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β-Cyclodextrin as an excipient in solid oral dosage forms: in vitro and in vivo evaluation of spray-dried diazepam-β-cyclodextrin products

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Summary

Diazepam-β-cyclodextrin and diazepam–lactose products were prepared by spray-drying. Complex formation could be demonstrated by differential scanning calorimetry and by application of a so-called "ether-wash" method, for diazepam-β-cyclodextrin but not for diazepam–lactose. Intrinsic dissolution rates were measured using a rotating disc method. The results indicated that, for the drug tested, complexation played only a minor role in dissolution rate enhancement. Both the processing of the drug and the excipient as well as the solubility and amount of the excipient used seemed to be rate-determining factors. Release rates from tablets and capsules were measured using the USP paddle method. For the capsules an enhancement of the dissolution rate by complex formation of the drug with β-cyclodextrin, was only found when low stirring rates were used (20 rpm). The difference in dissolution rate, as obtained at 50 and 20 rpm, can be explained by the presence of an aggregate at the bottom of the beaker at low stirring rates. In the microenvironment around the aggregate the solubility of the drug is enhanced by complex formation. Absorption experiments in human volunteers showed also an increased absorption of diazepam by β-cyclodextrin complexation.

Introduction

During the past decades many methods to improve the dissolution rate of poorly soluble drugs from solid dosage forms have been described, e.g. the use of solid dispersion systems (Chiou and Riegelman, 1971), or hydrophilization with a hydrophilic polymer (Lagas, 1980). Among this variety of methods the use of cyclodextrins is a relatively new possibility.

Cyclodextrins (CDs) are well-known for their ability to form inclusion complexes with lipophilic drug molecules. In the past few years a number of reviews covering the pharmaceutical applications of cyclodextrins have been published (Pitha et al., 1983; Jones et al., 1984; Uekama and Otagiri, 1986).

Inclusion complexes of drugs may offer a number of advantages over the pure compounds, such as improved bioavailability and improved chemical and physical stability. Many reports have

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been published on improved drug dissolution by complex formation with cyclodextrins. However, little attention has been paid to the incorporation of drug–cyclodextrin complexes in solid oral dosage forms.

The aim of this study was to evaluate the application of cyclodextrins as complexing agents in solid dosage forms, as compared to the use of non-complexing excipients, such as lactose. The very slightly soluble and hydrophobic diazepam was used as the test drug. Both, solid diazepam–β-cyclodextrin complexes and diazepam–lactose products, were prepared by means of a spray-drying technique. The products were evaluated on their intrinsic dissolution properties. Next, micronized diazepam, spray-dried diazepam and spray-dried diazepam–β-cyclodextrin, respectively, were incorporated into tablet formulations. The tablets were tested on the in vitro release rate of the drug. Finally, micronized diazepam, a physical mix of diazepam with β-cyclodextrin, and the spray-dried products of diazepam with β-cyclodextrin or with lactose, respectively, were analyzed for both the in vitro dissolution and the in vivo absorption of the drug.

Materials and Methods

Materials

β-Cyclodextrin was a gift from Avebe (Veendam, The Netherlands). Lactose was a gift from DMV (Veghel, The Netherlands). Diazepam was obtained from Centrafarm (Etten-Leur, The Netherlands). All other chemicals and solvents used were of analytical grade.

Preparation of the spray-dried products

Spray-drying was performed in a Büchi 190M laboratory spray-dryer (Büchi, Flawil, Switzerland). Diazepam (2.13 g) was dissolved in 2.5 litres of 96% ethanol. The required amount of β-CD or lactose was dissolved in 2.5 litres of distilled water and the solutions were mixed, which yielded a clear, homogeneous solution that was fed into the spray-dryer. The drying conditions were: flow rate 750 ml/h, inlet temperature 170 °C, outlet temperature 70 °C, air flow rate 600 Normliter/h. The yield was 50%.

Characterization of the spray-dried products

The diazepam content was determined spectrophotometrically at 231 nm in phosphate buffer pH 7. The absence of degradation products of diazepam was confirmed by means of a thin-layer chromatography (TLC) method as described by Moffat et al. (1986). Complex formation was studied by differential scanning calorimetry (DSC) using a Dupont 99 Thermal Analyzer with a DSC cell 910 (sample size 5 mg, scanning rate 10 °C/min.

Complex formation was furthermore studied by an "ether-wash" method. An exactly weighted amount of powder was shaken with 30 ml diethyl-ether (dried on anhydrous magnesium sulphate). The particles were removed by filtration, and the ether evaporated. The remaining drug was then dissolved in 50% ethanol and determined spectrophotometrically.

Preparation of the physical mixtures

Physical mixtures were prepared in a Turbula mixer at 90 rpm during 15 min in a glass vessel which was filled to 25% of its capacity.

Production of the tablets

Tablets of 200 mg with a diameter of 9 mm were made with a hydraulic press (Hydro Mooi, Appingedam, The Netherlands). The die was lubricated with magnesium stearate before each compression. The tablets were standardized to a crushing strength of 80 ± 20 N (Table 2) and all showed disintegration times under 1 min (USP disintegration test).

Dissolution rate measurements

Non-disintegrating tablets were prepared by compressing 400 mg powder with a force of 30 kN for 5 min. Intrinsic dissolution rates of these tablets were measured using the rotating disc method described by Lagas (1980). The dissolution medium (0.001 M phosphate buffer, pH 7) was degassed before used and kept at 37 °C. Samples were taken manually and filtered through a 0.45 μm PTFE filter. The diazepam concentration was measured spectrophotometrically at 231 nm. β-Cyclodextrin was assayed with a method described by Vikmon (1982) and lactose concentra-

tions were measured after reactions with anthrone (Corrigan and Stanley, 1981). All experiments were carried out in triplicate. The dissolution rate measurement of diazepam from disintegrating tablets and capsules was performed according to the USP XXI paddle method at 50 or 20 rpm. The dissolution apparatus was equipped with PTFE tubing to prevent sorption of diazepam. Two dissolution media were used: 0.1 N HCl and 0.05 M phosphate buffer pH 7.0. The concentration of diazepam was measured spectrophotometrically at 242 nm (pH 1), 231 nm (pH 7) and 250 nm (capsules) using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands).

Experiments were carried out in triplicate, except for the 20 rpm dissolution rate measurements which were performed in 6-fold.

In vivo study design

The protocol was approved by the Ethical Committee of the University Hospital in Groningen. Eight healthy male volunteers (age 20–26 years, wt. 70–93 kg) participated in the study. They were informed of the nature of the study by an independent pharmacist and gave their written consent. No drugs were taken for one week prior to and during the experiment. The experiments were started at approximately 08.00 h after fasting overnight. Each subject was given one of the 4 capsule formulations (Table 3) with intervals of 7 days in a cross-over design. The capsules were swallowed with 100 ml of water. Blood samples of 7 ml were taken immediately before administration and at 10, 20, 30, 40, 60, 90, 120, 180 and 240 min after administration. Heparin was added to the samples to prevent clotting. Plasma was obtained by centrifugation at 3000 rpm and stored frozen until analysis.

Bioanalysis

To 1.0 ml of plasma were added 3.0 ml dichloromethane and 1.0 ml internal standard solution (nitrazepam 200 ng/ml in a saturated borax solution). The mixture was vortexed for 60 s and then centrifuged at 3000 rpm. The water layer was removed. The tube was placed in liquid nitrogen for 15 s and the dichloromethane layer was transferred to a centrifuge tube. The tubes were placed in water of 40 °C and the dichloromethane was evaporated under a gentle stream of nitrogen. To the residue 120 μl mobile phase was added and this was used as a sample for HPLC analysis. A calibration graph was prepared by the addition of known quantities of diazepam to blank plasma and extracted according to the above procedure. The peak-height ratio of diazepam : nitrazepam was plotted against the concentration of diazepam added. The concentration of diazepam in the test samples was calculated using the regression parameters obtained from the calibration graph.

The HPLC system consisted of a Perkin Elmer Series 10 Liquid Chromatograph. A Promis autosampler was used for injection of the samples: sample loop 100 μl, injection volume 50 μl, flush volume 50 μl. The analytical column was packed with Partisil 5 μm (150 × 3.0 mm i.d.). A guard column packed with Vydac (100 × 2.1 mm i.d.) was used before the analytical column. The mobile phase used was dichloromethane : tetrahydrofuran (94 : 6). The column was maintained at room temperature and the mobile phase flow rate was 1.0 ml/min. Column effluents were monitored at 254 nm with a Waters Associates Model 441 absorbance detector.

Pharmacokinetic and statistical analysis

From plasma data absorption profiles were calculated using numerical deconvolution (Proost, 1987). As a reference we used pharmacokinetic data following intravenous administration of 10 mg diazepam (Moolenaar et al., 1980). The areas under the curve (AUC) were calculated using the mixed integration algorithm (Proost, 1987). The fraction absorbed and the AUC_{60}, AUC_{120} and AUC_{240} were used as a measure of drug absorption. For each combination of two dosage forms the AUCs were compared in a two-way analysis of variance (ANOVA) (2 dosage forms, 8 subjects). Differences were considered to be significant if $P < 0.05$.

Results and Discussion

Preparation and characterization of the different products

Figs. 1 and 2 show the DSC curves of various diazepam–β-cyclodextrin physical mixtures, and

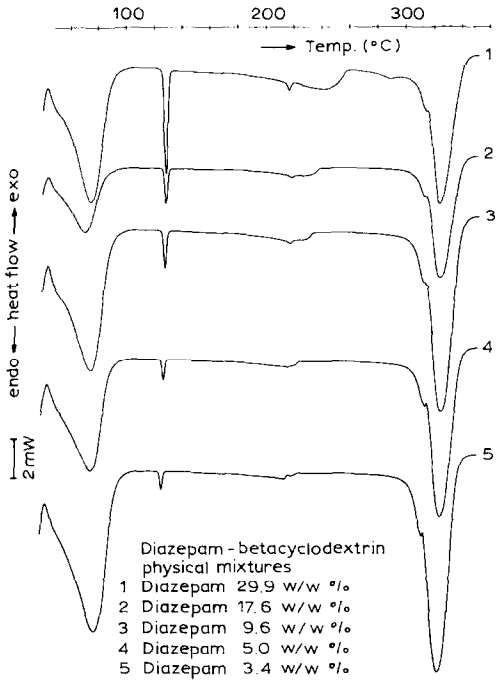

Fig. 1. DSC curves of various diazepam–β-cyclodextrin physical mixtures.

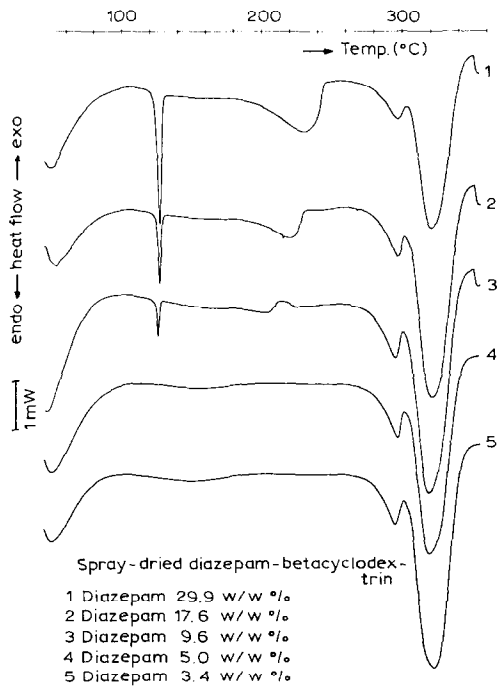

Fig. 2. DSC curves of spray-dried diazepam–β-cyclodextrin products.

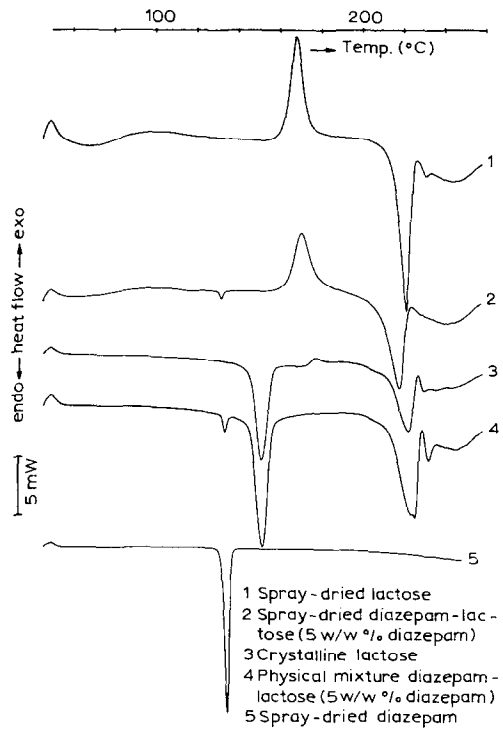

Fig. 3. DSC curves of different diazepam–lactose products.

of the spray-dried products, respectively. The results show the absence of the characteristic endothermic melting peak at 128° C for the spray-dried products containing 3, 4 and 5% (w/w) diazepam, as compared to the physical mixtures in which this peak is clearly visible. The absence of the melting peak for the spray-dried products indicates that the diazepam molecules are molecularly dispersed throughout a matrix of β-cyclodextrin molecules. In contrast to this, it is unlikely that a molecular dispersion of diazepam can be obtained by spray-drying the drug with a non-complexing excipient, like lactose. This is endorsed by the DSC curve of a spray-dried diazepam–lactose product (containing 5% w/w diazepam), still showing the characteristic diazepam melting peak (Fig. 3). Moreover, the "ether-wash" method revealed a free fraction of only 9% of the total diazepam content for the diazepam–β-cyclodextrin (5% w/w) spray-dried product, but 92% for the comparable diazepam–lactose product. TLC proved no decomposition of diazepam during spray-drying. De-

composition of β-cyclodextrin was excluded by determination of the β-cyclodextrin content of the products (according to Vikmon, 1982). From these data it was concluded that inclusion complex formation with β-cyclodextrin was indeed obtained for the spray-dried products containing 3.4% and 5.0% (w/w) diazepam, respectively. These results are in agreement with other studies concerning the preparation of cyclodextrin complexes by spray-drying (Kata and Haragh, 1981; Kata and Gyorgy, 1982; Kata and Wayer, 1985; Kata and Kedvessy, 1987). The diazepam–β-cyclodextrin complex appeared to be relatively stable as no changes in the DSC curves and diazepam content were observed after storage of the complex for a period of one year at ambient conditions (data not shown).

Intrinsic dissolution rate studies

The effect of β-cyclodextrin on the solubility of diazepam was studied by Andersen and Bundgaard (1982), and by Uekama et al. (1983). They showed that complexation resulted in an increased solubility of diazepam.

The intrinsic dissolution rates at pH 7 of diazepam and of β-cyclodextrin or lactose from the spray-dried products made, are presented in Table 1. The dissolution rate of the drug was found to increase from 7 $\mu g \cdot cm^{-2} \cdot min^{-1}$ for pure diazepam to about 130 $\mu g \cdot cm^{-2} \cdot min^{-1}$ for the spray-dried diazepam–β-cyclodextrin product containing 9.6% (w/w) diazepam. The β-cyclodextrin showed likewise increasing intrinsic dissolution rates with decreasing diazepam content. For the pure β-cyclodextrin and the spray-dried product with 5% (w/w) diazepam, however, no significant difference in dissolution rate was found. From the DSC curves recorded, and the results of the ether-wash method, it may be assumed, that tablets containing up to 5% (w/w) diazepam are made up of hydrophilic β-cyclodextrin and hydrophilic drug–cyclodextrin complex only. At higher diazepam contents the tablets will, however, contain free hydrophobic diazepam in addition. The slowly dissolving diazepam will, as described by Higuchi (1967), form a layer adjacent to the interface during the dissolution process. The tablet surface will therefore become increasingly hydrophobic with increasing diazepam content, resulting in decreasing intrinsic dissolution rates. This assumption is confirmed by the results of the dissolution tests of the diazepam–lactose products, showing a continuous increase in dissolution rate of both diazepam and lactose with decreasing diazepam content. From these results it is concluded that complex formation plays only a minor role in affecting the dissolution rate of slightly soluble hydrophobic drugs, when present alongside high percentages of highly soluble hydrophilic

TABLE 1

Intrinsic dissolution rates of spray-dried products at pH 7

mean ± S.D.

Diazepam content (%)	Molar ratio	Diss. rate of diazepam ($\mu g \cdot cm^{-2} \cdot min^{-1}$)	Diss. rate of β-CD ($\mu g \cdot cm^{-2} \cdot min^{-1}$)	Diss. rate of lactose ($\mu g/cm^2 \cdot min$)
Diazepam–β-cyclodextrin				
100.0	–	7.1 ± 0.4	–	
17.6	1: 1	89 ± 4	1345 ± 197	
9.6	1: 2	131 ± 5	1997 ± 104	
5.0	1: 4	115 ± 4	3357 ± 185	
0.0	–	–	3249 ± 599	
Diazepam–lactose				
100.0	–	7.1 ± 0.4		–
17.6	1: 3.5	7.5 ± 0.4		2729 ± 95
9.6	1: 7	145 ± 62		7225 ± 949
5.0	1:14	280 ± 20		10280 ± 982
0.0	–	–		16010 ± 1280

TABLE 2

Tablet formulations (9 mm, 200 mg)

Tablet	A	B	C	D
Diazepam-β-cyclodextrin spray-dried	49.4%			
Diazepam spray-dried		2.5%		
Diazepam micronized			2.5%	2.5%
β-Cyclodextrin			46.9%	
Sodium starch glycolate	4.0%	4.0%	4.0%	4.0%
Microcrystalline cellulose	25.0%	25.0%	25.0%	25.0%
α-Lactose monohydrate	21.6%	68.5%	21.65%	68.5%

excipients. The complex formation is likely to affect the dissolution rate at relatively high drug concentrations. The results show, at a content of 17.6% (w/w) diazepam, an intrinsic dissolution rate of the drug of 89 $\mu g \cdot cm^{-2} \cdot min^{-1}$ for the spray-dried β-cyclodextrin product, but of only 7.5 $\mu g \cdot cm^{-2} \cdot min^{-1}$ for the spray-dried lactose containing product.

In vitro release rate studies

The in vitro drug release was studied on differently formulated tablets (Table 2) and capsules (Table 3). The release profiles from the tables are illustrated in Figs. 4 and 5. At pH 7 totally different release rates were found for the different formulations. In 0.1 N HCl, however, no significant differences were observed. The latter is explained by the high solubility of diazepam at pH 1.

In order to eliminate the effect of disintegration of the tablet on the release rate of the drug, micronized diazepam, a physical mix of diazepam (5% w/w) with β-cyclodextrin, and the spray-dried products of diazepam (5% w/w) with β-cyclodextrin or with lactose, respectively, were filled into capsules (Table 3) and tested for dissolution at pH 7 (Fig. 6). The results show an increased release rate on addition of hydrophilic β-cyclodextrin to the very slightly soluble hydrophobic diazepam. Highest dissolution rates were found for the spray-dried products with β-cyclodextrin and lactose. It should be noted, that the spray-dried diazepam–lactose product dissolved even slightly faster than the diazepam–β-cyclodextrin complex ($P < 0.05$). The order of the sequence of dissolution rates, as obtained at 50 rpm of the paddle in the USP dissolution model, is consistent with the data of the intrinsic dissolution rates, but deviates from the in vivo absorption profiles (Fig. 9). Taking into account that the literature points to mild agitation in the gastrointestinal tract (Levy, 1963; Rothe and Schellhorn, 1977; Proost et al., 1983), the dissolution tests were also performed at 20 rpm of the paddle (Fig. 7). Now the results showed faster dissolution of the drug from the

TABLE 3

Capsule formulations

Capsule no.	Diazepam	β-Cyclodextrin	Lactose	Processing
1	5 mg	–	–	micronized
2	5 mg	93 mg	–	mixed
3	5 mg	93 mg	–	spray-dried
4	5 mg	–	93 mg	spray-dried

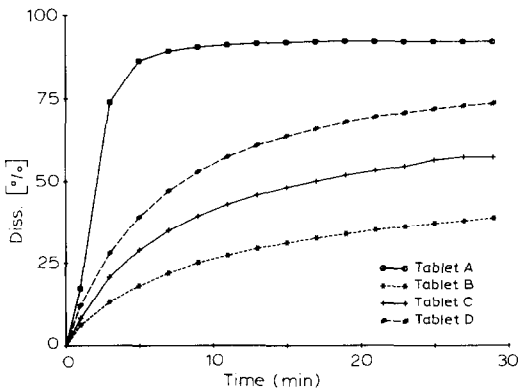

Fig. 4. Dissolution profiles of diazepam tablets, determined at pH 7, and 50 rpm (for tablet formulations see Table 2).

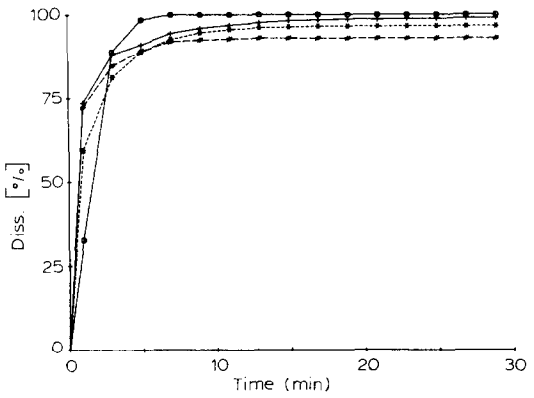

Fig. 5. Dissolution profiles of diazepam tablets, determined at pH 1, and 50 rpm (legend as in Fig. 4).

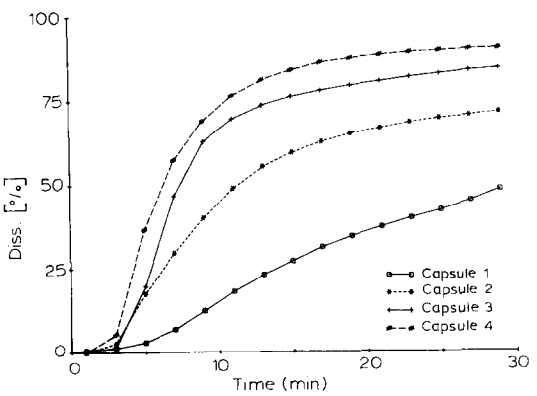

Fig. 6. Dissolution profiles of diazepam capsules, determined at pH 7, and 50 rpm (for capsule formulations see Table 3).

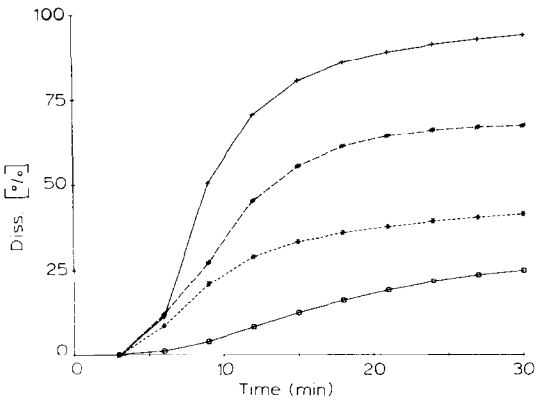

Fig. 7. Dissolution profiles of diazepam capsules, determined at pH 7, and 20 rpm (legend as in Fig. 6).

capsule containing the diazepam–β-cyclodextrin complex as compared to the spray-dried diazepam-lactose product. The difference in the results obtained at the two agitation intensities may be explained as follows. At low stirring rates the powders form an aggregate on the bottom of the beaker with a relatively large boundary layer. In the microenvironment, surrounding the aggregate, β-cyclodextrin causes an increase in diazepam solubility. This increase in solubility results into a more rapid dissolution of diazepam. This effect is of course not shown by lactose, as this substance does not enhance the diazepam solubility. This additional dissolution rate-enhancing effect of β-cyclodextrin is absent when higher stirring rates

TABLE 4

Diazepam plasma levels of the human volunteers

Mean ± S.D.

Time (min)	Diazepam plasma concentration (μg/l)				
	Reference	Capsule 1	Capsule 2	Capsule 3	Capsule 4
0		0 ± 0	0 ± 0	0 ± 0	0 ± 0
10	542 ± 123	2 ± 5	0 ± 0	5 ± 9	0 ± 0
20	472 ± 100	6 ± 7	20 ± 32	30 ± 24	28 ± 63
30	416 ± 88	21 ± 17	70 ± 49	107 ± 61	78 ± 77
40		58 ± 47	95 ± 49	160 ± 61	104 ± 49
60	347 ± 90	82 ± 39	130 ± 38	174 ± 31	155 ± 25
90		94 ± 38	140 ± 21	179 ± 28	155 ± 24
120	268 ± 83	94 ± 23	123 ± 15	154 ± 30	126 ± 16
180	216 ± 73	81 ± 19	99 ± 22	119 ± 19	98 ± 17
240	195 ± 53	74 ± 15	85 ± 25	99 ± 28	86 ± 19

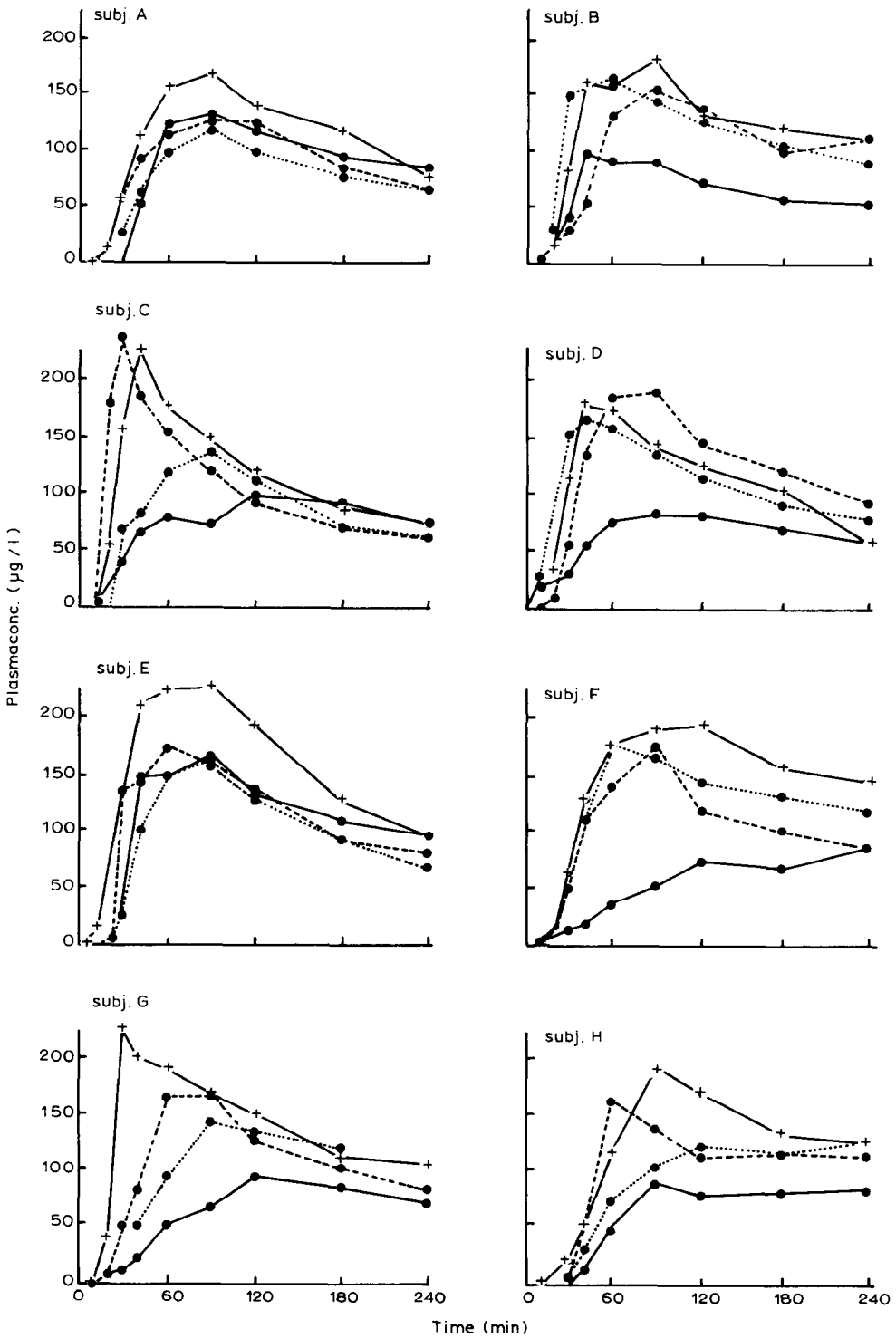

Fig. 8. Individual plasma of diazepam calculated using numerical deconvolution (legend as in Fig. 6).

are applied. This is explained by the dispersion of the dissolving particles over the entire beaker, resulting in small boundary layers. As the β-cyclodextrin amount is too low to increase the diazepam solubility in the bulk significantly, its additional dissolution rate-increasing effect is not observed here. It is thus evident that stirring speed is a critical parameter in the evaluation of the described products.

In vivo results and their correlation to in vitro data

The 4 differently formulated capsules (Table 3) were given to 8 male volunteers. In Table 4 and Fig. 8 the (mean) plasma levels are presented. The differences observed between the different formulations, indicate that the in vivo dissolution occurs not only in the acidic stomach fluids, but also in the small intestine. This is in accordance with the short transit times of solid dosage forms in the stomach, as observed by Davis (1986) in fasted volunteers.

As the absorption behaviour was the main interest of this study, plasma data were calculated in absorption profiles by numerical deconvolution. The numerical deconvolution was applied using the i.v. data obtained by Moolenaar et al. (1980) as reference. Table 5 and Fig. 9 present the results of this treatment.

The t_{max} and C_{max} were considered to be inappropriate absorption parameters in this study, as

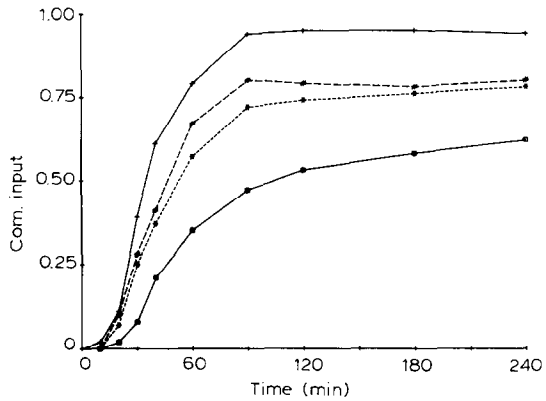

Fig. 9. Mean absorption profiles of diazepam calculated using numerical deconvolution (legend as in Fig. 6).

the determination of t_{max} depends strongly on the sample times; the C_{max} is of little value because of the slow elimination of diazepam as compared to absorption rate.

AUCs at 60, 120 and 240 min were calculated as a relative measure of absorption (Table 6). In order to see whether the differences found were statistically significant, the results were compared using an ANOVA (Table 7). From the AUC data it follows that the capsules, except for the formulations 2 and 4, show significantly different absorption behaviour. Capsule 3 gave the highest absorption, followed by the capsules 2 and 4, while capsule 1 was lowest. Moreover, the AUC data particularly point to differences in absorption rate of the drug, rather than the extent of absorption, as the relative differences in the AUCs are largest at 60 min and smallest at 240 min. The AUC data are also found to be in good agreement

TABLE 5

Amounts diazepam absorbed, as fraction of the total dose, calculated using numerical deconvolution

Mean ± S.D.

Time (min)	Cumulative input			
	Capsule 1	Capsule 2	Capsule 3	Capsule 4
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10	0.01 ± 0.02	0.00 ± 0.00	0.02 ± 0.03	0.00 ± 0.00
20	0.02 ± 0.03	0.07 ± 0.11	0.11 ± 0.09	0.10 ± 0.22
30	0.08 ± 0.06	0.25 ± 0.18	0.39 ± 0.22	0.28 ± 0.29
40	0.21 ± 0.17	0.37 ± 0.20	0.61 ± 0.24	0.41 ± 0.22
60	0.35 ± 0.17	0.57 ± 0.18	0.79 ± 0.17	0.67 ± 0.12
90	0.47 ± 0.20	0.72 ± 0.13	0.94 ± 0.13	0.80 ± 0.10
120	0.53 ± 0.15	0.74 ± 0.09	0.95 ± 0.15	0.79 ± 0.08
180	0.58 ± 0.14	0.76 ± 0.12	0.95 ± 0.12	0.78 ± 0.08
240	0.62 ± 0.13	0.78 ± 0.14	0.94 ± 0.16	0.80 ± 0.10

TABLE 6

Areas under the curve for the different capsules at different times

Mean ± S.D.

	AUC (60 min) (min·μg/l)	AUC (120 min) (min·μg/l)	AUC (240 min) (min·μg/l)
Capsule 1	1948 ± 1110	7423 ± 2966	17,274 ± 4681
Capsule 2	3622 ± 1719	11730 ± 2616	23837 ± 3576
Capsule 3	5536 ± 1984	15872 ± 2634	30524 ± 3908
Capsule 4	4124 ± 2026	13075 ± 2073	25131 ± 2344

TABLE 7

Results of the ANOVA of AUC at 60, 120 and 240 min

Degree of freedom for the capsules = 1; degree of freedom for the residuals = 7

Capsule reference : test	Probability of F		
	AUC (60 min)	AUC (120 min)	AUC (240 min)
1 : 2	0.024	0.015	0.035
1 : 3	< 0.001	< 0.001	< 0.001
1 : 4	0.015	0.002	0.005
2 : 3	0.046	0.006	0.001
4 : 2	0.605	0.182	0.292
4 : 3	0.040	0.007	0.008

with the deconvolution results of the mean plasma levels, as the same rank order is obtained.

Comparison of the in vivo absorption profiles (Fig. 9) with the in vitro dissolution rates of the drug from the differently formulated capsules (Figs. 7, 8) show a corresponding rank order, when the in vitro dissolution test was performed at 20 rpm of the paddle. No conformity was obtained at 50 rpm with regard to the position of capsule 4, as compared to capsule 3. This indicates, as mentioned before, that in vivo dissolution occurs under low agitation intensities. Under these circumstances the cyclodextrin is able to increase the solubility of diazepam in the microenvironment of the dissolving particles, and will thereby enhance the absorption of the drug.

Conclusions

The incorporation of the very slightly soluble and hydrophobic drug diazepam into highly soluble hydrophilic excipients, like lactose or β-cyclodextrin, was found to increase both the in vitro release rate, and the in vivo absorption rate of the drug from solid dosage forms. The spray-dried products showed higher release and absorption rates, as compared to the physical mixtures, pointing to the influence of the processing of drug and excipients.

Intrinsic dissolution measurements indicated that the effect of complex formation with the hydrophilic β-cyclodextrins was only of influence at a relatively high content of the hydrophobic diazepam. In the presence of high percentages of highly soluble hydrophilic excipients, complex formation plays only a minor role in determining the dissolution rate.

In vitro release rate experiments, however, showed that under low agitation intensities dissolution rate is enhanced by β-cyclodextrin complexation, due to the increased solubility of diazepam in the microenvironment of the dissolving particles. As the in vivo dissolution also occurs under low agitation intensities, the complex-forming ability of cyclodextrin leads to increased diazepam absorption rates.

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