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The effect of in-vivo dispersion and gastric emptying on glibenclamide absorption from a novel, rapidly dissolving capsule formulation

J. A. GANLEY*†, J. MCEWEN**, R. T. CALVERT† AND M. C. J. BARKER††

*Pharmaceutical Development Department, Hoechst Pharmaceutical Research Laboratories, Walton Manor, Walton, Milton Keynes, Bucks MK7 7AJ. **Clinical Pharmacology Department, Hoechst Pharmaceutical Research Laboratories, Walton Manor, Walton, Milton Keynes, Bucks MK7 7AJ. †Pharmacy Department, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX. ††Department of Nuclear medicine, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX UK

The in-vivo dispersion and gastric emptying of a novel glibenclamide dose form have been investigated using γ-scintigraphy and related to the absorption of glibenclamide determined by measuring glibenclamide plasma concentrations. Its absorption is determined by the rate of emptying of the dose form from the stomach with the lag time between dosing and the start of gastric emptying (and hence absorption of the dose) largely dependent on the in-vivo disintegration time. The presence of food in the stomach has a marked effect on in-vivo disintegration/dispersion of the dose form and hence on the lag time between dosing and the start of absorption.

A novel glibenclamide capsule formulation has been prepared by dissolving glibenclamide in a molten polyoxyethylene base and filling the resulting solution into hard gelatin capsules in which the melt solidifies on cooling (Walker et al 1982). The major difference between the performance of this product and conventional glibenclamide oral dosage forms is the rapid dissolution of drug. In healthy volunteers this is reflected by the attainment of effective glibenclamide plasma concentrations associated with a hypoglycaemic effect which is fast in onset and of relatively short duration (Lawrence et al, in press). This rapid and short-lived action suggests the possibility of matching the glibenclamide plasma profile to glucose absorption, with consequent improved control of post-prandial plasma glucose concentrations.

The rapid dissolution of glibenclamide from the novel capsule formulation may mean that dissolution is no longer the rate-limiting factor in glibenclamide absorption after oral dosing. A new rate-limiting stage in the absorption process will thus arise and it is likely to be related to the in-vivo behaviour of the capsule, particularly its disintegration, the dispersion of its contents and their emptying from the stomach from which, for reasons of relative surface area, little absorption would be expected.

γ-Scintigraphy is a useful non-invasive technique for the study of in-vivo behaviour of pharmaceutical dosage forms and the investigation of gastric emptying (Digenis et al 1976; Hunter et al 1980, 1982). The capsule formulation is ideally suited to investigations using γ-scintigraphy since the contents may be readily labelled using a solution containing Technetium 99 m to give a homogeneous mix. The small amount of radiolabelled solution required does not change the nature or performance of the dosage form and the homogeneity of the contents ensures that the behaviour of the radioactive marker reflects that of the unabsorbed drug.

We have attempted to relate the potential absorption rate-limiting factors—capsule disintegration, dispersion and gastric emptying of contents—to drug absorption as measured in plasma.

Since gastric emptying is considerably influenced by the presence of food, the study was with volunteers who had fasted and after they had had a light meal.

MATERIALS AND METHODS

Subjects

Four healthy male volunteers, 26–38 years, each within ±10% of the average weight for his height, underwent a comprehensive routine clinical and biochemical examination before entry to the study.

Study design

The study was on day 1 and day 3 of a three day period and was based on a balanced cross-over design related to food intake. The dose, one capsule containing 1 mg of glibenclamide together with 50 μCi of Technetium 99m–DTPA chelate, was administered with 100 ml of water (also labelled with

* Correspondence.

50 μCi of Technetium 99m–DTPA to outline the position of the stomach). Subjects remained seated for the first 90 min after dosing.

On each of the two study days, two of the subjects received the dose following an overnight fast, and they remained fasting for 90 min post dose. The other two subjects received the dose immediately following a standard breakfast of two slices of toast, 16 g of butter, a pack of marmalade and a cup of tea or coffee with sugar.

Preparation of the dose form

The polyoxyethylene matrix containing glibenclamide was prepared in bulk before the study by dissolving 1 g of glibenclamide in 120 g of molten base at a temperature not exceeding 60 °C. The resulting solution in 5·0 g amounts was distributed into 25 ml beakers, allowed to cool and solidify and then covered with paraffin film and stored at 5 °C. On the morning of each study day a solution of Technetium 99m (Diethylenetriaminepentacetic acid chelate : Technetium–DTPA) was prepared by reconstituting a commercial DTPA kit (CIS (UK) Ltd TCK.6.) with the eluate from a Technetium generator. The resulting solution was diluted with 0·9% NaCl (saline) to an activity of 5000 μCi ml^{-1}.

A 5 g amount of the pre-prepared matrix was melted at 60 °C in an oil bath and 0·40 ml of the solution of Technetium 99m–DTPA chelate in saline was added and mixed. Amounts of 130 mg of the resulting mixture were filled into size 2 hard gelatin capsules and allowed to cool and solidify. The capsules, each of which contained 1 mg of glibenclamide and 50 μCi of Technetium 99m, were check weighed before use. The homogeneity of the molten fill ensured that both glibenclamide and Technetium contents of individual capsules could be confirmed by fill weight determination.

γ-Scintigraphy

Each subject was seated on a high stool in front of the γ-camera (Elscint (GB) Ltd, Dymax Ltd, Dymax LF). Immediately after dosing, 60 serial 1 min scintiscans were recorded over the abdominal region and stored on magnetic tape. The time of the start of disintegration/dispersion of the capsule was determined by direct inspection of the serial scintiscans as were the boundaries of the stomach area. Gastric emptying was determined by counting the radioactivity remaining within the defined stomach area for each 1 min scintiscan and correcting the figures obtained for radionuclide decay. The resulting figures were corrected for the contribution of the water containing the radionuclide marker as follows.

Gastric activity not associated with the capsule was determined before capsule disintegration when capsule associated activity was easily measured and subtracted. An exponential emptying curve for the water was thus calculated and extrapolated post disintegration to enable gastric activity due to the radiolabelled water to be calculated at each time. Gastric activity due to the capsule contents was then obtained by subtraction.

Results were expressed as a percentage of the maximum value found.

Figures corrected for the contribution of the radiolabelled water did not differ greatly from uncorrected figures, probably reflecting the rapid dispersion of the hydrophilic capsule contents following disintegration.

Glibenclamide absorption

Samples of venous blood (5 ml in lithium heparin) were removed via an indwelling cannula before the dose and at the following times, post dose; at 3 min and then every 3 min up to 1 h, then at 75, 90, 105, 120, 150, 180, 210 and 240 min. Each sample was centrifuged immediately and the plasma was separated and frozen pending assay for glibenclamide.

Drug concentration in each plasma sample was determined by radioimmunoassay. The resulting drug plasma concentration profile was deconvoluted using the method of Wagner & Nelson (1963) to derive the drug absorption data for each subject on each study day. To enable easier comparison with gastric activity determined by serial scintiscans, the absorption data were expressed as a percentage (of the total drug absorbed) remaining to be absorbed at each time.

Pharmacokinetic analysis

Maximum drug plasma concentration and time to maximum value was obtained directly from the drug plasma profile for each volunteer. The profiles were subjected to an iterative curve-fitting procedure to obtain values for half-life. The area under the plasma concentration-time curve up to the last measured time (4) and the area under the curve extrapolated to infinite time were calculated using the trapezoidal rule (Yeh & Kwan 1978).

RESULTS AND DISCUSSION

The glibenclamide plasma concentration profiles for each subject, both in the fasting state and after food, are shown in Fig. 1. The pharmacokinetic paramet-

ers derived from these profiles are summarised in Table 1.

With all four subjects it was apparent that taking the dose after breakfast significantly delayed drug absorption. In subjects in the fasting state, glibenclamide was first detected in plasma between 12 and 24 min after dosing, but when the dose was taken after food the drug was not detectable until an hour or more post dose.

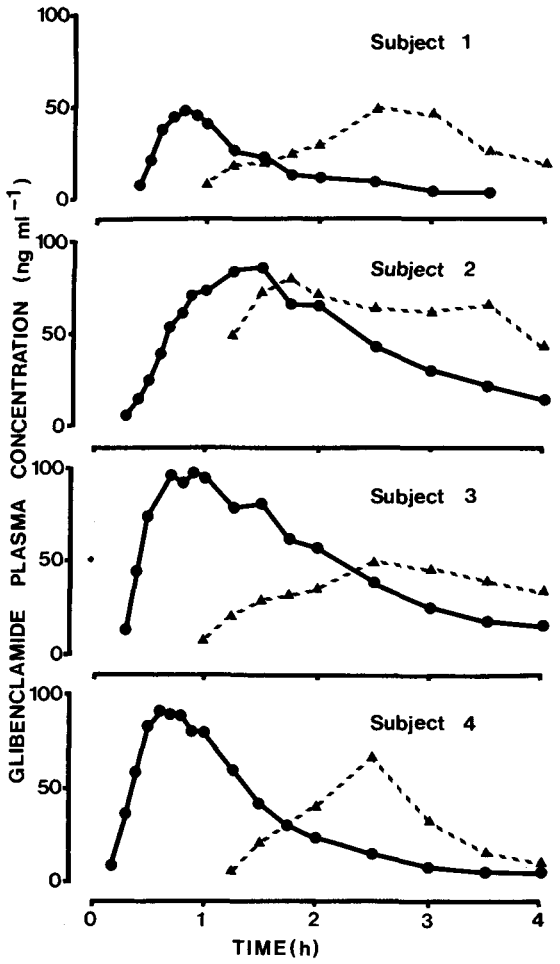

FIG. 1. Glibenclamide plasma profile for each subject dosed in the fasting state (●) and after a light meal (▲).

In the fasting state, the beginning of drug absorption indicated by its first appearance in the plasma, correlated well with the start of in-vivo capsule disintegration, as seen in the scintiscans (Table 2). In the four subjects the first detectable plasma values were seen within 4 min of the start of the disintegration/dispersion of the capsule. So the major component of the absorption lag time in the fasting state was the in-vivo disintegration of the capsule and the release of its contents.

When the dose was taken after food the capsule contents did not appear to disperse significantly in the subsequent 1 h in which scintiscans were taken, thereby preventing an accurate assessment of the start of in-vivo disintegration.

For each subject in the fasting state Fig. 2 shows the emptying of capsule-associated radioactivity from the stomach compared with the absorption of drug, in percentage terms for ease of comparison. The parameters derived from the absorption and gastric emptying curves are summarized in Table 2.

With subjects 2, 3 and 4 (Fig. 2) there was a clear relationship between gastric emptying and drug absorption. Although it was difficult to determine accurately the start of gastric emptying, because of inherent variations in the activity measurements, the start of drug absorption correlated well with the start of emptying assessed from the graph and also with the start of in-vivo disintegration. As can be seen from Table 2, absorption began within 1 to 4 min of the start of disintegration of the dose form.

The rate of drug absorption was also in excellent agreement with the rate of gastric emptying indicated by the slopes of the respective graphs. The shape and slope of the gastric emptying plot was remarkably paralleled by the corresponding glibenclamide absorption graph in Fig. 2. Although the

Table 1. Pharmacokinetic parameters derived from the plasma profile for each subject in both the fasting and non-fasting states.

	Fasting state				Non-fasting state			
Subject	1	2	3	4	1	2	3	4
Correlation coefficient	0·95	0·99	0·98	0·99	0·95	0·71*	0·97	0·99
Cp max (ng ml^{-1})	51	86	103	96	49	79	50	67
t max (h)	0·85	1·5	0·75	0·65	2·5	1·75	2·5	2·5
$t_{\frac{1}{2}}$ (h)	0·79	1·18	1·18	0·69	0·83	3·32	2·53	0·65
AUC 4 h (ng ml^{-1} h)	61	179	193	128	101	211	115	96
AUC ∞ (ng ml^{-1} h)	68	204	221	134	126	421	241	106

* Insufficient data for curve fitting.

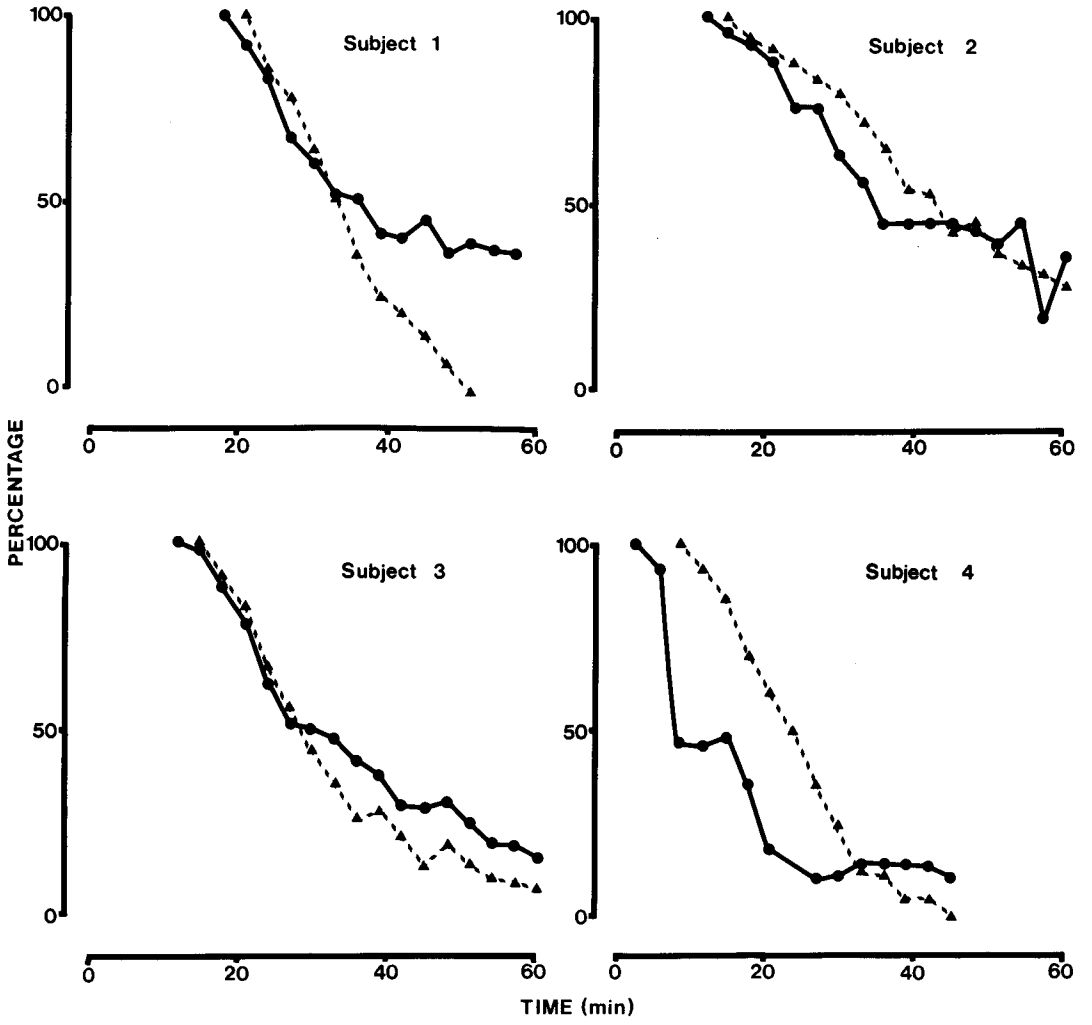

FIG. 2. Comparison of gastric emptying of the capsule contents (percent remaining in the stomach (●)) and absorption of glibenclamide (percent remaining to be absorbed (▲)) for each subject in the fasting state.

curves for gastric emptying were not readily amenable to a single simple mathematical model, rate constants for zero order absorption and emptying were derived by regression analysis of the linear portions of the curves to allow direct comparisons. These rates are shown in Table 2 and demonstrate that although there was significant inter-individual variation in absorption rate (1·9–3·7% min^{-1}) this was wholly mirrored by differences in emptying rate (2·2–3·7% min^{-1}). Individual differences in the shape of the absorption profile were similarly mirrored by differences in gastric emptying. Thus absorption of glibenclamide from this rapidly dissolving formulation was controlled by the emptying of the dose form from the stomach.

With subject 1 the relationship between gastric emptying and glibenclamide absorption was less obvious. Although the start of drug absorption correlated well with the start of in-vivo disintegration of the capsule and gastric emptying, the slopes of the emptying and absorption curves differed significantly. This appeared to be due to low bioavailability in this subject.

Low bioavailability was a surprising finding with such a rapid release product but was consistent with the data available. In the fasting state in subject 1, glibenclamide plasma concentrations were much lower than those for the other three subjects. This was evident both in a low maximum plasma concentration and in a lower area under the plasma

Table 2. Parameters derived from in-vivo capsule behaviour and drug absorption for each subject in the fasting state.

Subject	1	2	3	4	1*
Disintegration (min)	18	11	13	8	18
Emptying onset (min)	18	12	12	(3)	18
Absorption onset	21	15	15	9	21
Emptying rate % min^{-1}	2·4	2·1	3·8	3·8	2·4
Absorption rate % min^{-1}	(4·2)	1·9	3·6	3·7	2·5
Absorption/emptying	(1·75)	0·90	0·95	0·97	1·04

* Corrected for 60% bioavailability.

concentration curve (see Table 1 and Fig. 1). For subject 1, the area under the curve in the fasting state was also lower than that after food. Although the pharmacokinetic parameters were variable with all subjects, this higher area for post-food dosing reinforced the suggestion of a low bioavailability in the fasting state. The gastric emptying curve showed that a plateau was reached with about 40% of the activity remaining in the stomach and incomplete emptying would provide a reason for low bioavailability. Inspection of the scintiscans at later times indicated that the bulk of the residual activity in the stomach was high in the fundus—probably due to the attachment of a part of the dose form to the mucosa in an area where there was insufficient fluid to promote dissolution and dispersion.

Retention was almost certainly influenced by the complete lack of subject movement over the first hour of the test which was necessary to enable reproducible scintiscans to be obtained. It was surprising, however, that the effect persisted over the 4 h of the test as indicated by the absence of a second glibenclamide plasma peak.

Bioavailability considerations affect correlation between drug absorption and gastric emptying because the absorption percentages derived from the Wagner Nelson deconvolution are percentages of the amount of drug absorbed, whereas the emptying figures relate to the total dose administered. Unfortunately, an accurate assessment of bioavailability could not be made from the data available, but a figure of 60% for subject 1 in the fasting state, was estimated on the basis of a combination of relative intersubject plasma values and the area under the plasma concentration curve from the fasting state compared with that from the non-fasting state. When the absorption curve for subject 1 was corrected for the estimated 60% bioavailability, the correlation with gastric emptying was excellent and comparable with the other subjects (Fig. 3, Table 2).

When the capsule was taken after food neither emptying of the capsule contents from the stomach nor absorption of drug occurred during the 1 h when scintiscans were obtained, making correlation between gastric emptying and drug absorption impossible.

Inspection of the scintiscans in the post food studies indicated that the effect of the food was largely in inhibiting the dispersion of the drug from the dose form within the stomach. The food was expected to promote gastric motility and hence dispersion, but the need for the subject to remain motionless in front of the γ-camera may have influenced the outcome.

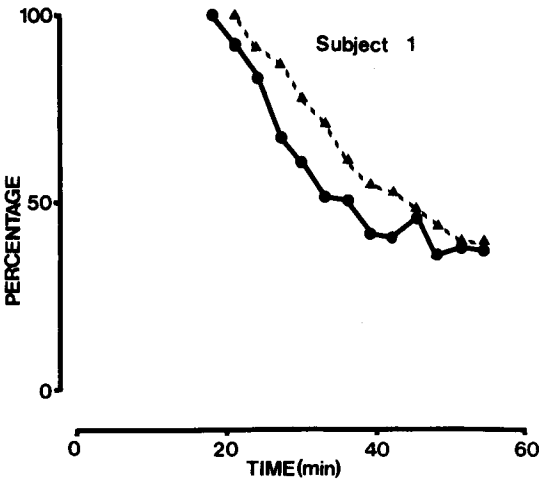

FIG. 3. Comparison of gastric emptying of the capsule contents (percent remaining in the stomach (●)) and absorption of glibenclamide (percent remaining to be absorbed (▲)) for subject 1 in the fasting state after correction for 60% bioavailability.

The implications of the results go beyond the specific novel dose form investigated. Gastric emptying has previously been found to be a rate limiting stage in the absorption of acetaminophen from a relatively large volume solution formulation (Clements et al 1978) and is likely to be a main factor with other oral dose forms, particularly those capable of rapid in-vivo dissolution, as these are likely to be sensitive to factors affecting gastric emptying.

Minimizing the variation in gastric emptying of dose forms, for example by the use of readily dispersible formulations, and by optimizing dosing instructions, should have a beneficial effect on the consistency of their performance. There are factors that could influence the reproducibility of gastric emptying—volume of liquid co-administered, timing of the dose relative to food, the influence of a second

drink shortly after dosing. These factors could repay investigation.

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