

Drug Marker Absorption in Relation to Pellet Size, Gastric Motility and Viscous Meals in Humans

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Received November 7, 1997; accepted November 21, 1997

Purpose. The objective of this study was to evaluate drug marker absorption in relation to the gastric emptying (GE) of 0.7 mm and 3.6 mm enteric coated pellets as a function of viscosity and the underlying gastric motility.

Methods. Twelve subjects were evaluated in a 3-way crossover study. 0.7 mm caffeine and 3.6 mm acetaminophen enteric coated pellets were concurrently administered with a viscous caloric meal at the levels of 4000, 6000 and 8000 cP. Gastric motility was simultaneously measured with antral manometry and compared to time events in the plasma profiles of the drug markers.

Results. Caffeine, from the 0.7 mm pellets, was observed significantly earlier in the plasma than acetaminophen, from the 3.6 mm pellets, at all levels of viscosity. Motility related size differentiated GE was consistently observed at all viscosity levels, however, less variability was observed with the 4000 cP meal. Specifically, the onset of absorption from the 3.6 mm pellets correlated with the onset of Phase II fasted state contractions ($r = 0.929$, $p < 0.01$).

Conclusions. The timeframe of drug marker absorption and the onset of motility events were not altered within the range of viscosities evaluated. Rather, the differences in drug marker profiles from the non-digestible solids were most likely the result of the interaction between viscosity and motility influencing antral flow dynamics. The administration of the two sizes of pellets and a viscous caloric meal with subsequent monitoring of drug marker profiles is useful as a reference to assess the influence of motility patterns on the absorption profile of orally administered agents.

KEY WORDS: gastric emptying; oral absorption; gastric motility; enteric coated; caffeine; acetaminophen; viscous meal.

INTRODUCTION

Discontinuous input rates following oral drug administration are often attributed to gastric emptying (GE). The design of

drug delivery systems to improve the consistency of oral absorption profiles is facilitated by understanding the physical factors involved in GE (1–4). Although particle size, particle density and viscosity are important parameters which influence size differentiated GE, the individual parameters have been shown to poorly correlate with GE of non-digestible solids (5). However, a strong correlation between the differential emptying of non-digestible solids has been observed when all the factors (diameter, density and viscosity) are integrated and described by a buoyancy term (5). This hydrodynamic relationship emphasizes that the interplay of these factors is important in the regulation of GE (5,6).

The intensity of antral peristaltic contractions in conjunction with pyloric resistance and duodenal feedback contribute to the forces involved in fed and fasted GE (7,8). Fed state motility is characterized by a pattern of low amplitude contractions which results in the relatively consistent GE of small solids through the pylorus (1). The fed state size cutoff for non-digestible solids is controversial with reports ranging from 2 mm (1) to 7 mm (2). Particles beyond this margin empty during the stronger contractions associated with Phase II and III of the fasted state cycle.

This investigation examined the influence of pellet size, gastric motility and viscosity on the timeframe of drug marker absorption. Each treatment phase was comprised of 0.7 mm caffeine (CAFF) and 3.6 mm acetaminophen (APAP) enteric coated pellets and a viscous caloric meal. The primary objective of this study was to evaluate the relationship between the physical parameter of particle size with the physiologic event of gastric motility as a function of meal viscosity. The hypothesis was that size differentiated GE of 0.7 mm and 3.6 mm enteric coated pellets administered with a viscous caloric meal would occur; with the smaller (0.7 mm) CAFF pellets emptying during the fed state and the larger (3.6 mm) APAP pellets emptying during the fasted state. Furthermore, the resulting drug marker absorption profiles would reflect the timeframe of GE and thus, provide an indirect measure of gastric motility events.

METHODS AND MATERIALS

Pellet Dose and Viscous Meal

The 0.7 mm CAFF (Lot 36913) and 3.6 mm APAP (Lot 36912) enteric coated spherical pellets for the human protocol were manufactured under cGMP guidelines in collaboration with The Pharmacia Upjohn Co. (Kalamazoo, MI) (9). Both pellet formulations began with sucrose non-pareils as the core, with several suspension layers sequentially coated (Glatt fluidized bed coater; Glatt Air Technologies; Ramsey, NJ) on the cores to achieve a target diameter, drug potency and enteric coat level. The target diameter was attained with talc suspensions and the final coat was methacrylic acid copolymer, NF (Eudragit L30D, Rohm Pharma, Inc.) at levels of 3.5 to 4 mg/cm². The pellet lots were submitted for stability testing at 30°C and 45% relative humidity, after which the release profile and potency were determined. The pellet formulations were placed in a rotating basket apparatus (USP 1) at 100 RPM and 37°C and sampled every 10 minutes. The pellets were placed in

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ABBREVIATIONS: CAFF, caffeine; APAP, acetaminophen; GE, gastric emptying; HPMC, hydroxypropyl methylcellulose.

pH 2.0 media (HCL/NaCl) with an ionic strength of 0.1. After 2 hours, the pH of the media (900 ml) was adjusted to 6.0 with an ionic strength of 0.137. This procedure was repeated at 0, 1, 3, 6, 9 and 12 months (9). A liquid pycnometer (10 ml Gay-Lussac, Thomas Scientific, Chicago, IL) was used to determine pellet density ($n = 3$). Pellet diameters were then calculated by applying the formula for sphere volume from the pycnometer data. This calculation was verified with direct digital micrometer (Mitutoyo; Tokyo, Japan) measurements with a sample size of 50 for each formulation ($n = 3$). The dose consisted entirely of single pellets, as all fused pellets were manually removed prior to weighing.

The viscous caloric meals consisted of hydroxypropyl methylcellulose (HPMC) (The Dow Chemical Co., Midland, MI), glucose and water. The target viscosities for the treatment phases (4K, 6K and 8K cP), were achieved with K15MP HPMC using the hot/cold dispersion method (10). Each 200 ml viscous meal treatment contained 100 kcal of glucose from the incorporation of a glucose tolerance beverage (General Medical Corp, Richmond, VA). The viscosity level of each meal was assessed at 37°C with the Rheo-Tech Visco-Elastic Rheometer (Rheo-Tech International Ltd) and was considered acceptable if it was within the limits of ± 200 cP of the target viscosity.

Human Protocol

Twelve healthy volunteers (2 female, 10 male, age range 22–39 years) gave written informed consent to participate in this three-way crossover study designed to assess size differentiated GE at three viscosity levels (4K, 6K and 8K cP). The study was conducted at the General Clinical Research Center at the University of Michigan Medical Center following approval by the Institutional Review Board. Subjects were deemed healthy based on a physical exam, medical history, complete blood count and serum chemistries. The volunteers were medication free, including over the counter medications, for at least 3 days prior to the study. Subjects refrained from ingesting xanthine containing foods and beverages (including caffeine) for 48 hours before each study phase. Following an overnight fast, subjects were admitted to the clinical research center and intubated with a gastric manometric catheter (PVC ICM³8 Arndorfer; Greendale, WI). Antral placement of the catheter was verified by fluoroscopy. After a 10 minute quiescent period (Phase I) in the fasted state, the subjects were administered the viscous meal in two parts. The first 150 ml portion of the viscous caloric meal was administered over 5 minutes and was given to induce the fed state. Fifteen minutes later, the remaining 50 ml of the viscous caloric meal and the entire pellet dose was administered simultaneously. The pellet dose consisted of 0.7 mm enteric coated pellets containing 100 mg of CAFF and 3.6 mm enteric coated pellets containing 500 mg of APAP. Subsequently, the subject's mouth was rinsed twice with water (~4 mL each) to ensure that pellets did not remain in the oral cavity. Motility monitoring continued for four hours post-dose as the subject remained seated upright.

Motility Recording and Analysis

The manometric catheter was designed to lay in the antrum and assess gastric motility patterns. A 5 cm weighted tip

was located at the distal end with side holes placed radially 1.5 cm apart starting 1 cm from the tip. A pH probe was located 13.5 cm from the distal end of the catheter. The pressure/motility recordings were measured with a capillary infusion pump system with pressure transducers connected to a meter, a transducer amplifier and a Model 4600 Data acquisition signal analysis system (Gould Inc., Valley View, OH). The readings were recorded on a thermal chart recorder (TA2000) and with the DASA VIEW II (Gould Inc., Valley View, OH) computer software at a data sampling rate of 10 per second. Subsequently, the most active channel was analyzed using software designed in our lab. In brief, this program allows the motility data file to be analyzed using filtering variables including: the sampling rate, minimum slope, minimum peak height and minimum width. After the noise was filtered and peak detection was complete, the contractile activity was summarized according to peak timing, frequency and area under the motility peak (normalized to maximum peak area for each study).

Time events in the motility cycle were defined according to the normalized peak area and peak frequency. Characterization of time events in the motility file were isolated in terms of time to the start of Phase II (T_{Ph-II}), time to the start of Phase III ($T_{Start-Ph-III}$), and the time to the end of Phase III ($T_{End-Ph-III}$). The criteria for T_{Ph-II} was a minimum normalized peak area of 0.05 with additional contractile activity following within 30 minutes. Selection of $T_{Start-Ph-III}$ was chosen at the onset of activity in which there were frequent and high peak area measurements separated by no more than 2 minutes until the $T_{End-Ph-III}$ where contractile activity ceased.

Drug Marker Analysis

Blood samples (3cc) were obtained through a forearm venous catheter placed in the left arm for multiple blood draws and placed in heparinized Vacutainer® vials (Becton Dickinson; Rutherford, NJ). The sampling points were: pre-dose, every 15 minutes for 4 hours, then every hour for 4 hours and then at 12 and 24 hours after the dose for a total of twenty-three sampling points for each phase of the study. The samples were centrifuged, and the plasma harvested, stored at -20°C and later analyzed via a modified HPLC assay with a lower limit of quantification for both compounds at 0.05 µg/ml (11,12).

The non-compartmental pharmacokinetic parameters t_{max} , C_{max} , AUC, MRT and $t_{1/2}$ for CAFF and APAP were determined with Topfit® Ver. 2.0 software program (Gustav Fischer, Stuttgart, Germany). AUC was calculated using the linear trapezoidal rule extrapolated to infinity from the last data point. The elimination rate was calculated from the linear portion of the log-linear terminal elimination phase. Statistical analysis was performed with Statistica® Release 4.5 (StatSoft, Tulsa, OK). A two-way multiple measures ANOVA was used to test for potential differences among the viscosity treatment levels (levels 4, 6 and 8K cP) and for period effects (influence of viscosity sequence). Critical levels of significance were set at $p = 0.05$.

Plasma profiles were assessed for the time event defined as: the first measurable timepoint for the drug marker ($t_{Initial-CAFF-0.7mm}$ and $t_{Initial-APAP-3.6mm}$). A comparison of $t_{Initial-CAFF-0.7mm}$ and $t_{Initial-APAP-3.6mm}$ was performed to evaluate the influence of diameter on the timeframe of the onset of absorption. The relationship between the independently deter-

mined time events from the motility analysis and drug marker profiles were evaluated to assess the influence of gastric motility and the viscous meal level on the resulting plasma profiles of the drug markers from the 0.7 and 3.6 mm enteric coated pellets.

RESULTS

In-Vitro Characterization of Pellets

The pellet diameter values assessed by both indirect and direct methods were in agreement and were not significantly different from one another. The pycnometer calculated diameters were 0.68 ± 0.004 mm for CAFF and 3.62 ± 0.001 mm for APAP (mean \pm sd) and the micrometer readings were 0.62 ± 0.044 mm and 3.62 ± 0.162 mm, respectively. The enteric coated pellets, nominally referred to as 0.70 mm CAFF and 3.6 mm APAP, had a mean density (\pm sd) of 1.57 ± 0.032 g/cm³ and 1.53 ± 0.007 g/cm³, respectively which were not significantly different.

The stability studies demonstrated no appreciable change in the release rate or drug loading for a 12 month period for the 0.7 mm and 3.6 mm pellets (9). Drug release was not detected in the pH 2.0 media for 2 hours. The onset of DM release was detected within 10 minutes at pH 6.0 for both formulations with a release fraction between 0.8 and 1.0 at the 20 minute sample (Fig. 1). The drug marker loading of the pellets were 30.8 and 19.7 (%w/w) for the CAFF and APAP pellets, respectively. The 100 mg dose of CAFF corresponded to 325 mg of 0.7 mm enteric coated pellets and the 500 mg dose of APAP was administered in 2.538 g of 3.6 mm enteric coated pellets.

Drug Marker Profile Analysis

Of the total 36 conducted studies, five were excluded from the motility and drug marker profile analysis due to protocol

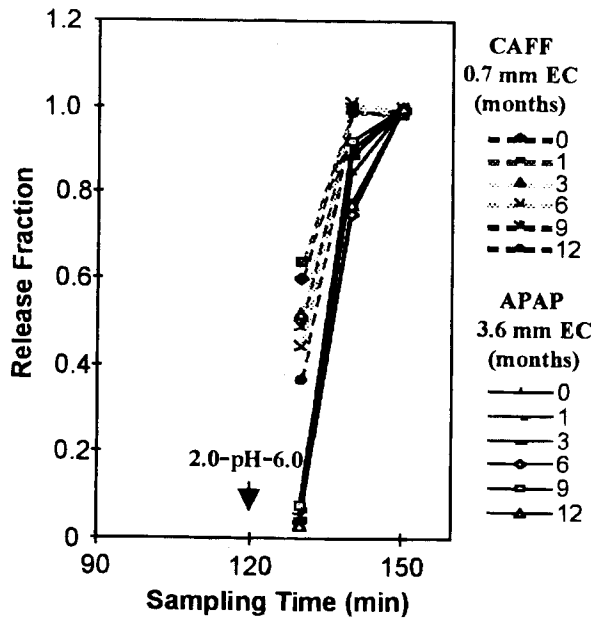


Fig. 1. Release profiles for 0.7 mm EC CAFF and 3.6 mm EC APAP pellets in pH 2.0 media and pH 6.0 buffer during 12 months of stability testing at 37°C and 45% RH.

Table I-A. Plasma Pharmacokinetic Parameters for CAFF from 0.7 mm EC Pellets (mean \pm sem) at 4K, 6K and 8K cP Meal Viscosities

| Meal Viscosity | 4000 cP | 6000 cP | 8000 cP |
|----------------------------------|-------------------------|---------------------------|-------------------------|
| AUC (μ g*hr/L) | 15.83 (± 5.56) | 15.84 (± 5.67) | 17.06 (± 5.49) |
| MRT (hr) | 8.38 (± 1.93) | 8.84 (± 2.26) | 9.07 (± 1.72) |
| t _{1/2} (hr) | 4.69 (± 1.45) | 4.90 (± 1.85) | 5.29 (± 1.32) |
| C _{max} (μ g/ml) | 2.11 (± 0.37) | 2.17 (± 0.34) | 2.18 (± 0.48) |
| t _{Initial-3.6mm} (min) | 45 (± 12) | 54.55 (± 15.12) | 61.5 (± 11.1) |
| t _{max} (min) | 144 (± 33) | 173.18 (± 44.38) | 156 (± 24) |

infringements or instrument error. Therefore, thirty-one studies were included in the motility and drug marker profile analysis (4K cP n = 10, 6K cP n = 11, 8K cP n = 10).

The calculated non-compartmental plasma pharmacokinetic parameters for CAFF (0.7 mm) (Table I-A) and APAP (3.6 mm) (Table I-B) are presented according to meal viscosity levels (4K, 6K and 8K cP) as well as the drug marker events of t_{Initial-CAFF-0.7mm} and t_{Initial-APAP-3.6mm}. There were no significant differences observed for the parameters among the three viscosity levels for either CAFF or APAP.

The relative onset and range of t_{Initial} values for the drug markers (t_{Initial-CAFF-0.7mm} and t_{Initial-APAP-3.6mm}) at the three viscosity levels are presented in Fig. 2. The positive slope connecting the two time events (except one subject at 8K cP) demonstrates that CAFF from the 0.7 mm enteric coated pellets are consistently measured in the plasma prior to the APAP from the 3.6 mm enteric coated pellets. The plasma profile time event parameters, t_{Initial-APAP-3.6mm} and t_{Initial-CAFF-0.7mm}, were significantly different (p < 0.005) when compared within each of the viscosity levels. The average corresponding time between t_{Initial-APAP-3.6mm} and t_{Initial-CAFF-0.7mm}, (Δ t_{Initial}) is relatively consistent across the viscosity levels with 49.5 ± 11.4 min. at 4K cP, 54.6 ± 25.8 min. at 6K cP and 45.0 ± 18.0 min. at 8K cP (mean \pm SEM).

Table I-B. Plasma Pharmacokinetic Parameters for APAP from 3.6 mm EC Pellets (mean \pm sem) at 4K, 6K and 8K cP Meal Viscosities

| Meal Viscosity | 4000 cP | 6000 cP | 8000 cP |
|----------------------------------|-------------------------|---------------------------|-------------------------|
| AUC (μ g*hr/L) | 23.92 (± 5.23) | 22.92 (± 4.90) | 22.13 (± 3.80) |
| MRT (hr) | 7.10 (± 0.50) | 7.22 (± 0.90) | 6.89 (± 0.53) |
| t _{1/2} (hr) | 3.59 (± 0.45) | 3.45 (± 0.55) | 3.33 (± 0.50) |
| C _{max} (μ g/ml) | 4.74 (± 0.75) | 4.56 (± 0.93) | 4.17 (± 0.88) |
| t _{Initial-3.6mm} (min) | 94.5 (± 17.4) | 109.10 (± 30.50) | 106.5 (± 16.8) |
| t _{max} (min) | 190.5 (± 23.4) | 203.18 (± 45.87) | 225 (± 36) |

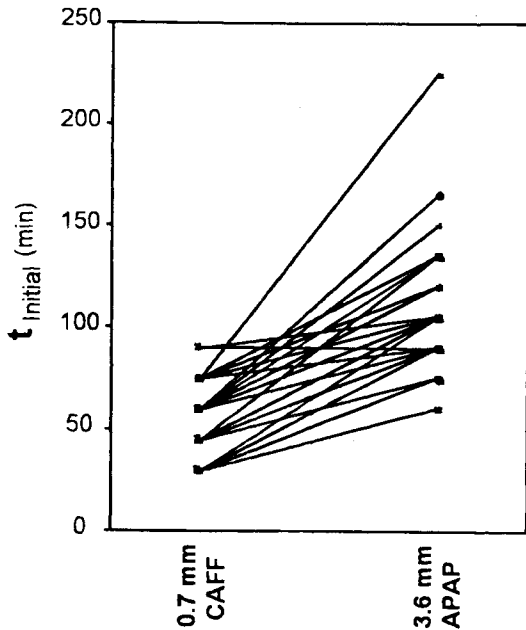


Fig. 2. The comparison of $t_{initial}$ (the first measurable drug marker timepoint) values for CAFF (0.7 mm) and APAP (3.6 mm) in plasma. Combined data for the 4000, 6000 and 8000 cP viscous caloric meals.

Motility and Drug Marker Time Event Analysis

The fasted state motility time events: T_{Ph-II} , $T_{Start-Ph-III}$ and $T_{End-Ph-III}$, were determined for each study and are summarized according to viscosity level in Fig. 3. There were no significant differences in each of the motility time event parameters among the three viscosity levels. Increasing meal viscosity was not associated with a lengthening of the onset of fasted state contractions or the ensuing Phase III time event. The duration of the fed state was not quantitated due to the lack of contractile measurements obtained during this phase. The lack of measurement was potentially due to a combination of low amplitude fed state contractions and the possible dampening effects of the viscous meal. During the period of conversion from the fed to fasted state, the motility did not revert

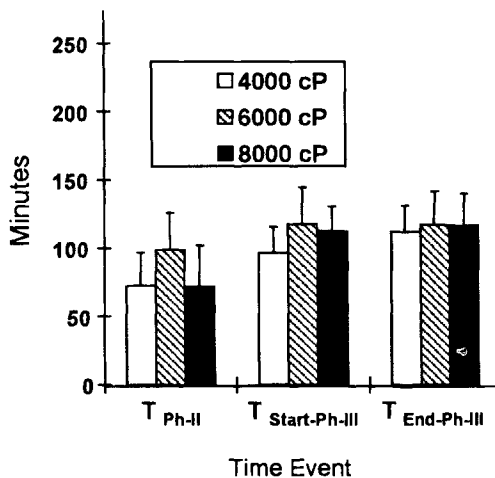


Fig. 3. Comparison of motility time events at 4000, 6000 and 8000 cP.

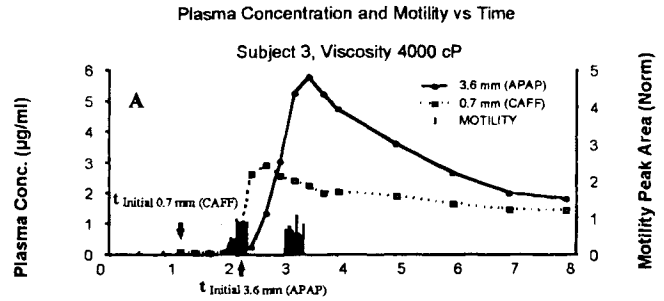


Fig. 4. Profile of drug markers from 0.7 mm CAFF (□) and 3.6 mm APAP (●) enteric coated pellets overlaid on the corresponding antral motility (I) with the respective $t_{initial}$ timepoints, administered with a 4000 cP viscous caloric meal (100 kcal/200ml).

immediately to Phase III but alternatively entered into either Phase I or II.

The influence of motility and pellet diameter relative to the timeframe of absorption with the 4K cP meal is depicted in Fig. 4. The plasma profiles of the drug markers are superimposable with the underlying motility pattern relative to the timing of the pellet dose. CAFF from the smaller pellets was observed in the plasma prior to the spikes representing fasted state Phase II motility. In contrast, the first measurable time event for the larger APAP pellets was observed following the onset of fasted state contractile activity. A differential emptying pattern was consistently observed between the 0.7 mm CAFF and the 3.6 mm APAP pellets at each viscosity level.

The relationship between $t_{Initial-APAP-3.6mm}$ vs. T_{Ph-II} exhibited a strong linear correlation with the 4K cP meal ($r = 0.929$, $p < 0.01$) (Fig. 5) however, as the viscosity increased the correlation decreased (6K cP $r = 0.799$, $p < 0.01$, 8K cP $r = 0.523$, $p > 0.05$). The average (\pm sem) interval between the onset of Phase II activity and $t_{Initial-APAP-3.6mm}$ (4K cP = 21.9 ± 10.7 ; 6K cP = 10.36 ± 18.94 ; 8K cP = 34.7 ± 27.64) exhibited the least variability at

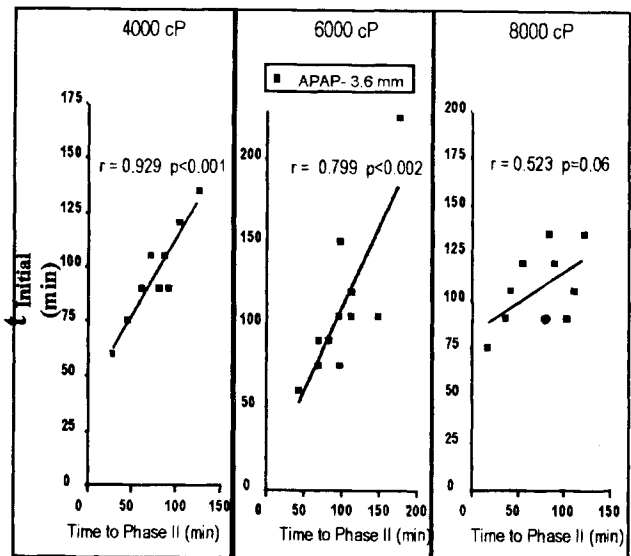


Fig. 5. The correlation of parameters $t_{initial}$ (the first measurable drug marker timepoint in plasma) with T_{Ph-II} (time to the onset of Phase II fasted state motility) at 4000, 6000 and 8000 cP meal viscosities for 3.6 mm EC APAP pellets.

the 4K cP level. Significant linear correlations were also noted between t_{\max} for CAFF (0.7 mm) and APAP (3.6 mm) and the motility events, $T_{\text{Ph-II}}$ and $T_{\text{Start-Ph-III}}$, at the 4K and 6K cP viscosities but was lacking at 8K cP (data not shown). Based on the low degree of variability with the 4K cP viscous meal and the increasing variability observed with the higher viscosities, the 4K cP viscous meal was deemed optimal.

DISCUSSION

The current investigation indirectly assessed several integral parameters involved in gastric flow dynamics (i.e., particle size, viscosity and gastric motility) that are known to influence size differentiated GE. The objective was to gauge this event by determining the relative timeframe of the emptying for the 0.7 mm and 3.6 mm pellets by assessing their respective drug marker absorption profiles. Important considerations in the design of this study included the choice of drug marker, particle diameter, density, drug marker release profile of the dosage form and the viscosity level.

GE dependent absorption has been reported for CAFF (13,14) and APAP (15), indicating rapid intestinal absorption. The drug markers are both rapidly absorbed from orally administered solutions with comparable mean t_{\max} values of 29.8 and 22 minutes for CAFF (16) and APAP (17), respectively. Utilizing differences in the onset of absorption of the rapidly absorbed drug markers would then correspond to the timeframe in which GE occurred. Previous attempts with this general approach have been inconclusive (18). Previous disparate findings potentially may have resulted from the confounding of the absorption parameter with dosage form inconsistencies and/or study design issues (18). In order to minimize potentially confounding factors, the *in-vitro* properties of the enteric coated pellets, utilized in this trial, met several critical criteria specified in the study design such as narrow size distribution and similarly rapid dissolution rates.

Although HPMC viscosity is sensitive to dilution with gastric secretions, the viscosity range was chosen below 10K cP based on preliminary studies in our laboratory in which viscosities $\geq 10K$ cP level did not demonstrate consistent size differentiated GE (unpublished data). Similar observations were made with high HPMC viscosity levels by Sirois *et al.* (5). The meal viscosity levels of 4K, 6K and 8K cP, did not significantly effect the overall extent and rate of absorption for the individual drug markers as observed by similarities in the AUC, C_{\max} and t_{\max} . At higher HPMC meal viscosities, 15K and 30K cP, a decrease and delay of glucose absorption has been reported (19). Statistically different drug marker profile events between $t_{\text{Initial-0.7mm-CAFF}}$ and $t_{\text{Initial-3.6mm-APAP}}$ were observed at each viscosity level and indicates the occurrence of size differentiated emptying of the 0.7 mm and 3.6 mm pellets.

Manometric characterization of fasted state motility was effective with the placement of our modified catheter design in the antrum. Previous manometry studies have also reported the lack of contractile measurements in the fed state (20). The delay of fasted state motility events ($T_{\text{Ph-II}}$, $T_{\text{Start-Ph-III}}$ and $T_{\text{End-Ph-III}}$) did not occur with increasing viscosity levels, however, the correlation between $t_{\text{Initial-APAP-3.6mm}}$ and $T_{\text{Ph-II}}$ was improved at the 4K cP level. This suggests that the influence on drug marker absorption stemming from viscosity levels is not

due to altered motility, but rather the result of modified flow dynamics in the stomach. A decreasing correlation with increasing viscosity suggests that the fed state size cutoff may vary according to meal composition and motility, which concurs with the buoyancy factor described by Sirois *et al.* (5).

Size differentiated GE at 4K cP in the fed and fasted state is further demonstrated by the t_{Initial} values for the drug markers in Fig 4. 0.7 mm pellets were able to empty during the fed state, whereas the drug marker from the 3.6 mm pellets is first observed after the onset of Phase II activity. The correlation ($r = 0.929$, $p < 0.01$) between $t_{\text{Initial-APAP-3.6mm}}$ and $T_{\text{Ph-II}}$ indicates that the motility event of Phase II governs the emptying of the larger pellets with the subsequent absorption of the drug marker.

The dosing protocol of the meal and dosage form appears critical for an ordered fed state emptying pattern, which is conventionally perceived as the pattern of low amplitude peristaltic contractions resulting from intestinal feedback. To ensure the induction of fed state motility, a 15 minute delay was specified in our dosing protocol between the meal and the pellets. In concurrence with previous reports, (20,21) we observed that meal administration during Phase II of the MMC does not ablate the contractile cycle and convert to the characteristic fed state motility pattern, rather the contractions continue and often follow through to complete Phase III activity. An adjustment period is referred to by Mojaverian *et al.* (22) where the administration of indigestible solids were delayed for 30 minutes after the ingestion of a meal to ensure baseline conditions. In studies where large indigestible solids are administered without an equilibrium period after meal ingestion, GE was observed within minutes of oral dosing (2). Differences between meal ingestion and the relative dosing time of test solids may explain some of the conflicting observations of large non-digestible solids emptying early in the proposed fed state.

The current pellet and viscosity study controlled for various physical influences on GE in order to isolate a physiologic influence on the timeframe of absorption. The timeframe of absorption for orally administered drugs is an important component of pharmaceutical claims such as bioequivalence and in labeling statements regarding the onset of action. Both fed and fasted state studies are important since the onset and extent of absorption can be significantly different under these conditions. An appropriately controlled dosing protocol and meal is necessary to adequately compare absorption parameters. Having established a relationship between motility and the timeframe of absorption with this pellet and viscous meal system, a potential application would be to apply this as a reference in determining the influence of normalized fed and fasted state motility on the absorption of a co-administered experimental compound or formulation. We have determined conditions under which the onset of drug absorption is directly related to fed and fasted state size differentiated GE corresponding to specific gastric motility states. The underlying motility assessed by the drug marker profile could be used to evaluate the influence of motility on the absorption timeframe of orally ingested agents and may indicate whether the rate limiting step to absorption is controlled by GE or intestinal absorption.

ACKNOWLEDGMENTS

This work was supported in part by an American Foundation for Pharmaceutical Education (AFPE) Fellowship

and by NASA Grant NAGW-4981. The authors would like to acknowledge the Pharmacia & Upjohn Company for the generous donation of resources and materials in the manufacture of the pellets and the General Clinical Research Center (GCRC), University of Michigan funded by a Grant (M01 RR00042) from the National Center for Research Resources, National Institutes of Health, US PHS.

The results in part were presented at the 1996 annual meeting of AAPS in Seattle, Washington.

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