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ORAL DOSAGE FORMS WITH CONTROLLED GASTROINTESTINAL TRANSIT

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ABSTRACT

The present investigation concerns the development of new dosage forms which, after oral administration, exert an active influence on their gastrointestinal transit. The dosage forms release excipients which aim to increase the lenght of time the drug spends in the absorbing section of the duodenum and small intestine. A delayed gastrointestinal transit is intended to achieve a more complete and longer lasting absorption of drugs with a limited duration of absorption.
The present study examined whether, by incorporating triethanolamine myristate (165 mg) as an excipient in tablets containing riboflavine (20 mg) as an example of a drug with limited absorption, the gastrointestinal transit of riboflavine could be delayed and hence its absorption improved.
Five subjects took part in the in vivo studies and a

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pH-telemetering device (Heidelberg capsule) was used to determine gastric residence time.
The investigations showed that in 4 out of 5 subjects, the gastric residence time of the pH-telemetering capsule could be prolonged and the renal elimination of riboflavine increased. The increase in renal elimination of riboflavine in the presence of triethanolamine myristate was statistically significant in the 4th urine collection period ($0.05 > p > 0.0025$).

MATERIALS AND METHODS

The following substances were employed:
Riboflavine, Ph. Eur. (Hoffmann-La Roche, Grenzach,FRG)
Triethanolamine, pure (Hüls, Marl, FRG)
Sodium bicarbonate, Ph. Eur. (Mainland, Frankfurt, FRG)
L(+) Tartaric acid, Ph. Eur. (Merck, Darmstadt, FRG)
Potato starch, Ph. Eur. (Mainland, Frankfurt, FRG)
Lactose, Ph. Eur. (Mainland, Frankfurt, FRG)

Triethanolamine myristate was obtained by melting together equivalent amounts of myristic acid and triethanolamine.

Manufacture of the dosage forms:
Tablet press: Betema hand-operated press with compression tool for tablets. Punch diameter 12 mm, flat-faced, facetted (Betema, Berlin, FRG).
The composition of the myristic acid-containing tablet is given in Fig. 1. The tablet consists of two layers, one with the active ingredient (20 mg riboflavine) and the other with the transit delaying excipient (165 mg triethanolamine myristate). At first the active ingredient layer was compressed.
As a comparative preparation the active ingredient layer was used containing only 20 mg riboflavine in Granulatum simplex (Ph. Dan.).

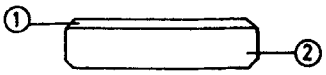
<table>
<tr><td>DOSAGE FORM: TWO-LAYER TABLET</td><td>DRUG: RIBOFLAVINE</td></tr>
<tr><td rowspan="2">  </td><td>DOSE: 20 mg</td></tr>
<tr><td>EXCIPIENT (TRANSIT-DELAYING):
TRIETHANOLAMINEMYRISTATE</td></tr>
<tr><td>ø = 12 mm, ROUND, BIPLANAR, FACETTED</td><td>DOSE: 165 mg ≙ 100 mg Myr. acid</td></tr>
<tr><td>① ACTIVE INGREDIENT LAYER
Riboflavine 20 mg
Granulatum simpl. 300 mg</td><td>② EXCIPIENT LAYER
Triethanolaminemyristate 165 mg
Na bicarbonate 50 mg
Tartaric acid 25 mg
Granulatum simplex 300 mg</td></tr>
<tr><td>320 mg / tablet</td><td>530 mg / tablet</td></tr>
<tr><td colspan="2">TOTAL WEIGHT OF TABLET: 850 mg</td></tr>
</table>

FIGURE 1

Composition of the Myristic Acid-containing Tablet

TABLE 1

Age and Body Weight of the Subjects

Subject	Age (years)	Body weight (kg)
1	25	83
2	22	83
3	24	70
4	39	84
5	25	73

Clinical studies:

Five healthy male subjects aged 22-39 years and weighing 73-84 kg took part on the cross-over in vivo studies (Table 1).

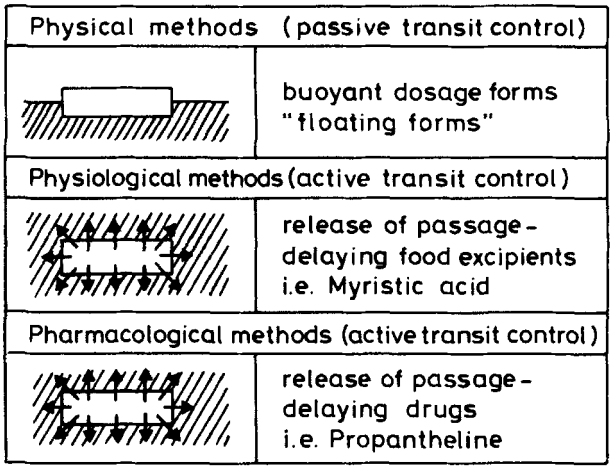


FIGURE 2
Methods of controlling Transit

Two preparations were tested. The subjects were fasted over night. At 09.00 hr the subjects swallowed one of the dosage forms followed immediatedly afterwards by the Heidelberg capsule (Telefunken, Berlin, FRG) with a total of 200 ml water. The pH-time profile of the pH-telemetering capsule was continuously recorded. From 11.00 hr onwards, 100 ml water was drunk at hourly intervals and at 14.00 hr, a standard meal consisting of two buttered rolls containing sliced sausage and cheese was eaten. Urine was collected hourly. The content of riboflavine was determined by densitometry (Chromatogramm Spektralphotometer KM 3; Zeiss, Oberkochem, FRG).
The statistical significance of the results was assessed using the student's t-test for paired values.

RESULTS AND DISCUSSION

The various ways that transit through the gastrointestinal tract may be actively and passively influenced are shown in Fig. 2.

In constructing floating forms[1], attempts are made to achieve the latest possible passage of the dosage form into the the duodenum without affecting gastric emptying. According to this control principle, the released and dissolved drug should reach the upper, absorbing part of the intestine from the stomach in small amounts, so that a complete and even absorption ensues.

By actively delaying transit, which was the concern of this study , the aim is to achieve a controlled gastrointestinal passage through the release of controlling substances from the drug form. Drugs such as propantheline or physiologically active constituents of foodstuffs, eg certain fatty acids, could be added in low concentrations as controlling agents[2]. The use of physiologically active elements of foodstuffs to regulate the gastrointestinal transit of drugs was the new development of the present investigations.

The use of transit-controlling dosage forms is of special interest for those drug substances which are only absorbed over a limited period from the duodenum or the upper part of the small intestine.

The results of computer simulations of the effects of transit-delaying measures on the serum concentration of a drug with a limited duration of absorption from the gastrointestinal tract are depicted in Fig. 3.

Without a delay in transit, the limit of absorption (Line A) is reached more quickly. Absorption remains incomplete. By delaying gastrointestinal transit, the drug spends longer in the absorbing section (Line B) and is more fully absorbed.

To calculate the limited absorption of drugs from the gastrointestinal tract, a new pharmacokinetic parameter - the absorption probability F_{abs} - is used[3]. The absorption probability indicates what proportion of

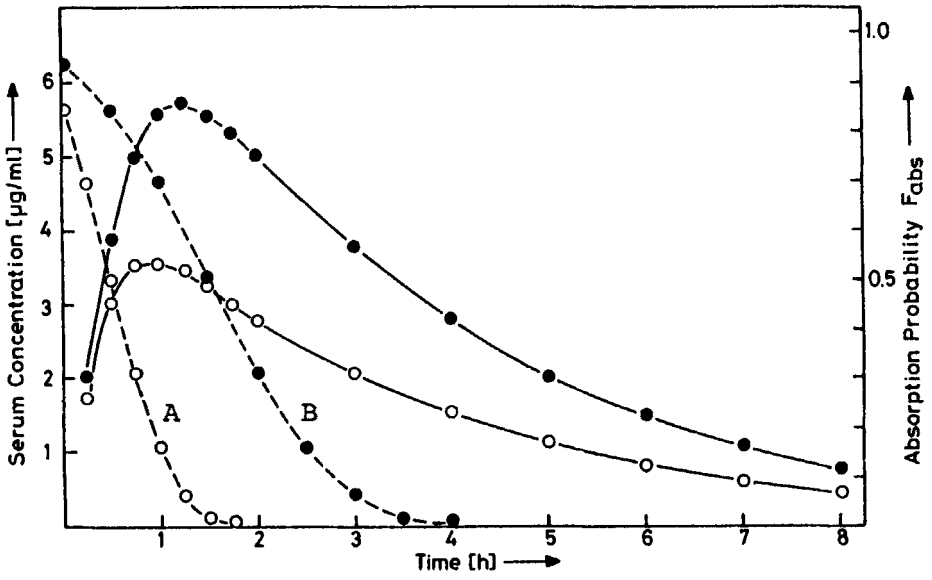


FIGURE 3

Effects of a transit-delaying Agent on the Serum Concentration of a Drug (Computer Simulation)
Dose: 100 mg, V_f = 10 l, k_a = 0.05 min^{-1}, k_e = 0.005 min^{-1}, k_f = 0.0385 min^{-1}

--o-- $F_{abs_{0.5}}$ = 30', σ = 30' (–o– Serum concentration)
--●-- $F_{abs_{0.5}}$ = 90', σ = 60' (–●– Serum concentration)

drug can still be absorbed after various times. The value F_{abs} = 0.5 states that only 50% of the drug present in the gastrointestinal tract can still be absorbed. The value 1 shows an optimal region of absorption. 0 indicates that no intact drug molecule can still be found in the absorbing section of the gastrointestinal tract.

To determine the distribution of drug molecules in relation to the absorbing section, the inverse cumulative probability distribution of the standard normal distribution ($F_{(c')}$) is used. $F_{(c')}$ is calculated from the following formula:

$$F_{(c')} = 1 - \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{c} e^{-c^2/2}\, dc$$

In the present study, $F_{(c')}$ is defined as absorption probability F_{abs} of a drug when the state of the probability distribution in relation to the time axis of the particular blood level-time relationship is specified. The indipendent variable c of the cumulative probability distribution is thus related to the independent variable t (time) of the blood level-time curve by the position of the point of inflection ($F_{abs\ 0.5}$) on the time axis and by the detailing of a defined time interval for the standard deviation.

The delay in gastric emptying after meals rich in fats is largely caused by the saturated fatty acids, with a chain length of C 10 to C 14, which arise after hydrolysis of fats present in foods in the duodenum[4]. In the present investigation myristic acid (C 14) was used as a transit-delaying agent.
Since by introducing fatty acids as transit-delaying agents, natural control mechanisms are invoked without involving systemic side effects as with drug substances (eg propanthelin), this principle is preferred.
To improve the solubility or dispersibility of myristic acid, the triethanolamine salt is included in the dosage form. The triethanolamine myristate, when present in aqueous dispersions (1%) has a pH of about 7.3, whilst the sodium salt for example, in a corresponding concentration has an alkaline pH of about 8.7.

The construction of the myristic acid-containing tablet is shown in Fig. 2. A two layer tablet has been developed consisting of a layer of drug containing 20 mg riboflavine as an example of a drug with a limited absorption in a potato starch-lactose granulate

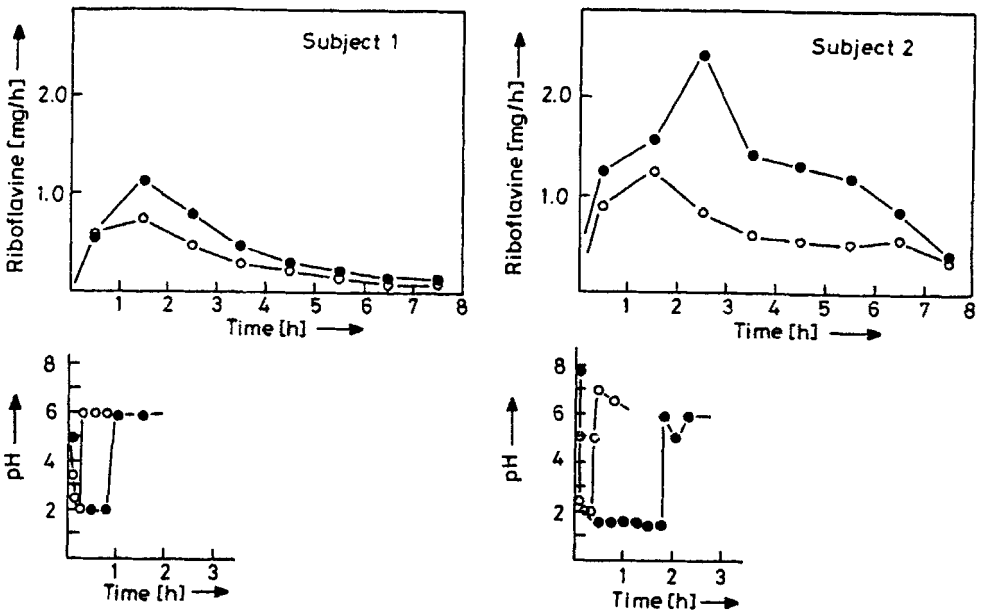


FIGURE 4

Gastric Transit of the pH-telemetering Capsule and renal Elimination of Riboflavine

- ● - with
- o - without

Triethanolamine Myristate

(7:3, Granulatum simplex Ph. Dan.) and a layer of excipient containing triethanolamine myristate. To ensure an optimal release of triethanolamine myristate, the substance is used with an effervescent mixture. For comparison with the two layer tablets, myristic acid-free tablets containing only 20 mg riboflavine in Granulatum simplex were included in the study. The tablets were investigated in a cross-over experiment in vivo in 5 fasting subjects. The renal elimination of riboflavine was determined at hourly intervals.

To discover to what extent triethanolamine myristate influenced the gastric transit times of drug forms,

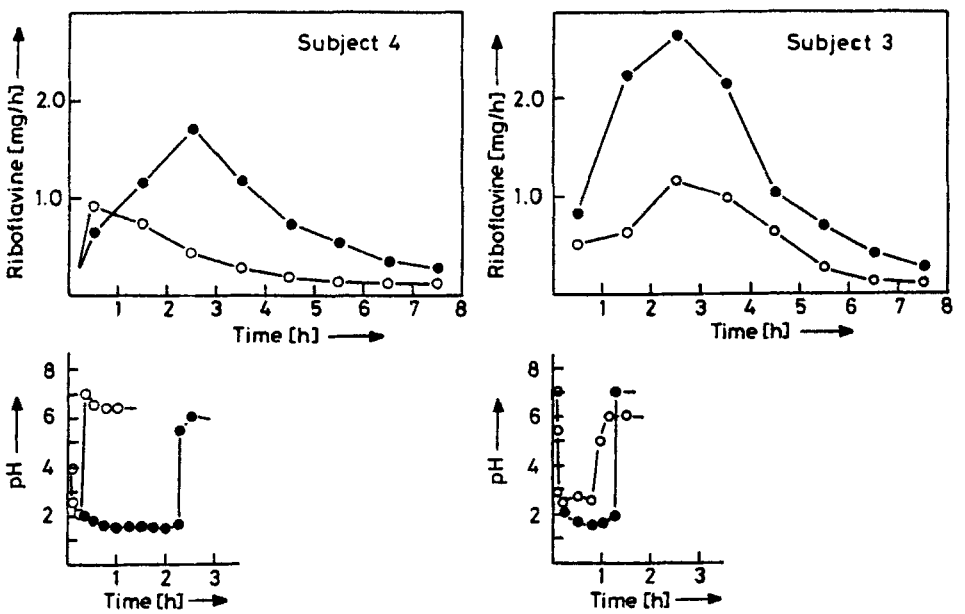


FIGURE 5

Gastric Transit of the pH-telemetering Capsule and renal Elimination of Riboflavine

- ● - with
- o - without

Triethanolamine Myristate

a pH telemetering device (Heidelberg capsule) was used as a model dosage form. The Heidelberg capsule continuously transmitted details of the pH of the fluid surrounding it and hence enabled conclusions to be drawn concerning the residence time in the stomach. Ultrasonic recordings were carried out in parallel experiments to determine the location of the capsule in the gastrointestinal tract.

The data concerning the renal excretion of riboflavine with and without triethanolamine myristate are compared with the pH-time profiles, which were obtained with the pH telemetering capsule, in Figures 4, 5 and 6.

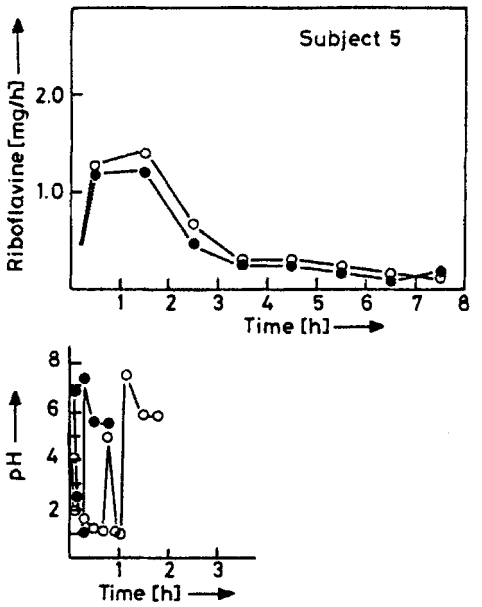


FIGURE 6

Gastric Transit of the pH-telemetering Capsule and renal Elimination of Riboflavine

- ● - with
- o - without

Triethanolamine Myristate

The investigations showed that the reaction of the subjects differed markedly. The greatest increase in renal elimination of riboflavine caused by incorporation of the salt of myristic acid were displayed by subjects 2, 3 and 4. Only subject 5 responded differently to the others. With this subject, no increase in the gastric residence time or improvement in renal elimination was obtained.

The mean values of renal elimination of riboflavine are shown in Fig. 7. The renal elimination of riboflavine in the collection period between the 3rd and 4th hours was statistically significantly increased

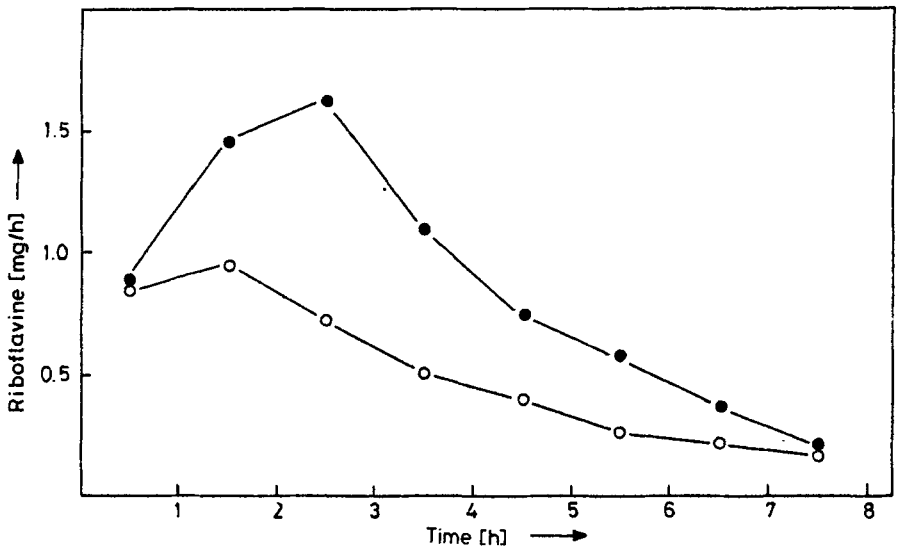


FIGURE 7

Effects of Triethanolamine Myristate as a physiological transit-delaying Agent on the renal Elimination of Riboflavine (n=5, $\bar{x}_{arith.}$)

- o - Tablet A, 20 mg Riboflavine
- ● - Tablet B, 20 mg Riboflavine + Triethanolamine Myristate

(0.05 >p >0.0025) in the presence of triethanolamine myristate.

The transit times of the Heidelberg capsule are compared with the renal elimination data of riboflavine in Tab. 2. The higher of each paired value is marked with a cross. The longer gastric residence time of the Heidelberg capsule correlates, in each subject, with the higher renal elimination of riboflavine.

CONCLUSIONS

A major problem in developing dosage forms with actively controlled gastrointestinal transit is at

TABLE 2

Residence Time of the pH-telemetering Capsule and Renal Elimination of Riboflavine

Subject	Residence time of the capsule in the stomach [min]		Renal elimination (% of administered dose)	
	A	B	A	B
1	15	48 (+)	13.35	18.75 (+)
2	26	102 (+)	28.32	50.72 (+)
3	60	78 (+)	22.54	51.90 (+)
4	20	135 (+)	15.48	33.30 (+)
5	67 (+)	15	22.50 (+)	19.50

A: without
B: with Triethanolamine Myristate

(+) Higher of the two paired values

present the highly differing interindividual reaction of subjects to controlling substances such as triethanolamine myristate. According to the experiences reported here, this reaction is not obtained at random, but is reproducible in each subject.

In future it will be necessary to find new controlling substances and to examine whether their combination in drug preparations can lead to a control of transit even in subjects who respond differently. In addition, combination of different principles of transit control as depicted in Fig. 1 should be further investigated.

Another important question is the dosage and rate of release of controlling substances. Work that we have carried out during the course of our studies with myristic acid has shown that in a relatively high

concentration of 400 mg molten in polyethylene glycol 6000, an acceleration of gastric transit after a standard breakfast occurs.

In the current study riboflavine was used as a model of a drug with a limited duration of absorption. The aim of our investigations is to develop optimal dosage forms for other drugs, whose bioavailability can be markedly improved by, for example, food.

REFERENCES

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4. Hunt, J.N. and Knox, M.T., J.Physiol. 201, 327 (1968)