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The effect of the swelling capacity of disintegrants on the in vitro and in vivo availability of diazepam tablets, containing magnesium stearate as a lubricant

J.H. Proost, G.K. Bolhuis and C.F. Lerk

Laboratory for Pharmaceutical Technology and Dispensing, University of Groningen, Groningen (The Netherlands)

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Summary

The disintegration and dissolution rate of diazepam tablets, containing the slightly swelling disintegrant, potato starch, depend on mixing time of the drug/excipient preblend with the lubricant magnesium stearate. During the mixing process, a hydrophobic lubricant film is formed on the excipient particles, which decreases the penetration of water into the tablet, and as a result, increases the disintegration time.

On the other hand, disintegration and drug dissolution rate of tablets with the strongly swelling disintegrant sodium starch glycolate, are hardly affected by mixing with magnesium stearate. The difference in effect of the lubricant on the disintegrants is explained by the difference in swelling capacity of the disintegrants.

The dissolution rate of tablets with potato starch strongly depends on both the dissolution model (i.e. USP XX basket-model and paddle-model) and stirring rate (i.e. 50 or 100 rpm.). For tablets with the strongly swelling sodium starch glycolate the dissolution rate is less affected by the dissolution method. The discrimination between the tablets is best using a method with mild hydrodynamic conditions.

The bioavailability of diazepam from these tablets was studied in human volunteers. Significant differences in absorption parameters were found. However, the influence of the swelling capacity of the disintegrant and the mixing time on absorption rate is less pronounced than was expected from the in vitro dissolution tests.

A correlation of in vitro dissolution and in vivo absorption has been found for the model with a relatively high stirring rate, which is less discriminating in vitro.

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Introduction

The disintegration of tablets and the dissolution of active ingredients are dependent on both tablet formulation and manufacturing process.

Usually, for purpose of a fast disintegration of tablets a swelling agent is added as a disintegrant. However, the presence of a disintegrant is no guarantee for a rapid disintegration (Bolhuis et al., 1981; Shah et al., 1977). In previous work (Bolhuis et al., 1981) it is shown that the efficacy of potato starch as a disintegrant is decreased by an increase of the mixing time of the ingredients with the lubricant magnesium stearate. The deleterious effect of magnesium stearate on disintegration, and as a result on dissolution of active principles, is caused by a lubricant film, which is formed during mixing of tablet excipient particles with the lubricant (Bolhuis et al., 1975; Lerk et al., 1977a and b; De Boer et al., 1978). This hydrophobic film around tablet excipients delays, or even inhibits, the penetration of water into the pores of the tablets, and thus masks the action of the disintegrant. Because this lubricant film never envelopes the disintegrant particles completely swelling is not inhibited at the surface of the tablet where the disintegrant particles are in direct contact with water. For disintegrants with a moderate swelling capacity, e.g. potato starch, the structure of the tablet is not disrupted spontaneously. In this situation disintegration is enhanced by mechanical factors, such as the presence of discs in the USP apparatus or high stirring rates in dissolution models, abrasing the partially disrupted structure at the tablet surface.

On the contrary, disintegrants that swell strongly in contact with water, like sodium starch glycolate, always disrupt the surface structure completely, permitting water to penetrate into the tablet. By this process the tablet disintegrates quickly, even without any mechanical influence. In this study the interaction of disintegrants and magnesium stearate is investigated and related to in vitro disintegration and dissolution, and to the in vivo availability of a model substance, i.e. diazepam.

Experimental

Materials

The materials used were: diazepam (Valium, Hoffman-La Roche, Basle, Switzerland), unmilled dicalcium phosphate dihydrate (Emcompress, Edward Mendell, New York), dried potato starch (moisture content about 8%) (Avebe G.A., Veendam, The Netherlands), sodium starch glycolate NF XV (Primojel, Avebe G.A., Veendam, The Netherlands) and magnesium stearate (Lamers and Indemans, 's-Hertogenbosch, The Netherlands). All reagents were analytical grade.

Methods

Mixing. Preblends of diazepam, filler and disintegrant were prepared by mixing (Turbula mixer, model 2P, W.A. Bachofen, Basle, Switzerland) the excipients for 15 min, using glass vessels with a loading of about 20% and a rotation speed of 90 rpm. After addition of 0.5% magnesium stearate mixing was continued for a specified period (2 or 30 min).

Tablet compression. The tablets were prepared by introducing manually 200 mg of the blend into a 9 mm die of a compression device, mounted between the plattens of an instrumented hydraulic press (Hydro Mooi, Appingedam, The Netherlands). Compression force was 10 kN.

Disintegration time. The disintegration time of the tablets was determined using the USP XX apparatus. The test was performed with and without discs. The data given are the mean values of 6 individual tablets.

Dissolution rate. The dissolution rate of diazepam was determined in 900 ml of deaerated water, using the rotating basket and the paddle method of USP XX. Stirring speed was 100 rpm for the rotating basket, and 50 rpm or 100 rpm for the paddle method. Samples of 5 ml were removed through a membrane filter (0.8 μm) at 2, 5, 10, 15, 20, 30, 45 and 60 min and replaced by 5 ml of water. 0.05 ml 2 N sulfuric acid was added to the samples and they were immediately analyzed spectrophotometrically at the absorption maximum of about 241 nm. The data given are the mean values of 4 determinations. A 3-factor analysis of variance (ANOVA) was made for the percentage dissolved in 60 min in the paddle model, using a 2^3-design (2 disintegrants, 2 mixing times and 2 stirring rates).

Human experiments

Ten healthy male volunteers (age 20–33 years, body weight 57–81 kg) participated in the cross-over study. No drugs were taken for two weeks prior to and during the experiment. The experiments were started at approximately 09.00 h after fasting overnight. No food was taken during the experiment (4 h). Each subject was given one of the 3 tablet formulations, containing 5 mg of diazepam in a randomized order with intervals of 10–14 days. The tablets were swallowed with 100 ml of water. Blood samples of 10 ml were taken at 10, 20, 30, 40, 60, 90, 120, 180 and 240 min after administration, using vacuum tubes (Venoject tubes, Terumo, Leuven, Belgium) with 15 mg EDTA-sodium. Plasma was obtained by centrifugation and was stored frozen until analysis.

Analysis of plasma samples. Diazepam concentrations in plasma were determined by HPLC, using the method of Westenberg en De Zeeuw (Westenberg and De Zeeuw, 1976).

Pharmacokinetic parameters. The absorption rate of diazepam was characterized by peak concentration (C_{max}), peak concentration time (t_{max}), plasma concentrations (C_t) and area under the curve (AUC_t) at specified times. AUCs were determined by trapezoidal rule. These parameters were compared in an analysis of variance (ANOVA) with two factors (3 dosage forms and 10 subjects). Differences between tablets were tested using Newman-Keuls' method. Differences were considered to be significant if $P < 0.05$.

Results and discussion

The tablet formulations are listed in Table 1.

TABLE 1

TABLET FORMULATIONS

Ingredient % (w/w)	Formulation			
	P-2	P-30	S-2	S-30
Diazepam	2.5	2.5	2.5	2.5
Dicalcium phosphate dihydrate	77	77	93	93
Potato starch	20	20		
Sodium starch glycolate			4	4
Magnesium stearate	0.5	0.5	0.5	0.5
Mixing time with magnesium stearate (min)	2	30	2	30

Disintegration time

The disintegration time of the tablets with sodium starch glycolate as a disintegrant (S-2 and S-30) is extremely short (Table 2), and is independent of mixing time with magnesium stearate, as has been expected from earlier results (Bolhuis et al., 1981). The presence of discs in the apparatus hardly affects disintegration time.

On the contrary, the tablets with potato starch (P-2 and P-30) are strongly influenced by mixing time. Disintegration time is prolonged after 30 min mixing with magnesium stearate (P-30), and is also strongly affected by the presence of the discs. Without the discs, P-30 does not disintegrate completely within 15 min, and 3 out of 6 not even within 30 min. These results show that the disintegration test without discs is more discriminating than the USP-method with the use of disks.

Dissolution rate

The dissolution rate of diazepam from the tablets is shown in Fig. 1 (rotating basket, 100 rpm), Fig. 2 (paddle method, 50 rpm) and Fig. 3 (paddle method, 100 rpm).

The dissolution of diazepam from the tablets with sodium starch glycolate is hardly influenced by mixing time with magnesium stearate. For tablets with potato starch as a distintegrant, the dissolution rate decreases with increasing mixing time.

TABLE 2

DISINTEGRATION TIME (±S.E.M.)

Formulation	Disintegration time (s)	
	with discs	without disc
P-2	12 ± 1	9 ± 1
P-30	32 ± 2	over 900
S-2	7 ± 1	6 ± 1
S-30	7 ± 1	7 ± 1

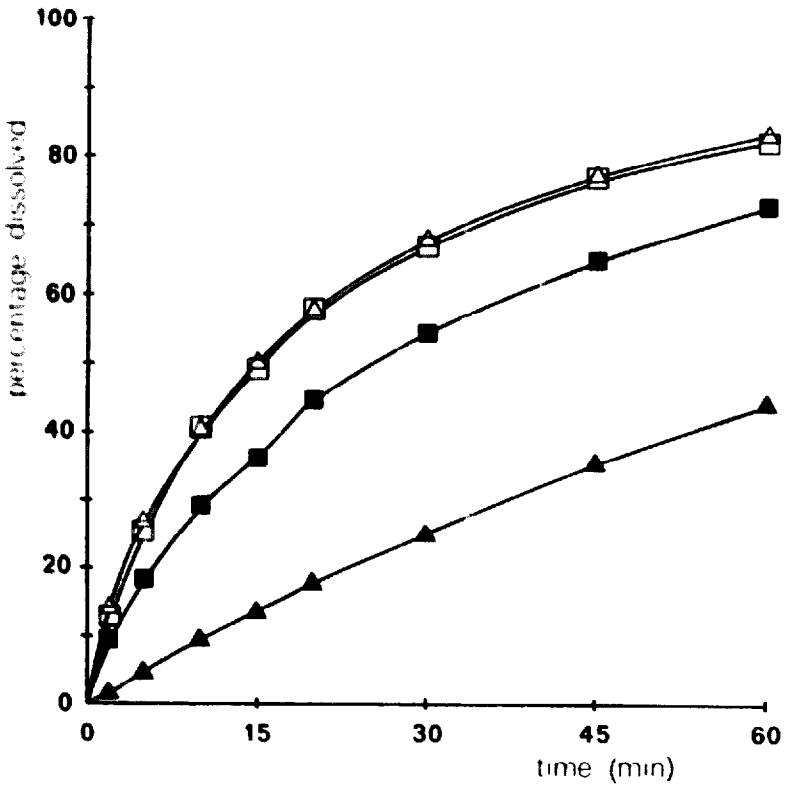

Fig. 1. Dissolution profiles of diazepam, determined with the rotating basket at 100 rpm. ■, P-2; ▲, P-30; □, S-2; △, S-30 (Abbreviations see Table 1).

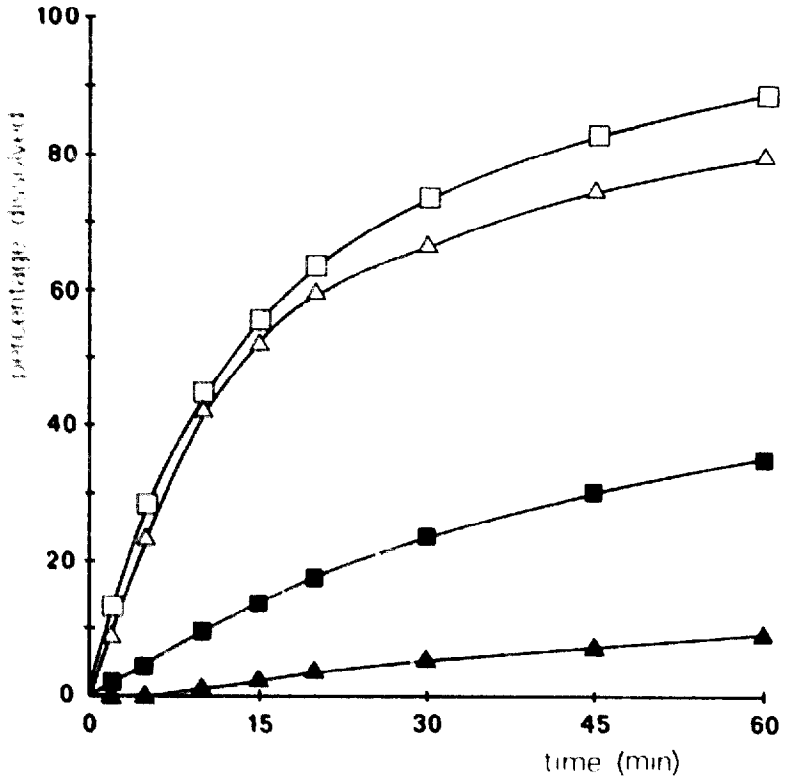

Fig. 2. Dissolution profiles of diazepam, determined with the paddle model at 50 rpm. Symbols as in Fig. 1.

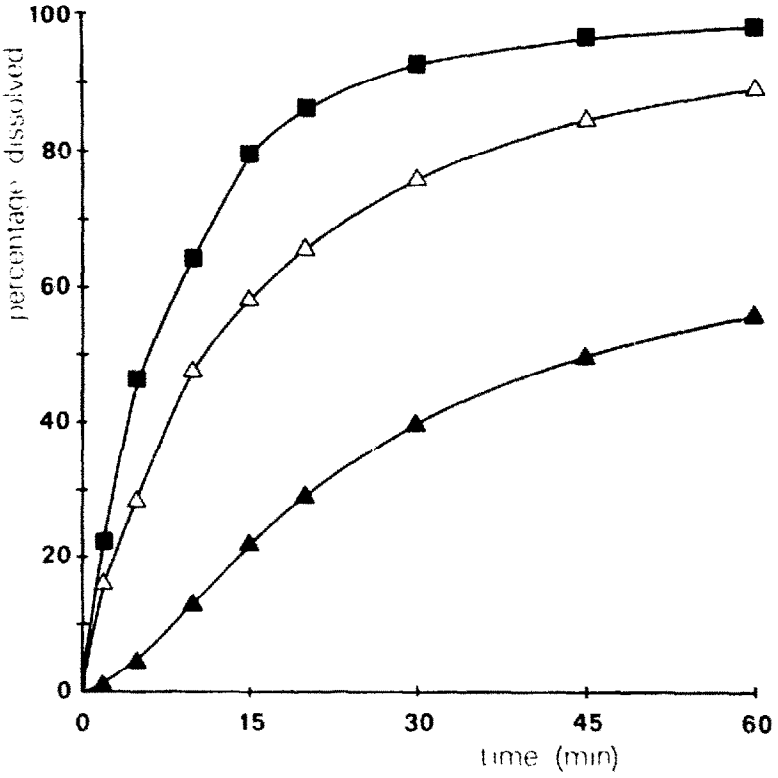

Fig. 3. Dissolution profiles of diazepam, determined with the paddle model at 100 rpm. Symbols as in Fig. 1.

In all dissolution tests, the tablets P-30 did not disintegrate completely within 60 min. For both P-2 and P-30, the dissolution rate is dependent on the stirring rate.

The analysis of variance of the percentage dissolved in 60 min in the paddle model is shown in Table 3. Two highly significant ($P < 0.001$) interactions can be

TABLE 3

THREE-FACTOR ANOVA OF PERCENTAGE DISSOLVED IN 60 MIN IN THE PADDLE MODEL AT 50 rpm AND 100 rpm

	Degrees of freedom	Mean square	F-ratio	Probability of F
Disintegrant (D)	1	12,386.59	245.2	$P < 0.001$
Mixing time (M)	1	3660.26	72.5	$P < 0.001$
Stirring rate (S)	1	8067.68	159.7	$P < 0.001$
Interaction D × M	1	1318.92	26.1	$P < 0.001$
Interaction D × S	1	4236.14	83.9	$P < 0.001$
Interaction M × S	1	129.93	2.57	NS [a]
Residuals	21 [b]	50.52		

[a] Not significant.

[b] Tablet S-2 at 100 rpm not performed; therefore the total degrees of freedom are $4 \times (2 \times 2 \times 2 - 1) - 1$, and no interaction D × M × S can be calculated.

seen: disintegrant × mixing time and disintegrant × stirring rate. This is the statistical equivalent of the results described above: the factor disintegrant is not independent of both mixing time and stirring rate. The dissolution test using the paddle model at 50 rpm seems to be more discriminating between tablets. Obviously here disintegration is mainly determined by the efficacy of the disintegrant. Therefore dissolution of P-30 is low. At higher stirring rates the disintegration is accelerated by abrasion of the tablet surface. This effect is only significant for tablets containing the slightly swelling disintegrant potato starch, which do not disintegrate spontaneously without any mechanical forces.

Human experiments

The tablets P-2, P-30 and S-30 were given to 10 human volunteers, and the results of the experiments are shown in Fig. 4 and Table 4. After two hours no difference can be seen between the formulations as has been expected from the pharmacokinetic profile of diazepam, which has a terminal half-life of about 20 h (Kaplan et al., 1974; Mandelli et al., 1978; Moolenaar et al., 1980). It is not possible to calculate the absorption rate (assuming first-order kinetics) from these data, because the kinetics of diazepam can only be described satisfactorily by a 2 or 3 compartment model (Kaplan et al., 1974; Mandelli et al., 1978; Moolenaar et al., 1980), and so more data are necessary.

Analysis of variance (two-factor ANOVA) was carried out for C_{max}, t_{max}, C_{30min}, AUC_{60min} and AUC_{240min}. Differences between tablets were statistically tested using Newman-Keuls' method. In Table 5 ANOVA of t_{max} is given as an example. Because of the slow elimination of diazepam, peak concentration (C_{max}) will be

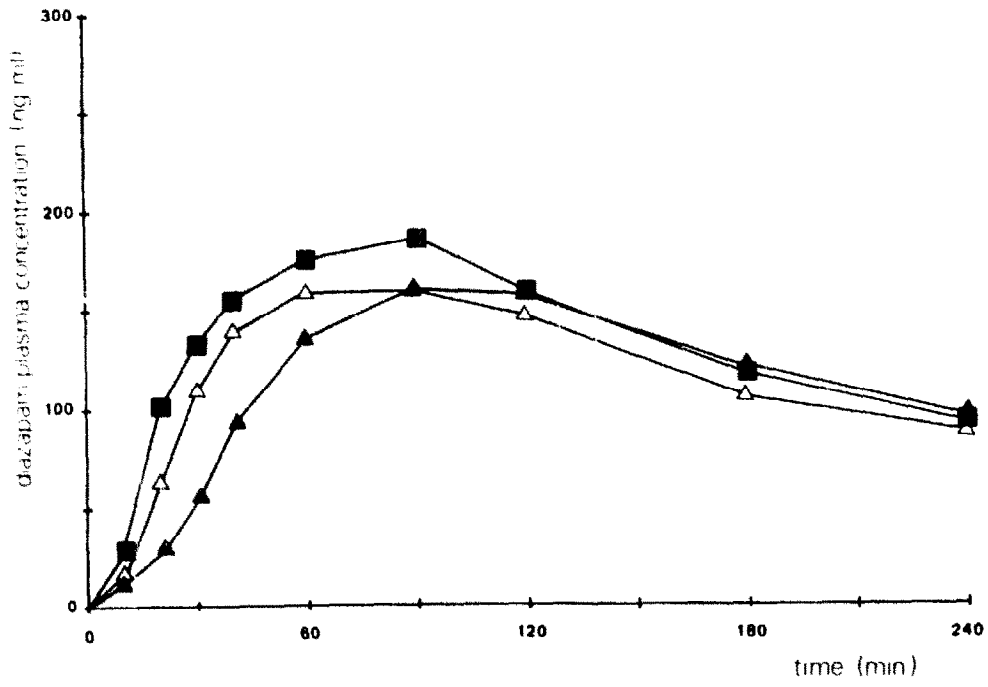

Fig. 4. Plasma concentration profiles of diazepam (mean of 10 subjects). Symbols as in Fig. 1.

TABLE 4

PARAMETERS OF DIAZEPAM PLASMA PROFILES (MEAN ± S.E.M.)

	P-2	P-30	S-30
C_{max}(ng/ml)	207 (±11)	187 (±9)	189 (±14)
t_{max}(min)	77 (±14)	107 (±11)	75 (±10)
C_{30min}(ng/ml)	132 (±24)	55 (±11)	109 (±20)
AUC_{60min}(h·ng/ml)	110 (±16)	61 (±8)	92 (±13)
AUC_{240min}(h·ng/ml)	529 (±32)	462 (±18)	471 (±30)

influenced only slightly by absorption rate. Therefore, C_{max} does not fit as an absorption parameter.

Differences in disintegration time may affect the initial absorption rate, and, as a result, plasma concentration during the absorption phase. Therefore, absorption rate was characterized by t_{max}, C_{30min} and AUC_{60min}. From Table 6 it can be seen that these parameters are significantly different ($P < 0.05$) for P-30 in comparison with P-2 or S-30. Although P-2 seems to show a faster absorption than S-30, no significant difference was found ($P > 0.10$ for all parameters).

Because AUCs of the 3 tablets did not show a significant difference, it can be assumed that an equal fraction of the dose is absorbed. Comparison with AUC from intravenous administration and from commercially available tablets (Moolenaar et al., 1980) suggests a complete absorption. The practical significance of the differences in the initial absorption rate depends on the therapeutic purpose. For chronic administration absorption rate is of minor importance, because plasma concentration is mainly determined by the total amount absorbed. However, if a rapid onset of drug action is desired (e.g. diazepam as a hypnotic), a fast initial absorption is necessary.

Correlation of in vitro / in vivo data

Comparison of in vivo and in vitro data shows a rank order correlation of absorption rate (as characterized by plasma concentrations during the first 60 min or AUC_{60min}) with dissolution rate in the paddle model at 100 rpm (as characterized by percentage dissolved during 60 min): P-2 > S-30 > P-30. In other studies (Barr,

TABLE 5

TWO-FACTOR ANOVA OF t_{max}

	Degrees of freedom	Mean square	*F*-ratio	Probability of *F*
Tablets	2	3063	6.56	$P < 0.01$
Subjects	9	3256	6.98	$P < 0.005$
Residuals	18	467		

TABLE 6

NEWMAN-KEULS' TEST ON DIFFERENCES BETWEEN TABLETS, BASED ON TWO-FACTOR ANOVA

	P-2/P-30	P-30/S-30	P-2/S-30
C_{max}	NS [a]	NS	NS
t_{max}	$P < 0.01$	$P < 0.025$	NS
C_{30min}	$P < 0.025$	$P < 0.05$	NS
AUC_{60min}	$P < 0.01$	$P < 0.05$	NS
AUC_{240min}	NS	NS	NS

[a] Not significant

1972; Levy, 1963; Rothe and Schellhorn, 1977) in vivo–in vitro correlations are found mostly with dissolution models with lower stirring rates and mild hydrodynamic conditions. A different rank order (S-30 > P-2 > P-30) is found for dissolution in the paddle model at the lower stirring rate, for dissolution in the rotating basket (100 rpm) and for disintegration (with and without using discs).

Our results can be explained by assuming that disintegration of tablets in the gastrointestinal system is enhanced by mechanical factors, caused by gastric or intestinal motility. Thus the absorption of drugs from dosage forms whose disintegration strongly depends on mechanical factors (i.e. P-2 and P-30) can be markedly faster than would be predicted from dissolution data obtained with low stirring rates.

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