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# Physicochemical aspects of drug release. V. The importance of surface coverage and compaction on drug dissolution from ordered mixtures

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## Summary

Two micronized drugs, griseofulvin and oxazepam, were used in the form of agglomerates from the sieve fraction 500–710 μm. Granulate mannitol and anhydrous lactose (250–450 μm) were chosen as carrier materials. Mixtures having different degrees of surface coverage were produced in a Turbula-mixer. In order to accellerate tablet disintegration, 5% Avicel and 2% Ac-Di-Sol were then admixed. Tablets were compressed at 100 and 200 MPa respectively. Dissolution rates for ordered mixtures and tablets were determined according to USP XX1 (100 rpm). All the mixtures and the tablets dissolved considerably faster than the agglomerated drug raw material alone. Low surface coverage (8%) resulted in an almost instantaneous dissolution, whereas higher additions of the drug gave a somewhat smaller improvement. Here, the drug particles probably formed a 'film' around the carrier material, thereby interfering with the instantaneous dissolution of the latter. The tabletting procedure did not impair the dissolution of the systems. Instead, a faster dissolution was obtained for the higher degrees of surface coverage. A probable explanation for this is, that the 'film' of drug particles was broken at the same time as the carrier material partly fragmented.

## Introduction

The concept of ordered mixture was first introduced to describe a specific type of distribution between mixing components, representing, in contrast to a random mixture, an ideal system regarding mixture homogeneity (Hersey, 1975). Since an ordered mixture, in principle, can be formed utilizing adhesive interactions between mixing components (Malmqvist and Nyström, 1984a), it is often better adopted to pharmaceutical, fine particulate materials, than the concept of random mixture (Hersey, 1977).

Many studies have therefore been undertaken to evaluate different aspects regarding the preparation of ordered mixtures. Here, especially dry mixing of a small amount of finely divided drug with a large amount of coarse carrier particles has been studied (Malmqvist and Nyström, 1984b; Staniforth, 1982). Although there still exist some difficulties regarding appropriate methods to elucidate whether an ordered system has been obtained or not, and subsequently how to de-

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termine the end-point of the mixing process, it is well documented that ordered mixing provides a means of obtaining mechanically stable systems of high mixing homogeneity.

In earlier studies from our laboratory (Nyström and Westerberg, 1986; Westerberg et al., 1986), the usefulness of ordered mixtures for improving the dissolution rate of fine particulate, low soluble drugs, has been demonstrated. By deagglomerating the drug by a dry mixing process, the discrete drug particles (or minor clusters of particles) could be distributed over the surface of carrier particles, and thus be directly available for the dissolution media. Using mixtures, where approximately 15% of the carrier particles were theoretically covered by discrete drug particles, it was shown that the dissolution rate was as high as for a well dispersed suspension of the drug (Nyström and Westerberg, 1986). It was later confirmed that a prerequisite for this fast dissolution was the more or less instantaneous dissolution of the carrier particles (Westerberg et al., 1986). This observation has been explained by the effect of particle size on the thickness of the diffusion layer around the dissolving unit (Niebergall et al., 1963). It is first when separate, fine drug particles are present, that the slow transport by diffusion of dissolved molecules, will not substantially slow down the dissolution process (Nyström and Westerberg, 1986).

In order to evaluate the usefulness of ordered mixing, in this context for drug formulation of low dose drugs into solid dosage forms, it seems important to gain experience regarding two principal aspects. Firstly, the amount of drug that could be incorporated is basically limited by the amount of carrier surface area available, in order to avoid "oversaturation" (Malmqvist, 1984) and reduced mixing homogeneity. However, since the carrier material must undergo fast dissolution, it can not be excluded that a lower limit for the maximum drug content must be applied. One aim of this study therefore was to evaluate the effect of carrier surface coverage on dissolution rate. Secondly, the incorporation of ordered mixtures into solid dosage forms, especially tablets, may decrease dissolution rate, due to the introduction of new rate-limiting steps, such as penetration of dissolution media into tablets and tablet disintegration. Another aim of the study therefore was to evaluate the effect of compact formation on dissolution rate, utilizing a tablet formulation that has been reported suitable for high dose drugs (Bolhuis et al., 1979).

## Materials and Methods

### *Materials*

#### *Components of ordered mixtures*

*Adhering materials.* Griseofulvin (fine particulate, Glaxo, U.K.) and oxazepam (micronized,

TABLE 1

*Primary characteristics of adhering materials*

| Material | Density $\rho_s$ (g/cm$^3$) | Aqueous solubility at room temperature $C_s$ (mg/liter) | Surface specific dissolution rate $G$ ($\mu$g min$^{-1}$ cm$^{-2}$) | Geometric volume diameter by weight $\bar{d}_v$ ($\mu$m) | Geometric S.D. $\delta_g$ ($\mu$m) | External specific surface area of primary particles $S_w$ (cm$^2$/g) [a] | Surface shape factor of primary particles $\alpha_s$ [b] |
|---|---|---|---|---|---|---|---|
| Griseofulvin [c] | 1.44 | 8.7 | 6.5 | 3.6 | 1.6 | 21 500 | 5.1 |
| Oxazepam | 1.48 [d] | 22 [e] | 15 [f] | 8.2 [f] | 2.0 [f] | 24 500 | 12.6 |

[a] Measured by permeametry (Blaine, Seger Tonindustrie, F.R.G.).

[b] According to Heywood (1954).

[c] The griseofulvin quality used was characterized by Nyström et al. (1985) and Nyström and Westerberg (1986).

[d] Measured with an air comparison pycnometer (Beckman, mod. 930, U.S.A.).

[e] Determined by spectrophotometry at 238 nm (KabiVitrum AB, Sweden).

[f] Measured with a Coulter Counter, mod. TAII (U.K.) (capillary diameter 100 $\mu$m).

TABLE 2

*Primary characteristics of carrier materials*

| Carrier | Density $\rho_s$ (g/cm$^3$) [a] | Harmonic mean diameter by weight $d_h$ ($\mu$m) | Surface to volume shape factor $\alpha_{sv}$ [b] | External specific surface area $S_w$ (cm$^2$/g) [c] |
|---|---|---|---|---|
| Lactose | 1.58 | 244 | 8 | 208 |
| Mannitol | 1.46 | 276 | 11 | 273 |

[a] Measured with an air comparison pycnometer (Beckman, mod. 930, U.S.A.).
[b] Estimated by microscopy, according to Heywood (1954).
[c] Calculated as described earlier (Westerberg et al., 1986).

Wyeth, F.R.G.), two fine particulate and sparingly soluble drugs, were used. In order to enhance the formation of ordered mixtures, the oxazepam was milled in a pin disc mill (Alpine, 63C, F.R.G.).

As a result of their cohesiveness, the two adhering materials tend to be strongly agglomerated. Agglomerates in the sieve fraction 500–710 $\mu$m, were used for all experiments. Primary characteristics of the two adhering materials are presented in Table 1.

*Carrier materials.* Lactose (anhydrous, De Melkindustrie Veghel, the Netherlands) and mannitol (granulate, Merck, F.R.G.) were used. The two materials are highly soluble in water and have irregular particle shapes with relatively rough surface textures.

The two carrier materials were fractionated by sieving (Fritsch Analyzette, F.R.G.) and the sieve fractions 250–450 $\mu$m were used. Primary characteristics of the two carrier materials are presented in Table 2.

*Tablet excipients*

*Binder.* Microcrystalline cellulose (Avicel PH 101, FMC, PA, U.S.A.) was used.

*Disintegrant.* Ac-Di-Sol (FMC, PA, U.S.A.) was used. It is a modified cellulose gum that strongly swells in water.

*Lubricant.* Magnesium stearate (crystalline, Kebo Grave, Sweden) was used in the form of a 1% ethanol suspension, that was applied externally on the die walls and the punch tips prior to each compaction.

*Methods*

*Preparation of ordered mixtures*

*Weight proportions.* In order to estimate the degree of surface coverage, a so called surface area ratio, $R_s$, has been used (Nyström et al., 1982). A surface area ratio of unity theoretically represents a system where all of the carrier surface area is covered by drug particles. The phenomenon of "oversaturation" (Malmqvist, 1984) is normally expected for surface area ratios exceeding unity. The surface area ratios tested were, for the griseofulvin mixtures 0.08, 0.50 and 1.0, and for the oxazepam mixtures 0.08, 0.50, 0.57 and 1.5.

*Mixing.* Mixing was performed in a Turbula mixer (2 litres, W.A. Bachofen, Switzerland), at a speed of 90 rpm. The size of the mixing jar was chosen to give a fill volume of approximately 50%. The standard mixing time was chosen to be 3000 min (Nyström and Westerberg, 1986), although 4000 min was used for one oxazepam system (Tables 7 and 8). The following respective amounts of griseofulvin and lactose were mixed: 0.153 g and 50.0 g ($R_s = 0.08$), 0.949 g and 50.0 g ($R_s = 0.50$), and 1.863 g and 50.0 g ($R_s = 1.0$). The respective amounts of oxazepam and mannitol were: 0.567 g and 135.0 g ($R_s = 0.08$), 3.990 g and 150.0 g ($R_s = 0.50$); 3.633 g and 150.0 g ($R_s = 0.57$), and 3.000 g and 50.0 g ($R_s = 1.5$). To evaluate the effect of mixing time on deagglomeration, surface coverage, and consequently on dissolution rate, the mixing time for some mixtures was varied between 750 and 6000 min. To test if

ordered mixtures were formed, the mixtures were characterized by a sieve classification method (Malmqvist and Nyström, 1984b) (Tables 3 and 4). In this study, 2 g samples were assayed according to this earlier described technique.

*Admixing of tablet excipients*

Here, the ordered mixtures obtained after standard mixing time (3000 or 4000 min) were used for the further evaluation of tabletting behaviour. These ordered mixtures, the binder (Avicel PH 101) and the disintegrant (Ac-Di-Sol) were dry mixed in the Turbula mixer for 30 min at a speed of 90 rpm. The proportions of Avicel and Ac-Di-Sol were chosen to be 5 and 2 w/w% respectively.

*Compaction*

The tablets were made through direct compression in an instrumented excenter press (mod. EK 0, Korsch, F.R.G.) at 100 and 200 MPa, respectively. The diameters of the griseofulvin compacts were 1.13 cm ($R_s = 0.08$), 0.90 cm ($R_s = 0.50$) and 0.60 cm ($R_s = 1.0$). For the oxazepam compacts the diameter was 1.13 cm. The lubricant, magnesium stearate in a 1% ethanol suspension, was applied externally on the die walls and the tips of the punches prior to each compaction. Before the evaluation of the tablets, they were stored for at least 48 h at 45% RH and at ambient temperature.

*Evaluation of tablets*

*Tablet weight.* The tablets were weighed on analytical balances (Sartorius 2442 and Sartorius 1602 MP, F.R.G.).

*Tablet strength.* The crushing strengths and the radial tensile strengths (Fell and Newton, 1970) derived from these were determined (Heberlein, mod. 2E/205, Switzerland and Erweka TBH 28, F.R.G.).

*Tablet thickness.* The tablet thicknesses were measured with micrometer calipers (Luna 7321, Sweden and Mauser, F.R.G.).

The physical characteristics of the tablets are presented in Tables 5 and 6.

*Dissolution studies*

*Dissolution test.* The dissolution test was designed according to the USP XXI, paddle method. The measurements were performed at a rotational speed of 100 rpm at a constant temperature of 22° C. Each of the ordered mixtures, the tablets made from these mixtures, and pure agglomerates were tested. The dissolution media consisted of 0.9 w/w% solution of sodium chloride in distilled water. To ensure adequate wetting conditions, 0.01 w/w% of Tween 80 was added to the dissolution media (Nyström and Westerberg, 1986). To obtained near-sink conditions during the dissolution test, amounts of griseofulvin and oxazepam corresponding to approximately 10% of their solubilities were added to the dissolution media. In this study 0.7 mg of griseofulvin agglomerates and 2.0 mg of oxazepam agglomerates were added to 1 litre dissolution medium. Amounts of ordered mixtures corresponding to these respective values were used. Samples from the ordered mixtures were obtained by scooping.

The drug contents of the tablets were chosen to be 0.7 mg ($R_s = 0.08$) and 3.5 mg ($R_s = 0.50$ and 1.0) of griseofulvin, and 2.0 mg ($R_s = 0.08$) and 10.0 mg ($R_s = 0.57$ and 1.5) of oxazepam. These amounts gave tablet dimensions that were practical to handle. Since the calculation of dissolution rate data was performed only until 30% of the charged amounts was dissolved, also these experiments were considered to have been conducted under near-sink conditions.

*Calculation of dissolution rate constants*

In order to evaluate the capacity of the tested systems regarding the dissolution rate of drug molecules, a simplified quantification of the experiments was performed. The values so obtained were compared with calculated values of the theoretical maximum dissolution rates.

*Experimental dissolution rate $K_E$.* The dissolution rate is normally defined by a simple differential equation:

$$\frac{dw}{dt} = \frac{D}{h} \cdot S_c \cdot (C_s - C_t) \qquad (1)$$

where $dw/dt$ is the rate of dissolution, $D$ and $S_c$ are the respective diffusion coefficient and surface area of the dissolving material, $h$ is the thickness of the diffusion layer, $C_s$ is the equilibrium solu-

bility of the dissolving material, and $C_t$ is the concentration in the bulk solution at time $t$.

The dissolution will follow a zero order kinetic, only if true sink conditions are maintained, and if the drug surface area is constant during dissolution. In all experiments, the dissolution rate ($K_E$) was calculated for the dissolution of 30% of the amounts of drug tested. Although, this procedure does not correspond to a true zero order dissolution kinetic (producing a straight line dissolution profile), it was believed to be adequate for a relative comparison with data obtained under similar conditions. The amount dissolved ($C_t$) in no calculation exceeded 14% of the drug solubility ($C_s$), and the decrease in surface area ($S_c$) was subsequently limited to 30% raised to 2/3 (Hixson and Crowell, 1931).

*Theoretical maximum dissolution rate $K_M$.* The maximum rate is here defined as the dissolution rate from well-dispersed suspensions of drug molecules. For such suspensions the surface specific dissolution rates ($G$), in $\mu g\ min^{-1}\ cm^{-2}$, were determined by a Coulter Counter technique (Nyström et al, 1985a). This technique is capable of monitoring both changes in dissolved weight and remaining surface area of the drug, as a function of time. The $G$-values were calculated for the initial dissolution according to a similar procedure as the one described above for $K_E$, except that the dissolving surface area ($S_c$) was directly monitored and used in the calculation. The maximum dissolution rate ($K_M$) then was calculated from knowledge of the external specific surface area of primary particles of the two drug materials,

$$K_M = G \cdot S_p \qquad (2)$$

where $S_p$ is the surface area in $cm^2$ of the amount of drug tested for dissolution in each experiment.

It should be noted, that the term maximum rate refers to a suspension of primary particles of the tested drugs. This is not identical to the term intrinsic dissolution rate (e.g. Nicklasson et al., 1981) referring to a pure mass transport of molecules from solid to dissolved state. However, it has been shown that for fine particulate materials, such as those used in this study, the diffusional transport is strongly reduced as compared to what is obtained for coarser particulate systems (Nyström et al., 1985a; Niebergall et al., 1963). For this reason, the effect of agitation intensity seems to be much lower than is normally expected (Nyström et al., 1985b; Nyström and Westerberg, 1986).

*Analytical procedure.* A semiautomatic sampling and analysis system was used. A pump transferred liquid from the dissolution vessels to the flow cells in a spectrophotometer (Beckman, mod. 35, U.S.A. and Zeiss PM 6, F.R.G.) where the UV absorbances were measured at 295 nm (griseofulvin) and 238 nm (oxazepam). The samples were first filtered through a filter tip of glass wool (griseofulvin) or through a membrane filter, pore diameter 0.6 $\mu$m (Nucleopore, CA, U.S.A.) (oxazepam) in order to obtain samples free from particles. At the beginning of each sampling period, compensation was made for the time it took for the solutions to move from the dissolution vessels, by the pump, and into the flow cells. This time was subtracted from the time of the first absorbance measurement. Presented results are mean values of two determinations (Figs. 1–4 and Tables 7 and 8).

## Results and Discussion

*Sieve classification test*

The distribution of griseofulvin and oxazepam in the ordered mixtures are summarized in Tables 3 and 4 respectively. It should be pointed out that the theoretical percentage values were calculated separately for each individual mixing system. The differences obtained reflect the sampling error involved, when analyzing a small sample size (2 g).

The results in Tables 3 and 4 indicate that both combinations of binary mixtures prepared, resulted in ordered or near-ordered mixtures. No large agglomerates ($> 500\ \mu m$) were detected. The drug particles were distributed on the carrier materials in approximate relation to the surface area properties in each sieve fraction. For one of the griseofulvin/lactose mixtures, however, a relatively high amount was found in the finest sieve fraction, as reported earlier (Westerberg et al.,

TABLE 3

*Distribution of griseofulvin in ordered mixtures with lactose* [a]

| Sieve fraction ($\mu$m) | Surface area ratio = 0.08 [b,c] | | Surface area ratio = 0.50 [d] | | Surface area ratio = 0.50 [c] | | Surface area ratio = 1.0 [e] | |
|---|---|---|---|---|---|---|---|---|
| | $T$ (%) | $E$ (%) | $T$ (%) | $E$ (%) | $T$ (%) | $E$ (%) | $T$ (%) | $E$ (%) |
| < 180 | 2.6 | 21.7 | 0.5 | 0.6 | 0.4 | 0.6 | 0.4 | 0.4 |
| 180–360 | 79.1 | 58.9 | 69.6 | 62.2 | 79.1 | 75.4 | 81.6 | 79.5 |
| 360–500 | 18.2 | 19.4 | 30.3 | 37.0 | 20.4 | 23.7 | 18.0 | 19.8 |
| > 500 | 0.1 | 0.0 | 0.0 | 0.2 | 0.0 | 0.3 | 0.0 | 0.3 |

$E$, amount of griseofulvin in sieve fraction as determined by experiment. $T$, theoretical value, corresponding to the external surface area fraction of carrier particles in the sieve fraction.

[a] Determined according to Malmqvist and Nyström (1984b).

[b] Values taken from Nyström and Westerberg (1986).

[c] Mixing time 3000 min.

[d] Mixing time 750 min.

[e] Mixing time 5000 min.

1986). This was probably due to loosely adhering griseofulvin particles.

*Dissolution studies on ordered mixtures*

The significance of different surface area ratios (mixing time 3000 min) for the dissolution rate is indicated in Figs. 1 and 2, where the amounts dissolved against time for ordered mixtures of griseofulvin and oxazepam together with agglomerates of the respective drugs are presented. Figs. 1 and 2 also illustrate the influence of mixing time on the dissolution rate for ordered mixtures of griseofulvin ($R_s = 0.50$ and 1.0) and oxazepam ($R_s = 0.50$) produced during 3 different mixing times. See Tables 7 and 8 for the theoretical maximum dissolution rates and the experimental dissolution rates, when 30% of the respective ordered mixtures and the agglomerates were dissolved. As a measure of the dissolution capacity of the tested systems, the ratios of the experimental and the maximum rates were calculated as percentage values. These values are hereafter used in the discussion of the different experiments.

For the lowest surface area ratio tested, both drugs showed extremely high dissolution rates. A comparison with the maximum rates (Tables 7

TABLE 4

*Distribution of oxazepam in ordered mixtures with mannitol* [a]

| Sieve fraction ($\mu$m) | Surface area ratio = 0.08 [b] | | Surface area ratio = 0.50 [c] | | Surface area ratio = 0.57 [b] | | Surface area ratio = 1.5 [d] | |
|---|---|---|---|---|---|---|---|---|
| | $T$ (%) | $E$ (%) | $T$ (%) | $E$ (%) | $T$ (%) | $E$ (%) | $T$ (%) | $E$ (%) |
| < 180 | 0.3 | 0.3 | 0.5 | 1.2 | 0.4 | 0.4 | 0.5 | 1.2 |
| 180–360 | 40.8 | 50.9 | 54.0 | 42.5 | 37.6 | 47.6 | 34.2 | 47.2 |
| 360–500 | 54.7 | 47.0 | 42.3 | 51.4 | 53.7 | 47.2 | 59.7 | 48.6 |
| 500–710 | 3.9 | 1.8 | 3.2 | 4.9 | 8.2 | 4.8 | 5.1 | 2.8 |
| > 710 | 0.3 | 0.0 | 0.0 | 0.0 | 0.2 | 0.0 | 0.4 | 0.2 |

$E$, amount of oxazepam in sieve fraction as determined by experiment. $T$, theoretical value, corresponding to the external surface area fraction of carrier particles in the sieve fraction.

[a] Determined according to Malmqvist and Nyström (1984b).

[b] Mixing time 3000 min.

[c] Mixing time 750 min.

[d] Mixing time 4000 min.

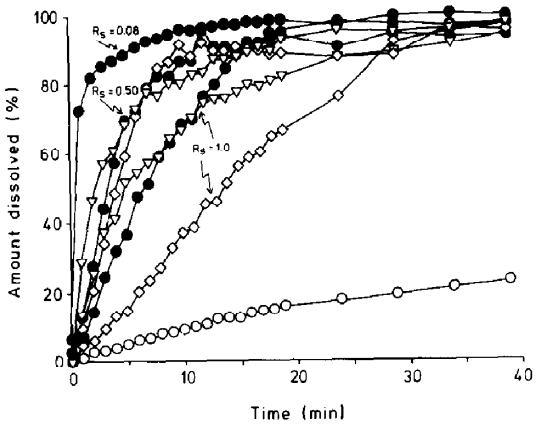


Fig. 1. Effect of surface area ratio ($R_s$) and mixing time (mt) on the dissolution rate of griseofulvin in ordered mixtures with lactose and as agglomerates. ▽, mt 750 min ($R_s$: 0.50 and 1.0); ●, mt 3000 min ($R_s$: 0.08, 0.50 and 1.0); ◇, mt 5000 min ($R_s$: 1.0) and 6000 min ($R_s$: 0.50); ○, agglomerates.

and 8) shows that these mixtures release the drug particles instantaneously. This also indicates that the dissolution rate is determined by the interfacial surface area between discrete drug particles and dissolution media, i.e. the degree of fineness of the tested compounds.

An increased addition of drug to the carrier materials substantially lowered the dissolution rate. For the intermediate surface area ratio (griseofulvin: 0.50, and oxazepam: 0.57) the dissolution rates for the mixtures prepared during 3000 min were 69 and 18% of the possible maximum rates. When the surface area ratio was increased to unity or above, the dissolution rate was further reduced.

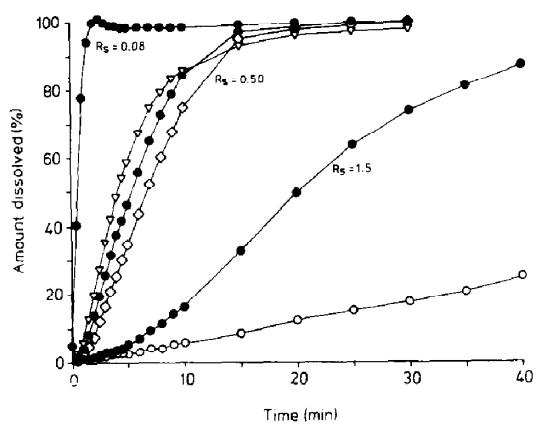


Fig. 2. Effect of surface area ratio ($R_s$) and mixing time (mt) on the dissolution rate of oxazepam in ordered mixtures with mannitol and as agglomerates. ▽, mt 750 min ($R_s$: 0.50); ●, mt 3000 min ($R_s$: 0.08 and 0.50); ●, mt 4000 min ($R_s$: 1.5); ◇, mt 6000 min ($R_s$: 0.50); ○, agglomerates.

The obtained effect of the amount of drug to carrier ratio could either be explained by an 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 order to investigate this further, also the mixing time was varied for some of the ordered mixtures of higher surface area ratios.

The results show that the dissolution rates decreased with mixing time. The highest dissolution rates were obtained for the mixtures that were mixed for 750 min ($R_s = 0.50$ and 1.0 for griseofulvin, and $R_s = 0.50$ for oxazepam). Here, the dissolution rates amounted to 102% and 63% (griseofulvin) and 30% (oxazepam). Mixing for 3000 and 6000 min gave values of 69% and 59% (griseofulvin) and 24% and 18% (oxazepam), respectively. A plausible explanation to these results is, that the primary drug particles formed a "film" around the carrier particles. The longer the mixing time, the more uniform and complete the surface coverage of the carrier particles became. In such a system the dissolution of the carrier and consequently the release of discrete primary drug particles will be delayed. A carrier particle that is almost completely coated with hydrophobic drug particles will probably initially dissolve with a rate governed by the penetration rate of dissolution media through the layer of adhering drug particles.

*Dissolution studies on tablets*

The effect of compaction on the dissolution rate for ordered mixtures are presented in Figs. 3 and 4. Here mixtures with varying surface area ratios, regarding admixed drug content, obtained after standard mixing time (3000 and 4000 min) are compared with the corresponding tablets, compressed at 100 and 200 MPa. In Tables 5 and 6 important tablet characteristics are summarized, whereas in Tables 7 and 8, the experimentally obtained dissolution rates are compared with cor-

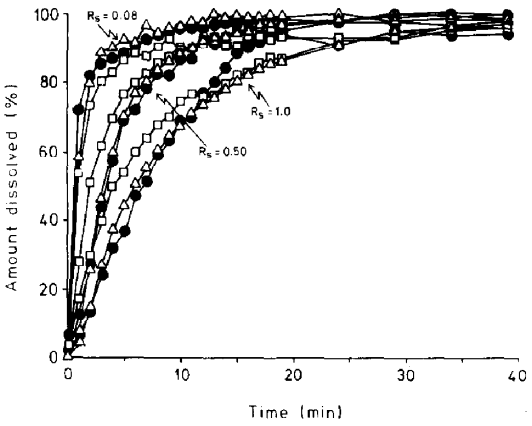


Fig. 3. Effect of surface area ratio ($R_s$: 0.08, 0.50 and 1.0) and compaction (upper punch pressure, UPP) on the dissolution rate of griseofulvin in ordered mixtures with lactose (mt 3000 min). ●, ordered mixture; □, UPP: 100 MPa; △, UPP: 200 MPa.

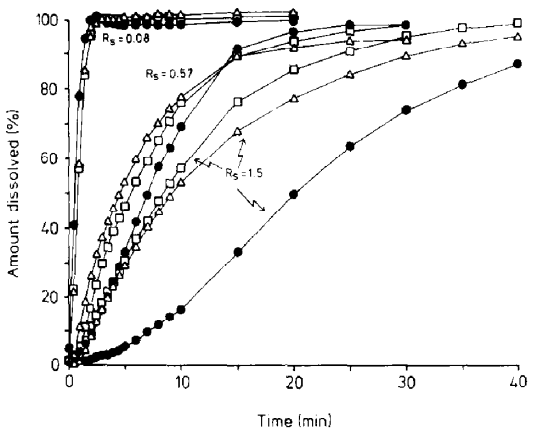


Fig. 4. Effect of surface area ratio ($R_s$: 0.08, 0.57 and 1.5) and compaction (upper punch pressure, UPP) on the dissolution rate of oxazepam in ordered mixtures with mannitol (mt 3000 min). ●, ordered mixture; □, UPP: 100 MPa; △, UPP: 200 MPa.

responding theoretical, maximal dissolution rates. The ratios between these pairs of data are calculated as percentage values.

Results in Tables 5 and 6, demonstrate that the chosen compaction loads, 100 and 200 MPa, gave tablets of sufficient mechanical strength. For the highest drug content, corresponding to $R_s = 1.0$ for griseofulvin and 1.5 for oxazepam both the 100 and 200 MPa tablets showed higher dissolution rates than the ordered mixtures alone. The increases in dissolution rates due to compaction may have been attributed to a breakage of the carrier particles on one hand, and the possible "film" of primary particles around these former on the other. As a result of both, the total external surface area of carrier material exposed to the dissolution media, would have been increased, subsequently resulting in a faster release of descrete drug particles to the dissolution media (Westerberg et al., 1986). The tablets made from mixtures with intermediate surface area ratios (0.50 and 0.57), in all cases gave higher dissolution rates than the ordered mixture alone, especially for 100 MPa tablets of griseofulvin.

All the tablets made from the mixtures with low surface area ratio (0.08), resulted in dissolu-

TABLE 5

*Characteristics of griseofulvin tablets* [a]

| Amount of griseofulvin (mg) | Surface area ratio $R_s$ | Maximum upper punch pressure $UPP_{max}$ (MPa) [b] | Crushing strength $P_x$ (kp) | Radial tensile strength $\sigma_x$ (MPa) | Tablet diameter $d$ (cm) | Tablet weight $w$ (mg) | Tablet thickness $t$ (cm) |
|---|---|---|---|---|---|---|---|
| 0.7 | 0.08 | 98 | 3.0 | 0.83 | 1.13 | 245 | 0.197 |
| 0.7 | 0.08 | 200 | 7.6 | 2.31 | 1.13 | 245 | 0.180 |
| 3.5 | 0.50 | 102 | 5.4 | 1.24 | 0.90 | 196 | 0.241 |
| 3.5 | 0.50 | 199 | 9.6 | 2.38 | 0.90 | 197 | 0.223 |
| 3.5 | 1.0 | 98 | 3.2 | 0.62 | 0.60 | 100 | 0.282 |
| 3.5 | 1.0 | 200 | 7.0 | 1.47 | 0.60 | 100 | 0.261 |

[a] Mean values of 5 determinations.

[b] $UPP_{max}$ variations allowed: 100 MPa ± 3 MPa and 200 MPa ± 5 MPa.

TABLE 6

*Characteristics of oxazepam tablets* [a,b]

| Amount of oxazepam (mg) | Surface area ratio $R_s$ | Maximum upper punch pressure $UPP_{max}$ (MPa) [c] | Crushing strength $P_x$ (kp) | Radial tensile strength $\sigma_x$ (MPa) | Tablet weight $w$ (mg) | Tablet thickness $t$ (cm) |
|---|---|---|---|---|---|---|
| 2.0 | 0.08 | 99 | 7.3 | 0.91 | 514 | 0.441 |
| 2.0 | 0.08 | 200 | 16.4 | 2.23 | 516 | 0.404 |
| 10.0 | 0.57 | 98 | 5.1 | 0.63 | 503 | 0.442 |
| 10.0 | 0.57 | 203 | 14.1 | 1.56 | 504 | 0.496 |
| 10.0 | 1.5 | 99 | 3.1 | 1.03 | 190 | 0.165 |
| 10.0 | 1.5 | 204 | 7.2 | 2.63 | 191 | 0.151 |

[a] Mean values of 5 determinations.
[b] Tablet diameter: 1.13 cm
[c] $UPP_{max}$ variations allowed: 100 MPa ± 3 MPa and 200 MPa ± 5 MPa.

tion rates, that were very high and of the same order as those of the ordered mixtures alone.

The high experimental dissolution rates obtained, compared with the calculated maximum rates (values exceeding 100%) as presented in Tables 7 and 8, do probably reflect the problems involved in estimating slope values from profiles with almost instantaneous rise to the maximum. However, it could not be excluded that mixing and compaction of the drug compounds could change physicochemical properties is such a way that the intrinsic dissolution rate is enhanced.

## Conclusions

It has been shown earlier (Nyström and Westerberg, 1986) that the dry formation of ordered mixtures could substantially increase the dissolution rate for finely divided, sparingly soluble drugs

TABLE 7

*Dissolution rate data for griseofulvin preparations*

| Surface area ratio $R_s$ | Amount of griseofulvin (mg) | Mixing time $mt$ (min) | Compaction pressure $UPP_{max}$ (MPa) | Experimental dissolution rate $K_E$ (μg/min) | Maximum dissolution rate $K_M$ (μg/min) | Ratio of $K_E$ and $K_M$ (%) |
|---|---|---|---|---|---|---|
| 0.08 | 0.7 | 3000 | – | 156 | 98 | 159 |
| 0.08 | 0.7 | 3000 | 100 | 136 | 98 | 139 |
| 0.08 | 0.7 | 3000 | 200 | 136 | 98 | 139 |
| 0.50 | 0.7 | 750 | – | 100 | 98 | 102 |
| 0.50 | 0.7 | 3000 | – | 68 | 98 | 69 |
| 0.50 | 0.7 | 6000 | – | 58 | 98 | 59 |
| 0.50 | 3.5 | 3000 | 100 | 500 | 489 | 102 |
| 0.50 | 3.5 | 3000 | 200 | 339 | 489 | 69 |
| 1.0 | 0.7 | 750 | – | 62 | 98 | 63 |
| 1.0 | 0.7 | 3000 | – | 45 | 98 | 46 |
| 1.0 | 0.7 | 5000 | – | 22 | 98 | 23 |
| 1.0 | 3.5 | 3000 | 100 | 350 | 489 | 72 |
| 1.0 | 3.5 | 3000 | 200 | 244 | 489 | 50 |
| Griseofulvin agglomerates | 0.7 | – | – | 2.6 | 98 | 2.7 |

TABLE 8

*Dissolution rate data for oxazepam preparations*

| Surface area ratio $R_s$ | Amount of oxazepam (mg) | Mixing time *mt* (min) | Compaction pressure $UPP_{max}$ (MPa) | Experimental dissolution rate $K_E$ ($\mu$m/min) | Maximum dissolution rate $K_M$ ($\mu$g/min) | Ratio of $K_E$ and $K_M$ (%) |
|---|---|---|---|---|---|---|
| 0.08 | 2.0 | 3000 | – | 1718 | 744 | 231 |
| 0.08 | 2.0 | 3000 | 100 | 979 | 744 | 132 |
| 0.08 | 2.0 | 3000 | 200 | 974 | 744 | 131 |
| 0.50 | 2.0 | 750 | – | 226 | 744 | 30 |
| 0.50 | 2.0 | 3000 | – | 179 | 744 | 24 |
| 0.50 | 2.0 | 6000 | – | 135 | 744 | 18 |
| 0.57 | 2.0 | 3000 | – | 147 | 744 | 18 |
| 0.57 | 10.0 | 3000 | 100 | 1135 | 3720 | 31 |
| 0.57 | 10.0 | 3000 | 200 | 1310 | 3720 | 35 |
| 1.5 | 2.0 | 4000 | – | 44 | 744 | 5.9 |
| 1.5 | 10.0 | 4000 | 100 | 598 | 3720 | 16 |
| 1.5 | 10.0 | 4000 | 200 | 598 | 3720 | 16 |
| Oxazepam agglomerates | 2.0 | – | – | 14 | 744 | 1.9 |

compared to agglomerated forms of untreated compounds. It has also been shown that a prerequisite for such an improvement is, that the carrier material is highly soluble, thereby rapidly delivering the drug in the form of discrete primary particles (Westerberg et al., 1986). In this paper it has been shown that a fast dissolution of the carrier unit also requires that the surface coverage is kept relatively low. Although this could be obtained by an incomplete deagglomeration of the drug, such a procedure will not correspond to an optimum system, where the whole surface area of the primary drug particles instantaneously is exposed to the dissolution media. Therefore, the approach of utilizing ordered mixtures, here seems to be limited to formulations containing very potent drugs with a drug content normally not exceeding 2–5 mg per dose. However, different approaches to increase this level are under investigation at our laboratory. The paper also demonstrates, that initial penetration of liquid and subsequent disintegration of compacted ordered mixtures does not seem to impair the rate of drug release. With a proper choice of tablet excipients, it was possible to obtain dissolution rate profiles almost identical to those obtained for the drugs in the form of well-dispersed suspensions.

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