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Physicochemical aspects of drug release. IX. Investigation of some factors that impair dissolution of drugs from solid particulate dispersion systems

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Summary

Solid dispersions of different concentrations of griseofulvin (3, 10 and 20 w/w%) have been prepared by the melting method with polyethylene glycol (PEG) 3000 as a carrier. Different concentrations of the viscosity-enhancing agent Aerosil, colloidal silicon dioxide, and Ac-Di-Sol, a disintegrant of an internally cross-linked form of sodium carboxy methyl cellulose, alone or in combination, were added to the melts before solidification. In all samples investigated the PEG and griseofulvin phases were identified by X-ray powder diffraction. No solid solution or intermediate phase was observed. The dispersions were present as physical mixtures of the carrier and the drug. Dissolution rate measurements were performed according to USP XXI, paddle method 100 rpm, at 21 ± 1° C in a medium of deionized water with 0.9% sodium chloride and 0.01% polysorbate 80. The fastest dissolution of griseofulvin was obtained for dispersions containing the lowest concentration of drug, in the absence of additives. An increase in drug content, to 10 and 20 w/w%, or the addition of Aerosil markedly decreased the release and dissolution rate of griseofulvin. The further addition of Ac-Di-Sol improved the dissolution only for dispersions containing Aerosil, but no such effect was obtained for dispersions with higher concentrations of drug. A high concentration of fine particulate griseofulvin in the dispersion corresponds to a dissolution surface area of pronounced hydrophobic nature. In these systems inadequate wetting may be the rate-limiting step in the dissolution process, and the incorporation of the disintegrant does not affect the dissolution. The observed decrease in drug dissolution for systems with Aerosil incorporated may be explained by a lower solubility of PEG 3000 due to a change in its crystallinity, as observed by X-ray powder diffraction. The change in crystallinity was confirmed by DSC measurements where the heats of fusion for samples containing Aerosil, were increased compared to predicted values.

Introduction

The dissolution of sparingly soluble drugs can be enhanced by the preparation of solid solutions and solid dispersions. In this paper solid particulate dispersions have been investigated and the separate drug and carrier phases identified by X-ray powder diffraction. By incorporating the drug in an easily soluble carrier the drug is released as primary particles when the carrier dissolves. However, an increase in drug concentration generally gives a decrease in dissolution rate.

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Possible explanations for this phenomenon are an increase in drug particle size (Sjökvist and Nyström, 1988) or a reduced dissolution rate of the carrier (Corrigan et al., 1979; Sjökvist and Nyström, 1988). This latter effect is probably due to an impaired wetting of the dispersion particles or to a decrease in carrier solubility.

In an earlier study (Sjökvist and Nyström, 1988) it was shown that for solid dispersions of griseofulvin in polyethylene glycol 3000 (PEG), prepared by a solvent method, there was a direct relationship between an increase in particle size with increased drug concentration and a decreased dissolution rate. In solid dispersions prepared by the melting method, griseofulvin is dispersed in fine particulate form, even for higher contents of drug (10 and 20 w/w%). Nevertheless it was shown that the dissolution rate decreased with an increase in drug concentration and was not as high as might have been expected considering the fine particulate form of the drug. For these systems the dissolution of the carrier seemed to be the rate-limiting step in the delivery of dissolved drug to the dissolution medium.

To utilize solid dispersions as an effective formulation principle for the fast release of sparingly soluble drugs, it is important to find means to counteract the retarded carrier dissolution, when incorporating high doses of drug.

The aim of this study was to investigate possible mechanisms behind an impaired drug dissolution from solid dispersions. The influence of the incorporation of two different additives, a viscosity-enhancing agent and a disintegrant, on carrier and drug properties in solid dispersions was also studied.

Materials and Methods

Materials

Griseofulvin microsized (Glaxo, UK) was used as a model substance of a fine particulate, sparingly soluble drug. The material is strongly agglomerated due to its cohesive nature. Primary characteristics of the griseofulvin quality used have been characterized and described earlier (Nyström et al., 1985; Sjökvist and Nyström, 1988): true density, 1.44 g/cm^3; geometric mean diameter by weight, 3.0 μm; aqueous solubility, 7.6 mg/l at 21° C; melting point, 219–221° C.

Polyethylene glycol (PEG) 3000 (Apoteksbolaget, Sweden) was used as an easily soluble carrier. The melting point is 56–58° C, measured with a DSC 20 (Mettler, Switzerland) and the aqueous solubility is 1 : 2 (Martindale, 1982).

Aerosil 200 (Degussa, F.R.G.), a form of colloidal silicon dioxide, was used as a viscosity-enhancing agent. The degree of viscosity increase depends on the polarity of the liquid, i.e. polar liquids generally require higher concentrations than non-polar liquids (Handbook of Pharmaceutical Excipients, 1986). The average size of the primary particles is estimated to be approximately 16 nm (Katalog Pharmazeutischer Hilfstoffe, 1974).

Ac-Di-Sol (FMC Corp., U.S.A.) is an internally cross-linked form of sodium carboxymethylcellulose. It is essentially water-insoluble, but the particles are highly absorbent and swell strongly in contact with water. The material is a commonly used disintegrant in tablet formulation.

Methods

Preparation of solid dispersion

Solid dispersions (100 g) were prepared by the melting method. PEG 3000 was melted and griseofulvin was added in order to obtain 3, 10 and 20 w/w% solid dispersions. When no particles of griseofulvin could be observed visually, the melt was cooled at ambient temperature (21° C) and stored for at least 24 h before pulverizing it in a mortar. In all experiments the sieve fraction 300–500 μm was used, if not stated otherwise.

When Aerosil or Ac-Di-Sol were incorporated in the preparation, they were added to the melt after griseofulvin had dissolved completely in the carrier. The additives were incorporated under constant stirring until no clusters or agglomerates could be visually observed. When a combination of the additives was incorporated, Aerosil was added first.

Dissolution studies

Dissolution method. The USP XXI dissolution test (Prolabo, France) was used with a rotational paddle speed kept constant at 100 rpm and the water bath was equilibrated to room temperature ($21 \pm 1°$ C). 1000 ml of a dissolution medium of deionized water containing 0.9% sodium chloride and 0.01% polysorbate 80 was used in all experiments (Sjökvist and Nyström, 1988).

The sieve size fraction used was 300–500 μm, since it has been shown earlier that this fraction does not give problems with flotation or sedimentation (Sjökvist and Nyström, 1988).

In order to obtain near 'sink conditions' during the entire dissolution test, the amount of solid dispersion particles added to the medium was chosen to contain 0.6 mg griseofulvin. In the solid dispersions of 3, 10 and 20 w/w% griseofulvin this corresponds to additions of 20, 6.0 and 3.0 mg of solid dispersions, respectively.

Samples were transferred to a UV spectrophotometer flow cell where the absorbance was measured at 295 nm. The results presented are mean values of 3 determinations.

Calculation of dissolution rate constants. The initial dissolution rate, in μg/min, was calculated from the initial slope of the dissolution rate profile for the dissolution of about 30% of the amount of griseofulvin added. Here the amount of drug dissolved does not exceed 5% of the drug solubility and the dissolution approximately followed zero order kinetics.

Calculation of external surface area of solid dispersion particles. To relate the initial dissolution rate to the size of the solid dispersion particles, i.e., the surface of the carrier that initially is in contact with the dissolution medium, the external surface area (S) of the solid dispersion particles, in cm^2, was calculated according to:

$$S = \frac{\alpha_{sv} \cdot w}{d \cdot \rho_s}$$

where:

α_{sv} = surface to volume shape factor of 6 (Heywood, 1954)

w = amount of solid dispersion added (g)

d = arithmetic mean (cm) of the sieve size range of tested material

ρ_s = density of PEG 3000 (g/cm^3)

Characterization of carrier properties

Dissolution testing. The USP XXI disintegration test, basket rack assembly (Erweka, F.R.G.), was used as a simplified dissolution rate test, using a medium of 0.9% sodium chloride and 0.01% polysorbate 80 at $21 \pm 1°$ C. Here tablets of pure PEG 3000 and of solid dispersions with and without the incorporation of Aerosil and Ac-Di-Sol, alone or in combination, were made and tested for disintegration times. The unlubricated carrier or solid dispersion particles were weighed on an analytical balance and filled manually into the die, and compressed by hand in an instrumented single punch press (Korch EK 0, F.R.G.) to give flat-faced tablets (diameter 1.13 cm). The weighed amount of sample (Table 2) was chosen to keep the maximum upper punch pressure constant at 100 MPa. The results are mean values of 3 determinations.

X-ray diffraction. Phase analysis and determination of unit cell dimensions were made by X-ray powder diffraction using a Guinier-Hägg type focusing camera with CuK_α radiation and Si ($a = 5.431065$ Å) (Deslattes and Henins, 1973) as the internal standard. The cell dimensions were evaluated using a local program, CELL, (Ersson, 1988a) which includes a least-squares refinement of the cell dimensions. The positions of the lines on the X-ray film and their intensities were evaluated by means of a computer-controlled film scanner system constructed at the Institute of Chemistry, Uppsala University (Ersson, 1988b). All phases present could be identified by means of characteristic non-overlapping lines. For the lattice parameter determination of the PEG phase only lines free from overlap were used in the least-squares refinement.

Differential scanning calorimetry. Samples (3.5–4.5 mg) were examined using a DSC 20 differential scanning calorimeter (Mettler, Switzerland). A heating rate of 10 °C/min was used from 22–260 °C in an atmosphere of nitrogen with the samples kept in aluminium pans. The values of

heats of fusion were derived from integration in the temperature range 30–200 °C, if not stated otherwise. This is the melting range for the two-phase dispersions. Indium was used as standard (melting point 156.6 °C, heat of fusion: 28.45 J/g). The results presented are mean values of at least 4 determinations.

Characterization of drug particle size and shape in solid dispersion

Particle size. To study the particle size of griseofulvin and Aerosil in solid dispersions, alone or in combination, a Coulter Counter TA II fitted with a 30 μm aperture tube was used, as described earlier (Sjökvist and Nyström, 1988).

External surface area. The specific surface area of griseofulvin particles within the solid dispersion (3, 10 and 20 w/w%) was measured by light-blocking using an EEL photo sedimentometer, as described earlier (Sjökvist and Nyström, 1988).

Results and Discussion

Drug dissolution testing

Dissolution tests were made on solid dispersion particles of different concentrations of griseofulvin in PEG 3000 with or without additives and the results are presented in Figs. 1 and 2. The fastest dissolution rate for griseofulvin was obtained for the solid dispersion with the lowest concentration of drug (3 w/w%). An increase in concentration of Aerosil, Fig. 1, or an increase in drug content, Fig. 2, significantly reduced the dissolution rate. The particulate fineness of griseofulvin within the solid dispersion systems was high (approximately 2 $m^2 \cdot g^{-1}$) and of the same order for all systems (Table 1) as tested by the light-blocking technique. This indicates that the reduction in drug dissolution rate may be due to a reduced dissolution of the carrier and not to an increased drug particle size.

The results show that the release of griseofulvin from solid dispersions is considerably reduced when Aerosil is incorporated (Fig. 1). This decrease in dissolution rate becomes more pronounced as the concentration of Aerosil increases. During the dissolution test any solid dispersion particles remaining could be observed visually for

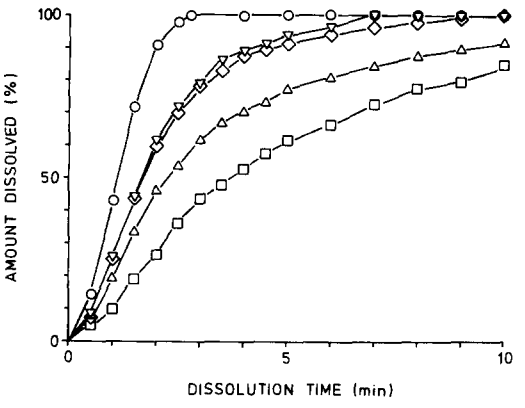

Fig. 1. Dissolution rate profiles for solid dispersions (sieve fraction 300–500 μm) of 3 w/w% griseofulvin in PEG 3000 with and without the incorporation of different concentrations of Aerosil: ○, 0 w/w%; ▽, 0.5 w/w%; ◇, 1 w/w%; △, 2 w/w%; □, 3 w/w%.

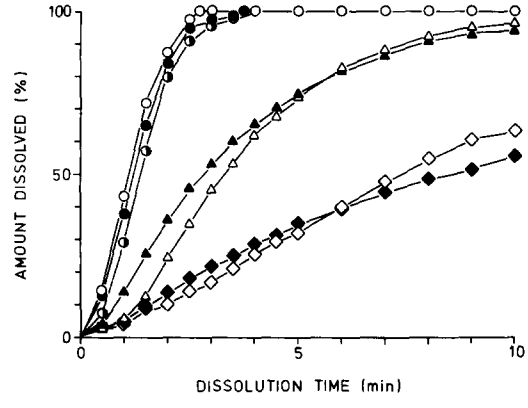

Fig. 2. Dissolution rate profiles for solid dispersions (sieve fraction 300–500 μm) of griseofulvin in PEG 3000. ○, ◑, ●, 3 w/w% griseofulvin; △, ▲, 10 w/w% griseofulvin; ◇, ◆, 20 w/w% griseofulvin. Open symbols: without Ac-Di-Sol; half-closed symbol: 1 w/w% Ac-Di-Sol; closed symbols: 10 w/w% Ac-Di-Sol.

TABLE 1

External specific surface area of griseofulvin particles in solid dispersions, as measured by a light-blocking technique

Content of griseofulvin (w/w%)	External specific surface area	
	S_v (cm^2/cm^3)	S_w (cm^2/g)
3	32400 ± 1700	22500 ± 1200
10	28400 ± 800	19700 ± 600
20	27000 ± 900	18700 ± 600

Values are mean ± S.D.

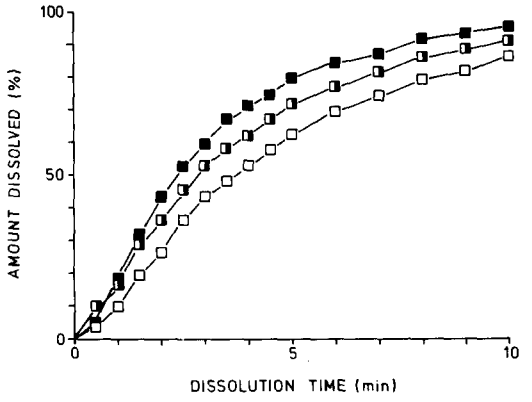

Fig. 3. Dissolution rate profiles for solid dispersions (sieve fraction 300–500 μm) of 3 w/w% griseofulvin and 3 w/w% Aerosil in PEG 3000. □, without Ac-Di-Sol; ◨, 1 w/w% Ac-Di-Sol; ■, 10 w/w% Ac-Di-Sol.

more than 10 min, especially for solid dispersions with the highest content of Aerosil. For the dispersion system without Aerosil there were no visible particles left after one min.

For the 3 w/w% griseofulvin solid dispersion the dissolution of the carrier was fast and the further addition of the disintegrant, Ac-Di-Sol, did not affect the dissolution of the drug (Fig. 2). Neither did the addition of disintegrant have any effect on the 20 w/w% solid dispersion and gave only a limited effect on the 10 w/w% solid dispersion. In these systems the rate-limiting process is probably the wetting of the dispersion particles. For the 3 w/w% dispersion with 3 w/w% Aerosil incorporated (Fig. 3), the dissolution was increased with the further incorporation of disintegrant. Dispersions containing Aerosil represent systems which are sensitive to incorporation of disintegrant and the corresponding increase in dissolution surface area.

Carrier dissolution testing

During the disintegration tests of compacts of solid dispersions, the compacts decreased in size by a slow erosion process. The results (Table 2) show that the disintegration time is prolonged with increase in drug content, which is in agreement with a previous study (Sjökvist and Nyström,

TABLE 2

Characterization of carrier (PEG 3000) dissolution from disintegration measurements of solid dispersion compacts containing griseofulvin, Aerosil and Ac-Di-Sol

Solid dispersions			Tablet weight (mg)	Tablet height (mm)	Disintegration time (min)
Conc. of griseofulvin (w/w%)	Conc. of Aerosil (w/w%)	Conc. of Ac-Di-Sol (w/w%)			
Pure recrystallized PEG 3000			496	4.21	12.6
3	–	–	493	4.21	14.7
10	–	–	507	4.30	18.8
20	–	–	511	4.26	23.5
–	0.5	–	491	4.17	13.1
–	1	–	495	4.18	13.6
–	2	–	498	4.19	14.1
–	3	–	499	4.19	14.5
3	0.5	–	495	4.19	15.1
3	1	–	496	4.17	16.7
3	2	–	497	4.18	16.7
3	3	–	500	4.18	17.6
3	–	1	493	4.16	14.7
3	–	10	507	4.18	15.2
10	–	10	521	4.35	19.1
20	–	10	523	4.25	23.3
3	3	1	502	4.15	16.6
3	3	10	513	4.16	17.4

Maximum upper punch pressure constant at 100 MPa.

1988). In that study it was concluded that dispersions with high drug content corresponding to a large number of fine hydrophobic drug particles with a large surface area of hydrophobic nature, probably possess poor wettability.

When Aerosil was incorporated in PEG 3000 the disintegration time was gradually prolonged with increase in Aerosil content. In dispersions of PEG 3000 containing both griseofulvin and Aerosil, the two components seem to provide an increased negative effect on the disintegration time.

Considering the results from the drug dissolution rate (Fig. 3), it was expected that the further addition of the disintegrant Ac-Di-Sol would decrease the disintegration time for compacts of dispersions with Aerosil, as the dissolution of these systems in particulate form was improved. However, no such effect was obtained that was independent of drug content and amount of Aerosil incorporated. This discrepancy from the results in Figs. 2 and 3 may be explained by the limited possibility for a disintegrant to act in a large, soft matrix of PEG, where the structure of the specimen is continuous and non-porous. The results indicate that dissolution rate studies on compacted dispersion materials probably are less sensitive to variations in formulation than the use of particulate solid dispersions (Sjökvist and Nyström, 1988).

Evaluation of factors controlling drug dissolution

Drug particle size. To investigate whether the reduced dissolution rate for dispersions containing Aerosil was due to particle growth of griseofulvin within the solid dispersion during the solidification, particle size characterizations were made with the Coulter Counter model TA II, as described earlier (Sjökvist and Nyström, 1988). The results are presented in Fig. 4. The particle size distribution of griseofulvin (3 w/w%) in the solid dispersion system, was in agreement with earlier reported results (Sjökvist and Nyström, 1988), where the geometric mean volume diameter by weight was 2 μm.

For the solid dispersion with 3 w/w% Aerosil in PEG 3000, no particles or very few particles were expected to be monitored, as the size of the Aerosil primary particles in dry state are within the colloidal range. However, the results show that the dispersions tested contained micron-sized particles, which were probably agglomerates of primary Aerosil particles.

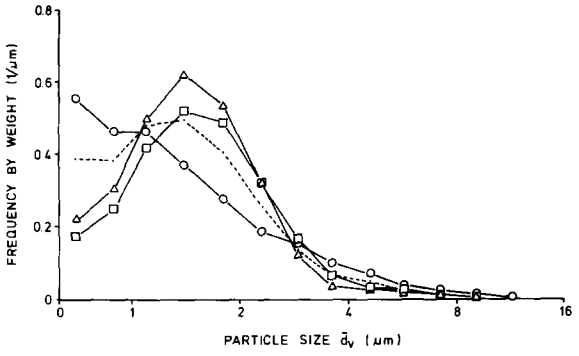

Fig. 4. Particle size distributions of griseofulvin and Aerosil, alone or in combination, in solid dispersions of PEG 3000 as measured by a Coulter Counter TA II. Concentrations of components in solid dispersion: ○, 3 w/w% griseofulvin; △, 3 w/w% Aerosil; □, 3 w/w% griseofulvin and 3 w/w% Aerosil; ------, predicted particle size distribution for solid dispersions with 3 w/w% griseofulvin and 3 w/w% Aerosil, calculated as the arithmetic mean of the distributions for griseofulvin (○) and Aerosil (△) respectively.

In Fig. 4 also the particle size distribution for the solid dispersion with both griseofulvin and Aerosil dispersed in PEG 3000 in equal amounts (3 w/w%) is shown. A calculated predicted distribution has been denoted, here defined as the arithmetic mean of the particle size distributions for griseofulvin and Aerosil, respectively. The results show that when the two components are combined in a solid dispersion, a somewhat larger particle size than expected is obtained, and that the number of smaller particles, e.g. < 1 μm, are less than in the calculated mean distribution. It cannot be excluded that the size of griseofulvin particles is somewhat increased, which could be due to Aerosil forming a small nucleus onto which the griseofulvin particles can start to grow. The difference in size distribution may have a limited effect upon the reduced dissolution rate after the addition of Aerosil (Fig. 1).

Surface area and dissolution of carrier

A more reasonable explanation to the dissolution results can be that the addition of Aerosil

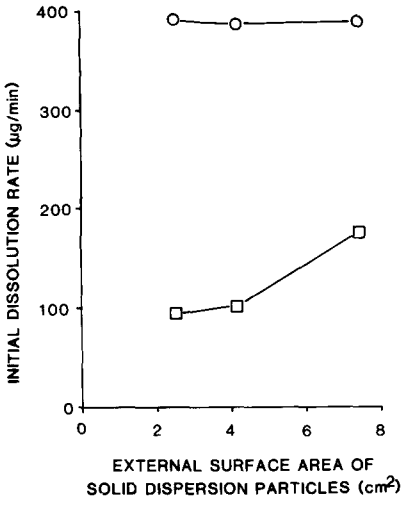

Fig. 5. Initial dissolution rate constant as a function of the calculated external surface area of solid dispersion particles of 3 w/w% griseofulvin in PEG 3000. The sieve size fractions used are 90–180, 180–300 and 300–500 μm: ○, without Aerosil; □, 3 w/w% Aerosil incorporated.

impairs the dissolution of the carrier, rather than promotes the growth of griseofulvin particles within the solid dispersion. This is supported by the findings presented above, that solid dispersion particles were observed during a longer period in the dissolution test when Aerosil was incorporated and that the further incorporation of the disintegrant improved the dissolution of the dispersion particles.

If the properties of the carrier are restricting for the dissolution of griseofulvin it should be possible to relate the drug dissolution rate to the particle size of the solid dispersion particles, i.e. the surface area of the dispersion particles that are initially in contact with the dissolution medium. Dissolution tests were made with 3 different sieve size fractions, 90–180, 180–300 and 300–500 μm, of solid dispersions of 3 w/w% griseofulvin in PEG 3000 with and without the addition of 3 w/w% Aerosil. The initial dissolution rate was calculated and presented in Fig. 5 as a function of the external surface area of the solid dispersion particles.

Without the addition of Aerosil the initial dissolution rate is relatively independent of the size of the solid dispersion particles. However, with Aerosil, the dissolution of griseofulvin from larger particles is delayed, which indicates that the dissolution of the carrier in this system is of importance for the release and dissolution of the drug.

Crystallinity and solubility of the carrier. The extent of crystallinity of PEG can influence the solubility of the polymer. An amorphous or metastable crystal form will dissolve at the fastest rate. To investigate qualitatively the degree of crystallinity, powdered unoriented samples were investigated by X-ray diffraction. The diffraction pattern should be sharply defined for highly crystalline materials and become increasingly diffuse with an increase in the amorphous content. The higher the diffraction angle 2 θ, the more the deviations from ordered structures will influence the diffraction pattern and make it more diffuse (Cullity, 1978).

In Table 3 the number of well-defined diffraction lines originating from the PEG structure is presented. The higher number of well-defined diffraction lines and the broader 2 θ range for PEG in the samples with Aerosil incorporated indicate a higher degree of crystallinity. This may correspond to a lower solubility of PEG. The result for the highest concentrations of griseofulvin (20 w/w%) indicates that the PEG crystallinity is

TABLE 3

X-ray powder diffraction analysis of PEG 3000 structure in solid dispersion systems

Sample	2θ	Number of diffraction lines originating from the PEG structure
PEG 3000	14–40°	16
PEG 3000 + 3 w/w% Aerosil	13–50°	26
PEG 3000 + 3 w/w% griseofulvin	13–40°	20
PEG 3000 + 3 w/w% Aerosil + 3 w/w% griseofulvin	13–53°	25
PEG 3000 + 10 w/w% griseofulvin	14–50°	19
PEG 3000 + 20 w/w% griseofulvin	14–36°	10

TABLE 4

Unit cell dimensions (Å) and volumes (Å^3) for PEG 3000 in solid dispersion systems with griseofulvin and Aerosil

Sample	Phases	Cell dimensions				
		a [1] (Å)	b [1] (Å)	c [1] (Å)	β [2] (°)	V [3] (Å^3)
PEG 3000 [4]	PEG	8.081 (8)	13.083 (14)	19.077 (35)	125.63 (12)	1 639 (5)
PEG 3000 + 3 w/w% griseofulvin	PEG + drug	8.081 (3)	13.091 (8)	19.086 (18)	125.61 (6)	1 641 (2)
PEG 3000 + 10 w/w% griseofulvin	PEG + drug	8.073 (10)	13.090 (13)	19.095 (30)	125.67 (16)	1 639 (5)
PEG 3000 + 20 w/w% griseofulvin	PEG + drug	8.065 (15)	13.076 (23)	19.030 (50)	125.48 (22)	1 634 (8)
PEG 3000 + 3 w/w% Aerosil	PEG	8.074 (6)	13.096 (11)	19.069 (19)	125.58 (7)	1 640 (3)
PEG 3000 + 3 w/w% griseofulvin + 3 w/w% Aerosil	PEG + drug	8.077 (3)	13.085 (7)	19.064 (15)	125.51 (5)	1 640 (2)
Griseofulvin	drug	8.969 (2)	– [5]	19.916 (10)	– [5]	1 601 (1)

[1] S.D.s in thousandth are given in brackets.
[2] S.D.s in hundredth are given in brackets.
[3] S.D.s in units are given in brackets.
[4] PEG 3000 has a unit cell which is monoclinic.
[5] Griseofulvin has a unit cell which is tetragonal.

reduced by the increased drug content. The results support the proposition that the lowered dissolution for dispersions with higher content of drug is not caused by a decreased solubility of the carrier, but rather by another mechanism, e.g. by a reduced wettability.

To investigate the occasional formation of a solid solution between drug and carrier, the lattice parameters for the monoclinic PEG phase in the different samples were determined. A systematic change in cell dimensions is an indication of solid solution formation. From the values of the PEG cell dimensions (Table 4) it is evident that there is no solid solution of the drug in the carrier phase, since all parameters are within the standard deviations.

The results from the DSC measurements (Table 5) are derived from integration in the 30–200 °C interval, which is the melting range for the two-phase dispersions. The results indicate a decrease in heat of fusion as the proportion of griseofulvin is increased. As the dispersions consist of the two phases PEG and griseofulvin, a predicted value of the heat of fusion for each solid dispersion tested has been calculated, assuming that the degree of PEG and drug crystallinity is unchanged. Using the value of 231 J/g for the pure PEG sample and 121 J/g for pure griseofulvin, an unchanged degree of crystallinity for the materials would have given heats of fusion of 228, 220 and 209 J/g for the dispersions containing 3, 10 and 20 w/w% griseofulvin, respectively. However, the heat of fusion values were somewhat reduced (Table 5), which might indicate a reduced degree of PEG crystallinity after the incorporation of the drug.

The heat of fusion values for PEG 3000 in solid dispersions with Aerosil incorporated showed that the experimental values were increased compared to the theoretical figures. These results support the increased crystallinity of PEG 3000 found by the X-ray powder diffraction technique.

TABLE 5

Heat of fusion of PEG 3000 and solid dispersion systems with griseofulvin and Aerosil

Sample		Heat of fusion		Deviation from theoretical value (%)
Content of griseofulvin (w/w%)	Content of Aerosil (w/w%)	Experimental (J/g) [a]	Theoretical (J/g)	
PEG 3000		231.2 ± 2.2	–	–
Griseofulvin [b]		121.5 ± 1.4	–	–
Solid dispersion				
3	0	223.6 ± 5.8	227.9	−1.9
10	0	209.1 ± 4.4	220.2	−5.0
20	0	193.1 ± 1.9	209.3	−7.7
0	0.5	237.7 ± 2.9	230.0	+3.3
0	1	241.6 ± 3.5	228.9	+5.5
0	2	238.0 ± 5.1	226.6	+5.0
0	3	243.6 ± 3.4	224.3	+8.6
3	0.5	229.3 ± 5.4	226.8	+1.1
3	1	226.9 ± 1.5	225.6	+0.6
3	2	229.7 ± 2.4	223.3	+2.9
3	3	229.1 ± 1.4	221.0	+3.7

The values of heat of fusion derive from integration in the temperature range 30–200 °C.

[a] Mean and standard deviation.

[b] The value of heat of fusion derives from integration in the temperature range 200–240 °C.

In the 3 w/w% drug dispersions with varying Aerosil content, the experimental heat of fusion values were unchanged for the two lowest Aerosil concentrations whereas an increase was obtained for the 2 higher Aerosil concentrations, compared to the theoretical values. In the 3 w/w% Aerosil sample the increase in heat of fusion was 3.7%, while separate drug and Aerosil dispersions changed the value with −1.9% and +8.6%, respectively. It appears that the increase in crystallinity of PEG, induced by the incorporation of Aerosil, to some extent is counteracted by the incorporation of griseofulvin. This is in agreement with the results from the X-ray diffraction method.

Conclusion

From the previous discussion it can be concluded that regarding release and dissolution properties of the drug the following main types of solid dispersions exist; none involves solid solutions.

For solid dispersions with low concentration of drug, in the absence of additives, the release of drug is fast. In these systems the dissolution of PEG is not affected by the incorporation of griseofulvin and the fine particulate form of the drug dissolves almost instantly.

If Aerosil is incorporated the crystallinity of PEG increases, which probably results in a decreased solubility. In such systems, where the particulate fineness of griseofulvin is high and the drug content is low, the impaired drug dissolution rate is due to a reduced dissolution of the carrier which gives a decrease in the release rate of drug particles.

Finally, for solid dispersions with a high concentration of drug, where the particle size is small, the reduced drug dissolution rate seems not to be due to a decreased solubility of the carrier. On the contrary, the characterisation of the carrier by X-ray diffraction and DSC indicates a decrease in crystallinity, which should give an increased solubility and dissolution rate of the carrier. In these systems the high content of hydrophobic drug probably produces dispersion particles of pronounced hydrophobic nature resulting in poor wettability, and this effect on dissolution of drug is not counteracted by the reduced crystallinity of the carrier in the system. The possibility to counteract a reduced dissolution rate of drug in solid dispersions by incorporating a disintegrant seems therefore to be valid only when the carrier solubility is relatively low.

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