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Effect of volume and viscosity of coadministered fluid on gastrointestinal distribution of small particles

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Abstract

The effect of volume and viscosity of a coadministered liquid on distribution and discharge kinetics of small particles of varying densities was studied in the fasted, cannulated dog. Particles of similar size (average diameter 1.0 mm), having densities of 0.5, 1.25, and 2.4 g/ml, were used in the study. Either 50 or 300 ml of Methocel solutions ranging in viscosity from 20 to 45 000 cps at 25°C were coadministered with the particles. All materials were administered orally during phase I in the fasted dogs, and discharged particles were collected from a permanent cannula situated 10–15 cm from the pylorus. Methocel solutions with viscosities up to 500 cps showed no effect on the distribution or transit times of particles as compared with water. However, viscosities of 5000 and 45 000 cps caused varying degrees of distribution of particles with densities of 0.5 and 1.25 g/ml. The discharge pattern of particles with density 2.4 g/ml is affected only with a viscosity value of 45 000 cps or greater. In general, a large volume (300 ml) distributed the particles better than a small volume (50 ml). The conclusion from these studies is that small non-digestible particles empty as a bolus during phase III when given with liquids of low viscosity, but when administered with liquids of viscosity higher than 5000 cps, they empty with the liquid and show a tendency of distribution.

Keywords: Gastric emptying; Gastrointestinal particle distribution; Viscosity; Methocel solution

1. Introduction

The fasted state in man, and other animals that consume food on a discrete basis, is characterized by a cyclic motility and secretory pattern of the GI tract (Weisbrodt, 1981; Quigly et al., 1984). This cyclic pattern of motility, which originates in the foregut and propagates to the terminal ileum, can be divided into four distinct phases: phase I – representing a quiescent period with no electrical activity and no contractions; phase II – the period of random spike activity or intermittent contractions; phase III – the period of regular spike bursts or regular contractions at the maximal frequency that migrate distally; and phase IV – the transition period between phase III and I. The average length of one complete cycle, commonly known as the interdigestive migrating motor complex (IMMC), ranges from 90

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to 120 min in both man and dog (Itoh and Sekiguchi, 1982). Phase III, also known as the housekeeper wave, serves to clear all indigestible materials from the stomach and small intestine. Non-digestible solids when administered during phase I are emptied from the dog stomach only during phase III (Ehrlein, 1980).

Gastric emptying of non-digestible solids appears to be affected by the strong contractions that occur during late phase II and the entire phase III. The process of gastric emptying of non-digestible solids during phase III is further aided by synchronized contractions in the proximal duodenum which propel the contents towards the jejunum (Ehrlein, 1980). During early and mid phase II, however, solids may be retropulsed back into the fundus (Ehrlein, 1980). Therefore, while contractions during phase II may be strong enough to propel solids out of the stomach, lack of synchronization of motility usually prevents emptying of solids during this phase.

Recent studies from our laboratory have shown that there is no sieving of particles during the fasted state (Gruber et al., 1987; Li, 1987). Solid non-digestible particles and powders closely follow the gastric motility pattern in the fasted dog. Onset of discharge of particles and powders correlated with late phase II and phase III activity. All particles and powders were emptied, more or less as a bolus, at the onset of high antral activity. This was attributed to strong interaction of particles with mucus in the stomach lining, which prevents any distribution of the particles. Also, gastric emptying of non-digestible particles is independent of size, density and surface characteristics as well as volume of coadministered saline. It was concluded that the residence time and distribution of oral dosage forms in the fasted, canine stomach are primarily dictated by two factors: the phasic activity of the motility pattern at the time of ingestion and bolus discharge due to particle-mucus interactions.

Dispersion of solid dosage forms, including tablets and capsules, has been reported to be poor in the stomach in the fasted state (Weiss et al., 1961; Levy, 1963; Hey et al., 1979). In summary, due to the nature of motility and particle-mucus interaction in the stomach, distribution of solid dosage form particles in the fasted state is poor.

The purpose of this study was to explore the effect of the volume and viscosity of the coadministered fluid on distribution and transit of small particles. In order to keep the number of variables small, three different spherical particles of similar size (about 1.0 mm) but different density were selected for the study. Also, all test particles were administered during phase I of the fasted state.

2. Materials and methods

2.1. Animals

Three adult, female dogs of mixed breed, weighing 15–20 kg. were used in the study. Each dog was prepared with a permanent duodenal cannula. The dogs were housed in a room with air and humidity control and a 12 h light/dark cycles. The animals were fed a standard laboratory diet once daily except before the studies, when they were fasted for 24 h to induce the fasted state. The animals were given free access to water at all times.

2.2. Dog preparation

The surgical procedure of Reinke et al. (1967) was followed to implant the cannula into the duodenum. After being anesthetized with 30 mg/kg of sodium pentobarbital (Nembutal sodium solution, 50 mg/ml; Abbott Laboratories, North Chicago, IL), the dogs underwent laparotomy under aseptic conditions. A modified Thomas cannula made of Derlin (o.d. 21 mm, i.d. 17 mm; The University of Wisconsin Physical Plant Machine Shop, Madison, WI) was implanted in the duodenum through a longitudinal cut about 15 cm from the gastroduodenal junction on the side free of mesenteric blood supply. The cannula was exteriorized through an opening in the abdomen and fixed to the abdominal wall at a site about 4 cm below the last rib and 2.0 cm from the midline cut. A recovery period of 2 weeks was allowed before the animals were used

Table 1
Various concentrations and corresponding viscosities of methocel solutions used

[Methocel] (% w/v)	Viscosity (cps) at 25°C
0.25	20
0.50	500
1.0	5000
2.0	45000

for studies. The dogs were trained to stand quietly, supported by slings (Alice King Chathman Medical Arts, Los Angles, CA) and to accept oral administration of liquids by natural swallowing.

2.3. Viscous solutions

High viscosity grade Hydroxypropylmethylcellulose (Methocel) was used as the viscosity inducing agent. The reason for choosing this material was the fact that it is non-digestible and does not have any caloric value. Using different concentrations of the material, it was possible to test a wide range of viscosities.

Since we now know that small and large volumes of fluids are handled differently, two volumes, representing a small and a large volume, were chosen. 50 ml was chosen as the small volume and 300 ml was used as the large volume because neither of these values is close to the critical volume of 100–150 ml which converts the stomach from the fasted to fed state. Table 1 lists the strengths and associated approximate viscosities of Methocel. Since Methocel is a pseudoplastic material, the listed values of viscosities were obtained at very small shear rates (0.2 rpm, SV II sensor system) where the values are relatively constant. A Haake RV 12 viscometer was used to measure all viscosities.

2.4. Particles

Three kinds of particles were chosen for this part of the study. Table 2 lists the name, size and specific gravity of the particles used. The size of all the particles averages about 1 mm in diameter, but they vary in density from 0.5 to 2.4 g/cm^3.

2.5. Administration of particles

Prior to each experiment, the dogs were fasted for 16–18 h but with free access to water. The duodenal discharge collected from the cannula can be used to ascertain the phase of activity at any given time, as explained previously (Gupta and Robinson, 1988, 1994). All meals were administered during phase I with intubation at the back of the mouth of the animals. In order to use the bile and mucus discharge to ascertain phasic activity, the cannula was opened and duodenal discharge allowed to drain. If bile and mucus discharge was observed on opening the cannula, then the arrival of the next cycle was awaited to time the first arrival of bile. After one complete phasic activity cycle was over, an additional 20 min period of no discharge was followed in order to make sure that the GI motility of the dog was in phase I. At this time, which was arbitrarily taken as time zero, the required volume of a test meal containing the particles at 20°C was instilled into the back of the dog's mouth by a flexible tube (5 mm i.d.) attached to a 200 ml syringe. The dog's mouth was held up and the meal instilled at a rate of about 150 ml per min which was swallowed comfortably. All particles were administered as a bolus with 50 ml of liquid. For 300 ml studies, the 50 ml suspension was followed by an additional 250 ml solution. The particles were not enclosed in capsules because the disintegration step in capsules constitutes yet another variable and may make interpretation of results more difficult. Therefore, the difference in transit or distribution pattern of these particles will be only

Table 2
Characteristics of particles used in the study

Particles (g/ml)	Size (diameter, mm)	Density (g/cm^3)
Foamed polystyrene [a]	1.0–1.2	0.50
Amberlite [b]	0.7–1.0	1.25
Glass [a]	0.8–1.0	2.40

[a] Gift from Dr Karl Thomae, Bieberach, West Germany.
[b] Amberlite synthetic ion-exchange resin, Rohm and Haas, Philadelphia, PA.

due to differences in their density or volume of fluid administered. Uniformity in the experimental set up with previous studies was ensured to keep the variables to a minimum and to make the comparison more meaningful.

2.6. Duodenal effluent collection

Following administration of water, all duodenal effluent was collected from the cannula at 2 min intervals for 10 min and at 5 min intervals thereafter. This included the volume discharged from the stomach as well as the secretions of the first 15 cm of duodenum. The particles were counted visually. Three repetitions at each volume were carried out on each dog, and the data from three dogs was pooled to calculate the mean and standard deviation.

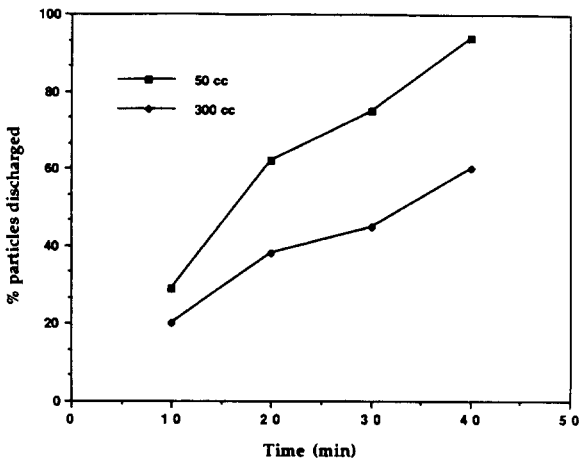

Fig. 1. Effect of volume of 2.0% Methocel on transit pattern of foamed polystyrene beads (size 1.0–1.2 mm, density 0.5 g/ml). Percent particles discharged are plotted as a function of time after the appearance of first particles. Each data point is the average value from nine studies.

3. Results and discussion

All the reported data are average values from nine studies (three studies in each of three dogs). The standard deviations have been left out in all the plots except the last one for the sake of clarity. Typically, standard deviations for all results were about 20% of the mean of nine studies. Also, the emptying patterns of 0.25–1.0% HPMC are not plotted because these viscosity values did not show significant difference in gastric emptying pattern of beads of any density. This fact has been discussed in the text.

3.1. Gastric emptying of particles

3.1.1. Polystyrene particles

When percent particles recovered from the duodenal cannula have been plotted against time after appearance of the first particle, the first particles appear only 30–40 min after ingestion of the particles. Discharge of polystyrene particles with small volumes of viscosities up to 500 cps, i.e., 0.25 and 0.5% HPMC show no difference when compared to water. However, higher viscosities do seem to distribute the particles better. While there is no difference between transit patterns with 1.0 and 2.0% Methocel solutions, there is a difference between these products and the lower viscosity systems.

With 300 ml of solutions of varying viscosities the pattern for 2.0% Methocel solution stands out from the rest. Almost 90% of the particles are discharged when ingested with a large volume of viscosity upto 500 cps. Fig. 1 summarizes the effect of volume of 2.0% Methocel on transit pattern of foamed polystyrene beads. When given with 50 ml solution the particles are discharged within 30 min of onset of discharge, which begins 30 min after ingestion. However, when ingested with 300 ml, discharge begins a few minutes after administration, but only 60% of the particles are discharged during 30 min.

With small volumes, onset of discharge of solids and liquids is simultaneous, unlike with water where the fluid phase empties first. This is because highly viscous material is not emptied until late phase II when the force is great enough to expel the solids as well. On the other hand, with large volumes, solids empty along with the solution. The percent of particles discharged corresponds roughly with the percent of fluid discharged during this time. This means that the particles, despite their low density remain uniformly suspended in the fluid and further support the hypothesis that large volumes of viscous ma-

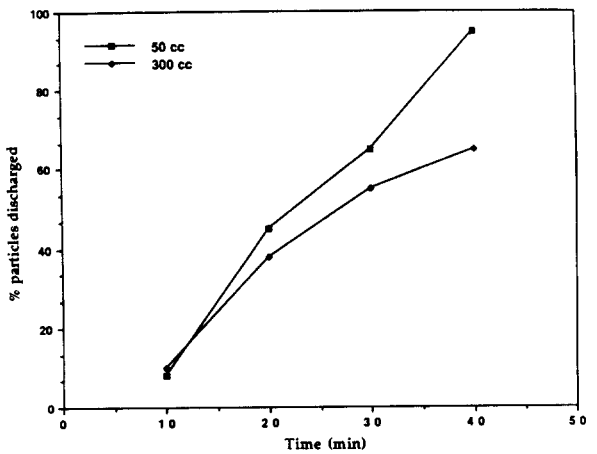

Fig. 2. Effect of volume of 2.0% Methocel on transit pattern of Amberlite beads (size 0.7–1.0 mm, density 1.25 g/ml). Percent particles discharged are plotted as a function of time after the appearance of first particles. Each data point is the average value from nine studies.

terials convert the stomach to a fed state.

3.1.2. Amberlite particles

Transit and distribution patterns of Amberlite beads show similar behaviour to polystyrene beads. This is despite the fact that the density of Amberlite beads is more than twice that of polystyrene beads. With small volumes, only 2.0% Methocel shows any significant distribution of particles, and the same is true for the large volume.

Fig. 2 summarizes the effect of volume of 2.0% Methocel on the emptying pattern of Amberlite beads. Once again, the recovery of particles with small volumes of fluid is virtually complete within 30 min of the onset of discharge whereas only about 60% of particles are recovered during this time when ingested with a large volume. This value corresponds to the volume of fluid emptied during this time, implying that there is adequate mixing in the stomach with large viscous volumes.

3.1.3. Glass beads

Unlike polystyrene and Amberlite beads, glass beads do not show any significant distribution during gastric emptying. With small volumes, the emptying of particles starts after 30–40 min and is complete within 20–30 min. However, the relationship between the discharge of liquid and particles is different. Even with 2.0% Methocel, the fluid leaves first and only then are the particles recovered. The glass beads, being heavier, probably sink to the body of the stomach and empty only during phase III. However, the time difference between the two is small. With large volumes most of the fluid is gone long before most of the particles empty and the particle discharge follows the same pattern as with 50 ml. Apparently, the degree of mixing during large viscous fluid emptying is not sufficient to keep the particles mixed with the gastric content. Another possibility is that both fluid and particles empty together but travel at different speeds in the duodenum. The observed difference in time may be due to slower movement of particles in the first 15 cm of the duodenum.

Fig. 3 summarizes the effect of volume on gastric emptying of glass beads when given with 2.0% Methocel. Since the initial time point in this curve is after the first appearance of particles, information is lost with respect to the onset of discharge. However, once discharge starts, over 90% of the particles are recovered within 30 min,

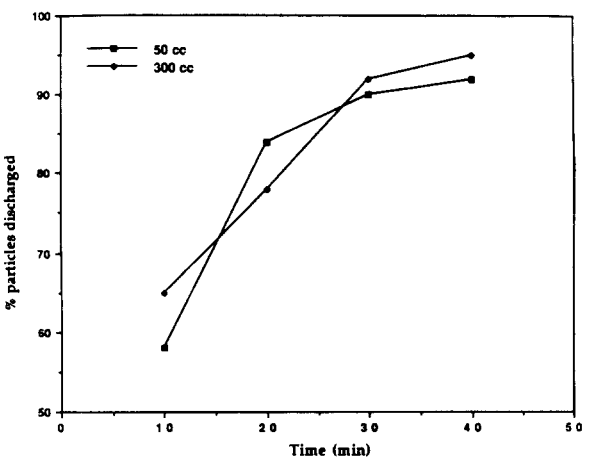

Fig. 3. Effect of volume of 2.0% Methocel on transit pattern of glass beads (size 0.8–1.0 mm, density 2.4 g/ml). Percent particles discharged as a function of time after the appearance of first particles. Each data point is the average value from nine studies.

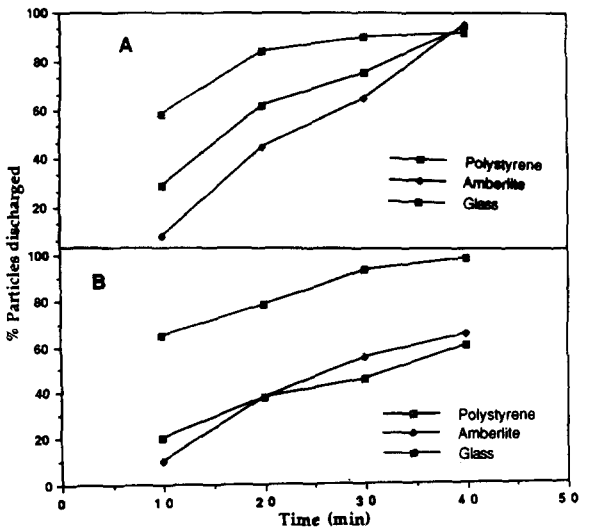

Fig. 4. Effect of density of particles on transit pattern of particles when coadministered with 50 ml (A) and 300 ml (B) of 2.0% Methocel solution. Percent particles discharged are plotted as a function of time after the appearance of first particles. Each data point is the average value from nine studies.

a pattern distinctly different from that of polystyrene and Amberlite beads.

3.2. Effect of particle density on discharge

Fig. 4A shows the effect of density of particles on the transit pattern of particles when ingested with a small volume of 2.0% Methocel solution. The curve for Amberlite particles is on the top, indicating that particles with a density closest to that of the gastric content empty at the fastest rate. Effect of density shows up when it is different from that of the medium. For glass beads (density 2.4 g/ml), the rate of gastric emptying picks up only after high antral activity, whereas most of the Amberlite particles are already emptied by then. Polystyrene beads demonstrate an intermediate curve.

Fig. 4B shows the effect of density of particles on their transit pattern when ingested with 300 ml 2.0% Methocel solution. The curve for glass beads is distinctly different from those of polystyrene and Amberlite. This shows that particles of density 1.25 or less empty slowly, with liquid, over a period of time. Particles of density 2.4, on the other hand, do not empty until most of the fluid is gone and high antral activity arrives. This implies that the fed state motility is not strong enough to empty glass particles.

Average gastric emptying of three kinds of particles as a function of time after administration (compared to time after the first appearance of particle) is shown in Fig. 5 and 6 for small and large volumes, respectively. Fig. 5 shows that while glass particles lag in their onset of discharge, they catch up once their discharge starts, resulting in a virtual overlap of curves. However, Fig. 6 shows a different curve for glass beads. It is clear from this plot that while Amberlite and polystyrene particles empty with the viscous fluid, glass beads empty only after most of the fluid is gone and high antral activity has arrived.

It is generally assumed that a dispersible dosage form randomly scatters through the GI tract (Becket, 1981). Dispersion of oral dosage forms is desirable for the following reasons. (i) Scattered particles can prevent the localization of drug in one area of the GI tract thereby reducing the incidence of GI discomfort with certain drugs. (ii) More uniform drug absorption may result from a distributed dosage form as compared to that from a single unit dosage form. This is be-

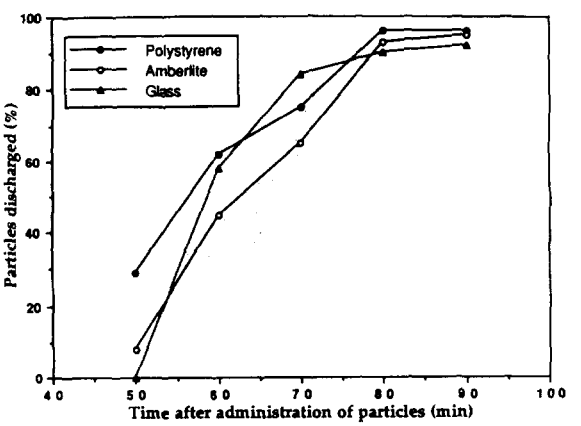

Fig. 5. Mean gastric emptying of particles of various densities when coadministered with 50 ml 2.0% Methocel solution. Percent particles recovered, as a function of time after administration. The error bars have been omitted for the sake of clarity. Each data point is the average value from nine studies.

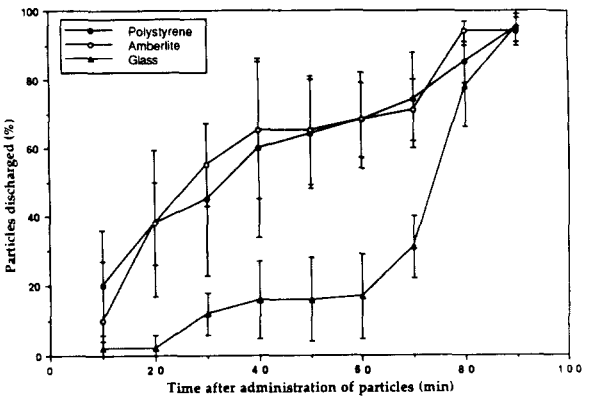

Fig. 6. Mean gastric emptying of particles of various densities when coadministered with 300 ml 2.0% Methocel solution. Percent particles recovered have been plotted as a function of time after administration. Each data point is the average value from nine studies.

cause in the fasted state, a single unit dosage form may travel through the stomach and the small intestine within a matter of minutes and the drug may not have the chance to dissolve and be absorbed. (iii) There is less chance of drug-release-control mechanism to fail for multiunit dosage forms. In a single unit dosage form, the failure of the drug-release-control mechanism may result in undesirable high levels of drug in the body.

When a meal consisting of liquid, digestible solids and non-digestible solids is given, the pattern of emptying of each component is different and independent of each other. When dogs were given a meal of 400 ml 1% dextrose, 50 g cubed liver, and 40 plastic spheres (diameter 7 mm; density 1.6), each component emptied differently (Hinder and Kelly, 1977). Liquid emptied most rapidly, more than 90% being emptied in about 1 h. Digestible solids, i.e., the liver cubes, emptied slowly and continuously over a period of about 4 h. In contrast, indigestible solids did not empty at all over a period of 4 h. This was attributed to retropulsion produced by simultaneous contractions of the terminal antrum and pylorus. In another study, larger non-digestible spheres (size > 6 mm, density 1.0) were not emptied until return of the interdigestive state and were emptied during late phase II and early phase III (Mroz and Kelly, 1977). Both size and density of non-digestible spheres affected their emptying in the presence of food in the range of 1–5 mm (Meyer et al., 1979). The same studies claimed that a density other than 1.0 slows gastric emptying of spheres of all sizes.

Due to recent advances in noninvasive techniques such as gamma scintigraphy, a number of studies of gastric emptying of solid dosage forms have been reported. Some of the earlier studies of gastric residence time of dosage forms reported that the onset of gastric emptying of enteric coated tablets was random and appeared to follow a log-normal and normal distribution in fasted dogs and man respectively (Wagner et al., 1958; Nelson, 1964). Based on these studies, it was suggested that gastric emptying of pellets would be continuous in the fasted state and that multiunit dosage forms would disperse very well throughout the GI tract (Wagner, 1971).

Using gamma scintigraphy, the onset of gastric emptying of pellets and large single unit systems has been reported to be within 2 h in the fasted state (Park et al., 1984; Smith and Feldman, 1986). Claims about the effect of density on gastric emptying have been conflicting. Some reports suggest that lower density particles empty slower than higher density particles (Sangekar et al., 1987), while others claim that there is no such difference (Sheth and Tossounin, 1984).

It has been reported that once past the pylorus, a dosage form has little, if any, chance of distributing itself (Davis et al., 1986; Davis et al., 1987). This means that distribution can be achieved only at the level of gastric emptying. The present studies have shown that by using viscosity inducing hydrophilic polymers, some degree of particle distribution can be achieved. One recent study has shown that the rate of gastric emptying of non-digestible particles is independent of the size of particles, but is influenced by their physical characteristics (Meyer et al., 1989). Using particles of hard or soft consistency, the authors have shown that soft particles emptied significantly faster than hard ones from the fasted human stomach. However, both the density and surface characteristics of the particles used in this study were different from each other and it is

possible that these differences contributed to the observed differences in rates of gastric emptying. Nevertheless, such results, combined with effect of the coadministered fluid on particle discharge from the stomach can set the stage for systems capable of dispersing in the GI tract. Additional studies in our laboratory have shown that it is possible to change the gastric motility and processing of its contents by administering partially hydrated swellable polymers orally (unpublished results). Such polymers presumably act by altering hydrodynamics in the stomach, and, by virtue of their viscosity, could help disperse the multiunit dosage forms.

It should be noted, however, that viscosities of the materials used in the present studies will change after ingestion. This is due to the fact that once in the stomach, a rise in temperature from 25 to 37°C and dilution from gastric secretions will tend to reduce the viscosity. Therefore, effective viscosities were lower than measured values. Also, surface characteristics of the particles are considerably different from each other. Interaction of the Methocel solution with the particle surface can affect wetting and hence mixing of particles with the solution. These factors have not been addressed in our studies.

The results from the present studies contradict the claims of longer gastric residence times of particles with high or low density in the fasted state. Also, claims about the distribution of multiunit dosage forms under normal dosing conditions seem to be questionable. However, these studies have indicated that it may be possible to create a condition in which some degree of particle distribution can be achieved in the fasted state.

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