

## Conteol of Crystal Growth in Drug Suspensions: 1) Design of a Conteol Unit and Application to Acetaminophen Suspensions)

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**CONTROL OF CRYSTAL GROWTH  
IN DRUG SUSPENSIONS**

**1) DESIGN OF A CONTROL UNIT AND APPLICATION TO  
ACETAMINOPHEN SUSPENSIONS\*)**

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**ABSTRACTS**

A monitor system is described for the control of particle growth by crystallization in real pharmaceutical

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\*) Dedicated to Prof. Dr. E. Nürnberg on the occasion of his 60<sup>th</sup> birthday

2341

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suspensions, based on the measurement of drug concentration in the liquid phase in contact with the drug crystals. The control unit consists of a thermostated vessel containing the drug suspension and a monitoring circuit including a dedector (i.e. refractive index, UV absorption). The concentration of the liquid supernatant is recorded in parallel with the actual temperature. Typical concentration-time curves indicate any dissolution or crystallization if temperature cycling ( $\Delta T \pm 10K$ ) is applied on the suspensions.

It is demonstrated by acetaminophen crystals that after decreasing the temperature the crystal growth appears significantly impeded even by very small amounts of PVP (3 ppm, mol mass 180,000). The polymer did not influence the rate of dissolution of the crystals at higher temperature. Surfactants reduce the protective action of PVP on crystal growth, in particular anionic surfactant which neutralize the protective action totally.

Crystal growth can be successfully inhibited by substances, which are irreversibly adsorbed to the crystal surface by specific interactions with their functional groups and a polymer structure of high molecular mass.

#### INTRODUCTION

Particle growth by crystallization is one of the most destabilizing physical processes in drug suspensions.

It is promoted by temperature changes during storage, especially if the solubility of the drug is strongly dependent on temperature. In this case the crystallised drug may dissolve with increasing temperature, followed by particle growth when the temperature decreases again. Supersaturated drug solutions are then formed, which stimulate crystallization. Crystal growth, however, favours rapid sedimentation and may finally lead to non redispersable sediments or caking (1). Several approaches are described in the literature both to monitor these processes and to impede crystallization from supersaturated solutions by the addition of polymers, surfactants, and dyes (2-7). We describe here a control unit designed to monitor crystal growth (and dissolution) even in highly-concentrated suspensions. The influence of additives on crystallization processes can also be evaluated.

#### CONTROL OF SUSPENSION STABILITY

##### 1. Measurement of particle size

In a suspension the total volume of the solid phase is the sum of the individual volumes of the single particles (i.e. crystals).

Any dissolution or crystallization process will change this solid phase volume. On cooling a drug suspension,

particle growth from supersaturated solution may be the preferred process, with the suspended crystals acting as nuclei. Consequently the particle size of the crystals increases. This can be evaluated from measurements of the particle size distribution in the suspension (2,8,9,10).

Different techniques have been described for example, the Andreasen pipette (9), the Coulter Counter (2,8,10) or the semi- or full automatic particle size determination from microscopic images (4). However, the analysis of representative samples from pharmaceutical (concentrated) suspensions is more or less an arbitrary procedure. Any pretreatment of the suspensions such as shaking, redispersion etc., as well as the sampling location in the suspension, are not standardized.

An alternative approach is the study of crystal growth on single crystals mounted under the microscope. Although this method is an elegant principle, it may be restricted to fundamental aspects such as the individual growth of different crystal faces, changes in crystal habit etc. It does not account for the mutual influence of solid particles in real suspensions. In addition, experimental difficulties arise from the need for proper mounting of the crystals

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