International Journal of Pharmaceutics, 33 (1986) 115–124
Elsevier

IJP 01110

Influence of polymer characteristics on drug loading into crospovidone *

F. Carli, I. Colombo, L. Magarotto, A. Motta and C. Torricelli

Physical Pharmacy Laboratory, Pharmaceutical Development, Farmitalia Carlo Erba, 20159 Milano (Italy)

(Received 28 February 1986)
(Accepted 26 May 1986)

Key words: Crospovidone – Drug loading in polymeric carrier – Improved dissolution system

Summary

Four "popcorn" and one chemically cross-linked polyvinylpyrrolidones were loaded with griseofulvin by swelling the polymers with a dimethylformamide solution of the drug. The particle size, surface area, microstructure, swelling properties and water soluble content of the 5 polymers were measured and related to the properties of the resulting loaded systems. Differential scanning calorimetry, X-ray diffractometry and electron microscopy were used to identify the physical state of the loaded drug, whereas X-ray photo electron spectroscopy was applied to identify the location of the drug molecules. By a prewashing treatment, the influence of the water soluble polymeric content on the final characteristics of the loaded system was evaluated. Finally, the dissolution properties of all the loaded polymers were measured and related to the basic physico-chemical properties of the polymers.

Introduction

The loading of drugs into cross-linked polyvinylpyrrolidone (crospovidone) has been recently proposed as a technique to increase the dissolution properties of slightly soluble drugs (Lippold and Lütschg, 1978; Takayama et al., 1982).

The main mechanism of the loading process is considered to be the molecular dispersion of the drug throughout the macromolecular network of the polymer, as supported also by X-ray photo electron spectroscopy (XPS) surface analysis (Carli and Garbassi, 1985). This dispersion brings about the amorphization of the loaded drug, which in turn gives origin to high supersaturation phenomena in the solubility pattern (Lippold et al., 1978; Carli and Garbassi, 1985).

The crospovidone commercially available is prepared by popcorn polymerization (Sanner et al., 1983) and is widely used as a disintegrant (Kornblum and Stoopak, 1973; Bronnsack, 1978); its monography is included in the National Formulary XV of the US Pharmacopeia under the name crospovidone, where identification and chemical analysis procedures are outlined. On the other hand, no particular attention has been given to the physico-chemical properties of the crospovidone, such as particle size, surface area, swelling volume, etc.

It is the object of this paper to fully characterize the crospovidone powder and to relate the physico-chemical parameters of the polymer to the

* Partially presented at the 4th Pharmaceutical Technology Conference, Edinburgh, 1984.

Correspondence: F. Carli, Physical Pharmacy Laboratory, Pharmaceutical Development, Farmitalia Carlo Erba, via Imbonati 24, 20159 Milano, Italy.

resulting characteristics of the drug–crospovidone systems. Furthermore, by studying also a chemically cross-linked povidone, the influence of the cross-linking technique on the characteristics of the loaded systems is also investigated.

Materials and Methods

Materials

The four "popcorn" crospovidones studied (lot 19-2143, hereafter called A; lot 48-3088, B; lot 12-1004, C; lot 99-1489, D) were used as received from BASF (F.R.G.). They were small experimental samples and may not represent the actually marketed Kollidon CL products. Also the chemically cross-linked povidone (lot 141-77/191/B/C, hereafter called E) was used as received (special sample from BASF, F.R.G.).

Griseofulvin (Glaxo Group Ltd., U.K.) was used as the drug model.

Methods

Polymer loading. The 5 crospovidones A, B, C, D and E were loaded with griseofulvin by swelling, under continuous mixing in a mortar, the polymer powders with a dimethylformamide solution of the drug. For each polymer a drug solution volume smaller than the maximum swelling capacity of the polymer was used; the drug solution concentration was chosen to give the desired drug–polymer ratio. After swelling, the loaded crospovidones were dried to constant weight in a vacuum oven (Vuototest, Mazzali, Italy), at 120°C, subsequently deaggregated with a 60-mesh sieve and homogeneously mixed (Turbula, Bachofen, Switzerland). Residual content of solvent was usually less than 150 ppm (Gas Chrom 2350, Carlo Erba Strumentazione, Italy).

Analysis of griseofulvin content. The griseofulvin content of the loaded polymers was checked by successive extractions with ethanol and subsequent spectrophotometric analysis (SP-8-100, Pye Unicam, U.K.). Usual griseofulvin content found was in the range 90–99% of the theoretical content.

Swelling measurement. The swelling volumes of the crospovidones were measured by the gravimetric centrifuge method of Kornblum and Stoopak (1973) or by directly registering the volumes of liquid uptake with an Enslin apparatus (Couvreur et al., 1976). The liquids used were: water, dimethylformamide, ethanol, acetone, chloroform and cyclohexane.

Pore Structure, particle size and surface area measurements. The microstructure characteristics, the particle size and surface area distribution of the 5 polymers were measured by microcomputerized mercury porosimetry (Mod. 200, Carlo Erba Strumentazione, Italy) and applying the method of Carli et al. (Carli et al., 1982, Carli and Motta, 1984).

Water soluble content. The water soluble content of the crospovidones was quantitatively determined by the pharmacopeial method (National Formulary XV). The presence of linear povidone was assessed by iodine complexation (Scholtan, 1953).

X-ray diffractometry. The X-ray diffractometer PW 1050/70 (Philips, The Netherlands) was used (CuKα as radiation source).

Electron scanning microscopy. The scanning electron microscope Stereoscan 604 (Cambridge, U.K.) was used.

Differential scanning calorimetry. Differential scanning calorimetry of the loaded systems was carried out with the TA 3000 system of Mettler (Switzerland), with the DSC 20 cell, under nitrogen flow and a heating rate of 10°C/min.

X-ray photo electron spectroscopy. The elemental composition of the surface of the griseofulvin loaded crospovidones was determined by X-ray photo electron spectroscopy (Mod. 548, Physical Electronics, U.S.A.).

Solubility measurements. The solubility of the loaded crospovidones was measured by placing an excess amount of the powdered systems in a flow cell containing 50 ml of pH 7.5 buffer solution, at 37°C, under constant magnetic stirring. The solution was filtered and pumped directly to a spectrophotometer cell (SP-8-100, Pye Unicam, U.K.)

Dissolution rate measurements. The dissolution rate (sink conditions) of the loaded crospovidones was measured by using an adequate amount of the sample powder and USP XX "paddle" method,

with 900 ml of pH 7.5 buffer solution, at 37°C, at 150 rpm.

Results and discussion

Physico-chemical properties of the crospovidones

The swelling volumes of the 5 polymers, reported in Table 1 and Fig. 1, show that the 4 popcorn crospovidones differ quite largely: polymer A and B swell more with all the solvents than polymer C and D. Furthermore the plot of the swelling volume against the polar component of the solubility parameter of the solvents points out that the 4 popcorn povidones are basically amphifilic, whereas the chemically cross-linked povidone exhibits a higher polarity.

The surface area of the 5 crospovidones ranged from 4.1 m^2/g of polymer A to 0.1 m^2/g of polymer E; these surface area values were simply related to the particle size and not to the presence of intraparticle pores. This was demonstrated both by mercury porosimetry analysis, presenting only unimodal pore size distribution related to interparticles voids and by gas adsorption analysis, which ruled out the presence of micropores.

The largely different particle size of the 5 crospovidones, found by porosimetry, was also confirmed by scanning electron microscopy (SEM). Furthermore the SEM analysis showed that the crospovidones A, B, C and D presented a very rough, "popcorn-like" appearance, whereas the chemically cross-linked povidone E presented a very smooth surface (Fig. 2).

As shown in Table 1, the water soluble content of the 4 popcorn crospovidones was under the USP upper limit (1.5%), but it did differ from one lot to the other one; on the contrary, the chem-

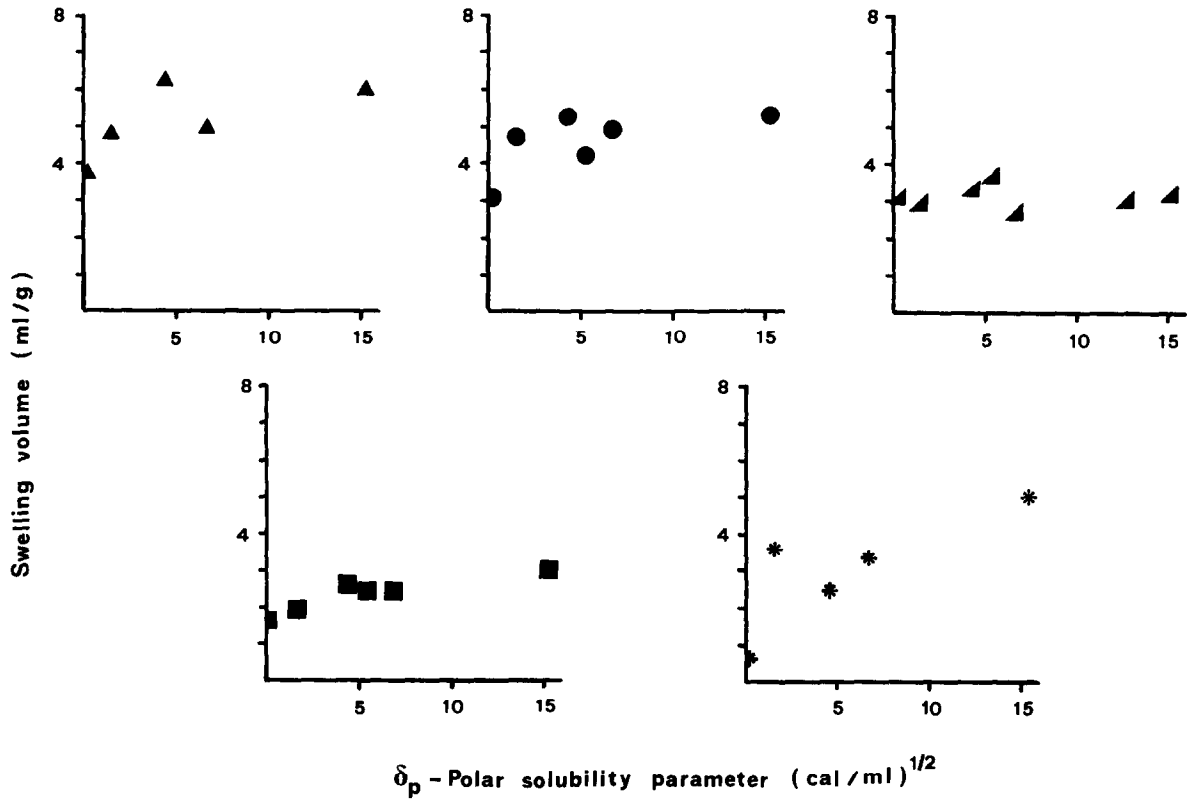


Fig. 1. Swelling of crospovidones A (▲), B (●), C (◢), D (■) and E (*) in various solvents: water (δ_p 15.3), formamide (δ_p 12.8), dimethylformamide (δ_p 6.7), acetone (δ_p 5.1), ethanol (δ_p 4.3), chloroform (δ_p 1.5) and cyclohexane (δ_p 0.0).

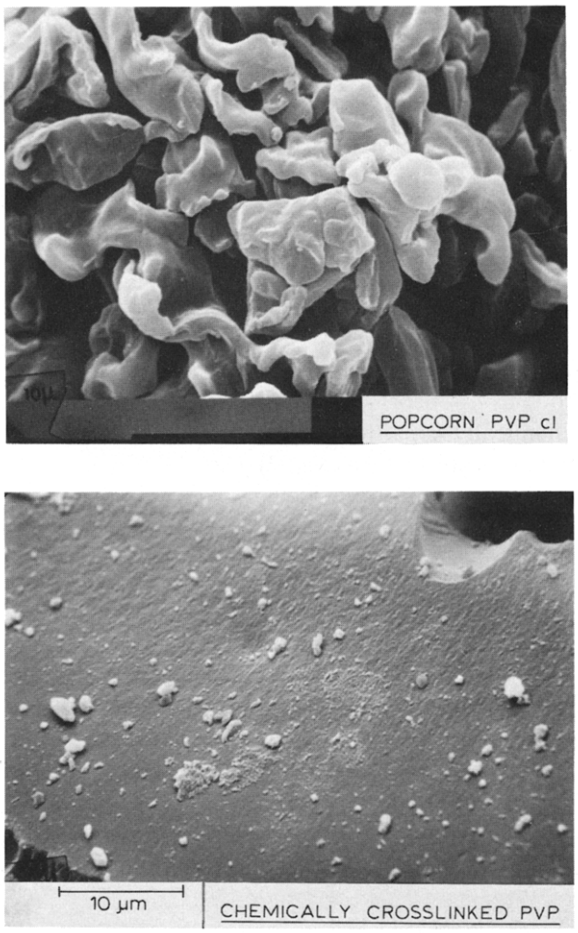


Fig. 2. Scanning electron photomicrographs of popcorn crospovidone (top) and chemically cross-linked crospovidone E (bottom).

ically cross-linked povidone presented a much higher water soluble content. Furthermore, by iodine complexation, it was possible to assess that in the case of the popcorn crospovidones the water soluble content was due to linear povidone residue, whereas in the case of the chemically cross-linked povidone it was essentially due to non-polymeric material.

Physical state of griseofulvin in the loaded crospovidones

The physical state of the griseofulvin loaded in the crospovidones has been assessed by differential scanning calorimetry and by X-ray diffractometry: from both techniques the residual percentage crystallinity has been derived (see Table 2), with a generally good agreement.

From the data presented in Table 2, the crospovidone A seems to have a high residual crystallinity at all the drug–polymer ratios, whereas the other popcorn crospovidones present a higher amorphization at the higher loading ratios (no residual crystallinity at 1/10 w/w). Furthermore, the chemically cross-linked povidone E presents no crystallinity at all the loading ratios.

It seems interesting to relate these crystallinity data to the water soluble content of each crospovidone: PVPcl A presents the highest content of linear polymer residue; during the solvent swelling loading process this polymeric residue may counterdiffuse from the inner core of the particles to the outer layers, slowing down the inward diffu-

TABLE 1

PHYSICO-CHEMICAL PROPERTIES OF THE CROSPOVIDONES

Crospovidone	Swelling volume of water (ml/g)	Swelling volume of DMF [a] (ml/g)	True density (ml/g)	Mean particle size [b] (µm)	Specific surface area [b] (m^2/g)	Water soluble content (%)	Type of water-soluble content [c]
A	6.1	4.9	1.22	13.0	4.15	1.10	linear PVP
B	5.3	5.0	1.18	9.5	2.98	0.43	linear PVP
C	3.2	2.6	1.23	32.0	0.52	0.46	linear PVP
D	2.9	2.4	1.20	49.0	0.34	0.35	linear PVP
E	5.0	3.4	1.23	165.0	0.10	3.80	low molecular weight species

[a] Dimethylformamide.
[b] By mercury porosimetry.
[c] By iodine complexation.

TABLE 2

PHYSICAL STATE OF GRISEOFULVIN IN THE LOADED CROSPOVIDONE SYSTEMS

Crospovidone	Drug–polymer ratio (w/w)	Differential scanning calorimetry (% crystallinity)	X-ray diffractometry (% crystallinity)
A	1/5	47	54
A prewashed	1/5	0	0
A	1/7	37	8
A	1/10	48	77
B	1/5	36	30
B prewashed	1/5	13	10
B	1/7	0	0
B	1/10	0	0
C	1/5	6.5	10
C prewashed	1/5	0	10
C	1/7	4.5	0
C	1/10	0	0
D	1/5	4	5
D prewashed	1/5	0	10
D	1/7	0	0
D	1/10	0	0
E [a]	1/5	0	0
E	1/7	0	0
E	1/10	0	0

[a] No significant difference between untreated and prewashed polymer.

sion of the drug molecules (see Fig. 3); this higher outer layer griseofulvin concentration may lead, in the drying process, to a higher surface crystallization.

This interpretation is supported by the data on the polymeric systems with prewashed crospovidones, i.e. crospovidones presenting no more polymeric residue after a prewashing treatment (no other physical change is found): as shown in Table 2, all the prewashed crospovidones, including PVPcl A, present an almost complete amorphization.

In the case of the chemically cross-linked povidone E the water soluble content is due only to non-polymeric material: this means that there is no strong slowing of the intraparticle drug diffusion process and consequently no crystallization effect in the surface layers.

It remains to mention that other information on the physical state of the loaded drug can be derived from the differential scanning thermograms; e.g., both the shape of the thermogram and the melting temperature can be related to the degree of drug dispersion over the surface of the carrier (Monkhouse and Lach, 1972). In fact, as shown in Fig. 4, there is a dramatic difference between the thermograms of the polymer loaded crystalline griseofulvin (presence of the sharp peak at the melting temperature of the pure drug and broad peaks at lower temperatures) and that of the pure drug. In a subsequent paper a detailed interpretation of this phenomenon will be given.

Surface analysis (XPS) of the griseofulvin loaded crospovidones

X-Ray photo electron spectroscopy (XPS), also known as ESCA, was used to analyze the elemental composition of the surface of the loaded crospovidones. The XPS technique is based on irradiating at a grazing angle X-rays over the surface of the samples, so that the inner electrons of the surface atoms (X-ray penetration depth for organic materials is 140 Å) are emitted and counted (Riggs and Parker, 1975; Hercules and Hercules, 1978): from the energy of the emitted electrons the element is identified, whereas from the electrons count the percentage of the element in the surface is derived. In the case of crospovidone loaded with griseofulvin the label atoms chosen to map the presence of griseofulvin in the surface layers were chlorine for the drug and nitrogen for crospovidone; from the absolute value of chlorine surface percentage and from the ratio Cl/N it was possible to follow the relative changes of the griseofulvin distribution over the polymer surface.

The basic observation which can be drawn from the data presented in Table 3 is that the chemically cross-linked povidone E shows a lower distribution of griseofulvin in the surface layers; i.e., the drug seems to be more impregnated in the inner core of the polymer particles. The 4 popcorn crospovidones have higher percentages of griseofulvin in the surface, as shown by the higher values of the Cl/N ratios. Furthermore, as amorphization increases, the griseofulvin molecules seem to spread more over the surface of the

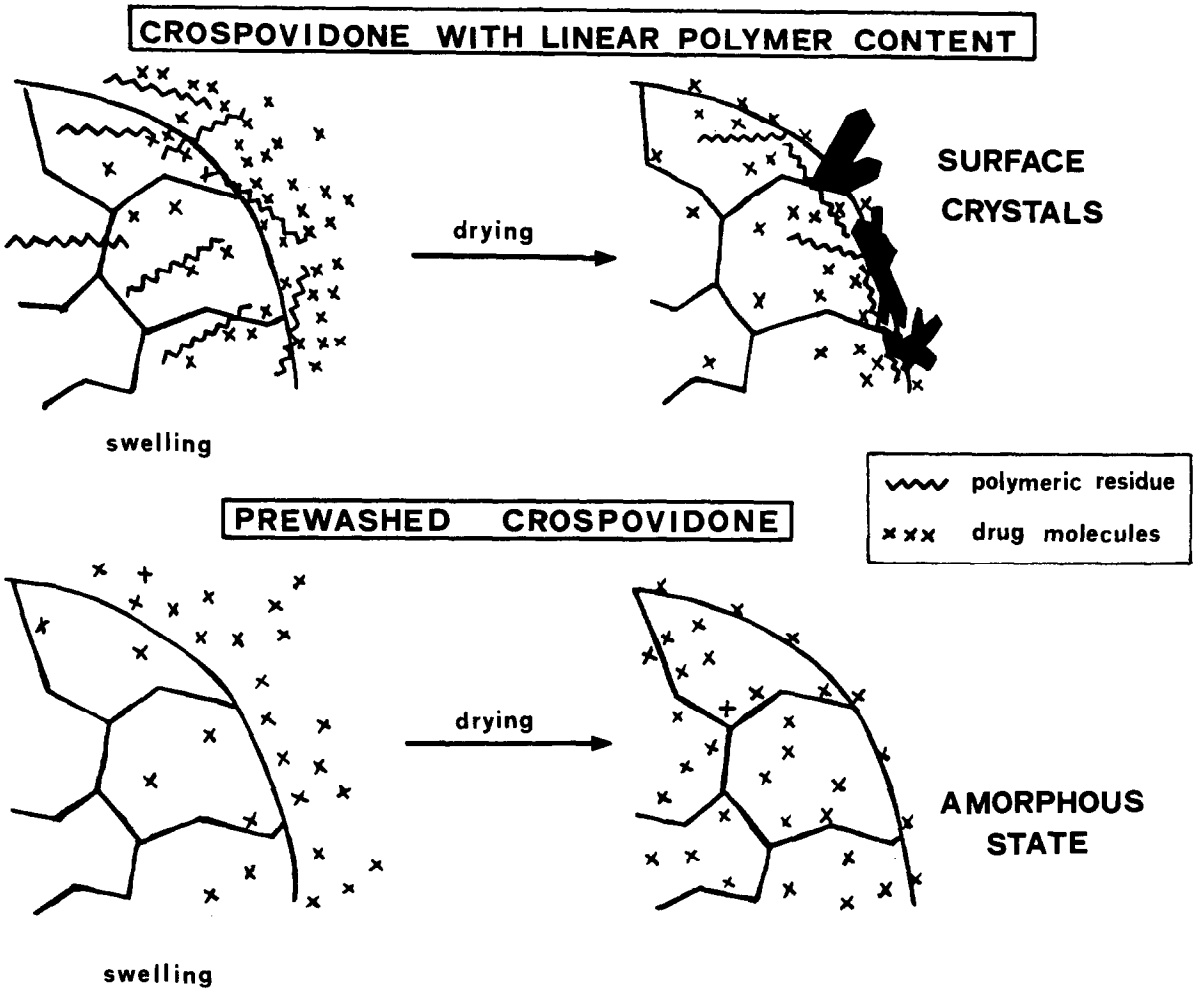


Fig. 3. Scheme of the drug loading in crospovidone, both for a non-washed and for a prewashed polymer.

popcorn crospovidones; this can be explained by considering that, as crystallinity decreases, a larger part of the surface is covered by the drug molecules, the tendency of the drug to diffuse in the inner core of the popcorn crospovidone particles being low (Carli and Garbassi, 1985).

In the case of the prewashed polymer systems, it is possible to observe a decrease of the Cl/N ratio: this can be explained on the basis of a higher intraparticle diffusion when no macromolecular counterdiffusion takes place. The only exception is polymer A, where the dramatic decrease of crystallinity due to the prewashing procedure actually increases the surface concentration of griseofulvin, largely counterbalancing the higher inner core diffusion effect.

Solubility and dissolution properties of the griseofulvin loaded crospovidones

In Fig. 5, the solubility data of the five 1/5 w/w drug–crospovidone systems are reported. All the systems show an oversaturation pattern, with higher oversaturation concentrations given by the systems with higher degree of amorphization. Furthermore, the fact that the chemically cross-linked povidone E originates the highest concentrations, may be related to a higher energy state of the griseofulvin molecules, as indicated both by the

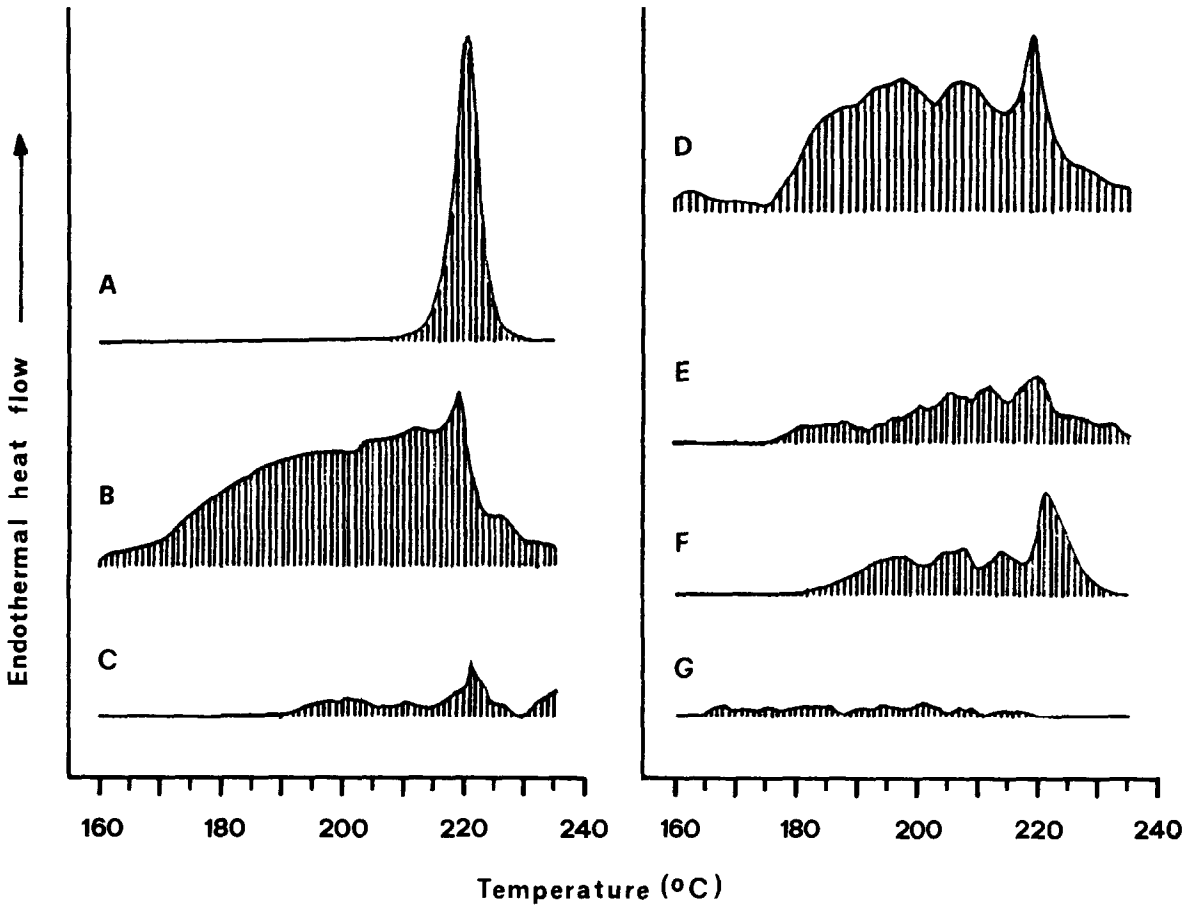


Fig. 4. Differential scanning calorimetry thermograms. Left: A, pure griseofulvin crystallized by DMF; B, griseofulvin/crospovidone A 1/5 w/w system; C, griseofulvin/prewashed crospovidone A 1/5 w/w system. Right: D, griseofulvin/crospovidone B 1/5 w/w system; E, griseofulvin/crospovidone C 1/5 w/w system; F, griseofulvin/crospovidone D 1/5 w/w system; G, griseofulvin/crospovidone E 1/5 w/w system.

complete amorphous state and by the higher dispersion of the drug molecules in the inner core of the crospovidone particles, as suggested by XPS data (Carli and Garbassi, 1985).

The role of lower residual crystallinity in originating higher oversaturation concentrations is stressed also in Fig. 6, where non-washed and prewashed polymer systems are compared: the prewashing treatment leads to a higher degree of amorphization and consequently a higher oversaturation pattern.

The dissolution rate data of the griseofulvin loaded systems prepared with the 5 different crospovidones are shown in Figs. 7, 8, 9, 10 and 11. For all the crospovidones it is possible to observe that lower drug loading ratios lead to higher dissolution rate concentrations. This may be related to higher drug–liquid interface area, due to higher amorphization and drug dispersion throughout the hydrophilic polymeric network. Only in the case of the crospovidone A less effect is exerted by the loading ratios; this may be due to the high crystallinity present also at the lowest drug–polymer ratios.

The dissolution rate of the prewashed popcorn polymer systems at 1/5 w/w drug–polymer ratio is shown in Fig. 12. Because the crystalline state was practically the same for all the 4 crospovi-

TABLE 3

SURFACE ANALYSIS (XPS) OF LOADED CROSPOVIDONE SYSTEMS (Cl/N = RATIO OF THE SURFACE PERCENTAGES OF CHLORINE AND NITROGEN)

Crospovidone	Drug/polymer ratio (w/w)	Cl/N
A	1/5	0.060
A prewashed	1/5	0.095
A	1/7	0.040
A	1/10	0.030
B	1/5	0.066
B prewashed	1/5	0.040
B	1/7	0.049
B	1/10	0.058
C	1/5	0.057
C prewashed	1/5	0.054
C	1/7	0.044
C	1/10	0.081
D	1/5	0.074
D prewashed	1/5	0.039
D	1/7	0.061
D	1/10	0.098
E [a]	1/5	0.055
E	1/7	0.036
E	1/10	0.038

[a] No significant difference between untreated and prewashed polymer.

dones, the dissolution rate seems to be influenced more by the surface area of the polymeric carrier and by the surface concentration of the drug (see XPS data).

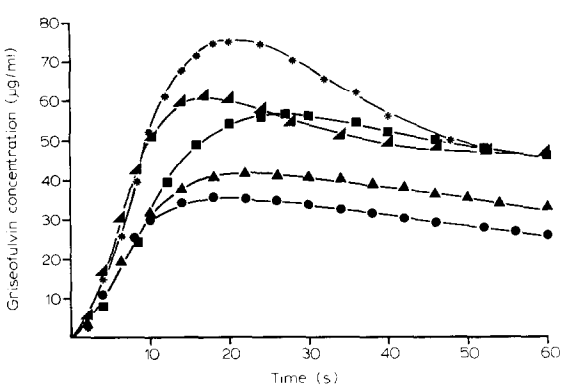


Fig. 5. Solubility (pH 7.5, 37°C) of the five 1/5 w/w griseofulvin/crospovidone systems obtained by loading the drug in crospovidones A (▲), B (●), C (◢), D (■) and E (*).

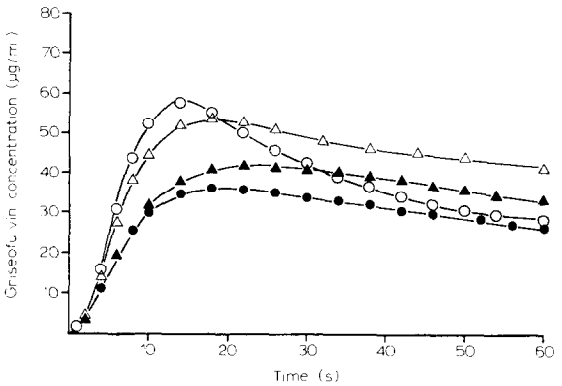


Fig. 6. Solubility (pH 7.5, 37°C) of griseofulvin loaded in non-washed crospovidones A (▲) and B (●) and in prewashed crospovidones A (△) and B (○). (Drug–polymer ratio: 1/5 w/w).

Practically all the 5 crospovidones studied presented one or more physico-chemical parameters different from the ones of the other polymers (specific surface area, water soluble content, etc.).

Two of these parameters had a particularly strong influence of the final characteristics of the drug loaded systems:

(a) the linear polymer residue, which influences the crystalline state of the loaded drug;

(b) the specific surface area, which influences the dissolution rate of the loaded systems.

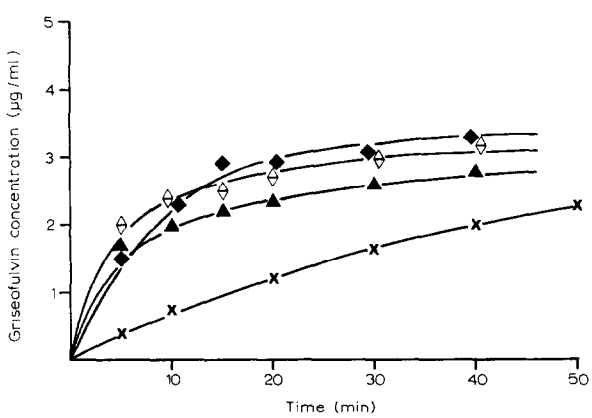


Fig. 7. Dissolution rate (pH 7.5, 37°C) of griseofulvin loaded in crospovidone A: 1/5 w/w drug–polymer system (▲); 1/7 w/w drug–polymer system (◈); 1/10 w/w drug–polymer system (◆). Pure griseofulvin dissolution profile is also shown (×).

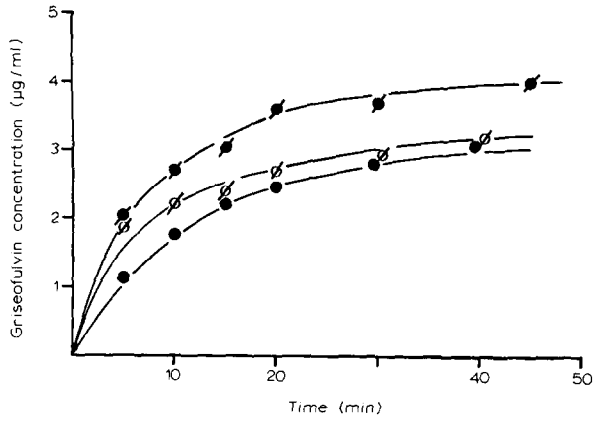


Fig. 8. Dissolution rate (pH 7.5, 37°C) of griseofulvin loaded in crospovidone B: 1/5 w/w drug–polymer system (●); 1/7 w/w system (Ø); 1/10 w/w system (◖).

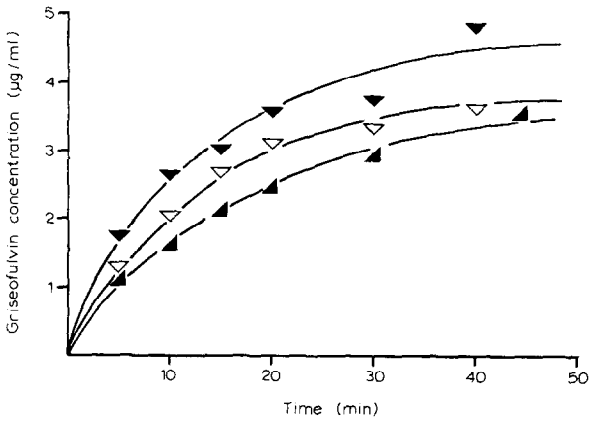
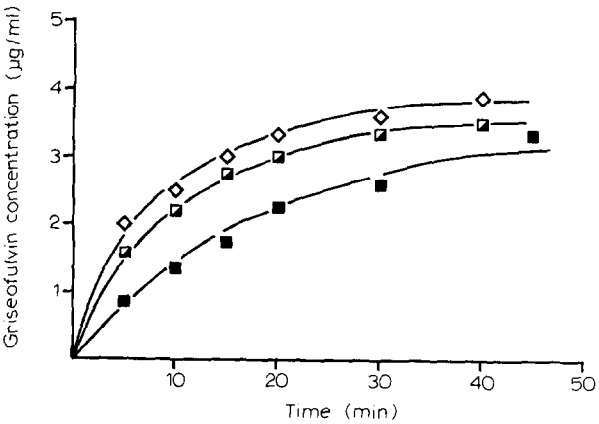


Fig. 9. Dissolution rate (pH 7.5, 37°C) of griseofulvin loaded in crospovidone C: 1/5 w/w drug–polymer system (◢); 1/7 w/w system (▽); 1/10 w/w system (▼).



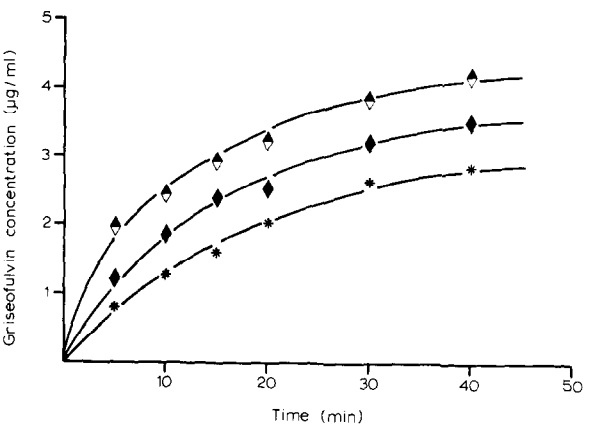


Fig. 11. Dissolution rate (pH 7.5, 37°C) of griseofulvin loaded in crospovidone E: 1/5 w/w drug–polymer system (*); 1/7 w/w system (◆); 1/10 w/w system (◆).

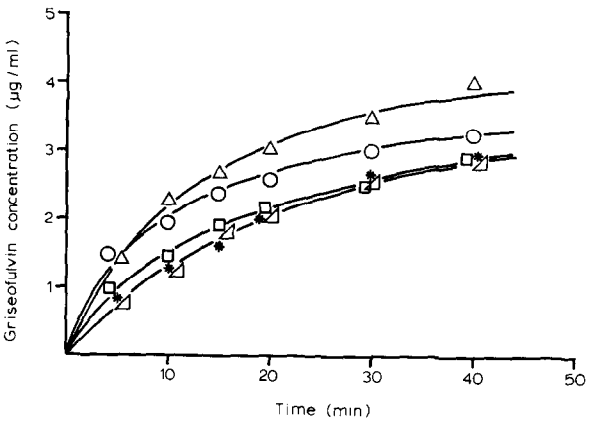


Fig. 12. Dissolution rate (pH 7.5, 37°C) of griseofulvin loaded in prewashed crospovidones A (△), B (○), C (△), D (□) and in crospovidone E (*). (Drug–polymer ratio 1/5 w/w).

On the other hand, once the solvent loading volumes have been appropriately chosen, the swelling properties of the crospovidones seem to exert no influence on the characteristics of the loaded systems.

As far as the relationship between the physical characteristics and the dissolution properties of the loaded systems is concerned, the most im-

←

Fig. 10. Dissolution rate (pH 7.5, 37°C) of griseofulvin loaded in crospovidone D: 1/5 w/w drug–polymer system (■); 1/7 w/w system (◪); 1/10 w/w system (◇).

portant considerations which can be made are the following:

(a) the solubility of the loaded systems is influenced practically only by the physical state of the loaded drug;

(b) the dissolution rate is influenced, besides the specific surface area, also by drug surface layers distribution.

Finally, it is important to stress the differences found between the chemically cross-linked povidone and the 4 popcorn crospovidones: in the former there is a higher tendency of griseofulvin molecules to disperse throughout the polymeric network, with consequent complete amorphization of the drug also at high drug–polymer ratio and lower drug concentrations in the surface layers. This higher degree of dispersion of the drug molecules lead to a higher oversaturation solubility pattern.

Acknowledgements

This research was partially sponsored by CNR (Consiglio Nazionale delle Ricerche). The assistance of Mrs. R. Fiannaca is gratefully acknowledged.

References

Bronnsack, A.H., Polyplasdone XL-Eigenschaften und praktische Erkenntnisse über den Einsatz als Tablettensprengund -bindemittel. *Pharm. Ind.*, 40 (1978) 1255–1263.

Carli, F., Motta, A., Ulivieri, M. and Italiano, P., Optimization of particle size analysis by microcomputer-controlled mercury porosimetry. In Stanley-Wood, N. and Allen, T. (Eds.), *Particle Size Analysis 1981*, Wiley Heyden, Chichester, 1982, pp. 103–112.

Carli, F. and Motta, A., Particle size and surface area distributions of pharmaceutical powders by microcomputerized mercury porosimetry. *J. Pharm. Sci.*, 73 (1984) 197–203.

Carli, F. and Garbassi, F., Characterization of drug loading in crospovidone by X-ray photoelectron spectroscopy. *J. Pharm. Sci.*, 74 (1985) 963–967.

Couvreur, P., Gillard, J. and Roland, M., Incidence des cinétiques d'absorption d'eau sur le délitement des comprimés pharmaceutiques à base d'agents amylaces. *Ann. Pharm. Franc.*, 34 (1976) 123–132.

Hercules, S.H. and Hercules, D.M., Surface characterization by electron spectroscopy for chemical analysis (ESCA). In Kane, P.F. and Larrabee, G.B. (Eds.), *Characterization of Solid Surfaces*, Plenum Press, New York, 1978, pp. 307–336.

Kornblum, S.S. and Stoopack, S.B., A new tablet disintegrating agent: cross-linked polyvinylpyrrolidone. *J. Pharm. Sci.*, 62 (1973) 43–49.

Lippold, B.C. and Lütschg, R., Einfluss von organischen, begrenzt quellfähigen Trägerpolymeren auf das Lösungsverhalten von schwerlöslichen Wirkstoffen. Erste Mitteilung. *Pharm. Ind.*, 40 (1978) 541–549.

Lippold, B.C., Lütschg, R. and Ullmann E., Einfluss von organischen, begrenzt quellfähigen Trägerpolymeren auf das Lösungsverhalten von schwerlöslichen Wirkstoffen. Zweite Mitteilung. *Pharm. Ind.*, 40 (1978) 647–653.

Monkhouse, O.C. and Lach, J.L., Use of adsorbents in enhancement of drug dissolution II. *J. Pharm. Sci.*, 61 (1972) 1435–1441.

National Formulary, XV Edition, Supplement 3, *United States Pharmacopeia*, Mack Publishing, Easton, PA, 1982, p. 368.

Riggs, W.M. and Parker, M.J., Surface analysis by X-ray photoelectron spectroscopy. In Czanderna A.W. (Ed.), *Methods of Surface Analysis*, Elsevier, Amsterdam, 1975, pp. 103–158.

Sanner, A., Straub, F. and Tschang, C.H., Chemistry, Structure and properties of polyvinylpyrrolidone. In Digenis, G.A. and Ansell, Joy (Eds.), *Proceedings of the International Symposium on Povidone*, Kentucky University, Lexington, 1983, pp. 20–38.

Scholten, W., Uber die Adsorptionsfähigkeit von wasserlöslichen polymeren Verbindungen, insbesonders von Polyvinylpyrrolidon. *Makromol. Chem.*, 11 (1953) 131–230.

Takayama, K., Imaizumi, H., Nambu, N. and Nagai, T., Factors affecting the dissolution and stability of drugs dispersed in polymers. *J. Pharm. Dyn.*, 5 (1982) S3.