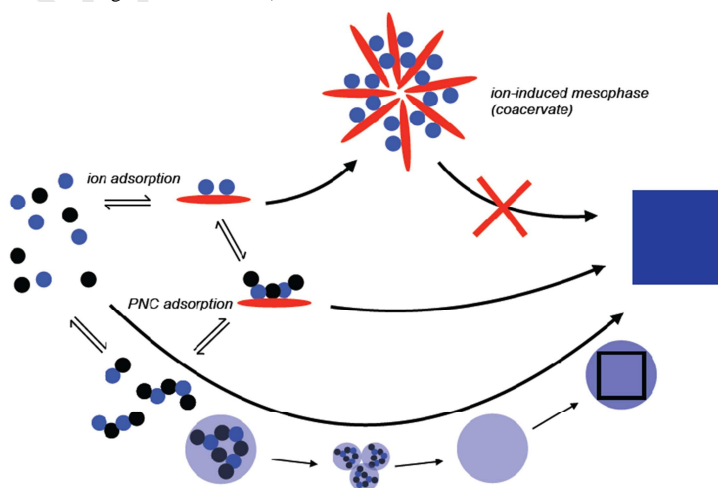
Table 1. Summary of the main works discussed about the influence of additives in reactive crystallisation

Reference	Precipitating System	Nature of the additive	Main effect	Mechanism
Nicoleau et al. [115]	Gypsum	Poly(acrylamide), Poly(acrylicacid), ...	Inhibition of nucleation and growth processes at various stages	Kinetics-based mechanism
Rabizadeh et al. [118]	Gypsum	Alkali and alkaline metal ions	Decrease in growth kinetics as a function of ionic strength and ion concentration	Not discussed
Bots et al. [119]	Calcium carbonate	Sodium sulfate	Adsorption of $[SO_4]^{2-}$ on facets retards the	Multi-stage growth process

			growth process	
Fdez.-Diaz et al. [120]	Calcium carbonate	Sodium sulfate	Increases the solubility of the stable phase	Dissolution-recrystallization process
Gebauer et al. [121]	Calcium carbonate	Poly(acrylic acid) and more	Inhibition of nucleation and growth processes at various stages	Multi-step growth process
Tong et al. [122]	Calcium carbonate	L-aspartic acid	Formation of a meta-stable phase	Growth- and fusion-limited aggregation mechanism
Shen et al. [123]	Calcium carbonate	Collagen	Formation of new crystal facets	Not discussed
Ruiz-Agudo et al. [124]	Calcium oxalate	Trisodium citrate	Stabilization of different intermediate states	Multi-step pathway
Ley-Ngardigal et al. [125]	Calcium pyrophosphate dihydrate	Metal ions	Formation of a less stable phase	Not discussed
Scheck et al. [126]	Iron(III) oxide polyaspartic acid	Polyaspartic acid	Promotes phase transformation	Multi-step precipitation process
Yi et al. [127]	Sodium yttrium fluoride	Ethylene diamine tetra acetic acid	Tuning the final size of nanoparticles	Not discussed
P. H. Hsu [116]	Pseudo-boehmite	Sodium chloride	Phase formation promoted due to the solvation of added salt	Not discussed

4.1. Modification of thermodynamic and kinetic parameters

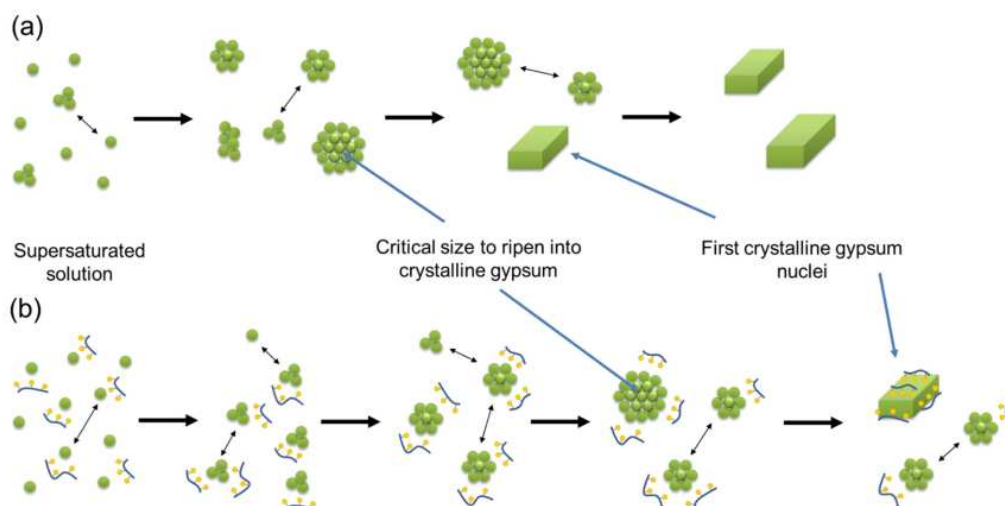
In the case of ionic systems, if spontaneous interactions exist with ions, one would expect that additives could be incorporated into crystal nuclei, inducing a decrease in their interfacial energy and lower the activation barrier. As a result, a reduction in induction times for nucleation would be expected, according to the CNT. However, on the thermodynamic side, the change in free energy barrier (ΔG^*) of a system to form a nucleus must be higher in presence of an additive than in the additive-free system (ΔG) [7]. Therefore, from a classical point of view, any possible formation of stable nuclei along with the additive is thermodynamically ruled out [114]. In this sense, Nicoleau et al. [115] found that as they increased the concentration of additive, the induction time for gypsum nucleation increased due to the enhanced interfacial energy. After nucleation, on the basis of CNT, the growth process could be inhibited by two routes: (i) The incorporation of additive impedes the ion-ion interactions and destabilizes the forming object and (ii) Strong interactions between additive and ions and/or high additive concentration can lead to the stabilization of intermediate mesophases or coacervates, instead of final crystals [114]. In contrast, in the framework of “non-classical” prenucleation clusters, weaker ion-additive interactions and/or low additive concentration would guide to final crystals. The favoured thermodynamic pathways in presence of various possible precursors are summarized in Figure 6 [114]. However, several questions remain unanswered: Do the additive incorporated nuclei have a higher free energy than supersaturated solution? Is. However, there are several questions that still remain unanswered: Have the additive incorporated nuclei a higher free energy than supersaturated solution? Are the existence of pre-nucleation clusters, together with a weaker interaction between additive and ions, the limiting factors to reaching the final crystals? Is the above mechanism valid for all solution-grown crystals, or limited to a particular crystal family (e. g: ionic crystals, metals, organic molecules...)?



- Figure 6. Schematic illustration proposed by D. Gebauer [114] of crystal nucleation with the ions and the pre-nucleation cluster pathways. The top and middle pathways show the potential effect of ions or pre-nucleation cluster adsorption on impurity or additive. The top pathway show that in case of high concentration of additives and/or strong ion-additive interactions, the formation of crystal is inhibited. Reproduced from Ref [114].

On the other hand, Nicoleau et al. [115] have shown by comparing the solution / nucleus interfacial properties (obtained by CNT and by wetting measurements), that pure thermodynamic interpretation of nucleation retardation is contradictory. Indeed, all the inhibitors used in

their study should instead favour nucleation by lowering the energetic barrier for the formation of the critical nucleus. The authors deduced that their experimental results were consistent with a kinetics-based mechanism, in which the polymeric inhibitor reduces the attachment frequency of monomers, within the framework of CNT (and acting on the pre-exponential factor of the nucleation law). They also analysed their data assuming a multistep (prenucleation clusters, liquid-like state amorphous, or highly hydrated particles) nucleation pathway. In this context, they propose that the polymer prevents the species from aggregating or reorganising. Consequently, the presence of additive lowers the probability of forming stable crystal seeds, and thus decreases the rate of crystal nucleation. The growth of clusters in solution can be limited by either reaction or integration in an existing cluster (reaction-limited cluster growth), by long-range diffusion, by aggregation and coalescence of larger units (preformed structures). As shown, in figure 7, for gypsum, in any cases, the presence of polymer inhibitor, hinders either diffusion, aggregation or fusion of the precursors, and in this way increases their kinetic persistence in solution.



- Figure 7. Nucleation pathway of Gypsum proposed by Nicoleau et al. [115]. (a) pure solution (b) with additive. Cluster are formed either by aggregation of monomer (CNT) or by aggregation / coalescence of pre associated entities (non-classical nucleation pathway). The collision probability and efficiency are reduced by the presence of the polymer; the live time of molecular entities in solution is increased as well as the induction time for crystal nucleation. Reprinted from [115], with permission from Elsevier.

4.2. Additives as inhibitors or promoters

Additives can directly or indirectly promote or inhibit reactive precipitation. However, while the effect of additives as inhibitors has been profusely reported in literature [117], reports concerning promoters are very scarce [116, 117]. For example, the effect of alkali ions on the kinetics of calcium sulfate dihydrate crystals was investigated using turbidity measurements [118], which is one of the most widely used techniques to determine nucleation/precipitation kinetics [117]. Turbidity was monitored as a function of reaction time to investigate the role of cations of different size on nucleation. It was observed that the higher the ionic strength, the stronger the affinity towards the CaSO_4 , and in turn, the higher the product solubility. As a result, nucleation and growth are inhibited by the presence of alkali ions, which delay the solvation of cations.

In another study, the influence of Na_2SO_4 on the crystallization of calcium carbonate was examined using X-ray scattering [119]. Again, both nucleation and growth rates were observed to decrease in presence of the sulphate $[\text{SO}_4]^{2-}$ molecules. However, the reductions in rates were not attributed to the incorporation of $[\text{SO}_4]^{2-}$ molecules in the growing nuclei, but to the adsorbed $[\text{SO}_4]^{2-}$ on growing faces which “poisoned” the vaterite spherulites surface. In this regard, if aggregation or growth of particles is to be prevented, a stabilizing agent is generally required. D’Addio and Prud’homme [83] rapidly mixed, using a MIVM mixer, a dissolved solute and stabilizing amphiphilic polymer with an antisolvent to create a high supersaturation promoting the formation of nanoparticles. The “poisoning” of the nanoparticles’ surfaces by adsorbed amphiphilic polymer uniformly stops growth, to produce nanoparticles with narrow particle size distributions.

The ability to promote the nucleation of a crystal phase has been inferred in two different systems by means of XRD and turbidity measurements: pseudo-boehmite [116] and iron(III) oxide-polyaspartic acid [126]. In the first case [116], a large excess of NaCl was incorporated to the system, enhancing the solvation of the salt at the cost of aluminium hydroxide ($\text{Al}(\text{OH})_3$) dehydration. As a result, the nucleation of pseudo-boehmite phase ($\text{AlO}(\text{OH})$) was favoured with respect to the nucleation of $\text{Al}(\text{OH})_3$. In the second case [126], the interaction mechanisms between polyaspartic acid and hydrolysed olation prenucleation clusters were observed by titration of the iron(III) (oxyhydr)oxide formation. It was observed that these interactions facilitate the formation of oxo-bridge compounds and leads to the formation of iron(III) oxide-polyaspartic acids. The mechanisms for inhibition or promotion have been reported on very few (CaSO_4 , CaCO_3) systems. A better understanding would require extending this study to other materials. In addition, other characterization techniques are required to prove in-situ the promotion/inhibition mechanisms. Using Raman spectroscopy, we can observe various interactions between

precursors and additives during a course of reaction, by tracking the intensity and position variation of specific Raman vibrations [128]. Similarly, using X-ray absorption spectroscopy (XAS) it is possible to follow the evolution of the oxidation state(s) for metals and their corresponding local environment in presence of additives, during a reaction [129].

4.3. Effect of additives on particles morphology and crystal structure

As mentioned above, the use of additives during a reactive crystallization, can not only modulate the growth rates but it can also tune and dictate final particles morphologies [105] and crystal structure (polymorph selection) [121, 130]. Thus, using additives in reactive crystallization would open the way to the control of a wide range of crystal morphologies (hexagonal, cubes, wires, etc.). This becomes particularly advantageous in various scenarios such as particle filtration [131], selective dissolution [132], luminescent labelling [127]. Various effects of additives on particle morphologies are discussed in literature: Guangshun Yi et. al. [127] demonstrated that the diameter of spherical NaYF_4 crystals can be varied from 37 to 166 nm by the addition of ethylene diamine tetra acetic acid (EDTA). However, the mechanisms by which EDTA is affecting particle growth are not explained. The role of alkali/alkaline earth metal ions on the morphology of calcium sulfate dihydrate (gypsum) crystals has also been examined [118]. Here, added ions were found to adsorb on the crystals high surface energy regions thus enhancing the growth in the perpendicular direction. With the increasing ionic strength of the media, gypsum crystals developed a higher aspect ratio with either almost same or reduced width. In other studies, the effect of additives on the particle morphologies and structure has been investigated in the case of biomaterials: namely in calcium carbonates, oxalates and phosphates crystallization [110, 122-124, 133]. The effect of collagen on the formation of CaCO_3 was investigated [123], finding that the increase of collagen concentration induced the formation of defects at edges (steps) and corners (kinks) of the crystals. Therefore, collagen moves towards high affinity distorted (i.e., high surface energy) regions and subsequently, it is incorporated into the sites, slowing down the growth process in those directions. This results in the formation of new crystal faces, thus modifying the crystal morphology. By increasing concentrations of collagen, the shape of CaCO_3 varied from rhombohedral to spherulitic, through the progressive thinning of crystal layer thickness. In another work, the synthesis of CaCO_3 , in presence L-aspartic acid (L-ASP), was performed [122], observing the progressive transformation of calcite to meta-stable vaterite with the increase of L-ASP concentration. Above 1.0 mg/ml of L-ASP, only vaterite precipitates. In this study, the observed mechanism was ill-defined and the vaterite formation was attributed to the high supersaturation concentration of precursor. Other authors investigated the formation of calcium oxalate in presence of trisodium citrate [124]. With the increasing trisodium citrate concentration, the induction time for nucleation was enhanced. Further, different intermediate phases were stabilized by the additive and consequently, delayed/postponed the formation of successive intermediate phase(s), as it has also been observed for calcium phosphate systems [110], where a template effect mechanism has been suggested to explain nanoparticle size stabilization. Owing to the stabilized amorphous phase, the dissolution and re-precipitation scenario of amorphous phase leads to high soluble meta-stable crystalline phase of calcium oxalate (caoxite).

Fernandez-Diaz et al. [120] investigated the transition of meta-stable vaterite into stable calcite, in presence of $[\text{SO}_4]^{2-}$. At the initial times (depending on $[\text{SO}_4]^{2-}$ concentration: even up to several hours), the added $[\text{SO}_4]^{2-}$ stabilizes the meta-stable vaterite phase over the stable calcite phase. Further, the added additive increases the solubility limit of the calcite and in turn, favours the reaction towards the vaterite formation. As a result, the majority of crystals obtained were vaterite instead of calcite. However, as reaction time progresses, the initially formed vaterite crystals were transformed to calcite. For some cases (for instance, molar ratio $[\text{SO}_4]^{2-}/[\text{CO}_3]^{2-} = 1.62$), this transformation was reported to take up to 350 hrs. In addition, Ley-Ngardigal et al. [125] have studied the influence of various ionic additives on the crystallization of triclinic calcium pyrophosphate dihydrate (t-CPPD). By combining, XRD and solid state P-NMR, they found that, even if the additives concentration were very low (trace), all the divalent ionic additives orient the crystallization calcium pyrophosphate from the stable phase (t-CPPD) to the less stable phase (m-CPPD) [134]. In the case of trivalent ions, crystallization was totally inhibited, and the formation of a very long lived amorphous phase was obtained. In addition, in all cases, they also prove that this change in crystal structure is induced by the incorporation of the additive in the crystal lattice.

5. Concluding remarks and open questions

This review focused on recent advances made for a better control of reactive crystallization processes, thanks to the progress made in three areas: i) the understanding of fundamentals of nucleation, ii) the control of precipitation kinetics by the improvement of mixing efficiency, and iii) the use of additives, either to control kinetics or to achieve desired particles properties (morphological, structural). Yet, much more remains to be done. Our understanding of the very first instants of fast nucleation events, which occur far away from the thermodynamic equilibrium, and in which disordered intermediate states are more likely to occur, is taking its first steps. Indeed, most of the experimental evidences that clearly show a "non-classical" nucleation behaviour have been performed on relatively slow nucleating systems, with time scales ranging from few seconds (calcium carbonate) to few hours or days (organic crystals or proteins), using stirred vessels or in static conditions. Due to the low energy involved in these processes (in the range of few k_bT), and because the position and path in the phase diagram are critical parameters, in some cases it would not be easy to determine up to which extent these findings could be a result of mixing artefacts (in the sense of a non-homogeneous mixing leading to a locally very high supersaturation) [135]. Moreover, in the cases where additives are involved in reactive crystallization, their effects on nucleation can hardly be explained without the presence of intermediate transient precursors to crystalline nuclei formation. The existence and possible detection of these precursors, already observed for very different systems, and pointing out to liquid-liquid phase separations, is highly dependent on the achievement of local supersaturation maxima, and thus on mixing. While the authors would dare to suggest that this mechanism could be generalized to all reactive and most of

non-reactive crystallization systems, on the one hand, in all the studies here presented, mixing effect has not been considered even though its relevance for the formation of transient precursors is hardly open to question. On the other hand, recent developments have shown that the presence of additives, even as trace, can orient crystallization, but also they can be used for stabilizing mesophases or prenucleation clusters. Taking into account that in the case of fast reactive crystallization, non-classical routes are likely to occur, we expect that this review will highlight the importance of mixing and the importance of additives for the control and for a better understanding of reactive crystallization.

In this context, we are convinced that the above-mentioned newly developed experimental setups based on micro- or millifluidic technologies [18, 31, 136, 137], will provide effective methodologies, not only for studying nucleation, but also for production purposes by multiple parallelization, in which a lot of effort have to be done. Indeed as they allow for a precise control on reactive crystallization operating conditions by means of a perfect control on mass and heat transfer, and mixing, they can provide a perfect environment for a better understanding of reactive precipitation processes (in the framework of non- classical nucleation), and for the rationalization of the use of additives. The combination of additives and micromixers, which can alter either the nucleation free energy landscape of nucleation, or the dynamics of phase transition, will definitely contribute to the development of valuable methodologies to orient or slow down the nucleation processes. From this perspective, we are convinced that the work of Fu et al. [90] pave the way of the use of combined micromixers for a precise control on reactive crystallization within sub-millisecond to millisecond timescales. Coupled with powerful time-resolved analytical techniques (SAXS, EXAF, XANES, High Energy XRD from a synchrotron source), these approaches will help us to improve our understanding of nucleation mechanisms, of the effect of additives or impurities on nucleation, and also to capture the structure and the composition of the nucleation intermediates.

Conflict of interest statement

Nothing declared.

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* of special interest

** of outstanding interest

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: