

Theophylline micronized

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your products.**

Breathe

 **BASF**

The Chemical Company

The Preface

Theophylline is still the standard drug for the therapy of bronchial asthma, chronic obstructive diseases of the respiratory tract, status asthmaticus, bronchial emphysema and shortness of breath caused by exposure of the right heart half as a result of obstructive diseases of the lungs.

Because of the narrow therapeutic range of theophylline, a plasma level between 8 and 20 $\mu\text{l/ml}$ should be attained. Higher plasma levels give rise to severe side effects such as spasms, sudden drops in blood pressure, ventricular arrhythmia or serious intestinal diseases such as bleeding. Lower plasma levels have no effect.

Plasma levels within the therapeutic range can be easily attained by the application of high-tech slow-release formulations over a longer period of time. The dissolution of the drug should be such that equilibrium is achieved between resorbed and eliminated theophylline. Today, pellet formulations are more widespread than bolus forms. Pellets are less dependent of how full the stomach is; they generally remain in the stomach for shorter periods than bolus forms so that no dosage dumping can occur, especially if their lacquers are damaged.

There are many different methods of manufacturing drug pellets, e. g. wet or melt extrusion or layering sugar beads with the drug substance.

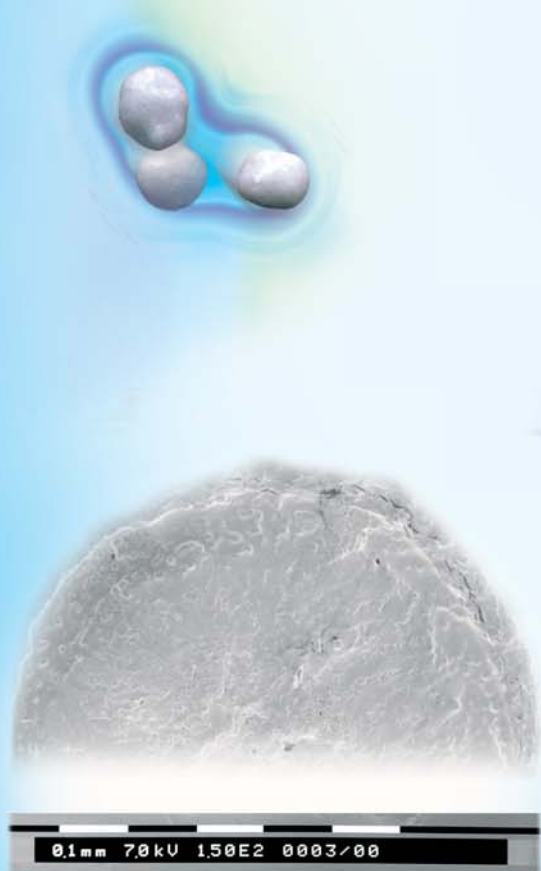
Direct coating is also a possibility with large particles. The pellets are coated with different polymers to control the correct

dissolution rate of the theophylline into the aqueous medium. In the past, the most common method used was to spray a solution of theophylline in an organic solvent together with a binding excipient onto sugar beads. In this way, consecutive layers could be applied to the seed particles, which were subsequently coated with a polymer solution or dispersion as slow-release coating.

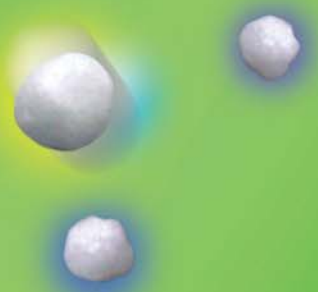
However, for both cost and environmental reasons (organic solvents), layering with dry powder or aqueous dispersion have become more common. These two methods are applicable, however, only when the surface of the pellets is very smooth, thick and free from the protruding peaks of crystals. Such crystal peaks cannot be adequately coated so that the characteristics of drug dissolution can vary from batch to batch.

Micronized theophylline powder is thus essential for these two methods.

BASF Fine Chemical Division, the world's largest manufacturer of theophylline and theophylline derivatives, can now supply micronized theophylline.



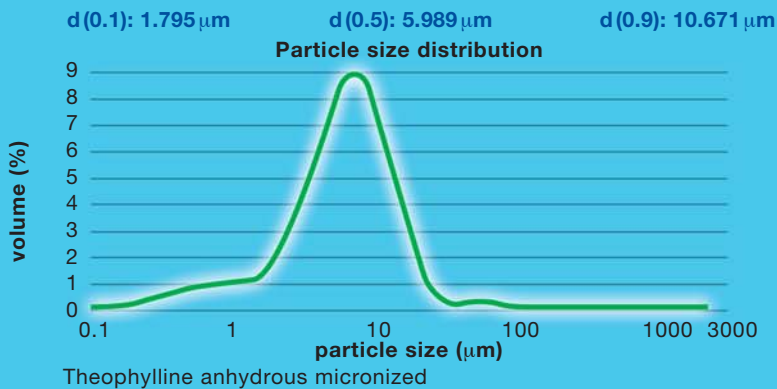
SEM photograph: section of a layered theophylline pellet including slow-release coating



Typical particle distribution curve of micronized theophylline

Measured by laser diffraction as a dry powder stream

Concentration: 0.0001 % VCI Weighted average D(4,3): 7.175 μm Specific surface: 1.92 m^2/g
 Width: 1.989 Uniformity: 0.633 D(3,2): 3.130 μm
 Distribution mode: Volume

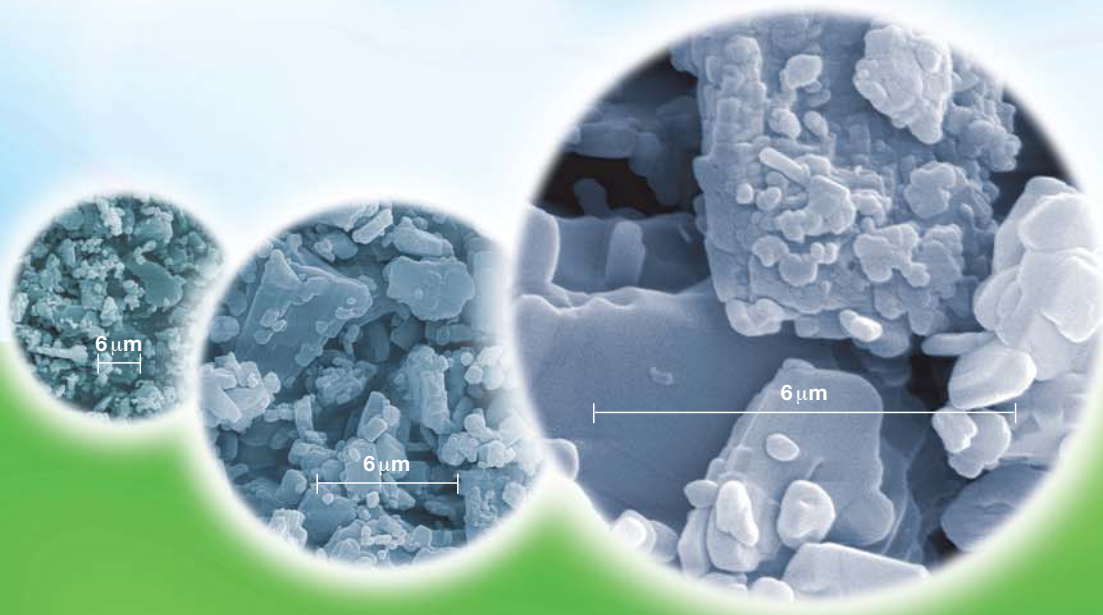


Typical values:

Lot:	d(0.1)	d(0.5)	d(0.9)
1	1.5 μm	6.3 μm	14.2 μm
2	1.3 μm	6.1 μm	14.1 μm
3	1.2 μm	6.0 μm	14.1 μm
4	1.4 μm	6.5 μm	14.8 μm
5	1.3 μm	6.1 μm	14.0 μm

The process of micronization has a high degree of reproducibility and only a small deviation of d(0.5) and d(0.9) values.

Particle specification: at least 90 % {d(0.9)} smaller than 20 μm



Theophylline anhydrous micronized

The Application

Manufacturing procedure:

Sugar beads of 0.4–0.5 mm diameter are mostly used as seed pellets.

Method 1:

In a fluid bed granulator, a 25 % aqueous solution of Kollidon® 30 or Kollicoat® IR as binding excipient is sprayed onto the sugar beads. At the same time, dry micronized theophylline powder is sprayed onto the wetted beads. Inlet air temperature is about 65 °C, outlet air temperature about 30 °C. Once the spraying process is complete, the pellets are dried until an outlet temperature of 38 °C is reached.

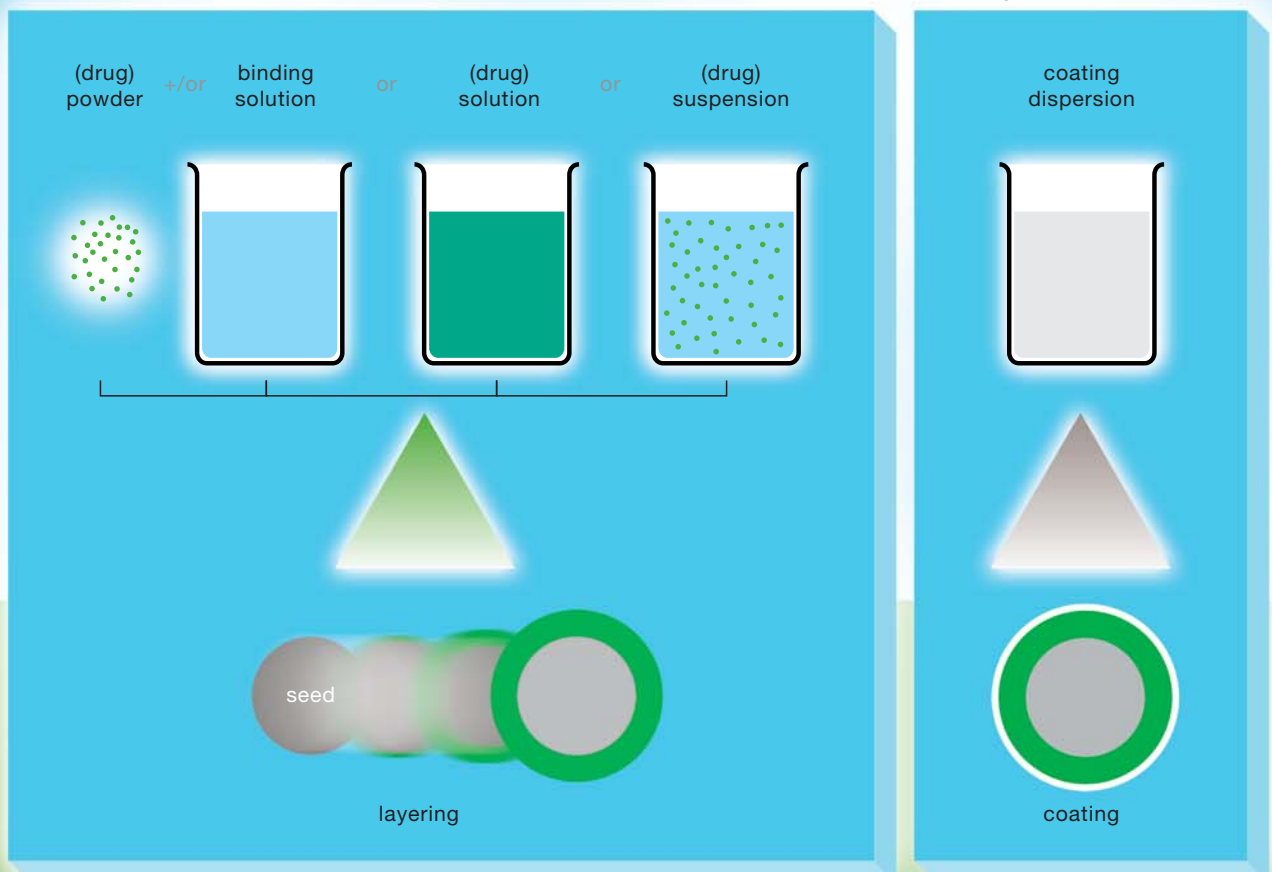
Method 2:

In a fluid bed granulator, an aqueous dispersion of micronized theophylline (see below) is sprayed onto sugar beads. Inlet air temperature is about 65 °C, outlet air temperature about 30 °C. Once the spraying process is complete, the pellets are dried until an outlet temperature of 38 °C is reached.

Composition of a typical aqueous theophylline dispersion:

- Water, demineralized: 70 %
- Theophylline micronized: 25 %
- Kollicoat® IR as a binding excipient: 5 %

Schematic of different methods for pellet coating



As the solubility of theophylline in water is slight (about 5 g/l at 20 °C), aqueous dispersions are easy to prepare. Only small quantities of the drug are dissolved and these can be used for coating using evaporation and crystallization.