Drug Development and Industrial Pharmacy, 22(12), 1173–1185 (1996)

RESEARCH PAPERS

A Survey of the Stability of Omeprazole Products from 13 Countries

A. G. Davidson and A. McCallum

Medicines Testing Laboratory, Royal Pharmaceutical Society of Great Britain, 34 York Place, Edinburgh EH1 3HU, United Kingdom

ABSTRACT

The results of an independent survey of the stability of omeprazole solid dosage forms (20 mg) show that products available in many countries worldwide exhibit a very wide range of stability characteristics. Stability testing under the ICH accelerated test conditions (40°C/75% RH; 6 months) was performed on a total of 34 products obtained in 13 countries by independent sampling officers. The samples were visually examined for physical change and analyzed for their total content of impurities, remaining omeprazole, and the amount of omeprazole released in vitro. Twenty-seven of the products (79%) exhibited a change in one or more of the stability-indicating parameters during the 6-month study. These included 16 products that had more than 10% of decomposition products at 6 months and 10 other products that contained 2–10% of decomposition products at 6 months. In most samples, the formation of decomposition products was accompanied by a corresponding measurable decrease in the content of omeprazole. Of the eight samples containing less than 2% of decomposition products after 6 months storage, one showed a large reduction in the amount of omeprazole released in vitro. Another product which contained 1.2% decomposition products at 6 months released lower amounts of omeprazole in vitro at all time points than most other products. Only six products (18%) were considered to demonstrate good physical and chemical stability over the course of the study, viz. Losec Capsules (Astra, Sweden), Losec Capsules (Astra, Korea), Losec Capsules (Astra, Turkey), Miracid Capsules (Berlin Pharm. Ind. Co., Thailand), Mopral Capsules (Astra-Ifesa, Spain), and OMP Tablets (Chon Kun Dang Corp., Korea).

INTRODUCTION

Since its launch in the late 1980s, omeprazole (Losec) has become one of the best-selling pharmaceuticals worldwide. It was the first proton pump inhibitor to be marketed in the U.K. and many other countries, and its licensed indications and uses have increased significantly in conditions requiring suppression of gastric acid secretion.

Omeprazole is a prodrug which is usually marketed as a gastro-resistant formulation because of its instability in an acidic environment. The world brand-leader, Losec Capsules, manufactured by the originator, Astra, contains beads incorporating the active ingredient in a matrix which is protected against acid degradation by polymeric layers. The capsules are usually packed in bottles with a desiccant in the lid to provide further protection.

In addition to Losec Capsules and other omeprazole products licensed by Astra, a number of omeprazole products are marketed by other manufacturers, either as registered generic products in countries which have limited patent protection or as unlicensed counterfeit products.

Despite its importance as a therapeutic agent and its known instability, omeprazole drug substance and its formulations have been the subject of very few published stability investigations (1–3). This survey was carried out to provide an independent study of the comparative stability of omeprazole in products marketed in several different countries. To provide a fair basis for comparison of the stability within a reasonable time scale, accelerated testing conditions complying with those agreed by the International Conference on Harmonisation (ICH) were adopted, i.e., 40°C ± 2°C/75% relative humidity (± 5%) for a maximum period of 6 months.

EXPERIMENTAL

Solvents and Reagents

Ethanol 95% v/v (Hayman analytical reagent grade)
Acetonitrile (Rathburn HPLC grade)
Ammonia (SG 0.91) prepared from ammonia SG 0.88 (Fisons)
Methanol (Rathburn HPLC grade)
Dichloromethane (Rathburn HPLC glass distilled grade)
Other chemicals were analytical reagent grade

Omeprazole reference substance was supplied as a gift by Astra Hassle, Sweden.

Samples

A total of 34 products (31 capsule formulations and 3 tablet formulations) from 13 countries worldwide were included in the survey. All the samples were obtained from the market and notarized as authentic by independent sampling officers. The products tested, their country of origin, manufacturer, and (where known) the batch number and expiry date are shown in Table 1.

Stability Storage

The samples were stored in two Patra humidity cabinets at 40°C ± 1°C and 75% relative humidity ± 3%. The cabinets were monitored by a thermometer calibrated to traceable standards and a hygrometer supplied with a certificate of compliance by the manufacturer (HANNA Instruments).

Appearance

The appearance of the capsule contents and of the tablets was assessed by viewing them against a white background in normal daylight. Any discoloration or other physical change was noted, in particular the uniformity of the color of the beads within different capsules and, where possible, between different containers of the same batch.

Assay of Omeprazole

The selective assay of omeprazole was carried out by liquid chromatography (LC). The LC system consisted of a pump (Beckman 110B), autosampler (Hewlett Packard, series 1050), spectrophotometric detector (Kontron Uvikon 735LC) set at 280 nm, column (Chromtech Nucleosil 120 C18 5 μ, 150 mm × 4.6 mm), guard column (Kromsil C8 7 μ 12 mm × 3.2 mm), and an integrator (Hewlett Packard HP 3396A).

The mobile phase was prepared by diluting 400 ml of acetonitrile and 250 ml of 0.0368 M phosphate buffer solution pH 7.6 to 1000 ml with water and deaerated by vacuum filtration before use. The flow rate was 1 ml/min.

The sample solution containing approximately 20 μg/ml was prepared by extracting ultrasonically an accurately weighed quantity of mixed beads from 10 cap-

Table 1

Products Examined

Sample	Product[a]	Manufacturer	Country	Batch No.	Expiry Date
1	Omezolan	Euro-Labor, S.A.	Portugal	94109	4/97
2	Proton	Laboratorio Medinfar	Portugal	3304	9/96
3	Lenar	Chemica	Greece	9401	5/96
4	Ezipol	Kleva	Greece	2593	5/96
5	Procelac	Syncro	Argentina	314162-1	3/96
6	Ulcozol	Laboratorios Bago S.A.	Argentina	314906-2	1/96
7	Ompranyt	Boehringer Mannheim	Spain	I-3	4/97
8	Pepticum	Andromaco	Spain	I-4	2/97
9	Mopral	Astra-Ifesa	Spain	I-04	5/97
10	Miracid	Berlin Pharm. Ind. Co. Ltd.	Thailand	944006	8/95
11	Desec	T. O. Chemicals Ltd.	Thailand	641301	Unknown[b]
12	Zefxon	Biolab	Thailand	303187	3/96
13	Losec	Astra	Korea	4002	17/3/97
14	Ramezol	Hanmi Pharm. Co. Ltd.	Korea	123038	5/4/97
15	OMP	Chon Kun Dang Corp.	Korea	NA00800	12/5/97
16	Omed	Sunk Yong Pharm. Ltd.	Korea	4006	30/10/97
17	Result	Choongwae Pharma Corporation	Korea	80000	2/10/96
18	Victrix	Americano de Farmacoterapia	Brazil	141	5/97
19	Perprazol	Libbs Farmaceutica Ltd.	Brazil	4 226 41	5/96
20	Ulconar	Laboratorios Frumtost	Brazil	9327	2/97
21	Togram	Laboratorios Silesia	Chile	1040394	3/97
22	Micromex	Laboratorios Recalcine	Chile	C94210	3/97
23	Omez	Dr. Reddy's Laboratories	India	OMO0744	1/96
24	Ocid	Cadila Chemicals Ltd.	India	4004	6/95
25	Omeprazoli	Jiangsu Changzhou	China	940323	Unknown
26	Omeprazole	Hainan San-Ye Pharm.	China	S930601	7/95
27	Omeprazoli	Liaoning Province Jinzhou	China	940301-5	Unknown
28	Inhibitron	Liomont	Mexico	40332	1/3/96
29	Ulsen	Senosiain	Mexico	4B04	2/96
30	Losec	Astra Hassle	Sweden	UD 5271	4/97
31	Losec	Astra	Turkey	403326	3/9/96
32	Demeprazol	Deva Holding A.S.	Turkey	312 3024	4/95
33	Omeprazid	Nobel Ilac	Turkey	4E 014	5/96
34	Omeprol	Ilsan Ilac	Turkey	402002	2/96

[a]All samples are 20-mg capsule formulations except 15, 16, and 17, which are 20-mg tablets.
[b]Manufacturing date: 29/7/93.

sules or of powder from 10 ground tablets, equivalent to 20 mg of omeprazole, with 60 ml of 0.1375 M phosphate buffer pH 11 for 10 min. Twenty milliliters of 95% ethanol were added and ultrasonication was continued for 5 min. The extract was then diluted with pH 11 phosphate buffer to 100 ml and filtered through Whatman No. 1 paper, and the filtrate was diluted 1 + 9 with water.

The standard omeprazole solution was prepared by dissolving about 20 mg of omeprazole reference substance, accurately weighed, in 20 ml of 95% ethanol and diluting to 100 ml in a volumetric flask with phosphate buffer pH 11. Five milliliters of this solution were diluted with water to 50 ml in a volumetric flask.

Injections (20 μl) of the sample and standard solution were made and the quantity of omeprazole in each dosage unit was calculated by using the average weight of the dosage unit and the proportional relationship that exists between the peak area and concentration of omeprazole.

Content of Impurities

The concentrations of decomposition products, synthetic impurities, and by-products were determined by LC. The LC system comprised a pump (Beckman 114M), autosampler (Waters 717), spectrophotometric detector set at 280nm (Milton Roy Spectromonitor 3100), column (Merck Superspher Si 60, Lichrocart, 125 mm × 4 mm), precolumn (Brownlee, Silica NewGuard, 7 μm, 15 mm × 3.2 mm), and a data-processing unit (Waters Millennium, version 2.00).

The mobile phase was prepared by diluting 25 ml of a mixture of ammonia (SG 0.91) and methanol (5:95) to 1000 ml with dichloromethane.

The sample solution was prepared by shaking 5 tablets or the pellets from the mixed contents of 5 capsules for 5 min with 60 ml of the LC mobile phase in a 100-ml volumetric flask protected from light and diluting to volume with the mobile phase. The solution was filtered through a glass microfiber filter prewashed with the mobile phase. Concentrations of the impurities were calculated as % area by normalization.

Dissolution of Omeprazole

The release of omeprazole from the dosage units was measured in vitro by using USP dissolution apparatus 2 (paddles) operated at 100 rpm and at 37°C. A conventional two-stage dissolution medium for a gastro-resistant formulation was used comprising 500 ml of USP simulated gastric fluid (without pepsin) for 2 hr followed by the addition of 400 ml of 0.235 M disodium hydrogen phosphate to provide a buffer of pH 6.8. After a further 30 min the concentration of omeprazole in the dissolution medium and hence the percentage of omeprazole released from each of 6 dosage units was determined by the LC assay method by diluting 5 ml of the filtered solution with 1 ml of 0.25 M sodium hydroxide solution.

Stability Testing Protocol

All samples were examined for appearance and tested for dissolution, impurities, and assay within 2 weeks of receipt. They were immediately stored at 40°C and 75% relative humidity. After 1 month the samples were visually examined and, if a significant change had occurred, the tests for dissolution, impurities, and assay were carried out. At 3 months and 6 months all samples were visually examined for appearance and tested for dissolution, impurities, and assay, except that if at any time point a sample was found to contain more than 10% of impurities, the dissolution test was not carried out. Also, if a sample was found to be extensively degraded at any time point, testing was discontinued. All tests were carried out before the expiry date of the samples (where known).

RESULTS

Appearance

The color of the capsule contents and of the tablets at each of the time points (0, 1, 3, and 6 months) is shown in Table 2. Most products were either off-white or pale brown when examined initially, which was consistent with the relatively low level of degradation products in the samples (4). However, many of the samples progressively darkened during the 6-month period, at the end of which some had a dark brown or very dark brown appearance. A discernible change of color at the 1-month time point was used as the criterion for carrying out the tests for assay, impurities, and dissolution at 1 month. The 6 products showing a marked change of color at 1 month were all shown to contain significant levels of decomposition products at 1 month (see below).

Assay of Omeprazole Content

Table 3 lists the assay results of each sample at each time point, expressed as a percentage of the label claim and as a percentage of the initial value. Samples are listed in the order of increasing instability as measured by the total decrease in content over the 6-month storage period. Interferences in the chromatograms of samples that were extensively degraded made it difficult to quantify accurately assay values below 10% of the label claim. Assay values less than 10% are listed in Table 3 as "< 10." For such samples, the result at the 3-month time point was used to rank the extent of degradation.

Of the 34 samples tested, 6 samples—viz. Zefxon Capsules (Thailand), Lenar Capsules (Greece), Ulconar Capsules (Brazil), Ocid Capsules (India), Perprazol Capsules (Brazil), and Inhibitron Capsules (Mexico)—on receipt gave assay results for omeprazole of greater than 105% of label claim, i.e., above the upper assay limit which is generally applicable for the release of

Table 2

Visual Examination of Samples

Sample	Product[a]	Month 0	Month 1	Month 3	Month 6
1	Omezolan Capsules	Pale brown	Pale brown	Grey-brown	Mottled grey-brown
2	Proton Capsules	Off-white	Off-white	Off-white	Off-white
3	Lenar Capsules	Pale yellow	Pale brown	Pale brown	Mottled grey-brown
4	Ezipol Capsules	Pale brown	Very dark brown	Very dark brown	NT[c]
5	Procelac Capsules	Pale yellow	Pale brown	Pale brown	Mottled brown
6	Ulcozol Capsules	Off-white/some grey	Pale brown/some grey	Dark brown/some grey	Very dark brown/some grey
7	Ompranyt Capsules	Pale brown	Pale brown	Dark brown/light brown[b]	Dark brown/light brown[b]
8	Pepticum Capsules	Off-white	Very pale brown	Pale brown	Pale brown
9	Mopral Capsules	Off-white	Off-white	Off-white	Off-white
10	Miracid Capsules	White	White	Off-white	Off-white
11	Desec Capsules	Pale brown	Pale brown	Pale brown	Pale brown
12	Zefxon Capsules	Pale brown/some white	Pale brown/some white	Pale brown/some white	Pale brown/some white
13	Losec Capsules	Off-white	Off-white	Off-white	Off-white
14	Ramezol Capsules	Off-white	Off-white	Pale brown	Brown-green
15	OMP Tablets	White core	Off-white core	Off-white core	Off-white core
16	Omed Tablets	Off-white core	Pale Yellow	Pale brown	Pale brown
17	Result Tablets	Off-white core	Greyish brown	Brown/dark brown	Dark brown
18	Victrix Capsules	Pale brown/green granules	Brown/green granules	Dark brown/green granules	Dark brown/green granules
19	Perprazol Capsules	Off-white	Off-white	Off-white	Pale brown/off-white[b]
20	Ulconar Capsules	Off-white/some red	Very pale brown/some red	Pale brown/some red	Pale brown/some red
21	Togran Capsules	Pale brown	Dark brown	Very dark brown	NT[c]
22	Micromex Capsules	Off-white	Very pale brown	Brown/pale brown[b]	Dark brown
23	Omez Capsules	Off-white/some darker 50/50	Off-white/some darker 50/50	Pale brown/some off-white	Mottled grey/some off-white
24	Ocid Capsules	Pale brown	Pale brown	Brown	Brown
25	Capsulae Omeprazoli	Pale brown	Brown	Brown	Dark brown
26	Omeprazole Capsules	Brown	Brown	Dark brown	Dark brown
27	Capsulae Omeprazoli	Brown	Dark brown	Dark brown	Mottled dark brown-green
28	Inhibitron Capsules	Brown	Dark brown, uneven in containers	Very dark brown/ dark brown[b]	Dark brown
29	Ulsen Capsules	Pale brown	Pale brown	Pale brown	Pale brown
30	Losec Capsules	Off-white	Off-white	Off-white	Off-white
31	Losec Capsules	Off-white	Off-white	Off-white	Off-white
32	Demeprazol Capsules	Pale brown	Brown	Dark brown	Very dark brown/ dark brown[b]
33	Omeprazid Capsules	Pale brown	Pale brown	Grey brown	Green-brown
34	Omeprol Capsules	Pale yellow	Pale yellow	Pale brown	Pale brown

[a]Appearance refers to the capsule contents or the interior of tablets.
[b]Samples where different rates of degradation occurred in different sample containers. Two descriptions relate to the extremes observed.
[c]NT = not tested.

Table 3

Assay Results[a]

Sample	Product	Month 0, % LC	Month 1, % LC (%T_0)	Month 3, % LC (%T_0)	Month 6, % LC (%T_0)
Capsules					
13	Losec	100.0	NT	100.5 (100.5)	99.5 (99.5)
29	Ulsen	104.5	NT	103.0 (98.6)	104.0 (99.5)
31	Losec	98.0	NT	98.5 (100.5)	97.5 (99.5)
2	Proton	100.0	NT	98.0 (98.0)	99.0 (99.0)
30	Losec	101.2	NT	102.0 (100.5)	100.5 (99.0)
12	Zefxon	111.0	NT	113.5 (102.3)	109.5 (98.6)
8	Pepticum	104.5	NT	102.0 (97.6)	102.5 (98.1)
3	Lenar	108.0	NT	107.5 (99.5)	105.0 (97.2)
10	Miracid	100.0	NT	97.3 (97.3)	97.0 (97.0)
9	Mopral	103.0	NT	99.3 (96.4)	99.5 (96.6)
11	Desec	102.5	NT	98.9 (96.5)	95.5 (93.2)
34	Omeprol	104.5	NT	102.0 (97.6)	96.5 (92.3)
5	Procelac	99.5	NT	90.5 (91.0)	91.0 (91.5)
20	Ulcanor	114.0	NT	105.0 (92.1)	103.5 (90.8)
23	Omez	104.8	NT	102.0 (97.3)	92.5 (88.3)
24	Ocid	106.4	NT	102.0 (95.9)	92.0 (86.5)
1	Omezolam	98.0	NT	89.0 (90.8)	81.0 (82.7)
19	Perprazol	107.8	NT	107.0 (99.3)	108.0/77.5 (100.2/71.9)[b]
33	Omeprazid	95.0	NT	83.5 (87.9)	50.0 (52.6)
18	Victrix	97.0	83.5 (86.1)	56.5 (58.2)	32.6 (33.6)
22	Micromex	103.0	NT	101.5/17.8 (98.5/17.3)[b]	23.9 (23.2)
7	Ompranyt	104.5	NT	102.5/70.0 (98.1/67.0)[c]	91.5/22.5 (87.6/21.5)[c]
14	Ramezol	103.5	NT	95.5 (92.3)	20.9 (20.2)
27	Omeprazoli	95.3	NT	50.5 (53.0)	13.4 (14.1)
25	Omeprazoli	104.8	NT	72.5 (69.2)	13.0 (12.4)
6	Ulcazol	101.0	NT	80.0 (79.2)	< 10
32	Demeprazol	100.0	92.5 (92.5)	78.0 (78.0)	78.5/< 10 (78.5/< 10)[b]
28	Inhibitron	106.0	101.0/91.0 (95.3/85.8)[b]	57.5/< 10 (54.2 < 10)[b]	< 10
21	Togran	94.1	76.0 (80.8)	12.0 (12.8)	NT
4	Ezipol	101.5	25.4 (25.0)	< 10	NT
26	Omeprazole	83.5	< 10	NT	NT
Tablets					
15	OMP	100.5	NT	106.5 (106.0)	102.0 (101.5)
16	Omed	87.5	NT	88.5 (101.1)	90.0 (102.9)
17	Result	101.0	95.5	88.5 (87.6)	61.5 (60.9)

[a]Assay results are presented as percent of label claim (%LC) and percent of initial value (%T_0). Listed in order of increasing instability. NT = not tested.

[b]Results from different containers from the same sample batch.

[c]Results from different capsules within the same sample strip-pack.

products to the market. Two samples (Omeprazole Capsules, China; and Omed Tablets, Korea) gave initial assay values of 83.5% and 87.5%, respectively.

As a result of discoloration, 7 samples were selected for testing after 1 month of storage (Victrix Capsules, Brazil; Demeprazol Capsules, Turkey; Togran Capsules, Chile; Inhibitron Capsules, Mexico; Ezipol Capsules, Greece; Omeprazole Capsules, China; and Result Tablets, Korea). Each exhibited a reduction in the content of remaining omeprazole. The Omeprazole Capsules from China exhibited almost total degradation of omeprazole, which suggested that its low initial value (83.5% label claim) was due, at least in part, to some decomposition having occurred before its receipt in the

laboratory. In the case of Inhibitron Capsules (Mexico), different degrees of discoloration were observed in the capsule contents from different containers of the same batch, which indicated that degradation may have occurred at different rates in different containers. This was confirmed by the different assay results for Inhibitron Capsules from different containers at both 1 month and 3 months.

At the 3-month time point, the majority of samples exhibited a reduction in the content of omeprazole which in the worst cases represented almost complete decomposition of omeprazole. Even greater losses of omeprazole were observed in the 6-month time point samples. Only 11 samples (32% of the total) gave assay values at 6 months that were within 3% of their initial value.

In addition to Inhibitron Capsules (Mexico), which showed different rates of degradation in different containers after 1-month storage, other products showed different levels of discoloration and different assay values in different containers of the same batch when tested at the 3-month and 6-month time points. These were Perprazol Capsules (Brazil), Micromex Capsules (Chile), and Demeprazol Capsules (Turkey). Also, a sample (Ompranyt Capsules; Spain) exhibited degradation that progressed at different rates in different capsules within the same strip-pack as shown by the different degrees of discoloration and correspondingly variable content of omeprazole.

Decomposition Products

The results for the content of decomposition products at each time point are shown in Table 4. As in Table 3, they are presented in order of their increasing degradation, as indicated by the increasing content of decomposition products over the 6-month storage period. In samples displaying extensive decomposition the chromatograms were too complex to permit accurate quantification of decomposition products. Results on samples containing more than 90% decomposition products are recorded as "$>90\%$."

Approximately half of the samples when tested initially showed levels of impurities of less than 1% of the omeprazole content. The remainder—except the sample of Omeprazole Capsules from China, which contained 4% of impurities—were found to contain a total content of impurities in the range 1–2%.

After storage for 3 months under the accelerated test conditions, all but 8 of the samples contained more than 1% of decomposition products and after 6 months only 6 samples (18%) contained not greater than 1% of decomposition products.

In general, there was a good inverse correlation between the content of remaining omeprazole and the content of decomposition products in each sample at each time point. However, with increasing levels of decomposition, the sum of the assay value and the content of the decomposition products increasingly deviated from the initial assay result for omeprazole. This increasing loss of mass balance is possibly due to the higher response factors of the decomposition products at 280 nm, the wavelength of detection in the tests for decomposition products and assay.

The identity of the decomposition products of omeprazole has not been published in the scientific literature. However, examination of the chromatograms of all the samples stored for 6 months in which the total content of decomposition products exceeded 1% of the omeprazole content comprised many peaks, the pattern of which appeared to be similar. Examples of chromatograms of products stored for 6 months, showing total impurity levels of 0.6% (Losec Capsules, Sweden), 16.1% (Ocid Capsules, India), and 81.1% (Victrix Capsules, Brazil) are shown in Fig. 1.

Dissolution

A summary of the percentage of the label claim of omeprazole released from the dosage forms into pH 6.8 phosphate buffer after a 2-hr preexposure to simulated gastric fluid (without enzyme) is shown in Table 5. The results are given for the mean and range of the 6 individual capsules.

When initially tested, 29 of the 34 samples gave a mean value greater than 75% and all individual values greater than 70% of the nominal content of omeprazole (20 mg). Two other samples gave slightly lower values (Proton Capsules, Portugal; and Ocid Capsules, India). Two samples gave very low amounts of omeprazole in the pH 6.8 buffer (Omeprazole Capsules, China; and Demeprazol Capsules, Turkey). During the testing of these products the capsule contents were observed to darken in the acid phase and take on a degraded appearance, indicating that the products do not offer sufficient protection during the preexposure to the acidic medium. Another sample (Omeprazoli Capsules, China; No. 27, Table 1) gave a very low release value owing to the failure of the capsule shells to disintegrate or dissolve during the test. These capsules also failed the European Pharmacopoeia disintegration test for capsules.

Table 4

Content of Total Impurities as % Area

Sample[a]	Product	% Area			
		Month 0	Month 1	Month 3	Month 6
Capsules					
30	Losec	0.3	NT	0.3	0.6
13	Losec	0.5	NT	0.6	0.9
10	Miracid	0.4	NT	0.4	0.9
9	Mopral	0.4	NT	0.4	0.9
2	Proton	0.6	NT	0.7	1.2
29	Ulsen	0.9	NT	1.4	1.5
31	Losec	0.2	NT	0.4	0.9
12	Zefxon	1.5	NT	1.5	2.5
20	Ulconar	1.0	NT	1.7	2.2
8	Pepticum	1.1	NT	1.5	2.5
34	Omeprol	1.1	NT	2.1	3.1
3	Lenar	1.4	NT	2.2	4.3
5	Procelac	0.8	NT	1.7	4.0
11	Desec	1.6	NT	2.3	5.1
23	Omez	0.5	NT	2.0	4.5
1	Omezolan	1.2	NT	4.9	7.7
24	Ocid	2.2	NT	6.5	16.1
19	Perprazol	0.8	NT	0.6	1.8/23.9[b]
33	Omeprazid	0.8	NT	10.7	38.4
7	Ompranyt	0.8	NT	3.1/44.3[c]	7.5/69.4[c]
18	Victrix	1.6	11.5	38.0	81.1
14	Ramezol	0.6	NT	3.7	86.7
6	Ulcozol	1.5	NT	12.0	>90%
32	Demeprazol	1.6	7.1	18.2	16.0/>90%[b]
25	Omeprazoli	1.0	NT	18.3	>90%
27	Omeprazoli	0.7	NT	39.3	>90%
28	Inhibitron	1.3	3.8/12.3[b]	33.9/83.3[b]	>90%
22	Micromex	0.9	NT	4.2/88.3[b]	69.5%
21	Togran	1.4	18.3	>90%	NT
4	Ezipol	1.9	56.4	>90%	NT
26	Omeprazole	4.0	>90%	NT	NT
Tablets					
15	OMP	0.7	NT	0.7	1.0
16	Omed	1.2	NT	2.3	2.7
17	Result	0.5	2.8	11.8	34.8

[a]Listed in order of increasing instability. NT = not tested.
[b]Results from different containers from the same batch.
[c]Results from different capsules within the same strip-pack.

Of the 29 samples exhibiting a minimum of not less than 70% dissolved from each of six dosage units when tested initially, only 17 showed similar dissolution after 3 months storage; and only 13, after 6 months. Some other samples were not tested as they had been shown to have undergone more than 10% decomposition. Five products that showed satisfactory dissolution initially and which contained less than 10% decomposition products after 6-month stability storage were found to comprise units that released less than 70% of the nominal omeprazole content at the 6-month time point. These were Omezolan Capsules (Portugal), Procelac Capsules (Argentina), Ompranyt Capsules (Spain), Omez Capsules (India), and Ulsen Capsules (Mexico). Another

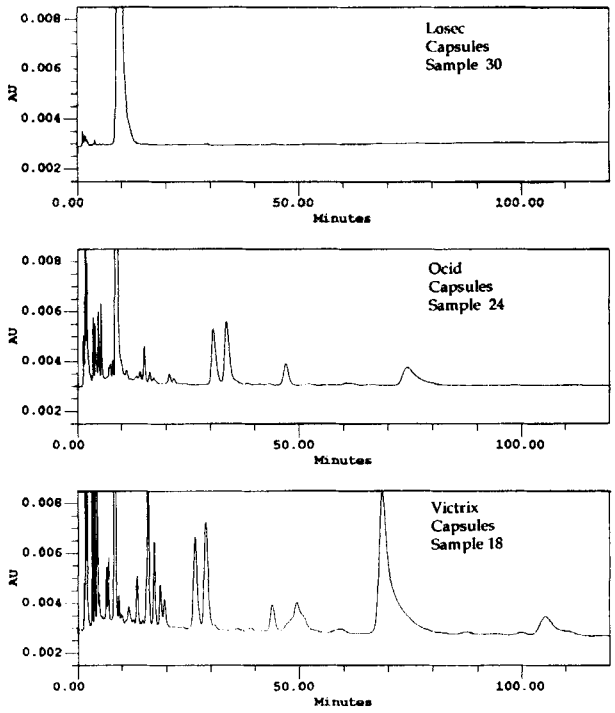

Figure 1. Chromatograms of 3 products after 6-month storage.

sample (Omed Tablets, Korea) exhibited a slight reduction in the amount of omeprazole dissolved and 1 of the 6 tablets tested at 6 months released less than 70%.

At the 3-month and 6-month time points, 2 samples displayed very wide intercapsule variability (Ompranyt Capsules, Spain; and Omez Capsules India). This was consistent, in the case of Ompranyt Capsules, with the intercapsule variability of the appearance and assay results on capsules within the same strip-pack (see above).

Additional Observations and Results

A number of samples tested on receipt showed evidence of extraneous material which was dissimilar to the omeprazole-containing beads. These were Ulcozol Capsules (Argentina), which had grey pellets among the off-white omeprazole-containing pellets; Victrix Capsules (Brazil), which contained green granules among the pale brown omeprazole-containing pellets; and Ulconar Capsules (Brazil), which contained red pellets among the off-white omeprazole-containing pellets. The extraneous material in these samples, isolated from the omeprazole-containing beads, was found to be devoid of omeprazole when assayed by the LC method.

Four other samples contained pellets that underwent color formation at different rates. These were Ulsen Capsules (Mexico), Omeprazole Capsules (China), Capsulae Omeprazoli (China) (Table 1, No. 27), and Zefxon Capsules (Thailand). In the case of Zefxon Capsules, white pellets among colored pellets remained at the end of the 6-month accelerated storage period, indicating either that omeprazole in the white pellets was stable or that the white pellets were devoid of omeprazole. The absence of omeprazole was confirmed when these pellets were assayed for omeprazole by liquid chromatography.

The presence of beads in these 7 samples with no or varying contents of omeprazole raised doubts about the uniformity of content of these products. The content uniformity of omeprazole in the 7 samples, stored after receipt at ambient temperature and humidity for approximately 7 months, was measured by applying the LC assay method to the contents of 10 individual capsules of each sample. The weight of each capsule contents was also measured and the relative standard deviations (RSDs) for weight variation (milligrams per capsule) and content uniformity (% label claim) in each capsule were calculated. For comparison, the corresponding RSDs of Losec Capsules (Sweden) were also determined.

The results in Table 6 show that 4 of the 7 samples comply with the acceptance criteria of the United States Pharmacopeia test for content uniformity (no capsule outside of 75% to 125% of label claim, at least 9 out of 10 capsules within 85% to 115% of label claim, and the RSD not greater than 6.0%). However, 2 of the 4 products, Victrix Capsules and Ulcozol Capsules, had RSDs for content uniformity of 5.8% and 5.2%, significantly higher ($p < 0.05$) than that of Losec Capsules, which had an RSD of 2.6%.

The sample of Omeprazole Capsules (China) failed the acceptance criteria by having 7 of the 10 capsules with less than 85% of label claim. This was consistent with the low assay result found at the start of the accelerated stability study. The sample of Zefxon Capsules (Thailand) failed the first level of the acceptance criteria by having an RSD on content uniformity of 8.1%. In contrast, the RSD for weight uniformity was only 2.4%, indicating that the poor content uniformity was due to a lack of homogeneity of the omeprazole in the capsule contents. The sample of Capsulae Omeprazoli (China) also failed the first level of the acceptance criteria by having an RSD on content uniformity of 6.3%. In this case, however, the variation appeared to be ac-

Table 5

Dissolution Results

Sample	Product	Country	%Dissolved (Mean %, Range %) Month 0	Month 1	Month 3	Month 6
1	Omezolan	Portugal	84, 80–86	NT[a]	73, 70–75	51, 48–56
2	Proton	Portugal	69, 66–71	NT	68, 63–75	65, 62–69
3	Lenar	Greece	105, 103–107	NT	97, 91–102	94, 88–97
4	Ezipol	Greece	95, 91–103	NT	NT	NT
5	Procelac	Argentina	87, 83–91	NT	82, 78–86	69, 64–73
6	Ulcozol	Argentina	93, 90–98	NT	NT	NT
7	Ompranyt	Spain	100, 86–101	NT	—, 12–89[b]	—, <1–79[b]
8	Pepticum	Spain	100, 98–104	NT	98, 96–104	100, 99–102
9	Mopral	Spain	80, 78–82	NT	83, 80–84	81, 77–83
10	Miracid	Thailand	93, 90–97	NT	94, 91–100	95, 91–97
11	Desec	Thailand	97, 95–102	NT	97, 96–98	87, 85–89
12	Zefxon	Thailand	98, 93–105	NT	96, 79–104	92, 86–106
13	Losec	Korea	83, 80–84	NT	87, 73–92	87, 83–92
14	Ramezol	Korea	88, 83–93	NT	70, 66–74	NT
15	OMP	Korea	91, 90–93	NT	87, 82–88	84, 83–86
16	Omed	Korea	78, 74–82	NT	75, 72–78	71, 65–73
17	Result	Korea	97, 94–103	96, 89–100	NT	NT
18	Victrix	Brazil	87, 83–96	NT	NT	NT
19	Perprazol	Brazil	100, 97–102	NT	98, 93–104	99, 90–103
20	Ulconar	Brazil	98, 93–100	NT	96, 90–101	93, 88–99
21	Togran	Chile	87, 71–94	NT	NT	NT
22	Micromex	Chile	95, 92–98	NT	93, 89–98	NT
23	Omez	India	93, 85–100	NT	—, 3–89[b]	26, 22–36
24	Ocid	India	65, 60–69	NT	48, 47–50	NT
25	Omeprazoli	China	92, 90–94	NT	NT	NT
26	Omeprazole	China	24, 22–26	NT	NT	NT
27	Omeprazoli	China	<2%	NT	NT	NT
28	Inhibitron	Mexico	92, 82–97	NT	NT	NT
29	Ulsen	Mexico	78, 71–83	NT	71, 51–82	42, 35–53
30	Losec	Sweden	91, 88–96	NT	92, 88–95	92, 87–95
31	Losec	Turkey	93, 89–97	NT	92, 85–95	91, 89–94
32	Demeprazol	Turkey	28, 26–29	28, 26–29	NT	NT
33	Omeprazid	Turkey	84, 81–89	NT	NT	NT
34	Omeprol	Turkey	96, 91–102	NT	98, 95–101	88, 83–93

[a]NT = not tested.

[b]The mean of these samples could not be meaningfully calculated due to the sample degrading at different rates.

counted for by a similarly wide variation in the weight of the capsule contents (RSD 5.4%). The last two samples were not retested (a retest is allowed by the USP) owing to a lack of further sample.

DISCUSSION

This independent survey of the stability of omeprazole products under accelerated testing conditions has concentrated on the critical quality parameters that may alter as a result of chemical or physical instability during storage. These parameters were appearance, content of omeprazole, content of decomposition products, and in vitro release of omeprazole.

The appearance of the product was shown to be an excellent predictor of the level of decomposition products in the formulation. Any tablet or capsule whose contents were more highly colored than pale brown contained a significant level of decomposition products. This observation was of value in demonstrating the different rates of decomposition of omeprazole in capsules

Table 6

Content Uniformity and Weight Variation

Sample	Product	Country	Content Per Capsule		Weight of Capsule Contents	
			Mean (%LC)	RSD%	Mean (mg)	RSD%
6	Ulcozol	Argentina	100.8	5.2	284.0	2.9
12	Zefxon	Thailand	100.4	8.1	290.6	2.4
18	Victrix	Brazil	94.6	5.8	256.8	2.1
20	Ulconar	Brazil	108.9	3.9	290.6	2.2
26	Omeprazole	China	81.9	4.6	225.5	3.2
27	Omeprazoli	China	97.3	6.3	222.0	5.4
29	Ulsen	Mexico	108.6	4.3	257.8	1.6
30	Losec	Sweden	100.8	2.6	232.4	2.4

from the same batch of some products in different containers, in different beads within the same capsule, and in different capsules within the same strip-pack.

A number of products exhibited a marked loss of omeprazole content during the 6-month study, which was explained by a corresponding marked increase in the level of decomposition products. In many other products the loss of omeprazole was less marked and, in the absence of statistical measures of analytical precision, it is not possible to conclude that these small losses are due to instability. However, for many of those products, the increase in decomposition products, which can be measured much more precisely than the loss of omeprazole, demonstrates that significant decomposition occurred.

There are no pharmacopoeial quality standards for omeprazole products, against which the levels of decomposition products formed during storage of the products can be assessed. However, the European Pharmacopoeia has recently published a monograph for omeprazole drug substance, in which the content of individual related substances is controlled to 0.1%. In the authors' experience of drug substances available in such a high degree of purity, a typical limit for total related substances, including decomposition products, in the dosage form at the end of shelf life might be of the order of 0.5% to 1.0%. It is essential, of course, that any limit for individual and total impurities is justified on safety grounds in relation to their toxicological properties. The levels of decomposition products in most of the products tested after accelerated stability storage exceeded 1%. Indeed, of the 34 products tested on receipt, 15 contained more than 1% of impurities; and at the end of the 6-month period of accelerated storage conditions, 26 products contained related substances in excess of 2% (in at least one container) including 10 that initially had contained less than 1% of impurities.

The dissolution test that was used to assess the stability of the dissolution characteristics was a conventional test for gastro-resistant oral dosage forms using a pH 6.8 phosphate buffer dissolution medium after a period of preexposure to simulated gastric fluid pH 1.2 (without enzymes). Because of omeprazole's acid lability, which results in the formation of colored products (5), it was not possible to determine the amount of omeprazole released into the acidic medium. However, any significant loss of omeprazole into the acidic medium was readily detected by the red to brown colour that developed. This was found to occur with 2 products and resulted in low amounts of omeprazole in the pH 6.8 buffer.

In the absence of publicly available quality standards for the amount of omeprazole that should be released during an in vitro release test, the typical pharmacopoeial acceptance criteria for oral dosage forms offer a reasonable alternative means by which the results of the dissolution test on the samples could be assessed. Although the various pharmacopoeias differ in their acceptance criteria, most solid dosage forms that are the subject of a pharmacopoeial monograph would comply with the criteria if almost all of the dosage units tested were at least 70% dissolved after 30 or 45 min. It is recognized by the pharmacopoeial authorities that, although compliance with the acceptance criteria does not guarantee bioavailability or bioequivalence of different products, it significantly reduces the likelihood of unsatisfactory bioavailability due to inadequate dissolution (6). Five products which initially gave results that complied with a limit of at least 70% released from all dosage units showed a significant reduction in the amount re-

leased after 6 months storage. This may also have been the case with other products whose dissolution was not tested at 6 months because the content of decomposition products exceeded 10% of the nominal omeprazole content.

When the 34 products were tested on receipt, 8 products gave assay results outside of the 90–105% limits that are often acceptable to registration authorities as end of shelf life limits, 15 had levels of total impurities greater than 1% (a typical limit for a solid dosage form of a drug substance that is available in a high degree of purity), and 3 products gave very low release of the active ingredient when subjected to a typical dissolution regimen for a gastro-resistant formulation. Two other products had mean values of 69% and 65% for the amount dissolved, which are slightly lower than values expected for this type of product. Thus, a total of 19 products (56%) on receipt did not comply with these generally acceptable shelf-life quality standards and, of these, 5 products did not comply on two of the three quantitative parameters and 2 products did not comply on all three parameters.

The results of the stability tests under accelerated test conditions indicate that omeprazole capsules and tablets sourced from many countries worldwide exhibit a wide spectrum of stability characteristics, ranging from highly stable even after 6 months storage to very unstable as demonstrated by almost complete decomposition after 1 month.

Accelerated stability testing is normally used to provide assurance of a product's stability under the recommended storage conditions: if a product is sufficiently stable under accelerated storage conditions, it is likely to be stable throughout its shelf life under the recommended storage conditions. (In addition, registration authorities normally require confirmation of "real-time" stability during shelf life under the recommended storage and transport conditions.) While the lack of stability under accelerated testing conditions does not preclude stability under normal ambient storage conditions, the marked instability of many of the products in this survey must cast serious doubt on the stability of the products under the relevant conditions for long-term storage and transport.

Based on the results of this survey, only 6 products—viz. Losec Capsules (Astra, Sweden), Losec Capsules (Astra, Korea), Miracid Capsules (Berlin Pharm. Ind. Co., Thailand), Mopral Capsules (Astra-Ifesa, Spain), Losec Capsules (Astra, Turkey), and OMP Tablets (Korea)—were stable over the 6-month period. These 6 products had no more than 1% of impurities at the end of the 6-month storage period, their assay and dissolution characteristics were almost unchanged, and the degree of discoloration was slight in comparison with most other samples. Two other products gave only a small increase in the content of impurities. One of them, Proton Capsules (Laboratorio Medinfar, Portugal), released lower amounts of omeprazole in the dissolution test, initially and at the end of the stability study, than most other products; and the other, Ulsen Capsules (Senosiain, Mexico), showed a considerable decrease in the amount of omeprazole dissolved when tested at the end of the storage period. All the other products contained levels of impurities greater than 2% at the end of the storage period, accompanied in most cases by a measurable decrease in the content of omeprazole. In some cases there was also a reduction in the amount of omeprazole released in the in vitro dissolution test. It is concluded that the design of the products showing significant changes during the stability study may not provide the necessary protection against environmental factors (heat and humidity) that cause decomposition.

The results obtained on some products indicate, not only that the products were unstable under the test conditions, but also that the instability could vary. Thus, different rates of decomposition of omeprazole in different containers bearing the same batch (lot) number and different rates of decomposition in different capsules in the same strip-pack were observed.

The results of the additional studies, on the homogeneity of the capsule contents, indicate that 4 products contain inert, non-omeprazole-containing extraneous material whose presence probably accounts for their poor uniformity of content. The function of these inert capsule constituents is not known but if they affect the stability of the omeprazole-containing constituents, their variable content may also result in variable stability of the omeprazole. The results also show that three other products appear to exhibit different rates of decomposition in different beads inside the same capsule as indicated by the different rates of discoloration of the beads. This apparent lack of homogeneity of the beads may account for the inferior content uniformity when compared to the original product, Losec Capsules from Astra, and lead to capsules undergoing different rates of decomposition within the same batch.

CONCLUSIONS

Six of the 34 omeprazole products tested (18%) were shown to be very stable when tested under the ICH conditions for accelerated stability testing. Another product was shown to be stable although the amount of omeprazole released initially and throughout the storage period was lower than that from most other products.

The vast majority of the omeprazole products tested (27 out of 34) failed to exhibit good stability. Chemical decomposition of omeprazole occurred to a significant extent, and this was often accompanied by significant physical changes in color and the amount released in the dissolution test. The inferior quality of these products raises concerns about their safety and efficacy.

REFERENCES

1. M. Mathew, V. Das Gupta, and R. E. Bailey, Drug Dev. Ind. Pharm., 21, 965 (1995).
2. A. Karlsson, J. Lindqvist, K. Lovgren, L. Rosen, and A.-M. Tivert, submitted for publication (personal communication).
3. S.-O. Jansson and J. Vessman, Mikrochim. Acta (Wien), II, 103 (1991).
4. K. Lovgren, A. Pilbrant, M. Yasumura, S. Morigaki, M. Oda, and N. Ohishi, U.S. Patent 4,786,505, 1987.
5. A. Pilbrant and C. Cederberg, J. Scand. Gastroenterol., 20(Suppl. 108), 113 (1985).
6. *British Pharmacopoeia 1993*, Addendum 1995, HMSO, p. A417.