Influence of Hydrodynamics and Particle Size on the Absorption of Felodipine in Labradors

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Purpose. To study the influence of GI hydrodynamics and drug particle size on felodipine absorption in the dog.

Methods. Labradors fistulated at midjejunum were used to selectively study the influence of hydrodynamics and particle size on the *in vivo* dissolution and absorption of the poorly soluble, lipophilic drug felodipine. A combination of infusion and oral administration of either normal saline or a 5% glucose solution was used to maintain "fasted" and establish "fed" state motility patterns, respectively. The absorption characteristics of both a micronized (8 μm) and a coarse fraction (125 μm) of felodipine were subsequently studied under these two motility patterns.

Results. A reduction in particle size led up to an approximate 22-fold increase in maximum plasma concentration and up to an approximate 14-fold increase in area under the curve, with a commensurate decrease in the time at which the maximum plasma concentration occurred. Although the absorption of felodipine from the solution and micronized suspension was not influenced by a change in the hydrodynamics, felodipine was absorbed from the coarse suspension almost twice as well in the "fed" state as under "fasted" conditions.

Conclusions. Absorption from coarse suspensions of felodipine was sensitive to luminal hydrodynamics, whereas micronized suspensions were not. However, the particle size seems to have a much more important influence on the bioavailability of felodipine than the hydrodynamics *per se*.

KEY WORDS: bioavailability; felodipine; fistulated dog model; hydrodynamics; particle size.

INTRODUCTION

Many poorly soluble drugs fail to be completely bioavailable after oral dosing due to inappropriately slow dissolution from the dosage form. In the case of dissolution rate-limited absorption, a variety of factors such as solubility, particle size, and the thickness of the boundary layer can influence the dissolution (1–3). The thickness of the boundary layer is, in turn, dependent upon the hydrodynamics (4). Although much is known about motility patterns and flow within the gastrointestinal (GI) tract under various conditions, until now it has been difficult to isolate hydrodynamic influences on drug dissolution from other factors that can play a role in absorption. The influence of fasted and fed state hydrodynamic conditions in the GI tract on dissolution and subsequent absorption remains an open question.

The aims of the present study were to investigate whether the GI hydrodynamics are important to *in vivo* dissolution and subsequent absorption of a poorly soluble drug, and to determine the relative importance of GI hydrodynamics and particle size in this process. We sought to create conditions *in vivo* that would enable us to specifically examine the relative importance of particle size and hydrodynamics on drug dissolution and absorption, using labradors fistulated at midgut. Experiments were conducted in two stages. In the first step, it was confirmed that the dosing conditions chosen would selectively influence the hydrodynamics, and in the second step these dosing conditions were applied to a pharmacokinetic study.

Felodipine was chosen as a typical example of a poorly soluble (aqueous solubility, 1 mg/l at 37°C) drug. Because it does not ionize over the pH range in the GI tract, variations in pH are not likely to influence its solubility. Furthermore, the high lipophilicity of felodipine (log P 4.5; personal communication, AstraZeneca, Mölndal, Sweden) indicates that permeability would not likely be a limitation to its oral bioavailability. Both micronized and coarse-grade felodipine were used, because it is well established that micronizing a poorly soluble drug can improve its bioavailability considerably (e.g., griseofulvin (5) and digoxin (6)).

MATERIALS AND METHODS

Materials

Felodipine and the internal standard (H 165/04), a structural analogue of felodipine, were supplied by AstraZeneca. Two particle sizes of felodipine were used: micronized powder (lot 41688–01) with a median particle size of 8 μm (95% confidence interval, 0–24.1 μm); and coarse grade powder (lot 14–01; sieve fraction, 100–200 μm) with a median particle size of 125 μm (95% confidence interval, 0–272 μm). Particle sizes were determined using a Coulter LS 130 (Coulter Electronics LTD, Fullerton, California) equipped with a fluid microvolume module and the corresponding software. All other chemicals were AR grade or equivalent and were purchased commercially.

Animals

Three male labradors, aged 2–3 years and weighing between 30 and 35 kg were used for the study. The dogs were obtained from Terje (Gammelsrud, Norway). All three labradors had a chronic nipple valve fistula in the mid-jejunum (approximately 76 cm below the pylorus) (7). The study was approved by the Animal Ethics Committee Gothenburg (ethics approval number, 2091997).

General Study Design

The first step was to establish an *in vivo* model simulating the different hydrodynamic conditions during the fasted and

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ABBREVIATIONS: C_{max}, maximum plasma concentration; GI, gastrointestinal; HPLC, high-performance liquid chromatography; PEG, polyethyleneglycol; t_{max}, the time at which the maximum plasma concentration occurred.

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the fed states in the GI tract. To maintain the fasted state motility pattern, 100 ml of a 0.9% saline solution was infused through the fistula into the gut, followed 15 min later by oral administration of 198 ml of a 0.9% saline solution containing 0.8% PEG 4000. To induce fed state motility, 100 ml of a 5% glucose solution was infused through the fistula into the gut (8), followed 15 min later by oral administration of 198 ml of a 5% glucose solution containing 0.8% PEG 4000. These caloric loads have been previously shown to be sufficient to convert the motility pattern (8,9) from the fasted to the fed state. Importantly, 5% glucose solutions were shown not to induce fluid secretion into the gut or to affect the solubility of felodipine, which could affect the dissolution rate. Any effect on the absorption profile between the 0.9% saline solution and the 5% glucose solution would result only from changes in the motility pattern, i.e., the hydrodynamics. For the pharmacokinetic studies, the dosing conditions established using the chyme studies were reproduced, with the modification that the fistula was closed after administration of the infusion at midgut and prior to oral administration.

In each dog, chyme collection studies were performed no more than twice a week, separated by at least 1 day; the different administrations were performed at least in triplicate for each animal. Pharmacokinetic studies were performed a maximum of once a week. Pharmacokinetic studies with the felodipine solution were performed once per animal, whereas the felodipine suspension experiments were each conducted in duplicate.

Study Protocol

Chyme Studies to Establish Dosing Conditions for the Pharmacokinetic Studies

Dogs were fasted for at least 16 h, and access to water was restricted 1 h before beginning the experiment, which typically began between 8:00 and 9:00 a.m. The dogs were fully conscious throughout the entire experiment. Fifteen minutes prior to the administration of the oral solution, 100 ml of either a 0.9% saline solution or a 5% glucose solution was infused through the fistula to maintain fasted or to induce fed state motility patterns, respectively. Shortly before oral dosing, a titanium cannula (internal diameter, 0.9 cm; external diameter, 1.1 cm; length, 8.2 cm) was inserted the exact length of the fistula, and the cannula was fixed in position with a bandage. A volume of 198 ml of either 0.9% saline solution ("fasted") or 5% glucose solution ("fed") containing 0.8% PEG 4000 was then administered via an orogastric tube over a period of 1–2 min. Ten milliliter chyme samples were collected serially from the cannula into graduated vials for up to 2 h postadministration. The time of each sample collection was noted for later calculation of the flow rate. The chyme sample was immediately centrifuged for 8 min at 4000 rpm and 4°C. Following centrifugation, the supernatant was transferred into a new vial, whereupon pH (PHM 93 reference pH meter, Radiometer, Copenhagen, Denmark) and osmolality (3 MO micro-osmometer, Advanced Instruments Inc., Norwood, Massachusetts) were measured. The supernatant was separated into various aliquots for analysis of felodipine solubility (selected samples) and PEG 4000 (all samples). All samples were stored at –20°C until assayed.

PEG Determinations

To determine the total chyme recovery and any net water flux, PEG 4000 0.8% was always included in the oral solutions. A 2-ml sample was removed from the diluent to confirm the PEG concentration, prior to its addition to the felodipine concentrate (oral solution), primary suspension (micronized oral suspension) or coadminstration with the powder (coarse grade oral suspension), respectively. The turbidity assay for PEG analysis was performed according to the method of Buxton *et al.* (10), with minor modifications.

Solubility Studies in Canine Chyme

An excess of felodipine was added to 5-ml glass vials containing approximately 3 ml canine chyme collected in the "fasted" or "fed" state. After equilibrium was achieved by gentle shaking in an oven at 37°C for 72 h, the chyme was filtered using a prewarmed Rezist (Schleicher & Schüll Dassel, Germany) 30/0.45 PTFE filter. The filtrate was immediately diluted with 99% (v/v) ethanol in preparation for the determination of felodipine concentration by high-performance liquid chromatography (HPLC).

HPLC Analysis

The concentration of felodipine in chyme samples was determined according to validated, in-house methods for the extraction and HPLC analysis of felodipine in physiologic fluids (including chyme and plasma). The chyme samples were extracted with toluene containing the internal standard, were evaporated to dryness, and were redissolved in mobile phase (acetonitrile/methanol/phosphate buffer pH 3, 40:20:40% v/v). A 100-μl volume of the sample was injected on a Nova PAK TM C18, 150 mm (5 μm) (Waters Corporation, Milford, Massachusetts) column. The flow rate was set at 1.0 ml/min, and detection was set at 362 nm. Typical retention times were 8.5 and 16.5 min for felodipine and the internal standard, respectively.

Statistics

Particle size distributions were not normally distributed, and results are presented as the median (95% confidence interval). Other data are presented as mean values (± SD). Student's unpaired *t* test was used to test for difference between the two prandial states. A P value <0.05 was considered to be significant (SigmaStat 2.0, SPSS, Chicago, IL).

Pharmacokinetic Studies

Orally Administered Felodipine Formulations

Solution. Ten milligrams of felodipine was weighed into a 200-ml volumetric flask, and 2 ml ethanol 99% (v/v) was added to fully dissolve the felodipine. This was followed by the addition of 20 ml polysorbate 80 1.5% (w/v) and adjustment of the volume to 198 ml using either 0.9% saline or 5% glucose solution containing 0.8% PEG 4000.

Suspension of Micronized Powder. Ten milligrams of micronized felodipine was weighed into a 50-ml Erlenmeyer flask, and 20 ml of a 1.5% (w/v) hydroxypropylmethylcellulose (HPMC) (6 cps) solution containing 0.8% PEG 4000 was added. The suspension was sonicated for approximately 1 min. This suspension was administered promptly with either 178 ml of 0.9% saline solution or 5% glucose solution containing 0.8% PEG 4000.

Suspension of Coarse-Grade Powder. Ten milligrams of coarse-grade felodipine was weighed into a weighing boat. After wetting the orogastric tube with approximately 40 ml of the 198 ml of either the 0.9% saline solution or the 5% glucose solution containing 0.8% PEG 4000, the felodipine was administered via a funnel into the orogastric tube and subsequently rinsed through with the remainder of the coadministered solution.

In each case, a total of 10.0 mg felodipine and 198 ml accompanying fluid was administered.

Blood Samples. Blood samples (2–3 ml) were taken from either the foreleg or neck surface veins. Samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, and 24 h after oral administration into Venoject heparin tubes (Terumo Europe N.V., Leuven, Belgium). Samples were stored on ice for no longer than 1 h, then centrifuged for 10 min at 4000 rpm and 4°C. The plasma was transferred in a new vial and stored at –20°C until assayed for drug concentration by gas chromatography according to the method of Ahnoff (11). Typical elution times were 13 min and 13.5 min, respectively, for felodipine and the internal standard. The dogs had access to food after 7 h.

Pharmacokinetic Calculations

Pharmacokinetic analysis consisted of the visual identification of the maximum plasma concentration (C_{max}) and the time at which this occurred (t_{max}) from the individual subject plasma concentration time profiles. The area under the plasma concentration vs. time curve from time zero to t (AUC_0^t) was calculated using Kinetica (demo version, InnaPhase Corporation, PA). Calculation of the mean values of the parameters and their SD was performed.

RESULTS

Chyme Experiments: 5% Glucose Solutions *vs.* Normal Saline Solutions

Using inclusion criteria of PEG 4000 recovery >80% and a volume recovery of >75%, a total of eight experiments were analyzed for the "fasted" state and seven for the "fed" state.

The mean chyme flow rate decreased from 25.8 ± 17.2 ml/min ("fasted" state) to 10.4 ± 11 ml/min ("fed" state), ($0.1 > P > 0.05$). Further, the chyme flow pattern was visually more regular for the "fed" compared to the "fasted" state. Two typical profiles showing the flow rate pattern in the "fasted" or the "fed" state are shown in Fig. 1.

No significant difference in felodipine solubility was observed in "fed" and "fasted" state chyme ("fasted" state, 77 ± 47 mg/l; "fed" state, 56 ± 34 mg/l). The mean pH value in chyme under "fasting" conditions (6.35 ± 1.32) was significantly higher ($P < 0.05$) than under "fed" conditions (4.93 ± 0.97), but there was no significant difference in osmolality between the "fasting" (277 ± 17 mOsmol/kg) and "fed" (293 ± 15 mOsmol/kg) states.

Pharmacokinetic Experiments

Pharmacokinetic parameters are summarized in Table 1, and the mean plasma profiles are shown in Fig. 2.

Mean C_{max} values were highest for the solution: 24.4 and 20.3 μg/l for the "fasted" and the "fed" states, respectively. Maximum concentrations after administering the micronized suspension reached 11.2 and 12.5 μg/l in the "fasted" and "fed" state, respectively, whereas after the coarse suspension

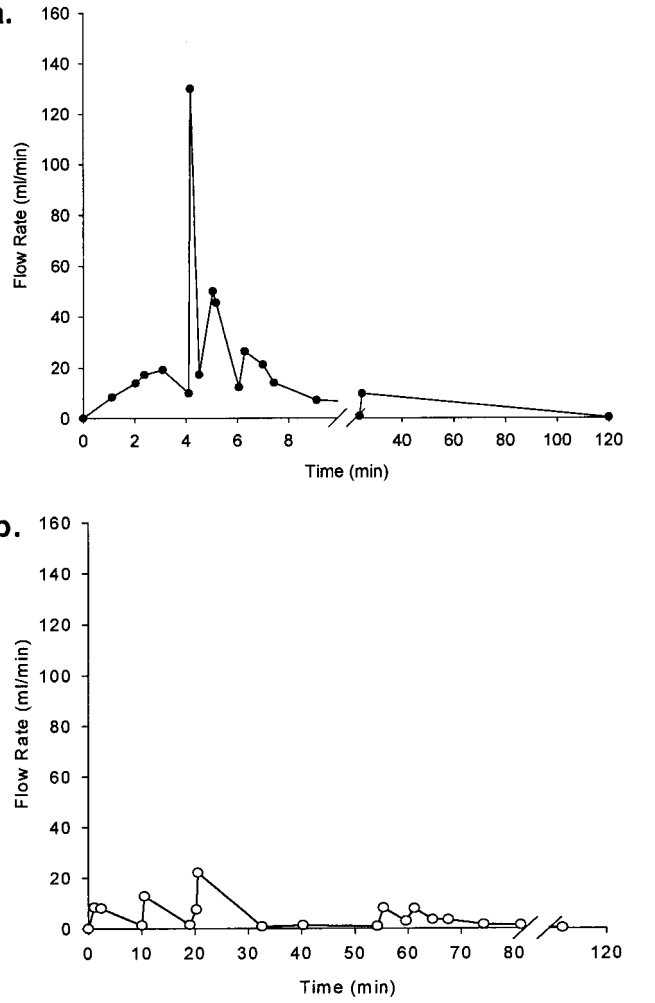

Fig. 1. Flow rates observed in dog 3 after infusion and oral administration of (a) 0.9% saline solution and (b) 5% glucose solution.

C_{max} values were much lower, around 0.5 and 1.2 μg/l, respectively.

The t_{max} values were commensurate with the C_{max} behavior. The times to peak were shortest for the solution ("fasted", 0.5 h; "fed", 0.4 h), somewhat longer for the micronized suspension (1.3 vs. 0.8 h, respectively) and much longer for the suspension containing the coarse grade felodipine (3.7 vs. 4.0 h, respectively). No significant difference in the t_{max} between the two dosing conditions was observed for any of the formulations.

The solution was more completely absorbed than either suspension, with AUC essentially the same under both "fasted" and "fed" conditions (33.9 vs. 35.1 μg/h/l). The relative bioavailability of the micronized suspension was about 75% and was independent of dosing conditions (24.5 vs. 25 μg/h/l). Absorption of the coarse-grade suspension was much poorer and varied with dosing conditions, about 5% (1.7 μg/h/l) in the "fasted" and just over 10% (3.7 μg/h/l) in the "fed" state.

DISCUSSION

"Fed" State *vs.* "Fasted" State: Validation

The objective of the chyme studies was to confirm that the dosing conditions used resulted in differences in hydro-

Table I. Mean Felodipine Pharmacokinetic Data following a 10-mg Dose of Felodipine, Administered Either as a Solution (n = 3) or as a Suspension (Micronized or Coarse Grade; n = 6) in Either a 0.9% Saline Solution or 5% Glucose Solution[a]

			Suspension			
	Solution		Micronized (8 μm)		Coarse (125 μm)	
Data	0.9% NaCl	5% Glucose	0.9% NaCl	5% Glucose	0.9% NaCl	5% Glucose
C_{max} (μg/l)	24.4 (±10.8)	20.3 (±14.2)	11.2 (±10.6)	12.5 (±10)	0.5 (±0.1)	1.2 (±0.6)
t_{max} (h)	0.5 (±0)	0.4 (±0.1)	1.3 (±0.5)	0.8 (±0.4)	3.7 (±2.3)	4 (±2)
AUC_7 (μg/h/l)	33.9 (±15.2)	35.1 (±29)	24.5 (±13.3)	25 (±17.2)	1.7 (±0.7)	3.7 (±2)

[a] Values given as mean (±SD).

dynamics, but not in other factors that could influence the absorption of felodipine.

The mean chyme flow rate (10.4 ml/min) obtained following the administration of 5% glucose solutions is in good agreement with the data from Brener *et al.* (9). They reported a gastric emptying rate of 2.13 kcal/min, which corresponds to a theoretical flow rate of 10 ml/min for a caloric load of 0.2 kcal/ml. The lower and more regular flow rate indicates that the 5% glucose converted the motility pattern from the fasted to the fed state.

The lack of effect of dosing conditions on felodipine solubility was verified by solubility determinations in chyme. Further, no water flux across the gut wall was induced by the administration of either the isotonic saline solution or the glucose solution and, hence, any effects on the dissolution rate/absorption could not be attributed to a difference in the fluid volume in the GI tract. Although the pH differed between the two sets of experimental conditions, the solubility of felodipine is not sensitive to pH in this pH range.

Thus, the dosing conditions selected for the "fasted" and "fed" states, although not representative of dosing conditions typically used in pharmacokinetic studies, allowed us to selectively study the influence of hydrodynamics on absorption of the poorly soluble felodipine.

Influence of Particle Size on Felodipine Absorption

The particle size of poorly soluble drugs can be of major importance for the dissolution and absorption process. *In vitro* studies have shown that initial dissolution rate increases as particle size is reduced (e.g., 12). *In vivo* studies have demonstrated the link between particle size and absorption for poorly soluble drugs. Examples include griseofulvin, for which a 4-fold increase in surface area resulted in a 2-fold enhancement in bioavailability (5,13), and digoxin. In the latter case, micronization of the drug (from 102 μm to 7–13 μm) doubled the bioavailability, bringing it to a level that was almost equivalent to the administration of an ethanolic solution (6). If there is lack of increase in the dissolution rate after micronization, this is usually attributed to agglomeration of the powder due to poor wetting properties (14). Under the conditions of the felodipine study, the low surface tension of GI fluids (15,16) was probably sufficient to circumvent aggregation problems. In any case, it is obvious from the current results that micronization has a profound effect on the *in vivo* dissolution and absorption of felodipine. The over 10-fold improvement in bioavailability obtained by micronizing the felodipine might be due to changes in surface morphology, i.e., an increase in edges, corners, and defects that lead to a higher surface free energy (17,18) and hence to a faster initial dissolution rate, as well as the simple increase in surface area per gram.

Influence of Hydrodynamics on Felodipine Absorption

In the GI tract, different hydrodynamic conditions are present, depending on the fasted or the fed state. In the fasted state the motility pattern is dominated by the interdigestive migrating motor complex, a cyclic pattern consisting of four phases with a duration of approximately 120 min in both dogs and humans (19). During phase I (which lasts approx. 60 min in the dog), residence times are long but there is barely any fluid movement, although in phase III (10–20 min)/IV (0–5 min) fluid movement is so rapid that there is insufficient time for dissolution to occur prior to reaching the absorptive sites. Only in phase II (20–40 min) is the combination of contraction pattern and flow rate conducive to drug dissolution. In contrast, the motility pattern of the fed state is more regular. The chyme is in continuous movement and, due to the rhythmic segmentation contractions, a more frequent local acceleration of the chyme can be assumed. It is likely that not only the rate but also the type of flow (laminar vs. turbulent) is different in the fed than in the fasted state and that this could lead to changes in dissolution, dependent on the sensitivity of the formulation. Taking these physiologic variations into consideration, the dissolution of poorly soluble drugs and the release from formulations sensitive to hydrodynamic changes is expected to be more effective in the fed than the fasted state.

Armenante and Kirwan (20) postulated that a different mass transfer process applies for microparticles than for larger particles. Although the development of a boundary layer is the main mass transfer mechanism for both macroparticles and microparticles, their behavior in micro-eddy regions differs. Local turbulences occur at milder hydrodynamic conditions for microparticles than for macroparticles, making them less sensitive to differences in the bulk hydrodynamics. A further explanation lies in slip velocity arguments. Harriott (21) investigated the dependence of the boundary layer thickness upon the slip velocity. He found that the slip velocity, the relative velocity of the solid to the fluid, was negligible for very small, suspended particles. Thus, bulk agitation will have relatively little influence on the dissolution rate of microparticles. In contrast, the slip velocity becomes an important factor in the dissolution process of larger particles.

Until now, no *in vivo* model has been available to directly test the influence of GI hydrodynamics accompanying the change from the fasted to the fed state. With our model, we were able to investigate these effects in a selective manner. Our results demonstrate that, depending on particle size, the

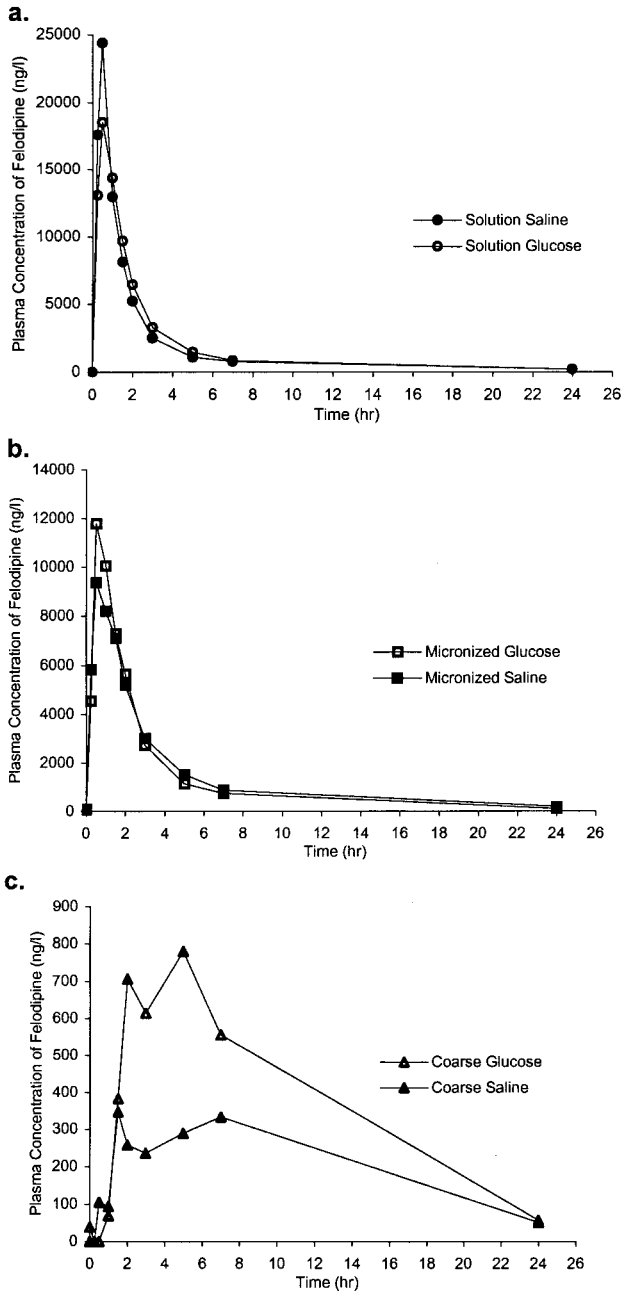

Fig. 2. Mean plasma concentrations following the administration of (a) felodipine solution (n = 3), (b) felodipine suspension-micronized powder, 8 μm (n = 6), and (c) felodipine suspension coarse-grade powder (125 μm [n = 6]; dose, 10 mg in either the 0.9% saline or 5% glucose solution.

hydrodynamics can influence drug absorption. The dissolution of the coarse-grade powder was improved by the "fed" state hydrodynamics, as reflected in the doubled extent of absorption. The micronized powder, by contrast, showed little or no sensitivity to hydrodynamics. These results concur with the expected differences in hydrodynamic behavior of macroparticles and microparticles, as outlined above.

CONCLUSIONS

The hydrodynamic influence on drug absorption seems to be particle size dependent for felodipine. Coarse-grade felodipine seems to be more sensitive to hydrodynamics than the micronized variety. However, the particle size itself seems to have a much more important influence on the bioavailability of felodipine than the hydrodynamics *per se*.

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