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ORIGINAL ARTICLE

Generic omeprazole delayed-release capsules: in vitro performance evaluations

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Abstract

Background: After the patent on omeprazole delayed-release capsules expired, Food and Drug Administration (FDA) approved several generic omeprazole delayed-release capsule applications. FDA has received some complaints concerning a lack of therapeutic effect of the generic omeprazole delayed-release capsules. *Aim*: To investigate the quality of five different marketed generic omeprazole delayed-release capsules. *Method*: The dissolution characteristics of these generic omeprazole delayed-release capsules were determined according to the United States Pharmacopeia (USP). Additional dissolution studies under simulated in vivo physiological conditions were also conducted to determine whether generic omeprazole capsules would perform similarly under these conditions. *Results*: The experimental data show that all the generic omeprazole delayed-release capsules met the USP standards. The in vitro dissolution of generic drugs is similar to that of the brand omeprazole product. *Conclusions*: There is no scientific evidence to support the claims that the generic omeprazole delayed-release capsules perform differently from the brand omeprazole product in vitro.

Key words: *Delayed-release capsules; dissolution; generics; omeprazole; stability*

Introduction

Omeprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, is the active ingredient in antiulcerative drug products. The omeprazole drug product is known to degrade in acid media as a function of pH but has acceptable stability under alkaline conditions[1]. Consequently, omeprazole delayed-release capsules contain an enteric-coated granule formulation that is designed to resist gastric conditions and release the active omeprazole in a more basic pH environment so that the product provides targeted therapeutic action.

After the patent on omeprazole delayed-release capsules expired, the Food and Drug Administration (FDA) approved several generic omeprazole delayed-release capsule applications (http://www.fda.gov/cder/ob/default.htm). These approvals were based on strict quality, bioequivalence, and labeling evaluations. Nevertheless, since the approval of generic products, the FDA has received some complaints concerning a lack of therapeutic effect of the generic omeprazole delayed-release capsules[2]. These complaints prompted the FDA's investigation to ensure the high quality and effectiveness of generic omeprazole capsule products.

Among the FDA's investigations, the FDA laboratory surveyed the generic delayed-release capsule products currently available on the market and examined their dissolution characteristics according to United States Pharmacopeia (USP) standards. Additional dissolution studies under simulated in vivo physiological conditions were conducted to determine whether generic omeprazole capsules would perform similarly under these conditions. These laboratory investigations concluded that there is no scientific evidence to support the claims that these generic omeprazole delayed-release capsules perform differently from the brand omeprazole product in vitro.

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Materials and methods

Materials

Brand and generic omeprazole delayed-release capsules were purchased from Washington Wholesale Drug Exchange, Savage, MD, USA, and used 'as is'. The samples consisted of five currently marketed generic delayed-release products and the brand product, Prilosec®. All products were labeled 20 mg omeprazole per capsule, and all products were tested before their expiration date. All reagents used in the high-performance liquid chromatography (HPLC) assay were of analytical grade: monobasic sodium phosphate (Mallinckrodt Chemicals, Phillipsburg, NJ, USA), dibasic sodium phosphate (Fisher Chemicals, Fair Lawn, NJ, USA), sodium borate decahydrate (Fisher Chemicals), dehydrated alcohol (Acros, Fair Lawn, NJ, USA), glycine (Sigma-Aldrich Co., St. Louis, MO, USA), hydrochloric acid (EM Science, Gibbstown, NJ, USA), 50% sodium hydroxide (Taylor Chemical Co., St. Louis, MO, USA), HPLC grade acetonitrile and methanol (EMD Chemicals Inc., Gibbstown, NJ, USA), and omeprazole (United States Pharmacopeia, Rockville, MD, USA).

The pH 11.0 assay diluent was prepared according to USP 30 page 2798 by dissolving 7.6 g of sodium borate decahydrate and 1.0 g edetate disodium in about 800 mL water, adjusting to pH 11.0 with 50% sodium hydroxide, transferring to a 2000 mL volumetric flask, adding 400 mL dehydrated alcohol and diluting with water to volume.

The pH 6.8 phosphate buffer used for the USP Dissolution Test 2 was prepared according to USP 30 page 2797 by adding 400 mL of 0.1 N HCl to 320 mL of 0.235 M dibasic sodium phosphate (previously adjusted to pH 10.4 with NaOH) then adjusting with HCl or NaOH to pH 6.8.

The pH 5.0 and 5.5 phosphate buffers used for the drug substance stability study were prepared by adding 400 mL of 0.1 N HCl to 320 mL of 0.235 M dibasic sodium phosphate (previously adjusted to pH 10.4 with NaOH) and adjusting the final pH to either 5.0 or 5.5 with HCl or NaOH.

The pH 6.8 phosphate buffer used for the USP Dissolution Test 1 was prepared in the vessel itself by adding 400 mL of 0.235 M dibasic sodium phosphate solution (previously adjusted to pH 10.5 with NaOH) to the vessels containing 500 mL of 0.1 N HCl from the acid stage, resulting in a pH of 6.8.

Methods

Assay

All products were assayed to verify that they contained the correct amount of omeprazole. A composite sample of 20 capsule contents (intact pellets) for each product was made. Three weighed portions of the composite sample equivalent to 20 mg of omeprazole were analyzed by USP assay procedure[3]. The average assay values were used in the calculation of % dissolved during dissolution testing for USP Test 2 acid stage.

Dissolution

All dissolution tests were performed with a Distek Dissolution System 2100A (Distek Inc., North Brunswick, NJ, USA) set up as apparatus 1 or apparatus 2 at 100 rpm. For apparatus 2, each of six capsules was placed in a USP sinker made according to the USP General Chapter <1092> specifications for capsule shell types 1 and 2 (4). To mimic the physiological conditions, the USP dissolution testing of delayed-release capsules is conducted in two stages: acid resistance stage and buffer stage. Currently, there are two dissolution tests for omeprazole delayed-release capsules.

USP Dissolution Test 1. Test 1 specifies two stages of testing: the acid resistance stage, 0.1 N HCl, 500 mL, apparatus 2, 100 rpm, 2 hours; and the buffer stage, pH 6.8 buffer, 900 mL, apparatus 2, 100 rpm, 30 minutes. For the acid resistance stage at the end of 2 hours, the dissolution medium containing the pellets was filtered through an 80 mesh (180 μm) sieve. The collected pellets were transferred to a volumetric flask and prepared according to USP dissolution procedure and analyzed by HPLC. For the buffer stage, a new set of capsules was tested using the acid stage procedure. At the end of 2 hours, 400 mL of 0.235 M dibasic sodium phosphate, which was previously adjusted to pH 10.5 with NaOH, was added to the vessels containing the 500 mL of 0.1 N HCl resulting in a pH 6.8 buffer. At the predetermined time points, an aliquot was taken, neutralized with 1 mL of 0.25 M sodium hydroxide, filtered, and analyzed by HPLC.

USP Dissolution Test 2. Test 2 also specifies two stages of testing: the acid resistance stage, 0.1 N HCl, 900 mL, apparatus 1, 100 rpm, 2 hours; and the buffer stage, pH 6.8 phosphate buffer, 900 mL, apparatus 1, 100 rpm, 45 minutes. At the end of 2 hours, the remaining pellets in the basket were transferred to a volumetric flask and prepared according to USP dissolution procedure and analyzed by HPLC. If the product had no remaining pellets in a basket after 2 hours, a value of 100% dissolution was assumed. For the buffer stage, a new set of capsules was tested using the acid stage procedure. At the end of 2 hours, the acid media was removed and replaced with 900 mL of pH 6.8 phosphate buffer and the dissolution was resumed. At the predetermined time points, an aliquot was taken, filtered, and analyzed by UV.

Dissolution under simulated GI physiological conditions

The current USP dissolution test for omeprazole delayed-release capsules has a 2-hour 0.1 N HCl stage followed

by a pH 6.8 buffer stage. It has been reported in the scientific literature[2] that the gastric pH of some patients can be as high as 5 or 6. If a patient has a higher gastric pH, these delayed-release omeprazole capsules could release the active omeprazole in the stomach causing drug degradation and diminution of therapeutic effect. To test this hypothesis, the acid stage medium was modified by replacing 0.1 N HCl with 0.235 M sodium phosphate solution adjusted to pH 4.0, 4.5, 5.0, or 5.5 with HCl. The USP Test 1 acid stage dissolution procedure for delayed-release omeprazole capsules was followed.

Omeprazole stability

For omeprazole drug substance stability, an accurately weighed quantity of omeprazole drug substance (USP) was dissolved in assay diluent (pH 11.0) to obtain a concentration of 4 mg/mL. A volume of 500 mL of pH 5.0 or 5.5, degassed phosphate buffer at 37°C, was placed in a dissolution vessel with paddle turning at 100 rpm. Stability studies were conducted using pH 5.0 and 5.5 media because all products remained intact below pH 5.0 (no drug release), and at pH 5.5, all products appeared to be mostly dissolved. An aliquot of 5.0 mL of the prepared 4 mg/mL omeprazole solution (equivalent to 20 mg omeprazole in 500 mL of 0.1 N HCl, USP Dissolution Test 1 acid stage) was added to the vessel. Aliquots of 5.0 mL were taken at 5-minute intervals for 1 hour and at 15-minute intervals thereafter for an additional hour. The aliquots were immediately transferred into 25-mL volumetric flasks that contained 15 mL of pH 11.0 diluent. The solutions were allowed to cool to room temperature, brought to volume with diluent and analyzed by HPLC as described below.

HPLC analysis

A Shimadzu HPLC System with Shimadzu SCL-10A controller, LC-10AD pump, SPD-10AV detector, CTO-10AS oven, and SIL-10AD autoinjector was used for the HPLC analysis. The USP omeprazole delayed-release capsule HPLC assay procedure was used to determine the omeprazole content of the capsules, USP Dissolution Test 2 acid resistance stage, and omeprazole stability study. An Agilent Eclipse XDB-C8 column, 4.6×150 mm^2, 5 µm particle size, was operated at ambient temperature, and the UV detector set at 305 nm, the USP recommended wavelength. The USP Dissolution Test 2 buffer stage procedure specified using the wavelength of maximum absorbance of omeprazole, which was determined to be 301 nm using an Agilent 8453 UV spectrophotometer.

The USP Dissolution Test 1 HPLC method was used for Test 1 acid resistance stage and Test 1 buffer stage. A Waters Symmetry C8 column, 3.9×150 mm^2, 5 µm particle size, was operated at ambient temperature and the UV detector at 280 nm, which was the specified USP wavelength. The mobile phases and sample solvents used for the USP HPLC methods for Dissolution Test 1 and Test 2 are different, which accounts for the different USP specified wavelengths.

Results

Assay

All products met USP assay specification of not less than 90.0% and not more than 110.0% of the labeled amount of omeprazole. The assay results are presented in Table 1.

USP dissolution

Acid resistance stage

Table 2 shows the dissolution results of omeprazole delayed-release capsules at the end of the acid resistance stage. For the USP Dissolution Test 1 for omeprazole delayed-release capsule, the USP acceptance criteria for this stage are as follows: L1, no individual value exceeds 15% of omeprazole dissolved; L2, the average of 12 units is not more than 20% of omeprazole dissolved, and no individual unit is greater than 35% of omeprazole dissolved; and L3, the average of 24 units is not more than 20% of omeprazole dissolved, no more than two units are greater than 35% of omeprazole dissolved, and no individual unit is greater than 45% of omeprazole dissolved. For the USP Dissolution Test 2 for omeprazole delayed-release capsule, the USP acceptance criteria are as follows: L1, the average of six units is not more than 10%; L2, the average of 12 units is not more than 10%; and L3, the average of 24 units is not more than 10%.

As shown in Table 2, generic product 5 failed L1 but passed L2 acceptance criteria. The five other products met L1 acceptance criteria.

Regulatory requirements including labeling require Test 2 for generic products 2 and 4 and Test 1 for Prilosec® and generic products 1, 3, and 5.

Buffer stage

The buffer remained at pH 6.8 ± 0.05 during drug release testing. All products contained pellets of various shapes and sizes. Visual observations during the drug release test showed that the capsule's contents for the majority of products disintegrated into fine particles in

Table 1. Assay results in % label claim (average 3).

Product	Omeprazole content	% RSD
Prilosec®	99.0	0.2
Generic product 1	101.3	0.6
Generic product 2	96.5	1.7
Generic product 3	98.8	0.2
Generic product 4	98.3	1.3
Generic product 5	96.8	1.6

Table 2. Dissolution results of the acid resistance stage.

Firm	USP test	High % label claim	Low % label claim	Avg. (6) % label claim	% RSD	Result
Prilosec®	1	12.8	9.3	11.1	13.5	L1: pass
Generic product 1	1	8.6	0.0	5.5	58.2	L1: pass
Generic product 2	2	9.6	0.0	2.8	124.3	L1: pass
Generic product 3	1	8.5	4.2	6.4	21.9	L1: pass
Generic product 4	2	1.5	0.0	0.4	146.1	L1: pass
Generic product 5	1	17.3	7.4	10.8	36.1	L1: fail
		17.3	6.2	Avg. (12) = 9.4	33.0	L2: pass

the buffered medium. The drug substance remaining in the intact pellets and particles may account for the lower drug release rates for these products. All results were calculated and some plotted as dissolution profiles (% cumulative dissolved drug versus time). Figure 1 shows the percent of drug release profiles during the buffer stage testing for the USP Dissolution Test 1 results for the average of the first six capsules tested. The decrease in % dissolution after the first 10–20 minutes may be the result of drug degradation from diffusion of media into the capsule.

The USP lists the following acceptance criteria for the buffer stage of the omeprazole delayed-release capsule dissolution for both Test 1 and Test 2: B1, each unit is not less than 80%; B2, average of 12 units is equal to or greater than 75%, and no unit is less than 60%; and B3, average of 12 units is equal or greater than 75%, not more than two units are less than 60%, and no unit is less than 50%. As shown in Table 3, the brand name and generic products 1, 3, and 5 passed the stage 1 dissolution testing B1 while generic products 2 and 4 passed the stage 2 dissolution testing B2.

Dissolution of products at different pH

With an acid stage of pH 4.0 or 4.5, less than 10% of the active pharmaceutical ingredient was dissolved from the capsule beads for all products. At pH 5.0, dissolution was still minimal for generic products 2 and 4; approximately 33% was dissolved for generic product 1, 79% for generic product 5, and almost 100% dissolved for the brand and generic product 3. As generic products 2 and 4 showed minimal dissolution in pH 5.0, these two products were not tested with pH 4.5 medium. Almost all omeprazole was dissolved from the capsule beads for all products in 2 hours at pH 5.5. All results are the average with standard deviation of three capsules except for pH 4.0 results that are the average with standard deviation of six capsules.

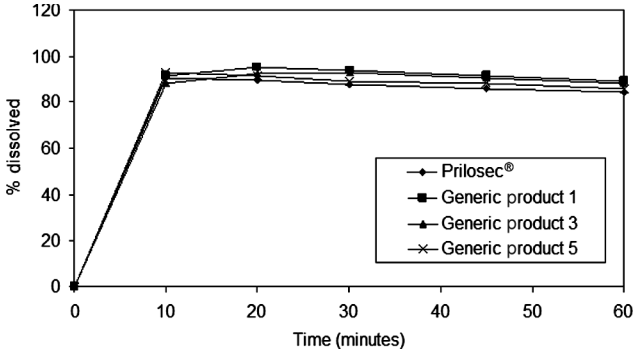

Figure 1. Percent of drug release profiles during the buffer stage testing for the USP Dissolution Test 1 for omeprazole delayed-release capsules.

Stability

Omeprazole drug substance immediately began to degrade in both pH 5.0 and 5.5 phosphate-buffered dissolution media (Figure 2). Complete degradation occurs in less than 1 hour in pH 5.0 and only 10% remains in pH 5.5 medium after 2 hours.

Discussion

Consumer complains about lack of therapeutic affect with generic products prompted this study. The samples surveyed in this study showed that the contents of all the omeprazole delayed-release capsules studied complied with the USP standards regardless of the source. Therefore, consumers can be assured that the omeprazole delayed-release capsules they are taking contain the amount of drug claimed on the label.

The dissolution studies revealed that at the acid resistance stage, capsules should release as little drug as possible as any drug released at the acid stage will rapidly be degraded. Data in Table 2 suggest that all the omeprazole delayed-release capsules met the USP L1 or L2 acceptance criteria. These results showed that the omeprazole delayed-release capsules are equivalent to the brand omeprazole product with respect to resistance in the acid media dissolution.

Figure 1 and Table 3 indicate that all the omeprazole delayed-release products at the buffer stage meet the USP standards although generic products 2 and 4 have lower values. It should be noted that the generic products 2 and 4 were tested using the USP Test 2. When generic manufacturers propose a different dissolution

Table 3. Dissolution results, USP Test 1, buffer stage, 30 minutes, and USP Test 2, buffer stage, 45 minutes.

Firm	USP test	High % label claim	Low % label claim	Avg. (6) % label claim	% RSD	USP acceptance criteria
Prilosec®	1	90.2	85.8	87.8	2.0	B1: pass
Generic product 1	1	99.9	87.9	93.6	5.3	B1: pass
Generic product 2	2	80.6	72.3	75.8	3.4	B2: pass
Generic product 3	1	93.9	91.4	92.6	1.1	B1: pass
Generic product 4	2	88.5	74.4	81.9	4.9	B2: pass
	1	81.1	71.0	76.8	3.9	B2: pass
Generic product 5	1	92.2	87.3	89.2	1.9	B1: pass

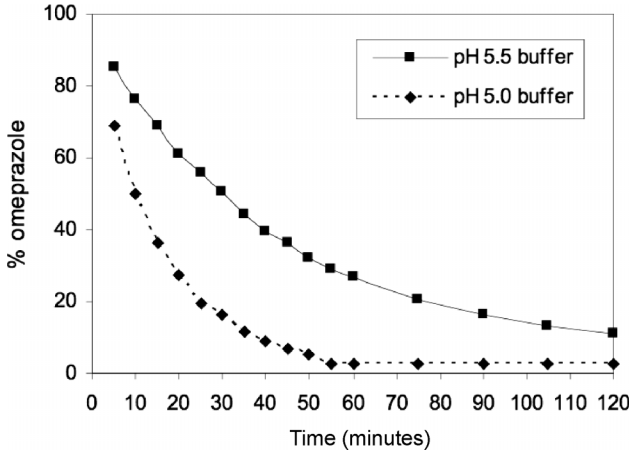

Figure 2. Omeprazole solution stability in the relevant dissolution media at the corresponding concentration.

test, FDA reviewers make thorough evaluation before approval of such test. Therefore, it is common that the generic product and the brand product have different dissolution methods. It can be concluded from Table 3 that there is no scientific evidence to believe that the generic products will perform differently from the brand name products in terms of dissolution at the buffer stage.

The FDA hypothesized that generic products may release more drug than the brand omeprazole product if they are exposed to pH between 4 and 5.5 in the acid stage. If this were true, due to the instability of omeprazole at these pHs, it is possible that the omeprazole in the generic products could have degraded while the brand name product does not. Table 4 shows the amounts of drug release at pH ranging from 4.0 to 5.5. All products release less than 10% omeprazole in pH 4.0 and 4.5 medium, consistent with the release in the USP acid stage medium of 0.1 N HCl. Some generic products remain intact at pH 5.0 and thus protect omeprazole from degradation; however, the innovator product and one generic have completely released the omeprazole. Stability studies of the drug substance show that any drug released at this pH will degrade within an hour. All products dissolve completely in pH 5.5 medium. Because omeprazole is not stable in acid medium pH 5.0 or 5.5 at 37°C, any dissolution that might occur at these pHs could result in loss of efficacy.

Table 4. Dissolution Test 1 results after 2 hours in acid media (% dissolved).

Product	pH 4.0	pH 4.5	pH 5.0	pH 5.5
Prilosec®	5 ± 5	6 ± 3	100 ± 0	100 ± 0
Generic product 1	4 ± 4	8 ± 2	33 ± 8	100 ± 0
Generic product 2	2 ± 1	—	5 ± 2	99 ± 0
Generic product 3	2 ± 1	4 ± 1	98 ± 2	100 ± 0
Generic product 4	4 ± 3	—	6 ± 2	89 ± 2
Generic product 5	7 ± 3	6 ± 2	79 ± 29	93 ± 12

—, Test not performed.

Conclusion

It can be concluded from these laboratory evaluations that the generic omeprazole delayed-release capsules manufactured by these five generic companies met relevant USP standards. Our investigation under simulated in vivo physiological conditions further indicated that generic omeprazole capsules perform similarly as the brand product under these conditions. Therefore, we found that there is no scientific evidence to support the claims that the generic omeprazole delayed-release capsules perform differently from the brand omeprazole product in vitro.

Declaration of interest: The authors report no conflicts of interest.

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