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Report

Thermal Stability of Mefruside–Polyvinylpyrrolidone Solid Dispersions

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The stability of mefruside–polyvinylpyrrolidone (PVP) 30 solid dispersions at ratios of mefruside/PVP 30 of 9/1, 7/3, and 5/5 (g/g) after mechanical (tableting) and allothermic stressing (50, 60, and 70°C up to 240 hr) was investigated. Only the 5/5 (g/g) solid dispersion showed no recrystallization of mefruside, whereas a slight increase in crystallinity in the 7/3 (g/g) solid dispersion and a strong increase in the 9/1 (g/g) product were detected. The mechanisms of drug recrystallization in such "high-energy products" are discussed.

KEY WORDS: mefruside; thermal stability; solid dispersions; polyvinylpyrrolidone.

INTRODUCTION

Drug absorption depends to a great extent on the solubility of the drug. Poorly soluble drugs therefore often show poor bioavailability. In this case the dissolution rate of the drug is the rate-determining step. Numerous efforts have been reported in the literature in the last two decades to change the physicochemical properties of poorly soluble drugs in order to improve their solubility (1–3). One possibility of increasing the solubility is the incorporation of a poorly soluble drug into a rapidly dissolving carrier to form a solid dispersion. This method of improving the dissolution rate was first proposed by Sekiguchi and Obi in 1962 (4). A classification of six different types of solid dispersions which are the most frequently described systems is given by Chiou and Riegelman (3).

The industrial application of these systems that are often called "high-energy products" is scarce. In 1983 only two solid dispersion systems seemed to be on the market (1). The striking gap between research efforts and industrial application must be found in the poor stability of these systems during the shelf-life time, especially after a mechanical or thermal stress during the manufacturing process.

In this study mefruside was used as a model substance to investigate the stability of mefruside–polyvinylpyrrolidone (PVP) solid solutions during allothermic storage. Embedding mefruside in PVP by means of a spray drying technique was the best method to achieve solid solutions (molecular dispersion of the drug in the carrier) which show improved dissolution rates in comparison with the micronized drug (5). The results of *in vitro* dissolution tests are shown in Fig. 1. The aim of this study is to investigate the thermal stability of the mefruside–PVP solid solutions.

MATERIALS AND METHODS

Mefruside (Baycaron mikrofein, Bayer Leverkusen, FRG) and PVP 30 (Kollidon 30, BASF, Ludwigshafen, FRG) in ratios of 9/1, 7/3, and 5/5 (g/g) were dissolved in a chloroform–methanol mixture (7/3, v/v) and spray-dried as described elsewhere (5,6). The spray-dried products were further dried under reduced pressure (10^{-5} mPa) to a constant weight and stored in air-tight containers.

Tablets of the spray-dried products were made using an excenter tableting machine (E XI, Fette, Hamburg, FRG) equipped with strain gauges connected to a carrier wave-frequency bridge (PR 9307, Philips, Eindhoven, NL), pressure force, 5–6 kN. X-ray diffraction measurements: X-ray gen-

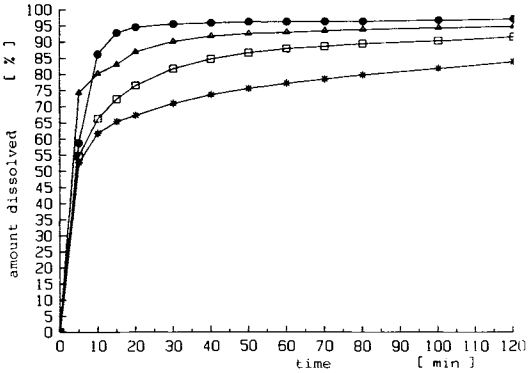

Fig. 1. Dissolution rate of mefruside–PVP 30 spray-dried products (5). (—●—●—) Mefruside–PVP 30 (5/5, g/g); SD, 1.52%. (—△—△—) Mefruside–PVP 30 (7/3, g/g); SD, 1.39%. (—□—□—) Mefruside–PVP 30 (9/1, g/g); SD, 0.57%. (—*—*—) Mefruside (reference); SD, 0.96%.

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erator (Philips PW 1730) with X-ray tube (Philips PW 2253/11); Cu anode; Ni filter; high voltage, 50 kV; tube current, 40 mA; diffractometer (Philips 1050/25); scanning speed, 0.02° 2 θ/sec; pulse count, $5 \cdot 10^4$/sec; scan range, 15–22° 2 θ; and one-line recorder (Philips PM 8203 A).

Semiquantitative Procedure by Means of X-Ray Diffraction

To study a possible mefruside recrystallization of the mefruside–PVP 30 solid solutions during allothermic treatment, a semiquantitative X-ray diffraction procedure was used as described by Chatten (7). To ascertain that the intensity of a diffracted beam of X-rays is a function of the amount of diffracting material, calibration curves were made. Pure mefruside heated for 240 hr at 70°C was used as a crystallinity standard and blended with PVP 30. The measured intensities of four peaks (2 θ: 16.1, 17.0, 18.6, and 21.0°) fitted well with this prerequisite. These four peaks were chosen in order to equilibrate statistically texture effects due to the preparation technique and to recognize in an early state a possible shift in the ratio of different crystal planes. The measured intensities of the four peaks were digitalized and the arithmetic value was calculated. To measure the basic intensity (noise) a scan range (2 θ = 19.9 to 20.4°) was used which did not interfere with any peak range. After calculating its arithmetic value, the basic intensity was subtracted from the peak value. Figure 2 shows reference goniometer diffractograms from pure mefruside, PVP 30, and the sample holder.

The intensity of the diffracted beam was measured for the spray-dried products and the tablet formulations after 2, 4, 6, 8, 12, 24, 48, 72, 120, and 240 hr during storage at 50, 60, and 70°C.

Scanning Electron Microscopy

The spray-dried samples were sputtered with gold (Sputter Anlage SCD, Balzers, Liechtenstein) and pictures were taken with a Stereoscan 600 SEM (Cambridge Scientific Instruments, Cambridge, GB).

RESULTS

Mefruside–PVP 30 (9/1, g/g) Spray-Dried Products

Figure 3 shows the results of recrystallization of mefruside in the above-mentioned solid dispersion after a storage period of 240 hr at 50, 60, and 70°C. Before heating the product it was confirmed by X-ray diffraction to show weak crystallinity. Figure 3 shows quite clearly the significant difference in the degree of recrystallization depending on the three different temperatures. Under storage conditions of 50°C, only a very slight increase in crystallinity is seen over the whole measured period. With storage at 70°C, within 24 hr a very strong increase in crystallinity is seen, reaching 70% of the crystallinity index of the standard within 240 hr. The results of the tablet formulation are shown in Fig. 4. Identical results are found at 50°C compared with the spray-dried powder (cf. Fig. 3). At 60°C, however, a significantly faster increase in crystallinity in the tablets is found in comparison with the spray-dried powder product. At a storage temperature of 70°C the results of the spray-dried powder and the tablets are nearly the same. These results demonstrate that in the temperature range between 50 and 60°C, an activating barrier for recrystallization of mefruside has to be assumed. During the tableting process additional mechanical energy enhances the recrystallization rate of mefruside.

Figure 5 shows a scanning electron micrograph. Only a few mefruside crystals can be seen at the surface of the spray-dried particle. Figure 6 shows a micrograph of a

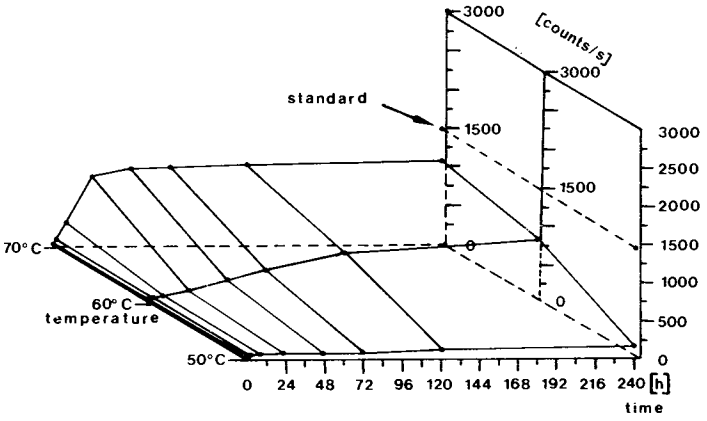

Fig. 3. Recrystallization of mefruside in a mefruside–PVP 30 (9/1, g/g) spray-dried product as a function of temperature and time. Standard: pure mefruside heated for 240 hr at 70°C.

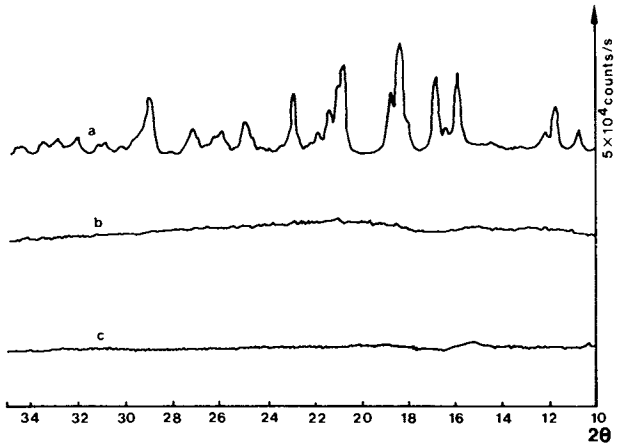

Fig. 2. Reference goniometer diffractograms. (a) Mefruside (crystallinity standard quality); (b) PVP 30; (c) sample holder.

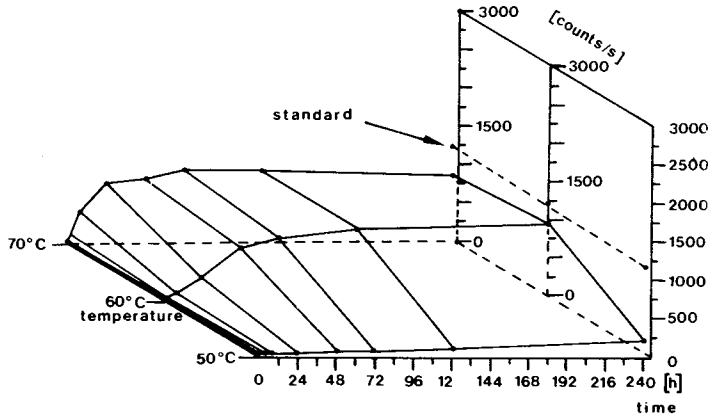

Fig. 4. Recrystallization of mefruside in a mefruside–PVP 30 (9/1, g/g) spray-dried product after tableting as a function of temperature and time. Standard: pure mefruside heated for 240 hr at 70°C.

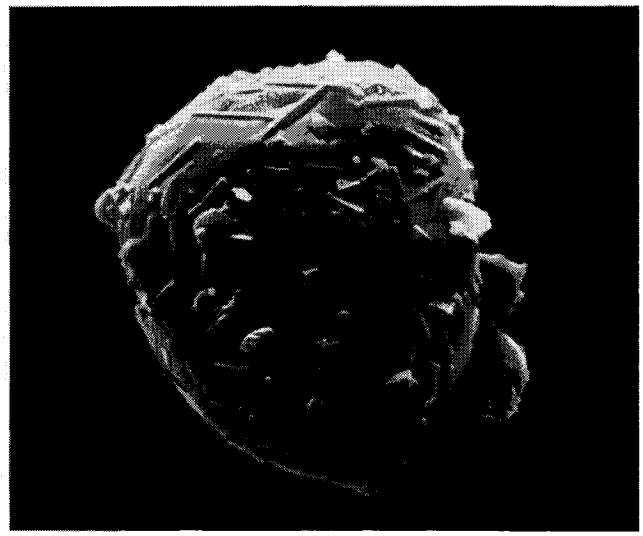

Fig. 5. Micrograph of particles of a mefruside–PVP 30 (9/1, g/g) spray-dried product. Magnification, 2000×.

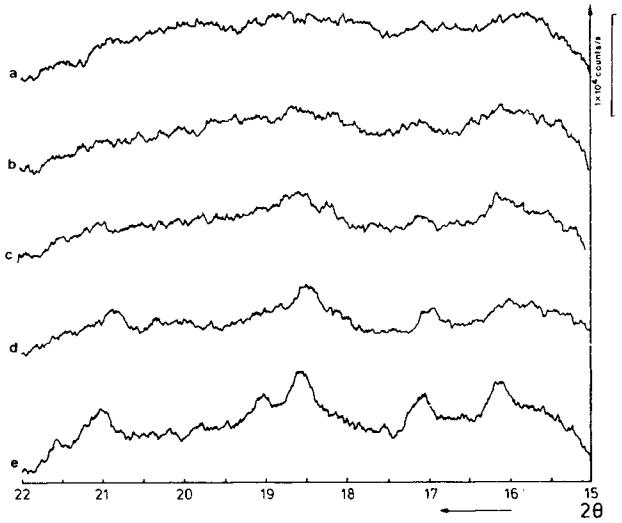

Fig. 7. Goniometer diffractograms of mefruside–PVP 30 (7/3, g/g) solid solutions. Storage periods at 70°C: (a) unheated reference; (b) 8 hr; (c) 24 hr; (d) 120 hr; (e) 240 hr.

spray-dried particle after a storage period of 240 hr at 50°C. A strong increase in crystallinity at the particle's surface can be easily detected. These micrographs show that during the storage period at 50°C, mefruside diffuses to the particle's surface to crystallize. It is possible that small amounts of the methanol–chloroform mixture that are still present in the particle after drying evaporate during storage and enhance diffusion of mefruside from the inside of the particle to its surface.

Mefruside–PVP 30 (7/3, g/g) Spray-Dried Products

Storage of mefruside–PVP 30 spray-dried products at 50°C over a 240-hr period did not show an increase in the crystallinity of mefruside. The same was true for tablets stored under the same conditions. Only a slight, but not significant, increase in crystallinity could be detected in the spray-dried powder and in the tablets after a storage period of 240 hr at 60°C.

The results of the allothermic storage of the spray-dried powder at 70°C are shown in Fig. 7. After a storage period of only 24 hr crystallinity of mefruside can be noticed which increases slightly but significantly up to 240 hr. These results were also confirmed by SEM. In Fig. 8 small crystals can be detected at the particle's surface after a storage period of 240 hr at 70°C.

Mefruside–PVP 30 (5/5, g/g) Spray-Dried Products

None of the products investigated (powder and tablets) show detectable recrystallization of mefruside after a storage period of 240 hr at 70°C neither by means of X-ray diffractometry (Fig. 9) nor by SEM (Fig. 10).

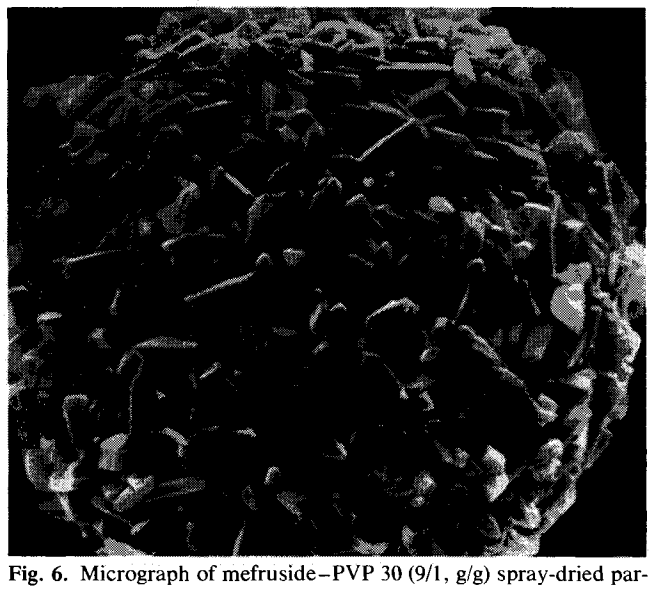

Fig. 6. Micrograph of mefruside–PVP 30 (9/1, g/g) spray-dried particles after a storage period of 240 hr at 50°C. Magnification, 5000×.

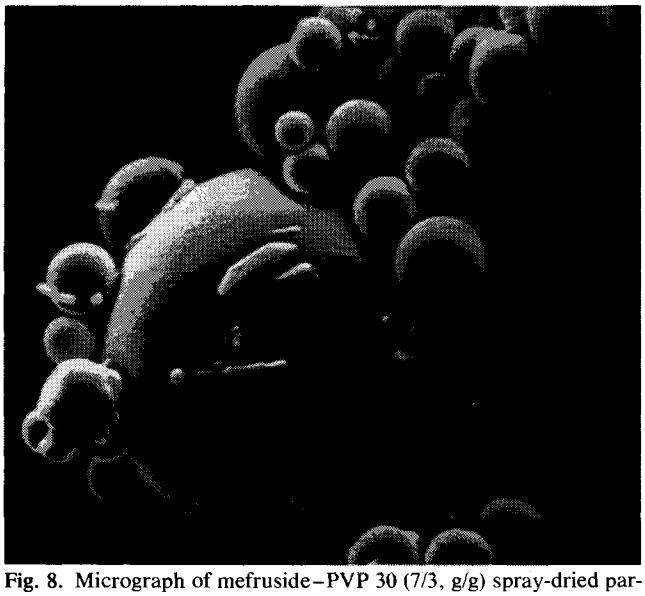

Fig. 8. Micrograph of mefruside–PVP 30 (7/3, g/g) spray-dried particles after a storage period of 240 hr at 70°C. Magnification, 5000×.

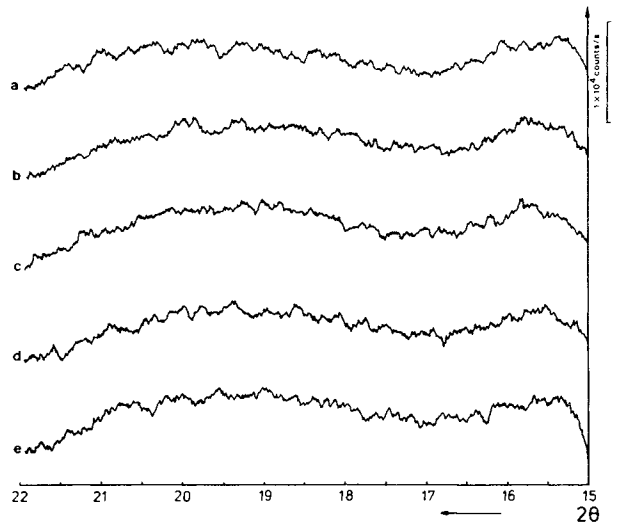

Fig. 9. Goniometer diffractograms of mefruside–PVP 30 (5/5, g/g) solid solution. Storage periods at 70°C: (a) unheated reference; (b) 8 hr; (c) 24 hr; (d) 120 hr; (e) 240 hr.

DISCUSSION

For drug–PVP complexes a maximal binding capacity of the drug (maximal drug load of the polymer in the state of a solid solution) has been reported (8–10). For phenacetin this maximal binding capacity is reached at a ratio of 1 drug molecule to 4 vinylpyrrolidone units; for phenol, paracetamol, and griseofulvin, a 1:1 ratio of drug to monomer units represents the maximal binding capacity. Drug–PVP complexes in the state of maximum binding capacity are very sensitive to recrystallization, especially after mechanical stresses (11). The tendency to recrystallize, however, is drastically hampered if the ratio of drug to monomer units is shifted from 1:1 to 1:5 in the case of griseofulvin.

Unfortunately, a maximum binding capacity for a mefruside–PVP complex could not be determined (6). The 9/1 (g/g) ratio of mefruside to PVP 30 used experimentally results in a 2.6/1 ratio stoichiometrically. Although the maximum binding capacity of PVP, which is thought to be a 1/1 complex, is exceeded by far, only a weak crystallinity in the product after spray-drying could be detected due to the low crystallization tendency of mefruside (6). The 7/3 (g/g) ratio of mefruside to PVP 30 equals statistically a ratio of 1 drug molecule to 1.47 monomer units. The 5/5 (g/g) ratio of mefruside to PVP 30 results in a 1/3.45 ratio of drug molecules to monomer units. This ratio is thought to be sufficiently high to obtain a stable high-energy product.

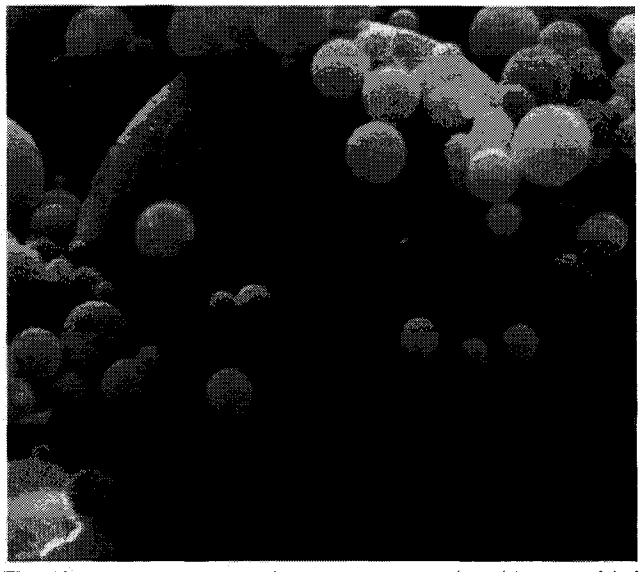

Fig. 10. Micrograph of mefruside–PVP 30 (5/5, g/g) spray-dried particles after a storage period of 240 hr at 70°C. Magnification, 5000×.

At a maximum load of PVP with drug (e.g., 1/1 ratio of drug molecules to monomer units), the network structure of the PVP chains is strongly enlarged because of the adherence of the drug molecules on the polymer. As a consequence, recrystallization of the drug takes place very easily even at low temperatures and especially after mechanical stresses because of the enhanced possibility for the drug molecules to diffuse. Increasing temperatures further facilitate the volume diffusion of the drug molecules.

If the ratio of drug molecules to monomer units is changed from 1:3 up to 1:5, the polymer is able to form a closer network structure compared to the 1:1 ratio. In this state (glassy state) the drug molecule is entrapped by the polymer chains; interactions of the drug with the polymer are possible as well. Increasing temperature also results in a higher kinetic energy of the molecules and in a loosening of the polymer network according to its glass transition temperature, which depends on the drug load of the polymer. At a ratio of 7/3 (g/g) of mefruside to PVP 30, the glass transition temperature of this solid solution is approximately 60°C. As a consequence, thermal stressing of this product at 60°C for 240 hr results in an increase in crystalline mefruside. This increase in crystallinity is still enhanced when the product is stressed mechanically during tableting.

At a ratio of 5/5 (g/g) of mefruside to PVP 30, the glass transition temperature of this solid solution exceeds 70°C, and within the chosen conditions no recrystallization of mefruside was detectable.

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REFERENCES

1. J. Kreuter. In D. D. Breimer and P. Speiser (eds.), *Topics in Pharmaceutical Sciences*, Elsevier, Amsterdam, 1983, pp. 359–370.
2. S. Keipert, J. Becker, H. Schulze, and R. Voigt. *Pharmazie* 28:145–183 (1973).
3. W. L. Chiou and S. Riegelman. *J. Pharm. Sci.* 60:1281–1302 (1971).
4. K. Sekiguchi and N. Obi. *Chem. Pharm. Bull.* 9:866–872 (1961).
5. H. Junginger and M. Wedler. *Acta Pharm. Technol.* 30:68–77 (1984).
6. M. Wedler. Thesis, Technical University Braunschweig, FRG, 1985.
7. L. G. Chatten. *Pharmaceutical Chemistry, Vol. 2, Instrumental Techniques*, Marcel Dekker, New York, 1969, pp. 380–391.
8. H. Junginger. *Pharm. Ind.* 38:461–471 (1976).
9. D. E. Guttman and T. Higuchi. *J. Pharm. Sci.* 45:659–664 (1956).
10. H. Junginger. *Pharm. Ind.* 39:383–388 (1977).
11. E. Nürnberg. *Habilitationsschrift*, University of Marburg, FRG, 1970.