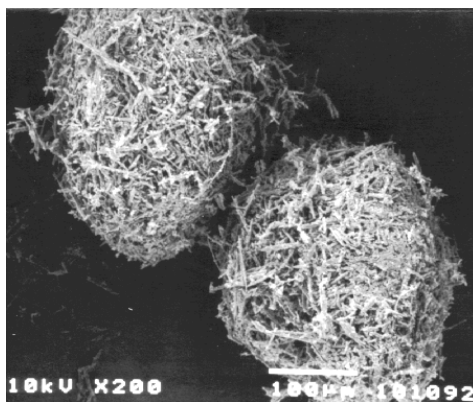


## Spherical Crystallization

Author: Karol Horvath, Director of Crystallization Services, Syntagon

**Introduction:** Small needle-shaped crystals typically display a fast dissolution rate, which is an often-desired property for a pharmaceutical formulation. On the other hand a crystallization process affording small needle-shaped crystals will normally result in problematic down-stream processing with long filtration times and difficult washings. The traditional solution for the API manufacturer is to strive for larger sized crystals and adding one or several processing steps, such as micronization, in order to produce crystals of the desired dimensions.

Spherical crystallization (SC) is a multiple unit process in which crystallization, agglomeration and spheronization is performed in one pot (Figure 1).<sup>1</sup> The resultant crystals, which may be needle-shaped, form spherical agglomerates that are easily isolated by filtration. SC has been used in several examples to improve filterability<sup>2</sup> but also other properties are improved such as flowability and compressibility.<sup>3</sup> In some instances direct tableting or coating is possible without further processing (mixing, agglomeration, sieving, etc.).<sup>4</sup>



**Figure 1:** Spherical agglomerate of drug candidate currently in development<sup>5</sup>

<sup>1</sup> Kawashima et al *Science*, **1982**, 216, 1127-1128

<sup>2</sup> Karol Horvath unpublished work

<sup>3</sup> S. Bhadra et al *Pharmaceutical Technology*, February 2004

<sup>4</sup> Karol Horvath WO/2000/076504

<sup>5</sup> Spherical agglomerates of drug candidate produced on 500 L reactor scale: *unpublished work Karol Horvath*

Fluvastatin sodium, an HMG-CoA reductase inhibitor, is known to exist in two crystal forms: Form A - lyophilized, hygroscopic, partially amorphous, partially crystalline flakes and Form B - non-hygroscopic, highly crystalline needles which crystallize from a mixture of one or two organic solvents and water.<sup>6</sup>

Form B was shown to display better photo- and temperature stability compared to Form A. In order to further improve the micromeritic properties to facilitate tableting and to solve a difficult filtration process SC was evaluated for the crystallization of Fluvastatin sodium. Two methods for SC have been reported:<sup>7</sup> *Spherical Agglomeration (SA)* method is carried out in a partially miscible solvent system and *Emulsion Solvent Diffusion (ESD)* method where the drug crystallizes inside "quasi -emulsion" droplets. In the example described herein the ESD technique was evaluated to improve the filterability and other micromeritic properties of Fluvastatin sodium,

## Results and Discussion

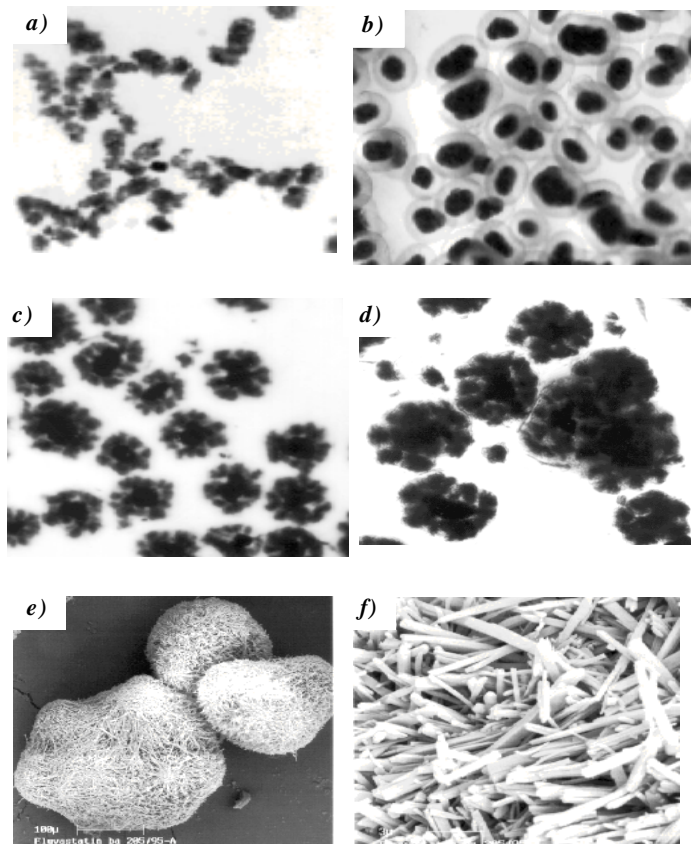
Lyophilized Fluvastatin sodium was dissolved in a mixture of ethanol and water at ambient temperature. Acetonitrile was added as a precipitating solvent and the solution was seeded with Form B crystals suspended in a small amount of acetonitrile. During the crystallization process, samples were continuously taken out for microscopic observations. A few minutes after seeding, the seed crystals began to flocculate. A microscopic examination revealed that the flocculation was caused by a viscous precipitate (Figure 2a). About three hours after seeding, the seed crystals were enveloped in a gel-like precipitate (Figure 2b).

After an additional two hours, nucleation was observed in the gel (Figure 2c, d) and also the slurry had become thicker. Finally, seven hours after seeding the entire gel had crystallized and formed spherical agglomerates. The agglomerates were 100 - 300  $\mu\text{m}$  in diameter, soft and porous. The agglomerates were comprised of needle shaped crystals with a thickness of less than 1  $\mu\text{m}$  and a length of less than 20  $\mu\text{m}$  (Figure 2e, f).

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<sup>6</sup> K. Horvath, *PCT Int. Appl.* WO 97/49681, (1997)

<sup>7</sup> Y. Kawashima, in *Powd. Techn. and Pharm. Processes*, Chapt. 14, Part 1, (1994)



**Figure 2:** Spherical crystallization of Fluvastatin sodium

The formation of the gel and thereby the possibility of producing spherical agglomerates depends on the solvent used, the solvent composition and the temperature. When other solvents were used or the crystallization was performed at a higher temperature, no gel formation was observed, and the formed product after equilibration was only comprised of single needle shaped crystals.

## Conclusions

The filtration and washing process of the spherical agglomerate was greatly improved as compared to the crystal slurry obtained from a traditional crystallization process. Furthermore the spherical agglomerates of Form B were later shown to display good tableting properties.