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Physicochemical aspects of drug release. XI. Tableting properties of solid dispersions, using xylitol as carrier material

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Summary

A set of tests, including characterization of carrier fragmentation tendency, radial and axial tablet tensile strength, friability, disintegration time and dissolution rate, is presented for the evaluation of the suitability of substances to be used as carriers in solid dispersions prepared by the melting method. The carrier used as a model substance was the sugar alcohol xylitol. Solid dispersions of the sparingly soluble drug griseofulvin were prepared at three concentrations (2, 10 and 20% w/w) by the melting method. Tablets were made of pure untreated xylitol, of fused/recrystallized xylitol and of solid dispersions with external lubrication or with lubricant included in the composition. In some of the compositions the binding/disintegrating agents Avicel and Ac-Di-Sol were included. It was observed that xylitol fragments extensively. The tableting properties were somewhat improved if xylitol was fused/recrystallized. The incorporation of griseofulvin increased the tablet tensile strength. This indicates that conclusions regarding tableting properties cannot be made directly from studies of an untreated carrier. Thus, the set of tests can be a valuable tool in tablet formulation. The fastest drug dissolution was obtained with solid dispersions of the lowest concentration of drug in both particulate and tablet form. An increase in drug content and compression pressure and a decrease in rotational paddle speed decreased the dissolution rate. Internal lubrication with the admixing of 0.5% magnesium stearate prior to tablet compression had a limited retarding effect on the dissolution rate.

Introduction

For drugs with low aqueous solubility, a reduction of the particle size, i.e. an increase in the specific surface area, can enhance the dissolution rate and may thereby improve the bioavailability (Atkinson et al., 1962; Duncan et al., 1962). To avoid the formation of agglomerates, which would result in a decrease in the effective surface area taking part in the dissolution, the drug can be dispersed in an easily soluble carrier to form a solid dispersion.

Important requirements for carriers used in solid dispersions prepared by the melting method include, for example, that they are solid at room temperature and have a low melting point which is separated from the temperature of degradation. In tablet formulation, the carrier should be easily powdered and have good tableting properties.

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Especially, when a fast drug release is desired, the tablet formulation should exhibit rapid disintegration followed by a fast dissolution of the drug. It might also be advantageous if the materials fragment extensively, which could result in higher tablet strength. For such fragmenting excipients, internal lubrication can be used, without a substantial reduction in drug release and dissolution, since new carrier surfaces are created which are not covered by the hydrophobic lubricant.

Normally in studies on solid dispersions it is only the dissolution properties of the carrier systems that are evaluated, and not the tabletting properties. However, if solid dispersions are going to be used in tablet formulations it is of importance to investigate thoroughly the suitability of the carriers to be used.

Suitable tests for tableting properties of carriers to be used in solid dispersions ought to include characterization of fragmentation tendency during compaction (Alderborn et al., 1985b), tablet strength, friability and disintegration time and drug dissolution rate. When the melting method is used it is also of interest to investigate if the tableting properties are changed when the carrier has been melted and when a drug is incorporated.

Polyethylene glycols, which are frequently used as carriers in studies of solid dispersions, possess poor tableting properties especially regarding tablet disintegration (Sjökvist and Nyström, 1988; Sjökvist et al., 1989).

Xylitol, a sugar alcohol, has previously been used in solid dispersions prepared by the melting method (Sirenius et al., 1979; Bloch et al., 1982) and in direct compression of tablets (Laakso et al., 1982). Xylitol is easily soluble in water, has a melting range of 92–95°C and begins to decompose at 179–186°C (Sirenius et al., 1979). The tableting properties of xylitol have not been studied in detail. It has been shown that the tableting properties of mannitol, a compound similar to xylitol, were improved when it was fused and used in direct compression (Kanig, 1964).

The aims of this study were firstly, to present a set of possible tests for the characterization of the tableting properties of a carrier to be used in solid dispersions prepared by the melting method, using xylitol as a model carrier; and, secondly, to study the release of a drug from solid dispersions of xylitol both in particulate form and in tablets. The usefulness of xylitol as a carrier in solid dispersions was thereby investigated.

Experimental

Materials

Griseofulvin, microsized (Glaxo, U.K.) was used as a model substance of a fine particulate, sparingly soluble drug. The solubility in 0.1 M HCl with 0.01% polysorbate 80, the dissolution medium used in this study, was approximately 55 mg/l at 37 °C. The geometric mean volume diameter by weight of the raw material was 3.0 μm as characterized by a Coulter Counter TA II and the melting range was 219–221 °C (Sjökvist and Nyström, 1988; Sjökvist et al., 1989).

Xylitol (Finnish Sugar, Finland), a sugar alcohol, was used as an easily soluble carrier. The solubility is 64 g/100 ml water at 20 °C and the melting range is 92–95 °C (Handbook of Pharmaceutical Excipients, 1986). The decomposition temperature is 179–186 °C (Sirenius et al., 1979).

Avicel PH 101 (FMC Corp., U.S.A.) microcrystalline cellulose, was used as a tablet binder and also as an agent improving the disintegration properties (Bolhuis et al., 1979).

Ac-Di-Sol (FMC Corp., U.S.A.), an internally cross-linked form of sodium carboxy methyl cellulose, was used as a disintegrant.

Magnesium stearate (Apoteksbolaget, Sweden), in a 1% w/w suspension of ethanol, was used for external lubrication. The die wall and punch faces were pre-lubricated with the suspension before each compaction. In some of the compositions 0.5% w/w magnesium stearate was mixed with the rest of the composition for 2 min in a Turbula mixer (W.A. Bachofen A.G., Switzerland) before compression.

Hydrochloric acid 0.1 M, diluted from Titrisol HCl 1 mol/l (Merck, F.R.G.) with 0.01% polysorbate 80 (Tween 80, Kebo Lab, Sweden) was used as dissolution medium at 37 °C.

Methods

Preparation of solid dispersions

Solid dispersions were prepared by the melting method. The griseofulvin supplied has a primary particle size of approx. 3 μm, the particles being present in agglomerated form with sizes up to a few millimeters. To obtain a more or less ordered mixture (Hersey, 1975) before the melting procedure, i.e. to ascertain a homogeneous melt, xylitol and amounts of griseofulvin corresponding to 2, 10 and 20% w/w were mixed in the Turbula mixer for 24 h to deagglomerate the griseofulvin. This rather long mixing time has been shown to be necessary for deagglomeration on a small scale. However, the mixing time can be decreased considerably as the batch size is increased (Malmqvist and Nyström, 1984).

In the mixtures with 2 and 10% w/w griseofulvin no agglomerates could be visually observed. However, in the 20% w/w mixture there was still some agglomerates present after the mixing. The mixtures were melted at 160 °C over 30 min. The resulting dispersion of drug in melted xylitol was cooled to ambient temperature (21 °C), for which a period of 2–4 h was needed, and stored for at least 72 h to give a solid which could be pulverized. The resulting solid was pulverized using a laboratory apparatus of extruder type (Assistent, Electrolux, Sweden) to obtain coarse particles and then further pulverized in a mortar to obtain the fractions 180–300, 300–500 and 500–710 μm. Xylitol, without the addition of griseofulvin was also fused at 160 °C over 30 min and recrystallized and pulverized to obtain the fraction 300–500 μm.

Primary characterization of solid dispersions

Drug external surface area. The specific surface area of griseofulvin within the solid dispersion was measured by a light-blocking technique using a photo sedimentometer (EEL, U.K.) (Sjökvist and Nyström, 1988). The basic technique for estimating specific surface area from photo extinction data has been described earlier (Rose and Sullivan, 1959; Barnett et al., 1980). Griseofulvin alone or solid dispersions, containing 2.5 mg griseofulvin, were suspended in 100 ml of a griseofulvin-saturated aqueous medium containing 0.01% polysorbate 80. The resulting suspension of griseofulvin was dispersed in an ultrasonic bath for 5 min prior to measurement. The results presented are mean values of three determinations from three suspensions of each sample. The light transmission was 55–71% in all experiments.

Apparent particle density. The density was measured with an Air Comparison Pycnometer (Beckman 930, U.S.A.). The results presented are mean values of three determinations. Air was used as penetrating medium in all samples, except for pure griseofulvin where helium was used as medium.

X-ray diffraction. Phase analyses were made by X-ray powder diffraction using a STOE Position Sensitive Detector (PSD) system, with Ge monochromatized CuK_{α} radiation. A curved-wire detector ($r = 130$ mm) was used with an angular range of 45° in 2θ and was operated in a stationary mode. The phases present could be identified by means of characteristic non-overlapping lines.

Compression of tablets

Before tabletting all powdered samples were stored for at least two days at 21 °C in a desiccator at 45% relative humidity. A weighed amount of powder was manually filled into the die and tablets were compressed at a series of pressures (100–300 MPa) in an instrumented single-punch press (Korch EK 0, F.R.G.) to give flat-faced tablets (diameter 1.13 cm). Variation in pressure within ±3% was accepted. The fill weight was adjusted to give a compact thickness of 0.3 cm at maximum compaction load.

The die wall and punch faces were lubricated before each compaction with the 1% w/w magnesium stearate suspension if not stated otherwise. Before any characterization of the tablets, the tablets were stored for at least two days under the same conditions as described above.

Tablets of four categories were prepared. Categories 1, 2 and 3 were prepared with external lubrication.

Category 1. Tablets of untreated xylitol (300–500 μm) without (I) and with (II) the addition of binding/disintegrating agents and of fused/recrystallized xylitol (300–500 μm) without (III) and with (IV) the addition of binding/disintegrating agents were compressed at 100, 150, 200, 250 and 300 MPa. The addition of binding/disintegrating agents here means the admixing of 5% w/w Avicel and 2% w/w Ac-Di-Sol for 30 min in the Turbula mixer.

Category 2. Tablets of solid dispersions of 2, 10 and 20 w/w% griseofulvin (300–500 μm) without and with the addition of 5% w/w Avicel and 2% w/w Ac-Di-Sol were compressed at 100, 150, 200, 250 and 300 MPa. Tablets of category 1 and 2 were used for the characterization of tablet properties and not for dissolution rate studies.

Category 3. To test drug dissolution from tablets, mixtures of fused/recrystallized xylitol (300–500 μm), solid dispersion (300–500 μm), 5% w/w Avicel and 2% w/w Ac-Di-Sol were compressed at 100, 200 and 300 MPa. The tablet weight was kept constant at 500 mg and the amount of solid dispersion particles was chosen to give a drug content of 0.6 mg/tablet. The low drug content was chosen to give dissolution tests at 'sink conditions' and to be able to compare the dissolution rate data with earlier results obtained at our laboratory.

Category 4. To study the effect of admixing magnesium stearate, tablets of category 3 containing the solid dispersion of 10% w/w griseofulvin were chosen. Magnesium stearate (0.5% w/w) was mixed for 2 min in the Turbula mixer with the rest of the composition, prior to the compression of tablets. The compaction pressure used here was 100 and 200 MPa.

Characterization of tableting properties

Fragmentation tendency. The fragmentation tendency during compaction of particles (300–500 μm) of untreated xylitol, of fused/recrystallized xylitol and of solid dispersions of 2, 10 and 20% w/w griseofulvin, was characterized by permeametry measurements of tablets using a Blaine apparatus (Alderborn and Nyström, 1985; Alderborn et al., 1985a,b). Approximately 20 tablets of each sample were compacted at a series of pressures up to 100 MPa.

The initial linear slope for the compaction up to 70 MPa was calculated and was used as a means to characterize the fragmentation tendency. The higher the slope value, the more fragmentable the material is (Alderborn and Nyström, 1985; Alderborn et al., 1985b).

Tablet strength. The mechanical strength of tablets was measured as axial (Nyström et al., 1977, 1978) and radial tensile strength (Fell and Newton, 1970). The latter was calculated from results obtained by a diametral compression test apparatus (Erweka TBH 28, F.R.G.). For tablets of category 1 and 2 the results presented are the mean values of 15 and 9 determinations, respectively.

Friability. Tablet friability was tested in a Roche friabilator (Erweka, F.R.G.) for 12 tablets over 4 min at 25 rpm. The tested tablets were compressed at 100, 200 and 300 MPa. For tablets of category 1 the presented results are mean values of three determinations, and for tablets of category 2 single determinations were made.

Disintegration time. The test was performed according to the USP XXI disintegration test, basket rack assembly (Erweka, F.R.G.) in a medium of 0.1 M HCl with 0.01% polysorbate 80 at 37 °C. The results presented are mean values for six tablets.

Drug dissolution

The dissolution rate was tested according to USP XXI, with rotational paddle speeds of 25, 50 and 100 rpm, in a medium of 0.1 M HCl with 0.01% polysorbate 80 at 37 °C. The dissolution tests were performed at 'sink conditions' where amounts of solid dispersion, corresponding to 0.6 mg griseofulvin, in particulate form and in tablets were added to 1000 ml of the medium. Samples were transferred to a UV spectrophotometer flow cell (Ultrospec II, LKB, Sweden) where the absorbance was measured at 295 nm. The results presented are mean values of at least six determinations.

The initial dissolution rate, in μg/min, was calculated from the initial linear slope of the dissolution rate profile (Sjökvist et al., 1989).

Results and Discussion

Primary characteristics of solid dispersions

Drug external surface area. The external surface area of the griseofulvin particles within the solid dispersion was of the same order for all the dispersions and similar to the raw material (Table 1). Compared to earlier studies (Sjökvist and Nyström, 1988; Sjökvist et al., 1989) where polyethylene glycol, PEG 3000, was used as carrier, the particle size of drug within the solid dispersion is somewhat higher when xylitol is used as carrier. This is because the griseofulvin has not dissolved in xylitol before solidification, which it has in dispersions of PEG 3000. The solidification process was also much longer for xylitol, which may have resulted in a limited growth of the griseofulvin particles.

Apparent particle density. The density of xylitol was unchanged after it had been fused/recrystallized (Table 1). As the concentration of griseofulvin in the solid dispersions increased, the density was decreased. A theoretical value of the density for each solid dispersion tested was calculated. Using 1.51 g/cm^3 for the fused/recrystallized xylitol and 1.45 g/cm^3 for griseofulvin, the theoretical values for the density of physical mixtures of the two components would give values as presented in Table 1. However, it was observed that the actual density values were less than the theoretical values. This probably reflects the presence of closed/entrapped pores which are not picked up using gas pycnometry. These pores could perhaps be caused by incomplete wetting of the hydrophobic particles in the xylitol melt.

X-ray diffraction. The results from the X-ray powder diffraction analyses (Fig. 1) showed that both griseofulvin and xylitol were present as pure crystalline phases, in all solid dispersions. The quantitative relation between phases, expressed as the intensity of the diffraction line with strongest intensity for each phase, indicates that the whole amount of griseofulvin exists as a pure crystalline phase dispersed in xylitol.

In the diffraction pattern for the raw material of xylitol, the peaks present at the 2θ values of approx. 12° and 19°, respectively, probably originate from the presence of small quantities of sorbitol (Handbook of Pharmaceutical Excipients, 1986).

Tableting properties

Fragmentation tendency. The fragmentation tendency during compaction is presented in Table 2. All samples showed a considerable increase in surface area with pressure. Between 10 and 70 MPa the increase in surface area was 4- to 5-fold. According to e.g. Alderborn et al. (1985b) such an increase indicates that a material is extensively fragmentable. The relatively high correlation coef-

TABLE 1

Characteristics of raw materials and solid dispersions

Sample	Density (g/cm^3)		External specific surface area of drug particles within the solid dispersions [b]	
	Experimental [a]	Theoretical	S_v (cm^2/cm^3)	S_w (cm^2/g)
Untreated xylitol	1.51 ($\pm 2.3 \times 10^{-3}$)	–	–	–
Fused/recrystallized xylitol	1.51 ($\pm 7.1 \times 10^{-3}$)	–	–	–
2% w/w griseofulvin/xylitol	1.50 ($\pm 1.5 \times 10^{-3}$)	1.51	18 200 ± 1 100	12 700 ± 700
10% w/w griseofulvin/xylitol	1.48 ($\pm 3.8 \times 10^{-3}$)	1.51	16 300 ± 700	11 300 ± 500
20% w/w griseofulvin/xylitol	1.46 ($\pm 1.1 \times 10^{-2}$)	1.50	18 400 ± 500	13 000 ± 300
Griseofulvin	1.45 ($\pm 1.3 \times 10^{-2}$)	–	22 000 ± 1 200	15 300 ± 800

[a] The 95% confidence intervals for the means are given in parentheses.
[b] Mean and standard deviation.

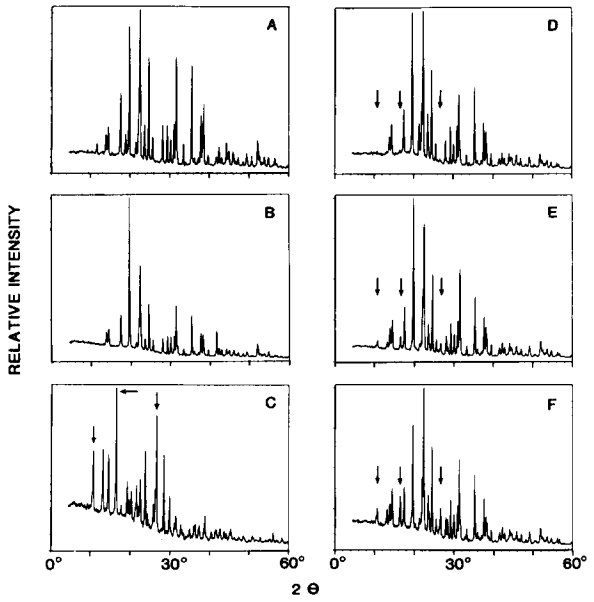

Fig. 1. X-ray powder diffraction spectra for pure materials and solid dispersions: A, untreated xylitol; B, fused/recrystallized xylitol; C, griseofulvin; D, 2% w/w griseofulvin dispersion; E, 10% w/w griseofulvin dispersion; F, 20% w/w griseofulvin dispersion. The three arrows in the spectra for the dispersion systems mark the positions for characteristic griseofulvin lines.

ficients indicate that the use of slope values was an acceptable means for quantification of the fragmentation tendency.

TABLE 2

Fragmentation tendency of xylitol and solid dispersions as characterized by tablet permeametry

Sample (−)	Fragmentation tendency [a] (m^2/g per MPa)	Correlation coefficient [b]
Untreated xylitol	4.25×10^{-3}	0.998
Fused/recrystallized xylitol	6.70×10^{-3}	0.987
2% w/w griseofulvin /xylitol	5.60×10^{-3}	0.955
10% w/w griseofulvin /xylitol	5.57×10^{-3}	0.993
20% w/w griseofulvin /xylitol	6.64×10^{-3}	0.997

[a] Values obtained from linear regression of the slope of specific surface area of tablets vs maximum upper punch pressure during compression.

[b] The correlation coefficient of linear regression.

The fragmentation tendency was somewhat more pronounced for fused/recrystallized xylitol and for solid dispersions of griseofulvin compared to untreated xylitol. In solid dispersions this may be because the particles contain a limited amount of closed pores, as indicated by the relatively low density values (Table 1). Such pores could then function as starting points for crack propagation and growth. Another explanation is that smaller cracks may have been introduced during the pulverization process.

SEM photomicrographs were made of xylitol particles. The untreated xylitol was sieved to obtain the sieve fraction 300–500 μm and the fused/recrystallized xylitol was milled and sieved to obtain the same fraction. The SEM photomicrographs (Fig. 2) show that the particles of fused/recrystallized xylitol were more irregular in geometrical form but had a smoother surface texture compared to untreated xylitol. The recrystallization of xylitol, as performed in this study, seems to result in a change regarding particle appearance and it cannot be excluded that the solid structure could have been slightly altered.

Tablet strength. The effects of compaction pressure on the radial and axial tensile strength for tablets of category 1 (untreated xylitol and fused/recrystallized xylitol) are presented in Fig. 3. Tablets made of untreated xylitol without disintegrating agents showed cracks in some tablets at higher pressure (250 MPa) and it was not possible to make tablets at the highest pressure, 300 MPa, due to extensive capping. When xylitol was fused/recrystallized and when disintegrating agents were included in the composition it was possible to make tablets without any visible cracks even at the highest pressure.

For practically all samples an increase in pressure resulted in an increase in radial tensile strength. A similar increase was also observed for the axial tensile strength for tablets made of fused/recrystallized xylitol with and without disintegrating/binding agents. However, for untreated xylitol the axial tensile strength increased initially, but at higher pressures the strength values decreased again, reflecting the capping tendency described above (Nyström et al., 1978; Alderborn and Nyström, 1984).

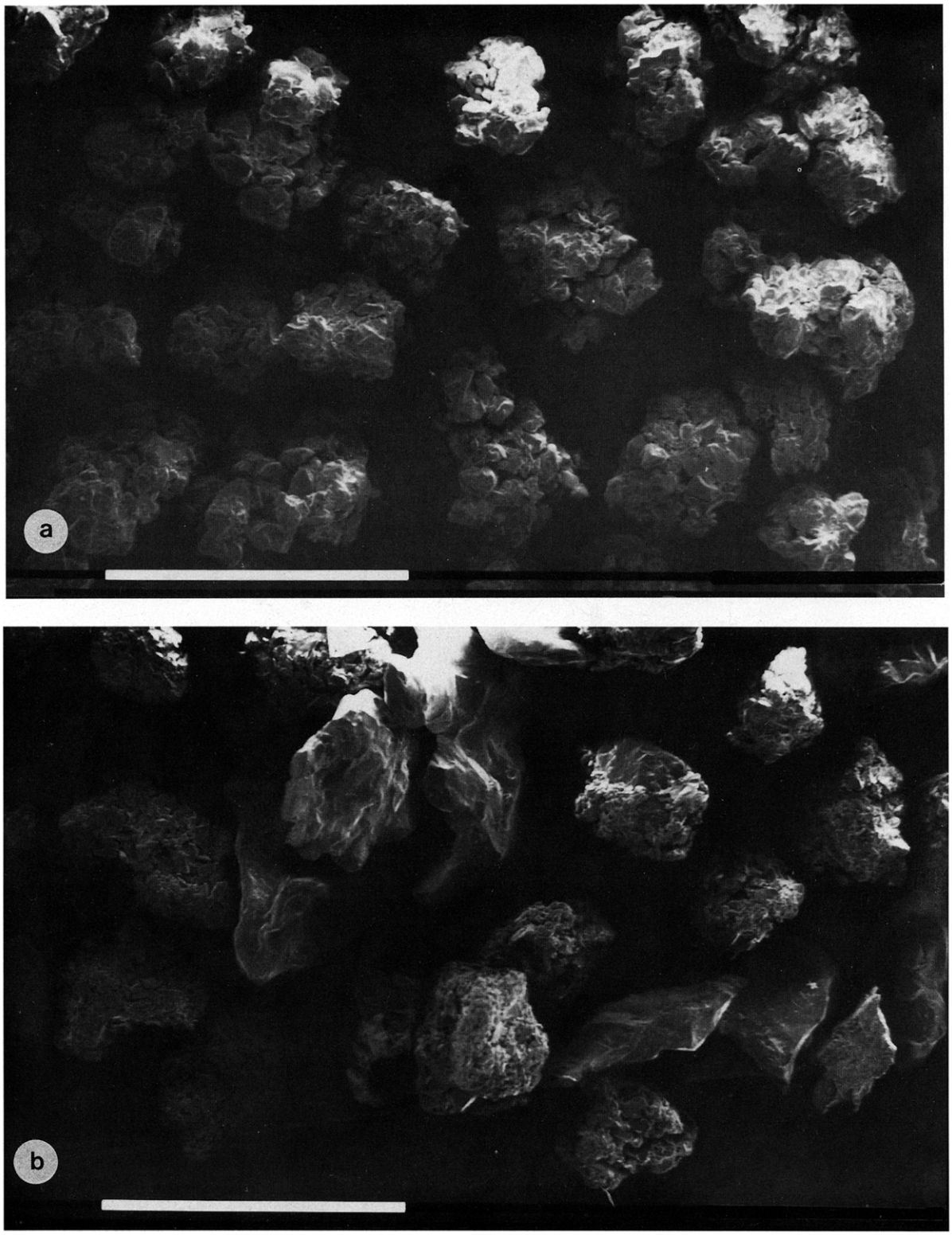

Fig. 2. Scanning electron photomicrographs of xylitol, sieve fraction 300–500 μm. A, untreated xylitol; B, fused/recrystallized xylitol. The white bars denote 1 mm.

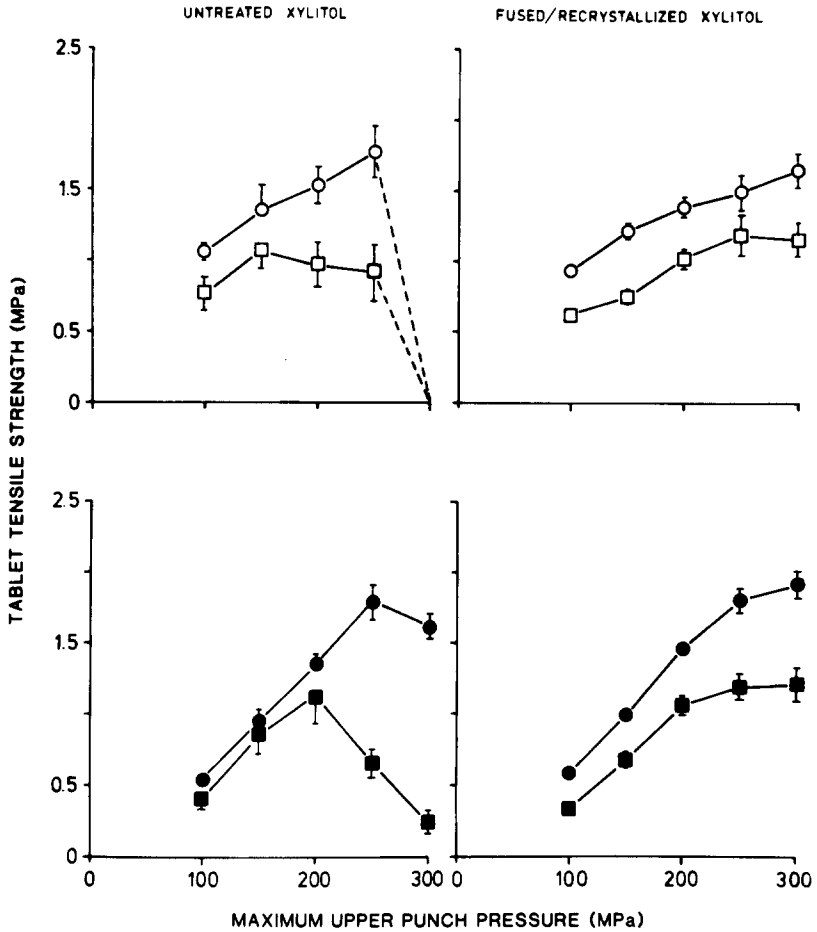

Fig. 3. Tensile strength of tablets (category 1) made of untreated xylitol and of fused/recrystallized xylitol: (○, ●) radial tensile strength; (□, ■) axial tensile strength. Open symbols: no disintegrating/binding agents; Closed symbols: composition containing 5% w/w Avicel and 2% w/w Ac-Di-Sol. Error bars represent the 95% confidence intervals for the means.

For tablets of category 2 (solid dispersions), an increase in pressure generally resulted in an increase in radial as well as axial tensile strength (Fig. 4), and it was observed that the radial tensile strength was of the same order for tablets of categories 1 and 2. However, the axial tensile strength was generally higher for tablets of category 2. It was observed that the surface texture of tablets of category 2 was smoother while tablets of category 1, especially when prepared at lower pressure, were softer and the edges were often ruptured. The addition of binding/disintegrating agents to the composition did not improve tablet tensile strength to any larger extent, either for tablets of category 1 or for tablets of category 2.

The low axial tensile strength of tablets made at the higher compaction loads of untreated xylitol resulted in a pronounced capping tendency. This was substantially counteracted by the fusion/recrystallization procedure. Untreated xylitol particles may possess a relatively high elastic component (Duberg and Nyström, 1986). This is probably to a large extent reduced by the recrystallization procedure and especially by the incorporation of drug particles. Such treatments probably result in solid structures with a higher concentration of

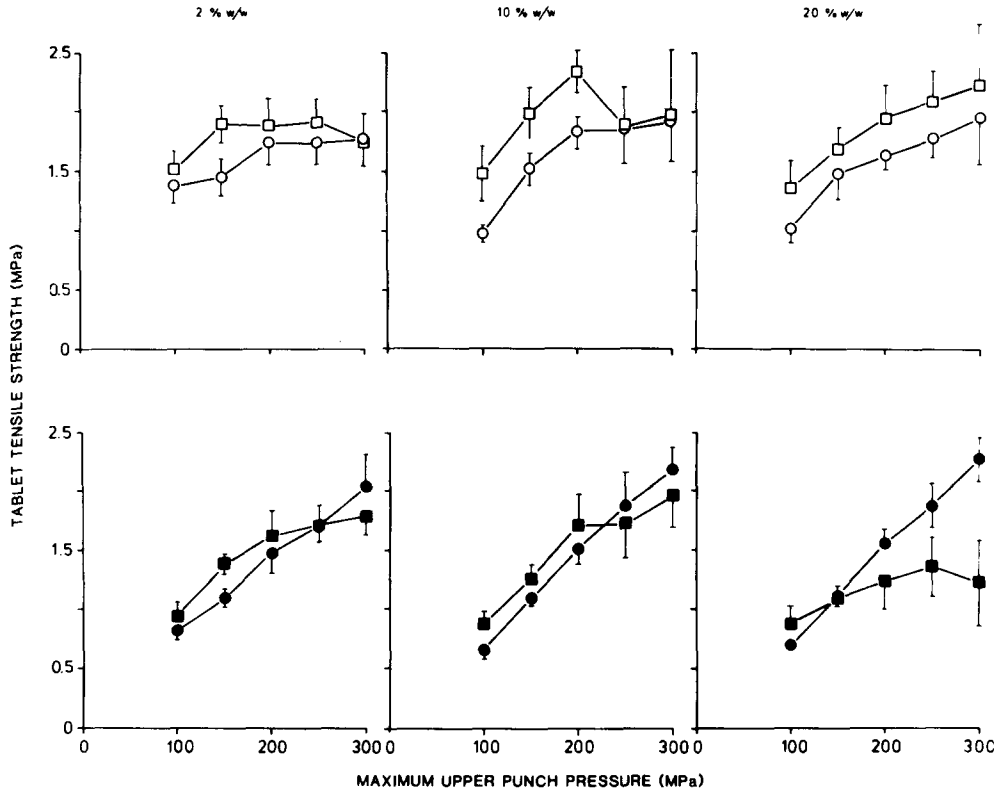

Fig. 4. Tensile strength of tablets (category 2) made of solid dispersions of 2, 10 and 20% w/w griseofulvin in xylitol. Symbols as in Fig. 3.

defects and crystal lattice imperfections, which enhances both the brittleness and the possibilities for plastic flow of the material. Another explanation can be that the change towards a more irregular particle shape and surface texture can result in an improved compactability (Alderborn and Nyström, 1982). It has also been claimed that the grinding process itself causes an activation of the surface and thereby results in a stronger bonding within the tablets (Hüttenrauch, 1983).

Friability and disintegration time. The friability results are presented in Tables 3–5. For tablets of untreated xylitol (Table 3) the friability was approx. 2% for the two pressures studied. With the addition of disintegrating agents the friability for tablets made at 100 MPa was increased due to the above mentioned tendency for the tablet edges to rupture. At the highest pressure, 300 MPa, the friability was increased to approx. 4.7%, reflecting the capping tendency observed from the tests of axial tensile strength.

For tablets of fused/recrystallized xylitol, with and without disintegrating agents, the friability was decreased with an increase in pressure. However, only tablets of fused and recrystallized xylitol with disintegrating agents made at the highest pressure gave values $< 1\%$.

For tablets of category 2 (Tables 4 and 5) it was observed that the friability was generally higher for tablets made at 100 MPa and that the friability decreased for tablets made at 200 and 300 MPa. There was also a general tendency for the friability to decrease with an increase in drug content in the solid dispersions.

An observed decrease in the friability gave tablets with somewhat longer disintegration times (Tables 3–5). A probable explanation is that with an increase in compaction pressure the compacts

TABLE 3

Friability and disintegration times for tablets of category 1

Type of tablet	Maximum upper punch press (MPa)	Weight (mg)	Height (mm)	Friability (%)	Disintegration time [a] (s)
I	100	416	3.32	2.13	14 ± 5
	200	477	3.54	1.91	135 ± 7
II	100	414	3.42	3.26	< 7
	200	482	3.55	1.73	10 ± 3
	300	520	3.79	4.69	94 ± 16
III	100	437	3.49	2.13	61 ± 13
	200	488	3.54	1.54	139 ± 8
	300	529	3.71	1.47	169 ± 2
IV	100	429	3.45	2.17	< 7
	200	495	3.56	1.08	99 ± 18
	300	533	3.75	0.88	198 ± 3

I, untreated xylitol; II, untreated xylitol with 5% Avicel and 2% Ac-Di-Sol; III, fused/recrystallized xylitol; IV, fused/recrystallized xylitol with 5% Avicel and 2% Ac-Di-Sol.

[a] Mean and standard deviation.

become more dense. This reduction in porosity may then correspond to an increased penetration time for the water. When Avicel and Ac-Di-Sol were incorporated the disintegration times were decreased. However, at the highest pressure the disintegration times were still fairly long, indicating that the effect of the disintegrant Ac-Di-Sol was delayed, due to the longer time taken for water to penetrate.

Drug dissolution

Drug dissolution from solid dispersion particles. Dissolution rate profiles for the solid dispersions in particulate form (300–500 μm) at a rotational

TABLE 4

Friability and disintegration times for tablets of category 2 without binding/disintegrating agents, prepared with external lubrication

Content of griseofulvin in solid dispersion (% w/w)	Maximum upper punch press (MPa)	Weight (mg)	Height (mm)	Friability (%)	Disintegration time [a] (s)
2	100	425	3.37	3.00	47 ± 1
	200	488	3.52	2.00	165 ± 1
	300	532	3.75	2.24	184 ± 9
10	100	424	3.40	1.86	113 ± 23
	200	488	3.57	1.98	207 ± 13
	300	519	3.69	1.70	234 ± 13
20	100	418	3.31	2.35	78 ± 5
	200	479	3.52	1.51	264 ± 5
	300	517	3.70	1.60	324 ± 10

[a] Mean and standard deviation.

TABLE 5

Friability and disintegration times for tablets of category 2 with 5% Avicel and 2% Ac-Di-Sol, prepared with external lubrication

Content of griseofulvin in solid dispersion (% w/w)	Maximum upper punch press (MPa)	Weight (mg)	Height (mm)	Friability (%)	Disintegration time [a] (s)
2	100	431	3.35	2.88	< 7
	200	484	3.52	1.41	50 ± 18
	300	522	3.70	1.34	180 ± 4
10	100	421	3.36	2.95	< 7
	200	483	3.55	1.30	82 ± 14
	300	521	3.71	1.17	214 ± 7
20	100	417	3.35	2.48	14 ± 5
	200	476	3.54	1.21	163 ± 5
	300	516	3.71	1.02	260 ± 13

[a] Mean and standard deviation.

paddle speed of 100 rpm are presented in Fig. 5. A reference profile was obtained by adding a well-dispersed and size-characterized suspension of griseofulvin (particulate fineness approx. 1.5 m^2/g) to the dissolution medium.

As mentioned above, the particulate fineness of griseofulvin within the solid dispersion systems was of the same order for all drug concentrations.

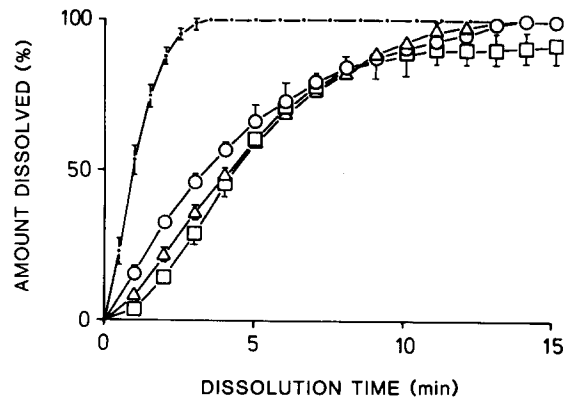

Fig. 5. Dissolution rate profiles for solid dispersion particles, sieve fraction 300–500 μm, of griseofulvin in xylitol. (○) 2% w/w griseofulvin; (△) 10% w/w griseofulvin; (□) 20% w/w griseofulvin; (----) suspension of griseofulvin. Error bars represent the 95% confidence intervals for the means.

In earlier studies (Sjökvist and Nyström, 1988; Sjökvist et al., 1989) the particulate fineness of griseofulvin in solid dispersions, with polyethylene glycol 3000 as carrier, was higher which resulted in faster drug dissolution. With xylitol as carrier, a more coarse particulate form of griseofulvin was obtained mainly because griseofulvin was not dissolved in the carrier prior to solidification. In addition to this it cannot be excluded that the long solidification process for xylitol (at least 72 h) resulted in an increase in griseofulvin particle size. This suggestion is supported by the fact that the particulate fineness of the raw drug material was higher than in the solid dispersion systems (Table 1).

The dissolution rate decreases somewhat with an increase in drug content. However, the rates are quite similar, which is in agreement with the results of an earlier study (Sjökvist and Nyström, 1988) where the dissolution from solid dispersions containing relatively coarse drug particles was directly related to the drug particle size. As the drug particle size is of the same order for all systems in this study, the dissolution rates are subsequently similar. However, during the initial phase, there is a tendency for dispersions with increased drug content to give a decreased dissolution rate. This

could probably be explained by a limited reduction in wettability of the dispersion particles when the content of hydrophobic drug is increased.

For the dispersion of 20% w/w drug the total amount of drug was not dissolved within 15 min as it was for the lower concentrations. This is probably because a fraction of the griseofulvin particles was in agglomerated form, as mentioned above. To obtain the value when 100% was dissolved, measurements were carried out at increasing paddle speeds until a final plateau value was reached.

To study factors possibly influencing the dissolution, dissolution rate tests were also performed on dispersion particles of 180–300 and 500–710 μm and at rotational paddle speeds of 50 and 25 rpm. The initial dissolution rates in μg/min were calculated from the dissolution rate profiles.

The dissolution for solid dispersions of the three drug concentrations was studied for the three sieve fractions at a rotational paddle speed kept constant at 100 rpm, (Fig. 6). The particle size is given as the mean of the size class limits of each sieve fraction. The effect of dispersion particle size is limited, indicating that the dissolution of the carrier is not a pronounced rate limiting step (Sjökvist et al., 1989).

The effect of rotational paddle speed on the dissolution, using the solid dispersion fraction

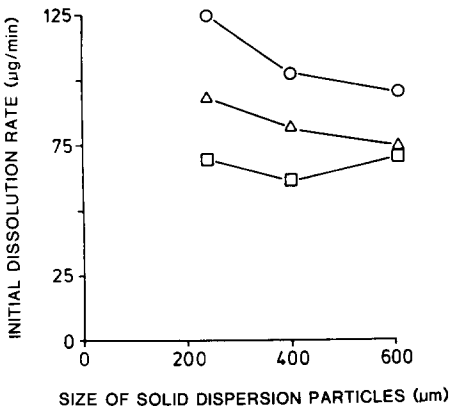

Fig. 6. Initial dissolution rate constant as a function of the particle size of the solid dispersions, at a rotational paddle speed kept constant at 100 rpm. Concentration of griseofulvin in solid dispersion: (○) 2% w/w griseofulvin; (△) 10% w/w griseofulvin; (□) 20% w/w griseofulvin.

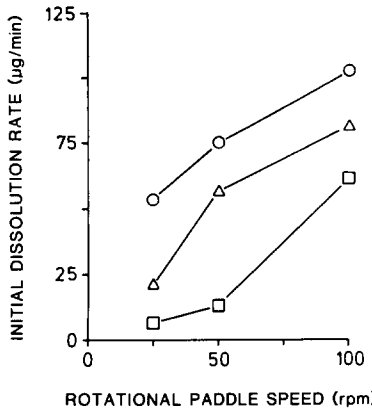

Fig. 7. Initial dissolution rate constant as a function of the rotational paddle speed for particles of the sieve fraction 300–500 μm. Symbols as in Fig. 6.

300–500 μm, is presented in Fig. 7. It was observed that the rotational paddle speed was important for the release and dissolution of the drug from the solid dispersions, as the dissolution for all drug concentrations was increased with an increase in paddle speed. The dissolution of griseofulvin from the well dispersed suspension is independent of agitation intensity, as 90% of the added amount is dissolved within 2.5 min for the three agitation intensities tested. These results support the interpretation that the dissolution of the carrier is not instantaneous. For the dispersion with 2% w/w drug, the effect of agitation intensity is more pronounced than would be expected if there was an instant release of drug particles.

Drug dissolution from tablets of solid dispersions. The dissolution of tablets of category 3 (fused xylitol, solid dispersion, 5% Avicel and 2% Ac-Di-Sol), each tablet containing 0.6 mg griseofulvin, was studied (Fig. 8). For tablets prepared at lower pressures the disintegration was instantaneous and subsequently the dissolution was fast. The dissolution rate decreased somewhat with an increase in drug content and the dissolution was further decreased with an increase in compaction pressure. This is in agreement with the results from the disintegration time studies (Tables 3–5). As the compaction pressure is increased, the tablets become more dense and subsequently the initial water penetration rate into the tablets is probably

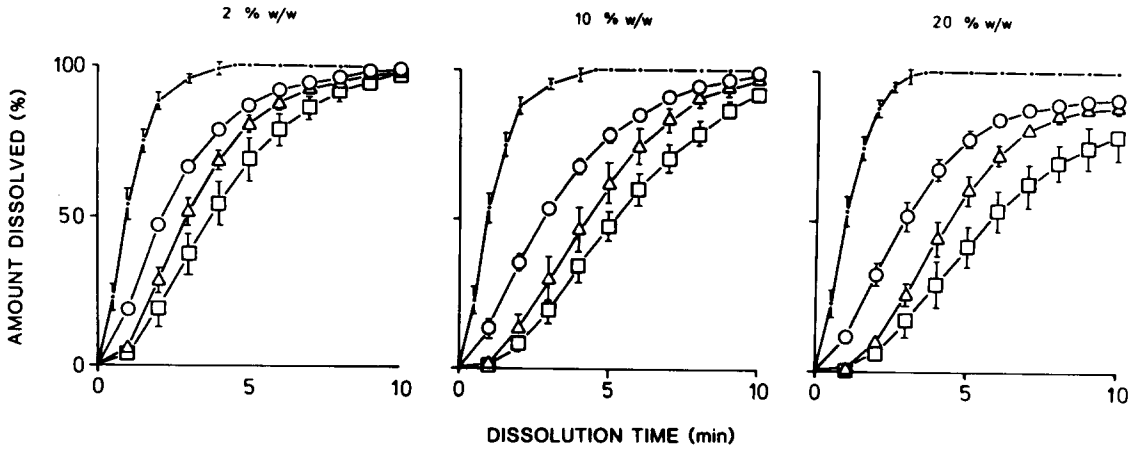

Fig. 8. Dissolution rate profiles for tablets (category 3), containing solid dispersions of 2, 10 and 20% w/w griseofulvin, respectively, at a rotational paddle speed kept constant at 100 rpm. Maximum upper punch pressure at which the tablets were prepared: (○) 100 MPa; (△) 200 MPa; (□) 300 MPa. (----) dissolution rate profile for suspension. Error bars represent the 95% confidence intervals for the means.

reduced resulting in a lag time before drug dissolution could be monitored.

It is not practical to use external lubrication if a larger batch size and a rotary press is going to be used. The use of internal lubrication is thus favourable. The admixing of a hydrophobic lubricant can, however, decrease the disintegration (Bolhuis et al., 1981) and drug dissolution (Levy and Gumtow, 1963; Lerk et al., 1982) especially for tablets made of carriers that show a low fragmentation tendency.

To study the influence of lubrication on the dissolution, dissolution rate studies were also made on tablets of dispersions of 10% w/w griseofulvin with internal lubrication (category 4). These tablets were prepared at 100 and 200 MPa and dissolu-

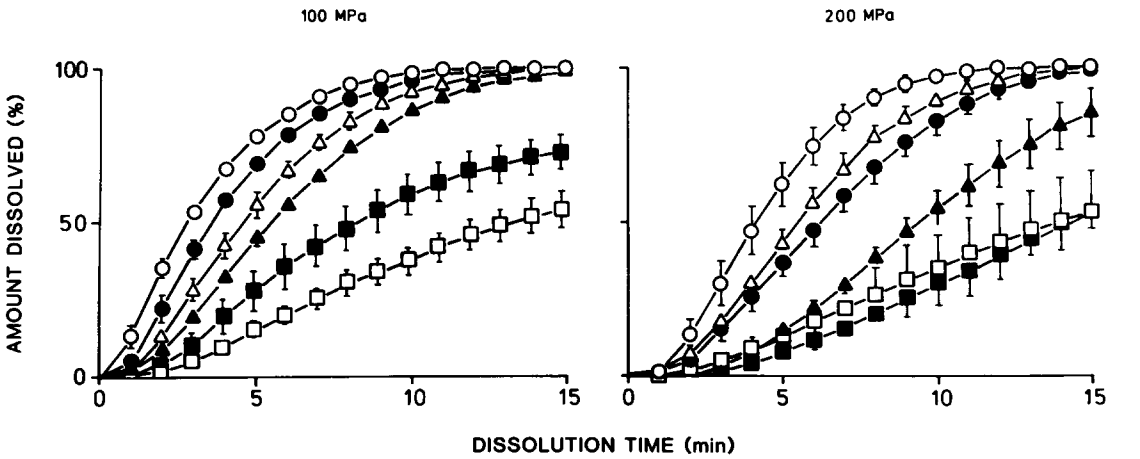

Fig. 9. Dissolution rate profiles for tablets of category 3 (containing 10% w/w griseofulvin) and category 4. Maximum upper punch pressures at which the tablets were prepared were 100 and 200 MPa. Rotational paddle speeds: (○, ●) 100 rpm; (△, ▲) 50 rpm; (□, ■) 25 rpm. Open symbols: external lubrication; Closed symbols: internal lubrication. Error bars represent the 95% confidence intervals for the means.

tion rate studies were made with rotational paddle speeds of 25, 50 and 100 rpm (Fig. 9).

For tablets made at 100 MPa it can be observed that the effect of internal lubrication is not pronounced. At the lowest rotational paddle speed, the tablets with internal lubrication even show a somewhat faster dissolution. However, at the higher pressure, the dissolution of tablets with internal lubrication is significantly retarded, except at the lowest rotational paddle speed.

Conclusions

By using treated xylitol (fused/recrystallized xylitol and solid dispersions) the tableting properties of this substance could be somewhat improved. Tablets could be made at higher pressures without capping and the friability was decreased. On the other hand, with an increase in tablet strength the disintegration time was slightly prolonged.

The results showed that the dissolution of griseofulvin from solid dispersions was fairly rapid. At the lowest pressure, 100 MPa, the tableting did not reduce the fast drug dissolution due to a fast disintegration of the tablets. With an increase in compaction pressure, a short lag time in the dissolution process was observed, due to the prolonged disintegration time.

The results indicate that xylitol can be used as a carrier in tablets of solid dispersions, when a fast drug release is desired. Some improvements might be achieved if the particulate fineness of drug within the solid dispersion can be increased and if the solidification time of xylitol can be decreased.

A set of tests for tableting properties, as described in this study, for materials to be used as carriers in solid dispersions, is valuable. If the solid dispersion is intended for use in tablet form, tests for tableting properties should be made in parallel with drug release and dissolution studies. The results in this study also demonstrate the need to characterize the properties of fused/recrystallized carriers, as demonstrated by the effect on axial tablet strength and the related capping tendency.

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