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Concomitant crystallization for in situ encapsulation of organic materials

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ABSTRACT

Concomitant crystallization leads to process intensification through the synergistic combination of the partial processes of particle formation and encapsulation within a single process step. Both cooling and electrospray crystallization in multi-component solutions were used to create (sub-)micron sized particles of different crystalline materials. Concentrations were varied to control core and shell material. Depending on the relative initial concentrations used, concomitant electrospray crystallization of isonicotinamide and caffeine leads to encapsulated particles. Only limited encapsulation was achieved during concomitant cooling crystallization. Concomitant cooling crystallization of cyclotrimethylenetrinitramine (RDX)–2,4,6-trinitrotoluene (TNT) resulted in separate RDX and TNT particles. Using electrospray crystallization, spherical nano-particles were produced, for which the component distribution within the particles could not be determined. Whereas crystallization from bulk solvent starts with a nucleus that grows gradually outward, whereby heterogeneous growth of a coating material on this core particle is not guaranteed, it appears that crystallization from evaporating solvent droplets starts at the surface of the droplets, and moves gradually inward. The resulting RDX–TNT powders have been tested for impact and friction sensitivity. The impact sensitivity has decreased compared to the raw materials, and the friction sensitivity did not change.

1. Introduction

In many fields of research (e.g. consumer products, foods, pharmaceuticals), products come in the form of organic, crystalline powders. Crystallization processes are used to produce and purify the solid materials and can be adapted to optimize properties like particle size, shape and purity. Such properties are for a large part responsible for the functionality of a product [1,2]. However, some functionalities, e.g. chemical and thermal stability [3], protection from external influences [4,5] and improved shelf life [6], cannot be achieved by optimizing the pure product properties. In such cases addition of another compound, to induce e.g. co-crystallization [7], salt formation [8], or microencapsulation, can tune the product to meet the customer's requirements.

Microencapsulation is the application of a thin coating layer around a core micro particle. Application of this technique to organic products has achieved several successes. In the field of energetic materials the sensitivity of an explosive, i.e. tendency to ignite due to external influences like shock or friction, is a serious safety issue [9,10]. In various studies the sensitivity of energetic materials was reduced, while maintaining their effectiveness, by encapsulating the product with a less sensitive energetic material [11,12]. In pharmaceutical research the transport of active pharmaceutical ingredients (API's) inside the human body is of major importance for the effectiveness of the drugs [13]. Rosenkranz et al. [14] achieved controlled release properties by encapsulating crystals of the protein BSA with paraffin, thereby retarding the dissolution of the compound.

In all aforementioned studies the core particles were preformed, and then seeded into a crystallization process of the coating material. As crystallization is already used for the particle formation and purification, intensification in the functional domain [15] by combining the encapsulation with the existing process step leads to several advantages. For example, direct core–shell formation reduces the number of processing steps, potentially leading to a compact, safe, energy-efficient, and environment-friendly sustainable process [16].

The integration results in the processing of complex solutions with two or more solutes. The crystallization of these solutes must be controlled in a way that they crystallize subsequently,

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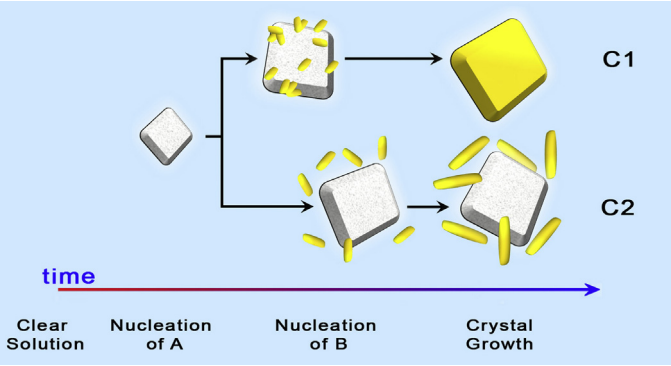

Fig. 1. Possible mechanisms in concomitant cooling crystallization. In mechanism C1 heterogeneous nucleation takes place of B onto A, leading to encapsulation, in mechanism C2 A and B form separate particles.

the resulting particles consisting of both component layers. If the concentrations in this process are chosen such that one of the solutes nucleates before the other is supersaturated, the nucleation behavior of the second solute can be influenced. Instead of nucleating at its own metastable zone limit, forming new particles, the second solute can heterogeneously nucleate on the surface of the first. Therefore, control is required over heterogeneous nucleation behavior, which is one of the major challenges in nucleation research [17]. We aim to crystallize particles that act as heterogeneous templates, onto which other particles form in the same processing step. We investigate how the crystal formation occurs in both cooling and electrospray crystallization processes.

Two model systems were investigated, the combination of the pharmaceutical compounds caffeine (CAF) and isonicotinamide (INA), and the combination of the energetic compounds cyclotrimethylenetrinitramine (RDX) and 2,4,6-trinitrotoluene (TNT). For the RDX–TNT system, it is important for safety reasons that the sensitivity of the explosive formulation is reduced. The resulting materials have been tested on composition, crystal shape, size and size distribution. Additionally, the energetic materials have been tested regarding their impact and friction sensitivity.

2. Potential concomitant crystallization mechanisms

With an aim to crystallize heterogeneous template particles and subsequently deposit particles of other compounds in the same processing step, the crystallization of both compounds from their complex solutions, containing multiple solutes, must be controlled. This concomitant crystallization process is studied in two different ways. Concomitant cooling crystallization is used to show the crystallization behavior in the free environment of bulk solvent, where it is imperative that the solutes have a certain affinity towards each other, in order to form particles consisting of both materials. With "affinity" we mean the effectiveness of the interaction between the different crystalline materials, with high affinity resulting in heterogeneous nucleation of one crystalline material onto the surface of previously formed crystals of the other. This requires a low interfacial energy between the crystalline material and the previously formed template crystal. Also the degree of structural and chemical match of these phases can be an important factor. Fig. 1 shows the possible mechanisms for a concomitant cooling crystallization process. In mechanism C1, where the compounds have a high affinity for each other, compound B heterogeneously nucleates on the surface of the previously crystallized compound A, thereby encapsulating this compound. In mechanism C2, where the affinity is low, compound B does not heterogeneously nucleate onto compound A, leading to separate particles of A and B.

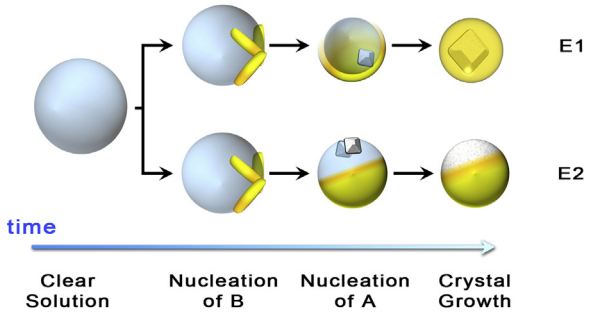

Fig. 2. Possible mechanisms in concomitant electrospray crystallization. In mechanism E1 heterogeneous nucleation takes place of A onto B, leading to encapsulation, in mechanism E2 particles are formed consisting of both A and B, but no real encapsulation takes place.

In order to reduce the dependence on the affinity between compounds on the resulting material, concomitant electrospray crystallization is used to study crystallization in a small confined space. Electrospray crystallization, similar to cold plasma crystallization [2], uses an alternative energy form to intensify the crystallization process. In electrospray crystallization [18] the solvent is dispersed in tiny, charged droplets using a high electric field, and subsequently fully evaporated, leading to the formation of small particles. Fig. 2 shows the possible mechanisms of particle formation in concomitant electrospray crystallization. In mechanism E1 compound A heterogeneously nucleates onto compound B, on the inside of the droplet. After removal of all solvent compound A is encapsulated by compound B. In mechanism E2 compound A does not heterogeneously nucleate onto compound B and no encapsulation will take place. However, due to the decreasing droplet size, particles will be formed consisting of both materials. Here it is tested whether concomitant electrospray crystallization always forms small particles consisting of multiple solids, where this cannot be achieved with concomitant cooling crystallization.

3. Experimental

3.1. Chemicals

INA (>99%) and anhydrous CAF (>99%) were purchased from Sigma Aldrich. The solvent used for these compounds was 92.5% ethanol. Ethanol (100%) was purchased from Sigma Aldrich and was diluted with ultrapure water in order to increase the caffeine solubility. TNT (2,4,6-trinitrotoluene) and class 2 RDX (cyclotrimethylenetrinitramine) were purchased from Chemring Nobel A.S., Norway. Acetone was used as solvent for these compounds. Acetone (99.8%) was purchased from Merck.

3.2. Cooling crystallization

The solubility of the compounds in the solvent and the metastable zone width (MSZW) of the solutions were determined using the Crystal16 multiple reactor setup (Avantium B.V.). Sixteen vials containing 1 ml solution were subjected to a preset temperature profile, to fully dissolve and subsequently crystallize the solutions three times, during which the saturation and nucleation temperatures were determined by measuring the transmissivity of the samples and linking that to the temperature with an average error of $\Delta T = 0.8\,^{\circ}C$. Resulting data were used to determine relative concentrations, to be used in cooling and electrospray crystallization experiments.

Concomitant cooling crystallization experiments were conducted using the Crystalline multiple reactor setup (Avantium B.V.). Vials of 8 ml with solutions containing multiple solutes were