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The Effect of Food on the Relative Bioavailability of Rapidly Dissolving Immediate-Release Solid Oral Products Containing Highly Soluble Drugs

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Abstract: The purpose of this study is to test the hypothesis that rapidly dissolving immediate-release (IR) solid oral products containing a highly soluble and highly permeable drug [biopharmaceutical classification system (BCS) class I] are bioequivalent under fed conditions. Metoprolol and propranolol (BCS class I) as well as hydrochlorothiazide (BCS class III) were selected as model drugs. The relative bioavailability of two FDA approved (Orange Book AB rating) solid oral dosage forms of metoprolol and propranolol/hydrochlorothiazide (combination tablets) was evaluated in human volunteers under fed conditions using a two-way crossover design. Equal numbers of male and female volunteers were recruited, and racial and/or ethnic minorities were not excluded. The plasma concentrations of metoprolol, propranolol, and hydrochlorothiazide were determined using validated high-performance liquid chromatography (HPLC) methods. Eighteen subjects completed the metoprolol study while 17 subjects completed the propranolol/hydrochlorothiazide combination tablet study. In the metoprolol study, the 90% confidence intervals of C_{max} and AUC_{inf} were 98−118% and 92−115%, respectively. For propranolol, the 90% confidence intervals of C_{max} and AUC_{inf} were 91−121% and 89−117%, and for hydrochlorothiazide, the 90% confidence intervals for C_{max} and AUC_{inf} were 96−107% and 97−106%, respectively. These study results appear to support the hypothesis that rapidly dissolving IR solid oral products containing a BCS class I drug are likely to be bioequivalent under fed conditions. In addition, BCS class III drugs may have the potential to be bioequivalent under fed conditions.

Keywords: BCS; food effect; HPLC; metoprolol; propranolol; hydrochlorothiazide

Introduction

Food may influence drug absorption as a result of physiological changes in the gastrointestinal (GI) tract or physical and/or chemical interactions between particular food components and drug molecules. Depending on the type and degree of interaction, drug absorption may be reduced, delayed, not affected, or increased by concomitant food intake.[1] Consequently, the bioavailability of a drug or the bioequivalence between test and reference products may be affected.

The mechanisms of food effect include physiological effects of food and physicochemical interactions between

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drug and food.[2] The physiological changes caused by food and fluid ingestion that may alter drug absorption include delaying gastric emptying, increasing intestinal motility, stimulating bile flow, changing GI pH, increasing splanchnic blood flow, altering luminal metabolism of a drug substance, and increasing the active absorption process. In addition to changes in drug absorption resulting from physiological effects, altered absorption may result also from direct drug−food or drug−fluid interactions. Absorption or adsorption interactions between drug and food molecules may influence drug availability. Complexation and chelation interactions between drugs and metal ions in meals and dairy products can decrease drug dissolution and subsequent absorption. Food may also act as a physical barrier, preventing drug access to the mucosal surface of the GI tract. This could affect both actively and passively absorbed compounds.

The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and, therefore, systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product.[3] This is why the Food and Drug Administration (FDA) recommends the use of high-calorie and high-fat meals during food-effect bioavailability and fed bioequivalence studies.[4]

The physicochemical properties of drugs play an important role in drug bioavailability changes caused by the food−drug interaction. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of bioequivalence.[5] The food effect is least likely to occur with rapidly dissolving, immediate-release (IR) drug products containing highly soluble and highly permeable drug substances because absorption of highly soluble and highly permeable drugs is usually pH- and site-independent and thus insensitive to differences in dissolution.[6] However, for some drugs in this class, food can influence bioavailability when there is a high first-pass effect, extensive adsorption, complexation, or instability in the gastrointestinal tract. Propranolol is a typical example of a high first-pass drug.[7] For rapidly dissolving formulations of biopharmaceutical classification system (BCS) class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying.

In August 2000, the FDA issued a guidance for industry on waiver of in vivo bioavailability and bioequivalence studies for IR solid oral dosage forms based on the BCS.[6] The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability.[8] When combined with the in vitro dissolution characteristics of the drug product, the BCS takes into account three major factors, namely, solubility, intestinal permeability, and dissolution rate, that govern the rate and extent of oral drug absorption from IR solid oral dosage forms.[6] A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0−7.5, while a drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. On the basis of this BCS guidance, biowaivers may be requested for high solubility and high permeability drugs (class I) formulated in IR solid oral dosage forms that exhibit rapid in vitro dissolution, provided the following conditions are met: (a) the drug is stable in the gastrointestinal tract; (b) excipients used in the IR solid oral dosage forms have no significant effect on the rate and extent of oral drug absorption; (c) the drug does not have a narrow therapeutic index; and (d) the product is designed not to be absorbed in the oral cavity.

However, this BCS guidance does not address the in vivo bioavailability and bioequivalence studies for IR solid oral dosage forms under fed conditions. The objective of the present studies was to test the following hypothesis: Highly soluble and highly permeable drugs formulated in IR solid oral dosage forms that exhibit rapid in vitro dissolution are unlikely not to be bioequivalent under fed conditions. Metoprolol and propranolol were selected as model drugs in this class. Hydrochlorothiazide was tested as a BCS class III drug.

Experimental Section

Materials. Metoprolol tartrate, dextrorphan tartrate, hydrochlorothiazide, hydroflumethiazide, labetalol, propranolol, and ultrapure acetonitrile were purchased from Sigma Chemical (St. Louis, MO). Octanesulfonic acid (OSA) was purchased from Kodak Corporation (Rochester, NY). HPLC grade methanol was purchased from Burdick and Jackson (Muskegon, MI). HPLC grade monobasic potassium phosphate and ACS grade hydrochloric acid were purchased from Fisher Scientific (Pittsburgh, PA). Filtered 18 MΩ water was supplied in house by a Millipore Milli-Q System (Bedford,

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MA). C-2, C-18, and CN-U (cyano) solid-phase extraction columns were purchased from Varian (Harbor City, CA). Blank human plasma was supplied by the NIH Blood Bank (Department of Transfusion Medicine, Bethesda, MD).

Model Drugs and Dosage Forms. Metoprolol and propranolol were selected as BCS class I model drugs, since metoprolol is usually used as an internal standard to determine the permeability classification of drugs[6] and propranolol has an extensive first-pass effect whose bioavailability is only 29% despite its absorption being complete.[9] Since there are a sufficient number of generic products for these drugs, two generic products with significant difference in dissolution profiles yet meeting the rapid dissolution criteria as outlined in the BCS guidance could easily be selected. Hydrochlorothiazide was selected because it was formulated with propranolol as a combination drug product. In addition, a previous study has shown that the concomitant intake of food had no effect on the area under plasma concentration time curves although the urinary recovery of the drug was higher under fed state than fasting state conditions.[10] The study outcome from hydrochlorothiazide may assist future BCS class III based biowaiver extension.[11,12] Generic metoprolol tablet products contained 100 mg of metoprolol. The bioequivalence study of propranolol and hydrochlorothiazide used two generic combination tablet products containing 80 mg of propranolol and 25 mg of hydrochlorothiazide.

In Vitro Dissolution Testing. The in vitro dissolution of generic products of metoprolol and propranolol/hydrochlorothiazide was determined using the USP apparatus II at 50 rpm in the following dissolution media (900 mL): 0.1 HCl, pH 4.5 buffer, and pH 6.8 buffer at the temperature of 37 °C. Six tablets of each drug product were tested.

Clinical Protocol. Two-way single dose crossover bioequivalence studies were conducted in 18 male and female healthy volunteers between 18 and 40 years of age. The research followed the tenets of the Declaration of Helsinki promulgated in 1964 and was approved by the Institutional Review Board of the University of Tennessee and the Risk Involving Human Subject Committee of the FDA. All subjects were provided written informed consent. All subjects were evaluated with a medical history and physical examination and with tests for clinical chemistry, complete blood count, urinalysis, and ECG prior to entering the study. The subjects were randomly divided into two groups, and each group received the two doses in a different sequence. One week elapsed between each of the two doses. On each of the two dosing days, the subjects reported to the clinical laboratory. Following an overnight fast the subjects received 180 mL of room temperature water in the morning and then ate a standard breakfast beginning consumption 15 min prior to dosing and completing consumption 5 min prior to dosing. The breakfast was two slices of toast, two pats of butter, one sausage patty, two scrambled eggs, 2 oz of hash brown potatoes, and 8 oz of whole milk. This breakfast had 53 g of fat for a total of 832 calories, with 58% of the calories derived from fat. The doses were one 100 mg metoprolol tablet for the metoprolol study and one 80 mg propranolol/25 mg hydrochlorothiazide tablet for the propranolol/hydrochlorothiazide study, given along with 240 mL of room temperature water. Subjects then received an additional 120 mL of water 2 h after the dose. All subjects received a standard lunch 5 h after dosing, a standard dinner 11 h after dosing, and a snack 15 h after each dose.

Sample Collection. Blood samples were collected immediately prior to the dose and 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 15, and 25 h after the dose. A 10 mL blood sample was obtained from each subject via a heparin lock or venipuncture. The plasma was isolated from whole blood by centrifugation at 4 °C and then transferred to plastic cyrovials, placed on dry ice until frozen, and then placed in a −80 °C freezer until analysis. All samples were collected and processed utilizing an Automatic Electronic Data Capture System (SureLynx from Data Capture International).

Sample Preparation: Metoprolol. Analytes were extracted from human plasma using silica-based solid phase extraction (SPE) C-2 cartridges. Internal standard (IS), dextrorphan, was added to the plasma samples. Plasma samples and standards were diluted 1:1 with water and vortexed for 30 s. The C-2 SPE columns were conditioned with 3 mL of methanol (MeOH) and 3 mL of water. Plasma samples were loaded onto the SPE column and then rinsed with 3 mL of water and 3 mL of 50:50 MeOH/water. Samples were eluted with 50:50 ACN/0.2 N hydrochloric acid (HCl). Samples were placed in a spin evaporator, dried under vacuum, and reconstituted in 150 μL of the mobile phase.

Sample Preparation: Hydrochlorothiazide and Propranolol. Analytes were extracted from human plasma using silica-based SPE C_{18} cartridges in combination with unendcapped Cyano (CN) SPE cartridges. Hydroflumethiazide (HFTZ) and labetalol were added to the plasma samples and served as IS in the two-phase continuous SPE extraction. Plasma was diluted 1:1 with water and vortexed for 30 s. Both the 500 mg C_{18} and 200 mg CN columns were conditioned with methanol. The CN column was placed on top of the C18 column with an adapter and then conditioned

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with water, liquid being allowed to pass through both columns. Sample was applied to the CN column, liquid being allowed to pass through the CN and C_{18} columns. One milliliter of diH2O was applied to the CN column while liquid was allowed to pass though the CN and C_{18} columns. The two columns were separated, and 2 mL of diH_2O was applied to each column. The CN column was eluted with 3 mL of 50:50 CH_3CN/0.1 N HCl, and the eluate containing propranolol and labetalol was collected. The C_{18} column was eluted with 3 mL of 25:75 CH_3CN/H_2O, and the eluate containing hydrochlorothiazide and hydroflumethiazide was collected. Samples were placed in a spin evaporator, dried under vacuum, and reconstituted in 150 μL of the mobile phase.

Plasma Analysis: Metoprolol. All standards and samples were analyzed on Hewlett-Packard 1090 (Wilmington, DE) HPLC system equipped with a Hewlett-Packard 1046A fluorescence detector, automated injector, and degassing and temperature control modules using a modified HPLC method reported previously.[13] Separation was obtained on a Metachem (Redondo Beach, CA) C-4 (4.5 × 250 mm) reverse phase HPLC column with a Supelco (Bellefonte, PA) LC-8 guard column (20 × 4.0 mm). The mobile phase was acetonitrile/tetrahydofuran/phosphate (pH = 3.0) with 0.13% octanesulfonic acid (15:2.25:82.75) delivered isocratically for 20 min. The flow rate was 1.75 mL/min. The injection volume was 50 μL. The fluorescence detection wavelengths were $\lambda_{ex} = 228$ and $\lambda_{em} = 320$ nm. The column temperature was maintained at 30 °C. The method was validated according to the FDA "Guidance for Industry", Bioanalytical Method Validation.[14] The method addressed all the guidance validation parameters and met all acceptance criteria. The metoprolol method was specific and linear ($r^2 > 0.99$) over the validated range of 1.85−148.0 ng/mL. Stability was established for all guidance stability endpoints. The mean recovery was greater than 98.2%. The mean intra- and interday precision was less than 10.4%.

Plasma Analysis: Hydrochlorothiazide and Propranolol. All standards and samples were analyzed on an Agilent 1100 (Wilmington, DE) HPLC system equipped with a 1315 series multiple wavelength detector and a 1046A fluorescence detector module using a novel HPLC method. Separation was obtained on a Phenomenex C18 Luna (2) (5 μM, 250 × 4.6 mm) reverse phase HPLC column (Torrance, CA) with a Beckman C18 (ODS) guard column (45 × 4.6 mm). The mobile phase was acetonitrile/20 mM phosphate (85:15, v/v) delivered isocratically for 40 min. The flow rate was 1.0 mL/min. The injection volume was 75 μL. The UV detection wavelength for hydrochlorothiazide was 272 nm. The fluorescence detection wavelengths for propranolol were $\lambda_{ex} = 232$ and $\lambda_{em} = 400$ nm. The column temperature was maintained at 27.5 °C. The method was also validated according to the FDA's guidance. The method for hydrochlorthiazide and propranolol met all acceptance criteria. The hydrochlorothiazide method was specific and linear ($r^2 > 0.99$) over the validated range of 10−150 ng/mL. Stability was established for all guidance stability endpoints. The mean recovery was greater than 90.2%. The mean intra- and interday precision was less than 7.5%. The propranolol method was specific and linear ($r^2 > 0.99$) over the validated range of 2.5−150 ng/mL. Stability was established for all guidance stability endpoints. The mean recovery was greater than 98.2%. The mean intra- and interday precision was less than 5.9%.

Pharmacokinetic and Statistical Analysis. The maximum plasma concentration (C_{max}) and time to reach the maximum concentration (T_{max}) were read directly from the observed concentration−time data. The area under the plasma concentration curve to 25 h (AUC_{0-25}) and the AUC to infinite time ($AUC_{0-\infty}$) were calculated by trapezoidal summation from time zero to the time of the final measurable concentration (CF), and then extrapolated to time infinity by adding the quotient CF/β to the corresponding AUC_{0-25}.

To determine average bioequivalence, the statistical analysis was performed using the GLM procedure from the SAS statistical package. The two one-sided tests were carried out by computing 90% confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using log-transformed data.

Results and Discussion

All the products evaluated met the rapid dissolution criteria: no less than 85% dissolved in 30 min in the dissolution media of 0.1 HCl, pH 4.5 buffer, and pH 6.8 buffer. Thus, these metoprolol and propranolol tablets can be considered for a biowaiver for fasted bioequivalence studies.

All 18 subjects successfully completed the metoprolol study. No side effects were reported, and no significant clinical abnormalities were observed in the poststudy clinical evaluations. Mean plasma concentration−time profiles for the two generic metoprolol products are shown in Figure 1. Bioavailability parameters are summarized in Table 1. Figure 1 and Table 1 show the absence of a significant difference between these two generic metoprolol tablet products, and the 90% confidence interval is within the limit of 80−125%.

Seventeen subjects completed the propranolol/hydrochlorothiazide study, and one dropped out from the study prior to second dosing. No side effects were reported and no significant clinical abnormalities were observed in the poststudy clinical evaluations. Mean plasma concentration−time profiles for the two generic propranolol/hydrochlorothiazide tablet products are shown in Figures 2 and 3. Bioavailability parameters are summarized in Table 1. Figures 2 and 3 and Table 1 show the absence of a significant difference between these two generic propranolol/hydro-

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Table 1. Results of Metoprolol and Propranolol/Hydrochlorothiazide Bioequivalence Studies

drug	pharmacokinetic parameters	product A mean (CV)	product B mean (CV)	ratio geometric mean	90% confidence interval
metoprolol	C_{max} (ng/mL)	179 (39)	189 (36)	1.07	98−118
	AUC_{0-t} (ng·h/mL)	1150 (75)	1108 (81)	1.03	92−114
	$AUC_{0-\infty}$ (ng·h/mL)	1215 (77)	1158 (84)	1.04	92−115
propranolol	C_{max} (ng/mL)	82 (37)	78 (36)	1.05	91−121
	AUC_{0-t} (ng·h/mL)	610 (32)	582 (32)	1.04	91−120
	$AUC_{0-\infty}$ (ng·h/mL)	658 (33)	636 (30)	1.02	89−117
hydrochlorothiazide	C_{max} (ng/mL)	138 (22)	135 (21)	1.01	96−107
	AUC_{0-t} (ng·h/mL)	906 (24)	889 (19)	0.99	96−106
	$AUC_{0-\infty}$ (ng·h/mL)	1040 (22)	1013 (18)	1.02	97−106

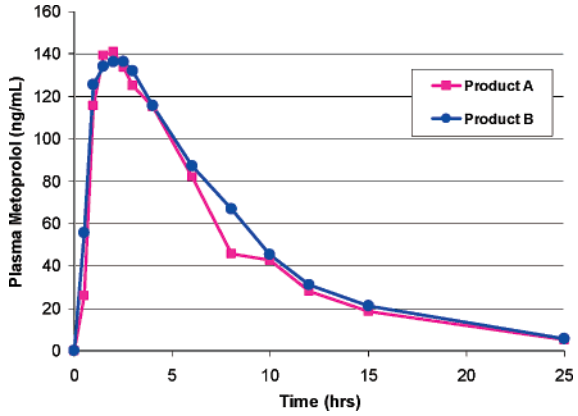

Figure 1. Mean metoprolol plasma concentration profiles after oral administration of 80 mg metoprolol generic tablet to healthy subjects under fed conditions.

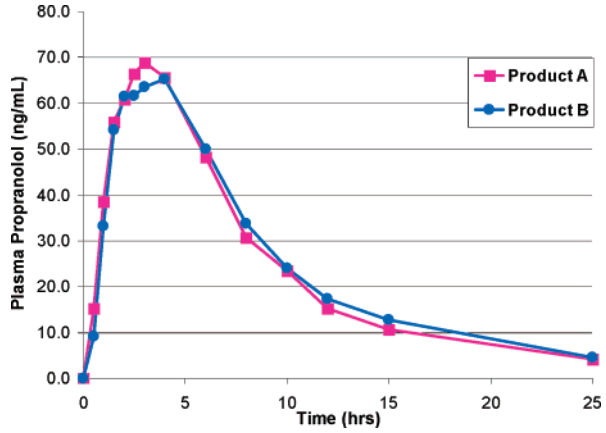

Figure 2. Mean propranolol plasma concentration profiles after oral administration of 80 mg propranolol and 25 mg hydrochlorothiazide generic tablet to healthy subjects under fed conditions.

chlorothiazide tablet products, and the 90% confidence intervals are within the limit of 80−125% for both propranolol and hydrochlorothiazide.

As suggested before, food effect on bioavailability, to some extent, depends upon the pharmaceutical properties of drugs.[9] The effect is least likely to occur with rapidly dissolving, IR drug products containing highly soluble and highly permeable drug substances because absorption of highly

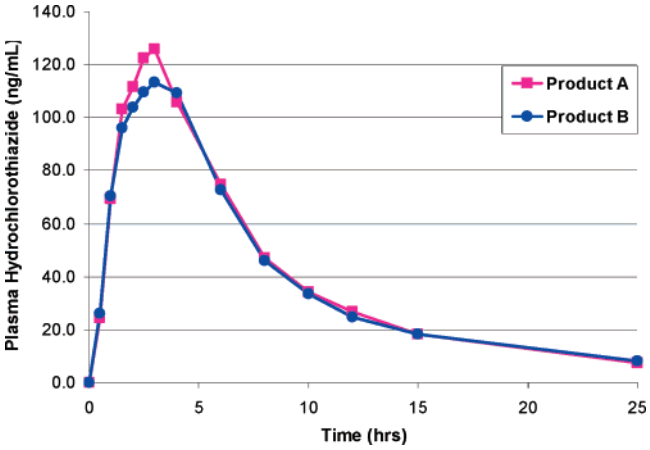

Figure 3. Mean hydrochlorothiazide plasma concentration profiles after oral administration of 80 mg propranolol and 25 mg hydrochlorothiazide generic tablet to healthy subjects under fed conditions.

soluble and highly permeable drugs is usually pH- and site-independent and thus insensitive to differences in dissolution. Melander et al.[15] reported that food did not systematically affect the rates of absorption and elimination of propranolol and metoprolol, but it enhanced the bioavailability and reduced individual variation of these two beta blockers. The results in this report demonstrate that, in general, there is a low risk with bioequivalence study waivers for highly soluble and highly permeable drugs formulated in the rapidly dissolving immediate dosage forms even for drugs with high first-pass effects.

Drugs with high solubility and low permeability are classified as BCS class III drugs. If the dissolution of a class III product is rapid under all physiological pH conditions, it can be expected that they may behave like an oral solution in vivo. In vivo bioequivalence studies generally are waived for oral solution drug products because the release of the drug from an oral solution is self-evident.[16] However, the drug absorption kinetics from the GI tract are influenced by a combination of physiological factors and biopharmaceutical properties such as gastrointestinal motility, permeability, and

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the interaction of drugs with excipients. In addition, class III compounds often exhibit site-dependent absorption properties[17,18] and thus the transit time through specific regions of the upper intestine may be critical for bioequivalence. Certain excipients have been shown to influence gastrointestinal transit time.[19]

The absorption of a class III drug is likely limited by its permeability and less dependent upon its formulation, and its bioavailability may be determined by its in vivo permeability pattern.

Our results suggest that permeability appears to make no difference with respect to the bioequivalence of highly soluble rapidly dissolving IR products. In fact, the 90% confidence interval of hydrochlorothiazide is much narrower than that of metoprolol or propranolol, demonstrating that BCS class III drugs may be better candidates for biowaiver, as suggested in the literature.[20] The major concerns with biowaiver extension to BCS class III drugs are the effects of excipients since BCS class III drugs are often transported by uptake and efflux transporters. Thus, if an excipient can strongly affect uptake or efflux transporters, it can significantly affect the oral absorption of drugs. In addition, the literature suggests more stringent requirement of in vitro dissolution for BCS class III drugs than BCS class I drugs for biowaiver.[21]

The BCS guidance generally is considered to be conservative with respect to the class boundary of solubility and permeability. It has been proposed to lower the limit of high permeability from 90% to 85% and change the solubility pH from 1−7.5 to 1−6.8.[22] It has been also suggested that many highly soluble drugs with less than 85% fraction dose absorbed pose no greater risk than class I drugs.[22] In addition, in vitro cell culture model, disk intrinsic dissolution rate, and computer prediction approaches have been proposed to directly classify drugs.[23−25]

These generic tablets of metoprolol or propranolol/hydrochlorothiazide were selected on the basis of the significant differences in dissolution profiles while still meeting the rapid dissolution criteria: no less than 85% dissolved in 30 min in 0.1 HCl, pH 4.5 buffer, and pH 6.8 buffer. The actual testing tablets were purchased and used as is without any prior testing. These generic tablet products are demonstrated to be bioequivalent, suggesting the high quality of generic products. These generic products can be substituted for each other; safety and efficacy of these generic products can be assured.

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