

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

K. H. Ziller & H. Rupprecht

To cite this article: K. H. Ziller & H. Rupprecht (1988) Conteol of Crystal Growth in Drug Suspensions: 1) Design of a Conteol Unit and Application to Acetaminophen Suspensions), Drug Development and Industrial Pharmacy, 14:15-17, 2341-2370, DOI: [10.3109/03639048809152019](https://doi.org/10.3109/03639048809152019)

To link to this article: <http://dx.doi.org/10.3109/03639048809152019>



Published online: 20 Oct 2008.



Submit your article to this journal [↗](#)



Article views: 77



View related articles [↗](#)



Citing articles: 10 View citing articles [↗](#)

Full Terms & Conditions of access and use can be found at
<http://www.tandfonline.com/action/journalInformation?journalCode=iddi20>

**CONTROL OF CRYSTAL GROWTH
IN DRUG SUSPENSIONS**

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

K.H. Ziller and H. Rupprecht

Department of Pharmaceutical Technology
University of Regensburg
Universitätsstr. 31
D-8400 Regensburg, FRG

ABSTRACTS

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

*) Dedicated to Prof.Dr. E. Nürnberg on the occasion
of his 60th birthday

2341

Copyright © 1988 by Marcel Dekker, Inc.

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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.