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Research Papers

Physicochemical aspects of drug release XVII. The effect of drug surface area coverage to carrier materials on drug dissolution from ordered mixtures

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Summary

Two micronized drugs (oxazepam and griseofulvin) and two carrier materials (mannitol and sodium chloride) were used to prepare ordered mixtures with different degrees of surface area coverage. The in vitro dissolution rate of the drugs and the carrier materials were determined. Suspensions of the drugs were used as references. The dissolution of a drug in an ordered mixture with a low degree of surface area coverage was very fast, even faster than from a well-dispersed suspension. It was proposed that differences in diffusional distance, which in turn is related to hydrodynamics, could be used to explain the obtained results. If the degree of surface area coverage was increased the dissolution rate of the drug was decreased. This decrease in dissolution rate could be because the dissolution of the carrier material was prevented by the high amount of hydrophobic drug present on the carrier unit. In this study it was, however, shown that the carrier materials dissolved quickly even when the degree of surface area coverage was high. This indicates that the drugs were present as small agglomerates instead of discrete primary particles thereby causing a decrease in the dissolution rate of the drugs.

Introduction

Ordered mixtures have been used in earlier studies to demonstrate improvement in the dissolution rate of poorly soluble, fine particulate drugs (Nyström and Westerberg, 1986). It has been shown that a prerequisite for such improvement is for the carrier material to be highly soluble, thereby rapidly delivering the drug in the form of discrete primary particles (Westerberg et al., 1986). For rapid dissolution of the carrier particles, the degree of surface area coverage (i.e., the amount of drug on the carrier unit) should be kept relatively low (Nilsson et al., 1988). When this surface area coverage is low, the dissolution medium can come in contact with the carrier material instantaneously and dissolve it rapidly. If the degree of surface area coverage was high enough, the carrier material could theoretically be completely coated with hydrophobic drug particles (Nyström et al., 1982). The dissolution rate for such a system would probably be governed

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TABLE 1

Primary characteristics of adhering drug materials

Material	Density [a] ρ_s (g cm^{-3})	External specific surface area of primary particles [b] S_w (cm^2 g^{-1})	Weight and surface area utilized in dissolution testing		Mean volume diameters by weight [c]		Surface to volume shape factor [d] α_{sv} (−)
			w (mg)	S_c (cm^2)	Geometric d_G (μm)	Harmonic d_H (μm)	
Griseofulvin	1.44	21800	0.70	15.3	3.09	2.84	9.16
Oxazepam	1.48	30750 [e]	2.0	71.5	9.71	6.71	35.5

[a] Measured with an Air Comparison Pycnometer (Beckman, model 930, U.S.A.). Mean values of three determinations.
[b] Measured by permeametry (Blaine, Seger Tonindustrie, Germany). Mean values of three determinations.
[c] Measured with a Coulter Counter, model TAII (U.K.) (capillary diameter 70 μm). Both materials were approximately log-normally distributed. Mean values of two determinations.
[d] Calculated according to Allen (1981).
[e] Mean value of two batches of oxazepam.

initially by the penetration rate of the dissolution medium through the layer of adhering drug particles. In the study by Nilsson et al. in 1988, the effect of the degree of surface area coverage was investigated to only a limited extent, and it was therefore considered to be of interest to study a whole series with different degrees of surface area coverage.

In earlier studies, we have reported that the dissolution rate of a drug from an ordered mixture, with a relatively low degree of surface area coverage, can be much higher than that of a well-dispersed suspension of the drug (Westerberg and Nyström, 1989, 1991). This may seem surprising since a well-dispersed suspension is usually considered to be the ideal system in this context. Since the solid carrier material is the main difference between the two systems, it would seem important to obtain more information regarding the role of this carrier material in the dissolution process of the drug.

The aim of this study was thus to further evaluate the effects of different degrees of surface area coverage in ordered mixtures on the drug dissolution rate. The mechanisms behind the increasing dissolution rate with ordered mixtures compared to that with well-dispersed suspensions was also studied.

TABLE 2

Primary characteristics of carrier materials

Carrier	Density [a] ρ_s (g cm^{-3})	External specific surface area [b] S_w (cm^2 · g^{-1})	Harmonic mean diameter by weight [c] d_H (μm)	Surface to volume shape factor [d] α_{sv} (−)	Aqueous solubility at room temperature C_s (mg · l^{-1})
Mannitol	1.46	241	308	11	182 [e]
Sodium chloride	2.17	118	273	7	357 [f]

[a] Measured with an Air Comparison Pycnometer (Beckman, 930, U.S.A.). Mean values of three determinations.
[b] Calculated according to Allen (1981).
[c] Calculated from sieve data. Mean values of three determinations.
[d] Estimated by microscopy, according to Heywood (1954).
[e] Data from Merck Index, 11th Edn.
[f] Data from Handbook of Chem. Weast (1986).

Materials and Methods

Materials

Components of ordered mixtures

Adhering drug materials. Oxazepam (Wyeth, Germany) and griseofulvin (micronized, Glaxo, U.K.), two fine particulate and sparingly soluble drugs, were used as model substances. Oxazepam was milled in a pin disc mill (Alpine, 63 C, Germany) and griseofulvin was used as supplied. Both materials are cohesive and therefore strongly agglomerated. The primary characteristics of the two adhering materials are presented in Table 1.

Carrier materials. Mannitol (granulate, Merck, Germany) and sodium chloride (cubic, crystalline, puriss, Kebo Lab, Sweden) were used. These two materials are highly soluble in water. Both were fractionated by sieving (Fritsch Analyzette, Germany) and the 250–450 μm sieve fractions were used. The primary characteristics of the two carrier materials are presented in Table 2.

Methods

Preparation of ordered mixtures

Weight proportions. The degree of surface area coverage was estimated using the surface area ratio (Rs) (Nyström et al., 1982). In our earlier studies we have used Rs values between 0 and 1, but in this study we have chosen to express them as percentages. Eight different surface area ratios, between 5 and 102%, were tested for each combination of drug and carrier material.

Mixing. Mixing took place in a Turbula mixer (2 L, W.A. Bachofen A.G., Switzerland), at a speed of 90 rpm. The size of the mixing jar was chosen to give a fill volume of approx. 50%. The materials were mixed for 3000 min to achieve an almost complete deagglomeration (Malmqvist and Nyström, 1984).

Solubility studies

The solubilities of oxazepam and griseofulvin were determined by adding an excess of the drug to the dissolution medium. The suspensions were agitated for 48 h at room temperature (22 ± 1°C). After centrifugation (Beckman, J-21C, U.S.A.), the supernatant was assayed spectrophotometrically (Hewlett Packard, 8451A, U.S.A.) at 238 nm (oxazepam) or 295 nm (griseofulvin) for the amount of drug. Tests were made for pure drug both alone and in an ordered mixture. To determine the effect of the carrier materials on the solubility of the drugs, the solubility of the pure drug was measured in both ordinary dissolution medium and in dissolution medium containing dissolved carrier material. The amount of carrier material added to the dissolution medium corre-

TABLE 3

Solubilities (C_s) of oxazepam and griseofulvin alone and in ordered mixtures at 22 ± 1°C [a]

Material	Pure substance in water (mg l^{-1})	Pure substance in dissolution medium (mg l^{-1})	Pure substance in dissolution medium containing mannitol [b] (mg l^{-1})	Pure substance in dissolution medium containing sodium chloride [b] (mg l^{-1})	Pure substance in saturated solution of mannitol (mg l^{-1})	Pure substance in saturated solution of sodium chloride (mg l^{-1})	Ordered mixture with mannitol in dissolution medium (mg l^{-1})	Ordered mixture with sodium chloride in dissolution medium (mg l^{-1})
Oxazepam	22.1 [c]	23.3	24.7	22.5	27.4	7.69	25.7 [e]	23.7 [e]
Griseofulvin	8.66 [d]	8.41	9.28	7.56	5.96	0.585	17.4 [e]	7.12 [e]

[a] Mean values of three determinations.

[b] The amount of carrier material added to the dissolution medium corresponds to the amount used for an ordered mixture with a surface area coverage of 5%.

[c] Determined by Nilsson et al. (1988).

[d] Determined by Nyström et al. (1985).

[e] Values utilized in calculation of K_N (Eqn 1).

sponded to the amount used for an ordered mixture with a surface area coverage of 5%. The solubility of the pure drug was also measured in saturated solutions of the two carrier materials. The results shown in Table 3 are mean values of three determinations.

Dissolution studies

All dissolution tests were performed according to USP XXII, paddle method, using an agitation intensity of 100 rpm at room temperature (22 ± 2°C). A 0.9% w/w solution of sodium chloride (Kebo Lab, Sweden) in distilled water was used as dissolution medium, unless otherwise specified. In order to ensure optimal wetting conditions 0.01% w/w polysorbate 80 (Kebo Lab, Sweden) was added (Nyström and Westerberg, 1986).

Dissolution test for adhering drug materials. Quantities of ordered mixtures of oxazepam and griseofulvin corresponding to 10% of their solubility were added to 1 l of dissolution medium so as to obtain near sink conditions.

A semi-automatic sampling and analysis system was used. A pump transferred liquid from dissolution vessels to flow cells in a spectrophotometer (Beckman, model 35, U.S.A. and Hewlett Packard, 8451A, U.S.A.) where the UV absorbance at 238 nm (oxazepam) or 295 nm (griseofulvin) was measured. The samples were first filtered through glass wool to ensure that they were free from suspended drug particles. Results presented are mean values of two to four determinations.

Dissolution test for carrier materials. A 0.01% w/w solution of polysorbate 80 in distilled water was used for the dissolution test for sodium chloride. The weights of the samples tested correspond to the amounts used for the dissolution tests on the adhering materials. Samples were drawn manually using an automatic pipette with a filter holder containing a filter tip of glass wool. The volume of the dissolution medium was kept constant by replacing with fresh medium immediately after each withdrawal. The amount of sodium chloride in the dissolution samples was measured with a combination chloride electrode (Orion, model 96-17B, U.S.A).

The amount of mannitol was measured using a HPLC system consisting of a pump (Waters-Millipore, Waters 600, U.S.A.), an injector (Waters-Millipore, Waters WISP 710 B, U.S.A.), a pulse-damper (Scientific Inc., SSI LP-21, U.S.A.), a column (Supelco Inc., Supelcogel C-611-SP, U.S.A.), a column oven (LKB-Biotechnology, LKB 2155, Sweden), a detector (ERMA Inc., ERMA 7515-A, Japan) and an integrator (Shimadzu Corp., Shimadzu C-R3A, Japan). The mobile phase consisted of 0.0001 M NaOH (pH 10, Merck, Germany) and the flow rate was 1.0 ml min^{-1}.

To evaluate the effect of the adhering material on the dissolution process, both ordered mixtures and the carrier material alone were studied. The influence of the degree of surface area coverage was evaluated by testing both low (5%) and high (100 or 102%) degrees. Results presented are mean values of five determinations.

Dissolution studies on drug suspensions. Dissolution tests were performed on oxazepam and griseofulvin suspensions. Amounts of oxazepam and griseofulvin corresponding to 10% of their solubility were added to 1 l of dissolution medium. To study the effect of the carrier material, mannitol or sodium chloride was added to the dissolution medium simultaneously with the suspension. The amount of carrier material added to the dissolution medium corresponded to the amount used for an ordered mixture with a surface area coverage of 5%. The dissolution rate of the suspensions was also measured in saturated solutions of the two carrier materials. Results presented are mean values of five determinations.

Calculation of drug dissolution rate constants (K_E). The experimental dissolution rate (K_E) in $\mu g\ min^{-1}$ was calculated for the dissolution rate for 30% of the amounts of drug tested, as described earlier (Nilsson et al., 1988).

Calculation of drug dissolution rate constants normalized for solubility and external specific surface area (K_N). Oxazepam and griseofulvin have different aqueous solubilities and external specific surface areas. To be able to directly compare the intrinsic dissolution rates of the two drug substances tested, the experimental dissolution rate (K_E) was corrected for their different solubilities (C_s), characterized in the respective disso-

lution medium for the drug in the ordered mixture (Table 3), and external surface areas (S_c) (Table 1). The drug surface area (S_c) participating in the dissolution is presented in Table 1, and was obtained by multiplying the external specific surface area (S_w) and the weight of drug (w) utilized for the dissolution test. The expression for the normalized dissolution rate (K_N) will then be

$$K_N = \frac{K_E}{C_s \cdot S_c} \quad (1)$$

which theoretically is an expression for the diffusional transport of solute away from the dissolving particle to the solvent bulk. This type of dissolution rate parameter has earlier been utilized by Bisrat and Nyström (1988), Anderberg and Nyström (1990) and Bisrat et al. (1992).

Results and Discussion

Solubility studies

The results of the solubility measurements are presented in Table 3.

The solubilities of oxazepam alone and in an ordered mixture are nearly the same. A very

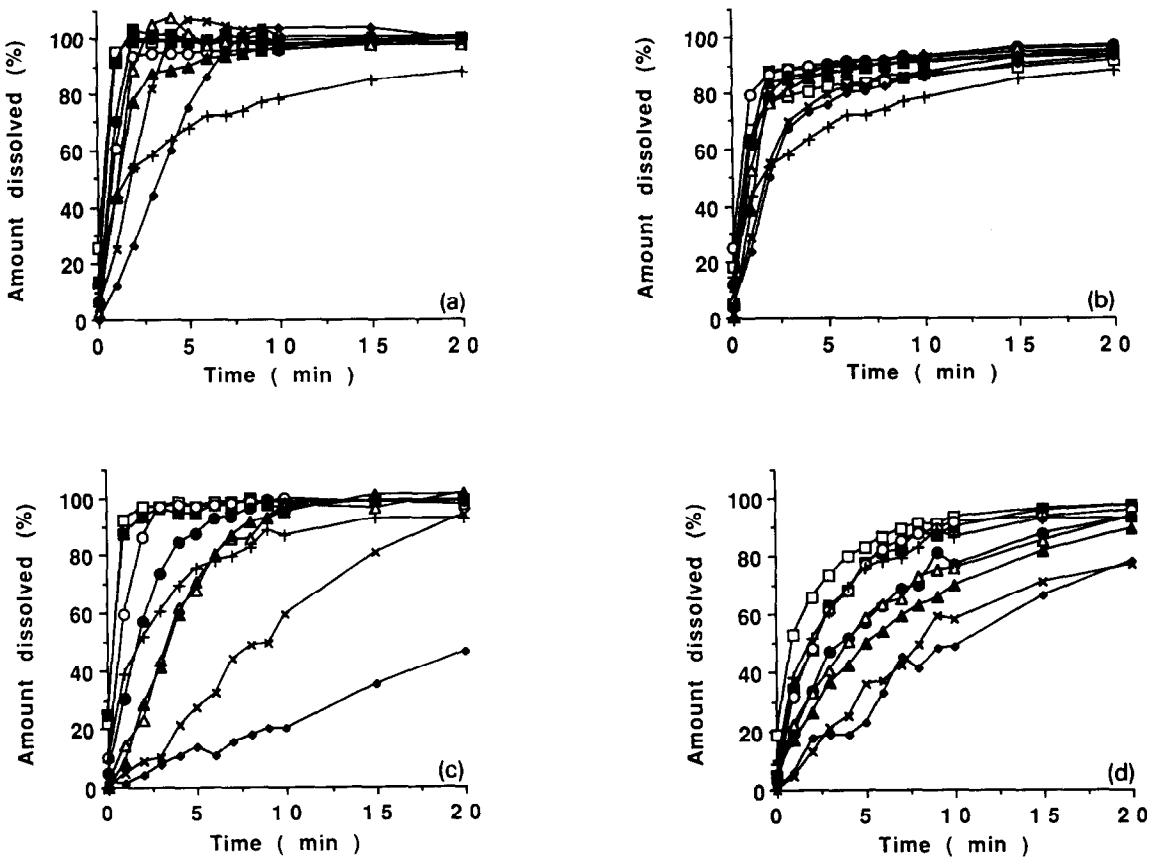

Fig. 1. Effect of the degree of surface area coverage on the dissolution rate of ordered mixtures. (a) Oxazepam in ordered mixtures with mannitol. □, 5% surface coverage; ■, 10% surface coverage; ○, 20% surface coverage; ●, 30% surface coverage; △, 40% surface coverage; ▲, 50% surface coverage; ×, 70% surface coverage; ◆, 100% surface coverage; +, suspension of oxazepam. (b) Oxazepam in ordered mixtures with sodium chloride. □, 5% surface coverage; ■, 14% surface coverage; ○, 20% surface coverage; ●, 29% surface coverage; △, 44% surface coverage; ▲, 50% surface coverage; ×, 73% surface coverage; ◆, 102% surface coverage; +, suspension of oxazepam. (c) Griseofulvin in ordered mixtures with mannitol. Symbols as in panel a. (d) Griseofulvin in ordered mixtures with sodium chloride. Symbols as in panel b.

slight increase in the solubility might be noticed in the presence of mannitol. This is especially seen in a saturated solution of mannitol. However, in a saturated solution of sodium chloride the solubility is markedly decreased.

The same pattern was observed for griseofulvin. However, when mannitol acts as a carrier material in an ordered mixture the solubility is doubled. This could probably be explained by a partial activation of the griseofulvin particles, resulting in regions of amorphous structures (Ahlneck and Zografi, 1990). The solubility of griseofulvin is decreased in saturated solutions of both carrier materials, especially sodium chloride.

Dissolution studies

The lagtime due to the transport of the medium from the dissolution vessels to the spectrophotometer has been estimated to be approx. 1 min and has been subtracted from the obtained results. Due to heterogeneity in the dissolution vessel immediately after the addition of the test sample and a built-in system error, the true lagtime, i.e., the amount dissolved at $t = 0$, could differ from zero. However, this affects the K_E values to only a minor extent.

The effect of different degrees of surface area coverage

The amount of drug dissolved, plotted against time for suspensions of oxazepam and griseofulvin and for ordered mixtures with mannitol and sodium chloride as carriers is presented in Fig. 1a–d.

Ordered mixtures of oxazepam and mannitol (Fig. 1a) show a fast dissolution rate and the 100% level is reached within 10 min for all mix-

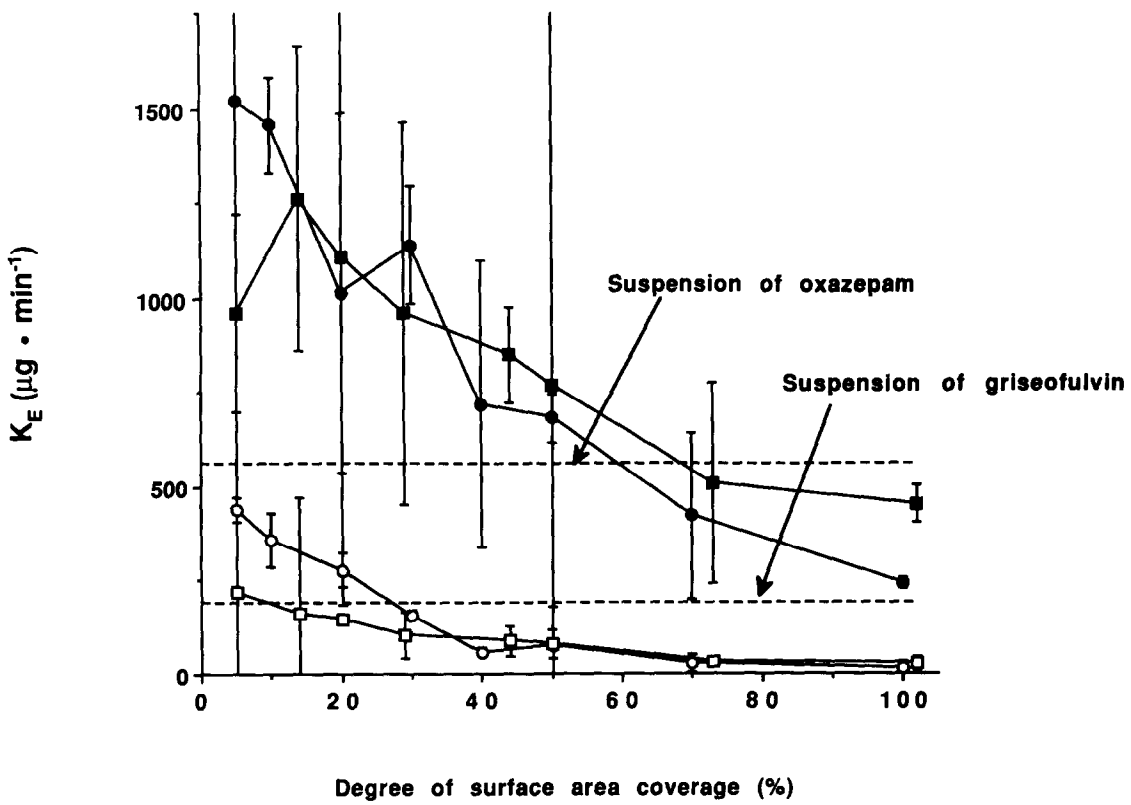

Fig. 2. Experimental dissolution rate (K_E), expressed in μg min^{-1}, as a function of the degree of surface area coverage. ●, oxazepam in ordered mixture with mannitol; ■, oxazepam in ordered mixture with sodium chloride; ○, griseofulvin in ordered mixture with mannitol; □, griseofulvin in ordered mixture with sodium chloride. Error bars represent the 95% confidence intervals for the means.

tures. The mixtures with a surface area coverage of 50% or less all show higher dissolution rates in comparison with the oxazepam suspension.

A fast dissolution rate, higher than for the griseofulvin suspension, was also seen for the ordered mixtures of griseofulvin and mannitol (Fig. 1c) with a degree of surface area coverage of 20% or less. When the degree of surface area coverage is increased (> 20%) the dissolution rates are substantially lowered.

Ordered mixtures of oxazepam and sodium chloride (Fig. 1b) and griseofulvin and sodium chloride (Fig. 1d) show somewhat different dissolution profiles compared to when mannitol is used as carrier material. The 100% level is reached much more slowly for the sodium chloride mixtures. This is especially emphasized for the griseofulvin and sodium chloride mixture. For the ordered mixtures of oxazepam and sodium chloride, where the degree of surface area coverage is 50% or less, the dissolution rates are faster than that obtained for the oxazepam suspension. The ordered mixtures with griseofulvin and sodium chloride have dissolution rates that are the same as or somewhat faster than those for a suspension of griseofulvin only when the degree of surface area coverage is 10% or less.

Fig. 2 shows the experimental dissolution rates K_E, expressed in $\mu g\ min^{-1}$. The suspensions of oxazepam and griseofulvin have been chosen as references to represent an ideal system with discrete primary particles. Here, the dissolution rate of the drug is not influenced by the presence of a carrier material. The highest dissolution rates are obtained when the degree of surface area coverage is low. The dissolution rate is much higher for many of the ordered mixtures than for the suspensions. It seems that the carrier material has a

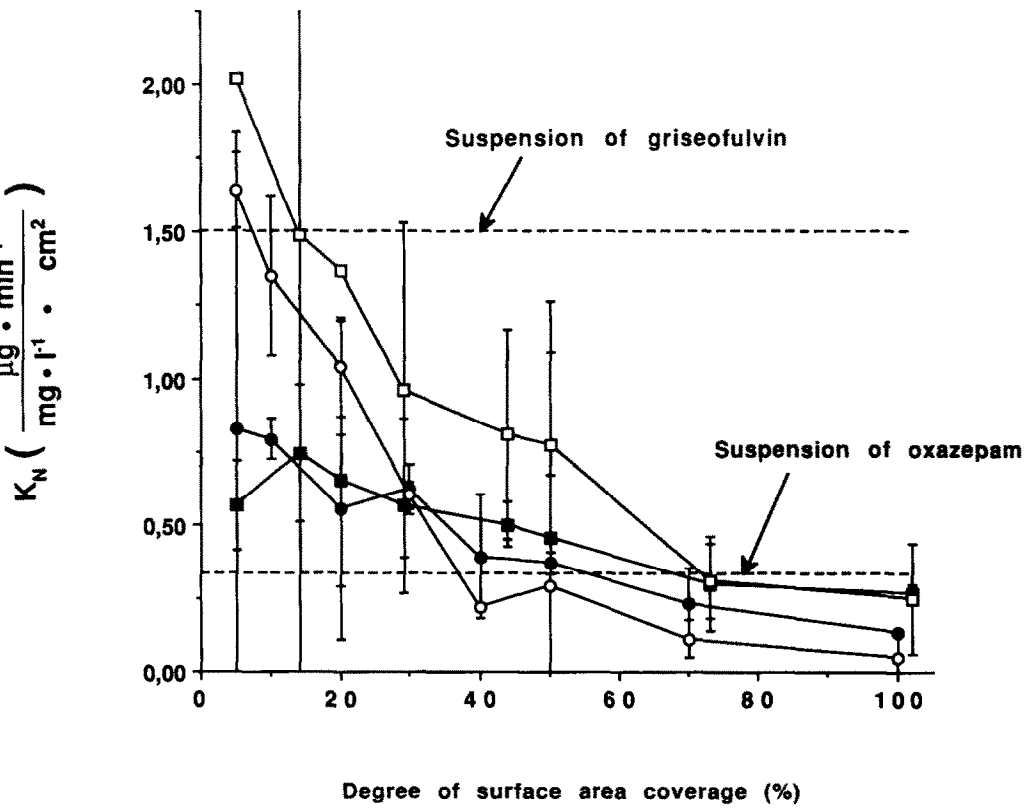

Fig. 3. Normalized dissolution rate (K_N), expressed in $\mu g\ min^{-1}/mg\ l^{-1}\ cm^2$, as a function of the degree of surface area coverage. Symbols as in Fig. 2. Error bars represent the 95% confidence intervals for the means.

positive effect on the dissolution rate of the drug. Ordered mixtures with a high degree of surface area coverage show a decrease in the dissolution rate, and for many mixtures the dissolution rate is lower than for the suspensions. There could be several reasons for this difference, between a low and a high surface area coverage, and this will be further discussed below.

The dissolution rate of oxazepam is markedly improved by incorporating it in an ordered mixture. The improvement is nearly the same irrespective of whether mannitol or sodium chloride is used as carrier material. Even if the amount of drug on the carrier material is rather high, up to 50% surface area coverage for both carrier materials, the dissolution rate is still faster than from a well-dispersed suspension.

For the lowest degree of surface area coverage (5%), for the ordered mixture of oxazepam and sodium chloride, the dissolution rate is lower than one perhaps would have expected. A low degree of surface area coverage for the drug means that the amount of carrier material which is added to the dissolution medium has to be relatively high in order to correspond to the desired amount of drug. When a large quantity of sodium chloride is added to the dissolution medium it agglomerates to form large particles. This decrease in surface area means that the dissolution of the carrier material is slowed and this consequently lowers the dissolution rate of the drug.

The dissolution rates of the griseofulvin and sodium chloride mixtures are in most cases not as fast as that of the griseofulvin suspension. Only the mixtures with a low degree of surface area coverage ($< 20\%$) are in good agreement with the well-dispersed griseofulvin suspension. The same pattern is shown for the griseofulvin and mannitol mixtures, with the exception of the mixtures with low degrees of surface area coverage ($< 30\%$) where the dissolution rates are much faster than that obtained for the griseofulvin suspension. This could be because the solubility of griseofulvin is markedly increased in an ordered mixture with mannitol as a carrier (Table 3).

The dissolution rate for the oxazepam suspension is higher than that for the griseofulvin suspension. This is because the two materials have different aqueous solubilities (Table 3). They also have different surface areas exposed to the dissolution medium (Table 1).

If the experimental dissolution rates are corrected for the differences in solubility (mg l^{-1}) and surface area (cm^2) between the two materials the results shown in Fig. 3 are obtained. It can be seen that the two suspensions have changed positions. Now it is the griseofulvin suspension that shows the highest intrinsic dissolution rate. The difference in dissolution rate between the two drugs may partly be explained by the difference in particle size (Table 1). Differences in particle size for relatively fine, sparingly soluble drugs in suspended form will affect the diffusion boundary layer thickness in the dissolution process. Small particles have a smaller diffusion boundary layer thickness resulting in faster transport of the dissolved molecules from the particle surface (Bisrat and Nyström, 1988).

The very high dissolution rate for the ordered mixture of griseofulvin and mannitol which is shown in Fig. 2 was not seen in Fig. 3. This indicates the need for solubility corrections to be made when an intrinsic dissolution rate is to be obtained. Thus, the intrinsic dissolution rate is similar for the two ordered systems of griseofulvin and for the two ordered systems of oxazepam.

Ordered mixtures with a high degree of surface area coverage (> 30–40%) show, as discussed above (Figs 1 and 2), a decrease in the dissolution rate. The dissolution rates are similar for the two drugs, which indicates that the effects of the difference in particle size have been smoothed out or have disappeared. This decrease with increasing surface coverage could be due to a change in the ordered units surface character to a more hydrophobic state which subsequently delays the wetting and dissolution of the carrier. This explanation was used in a previous study (Nilsson et al., 1988), where the increase in both drug amount and mixing time was reported to result in a more complete surface coverage of the carrier units. Consequently, it was suggested that the carrier dissolution rate was retarded which hindered the instant release of discrete primary drug particles. Another possible explanation for

the decrease in dissolution rate could be that the higher amount of drugs has an increased agglomeration tendency (Malmqvist and Nyström, 1984). In such a case, the carrier units could be rapidly dissolved, but the drug would then be released in the form of small agglomerates rather than as discrete primary particles. The reduction in drug dissolution rate would then be due to both a reduced surface area of the drug, effectively taking part in dissolution, and also due to an increased diffusional distance from the drug agglomerates, compared with the smaller drug primary particles (Bisrat and Nyström, 1988; Bisrat et al., 1992).

The importance of carrier dissolution for the drug dissolution from ordered mixtures

These tests were performed in an attempt to further evaluate the mechanisms behind the de-

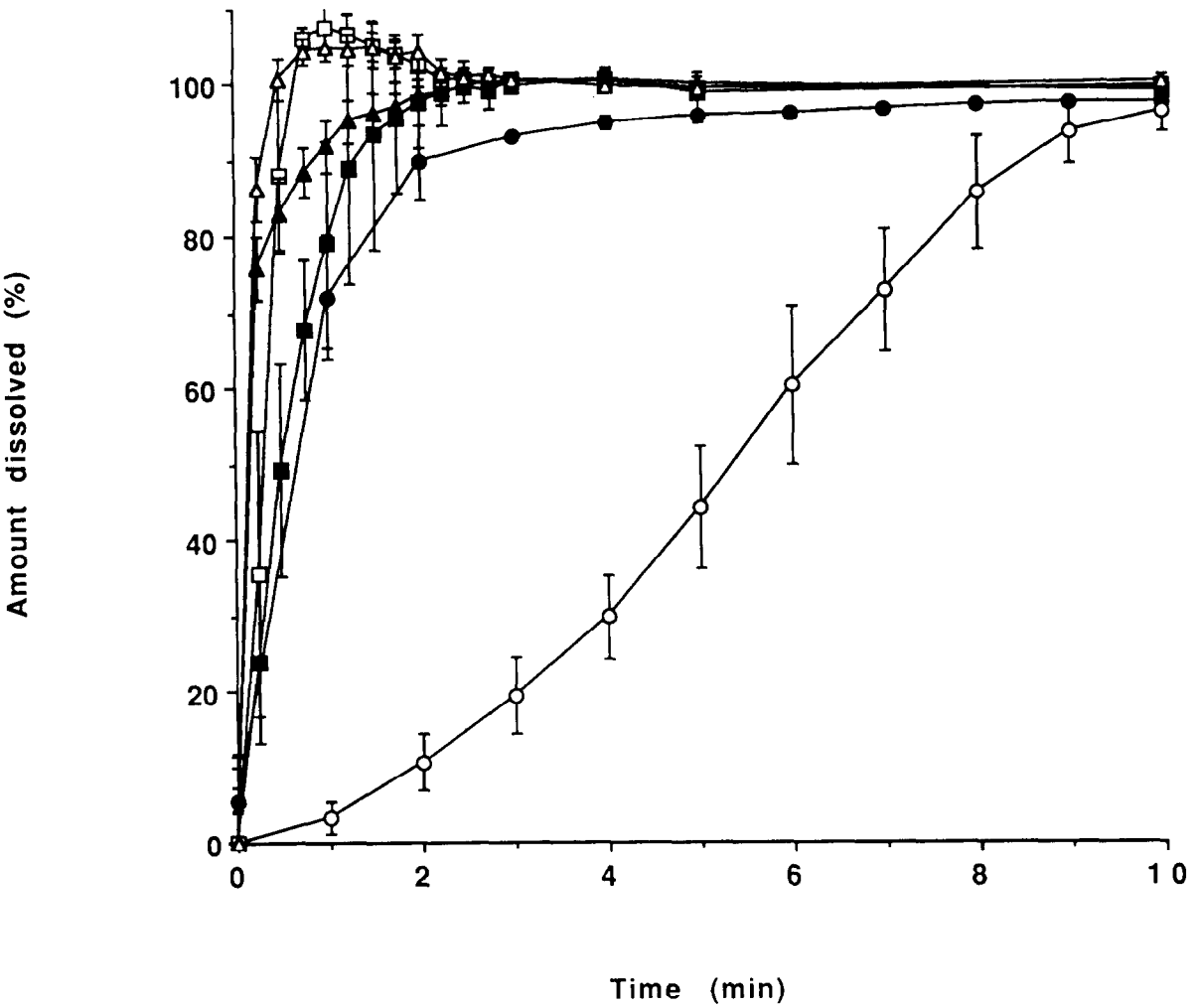

Fig. 4. Dissolution rate profiles for sodium chloride alone and in ordered mixtures with oxazepam. Degree of surface area coverage 5% (closed symbols) and 102% (open symbols). ●, ○, dissolution rate of oxazepam from an ordered mixture; ■, □, dissolution rate of sodium chloride from an ordered mixture; ▲, dissolution rate of sodium chloride alone (reference to a surface area coverage of 5%); △, dissolution rate of sodium chloride alone (reference to a surface area coverage of 102%). Error bars represent the 95% confidence intervals for the means.

crease in drug dissolution rate for ordered mixtures with high degrees of surface area coverage. Another aim was to study possible mechanisms for ordered mixtures with low degrees of surface area coverage and their higher dissolution rate compared to well-dispersed suspensions. The dissolution rates of the ordered mixtures of griseofulvin and sodium chloride were faster than that of the griseofulvin suspension only for the lowest degree of surface area coverage (5%), and therefore no tests were performed on these mixtures.

Dissolution studies on sodium chloride

Results for the dissolution tests of sodium chloride and oxazepam are shown in Fig. 4. Two different degrees of surface area coverage with ordered mixtures of oxazepam are compared, 5 and 102%. The dissolution profiles for both ox-

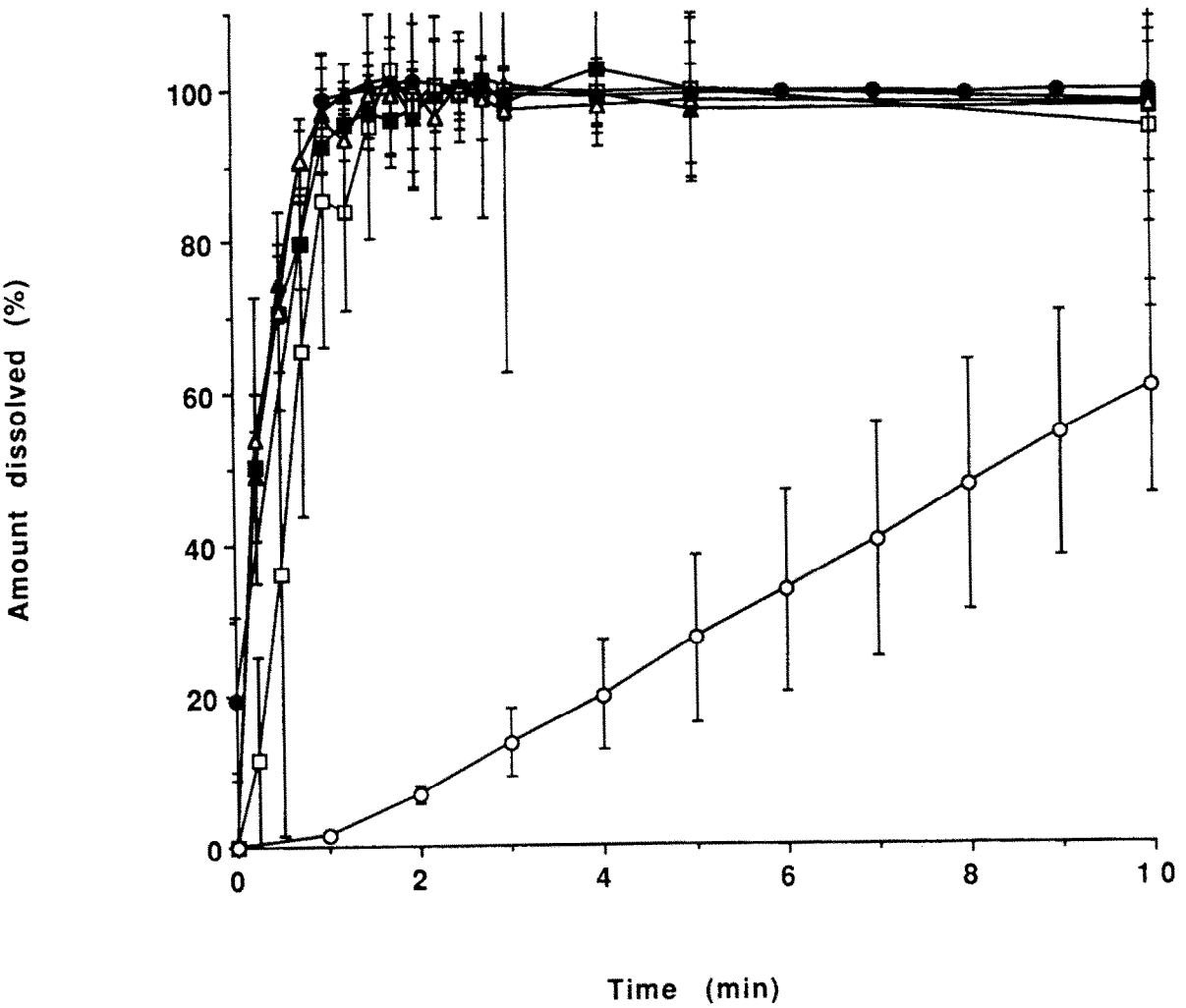

Fig. 5. Dissolution rate profiles for mannitol alone and in ordered mixtures with oxazepam. Degree of surface area coverage 5% (closed symbols) and 100% (open symbols). ●, ○, dissolution rate of oxazepam from an ordered mixture; ■, □, dissolution rate of mannitol from an ordered mixture; ▲, dissolution rate of mannitol alone (reference to a surface area coverage of 5%); △, dissolution rate of mannitol alone (reference to a surface area coverage of 100%). Error bars represent the 95% confidence intervals for the means.

azepam and sodium chloride in ordered mixtures are shown. The dissolution of pure sodium chloride, mixed for 3000 min, is used as a reference.

At a surface area coverage of 5% the dissolution rate of oxazepam is very fast, nearly the same as for sodium chloride (Fig. 4). The dissolution of sodium chloride seems to act as a driving force and thereby control the dissolution of the drug in the ordered mixture.

The dissolution of sodium chloride from the ordered mixture with 102% surface area coverage is fast, completed after only 1 min. The dissolution rate of oxazepam, however is slow, much slower than for a suspension. This indicates that the drug may be present as small agglomerates, thus corresponding to a reduced dissolution surface area and also a longer diffusional distance (Bisrat and Nyström, 1988). The carrier dissolution seems not to be a rate-limiting step as reported earlier for some ordered mixtures, where it was reported that an almost complete surface area coverage of an hydrophobic drug resulted in

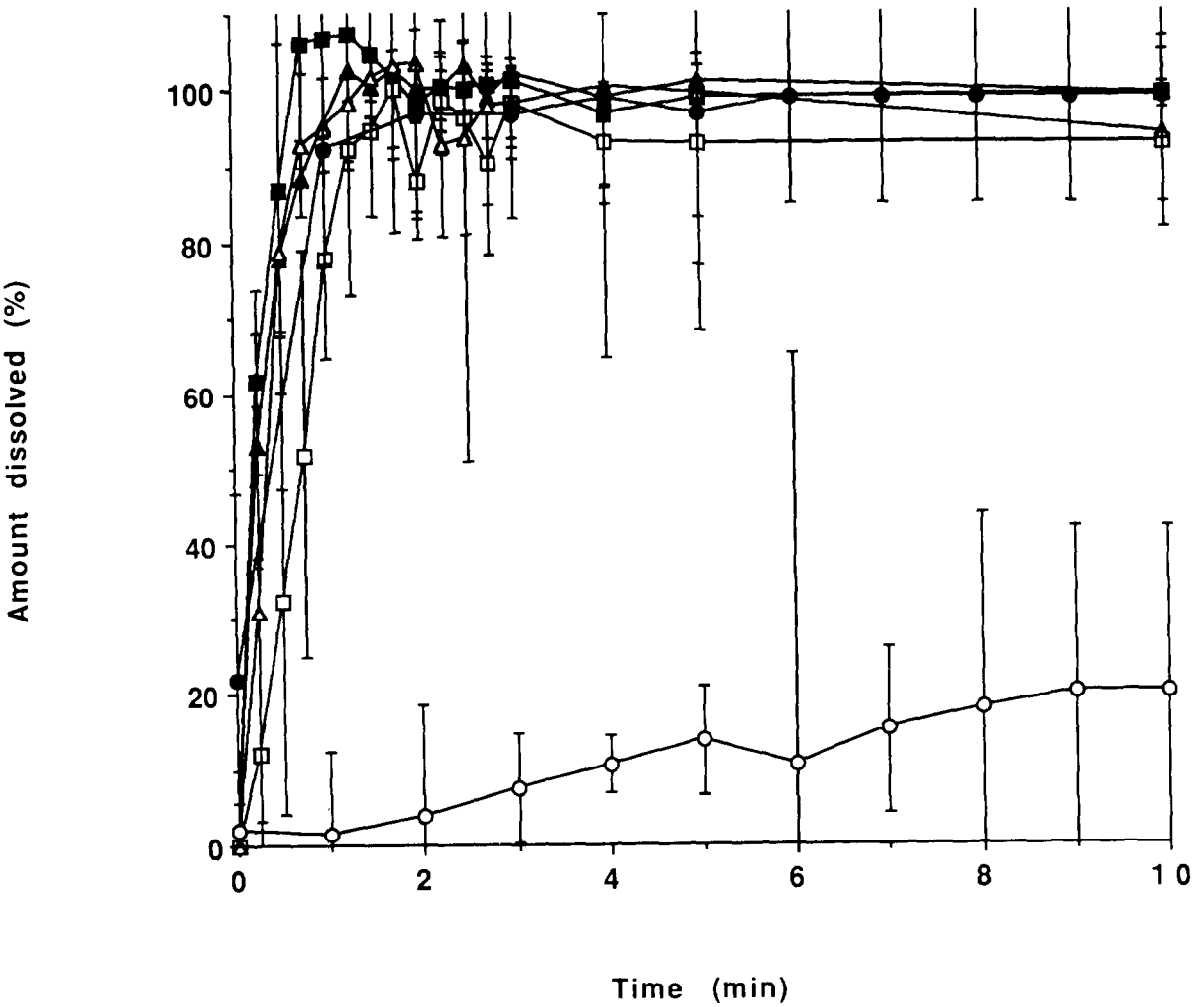

Fig. 6. Dissolution rate profiles for mannitol alone and in ordered mixtures with griseofulvin. Degree of surface area coverage 5% (closed symbols) and 100% (open symbols). ●, ○, dissolution rate of griseofulvin from an ordered mixture; ■, □, dissolution rate of mannitol from an ordered mixture; ▲, dissolution rate of mannitol alone (reference to a surface area coverage of 5%); △, dissolution rate of mannitol alone (reference to a surface area coverage of 100%). Error bars represent the 95% confidence intervals for the means.

inadequate wetting of the ordered units and a reduced release rate of discrete drug particles to the dissolution medium (Nilsson et al., 1988).

The dissolution rate of sodium chloride from an ordered mixture with 102% surface area coverage is somewhat faster than from an ordered mixture with a surface area coverage of 5%. This could be because the amount of sodium chloride differs. For the low degree of surface area coverage the amount of sodium chloride in the test sample is 2.3 g and for the higher degree the amount of sodium chloride is only 0.11 g. When a large quantity of sodium chloride is added to the dissolution medium it agglomerates to large particles and the dissolution rate is markedly decreased due to a decrease in surface area. This also lowers the dissolution rate of the drug as discussed above (Fig. 2). A low amount of carrier

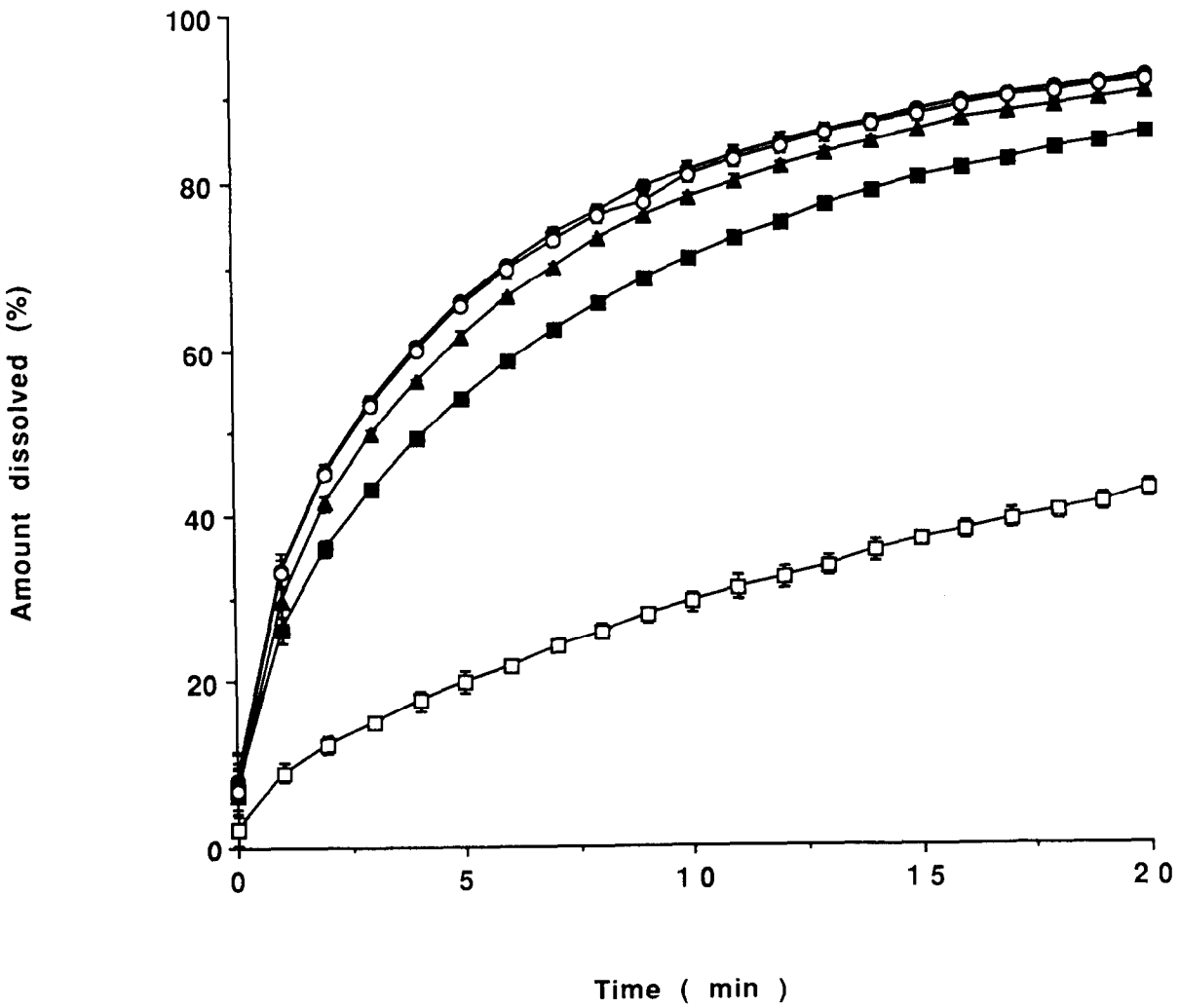

Fig. 7. Effect of addition of carrier material on the dissolution rate of oxazepam in suspension. ▲, oxazepam suspension in dissolution medium; ●, oxazepam suspension in a low amount of mannitol (corresponding to a surface area coverage of 5%); ■, oxazepam suspension in a saturated solution of mannitol; ○, oxazepam suspension in a low amount of sodium chloride (corresponding to a surface area coverage of 5%); □, oxazepam suspension in a saturated solution of sodium chloride. Error bars represent the 95% confidence intervals for the means.

material is more rapidly dispersed in the dissolution medium.

Dissolution studies on mannitol

Results for the dissolution tests of mannitol and oxazepam are shown in Fig. 5, and those results for mannitol and griseofulvin are depicted in Fig. 6. Two different degrees of surface area coverage with ordered mixtures of oxazepam and griseofulvin are compared, 5 and 100%. The dissolution profiles for oxazepam, griseofulvin and mannitol in ordered mixtures are shown. The dissolution of pure mannitol, mixed for 3000 min, is used as a reference. Figs 5 and 6 show that for a low surface area coverage, 5%, the dissolution rates of oxazepam, griseofulvin and mannitol are

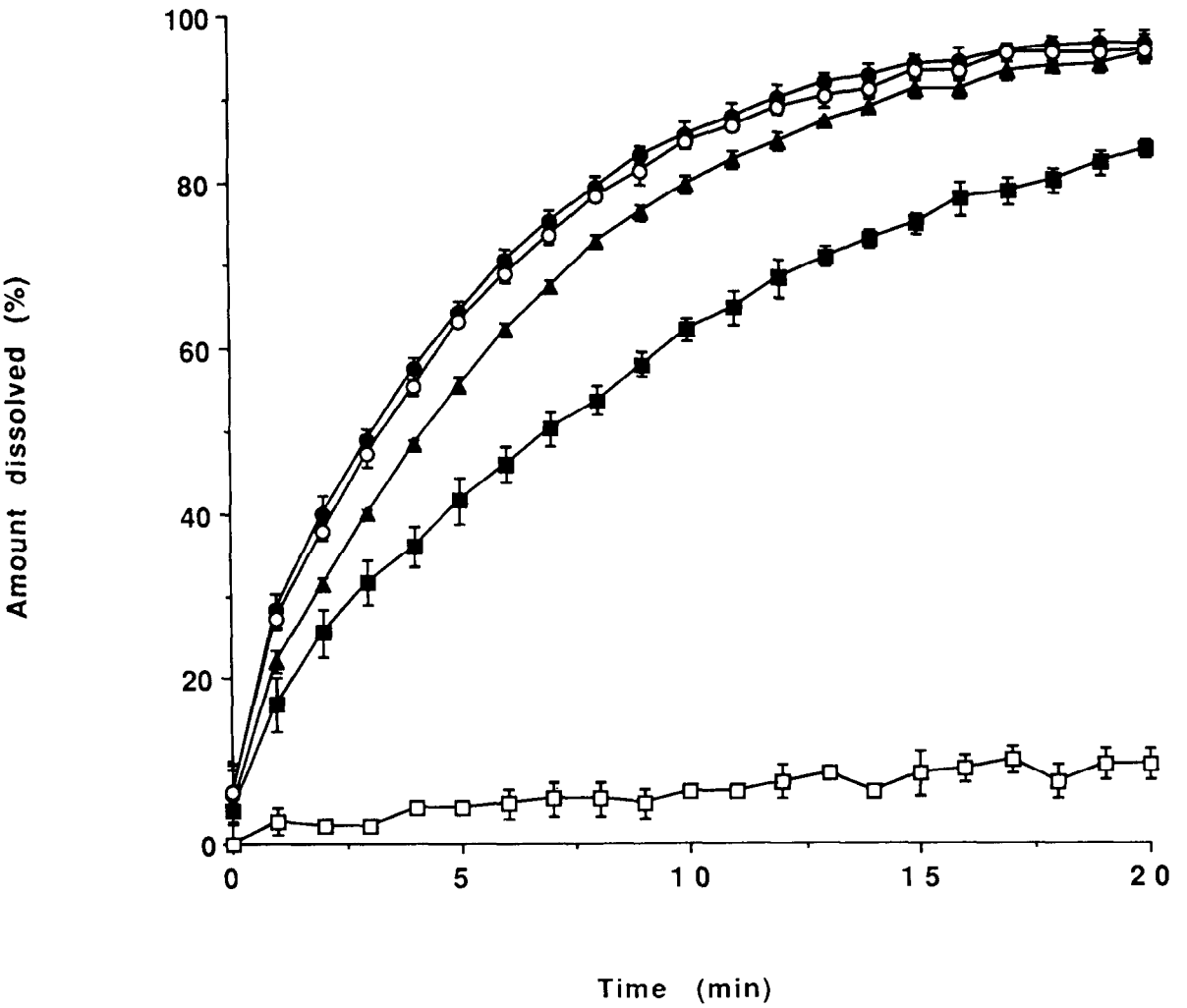

Fig. 8. Effect of addition of carrier material on the dissolution rate of griseofulvin in suspension. ▲, griseofulvin suspension in dissolution medium; ●, griseofulvin suspension in a low amount of mannitol (corresponding to a surface area coverage of 5%); ■, griseofulvin suspension in a saturated solution of mannitol; ○, griseofulvin suspension in a low amount of sodium chloride (corresponding to a surface area coverage of 5%); □, griseofulvin suspension in a saturated solution of sodium chloride. Error bars represent the 95% confidence intervals for the means.

fast. As for sodium chloride, mannitol seems to act as a driving force for the dissolution of the drug in the ordered mixture.

For a high surface area coverage, 100%, the dissolution rates of mannitol from the ordered mixtures of oxazepam and griseofulvin are also fast. The dissolution of pure mannitol is somewhat faster than the dissolution of mannitol from the ordered mixtures. This could be because the mannitol particles in the ordered mixture are completely covered with the hydrophobic drug, and a slower dissolution of the carrier is obtained due to poorer wetting and a decreased penetration rate of the dissolution medium into the carrier particle. However, this seems only to affect the initial dissolution rate of the carrier particle. After 2 min, both the pure mannitol and the mannitol from the ordered mixture, are completely dissolved. The dissolution rates of both oxazepam and griseofulvin are slow and this could initially be caused by the slower dissolution of the carrier, but the dominating effect is probably that the drug is present as small agglomerates instead of discrete primary particles, as discussed above for ordered mixtures of sodium chloride.

Dissolution studies on suspensions

The results for the oxazepam suspension are shown in Fig. 7. The amount of carrier material added to the dissolution medium corresponds to the amount of carrier material used in the ordered mixture with the lowest surface area coverage (5%). The dissolution rate for the suspension when low amounts of the carrier materials are added to the dissolution media is nearly the same as that for the suspension alone.

In a saturated solution of sodium chloride the dissolution rate of oxazepam is substantially lowered. This is probably due to the decreased solubility of oxazepam in a saturated solution of sodium chloride (Table 3). When the dissolution test is carried out in a saturated solution of mannitol, the dissolution rate of oxazepam is somewhat decreased.

The results for the griseofulvin suspension are shown in Fig. 8. The dissolution rates when low amounts of the carrier materials are added to the dissolution media are, as for oxazepam, nearly the same as for the dissolution rate of the suspension alone. In a saturated solution of mannitol the dissolution rate is lowered, and in a saturated solution of sodium chloride the dissolution rate is very low. This is probably explained by the change in solubility for griseofulvin in saturated solutions of the carrier materials (Table 3).

Mechanisms behind the impaired drug dissolution from ordered mixtures with a high drug surface area coverage

Theoretically, a surface area coverage of 100% means that the carrier particle is completely coated with hydrophobic drug particles. This ought to result in poorer wetting and a decreased penetration rate of the dissolution medium into the carrier particle, which would decrease the dissolution rates for both the carrier particle and the drug. However, this fact does not explain the obtained results, because the dissolution rate of the carriers tested is very fast in spite of the fact that a high amount of hydrophobic drug is present.

The value of the maximal surface area coverage (100%) carries a great deal of uncertainty. This is due to the simplified measurement of the external surface area of the carrier material. This surface area is calculated from the surface-to-volume shape factor estimated by microscopy (Heywood, 1954) and the harmonic mean diameter by weight measured using sieve analysis (Allen, 1981). For a test material with an extreme particle shape with respect to, e.g., flakiness it must be emphasized that the calculated surface area could be misleading regarding the estimation of coating capacity of the carrier. It therefore might be possible that a larger amount of drug is needed in order to achieve the theoretical coverage of 100%.

However, to explain the reduction in drug dissolution rate for these mixtures some additional mechanism involving the drug must be introduced. The most obvious explanation is that the drug is present as small agglomerates instead of discrete primary particles. This could be due to incomplete deagglomeration of the drug which is dependent on the deagglomeration capability,

during mixing, of the carrier material. It has been shown that for a high surface area coverage a more incomplete deagglomeration is achieved (Malmqvist and Nyström, 1984). The drug in the form of small agglomerates then corresponds to both a reduced dissolution surface area and an increased diffusional distance, compared to when the drug exists as discrete primary particles, as discussed above. Both factors will result in a decreased dissolution rate. The presence of small drug agglomerates will also result in a lower actual surface area coverage of the carrier particles and could thus also be used as an explanation for the rapid dissolution of the carrier.

Mechanisms behind increasing dissolution rate with ordered mixtures compared to well-dispersed suspensions

The mechanisms behind the increasing dissolution rate with ordered mixtures compared to well-dispersed suspensions can probably be related to the hydrodynamics of an agitated system of a suspended solid body (Bisrat and Nyström, 1988). Solids dispersed in a liquid medium under agitation are surrounded by zones of less movable liquid, i.e., a hydrodynamic boundary, reflecting a velocity gradient between the bulk fluid and the surface of the solid. For flow past a flat surface, the Prandtl boundary layer equation can be used to express the hydrodynamic boundary layer thickness (h_H).

$$h_H = k \cdot \frac{L^{1/2}}{V^{1/2}} \qquad (2)$$

where L is the length of the surface in the direction of flow and V denotes the relative velocity of the flowing liquid versus the flat surface. A decrease in particle size has been suggested to result in a decrease in V and a smaller value of L. Although these two effects counteract each other, it has been assumed (Niebergall et al., 1963) that the net effect is a decrease in h_H. It has been purported that a difference in particle size or diameter could correspond to a difference in the parameter L in Eqn 2 (Anderberg et al., 1988; Bisrat and Nyström, 1988; Bisrat et al., 1992). Therefore, a decrease in particle size corresponds to a reduced distance over which frictional forces could act, leading to a thinner region over which there is a velocity gradient. This would then correspond to a shorter diffusional distance (h_D) for dissolved molecules. The fraction of the hydrodynamic boundary layer thickness (h_H) in which diffusion dominates, constitutes this diffusion boundary layer thickness (h_D).

It is then possible to assume that the following combined effect could occur for an ordered mixture. Initially, the carrier particle is determining the hydrodynamic conditions and high values of L and V and subsequently a relatively long diffusional distance (h_D) are obtained. This long diffusional distance is permanent when insoluble carrier materials are used. When the carrier particle dissolves and the small drug particle is released, the drug particle has a high velocity (V) during the release-phase combined with a low particle size (corresponding to a small value of L) with a subsequently very low h_D value. Eventually the velocity (V) is decreased and h_D approaches to the same value as in a suspension system. However, the drug particle size has during this short release-phase now been substantially decreased and the diffusional distance (h_D) is thus shorter also during this second phase when it exist in free discrete form. A shorter diffusional distance especially during the initial release-phase, when the drug particle is ejected out in the medium from the dissolving carrier, could probably explain the higher dissolution rate for the ordered mixture in comparison with the suspension.

Conclusions

The dissolution of a drug in an ordered mixture with a low degree of surface area coverage is very fast, even faster than from a well-dispersed suspension. Increasing the proportion of drug in comparison to the carrier material substantially lowers the dissolution rate. This could be explained either as a result of incomplete deagglomeration, when the mixtures contain larger

amounts of drug, or by a decrease in the dissolution rate of the carrier particles when the surface coverage by the drug component increases. In this study it has been shown that the carrier materials (sodium chloride and mannitol) dissolve quickly even when the degree of surface area coverage is high. This indicates that the drug could be present as small agglomerates instead of discrete primary particles and this will cause a decrease in the dissolution rate of the drug, due to both a lowering of the drug dissolution surface area and to an increase in diffusional transport distance of dissolved drug molecules. The formation of smaller drug agglomerates, when higher amounts of drug is used, thus could reduce the effect of drug particle size found for mixtures with low surface area coverage. In Fig. 3, it was shown that the dissolution rate, corrected for differences in drug solubility and fineness was higher for griseofulvin than for oxazepam when mixtures of low surface area coverage were used. This was explained by a shorter diffusional distance for the smaller griseofulvin particles. This difference disappeared when higher drug amounts were admixed. Probably due to that agglomerates of similar size were present for the two drugs.

In an ordered mixture with a low degree of surface area coverage the dissolution rate of oxazepam follows the dissolution rate of the carrier materials (Figs 4 and 5). This ought to mean that the dissolution of oxazepam is taking place at a very high concentration of dissolved carrier material in solution in the micro-environment, compared to when the same amount of carrier material is added to the dissolution medium separately. To study the effect of a high concentration of carrier material, dissolution studies of a suspension of oxazepam were performed in saturated solutions of the carrier materials. In spite of the fact that the dissolution of the oxazepam suspension is markedly decreased in a saturated solution of a carrier material, an ordered mixture is not negatively affected when sodium chloride or mannitol are used as carrier materials. Therefore, the mechanism for the increased dissolution rate for the ordered mixture with a low degree of surface area coverage is probably not affected by the concentration of the carrier material in the micro-environment. The same explanation could be used for griseofulvin. Instead, it was proposed that the increase in drug dissolution rate compared to a suspension of the drug could be related to hydrodynamic factors. For a free suspended drug particle the apparent diffusional distance is relatively short and mainly a function of the particle size (Bisrat and Nyström, 1988). For the same drug particle just released from the dissolving carriers it is suggested that the diffusional distance is even lower, thus resulting in a very rapid dissolution process.

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