INTRODUCTION
The practice of medicine today is shifting toward an emphasis on preventive care and primary prevention of morbidities. With this change, the public has also developed increased health awareness. The potential role of mineral and multivitamins in prevention of certain morbidities and also the change in lifestyle has resulted in an increased trend in consumption of fortified foods. This is evident with the survival of multiple health food and nutritional supplement retail stores. It is also revealed in the food industry’s focus on food fortification. Foods are most often fortified with multivalent cationic minerals, such as calcium, iron, magnesium, and vitamins, like vitamins C, D, E, and B-complex. However, some fortified foods can contain up to 100% of the daily value (DV) of the U.S. recommended daily allowance (USRDA) or dietary reference intake (USDRI) within a single serving (Dietary Reference Intakes, 2000).

This concept has important implications from a pharmaceutical development and clinical pharmacology standpoint. While it is clear that certain drugs should not be taken with antacids, multivitamins, and mineral supplements, many patients do not consider the implications of taking their daily medications with food. Currently, the Food and Drug Administration (FDA) standardized meal used in the product labeling of drug-food interaction is a non-vegetarian, high-fat, high-calorie consisting of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. This diet provides only small amount of dietary vitamins and minerals (FDA 2001). As a result, many drugs are labeled “may be taken with or without food,” while they may be also labeled “do not take with antacids.” The biochemical mechanisms that cause drug-antacid interactions are the same mechanisms that cause drug interactions with fortified foods. Chelation and adsorption interactions, which cause decreased drug absorption, can certainly occur between fortified foods and drugs. The fact that some fortified foods contain a
quantity of polyvalent ions that approaches or exceeds that contained in antacid formulations, may produce changes in gastric pH, changes in urinary pH, and thereby decrease the absorption of some drugs.

Ciprofloxacin is a broadspectrum fluoroquinolone antibacterial agent. Since its introduction since 1980s, most Gram negative bacteria have remained highly susceptible to this agent in vitro; Gram positive bacteria are generally susceptible or moderately susceptible. It attains therapeutic concentrations in most of tissues and body fluids. It is one of a concentration-dependent and/or exposure dependent killing agents. As such, it must reach particular serum concentration or exposure to be effective (Davis et al., 1996).

Ever since the introduction of the fluoroquinolone antibiotics, it has been realized that they have significant interactions with substances containing multivalent ions (i.e., calcium, magnesium, aluminum, iron and zinc) and need to have their dosing separated from drugs containing these components (Nix et al., 1989, Kara et al., 1991, Frost et al., 1992, Li et al., 1994, Helena et al., 1995). As such, it has been relatively easy for prescribers and pharmacists to warn patients to space drugs such as antacids, sucralfate, and iron supplements from the dosing of fluoroquinolones by at least 2 to 4 hours to minimize and/or prevent an interaction and allow for optimal absorption of the antibiotic. In the situation of decreased absorption due to chelation, ciprofloxacin may not reach effectively therapeutic serum concentrations or exposures, although the bacteria are exposed to the antibiotic. Under circumstances such as this, bacteria are able to adapt to the presence of antibiotics and alter themselves to prevent destruction by antibiotics. At that point, the antibiotic will be ineffective, even in the most optimal conditions.

More recently, there has been an increasing trend in the food industry to offer products that have been fortified with essential vitamins or minerals. Although these products are thought to be innocuous in terms of causing problems in
patients, there is growing concern that some of these new food products may be leading to inadvertent drug-food interactions that may not have existed with food products prior to fortification. The concern is not just due to the potential for these interactions but the fact that they are not being investigated or characterized by either the drug or food industry during registration studies of their products.

Studies to characterize whether a drug needs to be spaced from food involve a high-fat/high-calorie meal (FDA, 2001). Ion interaction studies are typically conducted with antacids or mineral supplements (Helena et al., 1995, Nix et al., 1989). Dietary calcium interaction studies are typically extrapolated from milk (the main source of calcium in the Food and Drug Administration [FDA]–required food trials) or from studies with yogurt or milk alone, all of which have less calcium per serving than most calcium-fortified foods (Stass et al., 2001, Stanford et al., 1999). As such, even though the calcium content of a meal consisting of calcium-fortified foods may be as much as or exceed that contained in a calcium supplement, a patient is not warned by either the prescriber or the pharmacist to avoid such products if the drug has been shown to be safe when administered with a meal and/or dietary calcium because food products are not generally viewed as a “calcium supplement.” They are deemed a dietary source. Because of this, there may be the potential for the patient to take a dose of antibiotic with food to decrease gastrointestinal (GI) side effects, be 100% compliant with prescriber and pharmacist warnings about supplements and antacids, but suffer from an interaction similar in severity to that seen with supplements.

Whether the interaction occurs due to a large amount of a single polyvalent cation or small amounts of multiple polyvalent cations, the implications can be quite serious: pharmacologic treatment failure, antibiotic resistance, frequent dose changes, and increased morbidity and mortality. For the majority of the drugs, the interaction is one resulting in decreased drug absorption. Decreased absorption has the potential to lead to treatment failure, an undesirable result in any disease state. Since many of the drugs affected are antibiotics, it is important
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to consider the clinical consequences of antibiotic-cation interactions. Treatment failure in patients receiving antibiotics leads to prolonged illness, increased expense due to further antibiotic therapy, increased risk of developing a yeast infection in women on prolonged courses of antibiotics, increased risk of hospitalization with a worse form of infection, rapid increase in antibiotic resistance, and even death in critically ill patients.

The present study has, therefore, been planned to characterize whether or not ciprofloxacin drug administration with fortified foods is of significant severity that the bioavailability of a dose of ciprofloxacin may be compromised.