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Physicochemical aspects of drug release. XII. The effect of some carrier particle properties and lubricant admixture on drug dissolution from tableted ordered mixtures

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Summary

Four carrier materials with different degrees of fragmentation and different aqueous solubilities were used to prepare ordered mixtures of micronized oxazepam. The tablets were compressed and the influence of the addition of 0.2 and 1% w/w magnesium stearate, using different mixing times, on in vitro dissolution rates was studied. A suspension of oxazepam was used as a reference. The ejection force was used as a measure of friction during tableting. It was concluded that the negative effect of the lubricant on the dissolution properties can be counteracted by choosing carrier materials with both high aqueous solubility and a high degree of fragmentation. These results were further supported by testing a less hydrophobic lubricant (sodium stearyl fumarate) on a soluble nonfragmented carrier. Although the highest recommended surface area ratio, according to previous studies, was used, it was possible to obtain dissolution profiles from lubricated tablets almost identical to those obtained with a well-dispersed suspension by choosing a suitable carrier.

Introduction

Earlier studies (Nyström and Westerberg, 1986; Westerberg et al., 1986) have demonstrated the usefulness of ordered mixtures in improving the dissolution rate of finely particulate, poorly soluble drugs. The properties of the carrier material are also important (Westerberg et al., 1986). It was found that the more soluble the carrier, the faster the dissolution of the drug. When carrier materials with low solubility are used, the drug particles adhere to the coarse carrier particles and are less rapidly exposed to the dissolution medium as primary drug particles. A prerequisite for the fast dissolution of a drug seems to be more or less instantaneous dissolution of the carrier particles, thereby delivering the drug in the form of discrete primary particles.

It has been shown that the incorporation of ordered mixtures into tablets does not impair the dissolution of the system (Nilsson et al., 1988).

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The influence of lubricants was not investigated in this study. However, it is generally known that hydrophobic lubricants such as magnesium stearate can have a strong negative effect on the dissolution rate, disintegration time and strength of tablets.

The use of less hydrophobic lubricants, such as sodium stearyl fumarate, has been claimed not to have the disadvantages of magnesium stearate with respect to disintegration time and dissolution (Lindberg, 1972; Hölzer and Sjögren, 1979).

It has been reported that the negative effects of lubricants in tableting depend on the physical properties of the tablet excipients (Bolhuis et al., 1975; Hölzer and Sjögren, 1979). It has also been reported that materials which undergo fragmentation during compaction, thereby creating new contact points and an increased surface area of the material (Alderborn et al., 1985; Duberg and Nyström, 1986), are less sensitive to mixing with a hydrophobic lubricant such as magnesium stearate (De Boer et al., 1978).

The aim of this study was to evaluate the effects on drug dissolution rate when lubricants are incorporated in a tablet formulation based on ordered mixtures, using different carrier materials.

The carrier materials were also evaluated as to degree of fragmentation and aqueous solubility.

Materials and Methods

Components of ordered mixtures

Adhering material Oxazepam (micronized, Wyeth, Germany) was used as a model substance representing a fine particulate and sparingly soluble drug. In order to enhance the formation of ordered mixtures, the oxazepam was milled in a pin disc mill (Alpine, 63 C, Germany). The milled oxazepam was cohesive and therefore strongly agglomerated. Agglomerates in the sieve fraction 500–710 μm were used for all experiments.

Carrier materials Mannitol (granulate, Merck, Germany) represents a highly water-soluble material which fragments markedly during compaction. The particles have an irregular shape with a rough surface texture.

Sodium chloride (cubic, crystalline, puriss, Kebo Grave, Sweden) is a highly water-soluble material whose particles have a smooth surface texture. The degree of fragmentation during compaction is low (Alderborn et al., 1985).

Emcompress® (dicalcium phosphate dihydrate, E. Mendell, U.S.A.) represents a material with low water solubility and a high degree of fragmentation during compaction (Alderborn et al., 1985). The particles have a rough, granular-like structure.

Iron powder (Höganäs AB, Sweden) is insoluble in water and has a low degree of fragmentation during compaction (Nyström and Karehill, 1986). The particles have a smooth surface texture.

All the carrier materials were fractionated by sieving (Fritsch Analyzette, Germany) and the sieve fractions between 250 and 450 μm were used.

Tablet excipients

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

Disintegrant Croscarmellose sodium (Ac-Di-Sol®, FMC, PA, U.S.A.), a modified cellulose gum which swells strongly in water, was employed as disintegrant.

Lubricants Magnesium stearate (crystalline, Kebo Grave, Sweden) and sodium stearyl fumarate (PRUV®, Astra Pharmaceutical Production AB, Sweden) were used.

Primary characterization – carrier materials

Fragmentation The degree of fragmentation during compaction of the carrier materials was measured by a permeametry method (Alderborn et al., 1985) using an instrumented single-punch press (Korsch EK 0, Germany) and a Blaine apparatus (Seger Tonindustrie, Germany).

Primary characteristics of the four carrier materials are presented in Table 1.

Primary characterization — oxazepam

Density The density was measured as 1.47 g/cm^3 (mean value of three determinations) using an air comparison pycnometer (Beckman, model 930, U.S.A.).

Solubility The aqueous solubility at room temperature (23 $\pm$ 2 °C) was determined by spectro-

photometry at 238 nm (KabiVitrum AB, Sweden) as 22.1 mg/l.

Surface specific dissolution rate The dissolution rate was experimentally determined in an earlier study (Nilsson et al., 1988) as 15 μg/min per cm^2.

External surface area of primary particles The external surface area was determined by permeametry as 3.3 m^2/g (mean value of three determinations), using a Blaine apparatus (Seger Tonindustrie, Germany).

Preparation of ordered mixtures

Weight proportions The surface area ratio (R_s) was used to estimate the degree of surface coverage (Nyström et al., 1982). In order to obtain ordered mixtures of acceptable mechanical stability, the amount of drug substance should be limited to the maximum amount theoretically needed to obtain a monoparticulate layer covering the carrier particles. Surface area ratios exceeding unity are theoretically required. However, in order for the carrier particles to dissolve speedily, surface area ratios lower than 0.5 normally are used (Nilsson et al., 1988). The surface area ratios used in this study were 0.51 for the mannitol mixture, 0.41 for the sodium chloride mixture, 0.58 for the Emcompress mixture and 0.47 for the iron mixture.

Mixing The mixing was performed in a Turbula mixer (2 l, W.A. Bachhofen, Switzerland), at a speed of 90 rpm. The size of the mixing jar was chosen to give a fill volume of approx. 50%. In order to ensure total deagglomeration, the mixing was performed for 3000 min (Nyström and Westerberg, 1986).

Addition of tablet excipients

The ordered mixtures, the binder (Avicel PH 101; 5% w/w) and the disintegrant (Ac-Di-Sol; 2% w/w) were dry mixed in the Turbula mixer for 30 min at 90 rpm. The mixtures were then dry mixed with the lubricant. The amount of lubricant and the mixing time were varied. For the mannitol mixture, 0.2 and 1% w/w magnesium stearate were mixed in for 1, 10 and 100 min. The other mixtures were mixed with 1% w/w magnesium stearate for 10 min. The sodium chloride mixture was also mixed with 1% w/w sodium stearyl fumarate (PRUV) for 10 min. All mixing with lubricant was performed in the Turbula mixer at 90 rpm.

Compaction

Tablets were compressed at 200 MPa in an instrumented excenter press (model EK 0, Korsch, Germany). The diameter of the compact was 1.13 cm and the tablet weights were adjusted to include 2 mg oxazepam per tablet. For the mixtures without the addition of a lubricant, the punch faces and the die walls were prelubricated with a 1% w/w magnesium stearate suspension in ethanol. The tablets were stored for at least 48 h at 45% RH and at room temperature (23 ± 2°C) prior to evaluation.

TABLE 1

Primary characteristics of the carrier materials

Carrier material	Density [a] ρ_s (g/cm^3)	Harmonic mean [b] diameter d_H (μm)	Surface to volume [c] shape factor α_{sv} (–)	Specific surface [b] area S_w (cm^2/g)	Solubility [d] C_s (g/l)
Mannitol	1.46	321	11	235	182
Sodium chloride	2.17	263	7	123	357
Emcompress	2.32	257	9	151	< 0.1
Iron powder	7.72	280	9	42	insoluble

[a] Measured with an air comparison pycnometer (Beckman, model 930, U.S.A.).
[b] Calculated as described earlier (Westerberg et al., 1986).
[c] Estimated by microscopy, according to Heywood (1954).
[d] Aqueous solubility at 20°C from Handbook of Chemistry and Physics (53rd Edn).

Characterization of tablets

Tablet weight The tablets were weighed on an analytical balance (Sartorius 1602 MP, Germany).

Tablet thickness Tablet thickness was measured with a micrometer calliper (Mauser, Germany).

Tablet strength The crushing strengths and the radial tensile strengths (Fell and Newton, 1970) derived from these were determined (Pharma Test, Type PTB 301, Germany).

Disintegration time The disintegration time of the tablets was measured at 37 °C (Pharma Test, Type PTZ 1, Germany).

The physical characteristics of the tablets are presented as mean values of five determinations.

Determination of friction

The friction between the tablets and the die wall was evaluated by measuring the forces on the lower punch during ejection (EJF) using the instrumented excenter press equipped as described above. The ejection force, calculated per unit die contact area (EJF/A), was determined (Hölzer and Sjögren, 1978).

Before each individual material was tested, the punches and the die were cleaned with hot water and paper tissues, and ten tablets were compressed before five recordings were taken.

The tablet weight was, by calculation from the true density of the materials, chosen to give tablets of 0.3 cm thickness at zero porosity.

The ejection force was measured for all the carrier materials. The upper punch pressures (UPP) used were 100 and 200 MPa.

The EJF/A was also measured for mixtures containing ordered mixture, Avicel PH 101, Ac-Di-Sol and a lubricant. The tablet weight was adjusted to give a drug content of 2.0 mg oxazepam. The tablet height was measured immediately after ejection, with the micrometer calliper (Mauser, Germany). Here, the UPP used was 200 MPa.

Mixtures with oxazepam, Avicel PH 101 and Ac-Di-Sol were also tested with mannitol, the carrier material which resulted in the highest EJF/A value. EJF was measured after each addition of drug and tablet excipients. The UPP used were 100 and 200 MPa.

Dissolution studies

Dissolution test The dissolution test was performed according to the USP XXI, paddle method, using a rotational speed of 100 rpm at room temperature (23 ± 2 °C). A suspension of oxazepam, each of the ordered mixtures and tablets made from these mixtures were tested. A 0.9% solution of sodium chloride in distilled water was used as dissolution medium. To ensure optimal wetting conditions, 0.01% polysorbate 80 was added to the dissolution medium (Nyström and Westerberg, 1986). To obtain sink conditions during the dissolution test, 2.0 mg of drug was added to the dissolution medium, an amount corresponding to approx. 10% of the drug solubility. Amounts of ordered mixtures and tablets corresponding to this value were used.

Calculation of dissolution rate constants The experimental initial dissolution rate (K_E) was calculated for the dissolution of 30% of the amounts of drug tested, as described earlier (Nilsson et al., 1988).

The maximum dissolution rate (K_M) was here defined as the dissolution rate of a well-dispersed suspension of oxazepam. In this study an experimental value of 546 μg/min was obtained.

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, model 35, U.S.A.) where the UV absorbance was measured at 238 nm. In order to ensure samples free from suspended drug particles, the samples were first filtered through a filter tip of glass wool. At the beginning of each sampling period, compensation was made for the time it took for the solutions to move from the dissolution vessels, via the pump, into the flow cells. Presented results are mean values of two determinations.

Results and Discussion

Tableting properties

Fragmentation The effect of compaction pressure on the specific surface area of compacts of materials is presented in Fig. 1.

The results show, as expected, that both mannitol and Emcompress have a high degree of fragmentation during compaction, while for sodium chloride it is low. The iron powder did not form coherent compacts and the fragmentation tendency could thus not be determined.

Friction The friction between tablet and die wall was evaluated by measuring the forces on the lower punch during ejection (EJF/A). The results of the friction studies are summarized in Fig. 2 and in Tables 2–4.

The ejection force was measured for all the carrier materials. The results in Table 2 show that mannitol and Emcompress, both with a high degree of fragmentation during compaction (Fig. 1), attained the highest EJF/A of the tested carrier materials. These two materials therefore seem to have the greatest need for lubrication. Mannitol tended to adhere to the die and the punches. The two materials with a low degree of fragmentation, sodium chloride and iron powder, gave lower values of EJF/A.

For mannitol, which gave the highest EJF/A values, oxazepam, Avicel PH 101 and Ac-Di-Sol were added. EJF/A was measured after each addition of material. The results obtained are summarized in Table 3. At 100 MPa the ejection force was slightly decreased and at 200 MPa a slight increase was obtained after the addition of drug and tablet excipients.

Table 4 shows the obtained ejection forces at 200 MPa for oxazepam tablets 2 mg when the amount of lubricant and the mixing time were varied. For the mannitol mixture 0.2 and 1% w/w

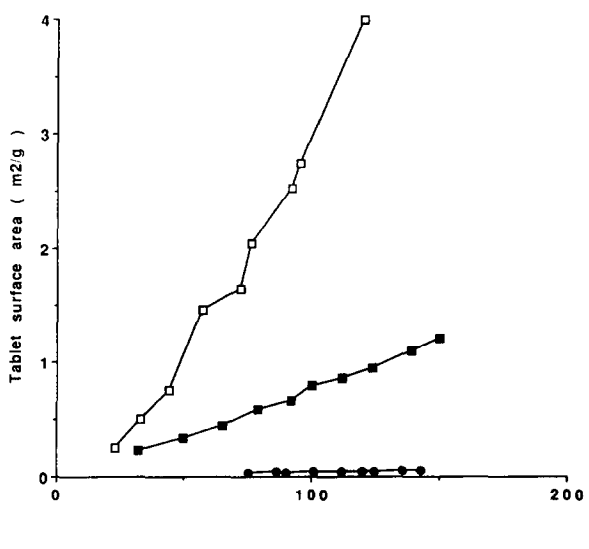

Fig. 1. Specific surface area of mannitol (□), sodium chloride (●) and Emcompress (■) tablets as a function of compaction pressure.

TABLE 2

Ejection force for the carrier materials compressed at 100 and 200 MPa [a]

Carrier material	Maximum upper punch pressure [b] UPP_{max} (MPa)	Ejection force EJF/A (kN/cm^2)
Mannitol	103	2.60
	205	1.69
Sodium chloride	101	0.35
	200	1.16
Emcompress	103	2.34
	209	2.00
Iron powder	202	0.30

[a] Mean values of five determinations.
[b] UPP_{max} variations allowed: 100 ± 5 MPa and 200 ± 10 MPa.

TABLE 3

Ejection force for mannitol after the addition of the drug and tablet excipients [a]

Material	Maximum upper punch pressure [b] UPP_{max} (MPa)	Ejection force EJF/A (kN/cm^2)
Mannitol + oxazepam [c]	100	2.14
	203	1.84
Mannitol + oxazepam + Avicel [d]	100	1.75
	205	2.00
Mannitol + oxazepam + Avicel + Ac-Di-Sol [e]	100	1.93
	204	2.05

[a] Mean values of five determinations.
[b] UPP_{max} variations allowed: 100 ± 5 MPa and 200 ± 10 MPa.
[c] $R_s = 0.51$.
[d] 5% w/w was added.
[e] 2% w/w was added.

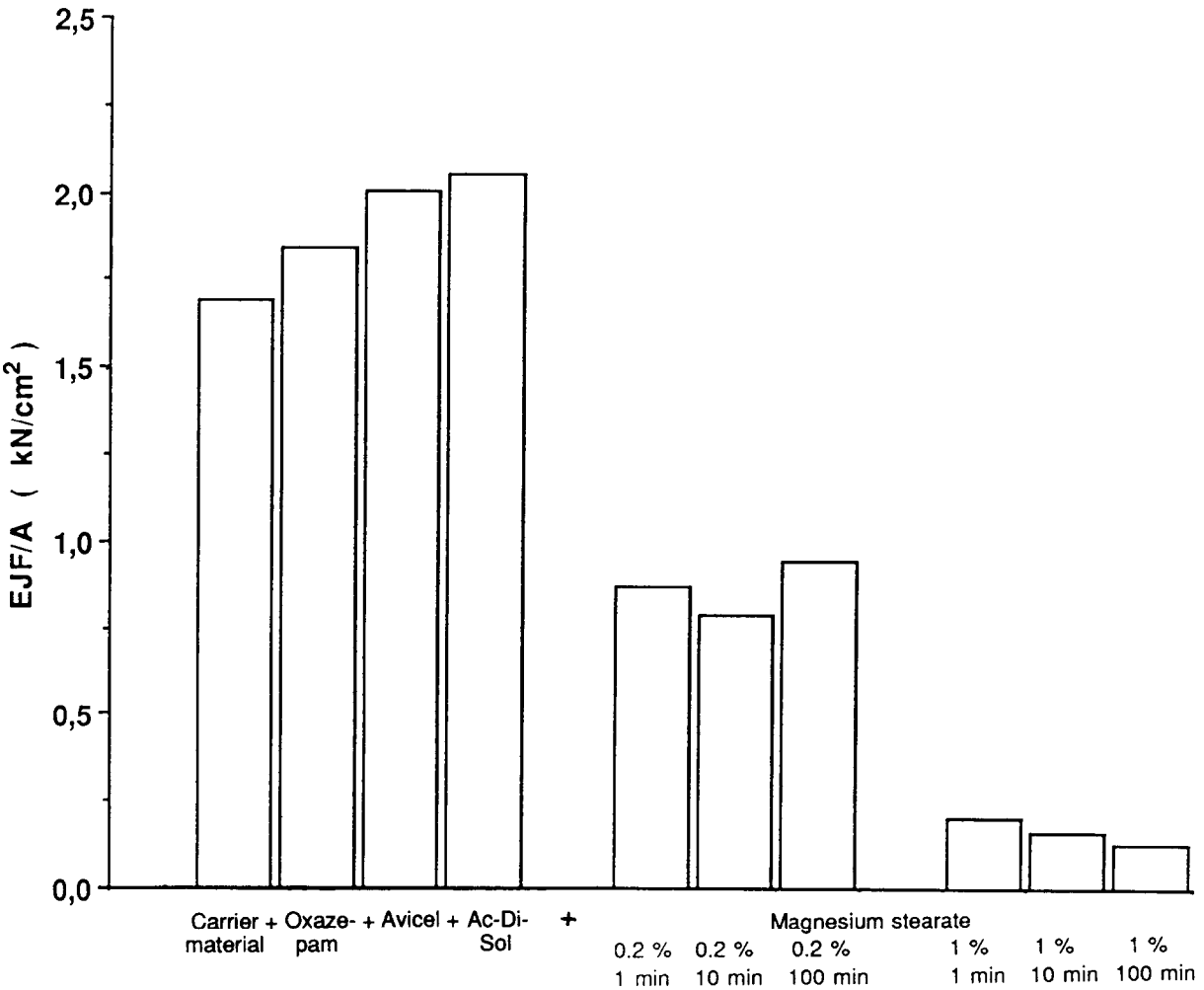

Fig. 2. The ejection forces obtained for the compression (200 MPa) of mannitol itself (carrier) and after addition of drug and tablet excipients. To the final mixture, the ejection forces for different additions of magnesium stearate are also presented.

magnesium stearate were mixed in for 1, 10 and 100 min. The results show that the addition of 0.2% w/w magnesium stearate strongly lowered the EJF/A. Addition of 1% w/w magnesium stearate caused a further decrease in the EJF/A. The effect of magnesium stearate was related to the concentration but not to the mixing time. All the EJF/A-values obtained at 200 MPA for mannitol alone and after addition of drug, binder, disintegrant, and lubricant are summarized in Fig. 2. The mixtures of the other carrier materials, which were mixed with 1% w/w magnesium stearate for 10 min, all caused a large decrease in the ejection force in comparison with that seen with the carrier alone. No difference in the EJF/A value could be seen for the sodium chloride mixture when sodium stearyl fumarate was used as the lubricant, compared to the effect of magnesium stearate.

Tablet strength and tablet disintegration

Relevant tablet characteristics are summarized in Table 5. In agreement with other studies, the incorporation of magnesium stearate reduced the tablet strength (e.g. Bolhuis et al., 1975; Ragnarsson et al., 1979). The tablets obtained with this

TABLE 4

Ejection force for oxazepam tablets 2 mg [a,b]

Carrier material	Lubricant	Amount of lubricant (% w/w)	Mixing time (min)	Maximum upper punch pressure [c] UPP_{max} (MPa)	Ejection force EJF/A (kN/cm^2)
Mannitol	Magnesium stearate	0.2	1	201	0.87
Mannitol	Magnesium stearate	0.2	10	205	0.79
Mannitol	Magnesium stearate	0.2	100	201	0.94
Mannitol	Magnesium stearate	1	1	202	0.20
Mannitol	Magnesium stearate	1	10	193	0.16
Mannitol	Magnesium stearate	1	100	199	0.13
Sodium chloride	Magnesium stearate	1	10	201	0.40
Sodium chloride	Sodium stearyl fumarate	1	10	194	0.45
Emcompress	Magnesium stearate	1	10	203	0.17
Iron powder	Magnesium stearate	1	10	205	0.03

[a] Mean values of five determinations.
[b] Tablet diameter: 1.13 cm.
[c] UPP_{max} variations allowed: 200 ± 10 MPa.

TABLE 5

Characteristics of oxazepam tablets 2 mg [a,b]

Carrier material	Lubricant	Amount of lubricant (% w/w)	Mixing time (min)	Surface area ratio R_s (−)	Maximum upper punch pressure [c] UPP_{max} (MPa)	Crushing strength P_x (kPa)	Radial tensile strength σ_x (MPa)	Disintegration time [d] (s)
Mannitol	–	–	–	0.51	200	4.1	1.50	38
Mannitol	Magnesium stearate	0.2	1	0.51	202	4.7	1.91	28
Mannitol	Magnesium stearate	0.2	10	0.51	200	2.6	1.04	20
Mannitol	Magnesium stearate	0.2	100	0.51	205	2.7	1.10	20
Mannitol	Magnesium stearate	1	1	0.51	199	1.4	0.61	35
Mannitol	Magnesium stearate	1	10	0.51	200	1.0	0.41	34
Mannitol	Magnesium stearate	1	100	0.51	200	0.4	0.16	92
Sodium chloride	–	–	–	0.41	198	5.5	1.58	29
Sodium chloride	Magnesium stearate	1	10	0.41	201	1.1	0.30	224
Sodium chloride	Sodium stearyl fumarate	1	10	0.41	205	2.2	0.64	205
Emcompress	–	–	–	0.58	199	3.0	1.36	23
Emcompress	Magnesium stearate	1	10	0.58	200	2.2	1.01	32

[a] Mean values of five determinations.
[b] Tablet diameter: 1.13 cm.
[c] UPP_{max} variations allowed: 200 ± 10 MPa.
[d] Mean values of six determinations.

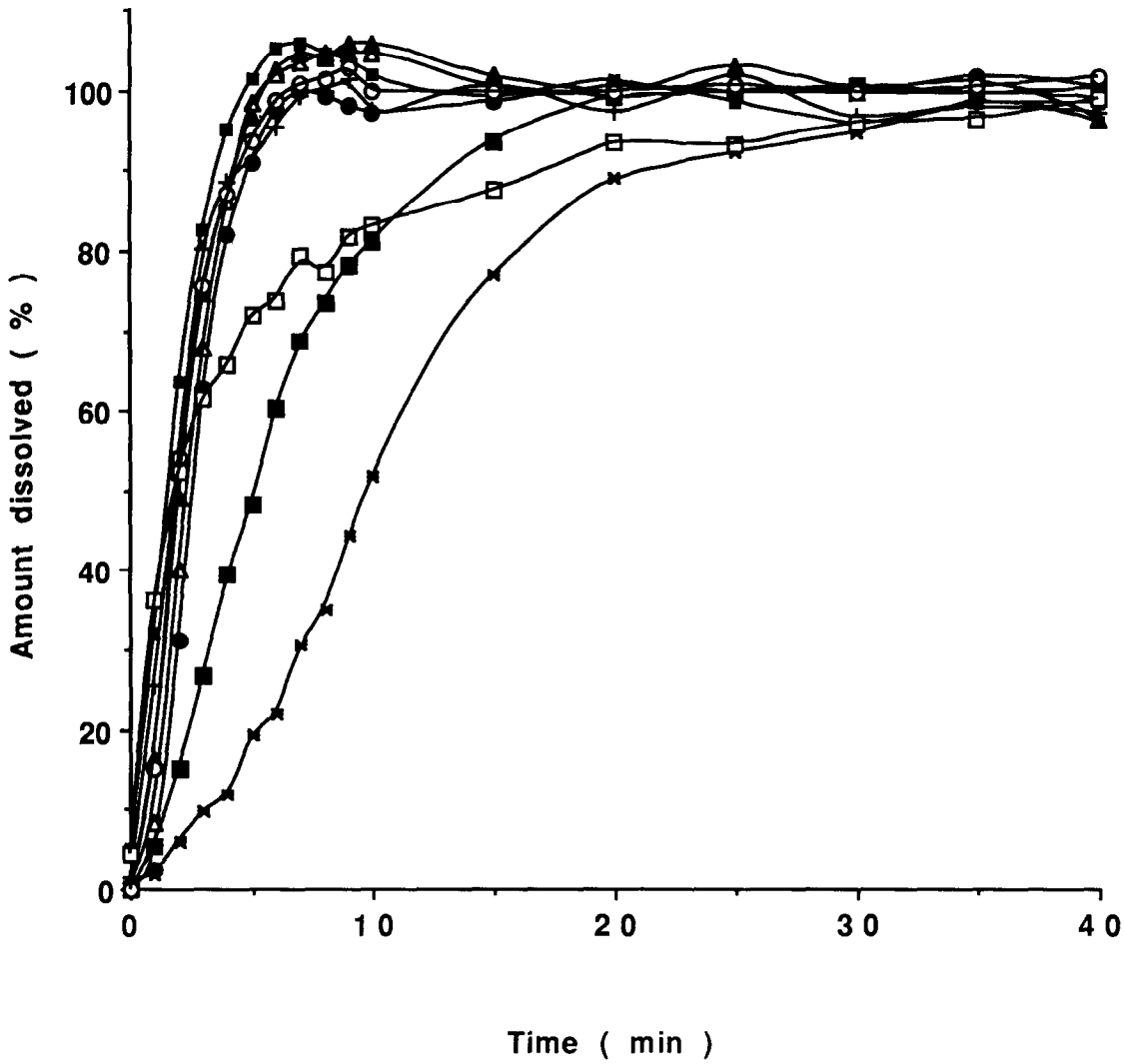

Fig. 3. Dissolution rate profiles obtained for mannitol as the carrier material. (□) Suspension of oxazepam; (●) ordered mixture. Compressed tablets containing 2 mg of oxazepam and tablet excipients. (○) External lubrication; (▲) 0.2% w/w magnesium stearate admixed for 1 min; (△) 0.2% w/w magnesium stearate admixed for 10 min; (⊠) 0.2% w/w magnesium stearate admixed for 100 min; (+) 1% w/w magnesium stearate admixed for 1 min; (■) 1% w/w magnesium stearate admixed for 10 min; (*) 1% w/w magnesium stearate admixed for 100 min.

mixture are very thin, which could also contribute to the reduction in tablet strength (Fell and Newton, 1970).

For the mannitol tablets, the crushing strength was markedly decreased when the amount of magnesium stearate was increased. The crushing strength decreased further when the mixing time was increased. The mannitol tablets disintegrated very quickly. A somewhat longer disintegration time was obtained when 1% w/w magnesium stearate was admixed for 100 min, however.

The addition of both magnesium stearate and sodium stearyl fumarate caused a substantial decrease in the crushing strength and an increased disintegration time for sodium chloride tablets. The value obtained with sodium stearyl fumarate was slightly better in comparison to that obtained with magnesium stearate.

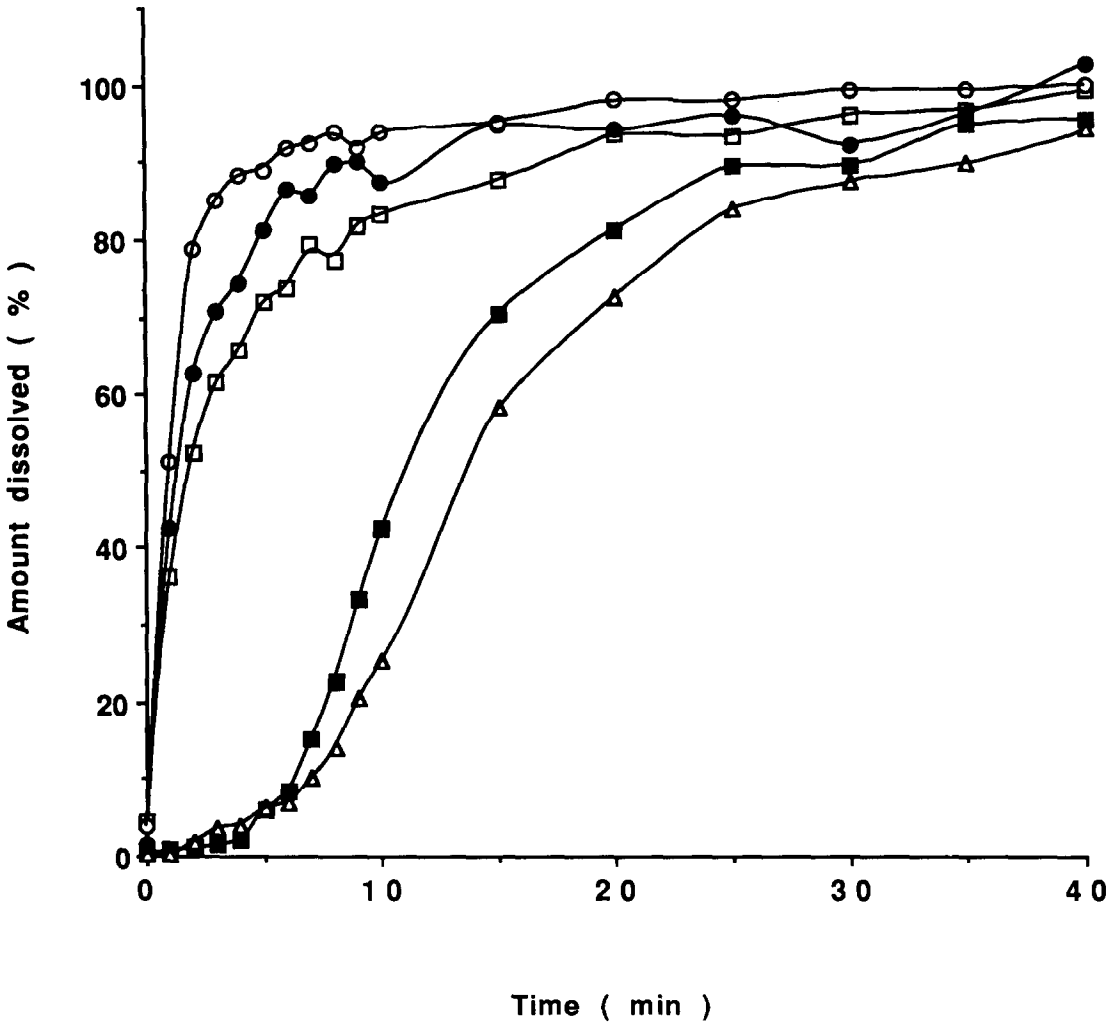

Fig. 4. Dissolution rate profiles obtained for sodium chloride as the carrier material. (□) Suspension of oxazepam; (●) ordered mixture. Compressed tablets containing 2 mg of oxazepam and tablet excipients. (○) External lubrication; (■) 1% w/w magnesium stearate admixed for 10 min; (△) 1% w/w sodium stearyl fumarate admixed for 10 min.

The crushing strength of the Emcompress tablets decreased moderately when the lubricant was added. Tablets both with and without lubricant disintegrated quickly.

The iron powder did not form coherent compacts and its tablet-forming properties could therefore not be characterized.

Dissolution properties

Results for the amount dissolved against time for a suspension of oxazepam, ordered mixtures and tablets made thereof with external and internal lubrication are shown in Figs 3–6. Tables 6 and 7 show the maximum dissolution rates of a suspension of oxazepam and the experimental dissolution rates, when 30% of the respective ordered mixtures and tablets were dissolved.

Mannitol All results obtained when using mannitol as carrier material are summarized in Fig. 3. The ordered mixture of mannitol and the tablets made with external lubrication demonstrated high dissolution rates, in fairly good agreement with the data obtained for the oxazepam suspension. The tableting procedure did not im-

TABLE 6

Dissolution rate data for ordered mixtures [a]

Carrier material	Surface area ratio R_s (–)	Experimental dissolution rate K_E (μg/min)	Ratio of K_E and K_M [b] (%)
Mannitol	0.51	255	47
Sodium chloride	0.41	701	128
Emcompress	0.58	104	19
Iron powder	0.47	44	8

[a] Mean values of two determinations.
[b] The maximum dissolution rate, K_M, was experimentally determined as 546 μg/min.

pair the dissolution of the systems. Instead the tablets showed a higher dissolution rate than the ordered mixture alone, as demonstrated earlier (Nilsson et al., 1988). Two concentrations of lubricant (0.2% w/w and 1% w/w) and three different mixing times (1, 10 and 100 min) were tested. The tablets with 0.2% w/w magnesium stearate showed high dissolution rates for oxazepam for all mixing times used. For the tablets with 1% w/w magnesium stearate a high dissolution rate for oxazepam was obtained with 1 min of admixing with the lubricant, but with 10 and 100 min of admixing the dissolution rate was decreased. Measurements of the ejection force during compaction showed acceptable levels for all lubricated systems, especially for mixtures containing 1% w/w magnesium stearate (Table 4). In spite of the fact that mannitol has a very high degree of fragmentation during compaction, there is a limitation to the amount of hydrophobic material that can be used

TABLE 7

Dissolution rate data for oxazepam tablets 2 mg [a]

Carrier material	Lubricant	Amount of lubricant (% w/w)	Mixing time (min)	Surface area ratio R_s (–)	Maximum upper punch pressure UPP_{max} (MPa)	Experimental dissolution rate K_E (μg/min)	Ratio of K_E and K_M [b] (%)
Mannitol	–	–	–	0.51	200	384	70
Mannitol	Magnesium stearate	0.2	1	0.51	202	357	65
Mannitol	Magnesium stearate	0.2	10	0.51	200	298	54
Mannitol	Magnesium stearate	0.2	100	0.51	205	495	91
Mannitol	Magnesium stearate	1	1	0.51	199	442	81
Mannitol	Magnesium stearate	1	10	0.51	200	163	30
Mannitol	Magnesium stearate	1	100	0.51	200	75	14
Sodium chloride	–	–	–	0.41	198	775	142
Sodium chloride	Magnesium stearate	1	10	0.41	201	58	11
Sodium chloride	Sodium stearyl fumarate	1	10	0.41	205	43	8
Emcompress	–	–	–	0.58	199	136	25
Emcompress	Magnesium stearate	1	10	0.58	200	44	8
Iron powder	–	–	–	0.47	204	63	12
Iron powder	Magnesium stearate	1	10	0.47	205	22	4

[a] Mean values of two determinations.
[b] The maximum dissolution rate, K_M, was experimentally determined as 546 μg/min.

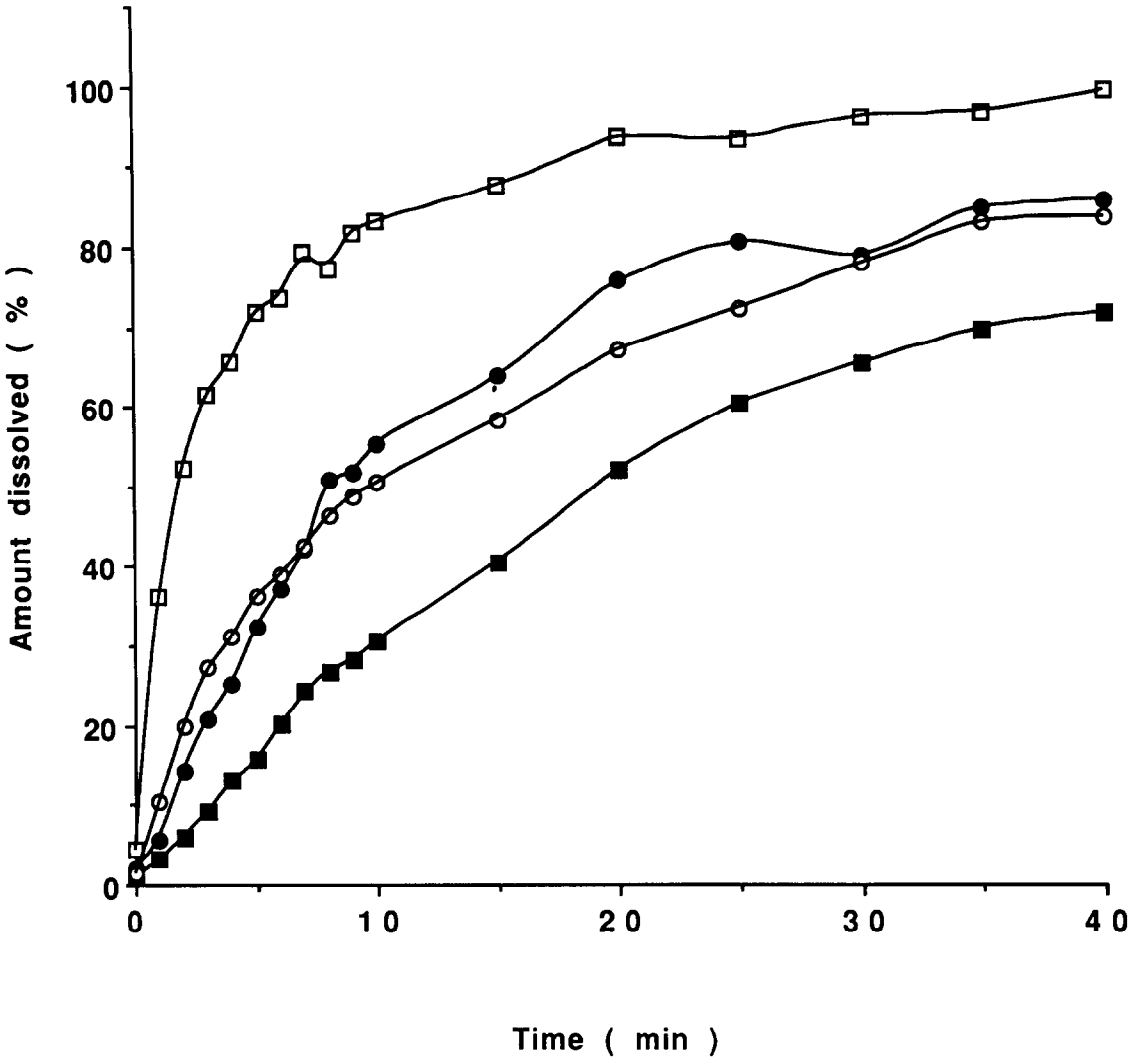

Fig. 5. Dissolution rate profiles obtained for Emcompress as the carrier material. (□) Suspension of oxazepam; (●) ordered mixture. Compressed tablets containing 2 mg of oxazepam and tablet excipients. (○) External lubrication; (■) 1% w/w magnesium stearate admixed for 10 min.

and still result in a high dissolution rate for the drug.

Sodium chloride The results obtained with sodium chloride as carrier material are summarized in Fig. 4. With the highly soluble sodium chloride, the ordered mixture and the tablets made with external lubrication gave very high dissolution rates for oxazepam, in fairly good agreement with the oxazepam suspension, as for mannitol.

Two different types of lubricants were tested, magnesium stearate and the less hydrophobic sodium stearyl fumarate. 1% w/w and 10 min mixing time were used for both lubricants. For the tablets made with internal lubrication the dissolution rate was substantially lowered. This was probably caused by the very low degree of fragmentation of sodium chloride during compaction (Fig. 1), thereby providing limited new, clean

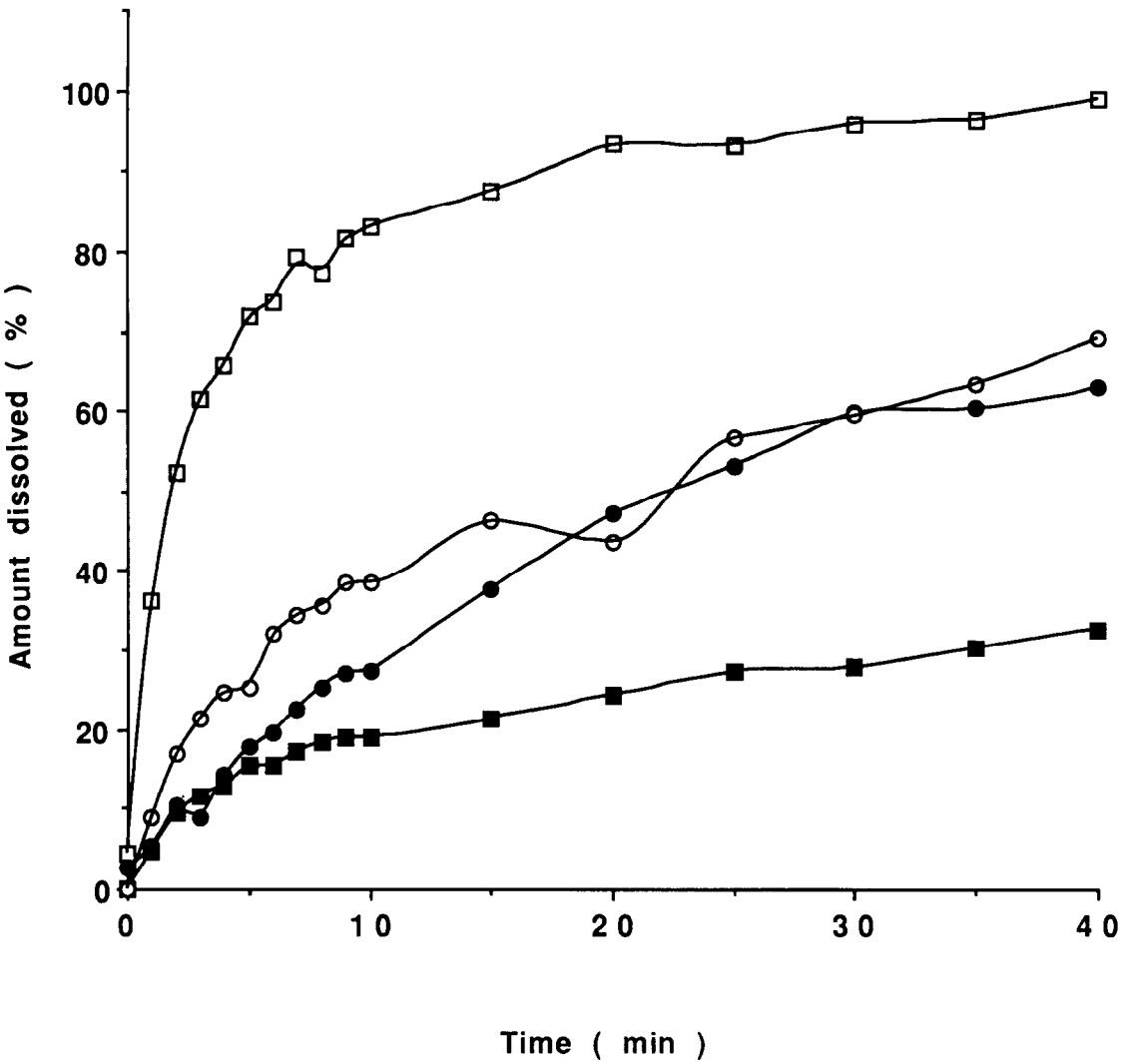

Fig. 6. Dissolution rate profiles for iron powder as the carrier material. Symbols as in Fig. 5.

surfaces, not coated with lubricant. In spite of the fact that sodium stearyl fumarate is regarded as a less hydrophobic lubricant, the drug dissolution rate was somewhat lower with this lubricant than with magnesium stearate.

Emcompress Fig. 5 shows the results obtained with Emcompress as the carrier material. For Emcompress, a material with very low aqueous solubility, the dissolution rates obtained for the ordered mixture and tablets with external lubrication were lower than those obtained for the oxazepam suspension. The result for the ordered mixture is in agreement with an earlier report (Westerberg et al., 1986). A lower dissolution rate was obtained for Emcompress because the drug particles are not rapidly exposed to the dissolution medium as primary particles, but remain adhered to the carrier particles. A thicker diffusion boundary layer may be developed for coarse carrier particles than for small drug particles (e.g. Niebergall et al., 1963; Bisrat and Nyström, 1988). It is first when separate fine drug particles are present that the slow transport of diffusion of dissolved molecules, will not substantially slow

down the dissolution process (Nyström and Westerberg, 1986). The dissolution rate was further decreased, with the tablets prepared by internal lubrication in spite of the fact that the material has a high degree of fragmentation during compaction. However, the differences between external and internal lubrication were in relative terms much less pronounced than the results for sodium chloride (Table 7).

Iron powder Fig. 6 shows the results when iron powder is used as carrier material. For iron powder, a material which is insoluble in water and has a very low degree of fragmentation, the dissolution rates obtained for the ordered mixture and the tablets made with external lubrication were substantially lower than for the oxazepam suspension. For tablets prepared with internal lubrication, the lowest dissolution rate of all tested systems was obtained.

Conclusions

It has been shown that the formulation of fine particulate, poorly soluble drugs into solid dosage forms, utilizing ordered mixtures, will be more effective regarding drug release when soluble excipients are used. For the dissolution rate in vitro it is important that the drug particles are in free suspended form and not attached to coarser solid units. This paper also demonstrates, that the negative effects of lubricants are counteracted if a carrier material with both high aqueous solubility and a high degree of fragmentation during compaction is used. The choice of carrier material appears to be more important for the dissolution rate than the choice of an alternative, less hydrophobic, lubricant. Although the highest recommended surface area ratio was used, it is possible to obtain dissolution rate profiles almost identical to those obtained for the drugs in the form of well-dispersed suspensions, with the proper choice of tablet excipients.

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