International Journal of Pharmaceutics, 28 (1986) 23–31
Elsevier

IJP 00928

Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from ordered mixtures

M. Westerberg, B. Jonsson * and C. Nyström **

KabiVitrum AB, S-112 87 Stockholm (Sweden)

(Received July 1st, 1985)
(Accepted August 22nd, 1985)

Key words: ordered mixture – dissolution rate – carrier particle – diffusional transport – micronized griseofulvin – surface area

Summary

Six different carrier materials (250–425 μm) were used to prepare ordered mixtures of micronized griseofulvin. These mixtures and pure griseofulvin (agglomerates 500–710 μm) were measured on dissolution rate at sink conditions, using a paddle method at two rotational speeds. Highly soluble carrier materials gave an extremely fast dissolution, probably due to the fact that the drug was delivered as free, well-dispersed primary particles, after rapid dissolution of the carrier particles. The surface area utilized for dissolution was shown to be close to the external surface area of the primary particles, as measured by permeametry. Practically insoluble carriers, gave a limited increase in dissolution rate as compared to the griseofulvin agglomerates. This was explained mainly by an increased influence of diffusional transport, and to some extent by a decrease in the surface area participating in dissolution. The use of a hydrophobic carrier, decreased the dissolution rate compared to griseofulvin agglomerates.

Introduction

In an earlier study (Nyström and Westerberg, 1985) the use of ordered mixtures, for improving the dissolution rate of a poorly soluble, fine particulate drug (griseofulvin) was investigated. The mixtures were obtained by a dry mixing process, using cubic crystalline sodium chloride as carrier material. The ordered mixtures gave a rapid dissolution, almost independent of agitation intensity and surfactant addition to the dissolution medium. This was in contrast to the dissolution of griseofulvin as a raw material, existing in agglomerated form, where the dissolution rate was lower and dependent upon the experimental conditions. It was believed that in the ordered mixture, individual drug particles were adhering to the carrier particles, and after a fast dissolution of sodium chloride the system could be regarded as a well-dispersed suspension of primary griseofulvin particles. The drug surface area taking part in dissolution was calculated and was found in agreement with the external surface area of the primary particles, as measured by permeametry. For the dissolution of griseofulvin agglomerates, the surfactant addition resulted in increased dissolution rate due to improved penetration of dissolution medium into the agglomerates followed by a partial disintegration, thereby increasing the surface area taking part in dissolution. The effect of increased

* *Present address*: Astra Läkemedel AB, Södertälje, Sweden.
** *Present address*: Department of Galenical Pharmacy, Biomedical Center, University of Uppsala, Box 580, S-751 23 Uppsala, Sweden
Correspondence: M. Westerberg, KabiVitrum AB, S-112 87 Stockholm, Sweden.

0378-5173/86/$03.50 © 1986 Elsevier Science Publishers B.V. (Biomedical Division)

agitation was explained mainly as an improved break up of the dissolving agglomerates.

In the previous study (Nyström and Westerberg, 1985) it was emphasized that the effective improvement obtained by ordered mixtures, could be due to the soluble nature of the carrier particles tested. Drug particles adhering to insoluble carriers would probably not be exposed to the dissolution medium as suspended primary particles, but be present in a smaller number of locations, each containing a higher quantity of drug (so called ordered units). The importance of the hydrodynamics would probably increase in such systems. It can therefore not be excluded that for poorly soluble carrier materials, both particle properties and experimental conditions could affect the dissolution rate. The objective of the present investigation was to prepare ordered mixtures using carrier materials of different solubility and surface texture, and to study the effect on dissolution rate.

Materials and Methods

Materials

Adhering material. As a model substance representing a fine particulate and sparingly soluble drug, griseofulvin (micronized, Glaxo, U.K.) was used as supplied. Due to its cohesive nature, the material is strongly agglomerated. Agglomerates in the sieve fraction 500–710 μm was used.

Carrier material-1. Sodium chloride (cubic, crystalline, puriss, Kebo Grave, Sweden) represents a highly water-soluble material where the particles have a smooth surface texture.

Carrier material-2. Lactose (anhydrous, De Melkindustrie Veghel, The Netherlands) is highly soluble in water, with an irregular particle shape and rough surface texture.

Carrier material-3. Tricalciumdicitrate (puriss, Kebo Grave, Sweden) was slugged in a tablet press (Kilian type RL, Köln, F.R.G.). The slugs were milled in a granulator (Erweka type FGS, F.R.G.) and then fractionated by sieving. The material represents a substance with an intermediate solubility in water. The particle shape is irregular and the surface texture is rough.

Carrier material-4. Emcompress (dicalciumphosphatedihydrate, E. Mendell, U.S.A.). The material was chosen due to its low water solubility. The particles have a rough, granular-like structure.

Carrier material-5. Glass beads (microflint glass, Kebo Grave, Sweden) represents a water insoluble material where the particles have a very smooth and regular surface texture.

Carrier material-6. Paraffin (granules, m.p. 58–60°C, Kebo Grave, Sweden) was milled in a granulator (Erweka type FGS, F.R.G.) and then fractionated by sieving. The material is insoluble in water and was chosen due to its hydrophobic nature. The particle shape is irregular but the surface texture is fairly smooth.

All the carrier materials were fractionated by sieving (Fritsch analyzette, F.R.G.) and the fraction between 250 and 425 μm was used. Photographs of the materials (Fig. 1) were taken using a scanning electron microscope (JSM U-3, JEOL, Japan).

In the dissolution medium, Tween 80 (polysorbate 80, Kebo Grave, Sweden) and sodium chloride (crystalline, pro analysi, Kebo Grave, Sweden) were used.

Primary characterization — griseofulvin

The griseofulvin quality used has been characterized in earlier studies (Nyström and Westerberg, 1985; Nyström et al., 1985) giving the following data also used in this study.

Density: 1.44 g/cm^3
Water solubility at room temperature: 8.7 mg/l
Surface specific dissolution rate: 6.5 $\mu g \cdot min^{-1} \cdot cm^{-2}$
Geometric mean volume diameter by weight: 3.6 μm
Geometric standard deviation: 1.6
External specific surface area of primary particles: 21,500 cm^2/g
Surface shape factor of primary particles: 5.1
External specific surface area of agglomerates: 180 cm^2/g
Surface shape factor of agglomerates: π

Primary characterization — carrier materials

Density. The density was measured using an air

comparison pycnometer (Beckman, mod.930, U.S.A.). Presented results are mean values of 3 determinations.

External weight specific surface area of carrier particles. The specific surface area (S_w) was calculated in cm^2/g as (Allen, 1981):

$$S_w = \frac{\alpha_{SV} \cdot 10}{d_h \cdot P_s} \quad (1)$$

where α_{SV} is a surface-to-volume shape factor (Heywood, 1954) estimated by microscopy, d_h is the harmonic mean diameter by weight in μm which was calculated from sieve data and P_s is the density in g/cm^3. The primary characteristics of the carrier materials are summarized in Table 1.

Preparation of ordered mixtures

Weight proportions. In order to avoid oversaturation of drug substance on the carrier particles (Malmqvist, 1984) the so-called surface area ratio (Nyström et al., 1982) should not exceed unity. In this study 0.153 g griseofulvin and 50.0 g carrier material were used for all mixtures corresponding to surface area ratios between 0.061 and 0.299 for the six carrier materials tested (Table 2).

Mixing. Before mixing, the materials were stored at 45% RH for not less than 48 h. The mixing was performed in a Turbula mixer (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%. In order to ensure total deagglomeration, the mixing was performed for 3000–5000 min (Malmqvist and Nyström, 1984a; Nyström and Westerberg, 1985) (Table 2). To test that no agglomerates were present and if ordered mixtures had been formed, the mixtures were characterized by a sieve classification method (Malmqvist and Nyström, 1984b). Photographs of the ordered mixtures were taken using a scanning electron microscope (JSM U-3, JEOL, Japan).

Dissolution studies

The dissolution test was performed according to the USP XX, paddle method. Two rotational speeds, 22 and 100 rpm, were tested and the temperature was kept constant to 23°C. Both ordered mixtures and pure griseofulvin in the form of agglomerate were tested.

As dissolution medium 0.9 w/w % solution of sodium chloride in distilled water was used. In order to ensure optimal wetting conditions, 0.01 w/w % of Tween 80 was added to the dissolution medium (Nyström and Westerberg, 1985).

In order to obtain sink condition during the dissolution test, the quantity of drug added to the dissolution medium was chosen to be approximately 10% of the drug solubility. In this study 0.229 g of the ordered mixtures were added to 1 litre dissolution medium, which corresponds to 0.7 mg of griseofulvin. From the ordered mixtures samples were obtained by scooping.

Analytical procedure

A semi-automatic sampling and analysis system was used. A pump transferred liquid from the dissolution vessels to flow cells in a spectrophotometer (Beckman, mod.35, U.S.A.) where the UV absorbance was measured at 295 nm. The solution was first passed through a filter tip of glass wool in order to ensure samples, free from suspended drug particles. Presented results are mean values of two determinations.

Results and Discussion

Results from the sieve classification test of the ordered mixtures are presented in Table 3. Here, the percentages of griseofulvin revealed in each of four sieve fractions are compared with theoretical values, calculated as the external surface area fractions of the carrier tested (Malmqvist and Nyström, 1984b).

Additionally, scanning electron photomicrographs were taken of all mixtures. Only for the mixtures with glass beads it was possible to clearly visualize the adhering griseofulvin particles (Fig. 2). The results in Table 3 and Fig. 2, indicate that all carrier materials could be used to obtain ordered mixtures. In the sieve classification method, 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 lactose, however, a relatively high amount was found in

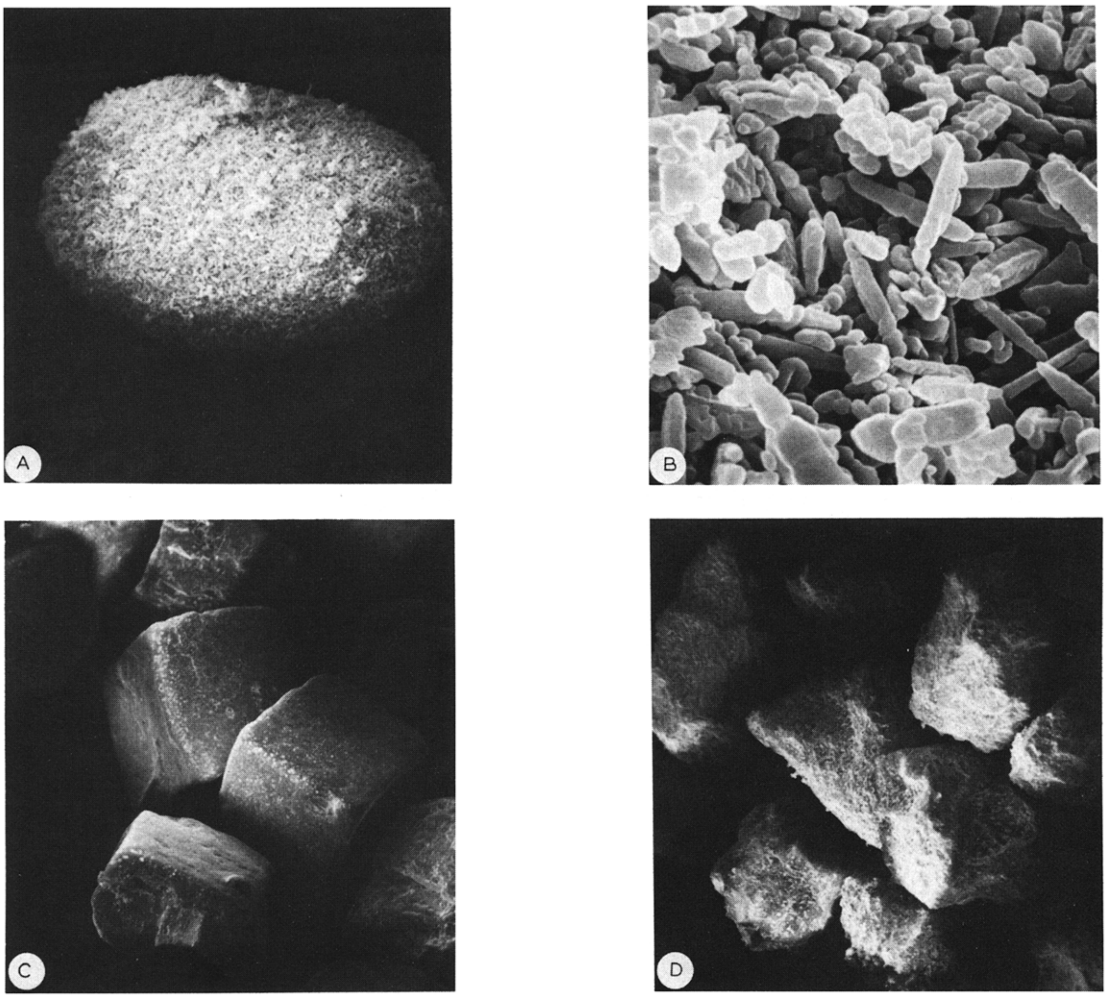

Fig. 1A–D.

TABLE 1

PRIMARY CHARACTERISTICS OF THE CARRIER MATERIALS

Carrier material	Density P_s (g/cm^3)	Harmonic mean diameter d_h (μm)	Surface-to-volume shape factor α_{SV}	Specific surface [a] area S_w (cm^2/g)	Solubility [b] (g/l)
Sodium chloride	2.17	322	7	100	357
Lactose	1.58	244	8	208	200
Tricalciumdicitrate	2.02	287	8	138	8.5
Emcompress	2.32	304	9	142	< 0.1
Glass beads	2.70	405	6	55	insoluble
Paraffin	0.93	398	10	270	insoluble

[a] Calculated from Eqn. 1.

[b] Water solubility at 20°C from Handbook of Chemistry and Physics, 53rd edn.

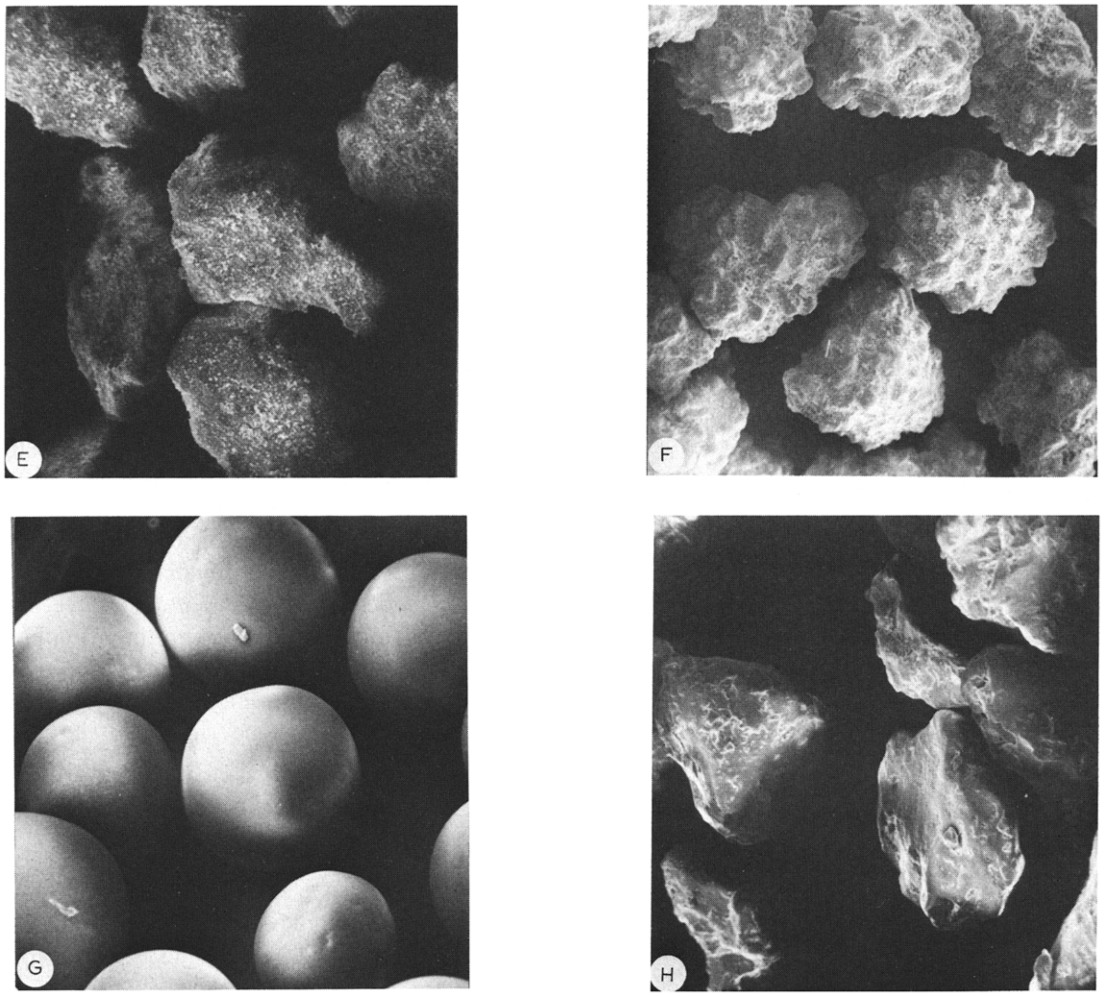

Fig. 1. Photomicrographs of materials: A, griseofulvin agglomerates; B, griseofulvin primary particles; C, sodium chloride; D, lactose; E, tricalciumdicitrate; F, Emcompress; G, glass beads; and H, paraffin.

TABLE 2

SPECIFICATIONS OF ORDERED MIXTURES OF GRISEOFULVIN

Carrier material	Mixing time (min)	Surface area ratio [a]
Sodium chloride	3000 [b]	0.164
Lactose	3000	0.079
Tricalciumdicitrate	3000	0.119
Emcompress	5000	0.116
Glass beads	5000	0.299
Paraffin	3000	0.061

[a] Calculated according to Nyström et al. (1982).
[b] 2000 min at 65 rpm and 1000 min at 90 rpm.

the finest sieve fraction, indicating the presence of loosely adhering particles or small agglomerates of griseofulvin. Also for tricalciumdicitrate a large amount was revealed in the smallest fraction, but since also a corresponding amount of carrier material was found here, it seems probable that the griseofulvin particles were adhering to the carrier material.

Data for the amount dissolved against time for both griseofulvin agglomerates and griseofulvin in the form of ordered mixtures are presented in Fig. 3 (100 rpm) and Fig. 4 (22 rpm). For both rotational speeds, a similar rank order between the

TABLE 3

DISTRIBUTION OF GRISEOFULVIN IN ORDERED MIXTURES [a]

Sieve fraction (μm)	Sodium chloride		Lactose		Tricalcium dicitrate		Emcompress		Glass beads	
	E (%)	T (%)	E (%)	T (%)	E (%)	T (%)	E (%)	T (%)	E (%)	T (%)
< 180	0.5	0.1	21.7	2.6	33.4	36.2	2.8	2.2	1.8	0.4
180–360	25.0	31.9	58.9	79.1	44.0	47.8	79.2	83.4	15.3	18.4
360–500	72.4	64.5	19.4	18.2	21.6	15.9	17.8	14.4	79.0	78.4
> 500	2.1	3.5	0.0	0.1	0.0	0.1	0.2	0.0	3.9	2.8

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

mixtures was obtained. The carriers possessing relatively high solubility in the dissolution medium (sodium chloride, lactose and tricalciumdicitrate) all gave extremely high dissolution rates, where most griseofulvin was dissolved already after 10 min. The effect of agitation intensity was minute. These results support earlier findings (Nyström and Westerberg, 1985) that after a rapid dissolution of the carrier particles, the griseofulvin particles probably are homogenously distributed throughout the medium and the system could be regarded as a well-dispersed suspension of primary particles. For such systems it has earlier been shown (Nyström et al., 1985) that the effect of agitation intensity was negligible, indicating that the dissolution process was not significantly diffusion controlled. The retarding dissolution rate obtained for tricalciumdicitrate mixtures at 22 rpm (Fig. 4), was possibly due to that the samples tested contained an erroneously low content of griseofulvin. Another explanation is that for this carrier material, with an intermediate solubility, some of the carrier particles did not dissolve instantanously, giving effects similar to the insoluble carriers (see below). The shape and surface texture of soluble carrier probably could effect the ordered mixing process, but are of no significant importance for the dissolution process.

For the two practically insoluble carrier materials, possessing hydrophilic surface properties (Emcompress and glass beads), the dissolution rate was lower than for the soluble carriers and influenced by the rotational speed (Figs. 3 and 4). The lower dissolution rate obtained, could for

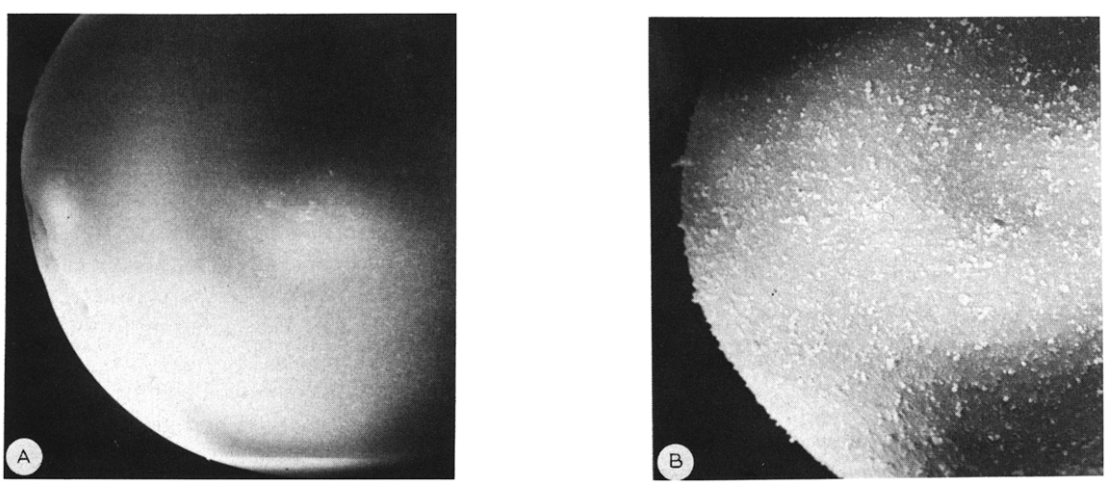

Fig. 2. Photomicrographs of glass beads: A, before and B, after mixing with griseofulvin.

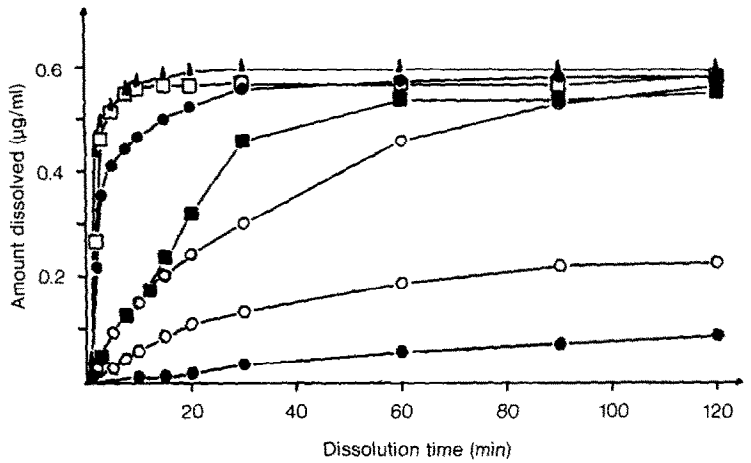

Fig. 3. Dissolution rate profiles for griseofulvin at 100 rpm, using a dissolution medium containing 0.01 w/w % Tween 80. Carrier material: ●, sodium chloride; ▲, lactose; □, tricalciumdicitrate; ○, Emcompress; ■, glass beads; ●, paraffin; ○, griseofulvin agglomerates.

these mixtures, partly be due to that drug particles are not rapidly exposed to the medium as primary particles, but remains adhering to the carrier particles. This might then prevent some of the surface area of the drug particles, faced against the carrier, from initially taking part in the dissolution. Since the drug particles probably do not exist as free particles during dissolution but are moved around in the medium attached to coarse carrier particles, also hydrodynamic differences ought to be considered. For the coarse carrier particles, a thicker stagnant diffusion layer may be developed, than for the small griseofulvin particles (e.g. Niebergall et al., 1963), resulting in a diffusional process of significant importance. The idea that the dissolution of griseofulvin from mixtures of the insoluble carriers, is substantially retarded by diffusion, is supported by the marked effect of agitation intensity. For the lower rotational speed, the dissolving materials were not randomly orientated in the medium, but preferably found at the bottom of the dissolution beaker. This could probably lead to

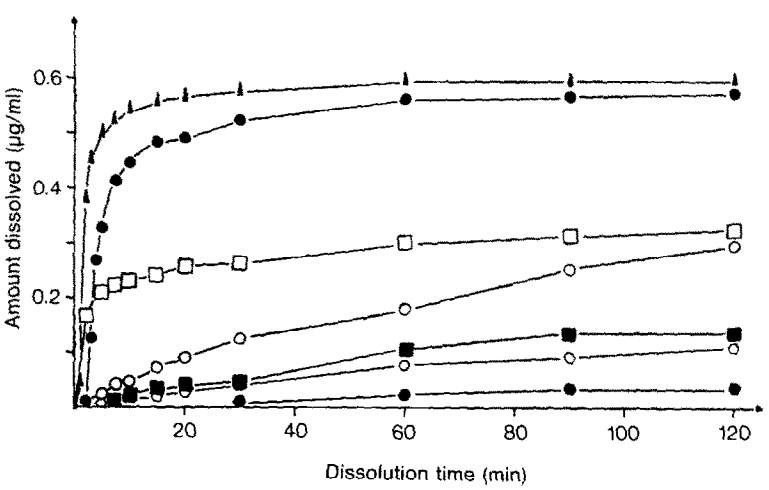

Fig. 4. Dissolution rate profiles for griseofulvin at 22 rpm, using a dissolution medium containing 0.01 w/w % Tween 80. Symbols as in Fig. 3.

further reduction in transfer rate, due to diffusion. The difference for the two rotational speeds could probably to some extent also be due to a separation of drug particles from the carrier, a phenomenon that would be facilitated at higher speeds. The similar results obtained for Emcompress and glass beads, indicate that the surface irregularity of the carrier particles, is not an important parameter for drug dissolution from ordered mixtures.

The only carrier material, causing a reduced dissolution rate, as compared to griseofulvin agglomerates, was paraffin (Fig. 3). This effect could be given several explanations. It was not possible to test by the sieve classification method, whether an ordered mixture was formed or not. Therefore griseofulvin agglomerates could have been present. The hydrophobic nature of the paraffin particles, could have caused an inadequate wetting of griseofulvin in these mixtures.

Conclusions

A prerequisite for fast dissolution from an ordered mixture, seems to be that the carrier particles dissolve rapidly, delivering a fine particulate suspension of drug particles. When the drug is coated on insoluble carriers, a limited improvement in dissolution rate is obtained. In order to evaluate if this effect is due to a decrease in contact surface area between drug and dissolution medium or due to a retarded transfer process by diffusion, the following procedure was utilized. For all mixtures tested, the initial contact surface area of griseofulvin taking part in dissolution, was calculated as described earlier (Nyström and Westerberg, 1985). This calculation is based upon the assumption that diffusion is not a rate-limiting step and subsequently the intrinsic dissolution rate for griseofulvin (6.5 $\mu m \cdot min^{-1} \cdot cm^{-2}$) as determined earlier (Nyström et al., 1985) was utilized for the calculation. Data for all mixtures are presented in Table 4. For the soluble carriers the contact surface area was between 9.4 and 33 cm^2. These values are of the same order of magnitude as the external surface area of primary particles for 0.7 mg griseofulvin, being approximately 16 cm^2, as calculated from the specific surface area (Table 2). The differences obtained for the three soluble carriers are probably of less significance, since the calculated values are extremely sensitive for small deviations in dissolved amounts during the steep, initial phase of dissolution (Figs. 3 and 4). The agreement with external surface area of the primary particles (Hoelgaard and Møller, 1973), supports the idea that diffusion is not a rate-limiting step for griseofulvin in free suspended form.

TABLE 4

CALCULATED SURFACE AREA OF 0.7 mg GRISEOFULVIN, INITIALLY TAKING PART IN DISSOLUTION [a]

Carrier material	Contact surface area at 100 rpm (cm^2)	Contact surface area at 22 rpm (cm^2)
Sodium chloride	17	10
Lactose	33	29
Tricalciumdicitrate	21	9.4
Emcompress	2.3	0.7
Glass beads	2.3	0.3
Paraffin	0.2	0.07

[a] Calculated according to Nyström and Westerberg (1985).

The calculated contact surface areas in mixtures using Emcompress and glass beads were for the higher rotational speed approximately 10%, and for the lower speed only 1–3% of the surface areas calculated for the soluble carriers. The attachment of drug particles to a carrier surface, is not likely to result in such dramatic decreases in surface area being in contact with a dissolution medium. Therefore it seems that the reduced dissolution rate is due to diffusional retardation. The use of intrinsic dissolution rate for the calculation of the surface area taking part in dissolution, seems then mainly to be applicable to systems where the drug is present as free primary particles.

The formulation of fine particulate, poorly soluble drugs into solid dosage forms, utilizing ordered mixtures, will probably be more effective regarding drug release, when soluble excipients are used.

The results in this study indicate that the dissolution rate in vitro is not only dependent upon the surface area of the drug in contact with the dissolution medium, but it is also of importance if the drug particles are in free suspended form or are attached to coarser solid units. In the latter

case, the thickness of a retarding, diffusional layer, will be governed by the large carrying unit. It could therefore be questioned how the improved dissolution profiles obtained in vitro, will be affected by an in vivo environment, where several possibilities for adhesion of drug particles exist, e.g. to the mucosa.

Acknowledgements

The authors are grateful to Glaxo, U.K. for supplying the griseofulvin samples used. We thank Dr. P. Kearny, Welsh School of Pharmacy, University of Wales, Institute of Science and Technology, for stimulating discussions. One of us (C.N.) also wishes to thank the Swedish Academy of Pharmaceutical Sciences for financial support.

References

Allen, T., Particle Size Measurement, 3rd edn., Chapman and Hall, London, 1981, p. 121.

Heywood, H., Particle shape coefficients. J. Imp. Coll. Chem. Eng. Soc., 8 (1954) 25–33.

Hoelgaard, A. and Møller, N., Studies on particle size problems. X. Evaluation of effective surface areas of micronized powders from dissolution rate measurements. Arch. Pharm. Chemi. Sci. Ed., 1 (1973) 1–13.

Malmqvist, K., Studies on the characterization of powders and powder mixtures. Ph. D. Thesis, Uppsala University, Uppsala, 1984.

Malmqvist, K. and Nyström, C., Studies on direct compression of tablets. IX. The effect of scaling-up on the preparation of ordered mixtures in double-cone mixers. Acta Pharm. Suec., 21 (1984a) 21–30.

Malmqvist, K. and Nyström, C., Studies on direct compression of tablets. VIII. A sieve classification method for the determination of agglomerates and distribution of fine particles in ordered mixing. Acta Pharm. Suec., 21 (1984b) 9–20.

Niebergall, P.J., Milosovich, G. and Goyan, J.E., Dissolution rate studies. II. Dissolution of particles under conditions of rapid agitation. J. Pharm. Sci., 52 (1963) 236–241.

Nyström, C., Mazur, J. and Sjögren, J., Studies on direct compression of tablets. II. The influence of the particle size of a dry binder on the mechanical strength of tablets. Int. J. Pharm., 10 (1982) 209–218.

Nyström, C., Mazur, J., Barnett, M.I. and Glazer, M., Physicochemical aspects of drug release. I. Dissolution rate measurements of sparingly soluble compounds with the Coulter Counter model TAII. J. Pharm. Pharmacol., 37 (1985) 217–221.

Nyström, C. and Westerberg, M., Physicochemical aspects of drug release. II. The use of ordered mixtures for improving the dissolution rate of low soluble compounds. J. Pharm. Pharmacol., submitted for publication.

Weast, R.C. (Ed.), Handbook of Chemistry and Physics, 53rd edn., The Chemical Rubber Co., Cleveland, OH, 1972–1973.