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Research Paper

A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol

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Purpose. To examine the effect of common excipients such as sugars (sorbitol *versus* sucrose) on bioequivalence between pharmaceutical formulations, using ranitidine and metoprolol as model drugs.
Methods. Two single-dose, replicated, crossover studies were first conducted in healthy volunteers ($N = 20$ each) to compare the effect of 5 Gm of sorbitol and sucrose on bioequivalence of 150 mg ranitidine or 50 mg metoprolol in aqueous solution, followed by a single-dose, nonreplicated, crossover study ($N = 24$) to determine the threshold of sorbitol effect on bioequivalence of 150 mg ranitidine in solution.
Results. Ranitidine Cmax and AUC(0–∞) were decreased by ~50% and 45%, respectively, in the presence of sorbitol *versus* sucrose. Similarly, sorbitol reduced metoprolol Cmax by 23% but had no significant effect on AUC(0–∞). An appreciable subject-by-formulation interaction was found for ranitidine Cmax and AUC(0–∞), as well as metoprolol Cmax. Sorbitol decreased the systemic exposure of ranitidine in a dose-dependent manner and affected bioequivalence at a level of 1.25 Gm or greater.
Conclusions. As exemplified by sorbitol, some common excipients have unexpected effect on bioavailability/bioequivalence, depending on the pharmacokinetic characteristics of the drug, as well as the type and amount of the excipient present in the formulation. More research is warranted to examine other 'common' excipients that may have unintended influence on bioavailability/bioequivalence.

KEY WORDS: bioavailability; bioequivalence; excipient; permeability; sorbitol.

INTRODUCTION

Drug absorption from the gastrointestinal (GI) tract is complex and can be influenced by a number of variables. Of all the possible factors, drug solubility and intestinal permeability are generally recognized to be critical determinants of the rate and extent of absorption (1). Accordingly, the Biopharmaceutics Classification System (BCS) based on the aqueous solubility and intestinal permeability of drugs has been used by pharmaceutical and regulatory scientists to identify potential drug candidates from immediate-release oral solid dosage forms for waiver of *in vivo* bioequivalence studies (2). In this context, most pharmaceutical excipients currently on the market are considered inert and thus, will not affect bioequivalence although certain 'active' excipients in the formulation have been reported to alter the rate and/or extent of drug absorption (3–17). As an example, sugars are commonly used as sweetening agents in oral liquid dosage forms. Literature data have revealed differential effects of various sugars on the GI transit and perhaps drug bioavailability. Mannitol solution at low concentrations relevant to pharmaceutical formulation was shown to reduce small intestinal transit time while sucrose solution did not appear to alter intestinal transit (6). In a study with cimetidine, the mean ratios of area under the plasma concentration–time curve (AUC), maximum concentration (Cmax), and time to peak concentration (Tmax) were 71, 46, and 167%, respectively, between mannitol and sucrose formulations (8). Sorbitol is isomeric to mannitol and both possess similar effects on the GI transit time. However, 10 Gm of sorbitol had minimal effect on the bioavailability of theophylline, expressed by AUC and Cmax (4). It is noteworthy that cimetidine has a low intestinal permeability whereas theophylline has a high permeability.

The influence of common excipients such as sugars on the outcome of bioequivalence has not been studied in the past. It is envisioned that the presence of an 'active' excipient in one formulation (but not in another) or in differing amounts between formulations may be one of the factors that contribute to the subject-by-formulation interaction

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observed in some bioequivalence studies (18). In light of the literature information, this research was first carried out to study the effect of two different sugars (sorbitol *versus* sucrose) on the bioequivalence status between formulations of drugs with low (ranitidine) and high (metoprolol) intestinal permeability. The results showed that sorbitol significantly influenced the bioequivalence outcome of ranitidine. Accordingly, another study was conducted to determine the threshold (minimal) amount of sorbitol required to affect ranitidine bioequivalence.

MATERIALS AND METHODS

Dosage Forms

In the study comparing sorbitol and sucrose, ranitidine dosage forms were prepared to contain 150 mg of ranitidine base (ranitidine HCl 168 mg — Ranbaxy Labs, Lot #3RNT115398) with either 5 Gm of sucrose (Sigma Lot 117H0056) or 5 Gm sorbitol (Sigma, Lot #1081491461) in a final aqueous solution of 15 ml. The dosing solution (15 ml) was administered using a 20 ml oral dosing syringe. The metoprolol doses were prepared to contain 50 mg metoprolol tartrate (Assia Chemical Lot 238002993) in an identical manner to the ranitidine solutions.

In the study determining the threshold of sorbitol effect, bulk ranitidine solution (Neuland Laboratories Limited, Batch #RHII0703021) was prepared by dissolving 150 mg ranitidine base (equivalent to 168 mg ranitidine HCl) with 5, 2.5, or 1.25 Gm sorbitol (Sigma-Aldrich, Lot #072K0097), or without sorbitol, in a final aqueous solution of 15 ml. The dosing solution (15 ml) was administered using a 20 ml oral dosing syringe.

In Vivo Study Designs

Sorbitol versus Sucrose

Two single-dose bioequivalence studies were conducted with 20 healthy volunteers (17 males and 3 females) in each trial. One study was on ranitidine and the other metoprolol. Both studies had a two-treatment, two-sequence, four-period, replicated crossover design. The research followed the 1964 Declaration of Helsinki and its amendments and was approved by the Institutional Review Board (IRB), University of Tennessee, and the Research Involving Human Subjects Committee (RIHSC), FDA.

The subjects, weighing between 50 and 96 Kg, were evaluated with a medical history, physical exam, ECG and clinical chemistry including CBC and urinalysis prior to receiving any doses. The volunteers were divided into two groups and each group ($N = 10$) received the two treatments in a different sequence: RTRT and TRTR. One week lapsed between doses. After an overnight fast, each subject received 180 ml of water to facilitate venous catheter placement. One hour later, each subject received the 15 ml oral dose (see "Dosage Forms") with 120 ml of water. No food was permitted until a standard lunch was served four hours after dosing. In the ranitidine study, blood samples were obtained prior to dosing and at 0.33, 0.67, 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4, 5, 6, 8, 10, and 12 h after each dose. In the metoprolol study, blood samples were obtained prior to dosing and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 15, and 25 h after each dose. For both studies, 7.5 ml blood samples were obtained from the indwelling catheter into a heparinized tube (Vacutainer®). Plasma was removed by centrifugation for 10 min at 4°C and stored at −80°C until analysis.

Threshold Level of Sorbitol Effect on Bioequivalence

This was a randomized, four-treatment, four-sequence, four-period crossover study. A total of 24 healthy volunteers (16 males and 8 females) completed the study. Subjects fasted for a minimum of 10 h prior to dosing. The volunteers were administered orally 4 single doses of aqueous solution containing 150 mg of ranitidine and either 0, 1.25, 2.5, or 5 Gm of sorbitol on 4 separate occasions with a 7-day interval between periods. Meals were given at 4 and 7 h post-dose. Blood samples, 7 ml, were collected prior to dose and serially for 12 h with similar sampling schedules as those for ranitidine in the first trial.

Analytical Methods

Ranitidine

A modified high-performance liquid chromatographic (HPLC) method (19) was used for determination of ranitidine concentrations. Ranitidine and n-propionyl procainamide (NPP, internal standard) were extracted from human plasma on Oasis HLB cartridge solid phase extraction (SPE) columns (Waters Corporation, Milford, MA). After extraction, samples were analyzed on a Hewlett-Packard 1050 Series HPLC with a quaternary pump equipped with a Hewlett-Packard diode array detector (DAD), automated injection, degassing and temperature controlled modules. Separation was achieved on a Phenomenex Luna C-18, reverse phase, 4.6×250 mm, 5 micron particle size, HPLC column (Torrance, CA), equipped with a Phenomenex C-18 Security guard cartridge. A temperature-controlled (30°C) gradient elution method was employed utilizing a mobile phase of 5–21% methanol/10 mM citrate/phosphate buffer, pH = 3.8 at a flow rate of 1 ml/min. for 32 min and increased to hold at 60% for 5 min. The flow rate was 1.0 ml/min. UV detection for ranitidine and NPP was at 272 nm and 317 nm, respectively. The injection volume was 100 µl.

In the study comparing sorbitol and sucrose, the precision of pre-study ($n = 20$) and in-study ($n = 60$) quality control (QC) samples was 1.3–6.1% and 4.5–12.3% (coefficient of variation, CV), respectively. The mean recovery of these samples was 87–92% and accuracy was 92–98%. The plasma calibration standards were linear over the range of 10–1,000 ng/ml. The limit of quantification was 10 ng/ml. In the subsequent study determining the threshold of sorbitol effect, the calibration curve was linear over the range of 25–750 ng/ml. The precision of QC standards ($n = 96$) ranged 2.9–4.2% CV, and the accuracy was 91–100%.

Metoprolol

A modified HPLC method (20) was used for determination of metoprolol concentrations. Metoprolol and dextrorphan (internal standard) were extracted from human plasma

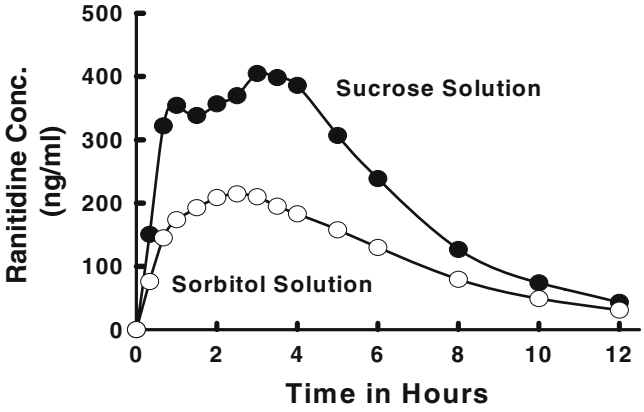

Fig. 1. Mean plasma concentrations of ranitidine in 20 healthy volunteers after administration of 150 mg ranitidine solution with addition of 5 Gm of sorbitol (*open circle*) or 5 Gm of sucrose (*solid circle*).

on C-2 SPE columns (Varian, Harbor City, CA). Samples were analyzed on a Hewlett-Packard 1090 Series HPLC with a tertiary pump equipped with a 1046A fluorescence detector, automated injection, degassing and temperature-controlled modules. Separation was achieved on the same type of C4/E HPLC reverse phase column with an LC-8 guard cartridge reported previously (20). A temperature-controlled (30°C) isocratic elution method was employed utilizing a mobile phase of 15% acetonitrile, 2.25% tetrahydrofuran, 0.13% 1-octane sulfonic acid, and 10 mM phosphate buffer (pH = 3.0) for 20 min. The flow rate was 1.75 ml/min. Metoprolol and dextrorphan were detected by fluorescence (excitation wavelength 228 nm, emission wavelength 320 nm). The injection volume was 50 μl.

The pre-study ($n = 20$) and in-study ($n = 40$) QC samples had precision of 3.9–11.8% and 6.8–8.7% CV, respectively. The QC standards had mean recovery of >95% and accuracy of 94–99%. The plasma standards were linear over the range of 1.5–100 ng/ml. The limit of quantification was 1.5 ng/ml.

Data Analysis

The area under the plasma concentration–time curve was calculated from time zero to infinity [AUC(0–∞)] using standard methods. Cmax was obtained by choosing the highest drug concentration from the plasma profile and Tmax was the corresponding time point for Cmax. Individual replicate data as well as the means of replicates were used for statistical analysis.

To determine bioequivalence, analysis of variance (ANOVA) was performed for ln-transformed data using General Linear Model (GLM) procedure from the SAS statistical package on a VAX 8000 computer. The statistical model was partitioned into sequence, subject within sequence, period and an error term. The two one-sided hypotheses at $\alpha = 0.05$ level of significance were tested for AUC(0–∞) and Cmax by constructing the 90% confidence intervals for the ratio of the geometric means between the test and reference products (21). Average bioequivalence was established for all ln-transformed bioavailability measures if their 90% confidence intervals fell within 80–125% (22).

For replicated design studies, statistical analysis was also carried out to estimate the variances of pharmacokinetic measures, including intra- and inter-subject variability and subject-by-formulation interaction (22,23). Subject-by-formulation interaction is a measure of subject-to-subject similarity (or dissimilarity) in the difference between a test and a reference product (24). Theoretically, if all individuals have similar differences between the two products, no subject-by-formulation interaction is present. If individuals vary considerably in their differences between the test and reference products, the subject-by-formulation interaction is large. The presence of a large interaction would inflate the error variance and thus might require more subjects to have the same power to pass average bioequivalence (24). The variance terms, intra-subject variability and subject-by-formulation interaction, were determined by the method of moments while inter-subject variability was determined by the restricted maximum likelihood (REML) method.

RESULTS

Ranitidine in Sorbitol Solution *versus* in Sucrose Solution

Figure 1 depicts the mean plasma concentration profile of ranitidine in 20 healthy subjects after oral administration of 150 mg ranitidine in sorbitol and sucrose solution. Although double or multiple peaks seemed apparent only in the mean profile of the sucrose solution, this phenomenon was evident in individual curves from both solutions. As shown in Table I, ranitidine Cmax was decreased by ~50% in the presence of sorbitol compared to sucrose. Likewise, ~45% decrease in AUC(0–∞) was found from sucrose to sorbitol solution. Both Cmax and AUC(0–∞) failed to meet the bioequivalence limits of 80–125%. Similar inter- and intra-subject variability was observed for Cmax between the two solutions. However, the inter-subject variability of AUC(0–∞) for the sorbitol solution was only half of the sucrose solution. The intra-subject variability of AUC(0–∞) was about 20% higher for the sorbitol solution. As indicated in Table I, a substantial subject-by-formulation interaction was found for both Cmax and AUC(0–∞), reflecting the lack of similarity in the difference between sucrose and sorbitol solutions across individuals. This large interaction was also exemplified by a stick plot connecting each individual's AUC(0–∞) data for the sucrose and sorbitol solution (Fig. 2). As shown, in several subjects the AUC(0–∞) values from the sucrose solution were about double those from the sorbitol solution whereas other subjects had similar values between the two formulations.

Metoprolol in Sorbitol Solution *versus* in Sucrose Solution

Unlike ranitidine, no double or multiple peaks were observed for metoprolol in either solution (Fig. 3). The absorption rate of metoprolol was slower in the presence of sorbitol compared with sucrose. Tmax was delayed by ~30 min for the sorbitol solution (average 1.6 h) relative to the sucrose solution. As shown in Table I, there was a 23% decrease in Cmax when metoprolol was dissolved in the sorbitol solution as opposed to sucrose solution. The 90% confidence interval for the average Cmax ratio between the sorbitol and sucrose (reference) solutions was outside the

Table I. Summary Data for the Study Comparing Sorbitol and Sucrose[a]

Parameter	Test	Reference	T/R ratio	90% confidence interval	Subject-by-formulation interaction
Ranitidine[b]					
Cmax					0.13
Geo. mean (ng/ml)	233.7	478.2	0.49	(44.0–54.2)	
Intersubj. SD[c]	0.236	0.225	1.05	–	
Intrasubj. SD	0.237	0.235	1.01	–	
AUC(0–∞)					0.15
Geo. mean (ng×h/ml)	1,514.7	2,681.1	0.56	(51.7–61.8)	
Intersubj. SD	0.132	0.243	0.54	–	
Intrasubj. SD	0.196	0.162	1.21	–	
Metoprolol[d]					
Cmax					0.12
Geo. mean (ng/ml)	49.3	63.8	0.77	(70.5–84.7)	
Intersubj. SD	0.477	0.476	1.00	–	
Intrasubj. SD	0.186	0.213	0.87	–	
AUC(0–∞)					0
Geo. mean (ng×h/ml)	292.7	316.4	0.93	(85.6–99.9)	
Intersubj. SD	0.612	0.654	0.94	–	
Intrasubj. SD	0.246	0.180	1.37	–	

[a]All analyses were conducted using ln-transformed data.
[b]Test: a 15-ml aqueous solution with 150 mg ranitidine and 5 gm sorbitol; Reference: a 15-ml aqueous solution with 150 mg ranitidine and 5 gm sucrose.
[c]Standard deviation approximates coefficient of variation (% CV) on the original scale.
[d]Test: a 15-ml aqueous solution with 50 mg metoprolol tartrate and 5 gm sorbitol; Reference: a 15-ml aqueous solution with 50 mg metoprolol tartrate and 5 gm sucrose.

acceptable bioequivalence range. However, the observed difference (7%) in the extent of absorption didn't achieve statistical significance and AUC(0–∞) was within the bioequivalence limits. The inter-subject variability for both Cmax and AUC(0–∞) was similar for metoprolol between the two solutions (Table I). In contrast, the intra-subject variability in the sorbitol solution was slightly lower for Cmax, but higher for AUC(0–∞). A sizable subject-by-formulation interaction was found for Cmax, but no interaction was evident for AUC(0–∞) (Table I). The presence of an interaction for Cmax may reflect the dissimilarity in the Cmax difference between the two solutions across individuals, and the two solutions may not be interchangeable if the Cmax of metoprolol is considered important in the clinical setting.

Ranitidine Solution with Various Amounts of Sorbitol

Figure 4 depicts the mean plasma concentration–time profiles of ranitidine in 24 healthy subjects after an oral administration of 150 mg ranitidine solution with various amounts of sorbitol. Double (or multiple) peaks were found in the individual profiles from all solutions either with or without sorbitol. This study data (Table II) was consistent with those from the first study (Table I). As shown in Table II, there appeared to be a linear relationship between the extent of reduction in ranitidine bioavailability and sorbitol dose added to the formulation. The presence of 5 and 2.5 Gm sorbitol significantly decreased the bioavailability of ranitidine, but 1.25 Gm of sorbitol did not affect bioequivalence based on the 90% confidence intervals (Table II).

Fig. 2. Stick plot for individual AUC(0–∞) values of ranitidine between sucrose and sorbitol solution, indicating a large subject-by-formulation interaction.

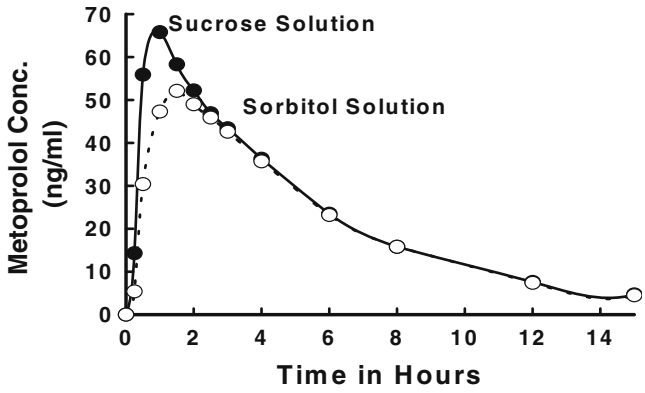

Fig. 3. Mean plasma concentrations of metoprolol in 20 healthy volunteers after administration of 50 mg metoprolol tartrate with addition of 5 Gm of sorbitol (*open circle*) and 5 Gm of sucrose (*solid circle*).

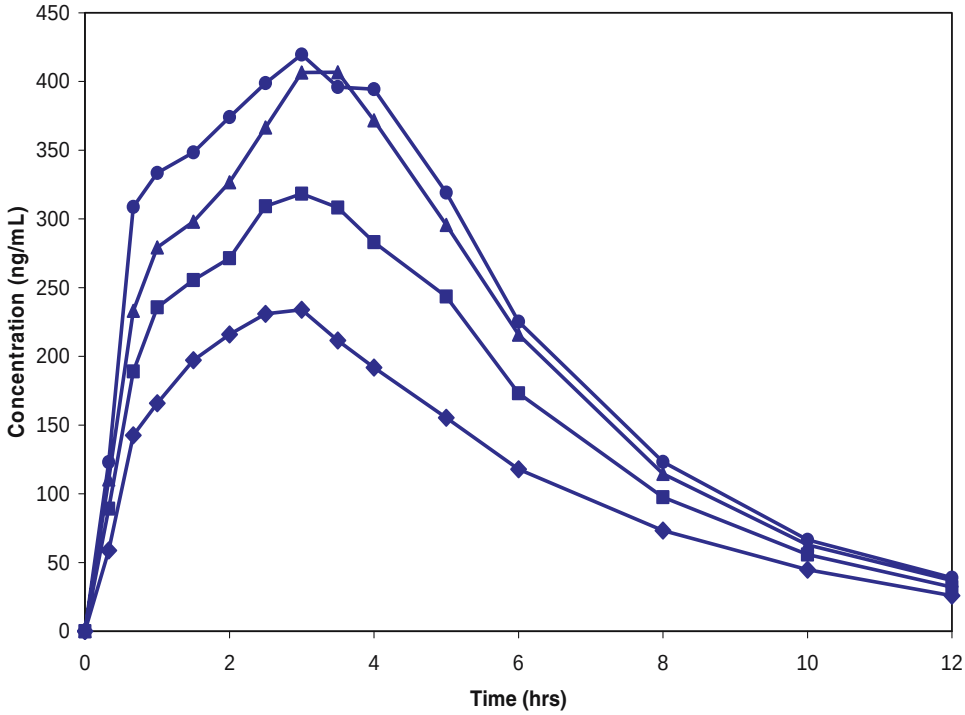

Fig. 4. Mean plasma concentrations of ranitidine in 24 healthy volunteers after administration of 150 mg ranitidine solution with addition of 0 (*closed circle*), 1.25 (*triangle*), 2.5 (*square*), and 5 Gm (*diamond*) of sorbitol.

DISCUSSION

Sorbitol has traditionally been used as an osmotic laxative in large quantity (25,26), and is known to cause GI distress or reduce small intestinal transit time at low concentrations (27–36). The difference in the bioavailability of ranitidine between the sorbitol and sucrose solution may be partly attributable to an increased GI fluid volume from the osmotic pressure of sorbitol (37), which decreased the concentration gradient of ranitidine in the GI tract, thereby reducing the drug absorption. Another mechanism may be the GI motility enhancement of sorbitol that reduces ranitidine contact time with the small bowel, a primary absorption site for the drug (38). Furthermore, the increased GI fluid influx and motility may cause insufficient time for drug absorption at the proximal intestinal region and drive most drugs to the distal region where ranitidine permeability is reported to be lower compared to the proximal site (39).

Sorbitol may have similar effects on the bioavailability of metoprolol although the extent of such influence was less pronounced than ranitidine. The contrast between metoprolol and ranitidine could be explained, in part, by their difference in the intestinal permeability. Unlike ranitidine, metoprolol has a relatively high permeability, which is pivotal for metoprolol absorption and thus, no significant difference in AUC(0–∞) was found between the sorbitol and sucrose solution although its Cmax was affected by sorbitol. Metoprolol is a high-hepatic extraction drug whose bioavailability may also be affected by transient alterations in hepatic blood flow (40). More recently, the human organic cation transporter (hOCT) 1 was suggested to play a major role in the intestinal absorption of ranitidine (41). Sorbitol has low intestinal permeability, and hence an interaction between sorbitol and hOCT1 could be another mechanism for the observed results in this study.

Double or multiple peaks were prominent in the individual plasma profiles of ranitidine from pure aqueous solution and sucrose solution, but less frequent from the sorbitol solution. Ranitidine is not well secreted into the bile (42) and thus enterohepatic recycling may be ruled out as a cause for the multiple-peak phenomenon. Double peaks have

Table II. Statistical Summary of Ranitidine Study with Various Amounts of Sorbitol[a]

Parameter	Geometric mean	% Reference[b]	90% confidence interval
Cmax, ng/ml			
Trt. 1	259	47.9	(43–53)
Trt. 2	378	70.3	(63–78)
Trt. 3	487	92.7	(83–104)
Trt. 4	528	–	–
AUC(0–∞), ng × hr/ml			
Trt. 1	1,464	54.5	(50–60)
Trt. 2	2,014	75.0	(68–82)
Trt. 3	2,493	92.8	(85–102)
Trt. 4	2,685	–	–

[a]Treatment (Trt.) 1: a 15-ml aqueous solution with 150 mg ranitidine and 5 gm sorbitol. Trt. 2: a 15-ml aqueous solution with 150 mg ranitidine and 2.5 gm sorbitol.Trt. 3: a 15-ml aqueous solution with 150 mg ranitidine and 1.25 gm sorbitol.Trt. 4: a 15-ml aqueous solution with 150 mg ranitidine and no sorbitol.
[b]Treatment 4 is the reference.

also been reported after an oral administration of cimetidine, which was attributed to the antral gastric motility in subjects (43). However, double peaks still occurred for ranitidine when the drug was administered directly to the jejunum (38), suggesting that gastric emptying may not be the single source. Using intestinal steady-state infusion technique, Grammatte *et al.* (39) showed the site-dependent absorption of ranitidine, i.e., highest absorption rate in the proximal duodenal–jejunum junction followed by the distal jejunum–ileum with no absorption in the mid-jejunum. They theorized the changes in water fluxes along the small intestine as a cause for discontinuous absorption profiles (i.e., double- or multiple-peak) of hydrophilic drugs. This theory might explain our finding for ranitidine in the sucrose solution. The enhancement of intestinal motility by sorbitol, however, could shorten the 'apparent' distance between the two absorption regions for ranitidine, and as a result, double or multiple peaks were less frequently observed with sorbitol as opposed to sucrose.

The use of replicated designs in the current study allowed for the assessment of variances between formulations in comparison. Notably, an appreciable subject-by-formulation interaction was observed for ranitidine Cmax and AUC(0–∞), as well as metoprolol Cmax. The presence of such interactions indicated a difference in the individual responses to the two formulations (i.e., sorbitol *vs.* sucrose solution). A relevant factor accounting for the subject-by-formulation interaction may relate to the unique effect of sorbitol on GI physiology observed in various subgroups of the general population (26–36). For example, in a study conducted on two continents (U.S. and India), an oral administration of 10 Gm of sorbitol caused 32% of the 124 healthy adults to develop abdominal symptoms, irrespective of ethnic origin (32). The orocecal transit time was significantly shorter in the sorbitol-intolerant group (72–79 min *versus* 110 min). In another study, sorbitol malabsorption was found in 12 diabetics and 23 nondiabetics with 6 diabetics (50%) and 13 nondiabetics (56.5%) developing abdominal symptoms after sorbitol ingestion (33).

The combined use of cathartics and activated charcoal has long been advocated for the management of drug overdose (44–46). Cathartics are intended to decrease drug absorption by accelerating the expulsion of the toxin–charcoal complex from the GI tract (47). Addition of sorbitol catharsis (130 Gm) produced a mean GI transit time of 0.9 h compared to 23.5 h with activated charcoal alone (48). However, studies with only sorbitol in large amounts (up to ~100 Gm) had no significant influence on the extent of absorption for aspirin or theophylline (49–51). Similar results were observed with charcoal–sorbitol combination for aspirin (49,52), acetaminophen (53) and theophylline (50,51). These findings appeared to be consistent with our metoprolol study. As with metoprolol, acetaminophen and theophylline are categorized as BCS I drugs (54). Aspirin (acetylsalicylic acid) may have a low permeability (55), but it is easily converted to salicylic acid (highly permeable) during and after absorption (56). The extremely high dose of aspirin (31×80 mg) employed in another study might have more acetylsalicylic acid (rather than salicylic acid) present in the GI tract during the early phase of poisoning, and thus a significant impairment of aspirin absorption was observed with sorbitol coadministration (57). The traditional use of sorbitol, in lieu of sucrose, as a cathartic in the management of poisoning may be attributed to the differential intestinal permeability and metabolic route between the two sugars. Sucrose has a high permeability and is rapidly metabolized at the intestinal wall to glucose and fructose (58,59). By contrast, sorbitol has a low permeability and hence, is capable of staying long in the lumen to exert its cathartic action (59). Sorbitol is slowly absorbed by the small intestine, and metabolized in the liver to glucose and fructose (60).

Sorbitol is a common sweetener in pediatric liquid medications given orally (61–63). It is also present in some fruits, juices, 'sugar-free' chewing gums and candies that are frequently consumed by infants and children (64–66). Poor absorption of carbohydrate in infants or children is well documented following juice consumption, especially when high in sorbitol (35,36). Conceivably, co-administration of sorbitol-containing medication (e.g., cough syrup) with another drug (e.g., antibiotics) may decrease the absorption and change the efficacy profile of the latter. Similarly, administration of a drug with sorbitol-containing juice may decrease the drug bioavailability.

While most excipients available in the marketplace may be devoid of pharmacologic action, the present study demonstrates the possible existence of an 'active' excipient that alters drug bioavailability, hence bioequivalence between formulations. The interactions observed between sorbitol and drugs may be partly derived from the sorbitol effect on GI physiology, thereby influencing drug absorption. The differential results between ranitidine and metoprolol may suggest that the bioavailability/bioequivalence of a drug with low intestinal permeability is more susceptible to the sorbitol effects than a drug with high intestinal permeability although other mechanisms are also possible. Conceivably, there might be other 'active' excipients that could influence bioavailability and/or bioequivalence through various mechanisms, such as inhibiting pre-systemic enzyme metabolism or intestinal membrane transporters, changing GI permeability, altering *in vivo* dissolution rate, complexating with drugs or degrading drugs in the gut. Further research is warranted to study the potential effects of other 'common' excipients on bioavailability and bioequivalence.

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