DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(15-17), 2341-2370 (1988)

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 occassion of his 60th birthday

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 irreversibely 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

and from necessity of a constant and equal flow of the feeding solution around the crystal (4,11,12).

2. Control of solute concentration in the liquid phase

Sekikawa (12) proposed control of crystallization in suspensions by monitoring the concentration of the drug in the liquid phase. In a closed suspension system dissolution and crystallization must change the concentration of the solute in the liquid phase. In this way coprecipitation and particle growth from ethanolic acetaminophen solutions have been controlled by intermittant measurement of the drug concentration in the supernatant liquid.

This method can, however, be improved by continously controlling the drug concentration in the liquid phase of a suspension both under isothermal and temperature cycling conditions, thereby simulating the stress on storage at varying temperatures.

According to Varney (14) the rate of crystal growth is dependent on a variety of parameters, such as the solubility of the drug (i.e. the saturation concentration) and their temperature dependence, the

degree of supersaturation, the temperature difference on storage and the frequence of temperature cycling. Any mechanical stress such as stirring must also be considered. Particles smaller than 1 μm may additionally exhibit Ostwald ripening.

3. Description of the Suspension Control Unit

The control unit was designed to measure drug concentration in the liquid phase and, simultaneously, the temperature in the suspension. Depending on the applied monitor system the concentration of additives influencing the crystallization can also be determined.

The main elements and their function are shown in Fig 1. A graduated Erlenmayer flask with a ground glass stopper (containing connecting passages) is used as a stirrer vessel [1]. This contains 50-100 ml of the liquid phase to which the solid drug is added. The suspension is then stirred by a magnetic stirrer [2] at ca. 300 RPM driven by a magnetic water turbine [4] (Feddeler, Essen FRG). Sliding bearings can adjust the stirrer shank in the stopper. The Erlenmeyer flask is contained in a thermostat (temperature adjustment better than ± 0,1K) and is equipped with heat

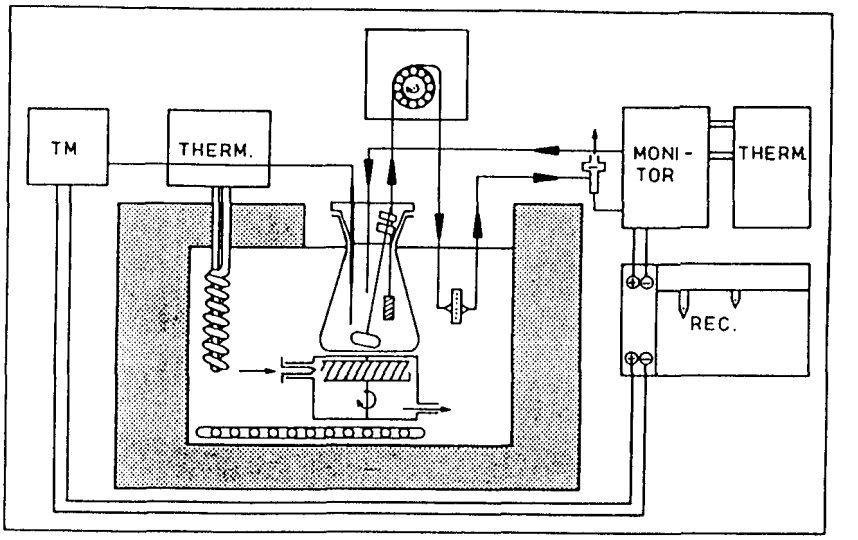

FIGURE 1:

System for monitoring the drug concentration in the liquid phase of suspensions during temperature cycling

1 stirrer vessel
2 stirrer with bearing, axis, magnetic pin
3 heat exchanger (heating and cooling)
4 turbine for the magnetic stirrer drive
5 temperature sensor
6 frit
7 membrane filter
8 peristaltic pump
9 septum for sample injection and sampling an bubble removement
TM temperature control
Therm. thermostat for temperature control of the suspension
Th. thermostat for the monitor system
MO monitor for drug concentration
Rec. twin-channel recorder

exchangers for heating and cooling [3] (supplied by a Braun Frigomix 1496/Thermomix 1480 BKV unit = [Therm]). A Pt-100 sensor [5] connected to a Knauer control unit [TM] controlls the temperature in the suspension.

A circuit is then established to control drug (and/or additive) concentrations. The liquid phase is transported through Teflon and Isoversinic tubes by means of a peristaltic pump (Gilson Miniplus [8]). The circuit starts with a glass frit G3 or G4 [6] to trap course solid particles. The liquid then passes through a membrane filter (d_{pore} 8 μm, cellulose nitrate, Sartorius) [7] and a HPLC-septum injector (Perkin Elmer) [9], so as to remove fine particles and bubbles before passing the monitor. The monitors applied were selected from HPLC equipment: a differential refractometer (Knauer), single beam UV spectrophotometer (Gilson spectrochrome U, Shimadzu UV 102 and UV 100-02), and double beam spectrophotometer (UV 210A Shimadzu) were used.

The flow-through cells in the monitor are maintained at temperatures 10K higher than the upper limiting temperature of any cycle (thermostats).In this way crystallization in the cuvettes is avoided. For UV measurements quartz cells (1-10 mm) are used (Hellma).

The following parameters have to be considered when selecting an appropriate monitor: linearity between the signal and the drug concentration (controlled by calibration), the sensitivity, the signal-to-noise ratio and the thermic drift compensation. Due to the high concentrations in saturated drug solutions it is better to measure concentration at a wave length apart from the absorption maximum. In this case the validity of the Lambert-Beer law has to be carefully evaluated. Temperature and concentration signals are recorded in parallel versus time, as is demonstrated in Fig 2.

The following criteria are prerequisites for an adequate control of a suspension system:

a) dissolution and crystallisation can be directly controlled by drug concentration without dilution steps;
b) the rates of dissolution and crystallization are relatively high;
c) polymorphism and pseudo-polymorphism are excluded;
d) interaction between drug crystals and excipients are well defined or can be independently determined;
e) influences on crystal growth can be independently measured by other methods (4-7,11-13).

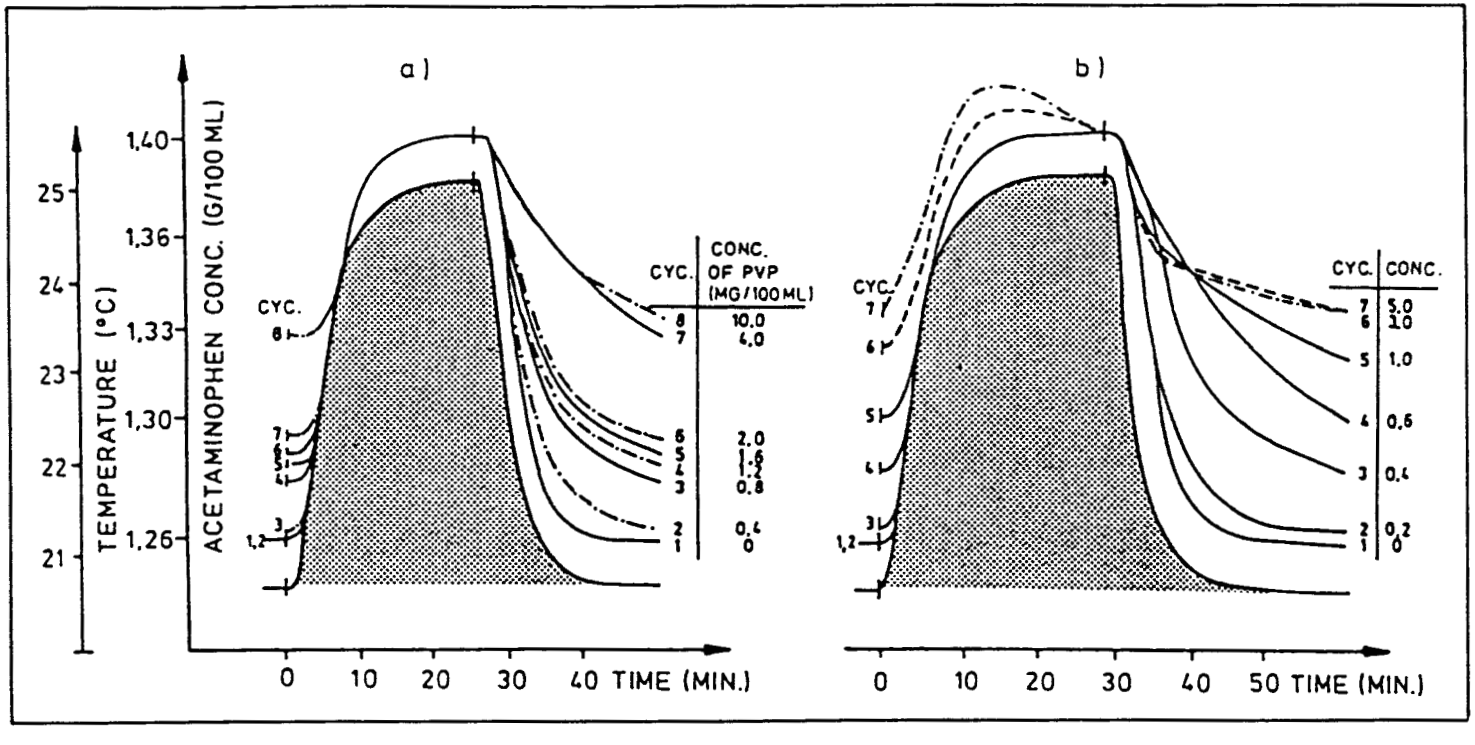

FIGURE 2:

Temperature cycling in aqueous acetaminophen suspensions (100 ml, 3%)

a) Additive PVP K17 (0.4 - 10 mg/100 ml)

b) Additive PVP K30 (0.2 - 5 mg/100 ml)

Temperature: curve over the hatched area (also in the following figures)

4. Design of Temperature Cycling

1-4g of drug (particle size 10 - 50 μm) are necessary for one experiment (suspended in 50-100 ml liquid phase). The experiments are carried out at room temperature - ΔT ± 10K - according to the temperature conditions during distribution and storage of drug preparation 60 min proved to be a reasonable compromise for one temperature cycle. Considering heating and cooling rates, the length of temperature plateau phases at the upper limiting temperature (to attain equilibrium) and a cooling period, limited to 30 min.

5. The Control of Crystal Growth of Acetaminophen in the Presence of PVP

The function and sensitivity of the control unit was evaluated by means of model suspensions, as to evaluate and predict suspension stability. Acetaminophen was selected as a drug model and polyvinylpyrrolidone (PVP) as an effective additive to inhibit crystal growth (4,12,15).

In Fig 2a/2b dissolution and crystallization of acetaminophen in aqueous suspensions during temperature cycling are demonstrated. PVPs of different molecular

mass were added to the suspensions. In the diagrams the temperature - curve over the hatched area and the concentration of the drug in the liquid phase versus the time are given. Locating marks indicate the points of temperature reversal. The number of temperature cycles are listed in the column "cyc" and the concentration of the added PVP in the column "conc". During the cooling periods the rate of crystallization obviously decreases with increasing amounts of PVP in the suspensions. Significant influences both on dissolution and crystallization are exhibited by PVP K30 (mol mass ≈ 43,000) and PVP K90 (mol mass ≈ 180,000)(Fig. 3a). The PVP K17 with its lower molecular mass of ≈ 9,000, has only a minor influence on these processes.

The number of temperatur cycles also influences the effectiveness of PVP. Starting with the 4^{th} cycle, supersaturated solutions are obtained during the dissolution period (related to the solubility at the upper limiting temperature). The concentration passes through a maximum after 8-10 min, then declines to the saturation concentration. Simultaneously the inhibiting action on crystallization (at the lower limiting temperature) appears more pronounced, and supersaturated suspensions are stabilized over several

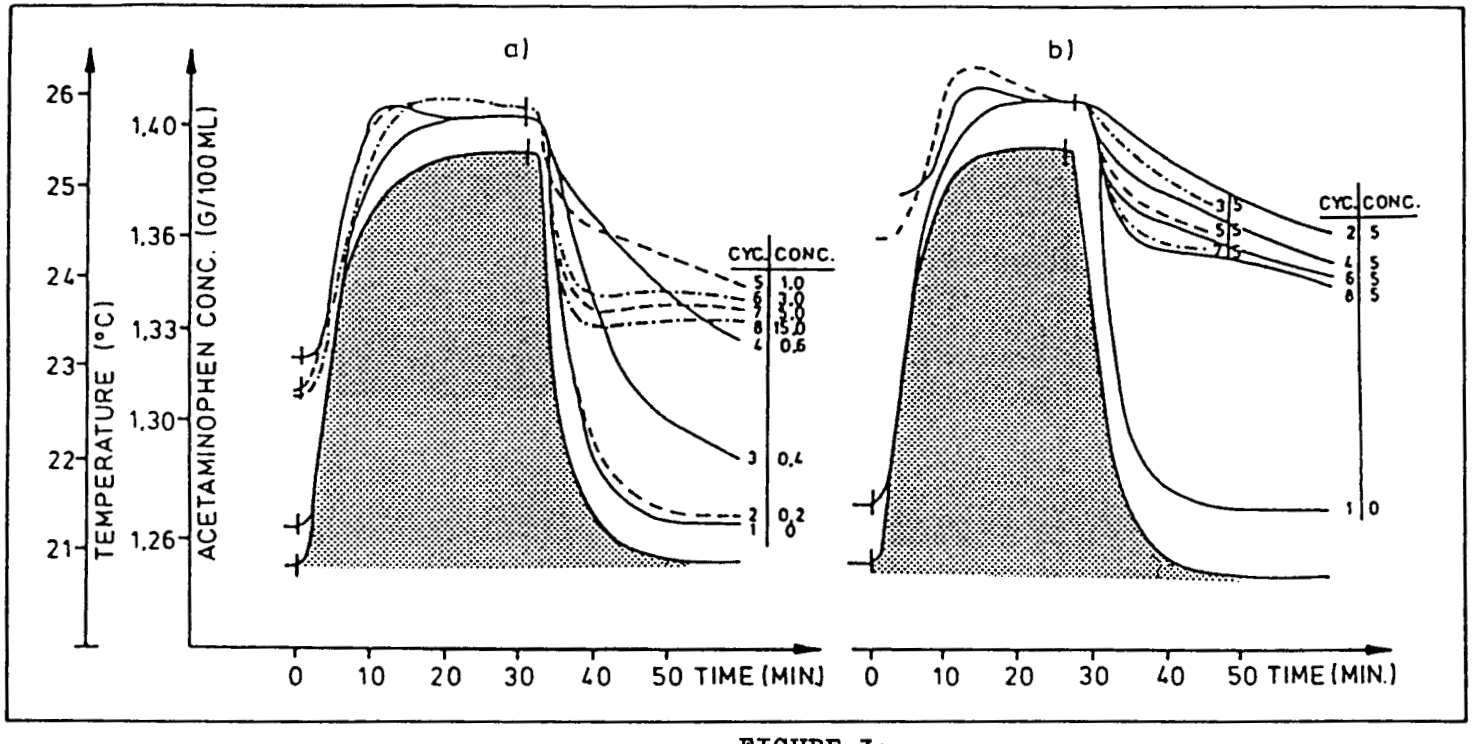

FIGURE 3:

Temperature cycling in aqueous acetaminophen suspensions (100 ml, 3%)

a) Additive PVP K90 (0.2 - 15 mg/100 ml)

b) Singular addition of 5 mg PVP K 90

hours. This is also demonstrated by temperature cycling at constant concentrations of PVP after the second cycle (5 mg/100 ml PVP K90) [Fig 3b]. Only a small decrease in concentration is observed during repeated cooling periods.

In Fig 4 acetaminophen concentrations are shown, obtained during the cooling periods of temperature cycling after 10 and 25 min, respectively. They are contrasted with the increasing amounts of PVP K17 and PVP K90 (semilogarithmic plot) added to the system. An effective inhibition of crystallization is indicated by high drug concentrations in the supernatant at low PVP concentrations and by a small difference between the concentration curves at 10 min and 25 min. It is thus confirmed that PVP K 90 is a potent crystallization inhibitor. With increasing frequency of temperature cycling the inhibiting action of PVP K90 is reduced to a fairly constant level, even after a further increase of polymer concentration (identical values were obtained by PVP K 30, not shown in this diagram).

From these experiments it is concluded that approximately 3mg PVP (= 30 ppm) K30 or K90 is the most effective amount of polymer to inhibite the crystallization of acetaminophen in suspensions.

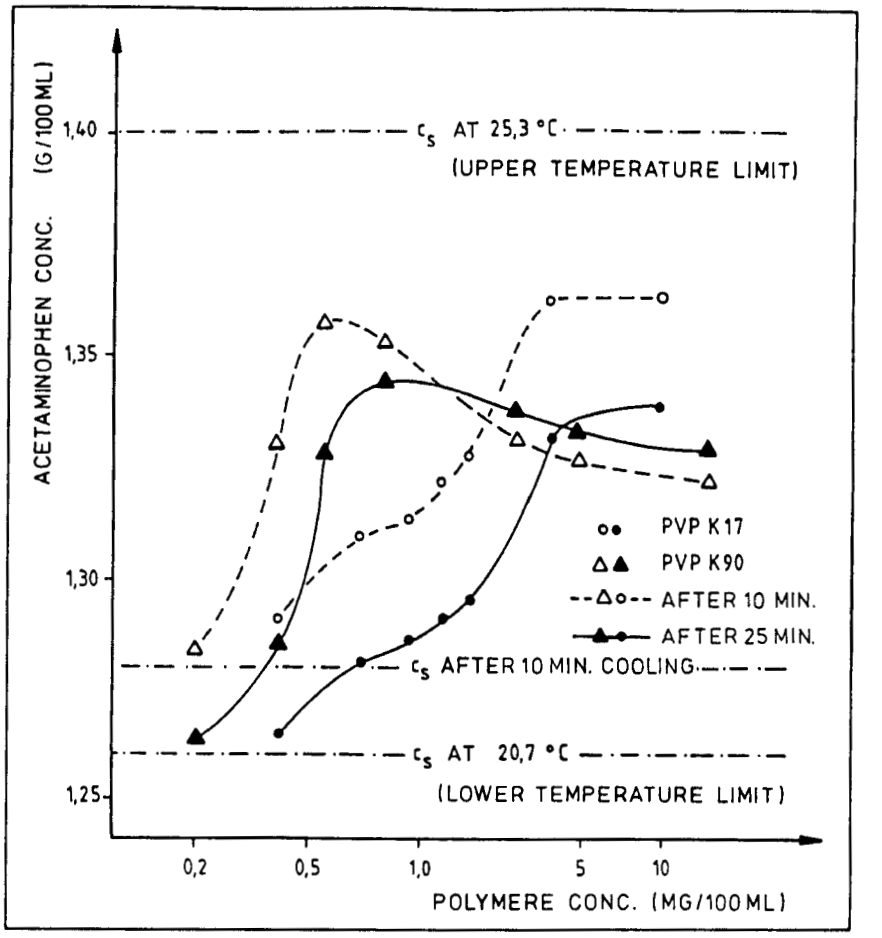

FIGURE 4:

Temperature cycling in aqueous acetaminophen suspensions. Drug concentration in the supernatant liquid phase in the presence of

o --- o PVP K17, 10 min o —— o PVP K17, 25min

Δ --- Δ PVP K90, 10 min Δ —— Δ PVP K90, 25 min

4-nitroacetanilide was introduced for comparsion as a drug model. The stucture of this molecule differs in the para-position to the acetamino groups (i.e. the OH group is replaced by a nitro group). In this way the influence of single functional groups on drug crystallization in the presence of PVP can be evaluated (Fig 5). The inhibitory effect of PVP K30 on the crystallization of 4-nitroacetanilide appears to be smaller, compared with acetaminophen. However, BSA, a polymer of the proteintype is also effective in crystal growth inhibition of 4-nitroacetanilide at concentration of 20 mg/100 ml (= 200 ppm). This may be due to the inability of the nitro group to form hydrogen bonds as a donor, leading to weaker interactions with PVP.

7. Influence of low molecular pyrrolidones, bovine serum albumin and surfactants on acetaminophen crystallisation

7.1. Addition of 1-methylpyrrolidone and piracetam

The crystallization of acetaminophen during the cooling period in temperature cycling is not significantly influence by either 1-methylpyrrolidone or piracetam [Fig 6]. Both substances are compounds of similar

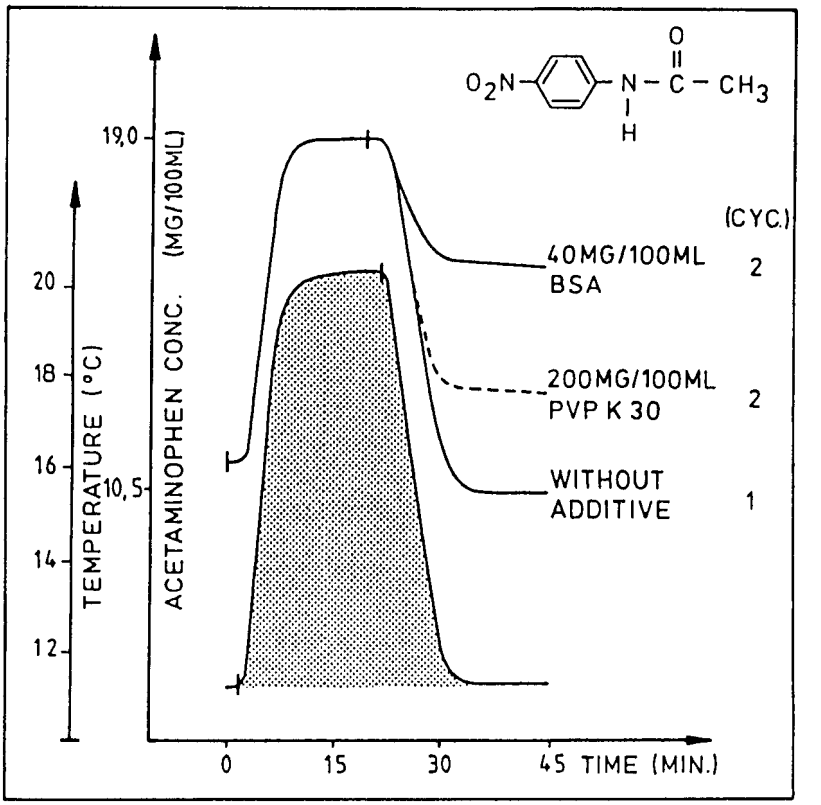

FIGURE 5:

Temperature cycling in aqueous 4-nitroacetanilide-suspensions (100 ml, 3%),. Additives PVP K30 and BSA

structure as the pyrrolidone monomers. Even relatively high concentrations of these additives (compared with PVP) are ineffective. During the third cycle PVP K30 was added, and was fully effective even in the presence of both additives. These experiments confirm the results obtained by Metha (11). He reported that

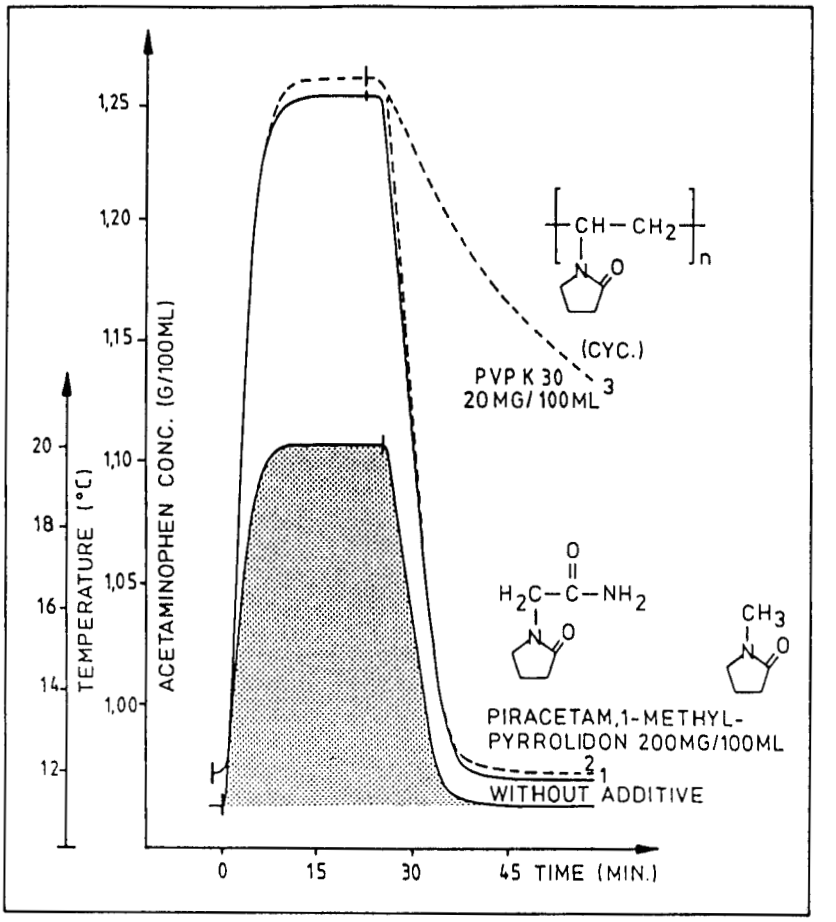

FIGURE 6:

Temperature cycling in aqueous acetaminophen suspensions (50 ml, 3%) piracetam and 1-methylpyrrolidone, respectively added in the second cycle

vinylpyrrolidone does not influence the crystallization of sulfathiazole, which is also a low molecular mass compound of similar structure. A specific influence of the pyrrolidone ring system on the protective action of PVP can, therefore, be ruled out.

7.2. Addition of BSA

Bovine serum albumin (BSA) was selected as an example of a polymer which shows strong interactions with a great number of drugs in aqueous solution (15-19). In Fig 7 the influence of BSA on acetaminophen concentration in the liquid bulk phase during temperature cycling of the suspension is given. This polymer inhibits the crystallization of acetaminophen to the same extent as PVP.

7.3. Combinations of PVP and surfactants

Surfactants are reported to influence crystallization by adsorption and solubilization effects (2,9,10,21,22). They are also widely used in suspension formulations as wetting agents and preservatives (23). We studied their possible interference with both the inhibiting polymer (24) and the crystal surfaces during

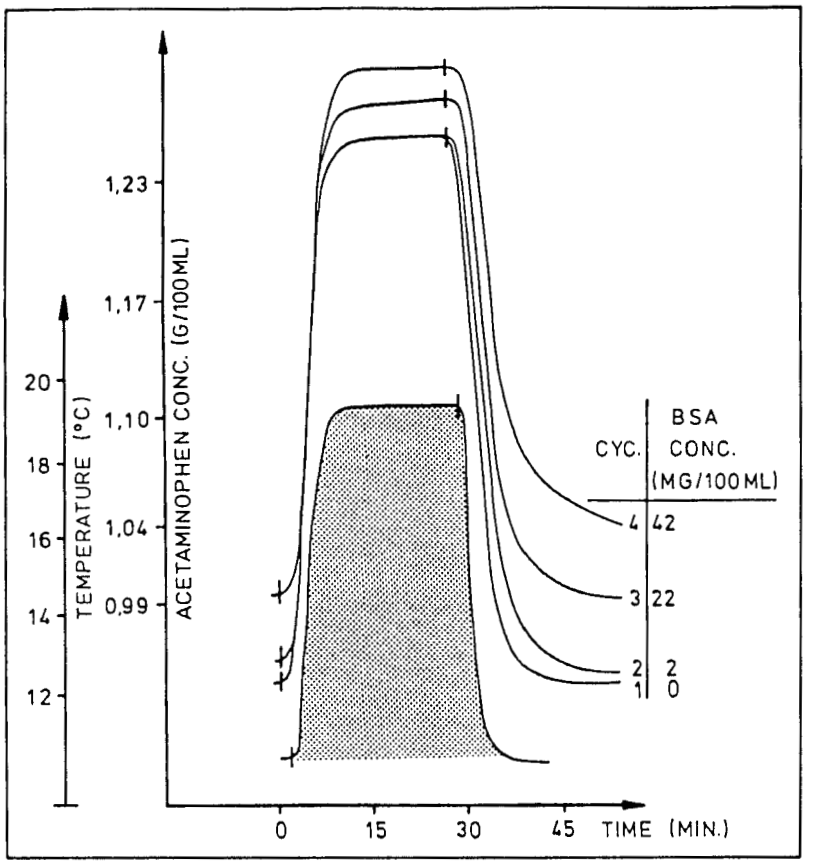

FIGURE 7:

Temperature cycling in aqueous acetaminophen suspensions in the presence of BSA (50 ml, 3%)

temperature cycling experiments with acetaminophen suspensions. The crystallization of acetaminophen is not influenced by the nonionic polyoxyethylene-polypropylene copolymer Pluronic F68.

In combination with PVP K17 the rate of crystallization is only slightly increased by the presence of the surfactant (Fig. 8).

The nonionic PEG-10-oleylether and hexadecylpyridinium cations both reduce the inhibiting effect of PVP on crystallization (Fig. 9a and b). These surfactants are reported to exhibit no significant interactions with PVP in solution (25,26), although they may be adsorbed to the crystal surfaces of the drug. In this way they can disturb the structure of the protective polymer at the crystal surface.
Hexadecylsulfate, however, neutralizes the protective action of PVP on acetaminophen crystallization almost completely (Fig 9b). This anionic surfactant aggregates with PVP in the aqueous phase (27), thus preventing the PVP from establishing protective layers on the drug crystals.

DISCUSSION

Specific and strong interactions between functional groups of the drug and a polymer are obviously a necessary, but not a sufficient, prerequisite to inhibit the crystallization from supersaturated solutions in drug suspensions. This is demonstrated by

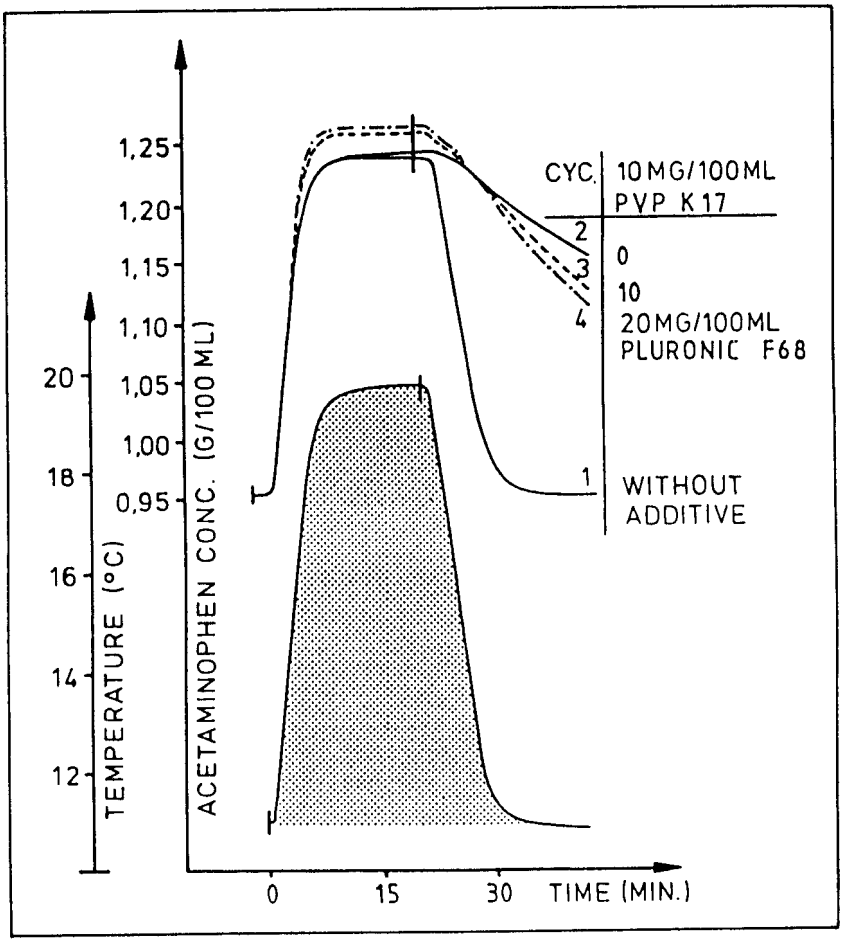

FIGURE 8:

Temperature cycling in aqueous acetaminophen suspension (50 ml, 3%) in the presence of PVP K17 and pluronic F68

the low molecular pyrrolidone compounds, which are more or less ineffective in influencing crystallization. The second, essential property of a protective substance seems to be the formation of an polymer adsorbate on the surface of the drug crystals. This impedes the

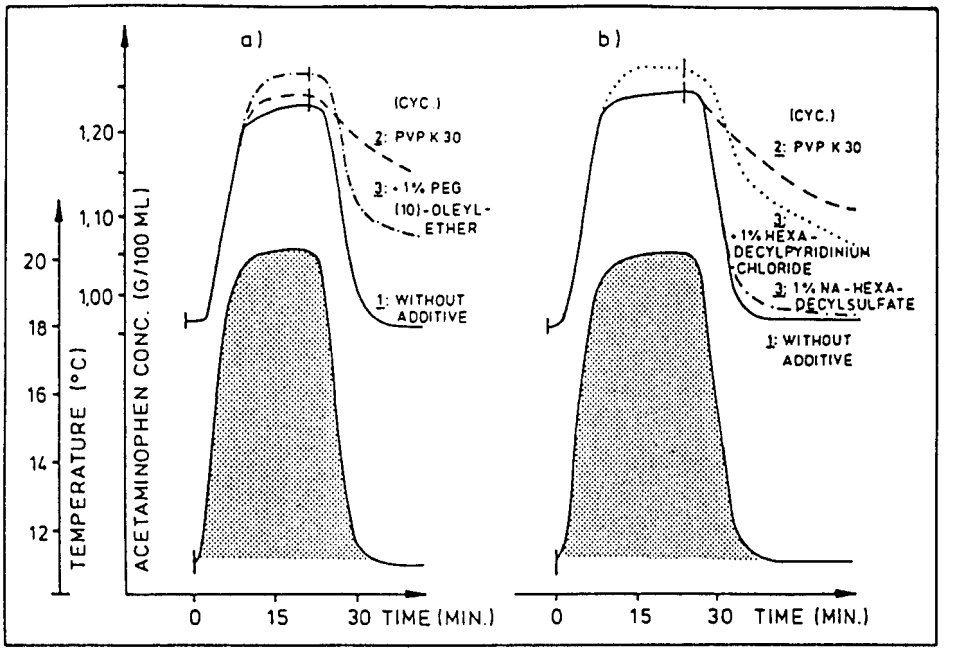

FIGURE 9:

Temperature cycling in aqueous acetaminophen suspensions (50 ml, 3%) in the presence of mixtures of PVP K30 (20 mg/100 ml) with

a) PEG(10)oleylether
b) hexadecylpyridinium chloride and sodium hexadecylsulfate, respectively

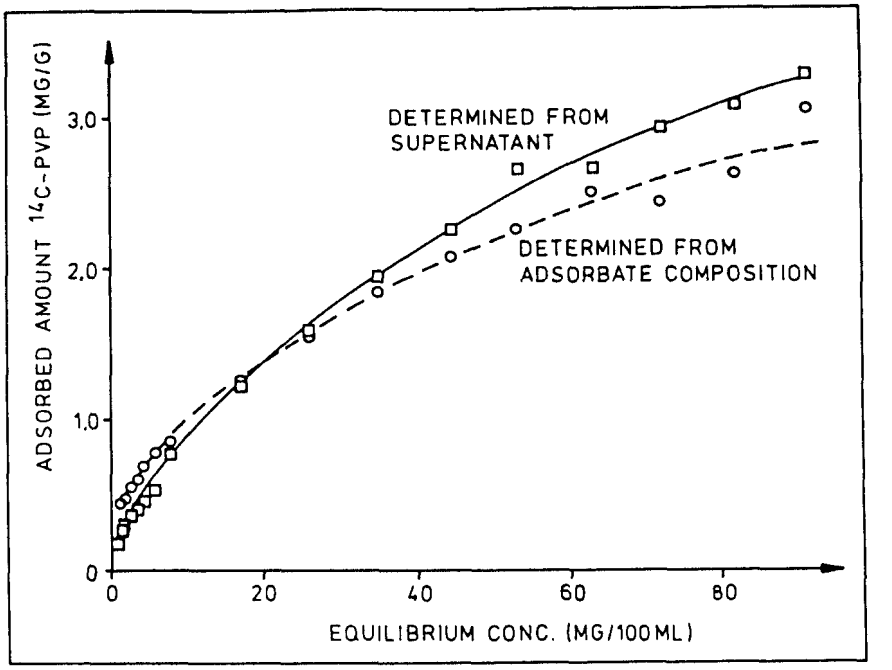

FIGURE 10:

Adsorption of PVP (^{14}C-K19/K17 1:50) onto acetaminophene crystals

approach of drug molecules from solution onto free spaces of the crystal lattice.

In the series of pyrrolidone compounds applied to acetaminophen suspensions only the high molecular mass polymers (PVP K30, PVP K90) show a pronounced protective action. The adsorption of PVP K17 on acetaminophen crystals is shown in Fig. 10. The

Langmuirian nature of the isotherm indicates that the adsorption is reversible, in contrast to the high molecular mass polymers. It can be imagined that the structures of PVP (and BSA) adsorbates formed on acetaminophen from the "good" solvent water (28) are responsible for the crystallization-inhibiting effect. The polymer is hydrated to a great extent in the adsorbate and attached to the crystal surface by some segments - so called trains (Fig. 11). Water molecules remain, therefore, in permanent contact with the crystal surface. On raising the temperature the dissolution process can start immediately and drug molecules dissolved from the crystal can diffuse through the adsorbate into the bulk liquid phase.

The inhibiting action of PVP on crystallisation is presumably a kinetic effect. PVP inhibits the introduction of drug molecules from solution into the crystal lattice by occupying the adsorption sites which are also free lattice sites. The adsorption of polymers onto solids is known to become progressively more irreversible with increasing chain length (28). This is also the case if only weak or medium adsorption forces are present on a single adsorption site. For the desorption of a polymer molecule the activation energy of desorption must be simultaneously achieved for every

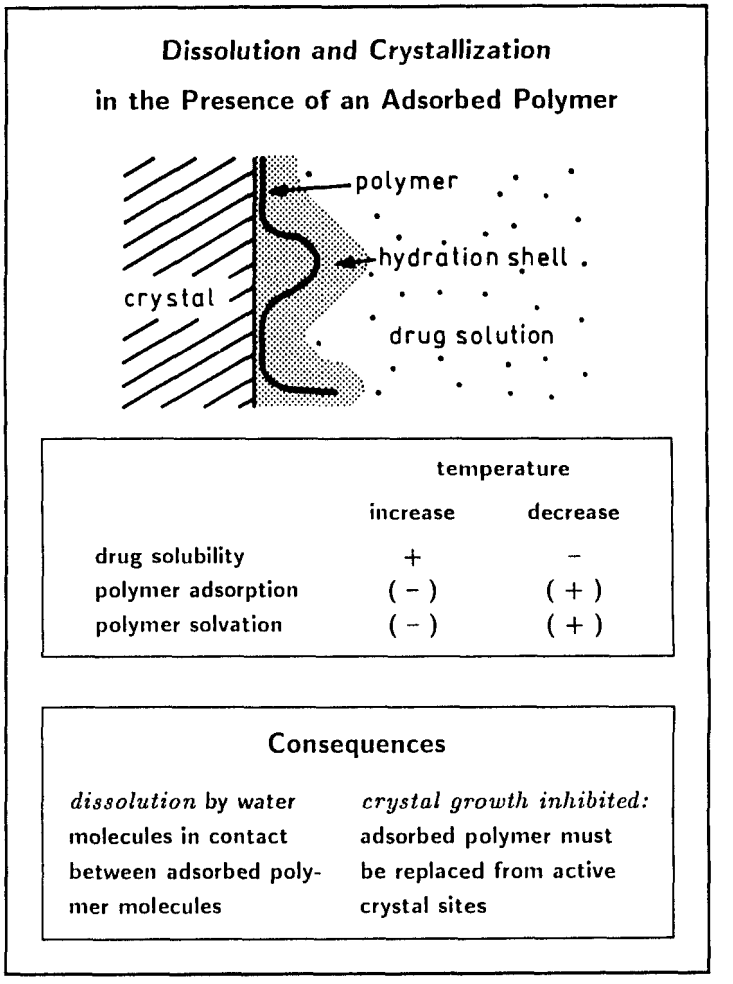

FIGURE 11:

Schematic sketch of the polymer adsorbate on a drug crystal and the influence of temperature cycling on the adsorbate

single contact point. In acetaminophen suspension only a gradual replacement of polymer contact sites on the crystals by drug molecules is envisaged. The adsorbed polymer may form a mechanical barrier against crystallization which has increasing protective action by increasing the polymer chain length and, consequently, the irreversible nature of adsorption.

When applying this method to suspensions of drugs which form polymorphs or pseudo-polymorphs it must be considered that the more stable crystal form may be formed as well as different crystal habits. This could influence the results of the temperature cycling experiments.

The method we presented in this paper may be a useful tool to detect and characterize the influence of additives on drug crystallization in suspensions. Even very small amounts - in the ppm range - show their protective action. It may succesfully be applied in the optimization of suspension stability and in the control of these dosage forms.

REFERENCES:

1) Florence, A.T. and D. Attwood, in: "Physicochemical Principles of Pharmacy", Macmillan, Houndmills, Basingstoke, London, 1981

2) Carless, J.E. and A.A. Forster, J.Pharm.Pharmacol. 18 (1966), 697-708

3) Moustafa, M.A., A.R. Ebian, S.A. Khalil and M.M. Motawi, J.Pharm.Sci. 64 (1975), 1485-1489

4) Simonelli, A.P., S.C. Mehta and W.I. Higuchi, J.Pharm.Sci. 59 (1970), 633-637

5) Nath, B.S. and R.V. Gaitonde, Ind.J.Pharm. 37 (1975), 77-80

6) Badawi, A.A., A.A. El-Sayed and I. Haroun, Pharm.International 5/6 (1977), 1-6

7) Nuernberg, E. and P. Kohl, Pharmaz.Ztg. 124 (1979), 523-529

8) Carless, J.E., M.A. Moustafa and H.D.C. Rapson, J.Pharm.Pharmacol. 20 (1968), 630-638, 639-645

9) Hasegawa, J. and T. Nagai, Chem.Pharm.Bull. 6 (1958), 129-137

10) Higuchi, W.I. and P.K. Lau, J.Pharm.Sci. 51 (1962), 1081-1084

11) Mehta, S.C., P.D. Bernardo, W.I. Higuchi and A.P. Simonelli, J.Pharm.Sci. 59 (1970), 638-644

12) Mehta, S.C., PH.D.Thesis Univ. Michigan 1969

13) Sekikawa, H., M. Nakano and T. Arita, Chem.Pharm.Bull. 26 (1978), 118-126

14) Varney, G., J.Pharm.Pharmacol. 19 (Suppl. 1967), 19s-23s

15) Motawi, A.M., S.A. Morbuda, F. El Khawas and K.L. El Khodery, Acta Pharm.Technol. 28 (1982), 211-215

16) Davison, C. and P.K. Smith, J.Pharmacol.Exptl.Therap. 133 (1961), 161-170

17) Eichman, M.L., D.E. Guttman, Q. van Winkle and E.P. Guth, J.Pharm.Sci. 51 (1962), 66-71

18) Keen, P.M., Brit.J.Pharmacol. 26 (1966), 704-712

19) Lindenbaum, A. and J. Schubert, J.Phys.Chem. 60 (1956), 1663-1665

20) Patel, N.K., P.-C. Sheen and K.E. Taylor, J.Pharm.Sci. 57 (1968), 1370-1374

21) Michaels, A.S. and A.R. Colville, J.Phys.Chem. 64 (1960), 13-19

22) Michaels, A.S. and F.W. Tausch, J.Phys.Chem. 65 (1961), 1730-1734

23) Higuchi W.I., Swarbrick J., Norman F.H., Simonelli A.P. and A. Martin; "Particle Phenomena and Coarse Dispersions" in: Remington's Pharmaceutical Sciences 17th, ed.; Geunaro A.R., Mack Publishing comp., Easton Pa, 1985, pp 301

24) Saito S., "Polymer Surfactant Interactions, in Nonionic Surfactants", M.J. Schick ed. Marcel Dekker Inc. New York, Basel, 1987, pp 881

25) Saito, S., Koll.-Z.u.Z.Polymere 249 (1971), 1096-1100

26) Saito, S. and K. Kitamura, J.Coll.Int.Sci. 35 (1971), 346-353

27) Saito, S., T. Taniguchi and K. Kitamura, J.Coll.Int.Sci. 37 (1971), 154-164

28) Tadros T.F., in: "Polymer Colloids", Buscall R., Corner T. and Stageman J.F. ed., Elsevier Applied Sci.Publ., London, New York, 1985, pp 105