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Reactive crystallization in pharma industry

Diwakar Z. Shende
Visvesvaraya National Institute of Technology, India

Reactive separation is a chemical process in which the synthesis of a substance (reaction) and the separation of by-products proceed simultaneously in one unit. In the chemical, refining and pharmaceutical industries, the interest in combining chemical reaction and separation in one hybrid process has been constantly growing. In traditional plants, reaction and separation proceed in units connected in a series: a reactor and generally numerous separation columns. In case of reactive separation, however, the reaction takes place in the reaction zone, and the separation of by products in the separation zone(s), of one and the same column.

Processes combining reaction and separation into a single, integrated operation become ever more attractive for chemical, pharmaceutical and related industries. Reactive separations show several important advantages like energy and capital cost reduction, increase of reaction yield and reduction of waste emission. As the product is continuously withdrawn from the reaction zone, the chemical equilibrium in case of equilibrium-limited reactions is shifted towards the products, which increases the conversion of the reactants. For exothermic reactions, the heat of reaction enhances the evaporation process and reduces in this way the demand of additional energy supply.

Reactive separation processes are: reactive distillation, extraction with reaction, reactive crystallization, reactive membrane separation, reactive absorption, adsorption with reaction.

Crystallization touches every aspect of our lives from the foods we eat and the medicines we take, to the fuels we use to power our communities. The majority of pharmaceutical products go through at least one crystallization step during their manufacture. Salt and sugar are delivered to our dinner tables as crystals.

Physical-chemical properties of the final product also depend on crystal characteristics. Crystallization process design in the pharmaceutical industry frequently targets crystal with controlled size, shape, purity and polymorphic form. In order to produce particles of small mean size directly, isolation techniques and equipment configurations producing uniformly high supersaturation, i.e. high rates of nucleation are needed. Reactive crystallization is known to produce very high levels of supersaturation.

When supersaturation of a crystallizing compound is created by chemical reaction, the operation is known as reactive crystallization. In reactive crystallization, reactions can be very fast compared to the mass transfer rates and growth rates to the crystals. It causes high local supersaturations. The high level of supersaturation results in high nucleation rates and small size crystal in the submicron to several micron range.

Production of crystals of small size in the manufacturing process of pharmaceutical compounds is important to improve properties such as dissolution rate, bioavailability, and tableting of the drugs, and to avoid additional downstream operations such as milling to reduce the particle size.

Many new pharmaceuticals have low water solubility, hampering their pharmaceutical activity upon administering. Half of the new active pharmaceutical ingredients (APIs) being identified are either insoluble or poorly soluble in water, solving bioavailability problems is a major challenge for the pharmaceutical industry.

Studies with poorly water-soluble drugs have demonstrated that particle size reduction to the sub-micron range can lead to an increase in the dissolution rate (the total amount of drug substance that dissolves per unit time) and a higher bioavailability. By decreasing the crystal product size, the surface-to-volume ratio is increased. Since smaller particles have a much higher specific surface area, an increase in the dissolution rate is expected at the same driving force for dissolution. Due to the relatively larger surface area, the dissolution rate is enhanced so that a higher concentration can be reached in shorter time frames. An increase in the solubility might be expected, since according to the Ostwald-Freundlich relation, smaller particles have increased solubility.

In the pharmaceutical industry, over 90% of the active pharmaceutical ingredients (API) are crystals of small organic molecules. The effectiveness of the API depends on key characteristics of the crystals. Two of the relevant characteristics are the mean crystal size and the crystal size distribution, which affect the transport of the API through the circulatory system to the target organs.

Reactive crystallisations can lead to the exclusive formation of the metastable polymorph of a system.

The phenomenon of polymorphism (the ability of a compound to exist in more than one crystalline structure) is of paramount importance in pharmaceutical products, as one polymorphic crystal may have good therapeutic effects and the other polymorphs may be inactive or may even have lethal effects. Researches involving polymorphisms is becoming increasingly important to the pharma industry because they change the effectiveness of the drug and are often the subject of lawsuits, e.g. Ranitidine-HCl is used for treatment of peptic ulcers and has two known polymorphic forms. Ritonavir (Novir) is a HIV protease inhibitor that has polymorphisms that have very different solubilities. In 1998, Abbott had to discontinue production of the drug until they corrected the polymorphism that they were using because it dissolved much slower than the polymorph they have used in earlier testing of the drug.

In view of the above, it is thought desirable to discuss the role of reactive crystallization for different significant drugs as basic tool in pharma industries and the advances therein.

Biography

Diwakar Z. Shende has completed his Ph.D. at the age of 35 years from Visvesvaraya National Institute of Technology (VNIT), Nagpur, Maharashtra, India and is serving VNIT Nagpur, a premier organization in technical education in India, as an assistant Professor of Chemical Engineering. He has published more than 12 papers in international journals of repute.