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Dosage forms with controlled gastrointestinal passage – studies on the absorption of nitrofurantoin

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Summary

The aim of the present investigation was to describe theoretically the influence of the rate of gastrointestinal passage on the absorption of drugs after peroral administration and to use this description in the practical development of new types of dosage forms. The intention in these studies was to devise peroral dosage forms that display a delayed gastrointestinal passage through the release of a passage-influencing excipient. The saturated fatty acid myristic acid was used as a substance for controlling gastrointestinal passage, since this acid, as a constituent of fat-rich food, delays transit through the alimentary tract. The ammonium salt was used to optimise the properties of myristic acid for use in oral dosage forms. In a comparative in vivo study with 5 healthy subjects, the effects of 107.5 mg ammonium myristate on the absorption of nitrofurantoin after the administration of sustained release preparations (dose: 100 mg) was determined indirectly on the basis of the renal excretion of the drug. A commercially available sustained release preparation in capsule form was used, that was given with and without ammonium myristate in a larger hard gelatine capsule. The addition of ammonium myristate led to an average increase of 23.8% of the total amount of nitrofurantoin excreted in the urine compared to the values obtained from the reference dosage form without the additional substance. The increase in renal excretion was statistically significant ($P < 0.01$). On evaluating the time course of urinary excretion of the drug, the amounts of nitrofurantoin excreted after administration of the dosage form with myristic acid were significantly higher ($P < 0.05$) in the 5th, 6th, 7th and 9th hours after dosage.

Introduction

Peroral drug preparations can show considerable differences in bioavailability despite their containing the same amount of active ingredient. One reason for the reduced absorption of a drug is that the optimum possible absorption only occurs in the upper parts of the intestine. Slow releasing drug preparations reach lower regions of the gastrointestinal tract where, despite complete release of the drug, its absorption is reduced because of the markedly decreased area of absorption and the possible degradation of drug by intestinal bacteria. A delay in passage caused by the presence of food can, in a few cases, lead to an improvement in the bioavailability of drugs (Beermann and Groschinsky-Grind, 1978; Kaumeier, 1980).

Attempts can be made by the development of special dosage forms that remain for a long period in the upper, absorbing part of the intestine, to

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achieve more complete absorption even with drugs that show a limited period of absorption.

The aim of the present studies was to develop dosage forms that, alongside the active ingredient, contain excipients that when released delay gastrointestinal passage of the drug.

Salts of myristic acid were used as controlling substances, because gastrointestinal investigations have suggested that myristic acid can be described as a model substance in the diet (Hunt and Knox, 1968). This fatty acid, formed by the hydrolysis of dietary fats in the duodenum, causes an inhibition of the forward movement of the chyme via receptors in the duodenum and jejunum. In previous studies, the prolongation of gastric residence time by low concentrations of the triethanolamine salt of myristic acid was demonstrated using a pH-telemetering capsule (Gröning and Heun, 1984).

Experimental

Pharmacokinetic calculations

Computer: Apple II e, Apple Computer Inc., USA-Cupertino. A computer program using the Gompertz function (Batschelet, 1980) was developed to calculate the drug concentrations that arise after oral application of dosage forms, taking into account limited regions of absorption.

The calculation of the values for the constants k, A and B was carried out in an iterative manner, based on the given time values $T1$ and $T2$, which define the duration of absorption of a drug. In the time interval between $T1$ and $T2$, the probability of absorption decreases from 0.9 to 0.1. The calculation of the amounts of drug A_1, A_2 and A_3 is carried out by numerical integration of the differential equation system. A program listing is available from the authors on request.

Manufacture of the double capsules

The double capsules were made individually. Capsules of size 0 (colourless) were filled with an inner drug capsule (Furadantin retard 50 Kapseln N2, Ch.B.: 73505403, Röhm Pharma, Darmstadt, F.R.G.) with and without ammonium myristate. The experimental dosage form contained, in the outer capsule: Ammonium myristate, 107.5 mg; granulatum simplex, 15.0 mg; aerosil 200, 2.0 mg. The control dosage form was filled with a mixture of: Granulatum simplex, 100.0 mg; aerosil, 2.0 mg.

Clinical experiments

Experimental plan. Table 1 shows the details of the subjects and the sequence in which the dosage forms were administered. The subjects were fully informed of the nature of the study which was carried out under medical supervision with ethical approval.

One hour before the administration, all subjects ate a standard breakfast consisting of 200 ml coffee and a buttered roll containing sliced sausage.

The dosage form was taken at 09.00 h with 200 ml water to ensure an adequate amount of urine for analysis. Urine was collected at hourly intervals for 9 h.

Polarographic determination of the nitrofurantoin excretion. The content of nitrofurantoin in the urine was measured by differential pulse polarography (Polarograph E 505, Metrohm, Herisau, Switzerland). The minimal detectable concentration was 0.2 μg/ml. The linearity range of the assay was between 0.2 and 5000 μg/ml. The coefficient of variation of 10 replicates of a concentration of 10 μg/ml in different urine samples was less than 2.1%.

Method: 10 ml phosphate buffer pH 7.2 (KH_2PO_4 34.0 g, NaCl 34.0 g, 1 N NaOH 189.0

TABLE 1

Details of the subjects and the application scheme

A, Capsule preparation without ammonium myristate; B, capsule preparation with addition of 107.5 mg ammonium myristate.

Subject no.	Age (years)	Sex	Body weight (kg)	Application 1	Application 2
1	25	male	88	A	B
2	24	male	76	B	A
3	28	female	50	A	B
4	24	male	75	B	A
5	41	male	83	A	B

ml (all 3 Merck, F.R.G) to 5000.0 ml purified water) are added to 10 ml samples of hourly excreted urine. The resulting mixture is de-aerated for 3 min with nitrogen, simultaneously maintained at 25.0 °C and then analysed by polarography. The determination is based on a previously constructed standard curve.

Results

Theoretical section and computer simulations

In the present study the Gompertz function

$$G(t) = A \times e^{-B \times e^{k \times t}} \quad (1)$$

was used to describe what proportion of a drug can still be absorbed after various times during gastrointestinal passage. The Gompertz function is a statistical function, that is originally used in connection with the mathematical description of mortality kinetics to calculate the time-dependent number of living individuals in a population where the mortality increases with time. In the Gompertz function, A and B are dimensionless constants, t is the time and k is a constant with the unit t^{-1}. The value of the constants can be determined by normalising the function to the initial value $G(0) = 1$ and by analysing the curve at the defined point of inflection $P_w(t_w \mid F(t_w))$. When the Gompertz function is used to describe gastrointestinal absorption, $G(0) = 1$ means that immediately after application, all the drug is available for absorption. Substituting with the initial condition $G(0) = 1$, one obtains:

$$1 = A \times e^{-B} \quad (2)$$

thus

$$B = \ln A \text{ or } A = e^{B} \quad (3,4)$$

Two independent constants remain, that can be calculated from the point of inflexion condition ($G(t_w) = 0$) and by substituting the coordinates of the point of inflexion in the original function:

$$B = 1 + \ln G(t_w) \quad (5)$$

$$k = -\ln(1 + \ln G(t_w))/t_w \quad (6)$$

Since with a slow decrease in absorption probability it is difficult to determine the centre of distribution or the point of inflexion, the estimation of the model constants B and k can be carried out more simply from the values of two points on the curve. By substituting the paired values for the 90% and 10% absorption probability, this gives, for example the following equation:

$$\ln 0.9 = B \times (1 - e^{k \times t_{90\%}}) \quad (7)$$

$$\ln 0.1 = B \times (1 - e^{k \times t_{10\%}}) \quad (8)$$

The equation system cannot be directly solved mathematically. The computer program devised in the present study to carry out pharmacokinetic calculations, therefore works with an iteration technique to determine the constants B and k for the Gompertz function. The time interval for a decrease of absorption probability from 90% to 10% is termed the absorption time limit. Various curves are shown in Fig. 1, that give the decrease in absorption probability with time according to the Gompertz function.

The values given for the duration of absorption relate to the period of decrease in absorption probability from 90% to 10% or from 0.9 to 0.1. The values of the constants B and k were calculated by iteration.

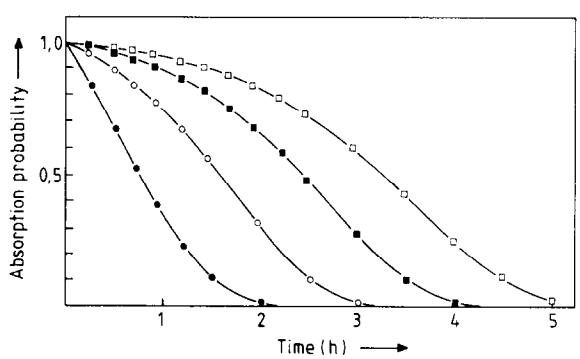

Fig. 1. Time course of the absorption probability calculated according to Eqn. 1. (-●-), Duration of absorption 0.17–1.15 h ($B = 0.498$; $k = 0.0192$ min^{-1}); (-○-), duration of absorption 0.5–2.5 h ($B = 0.134$; $k = 0.0193$ min^{-1}); (-■-), duration of absorption 1–3.5 h ($B = 0.0545$; $k = 0.0179$ min^{-1}); (-□-), duration of absorption 1.5–4.5 h ($B = 0.034$; $k = 0.0157$ min^{-1}).

To describe mathematically the uptake of the drug into the systemic circulation the superposition of the processes of release, absorption and statistical decrease in absorption probability must be taken into consideration. The following relationship applies to the amount of undissolved drug A_1 available in the gastrointestinal tract, independent of the release kinetics:

$$\frac{A_1(t)}{A_1(t-\Delta t)} = \frac{G(t)}{G(t-\Delta t)} \tag{9}$$

This equation can be transformed for the rate of decrease $dA_1(t)/dt$ by taking the limiting value:

$$\frac{dA_1(t)}{dt} = \frac{\dot{G}(t)}{G(t)} \times A_1(t) \tag{10}$$

which gives the following formula

$$\frac{dA_1(t)}{dt} = A_1(t) \times \frac{d}{dt} \ln G(t) \tag{11}$$

This produces the following differential equations for the mathematical description of the pharmacokinetic model:
(1) Amount of drug undissolved in the absorption area $A_1(t)$:

$$\frac{dA_1(t)}{dt} = k_f \times A_1(t) - A_1(t) \times \frac{d}{dt}(\ln G(t)) \tag{12}$$

(2) Amount of dissolved drug in the absorption area $A_2(t)$:

$$\frac{dA_2(t)}{dt} = -k_{01} \times A_2(t) + k_f \times A_1(t)\left[-A_2(t) \times \frac{d}{dt}(\ln G(t))\right] \tag{13}$$

(3) Central compartment $A_3(t)$:

$$\frac{dA_3(t)}{dt} = k_{01} \times A_2(t) - k_{10} \times A_3(t) \tag{14}$$

k_f: 1st order release rate constant
k_{01}: 1st order absorption rate constant
k_{10}: 1st order elimination rate constant

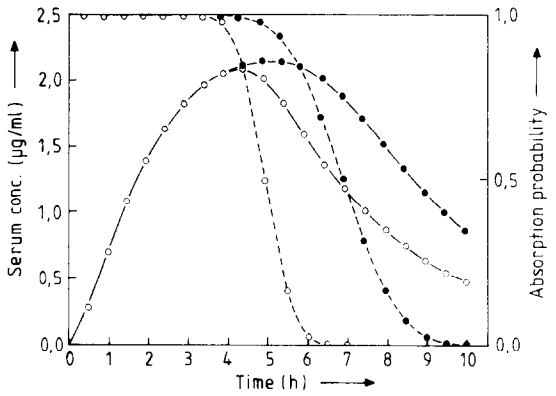

Fig. 2. Effect of passage delay on serum levels; computer simulation (100 mg; $V = 10$ l; $k_{01} = 0.05$ min^{-1}; $k_{10} = 0.005$ min^{-1}; $k_f = 0.02$; one compartment open model). (- -○- -) Duration of absorption 4.5–5.5 h; (-○-) serum level; (- -●- -) duration of absorption 5.5–8.5 h; (-●-) serum level.

By including the distribution volume V, a corresponding function $C_3(t) = A_3(t)/V$ can be given from the quantity function $A_3(t)$ to describe the change in concentration in the central compartment (plasma level, serum level).

The differential equation can be extended to include a distribution process in further compartments in the sense of a 2- or 3-compartment model.

The results of a computer simulation based on the mathematical model are given in Fig. 2. A drug that is only incompletely absorbed from a slow-releasing dosage form over 4.5 to 5.5 h shows better availability if its gastrointestinal passage is delayed.

In vivo investigations

Following investigations with riboflavin and triethanolamine myristate as model systems for dosage forms with active controlled gastrointestinal passage (Gröning and Heun, 1984), the aim of the present study was to determine whether the principle of delaying passage could improve the availability of nitrofurantoin from a commercial preparation (Furadantin retard capsules, 100 mg). It was also of interest to see whether the expected effect of delayed passage could also be demonstrated after a previously ingested light breakfast.

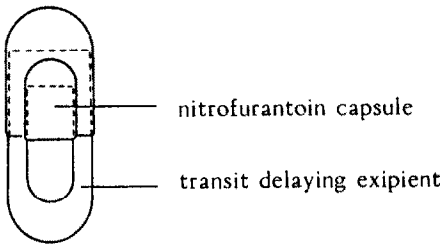

Fig. 3. Structural principle of the prepared dosage form.

Ammonium myristate was used as a substance for influencing gastrointestinal passage.

In order to affect the characteristics of the commercial preparation as little as possible, the investigations were carried out with a double capsule, whose structure is shown schematically in Fig. 3. The renal excretion of nitrofurantoin was used to assess the absorption of drug from the gastrointestinal tract.

The kinetics of urinary excretion show a significant increase in the rate of elimination in the region of the 5th, 6th, 7th and 9th hours after application (Fig. 4). Fitting the actual nitrofurantoin data to the previously described pharmacokinetic model the following results were obtained: Without ammonium myristate the duration of absorption ($T1$, $T2$) is 3 to 4 h. In the presence of ammonium myristate it is 4.5 to 5.5 h. The analysis of the data shows that the addition of ammonium myristate caused a delay of about 1.5 h in the transit time of the absorbing part of the gastrointestinal tract.

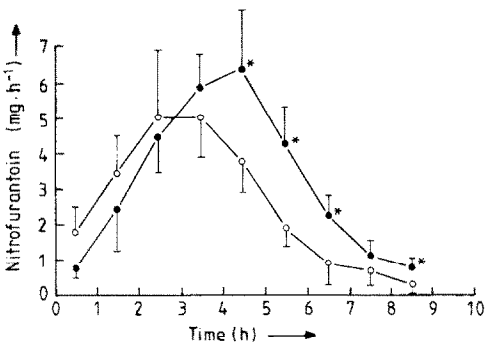

Fig. 4. Renal elimination of nitrofurantoin (dose: 100 mg; $n = 5$; mean $\pm$ S.D.; * $P < 0.05$). (-○-) Without ammonium myristate; (-●-) with ammonium myristate.

TABLE 2

Total renal elimination of nitrofurantoin

Subject	Furadantin retard with ammonium myristate	Furadantin retard without ammonium myristate
1	30.4	22.8
2	23.3	29.0
3	28.7	25.6
4	22.5	17.4
5	27.5	19.2
Mean	28.4	22.8
S.D.	13.9%	20.6%

As shown in Table 2, the total renal elimination in the presence of ammonium myristate was increased in all subjects. The mean renal elimination of nitrofurantoin expressed in terms of applied dose increased from 22.8 to 28.4%.

The t-test was used to statistically evaluate the paired data of the individual subjects. The 23.8% increase in total renal excretion of nitrofurantoin on addition of ammonium myristate as a passage-delaying substance compared to the control dosage form was statistically significant with a probability of error of less than 1%: $0.005 < P < 0.01$. The relative standard deviation of the individual differences fell at the same time from 20.6% with the control dosage form to 13.9% with the use of the active passage-controlling dosage form.

Discussion

In the present study it was possible to demonstrate that by addition of ammonium myristate, the availability of nitrofurantoin from a slow releasing dosage form can be improved. The effect on gastric residence time by similar substances has already been established in previous studies using a pH-telemetering capsule. A further indication of a comparable mechanism with ammonium myristate is given by the kinetics of renal elimination, that is characterised by the longer duration of urinary excretion.

In the present study, dosage forms were taken after a standard breakfast. However, the effect

achieved with ammonium myristate was over and above that of food.

Together with the increase in availability, a reduction in the interindividual variations in urinary excretion was also demonstrated. It may be possible, through the use of excipients, to make the conditions of absorption of drugs more uniform.

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