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FOOD-INDUCED THEOPHYLLINE RELEASE/ABSORPTION CHANGES FROM CONTROLLED-RELEASE FORMULATIONS: A PROPOSED IN VITRO MODEL

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SUMMARY

The rate and extent of absorption of theophylline from controlled-release products may change dramatically when these products are administered after a high fat meal and the direction of the change may vary with the formulation (1-3). In an effort to understand the reason for these changes the release rates of four theophylline controlled- release products

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were tested in a variety of fluids chosen to simulate the gastrointestinal environment. In vitro systems which combined fatty acid, high pH and bile salts resulted in release rate changes which showed the same direction of change as those observed after the high fat meal. These studies provide some insight into the possible interactions of gastrointestinal fluids with the rate controlling polymers of the controlled-release dosage forms.

INTRODUCTION

Controlled release theophylline preparations are frequently prescribed for maintenance therapy of obstructive airway disease. Presently there are as many as 20 products marketed in the USA for dosing twice a day. More recently, three products have been approved in the USA for once-a-day dosing. Theophylline has a narrow therapeutic window. Therefore, food induced absorption changes and/or variable theophylline absorption which have been reported with controlled release products can be a serious problem. (4-11).

In a study by Karim et al. (1, 2) four commercially available theophylline controlled-release products were dosed with a high fat breakfast and after a fast. Significant changes in absorption occurred

with the high fat meal, and the direction of the change varied with the controlled-release theophylline formulation.

In a 2nd study conducted by Karim et al., (3) Product A was dosed after a high, medium and low fat breakfast as well as after a fast. Only after a high fat breakfast was there a significant change in peak serum levels of theophylline.

The results of studies on immediate release formulations dosed with food do not explain the significant changes in rate and extent of absorption observed with controlled-release products. In studies by Welling (12) and Upton (13) the only statistically significant difference observed was a delay in tmax when the oral solution was dosed with food.

It may, therefore, be theorized that food or digestive fluids present after a high fat meal may interact with the rate controlling membrane or matrix and change the release rate.

To investigate this hypothesis changes in the release rates of the four theophylline controlled-release products used in the Karim study (1, 2) were measured when exposed to fluids chosen to simulate the environment of the gastrointestinal tract after a high fat meal.

To choose appropriate fluids it was useful to review what may happen to a dosage form when it is ingested with a high fat meal. In the mouth, lingual lipases begin the breakdown process of fats to fatty acids (14). In the stomach the dosage form may be in contact with fats, fatty acids, and high acid concentrations for a period of hours, since stomach emptying is slower after a high fat meal (15, 16). As the dosage form passes into the upper intestine, it will encounter higher pH and bile salts. Bile salts serve to emulsify fats so that further breakdown to fatty acids by pancreatic lipase may occur. In addition bile salts have been reported to solubilize and increase the absorption of many water insoluble drugs (17). These natural surfactants may also interact with the rate controlling polymers of the dosage form.

MATERIALS AND METHODS

Products Tested

The following commercially available dosage forms were studied: Product A was Theo-24 300 mg capsules (Lot 1283-873, G. D. Searle); Product B was Uniphyl 400 mg Tablets (Lot 09W, Purdue Frederick). Product C was Theo-Dur Sprinkle 125 mg capsules (Lot 385841), Key Pharmaceuticals); Product D was Theo-Dur 300 mg tablets (Lot 387281), Key Pharmaceuticals).

Standards and Reagents

Theophylline, USP anhydrous, was used as a standard for all analyses. All salts , acids and bases used in the preparation of dissolution media were reagent grade. Oleic acid was NF grade. Miglyol 812 was 65% caprylic (C8)/35% capric (C10) triglycerides.

Methods of Analysis

All dissolution testing was performed using USP apparatus I (baskets) at 100 rpm and 37°C. The release rates of the four products were determined in buffers of pH 1.2-8.0 and systems I-IV given in Table 1. Product A was additionally tested in systems V-X.

Products A and C, both encapsulated bead-type products, were removed from the capsule before testing in Systems III and IV. All products were placed in USP dissolution baskets which were then submerged in the soaking medium at 37°C. After the soaking period, the baskets were allowed to drain briefly before placing in dissolution media.

The concentration of theophylline in dissolution samples was determined by UV spectroscopy at λ=270 nm. The amount of theophylline released into the oleic acid after 1 hr of soaking was determined by HPLC utilizing an ODS column (DuPont Zorbax 25 x 4.6 mm i.d.) mobile

Table 1

Description of Dissolution Systems

System No.	Soaking Medium	Dissolution Medium
I	none	pH 6.6 buffer
II	none	0.04 M sodium deoxycholate
III	oleic acid	pH 6.6 buffer
IV	oleic acid	0.04 M sodium deoxycholate
V	propionic acid	0.04 M sodium deoxycholate
VI	linoleic acid	0.04 M sodium deoxycholate
VII	oleyl alcohol	0.04 M sodium deoxycholate
VIII	triolein	0.04 M sodium deoxycholate
IX	miglyol*	0.04 M sodium deoxycholate
X	oleic acid	0.04 M sodium cholate

*triglycerides of caprylic (C8) and capric (C10) acid

phase of 30% methanol/70% water, and UV detection at 254 nm.

RESULTS

The dissolution profiles for Products A-D in buffers of pH 1.2 - 8.0 are given in figure 1. (All dissolution results are reported as % of Label Claim, 95% confidence intervals are also indicated). Product A exhibited an increase in release rate with increasing pH. The other products showed no statistically significant change in release rate with pH ($\alpha = 0.05$).

The percent of theophylline released in 8 hrs from Products A, B, C, and D in Systems I - IV is given in Table 2. The percent of theophylline released from each product into oleic acid before transfer to the dissolution media was less than 3%.

Unpublished studies in our laboratories have demonstrated that the % dissolved in 8 hrs in System I correlated with AUC in studies with fasted subjects. Therefore, the percent dissolved at 8 hrs in System I was used as the *in vitro* reference to which all other *in vitro* results were compared.

Table 3 summarizes the direction of change in release rate of products A-D in systems II-IV relative to the reference system. For comparison the direction

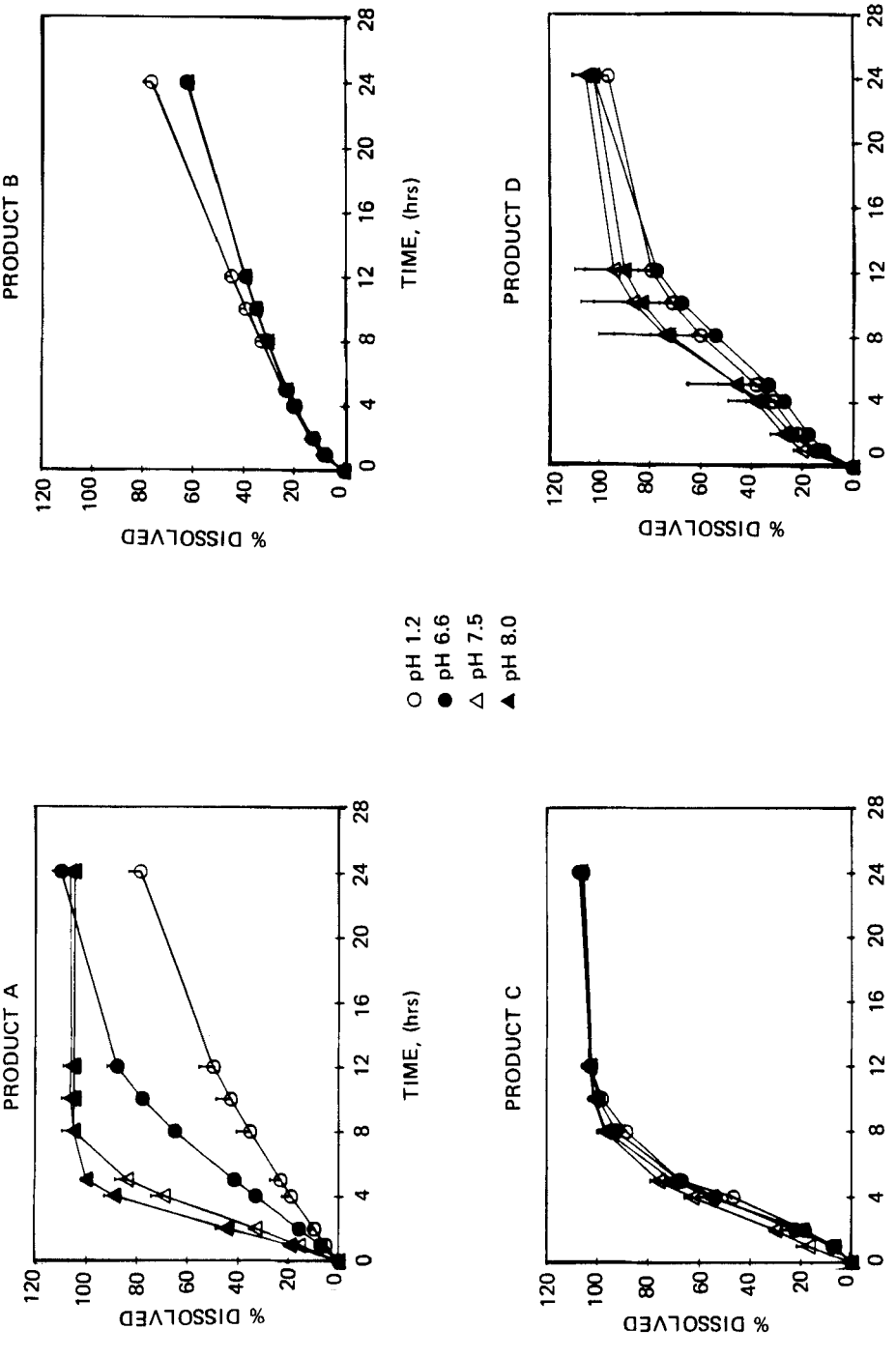

Figure 1: Mean % theophylline dissolved in vitro from Products A-D in buffers ranging in pH from 1.2 to 8.0. (Only +95% confidence interval indicated for clarity.)

Table 2

Dissolution values in systems I-IV

% Dissolved at 8 hrs

n (95% confidence interval)

System[1]:	I	II	III	IV
PRODUCT				
A	65.0	89.2	31.3	103.5
	12 (1.3)	3 (2.8)	3 (11.4)	3 (3.7)
B	30.6	53.4	------	53.4
	12 (0.6)	3 (3.2)	------	3 (2.18)
C	92.5	98.0	84.5	60.2
	3 (10.4)	3 (1.2)	3 (8.2)	6 (12.5)
D	57.6	69.3	76.5	62.7
	3 (22.1)	3 (8.4)	3 (18.4)	5 (22.3)

1. System I - pH 6.6 phosphate buffer
   System II - 0.04 M sodium deoxycholate, pH 8
   System III - 1 hr soak in oleic acid at 37°C
   followed by dissolution in pH 6.6 phosphate buffer.
   System IV - 1-3 hr soak in oleic acid at 37°C
   followed by dissolution in 0.04 M sodium deoxycholate

Table 3: Direction of change in release rate relative to the reference system, I, compared to direction of change in AUC fed/fasted. (+ increased; - decreased; nc no change)

Product	Change in 8 hr Release Rate			Change in AUC
	II/I	III/I	IV/I	NF/F[a]
A	+	-	+	+
B	+	nd[b]	+	+
C	nc	nc	-	-
D	nc	nc	nc	nc

a. NF = AUC from dose administered immediately after a high fat meal
F = AUC from dose administered under fasting conditions (1, 2)

b. No data

of change in AUC in the fed vs. fasted state is also given in Table 3.

A combination of lipid and bile salt, System IV appeared to give the same direction of change in release rate as in AUC. To further investigate this effect the lipid and bile salt were varied in Systems V-X and the effect on the release of Product A was studied. Figures 2 and 3 summarize these results.

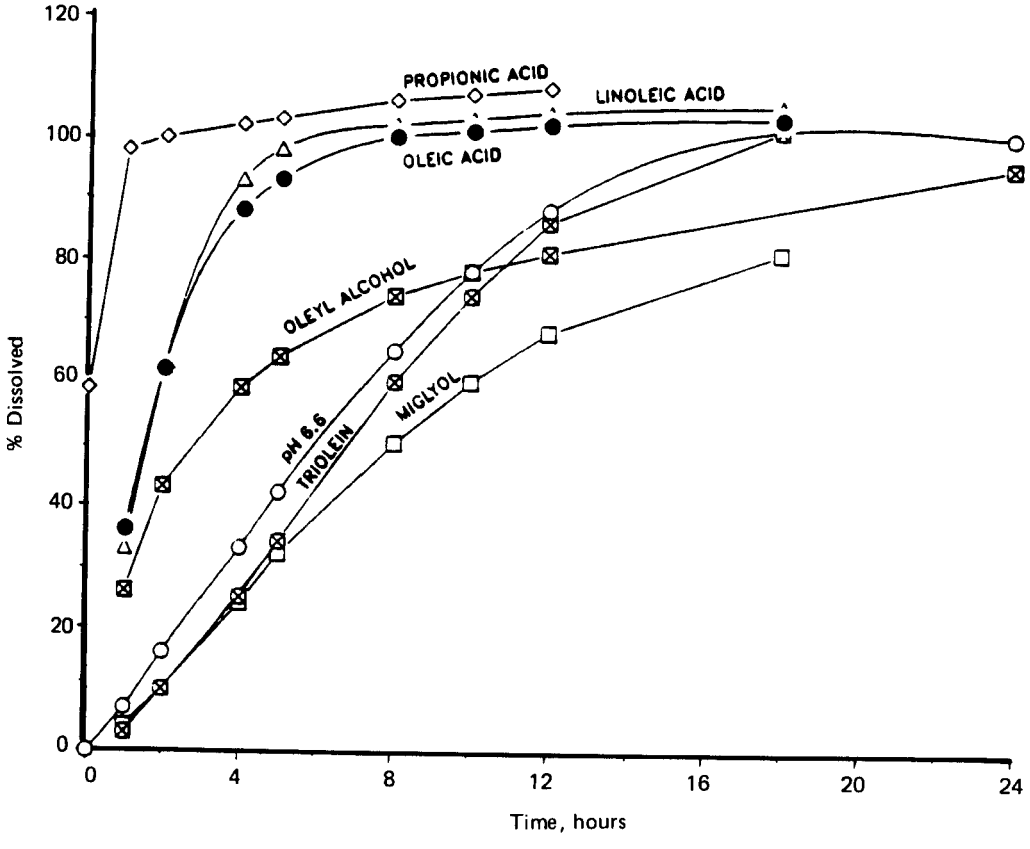

Figure 2:

Mean % theophylline dissolved from Product A in Systems V-IX.

DISCUSSION

Only product A exhibited a pH dependent profile; but products B and C also exhibited a change in absorption after a high fat meal. Therefore pH changes which occur in the gastrointestinal tract are not alone responsible for absorption/release changes which occur with these products.

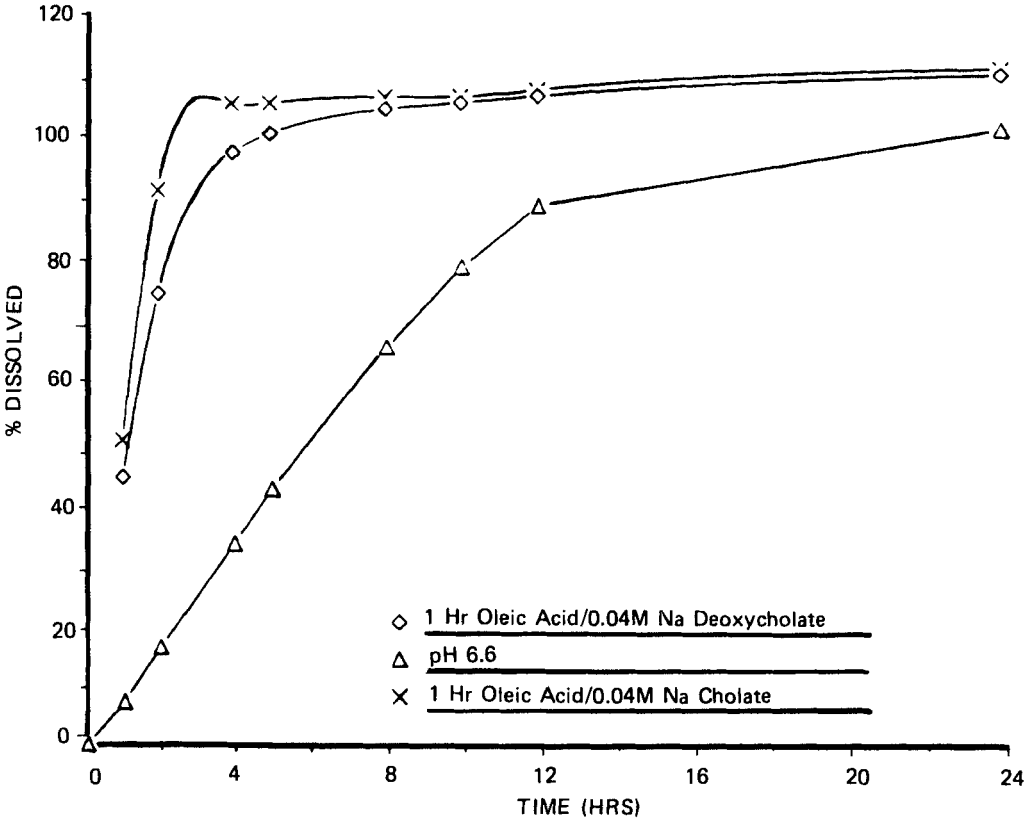

Figure 3:

Mean % theophylline dissolved from Product A in Systems I, IV and X.

A combination of a lipid and a bile salt were necessary to produce changes in release rate of the same direction as changes in AUC.

For product A the presence of a fatty acid was necessary to cause an increase in release rate. The effect from the fatty acid was independent of chain length which was varied from C3 to C18; or number of

double bonds which was varied from 0-2. With the triglycerides, triolein and miglyol, an increase in release rate was not exhibited, even though the dissolution medium was of alkaline pH (Figure 1 indicates that for Product A, an increase in rate was observed in alkaline pH without presoaking). The oleyl alcohol exhibited a release rate pattern in between that of the acids and the triglycerides.

A possible mechanism might be that the fatty acid is sufficiently lipopholic to permeate and/or solubilize the lipophilic components of the membrane or matrix. When the product is placed in dissolution media, the acid moiety reacts readily with the bile salt; further solubilizing the rate controlling polymers and an increase in rate is observed.

It is interesting that the same system (IV) produces a decrease in release rate for Product C. Visual observation of the product during testing is useful to explain this anomoly. After 1 hr in fatty acid the bead form of Product A is lost and an amorphous gel-like mass is formed. This mass is still observed after dissolution in bile salt. Thus a new rate controlling matrix is formed, whose surface area is much reduced, and whose release rate mechanism is altered. *In vivo* studies, such as external

scintigraphy would be necessary to confirm whether such a mass is actually formed in the intestinal tract. Figure 3 indicates that the dissolution profile with sodium cholate, the major component of human bile, is not significantly different from the results with sodium deoxycholate.

CONCLUSION

Although it is difficult to simulate the GI environment exactly, these data suggest that one of the causes of absorption changes observed with theophylline controlled-release products is due to the interaction of the rate controlling polymers with the fatty acid and bile salts present in the GI tract after a high fat meal.

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