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RESEARCH PAPER

Investigation of Prandial Effects on Hydrophilic Matrix Tablets

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ABSTRACT

*The prolonged release of drug from hydrophilic matrix tablets can be greatly affected by administration in connection with the intake of food. Changes of the tablet erosion are one of the main components of this effect. The aim of the present study was to identify the postprandial factors responsible for changes in tablet erosion and to develop predictive in vitro tests. Two formulations, one sensitive and the other robust to prandial effects in vivo, were investigated in vitro (*a*) in a complex physiological media simulating fasting and fed conditions; (*b*) according to a factorial experimental design that included agitation and pH concentrations of salt, surface-active agent, and nonionic solute as factors; and (*c*) at varying agitation intensities in three different sets of dissolution apparatus. Of the studied factors, only increased agitation enhanced the erosion of tablets in accordance with the in vivo effects of a meal. The other factors retarded erosion or had only minor effects. The hydrodynamic mechanical stress was thus considered to be the main factor responsible for postprandial effects on tablet erosion. The influence of changes in agitation and the opportunity to discriminate between sensitive and robust formulations differed among the three sets of dissolution apparatus. The modified USP II apparatus, operated at speeds of 50 and 100 rpm, is proposed as a discriminatory test.*
Key Words: *Food effects; Hydrophilic matrix tablets; In vitro dissolution; Tablet erosion.*

INTRODUCTION

The bioavailability of oral dosage forms is often affected by the timing of the administration in relation to meals. This is of special relevance for extended-release (ER) formulations, for which the dissolution pattern may be sensitive to prandial effects. Interactions can occur, for example, between food components and the formulation. The physiological changes in the gastrointestinal (GI) tract induced by food may also be important.

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Hydrophilic matrix tablets frequently use ER principles. The absorption from such hydrophilic matrix tablets in some cases has been found to be affected by administration with food (1–3). The drug release from a hydrophilic matrix is controlled by tablet erosion of the gel layer formed around the tablet after contact with GI fluids and diffusion through the gel layer. The former mechanism dominates, especially in the case of poorly soluble drugs (4–6). In vitro studies of hydrophilic matrix tablets have demonstrated that many factors, which may vary due to the prandial state, affect tablet erosion and drug release; they include solutes, surfactants, pH, and agitation (7–9). The in vivo relevance of such effects, however, is less clear.

In the work involved in developing ER products, the objective is to produce formulations that give the desired absorption profile with minimal inter- or intraindividual variation. It therefore is desirable to avoid formulations that are highly dependent on prandial effects, and there is also a need for discriminatory in vitro tests. Several attempts have been made to develop such tests, including the use of bile salts and lecithin, pH changes, fat emulsions, nutritional drinks, enzymes, pretreatment with oils, viscosity enhancement, and inert beads (10–16). No single method appears to cover the complexity of all potential factors induced by food. This implies that the available methods are not generally applicable for in vivo predictions of food effects for all kinds of dosage forms, and very few investigations have focused on hydrophilic matrix tablets.

In the present study, the erosion in vitro of two hydrophilic matrix tablets was compared. One (tablet A) had previously been shown to erode in the GI tract far faster postprandially than under fasting conditions, whereas the other (tablet B) was almost unaffected (1,17). The aims of the present study were to identify the main factors responsible for the prandial effects on the erosion rate of tablet A and to find an in vitro test system that was able to discriminate sensitive formulations from robust ones.

MATERIAL AND METHODS

Study Formulations

The study tablet compositions are given in Table 1. Both tablets were manufactured using conventional wet granulation and compressed to circular, convex tablets. The in vivo tablet erosion rates were determined by gamma scintigraphy in healthy human subjects after administration under fasting and fed conditions for tablets A and B (see Results and Discussion) (1,17). The drug dissolution and tablet erosion time curves were almost superimposable for both tablets (18), as might be expected as a result of the very low water solubility of both felodipine and nifedipine.

Table 1

Study Tablets

	A	B
Active drug (mg/tablet)		
Nifedipine	30	—
Felodipine	—	10
Matrix-forming excipients (mg/tablet)		
Hydropropyl methyl cellulose (50 mPas)	172	230
Ethylcellulose	20	—
Carboxypolymethylene	4.5	—
Other excipients, quantity sufficient for total tablet weight of:	340	470
Diameter (mm)	10	11
Prandial effect on tablet erosion	Yes	No

In Vitro Testing of Tablet Erosion

The in vitro evaluation was divided into three parts. Part I comprised testing in complex physiological test media with and without food components. Part II focused on the effects of different physical and physicochemical factors that could be induced by a meal, such as pH, ionic strength, surface activity, osmotic pressure, and agitation. Part III focused on an evaluation of hydrodynamic conditions using three different sets of equipment and agitation intensities.

A USP II paddle apparatus modified with a stationary basket (19), which kept the tablets in a standardized position to avoid random sticking to the beaker wall, was used in part I. The paddle stirring rate was 100 rpm, the volume was 500 ml, and the temperature was 37°C. The fasting experiment started with 0.1 M HCl for 1 hr, and the tablet was then moved to a Krebs-Henseleit Ringer buffer, pH 7.2, with an ionic strength of 0.1, which also included 5 mM sodium taurocholate (Sigma, Sweden) and 0.5% fat emulsion (Intralipid® 200 mg/ml, Pharmacia, Sweden). The experiment simulating fed conditions started with a multicomponent nutritional liquid (Nutrison®, Nutricia Nordica, Sweden), for which the pH had been adjusted to 5.6 by HCl. After 3 hr, the tablet was moved to the same buffer as in the fasting experiment, but including 20 mM sodium taurocholate and 5%

fat emulsion. All the media were homogeneous and stable for at least 24 hr. Enzymes were not added to avoid the digestion of meal components, thereby maintaining constant conditions.

Part II was performed using the same apparatus, volume, and temperature as in part I. To evaluate the influence of several factors, a factorial design shown to be an effective tool for investigations of this kind was used (20). The different variables in the design were pH, concentrations of sodium chloride, surface active agent, osmotic-pressure-enhancing agent, viscosity-enhancing agent, and paddle stirring rate. Polyoxyethylene monolauryl ether (Brij® 35, Fluka, Switzerland) was used as a surface-active ingredient, urea as a nonionic osmotic agent, and hydroxypropyl methyl cellulose (HPMC) (Methocel® E10M, Dow Chemicals) for viscosity adjustment. The low and high levels of each variable in the experimental design were designed to correspond to fasting and fed conditions, respectively. Although most of the components were not of physiological origin, the amounts that were added were chosen to create relevant in vivo physicochemical conditions. The different settings in all the experimental runs are summarized in Table 2. Runs 6 and 7 were made as replicates to determine variability.

The Modde® computer software (Umetri AB, Sweden) was used to set up the experimental design and to evaluate results by multiple linear regression. The model included only linear terms and no interactions. Since all the tablet erosion time curves were linear up to 90% erosion, the tablet erosion rate determined by linear regression was used as the response variable. Each test medium was characterized in terms of osmolarity by freeze-point reduction, viscosity by a cone-plate rheometer, surface activity by a de Noye-ring, and pH by a pH meter, while ionic strength was calculated.

All the experiments in part III were performed in phosphate buffer, pH 6.8, with an ionic strength of 0.1 at 37°C. Tablet erosion was measured in three different sets of equipment; the USP II apparatus modified with a stationary steel wire hook on which the tablet was placed 10 mm above the paddle; the USP III apparatus with top and bottom screens with a mesh size of 840 mm and 180 mm, respectively, and a 500-ml flask with four lateral inflections rotating at an angle of 45°C according to Koch (21). Each piece of apparatus was operated at three or four different agitation intensities (see Results and Discussion). The low and high levels of agitation intensity were stressed as much as possible with respect to practical factors such as apparatus design and the avoidance of gel tablets sticking to the walls. The tablet erosion rate was characterized by the time at which 50% of the tablets had eroded ($t_{50\%}$) since some deviations from linearity in the erosion time profiles were obtained.

In all three parts of the study, tablet erosion was measured by weighing the tablets after drying to constant weight, and the percentage of tablet erosion was calculated in relation to the initial dry weight of the tablets.

RESULTS AND DISCUSSION

Part I: Simulated Physiological Test Media

The erosion of tablets A and B in the media simulating fasting and fed conditions is shown in Figs. 1a and 1b. Tablet erosion was somewhat slower under fed conditions for both tablets. Careful visual inspection of the tablets did not reveal any adsorption of media components. The observed effects are probably due to interaction between the matrix polymers and food components increasing the strength of the gel layer around the tablets. The demonstrated effect on tablet erosion may well be relevant for the in vivo situation. However, since this interaction retarded the erosion, which is opposite to the observed effect of a meal in vivo, other factors are obviously more important for the postprandial effects on tablet A.

Part II: Physical and Physicochemical Factors

The physicochemical characterizations of test media are given in Table 2 for all experiments. The lower pH level is close to the normal fasting gastric pH of around 2.0, and the higher level was well within the normal range obtained in the intestine (22). The levels of ionic strength varied from 0.08 to 0.20 and were obtained by adding different amounts of sodium chloride, the two most abundant ions in the GI tract. Normal fasting levels for the ionic strength in the GI tract of 0.10–0.14 have been reported (23). Higher values, such as the upper level in the present study, might be transiently induced by food. The surface tension was about 70 mN/m in all the experiments without surfactant and HPMC. This value was decreased to 45–50 mN/m by HPMC and to 41–43 mN/m by Brij. Concomitant use of the two agents did not produce any additive effect. The surface tension of the gastric and intestinal fluid is reported to be 35–45 mN/m during fasting conditions (24). The osmolarity was controlled by urea and sodium chloride, and it varied

Table 2

Factors, Settings, and Physicochemical Characterizations of Test Media and Tablet Erosion Rate for All Experimental Runs in Factorial Design

Experiment No.	pH Nominal	NaCl (M)	Brij (mM)	Urea (M)	HPMC (M)	Paddle Speed (rpm)	pH Measured	Ionic Strength	Surface Tension (mN/m)	Osmolarity (mOsM)	Viscosity (mPas)	Erosion Rate (%/hr)	
												A	B
1	2.3	0.08	30	0.2	1	150	2.4	0.08	41	390	230	5	19
2	6.8	0.08	30	0	0	150	6.8	0.1	43	190	1	11	22
3	2.3	0.18	30	0	1	50	2.3	0.18	42	400	250	1.5	9.3
4	6.8	0.18	30	0.2	0	50	6.7	0.2	43	600	1	2.9	10
5	2.3	0.08	0	0.2	0	50	2.4	0.08	72	360	1	4.8	15
6A	6.8	0.08	0	0	1	50	6.8	0.1	49	190	270	2.9	14
6B	6.8	0.08	0	0	1	50	6.8	0.1	45	190	280	3	16
7A	2.3	0.18	0	0	0	150	2.3	0.18	72	350	1	13	25
7B	2.3	0.18	0	0	0	150	2.3	0.18	71	350	1	13	24
8	6.8	0.18	0	0.2	1	150	6.7	0.2	48	580	260	5.2	24
9	6.8	0.18	0	0	1	50	6.7	0.2	48	370	230	2.2	11
10	2.3	0.18	0	0	1	50	2.3	0.18	50	390	250	2.7	13

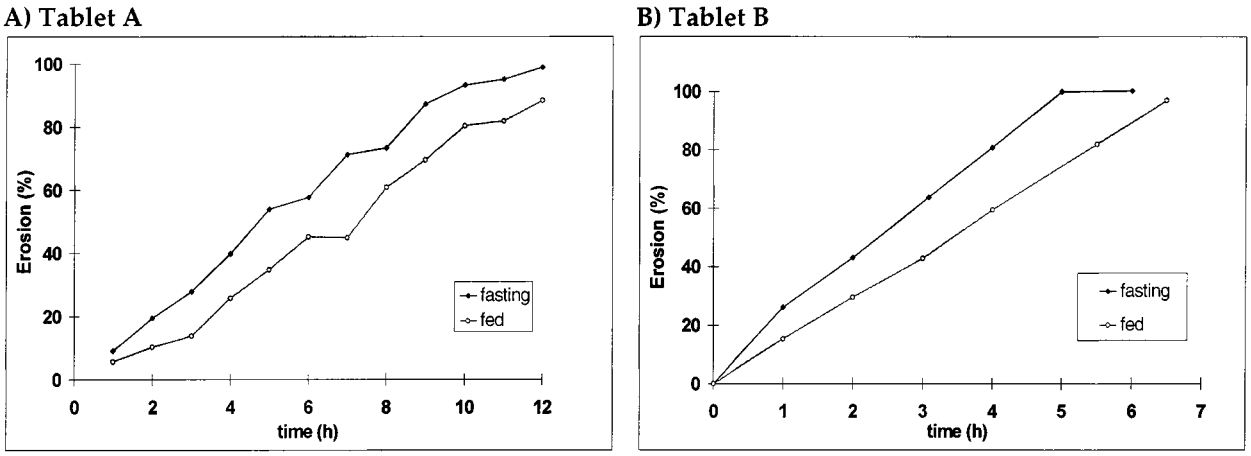

Figure 1. Tablet erosion time curves for tablets A and B under simulated fasted and fed conditions.

between 190 and 590 mOsM. The lower level was close to the fasting values of 200 mOsM reported for the stomach (23,24). The higher levels were regarded as relevant for the osmolarity obtained after the intake of a meal, although the size and type of meal has an obvious influence (25). The viscosity of the test media without HPMC was about 1 mPaS and corresponded to fasting conditions in the upper GI tract (24). The high level of 230–280 mPaS could be relevant after intake of food.

In the case of both tablets, the coefficients of determination r^2 of the individual erosion time data were all within 0.91–0.99, thereby supporting that the tablet erosion time profiles were approximately linear. The tablet erosion rate was strongly affected by variations in the experimental settings, as can be seen in Table 2. The model obtained from the multiple linear regression analysis of the different factors fitted the data very well, as r^2 for both A and B was above 0.99. The influence of the different factors on tablet erosion is shown in Fig. 2. NaCl, pH, and surfactant altered the erosion to a minor degree in relation to the in vivo effects of a meal and can thus be disregarded as factors responsible for the prandial effects on tablet A. Increased concentrations of urea and HPMC produced a pronounced retardation in the erosion of tablet A, but not of tablet B. Since administration after a meal enhanced the erosion of tablet A, these two factors do not explain the prandial effects. The paddle stirring rate was the only factor that increased the erosion rate in accordance with the in vivo food effect. Both tablets were affected, but tablet A appeared to be more sensitive. The far greater susceptibility of tablet A to changes in viscosity supports the conclusion that this tablet is more sensitive to hydrodynamic stress. Hydrodynamics/mechanical treatment is considered to be the most important factor when it comes to explanations of the faster erosion of tablet A when given postprandially. The significance of mechanical destructive forces in terms of the in vivo drug release has been demonstrated previously for other matrix tablets (26,27).

Part III: Hydrodynamic Conditions

The tablet erosion rate, expressed as $t_{50\%}$, in the three different sets of apparatus, is given in Fig. 3 together with in vivo data. In every set of apparatus, the erosion rate increased for both tablets as the agitation intensity increased, but to a varying degree. The range of $t_{50\%}$ obtained in all the tests was 1.6–11.1 hr for tablet A and 1.3–3.9 hr for tablet B. The far wider range for tablet A compared with table B confirmed the findings in part II that tablet A was more sensitive than tablet B to changes in hydrodynamic conditions.

To discriminate between tablets with different susceptibilities to hydrodynamic stress, it is desirable to find a simple method that requires few experiments. One approach is to obtain a reference value at mild agitation that is compared with another experiment performed under more forceful conditions. For the ideal method, a large difference between the two test conditions should be obtained for a sensitive tablet, and a more robust formulation should be almost unaffected. The best conditions in this respect were provided by the USP II method using paddle stirring speeds of 50 rpm for the reference value and 100 rpm or more for the stress test.

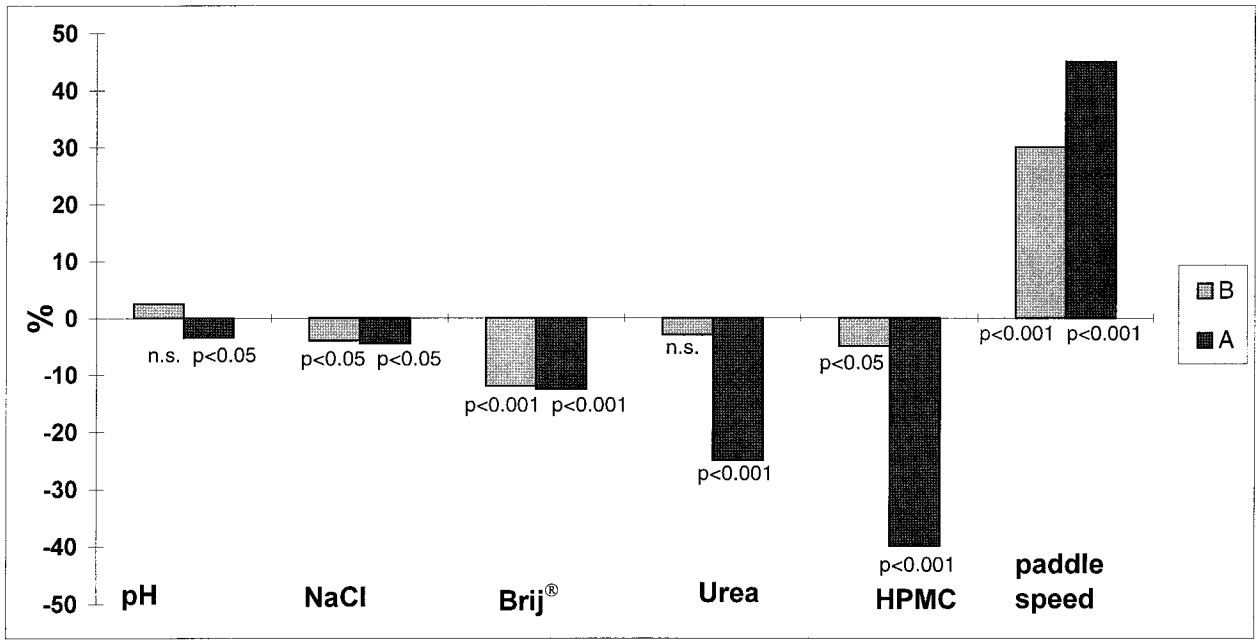

Figure 2. Influence of different factors on tablet erosion expressed as percentage change from low to high levels in experimental design and the statistical significance of the effects.

The rotating flask produced the fastest erosion rates of the three systems. A milder agitation intensity than that used in the present study has also been recommended for this apparatus in order to obtain realistic in vivo hydrodynamics (18). However, at lower rpm, the tablets frequently became stuck to the flask wall, and the equipment is obviously less suitable for this type of tablet.

In the studied range of agitations, the USP III apparatus provided the mildest treatment, apart from the very slow erosion of tablet A in USP II at 50 rpm. The discrim-

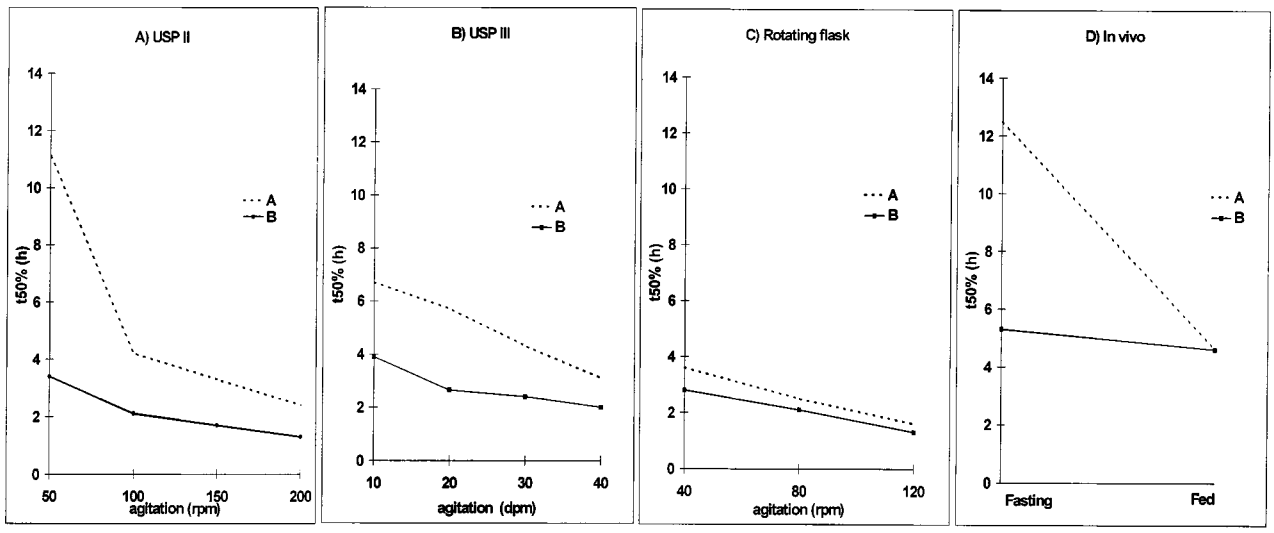

Figure 3. Time to 50% tablet erosion versus agitation intensity in vitro and for fasting and nonfasting administration in vivo.

ination between tablet A and B was not as good as with the USP II method. It therefore appears that the in vitro results cannot be directly transposed between the systems by tuning the agitation intensity. The same conclusion could be drawn from another study in which the drug dissolution from different hydrophilic matrix tablets was tested at different agitation intensities in the standard USP I, II, and III sets of apparatus (28). Different in vitro test systems apparently do not discriminate between tablets in the same way. It is desirable that the in vitro results also correspond to the in vivo data obtained under fasting and fed conditions to permit quantitative in vivo predictions. The best results in this respect were obtained in the modified USP II apparatus. The in vivo erosion for tablet A given under fasting or nonfasting conditions corresponded fairly well with the in vitro erosion at 50 and 100 rpm, respectively. The erosion of tablet B at 50 and 100 rpm was faster than in vivo, however. The different in vitro/in vivo correlations for the tablets illustrate that relationships of this kind can be formulation dependent.

CONCLUSIONS

Increased agitation in the GI tract, which exerts more intense mechanical stress on the tablets, appears to be the main determinant of the faster erosion rate obtained for a hydrophilic gel matrix tablet after intake with food. The choice of test apparatus and agitation intensities is critical for predictions of undesirable in vivo tablet properties of this kind. The modified USP II apparatus operated at 50 and 100 rpm provided the most suitable test.

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