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Continuous and reactive nanocrystallization: New concepts and processes for dual-use advances

Nanocristallisation continue et réactive : des concepts et des procédés nouveaux pour des avancées duales

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ABSTRACT

The nanocrystallization of organic pure and composite materials in amounts compatible with industrial demands opens an important challenge as such compounds are of high interest in the fields of pharmacy and defense. We demonstrate the versatility of the Spray Flash Evaporation (SFE) process which is a continuous technique and will establish a wider sphere of hierarchical nanocomposite structures and materials. The paper shows in detail the progress that is reached on the precise nanostructural tuning of composite matter, giving by the same way access to precise medical applications (e.g., advanced drug synthesis). Furthermore, SFE enables the production of energetic nanostructured precursors and therefore permits the synthesis by detonation of ultrafine nanodiamonds with pioneering sizes less than 5 nm. Without any doubt, the use of SFE opens a large fundamental research possibility and applicative issue for future products. To realize opportunities described in the manuscript for the materials conceived by SFE, we also introduce challenges to face in terms of structural characterization with high spatial and chemical resolution that were never reached in a combined manner before.

RÉSUMÉ

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La nanocristallisation de matériaux organiques purs ou composites dans des quantités industrielles est un défi majeur du fait qu'ils presentent un intérêt important pour la pharmacie et la défense. Dans cet article, nous démontrons la polyvalence du procédé *Spray Evaporation Flash* (SEF), une technique continue qui permet d'étendre l'accès à des matériaux nanocomposites hiérarchiques. L'article décrit les avancées obtenues en matière d'ajustement structural des nanocomposites, ouvrant par la même occasion la voie vers les médicaments de précision (e.g., élaboration de médicaments avancés). De plus, au travers de la production de précurseurs énergétiques nanostructurés, la technique SEF permet aussi la synthèse par détonation de nanodiamants ultrafins, avec des tailles de particules pionnières inférieures à 5 nm. Sans aucun doute, l'utilisation du SEF ouvre largement des possibilities en matière de recherche fondamentale et du point de vue des applications

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pour des produits nouveaux. Afin de concrétiser les opportunités des matériaux produits par SEF, qui sont décrites tout au long de l'article, nous évoquons également les défis qu'il faudra relever en matière de caractérisation structurale, avec des résolutions spatiale et chimique jamais atteintes conjointement jusqu'ici.

1. Introduction

Ascanio Sobrero discovered nitroglycerine in 1847. In 1879, William Murrell proposed to use it for the treatment of *angina pectoris*, due to the dilator properties of the chemical [1]. Until the beginning of the 20th century, nitroglycerine was the most used explosive in the world.

(3-Nitrooxy-2,2-bis(nitrooxymethyl)propyl) nitrate, also known as Pentaerythritol tetranitrate (PETN), a nitrate ester, is used for diagnosis and treatment for heart diseases [2,3]. It is still used worldwide in many detonators and/or priming systems. These two examples show the duality, which exists for some small organic molecules, which were used or known as medicaments, before being used as explosives. These nitroaromatics, nitramines, and nitrate esters are used in the defense area as well as in the medicament field. Furthermore, to show dual use applications of the process engineering research originally concentrated on the production of energetic nanomaterials, the work will also give the example of some purely small model medicament molecules, for example caffeine. Caffeine is well known as a stimulant of the nervous system and a muscle relaxant. Often, to enhance its bioavailability and to reduce sensitivity to humidity, caffeine is cocrystallized with oxalic acid, which is much more stable to humidity than the cocrystal caffeine/glutaric acid [4,5].

After seeing dual applications of some organic molecules in the explosive and medicament fields, one has to recognize that these molecules are always small organic molecules, with elements having low atomic numbers (H, C, O, and N). In the case of such substances, there is also a dual or shared need to produce them in the form of small particles and even in the form of nanoparticles. The smaller the particle size, the higher the bioavailability in the case of medicaments, and the higher the effectivity in the case of explosives. Another important need in the use of nanoparticles is the possibility to engineer nanoparticles in the form of nanococrystals to enhance further and precisely their performances. The specific properties can be tuned due to the cocrystal nature, by combining in a certain way the individual properties of each pristine molecule, which is part of the cocrystal. Within the medicament field, cocrystals introduce the precise or tuned Active Principle Ingredient (API) liberation through cocrystallization of an API with an adapted coformer [6]. In the energetic field, cocrystals offer the possibility to tune or to adjust the reactivity and sensitivity of an explosive formulation at the same time [7].

After advancing the high potential of these organic particles that are explosives and medicaments in the form of pure submicron- or nano-sized particles, in the pure or in the cocrystal state, one has to recognize the current poorness of the existing production technologies to face the challenge of producing these particles in high amounts – compatible with industrial needs. Therefore, present work will show the production of high amounts and the use of the presented technique for reactive synthesis: the production of nanodiamond particles with ultimate small sizes (<5 nm) and the need to characterize the organic materials as their size is regularly decreased in the last few years.

2. Continuous nanocrystallization: principle and production of model medicaments and energetic materials

Without having the objective to give an exhaustive review on available techniques and processes to nanocrystallize organic materials such as medicaments and explosives, one can cite among the ten most known techniques four main approaches that are conducted in the pharmaceutical and energetic fields. First one is the sol-gel approach. There are no intrinsic precursors, nor for medicaments nor for explosives, which are for example available in the case of the synthesis of nano-oxides, such as for example alkoxides. Nanoexplosives were elaborated, during the sol-gel synthesis of SiO_2 for instance [8,9]. This technique has in fact two drawbacks:

- First, it is hardly possible to recover the explosive within its original particle size and in its pure form after synthesis.
- Second, as the technique is discontinuous, it is also difficult to obtain high industrial amounts, with constant quality in terms of particle size distribution and morphology.

The second technique, which should be mentioned, is the so-called antisolvent technique. Using this process, medicaments and/or explosives are obtained in small particle sizes, by dissolving the compounds inside an organic solvent, and then, by rapidly mixing the solution into an anti-solvent, subsequently inducing a fast crystallization of the organic material [10,11]. Here again, despite that in this case it is possible to produce pure particles, it is also difficult to master a reproducible, narrow particle size distribution. Again – and even more important for energetic materials – batch techniques are very difficult to be upscaled for industrial purposes, as the risk is clearly enhanced by the amount of energetic materials. The latter is due to safety reasons. This trend will be more and more present in the future, with continuous severity increasing of the security rules.