Forced Degradation of Ibuprofen in Bulk Drug and Tablets

and Determination of Specificity, Selectivity, and the Stability-Indicating Nature of the USP Ibuprofen Assay Method

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This article discusses forced-degradation techniques and exposure studies on ibuprofen (IBP) bulk drug and IBP tablets and describes how the results were used to determine the specificity, selectivity, and the stability-indicating nature of the USP IBP assay method. The authors justify the use of the method for quantitation of IBP content and the limit of 4-IBAP in stability samples exposed to conditions stated in the stability protocol.

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Stability testing provides information about how the quality of bulk drug or drug product varies with time under the influence of various environmental factors such as temperature, humidity, and light and helps determine recommended storage conditions and establish retest periods and shelf lives (1). Assay analytical methods for evaluating the stability of drug substance or drug product should be specific and selective and should detect quantitative changes in drug substance and drug product over time (2). The specificity and selectivity of the method, or the method's ability to assess the analyte unequivocally in the presence of expected components, should be demonstrated to qualify the method as stability indicating (3). Subjecting the drug substance and drug product samples to forced degradation (stress testing) is necessary to generate degradation products that are used to demonstrate the specificity and selectivity of the method. Stress testing should demonstrate that the impurities and degradants from the active ingredients and drug product excipients do not interfere with the quantitation of active ingredient (2).

The purpose of this study was to evaluate the selectivity and specificity of ibuprofen (IBP) bulk drug and IBP tablet assay methods of the United States Pharmacopeia (USP) for the quantitation of IBP and the limit of 4-isobutylacetophenone (4-IBAP) and to demonstrate the stability-indicating nature of the method (4). To demonstrate the specificity and selectivity of the method, degradants were generated by subjecting the IBP bulk drug and IBP tablet assay preparations to stresses such as temperature, acid hydrolysis, base hydrolysis, light, and oxidation. High-performance liquid chromatography (HPLC) was used for the separation of the IBP peak from other peaks in the chromatogram representing degradants of IBP, impurities, and excipients. Peak separation was evaluated by retention time (RT), relative retention time (RRT, in which RRT = RT of an impurity peak ÷ RT of IBP), and peak resolution. Peak purity of IBP, 4-IBAP, and those peaks eluting closely to

Table I: Known impurities/ degradation standards.

Impurity/ Degradant	RRT
FPPA	0.36
MPPA	0.49
EPPA	0.58
PPPA	0.78
SBPPA	0.96
IBPPA	0.97
4-IBAP	1.57
BPPA	1.65

these compounds were examined by photodiode-array detection to assess separation of IBP and 4-IBAP peaks without interference from other peaks and in the absence of any coeluting peaks. A tablet assay preparation from a stability sample stored for 36 months (past the marketed product expiration date of 24 months) at 27 °C showed the degradation of IBP and the formation of degradation products. This sample was subjected to sunlight stress to further enhance degradation. The samples before and after sunlight exposure were evaluated to demonstrate the stability-indicating nature of the method.

Materials and methods

IBP bulk drug. The IBP bulk-drug substance was obtained from BASF Corporation (Mount Olive, NJ) and qualified as a secondary standard. The equivalency of the IBP secondary standard was determined to be 0.996 with the USP IBP reference standard using the USP IBP HPLC assay method (4). IBP, 2-(4-isobutylphenyl)-propionic acid (molecular formula: $C_{13}H_{18}O_2$, molecular weight: 206.28 daltons), is a colorless (white) crystalline stable solid with a melting point from 74 °C to 77 °C. It is slightly soluble in water (<1 mg/mL) but readily soluble in most organic solvents (e.g., ethanol, acetone, and acetonitrile).

Impurities and degradants of IBP. 4-IBAP, one of the main impurities of IBP as well as the major degradation product, was obtained from TCI America (Portland, OR) for this study. Impurity/degradation standards of IBP obtained from BASF Corporation included 2-(4-formylphenyl)propionic acid (FPPA), 2-(4-methylphenyl)propionic acid (MPPA), 2-(4-ethylphenyl) propionic acid (EPPA), 2-(4-*n*-propylphenyl)propionic acid (PPPA), 2-(4-secbutylphenyl)propionic acid (SBPPA), 2-(3-isobutylphenyl)propionic acid (IBPPA), 4-IBAP, and 2-(4-*n*-butylphenyl)propionic acid (BPPA) (see Figure 1). Approximate RRT values of standards are listed in Table I. When possible, the peaks in the chromatograms of the forced-degradation samples were assigned identifications on the basis of the RRT values of standards.

Drug product. The IBP tablets of 800-mg dosage stored for 12 months at 27 °C were used for stress testing because they showed no degradation products. In addition, the 36-month stability

Table II: 36-month stability sample preparations before and after sunlight exposure — relative retention time (RRT), peak quantitation by area percent, and peak purity and resolution of peaks in the chromatogram with their approximate retention times and identification. **(Table continued on page 32.)**

Sample	Area %/ Peak Purity	1.2 Unknown	1.4 Unknown	1.5 FPPA	2.0 MPPA	2.2 EPPA*	2.9 Unknown
Sample 1: 36-month	RT	1.23	1.35	1.45	2.01	2.17	2.89
stability sample	RRT	0.30	0.32	0.35	0.48	0.52	0.69
before sunlight	Area %	1.33	1.48	0.37	9.02	0.43	3.89
exposure	Peak purity	999	999	999	1000	999	1000
Sample 2: 36-month	RT	1.23	1.35	1.45	2.01	2.16	2.89
stability sample	RRT	0.30	0.32	0.35	0.48	0.52	0.69
before sunlight	Area %	1.23	1.27	0.35	9.63	0.50	3.73
exposure	Peak purity	999	999	999	1000	999	1000
Sample 3: 36-month	RT	1.23	1.35	1.45	2.01	2.16	2.89
stability sample	RRT	0.30	0.32	0.35	0.49	0.52	0.69
before sunlight	Area %	1.27	1.42	0.30	10.4	0.48	4.27
exposure	Peak purity	999	998	999	999	1000	1000
Sample 1: 36-month	RT	1.23	1.35	1.44	2.00	2.08	2.85
stability sample	RRT	0.30	0.33	0.35	0.49	0.51	0.69
stressed for 72 h	Area %	1.64	1.85	3.17	1.36	0.16	1.45
in sunlight	Peak purity	999	999	998	998	1000	1000
Sample 2: 36-month	RT	1.23	1.35	1.44	2.01	2.08	2.86
stability sample	RRT	0.30	0.33	0.35	0.49	0.51	0.69
stressed for 72 h	Area %	1.63	1.67	2.93	1.40	0.15	1.47
in sunlight	Peak purity	999	945	999	999	996	999
Sample 3: 36-month	RT	1.23	1.35	1.44	2.00	2.08	2.85
stability sample	RRT	0.30	0.33	0.35	0.49	0.51	0.69
stressed for 72 h	Area %	1.63	1.76	3.04	1.61	0.14	1.70
in sunlight	Peak purity	999	999	999	998	ND**	999

*Tentative identification because of poor peak resolution and peak broadening (2.1–2.4 min).
**ND = Not detected. Peak purity was not determined because of inadequate concentration as well as absorbance.

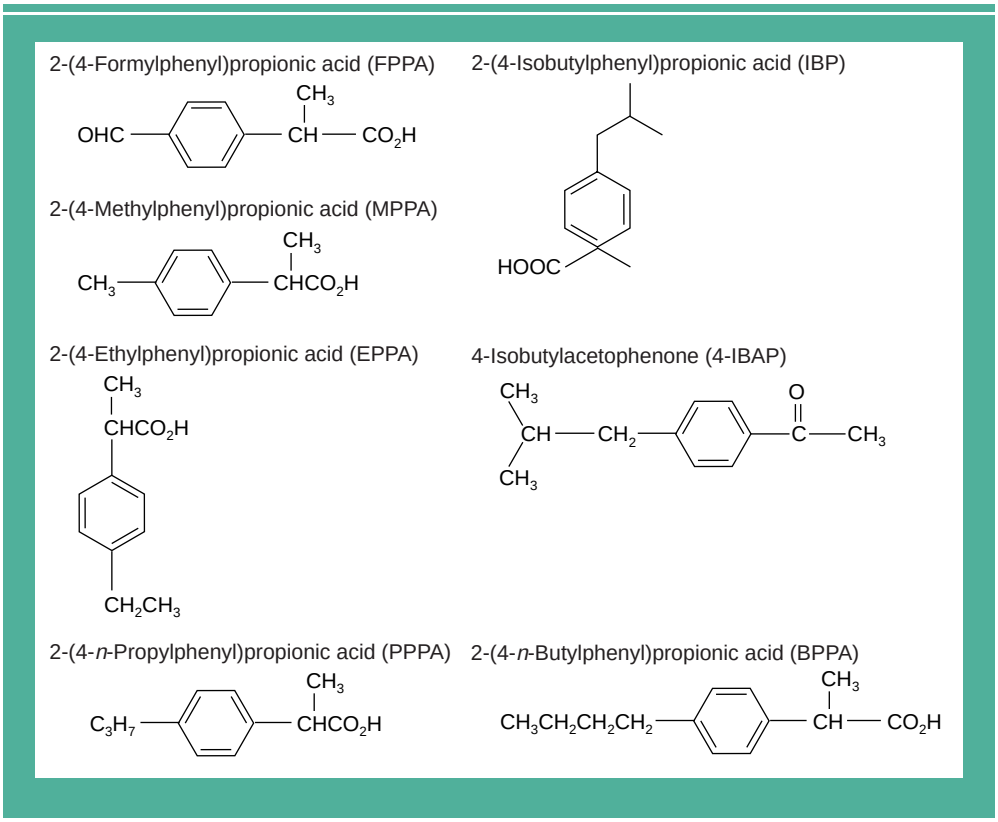

Figure 1: Structure of IBP and its known impurities.

samples of the same dosage strength also stored at 27 °C, which showed degradation products, were used to demonstrate the stability-indicating nature of the method. These samples were stored for 12 months beyond the product label expiration date of 24 months and represented a worst-case scenario. These samples also were subjected to light stress to further induce degradation products and to challenge the stability-indicating nature of the method.

Stresses used during the forced-degradation study. Bulk-drug and tablet preparations were subjected to forced degradation using the following stresses: acid — hydrochloric acid (2 N); base — sodium hydroxide (2 N); oxidation — hydrogen peroxide (10%); light — laboratory

Table II (continued from page 30): 36-month stability sample preparations before and after sunlight exposure — relative retention time (RRT), peak quantitation by area percent, and peak purity and resolution of peaks in the chromatogram with their approximate retention times and identification.

Sample	Area %/ Peak Purity	3.3 PPPA	4.1 IBP	4.9 Unknown	6.6 4-IBAP	6.9 BPPA
Sample 1: 36-month	RT	ND	4.17	ND	6.57	ND
stability sample	RRT	ND	1.0	ND	1.57	ND
before sunlight	Area %	ND	76.7	ND	6.76	ND
exposure	Peak purity	ND	1000	ND	1000	ND
Sample 2: 36-month	RT	ND	4.17	ND	6.57	ND
stability sample	RRT	ND	1.0	ND	1.57	ND
before sunlight	Area %	ND	73.3	ND	10.0	ND
exposure	Peak purity	ND	1000	ND	1000	ND
Sample 3: 36-month	RT	ND	4.17	ND	6.57	ND
stability sample	RRT	ND	1.0	ND	1.58	ND
before sunlight	Area %	ND	71.5	ND	10.4	ND
exposure	Peak purity	ND	1000	ND	1000	ND
Sample 1: 36-month	RT	3.29	4.11	4.89	6.44	6.94
stability sample	RRT	0.80	1.0	1.19	1.57	1.69
stressed for 72 h	Area %	5.04	38.3	0.24	42.1	4.35
in sunlight	Peak purity	976 (new peak)	1000	999 (new peak)	1000	1000 (new peak)
Sample 2: 36-month	RT	3.30	4.12	4.89	6.44	6.94
stability sample	RRT	0.80	1.0	1.19	1.56	1.69
stressed for 72 h	Area %	5.12	36.5	0.23	44.2	4.48
in sunlight	Peak purity	956 (new peak)	1000	999 (new peak)	1000	1000 (new peak)
Sample 3: 36-month	RT	3.30	4.11	4.89	6.44	6.94
stability sample	RRT	0.80	1.0	1.18	1.57	1.69
stressed for 72 h	Area %	4.98	34.9	0.21	44.8	4.75
in sunlight	Peak purity	963 (new peak)	1000	999 (new peak)	1000	1000 (new peak)

window (5660 lux), intensified-light cabinet (7300 lux), direct sunlight (129,000 lux); and temperature — oven at ~80 °C.

Preparation of extraction solution (ISTD solution). Components of the extraction solvent included chloroacetic acid and acetonitrile as extraction reagents and internal standard (ISTD) valerophenone as a marker for assay samples (4). A 1% chloroacetic acid solution was prepared by dissolving 40 g of chloroacetic acid in 4 L of water and adjusting the pH to 3.0 ± 0.05 with ammonium hydroxide. To prepare the extraction solution, 400 mL of 1% chloroacetic acid was mixed with 600 mL of acetonitrile, followed by the addition of 3.5 mL of ISTD.

Preparation of mobile phase. The mobile-phase constituents, 400 mL of 1% chloroacetic acid and 600 mL of acetonitrile, were mixed on line in an HPLC unit and degassed using a degasser–mixer.

Preparation of standard solutions. The 4-IBAP standard stock solution was prepared by transferring 60 mg of 4-IBAP into a 100-mL volumetric flask and diluting to mark with acetonitrile. The IBP standard solutions were prepared by transferring 1.2 g of IBP secondary standard into a 100-mL volumetric flask and 2.0 mL of 4-IBAP standard stock solution and diluting to mark with ISTD solution.

Preparation of nonstressed control samples. Samples were prepared in triplicate with a targeted IBP concentration of 12 mg/mL. One tablet or 0.8 g of IBP bulk-drug substance was added to 65 mL of extraction solution, and the contents were shaken for 1 h by a wrist-action shaker. The tablet extract or bulk-drug solutions were mixed well and filtered into autosampler vials using a Whatman 0.45-μm filter (5). These filtrates represented nonstressed, control sample preparations. The filtrates were analyzed by HPLC as specified by the USP IBP assay method (4).

Preparation of stressed samples. Samples for control and stress exposure were extracted in the same manner. After the volumetric flasks containing the extracts were removed from the wrist-action shaker, they were subjected to various stresses. This facilitated exposure of the active ingredient as well as the excipient components to various stresses and maximized the degradation of these components in solutions versus in intact tablets or bulk-drug powder.

Concentrated hydrochloric acid, sodium hydroxide, and 30% hydrogen peroxide were used for acid, base, and oxidation stresses, respectively, to arrive at a final stress concentration of 2 N, 2 N, and 10% final solution concentrations, respectively. Immediately after the addition of each of these three stresses, an aliquot of extract from a volumetric flask was taken and analyzed to determine whether an immediate degradation took place upon stress addition. These samples were designated as *initiation samples* to distinguish them from control and stress-exposed samples.

The volumetric flasks containing the extracted tablets or bulk drug were exposed to three types of light stresses: laboratory-window light (5660 lux), light cabinet (7300 lux), and sunlight (129,000 lux). The dark control samples were covered with aluminum foil to protect them from light. For temperature stress, the volumetric flasks containing the extracts were placed in a controlled-temperature oven at ~80 °C.

Duration of stress exposure. Samples were exposed to various stresses with the objective to achieve ~30% or more degradation of IBP and the formation of a number of degradation products, which are necessary to assess the method's specificity and selectivity. Initially, aliquots were sampled at 48 h and analyzed by HPLC. Degradation was minimal in some samples and nonexistent in others after 48 h. Therefore, the time of exposure was extended. The terminal sampling points for acid, light, temperature, and oxidation stresses were 240, 380, 244, and 216 h, respectively, at which times, at least with the light-stressed samples, a sufficient number of degradation products had formed so that the specificity and selectivity of the method could be evaluated. Base stress was not pursued because of the extensive precipitation when sodium hydroxide was added to bulk-drug and tablet assay preparations as a result of the IBP-free acid.

HPLC method and conditions. All samples were filtered using a syringe with a Whatman 0.45-μm filter attached to its tip, and the filtered extracts were transferred into HPLC autosampler vials (5). Analysis of filtered extracts was performed by HPLC (Agilent Technologies, Palo Alto, CA) using the following conditions: 254-nm detector wavelength; 40 °C column temperature; and 2 mL/min flow rate. The column used was a 4.6 mm × 25 cm Zorbax ODS (ODS column packing produced by chemically bonding dimethyl-octadecylsilane [C18] groups to Zorbax SIL silica particles). The "Statistics Report" function of Agilent's Chemstation software was used to integrate and analyze HPLC peak responses and to quantitate the peaks by area percentage. The evaluation of the selectivity and specificity of the method was accomplished by the RT, RRT, peak resolution, and peak purity values. Peak resolution of >2.5 was required for acceptable separation of a peak from its closely eluting peak. A diode array detector (DAD, Agilent) was used to determine the peak purity, and the peak-purity factor was determined by DAD software. A pure peak should have a purity factor of 990–1000.

Determination of IBP content in stressed and nonstressed bulk drug and tablets. Quantitation of the IBP peak and other components present in the chromatograms was performed by area percent. Individual peak area in the chromatogram was divided by total peak area, and the result was multiplied by 100 to calculate the area percent for each peak. Representative chromatograms (*x*-axis — retention time in minutes; *y*-axis — peak response in mAU) of stressed bulk-drug and tablet preparations are presented for selected stresses.

System suitability determination and specifications. System suitability samples were included for each analytical run during the forced-degradation study. Five standard injections were made, and the tailing factor, RTs, and resolution were determined for each run. The results from the analyses of samples were considered acceptable if the following system suitability acceptance criteria were met: RRTs were ~0.75 for IBP, ~1.0 for ISTD, and ~1.2 for 4-IBAP; the tailing factor for an individual peak was ≤2.5; the resolution *R* between the IBP, ISTD, and 4-IBAP peaks was ≥2.5; and the relative standard deviation (RSD) for five injections was ≤2.0% (4).

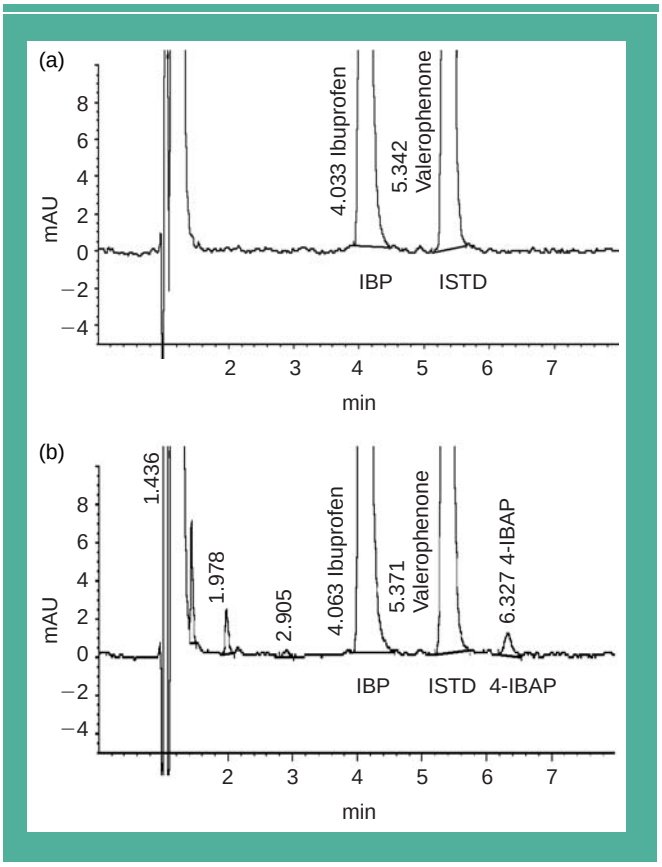

Figure 2: (a) Degradation of IBP in bulk-drug preparation from acid stress. (b) Degradation of IBP in tablet extracts from acid stress.

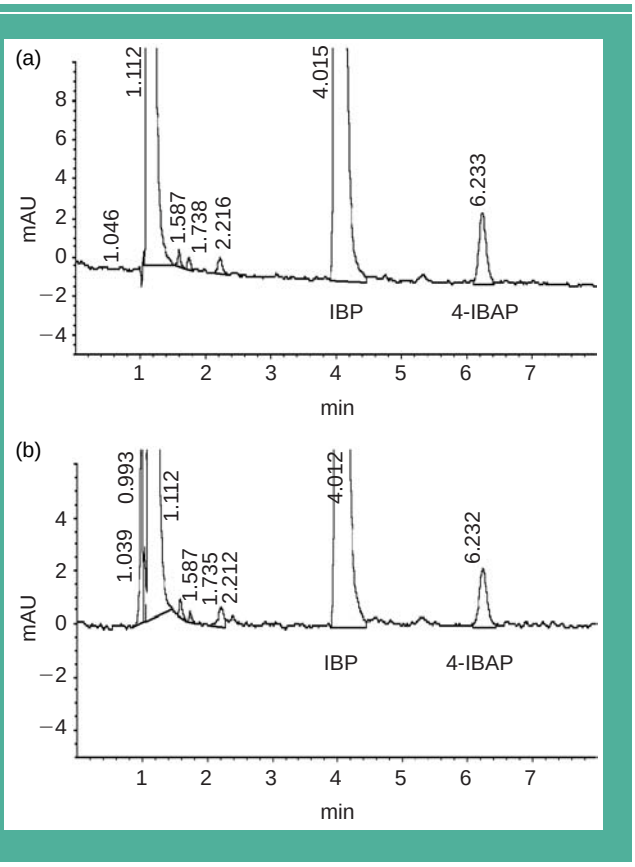

Figure 3: (a) Degradation of IBP in bulk-drug preparation from oxidation stress. (b) Degradation of IBP in tablet extracts from oxidation stress.

Results and discussion

System suitability specifications. The system suitability criteria were met for all run sequences during the forced-degradation study. The RRTs of IBP, ISTD, and 4-IBAP for a representative system suitability run were 0.75, 1.0, and 1.18, respectively. The tailing factors for IBP, ISTD, and 4-IBAP were 1.92, 1.20, and 1.17, respectively. The resolutions of the ISTD and 4-IBAP peaks with respect to the IBP peak were 7.73 and 4.97, respectively. System precision was demonstrated with recoveries of >99% for IBP and 0.1% for 4-IBAP from each of the five injections, with RSDs for the five injections for IBP and 4-IBAP being 0.30% and 0.50%, respectively.

Acid stress. IBP in bulk-drug assay preparations showed no degradation under acid stress (see Figure 2a). IBP showed some degradation under acid stress in tablet assay preparations with FPPA, MPPA, and 4-IBAP as the main degradation products (see Figure 2b). Some degradation of ISTD also was noticed, so it was decided to eliminate the use of ISTD in assay preparations for the forced-degradation study. For this reason, ISTD was not used for light, oxidation, temperature, or the 36-month stability sample experiments described in this article. In another published study, ISTD was shown to be highly susceptible to degradation under light and required adequate protection of samples during the assay of release and stability samples of the IBP drug product (6).

Base stress. When sodium hydroxide was added to the assay preparations designated for base stress, extensive precipitation resulted because the IBP-free acid that formed in the acidic extraction solution was precipitated by the addition of base stress. For this reason, experiments on this stress were discontinued and no data are presented.

Oxidation stress. Samples were exposed to oxidation stress using commercial 30% hydrogen peroxide, thereby creating a final sample concentration of 10% hydrogen peroxide. 4-IBAP was the major degradation product with ~2% in bulk drug and 1.2% in tablet preparations after 216 h of stress exposure (see Figures 3a and 3b). Four other degradant peaks were <0.4% in any replicate sample. Resolution of the IBP peak from the other peaks in the chromatogram was >2.5, thereby demonstrating the specificity of the method. The purity factors were 1000 for the IBP peak and 999 for the 4-IBAP peak, indicating a lack of any coeluting peaks. Degradation of IBP in bulk drug under oxidation stress was slightly higher than that in the tablet preparations.

Temperature stress. Bulk-drug and tablet sample preparations were exposed to 80 °C for 244 h. IBP degradation in bulk-drug samples ranged from 2.9 to 11.4% (see Figure 4a) and degradation of IBP in IBP tablet preparations ranged from 21.5 to 39.9% (see Figure 4b). In IBP bulk drug, the 4-IBAP peak at 6.3 min was the major degradation product, ranging from 1.43 to 4.94% for three replicate samples. Other degradation product peaks observed in bulk-drug preparations were two unknown peaks

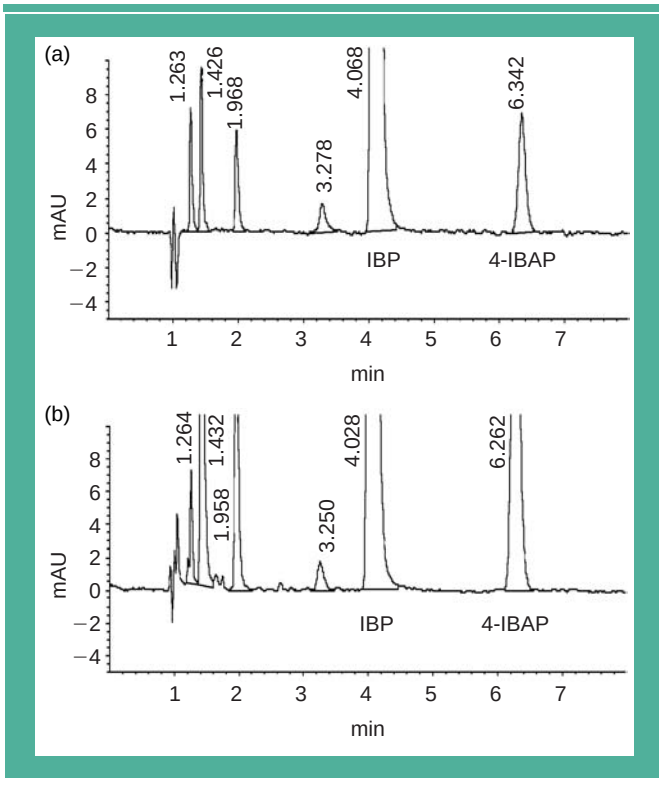

Figure 4: (a) Degradation of IBP in bulk-drug preparation from temperature stress. (b) Degradation of IBP in tablet extracts from temperature stress.

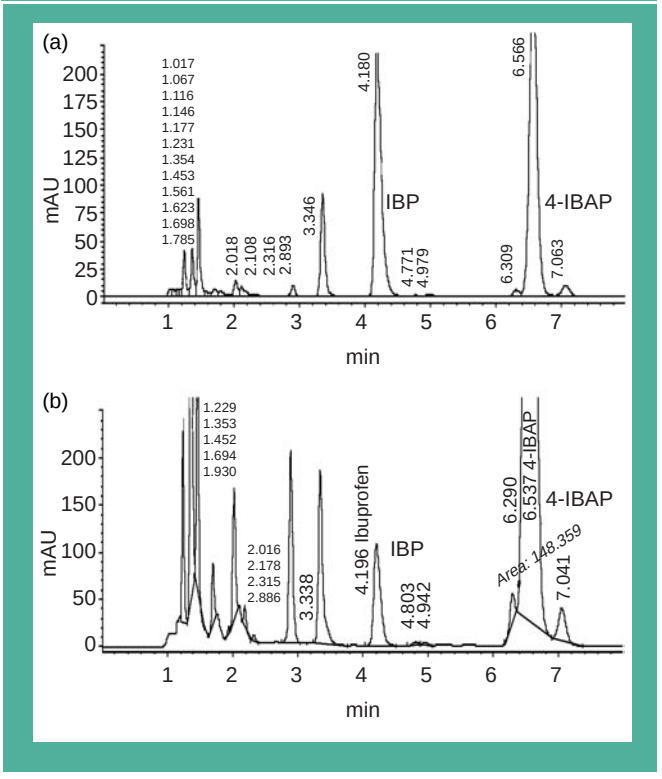

Figure 5: (a) Degradation of IBP in bulk-drug preparation from sunlight stress. (b) Degradation of IBP in tablet extracts from sunlight stress.

(at 1.3 and 1.4 min), MPPA, and PPPA, with none of these exceeding 2% by area percent. The degradation products formed from drug product and bulk drug were similar, although degradation was higher in tablet extracts. In tablet preparations, the peaks at 1.4 min (~8–18%) and the 4-IBAP peaks (~9–15%) were the major degradation products. Peak resolution was >2.5, indicating noninterference of peaks. IBP peak in bulk-drug and tablet extract samples had a peak-purity factor of 1000, confirming the absence of peaks coeluting with IBP. The major degradation product, 4-IBAP, also had a peak-purity factor of 1000.

Light stress in a light cabinet. IBP did not degrade under laboratory-window light conditions. Samples then were exposed to light in a light cabinet commonly used for accelerated stability storage conditions. Anticipating slow degradation of IBP in a light cabinet, and to accelerate degradation, acetone (1%) was added to samples as a sensitizer. Approximately 8% of IBP degraded in bulk-drug samples, whereas degradation of IBP in IBP tablet preparations ranged from ~11 to 18%. In IBP bulk-drug samples, the 4-IBAP peak was the major degradation product (peak area ~5%). Four other degradation product peaks resulted in >1% by area percent. In tablet preparations, 4-IBAP was the major degradant (peak area ~6%), and other degradant peaks were <3% by area percent. These degradant peaks were not present in the dark control samples. Resolution of the IBP peak from other peaks was >2.5, indicating noninterference of peaks with the IBP peak. IBP peaks in bulk-drug and tablet extract samples had a peak-purity factor of 1000, confirming the absence of peaks coeluting with IBP. The major degradation product, 4-IBAP, had a peak-purity factor of 1000. Because degradation of IBP was <30%, the effect of sunlight stress on degradation was investigated.

Sunlight stress. IBP in both the bulk-drug and tablet assay preparations degraded extensively, with ~70% and 98% (by area percent) degradation, respectively, in 380 h. The major degradation product formed was 4-IBAP (peak at ~6.6 min), ranging from 47.1 to 49.7% in bulk drug (see Figure 5a) and from 79.9 to 81.1% in drug product among three replicate samples (see Figure 5b). Degradant peaks were not present in dark control samples of bulk drug and tablets. Degradation of IBP and formation of 4-IBAP in tablet extracts were higher in drug product than in bulk drug. This difference indicates that one or more of the excipients may have acted as a photosensitizer (indirect photolysis), thus facilitating a higher amount of IBP degradation (see Figure 5b) in tablet extract preparations. Peak resolution of >2.5 indicated noninterference of peaks with the IBP peak, thereby demonstrating the specificity of the method. Purity of the IBP peak in bulk-drug and tablet extract samples was 100% (peak-purity factor of 1000), confirming the absence of peaks coeluting with IBP. The major degradation product in bulk drug, 4-IBAP, had peak-purity factors in replicate samples from 999 to 1000. However, resolution of the 4-IBAP peak (RT = 6.5 min), with peak at 6.2 min, ranged from 1.3 to 1.5 for the drug substance and tablet extract solutions, respectively. Resolution of the peak at 7.0 min with 4-IBAP ranged from 2.3 to 2.4. Peak-purity factors for peaks at 6.2 and 7.0 min ranged from 999 to 1000, indicating the absence of any coeluting peaks with these components in the case of bulk drug. However, for tablet preparations, peak purity ranged from 865 to 954 for 4-IBAP, indicating possible coelution or interference. The peak preceding the 4-IBAP peak (unknown) had peak-purity factors of 999, 917, and 999 for three replicates, respectively, and the peak succeeding it (BPPA) had a peak-purity fac-

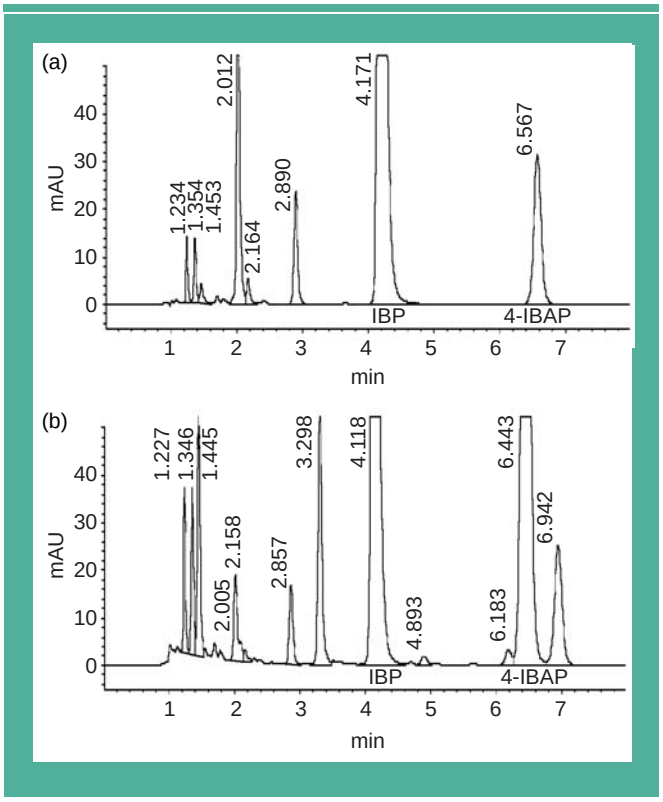

Figure 6: (a) Degradation of IBP in 36-month stability tablet extracts for nonstressed samples. (b) Degradation of IBP in 36-month stability tablet extracts in sunlight stress.

tor of 1000. The specificity and selectivity of the method for quantitation of 4-IBAP could not be demonstrated conclusively on the basis of the results for sunlight stress.

Degradation profiles of 36-month 27 °C stability samples. The peaks observed in 36-month stability samples before sunlight exposure had the following RTs in minutes: 1.2 and 1.4 (unknowns), 1.5 (FPPA), 2.0 (MPPA), 2.2 (EPPA), 2.9 (unknown), and 6.6 (4-IBAP). MPPA was the largest degradant by area percent quantitation, ranging from 9.0 to 10.4% among the three replicate samples. 4-IBAP was the second largest and ranged from 6.76 to 10.4%, followed by a peak at 2.9 min (unknown), which ranged from 3.73 to 4.27%. Other degradants were <2% individually in any replicate. IBP ranged from 71.5 to 76.7% among the three replicates. Peak resolution was >2.5, indicating noninterference of peaks with the IBP peak. Resolution of the 4-IBAP peak was >2.5, with the preceding peak, IBP. Purity of the IBP peak in all samples was 100% (a peak-purity factor of 1000), confirming the absence of peaks coeluting with IBP. 4-IBAP had a peak-purity factor of 1000. The 36-month stability sample showed that the USP IBP assay method is selective and specific for the quantitation of IBP and 4-IBAP and that the method is stability indicating (see Table II, Figure 6a).

Degradation profiles of sunlight-stressed 36-month 27 °C stability samples. Three replicates of 36-month stability samples were exposed to 72 h of sunlight to accomplish further degradation and to provide an assessment of the stability-indicating power of the method. Seven degradants were observed after exposure to sunlight and had the following RTs in minutes: 1.2 and 1.4 (unknowns), 1.5 (FPPA), 2.0 (MPPA), 2.2 (EPPA), 2.9 (unknown), 3.3 (PPPA), 4.9 (unknown), 6.4 (4-IBAP), and 6.9 (BPPA). The peaks at 3.3 min (PPPA, 5.0–5.1%), 4.9 min (unknown, 0.21–0.24%), and 6.9 min (BPPA, 4.35–4.75%) were the major new peaks resulting from sunlight exposure of the 36-month stability samples. The MPPA peak declined significantly (from 9.0–10.4% in three replicates of unexposed samples to 1.4–1.6% with light exposure). The IBP peak (RT = 4.1 min) declined nearly 50% (from 71.5–76.7% in unexposed samples to 34.9–38.3% in exposed samples). The peak at 2.9 min declined nearly 50% (from 3.7–4.3% in unexposed samples to 1.5–1.7 in exposed samples). The FPPA peak increased nearly 10-fold (from 0.30–0.37% in unexposed samples to 2.9–3.2% in exposed samples). The 4-IBAP peak increased nearly fourfold (from 6.8–10.4% in unexposed samples to 42.1–44.8 in exposed replicate samples). Thus, the sunlight-exposed samples showed not only a decline of degradation peaks but also the formation of new degradation peaks (see Figure 6b), which fully challenges the stability-indicating nature of the method. Peak resolution was >2.5, indicating noninterference of peaks with the IBP peak. Resolution of the 4-IBAP peak was 2.4, with its succeding peak, BPPA. Purity of the IBP peak in all samples was 100% (peak-purity factor of 1000), confirming the absence of peaks coeluting with IBP (see Figure 7). 4-IBAP had a peak-purity factor of 1000 (see Figure 8). The peak-purity factor for BPPA peak (RT = 6.9 min) was 1000. Although the resolution of 2.4 between 4-IBAP and BPPA was slightly below the targeted resolution of 2.5, the fact that both peaks had very high purity established their noninterference with each other as well as a lack of any coeluting peaks. These results conclusively demonstrated the selectivity and specificity and the stability-indicating nature of the method (see Table I, Figures 6–8).

Summary and conclusion

This forced-degradation study with IBP bulk-drug and tablet assay preparations has shown that IBP degraded under acid, oxidation, temperature, and light stresses. The specificity and selectivity of the method with samples under these stresses was demonstrated through the evaluation of RT, RRT, resolution, and purity data for all peaks in the chromatograms that exceeded 0.1%. IBP bulk drug did not degrade with acid stress, although MPPA and 4-IBAP were formed in drug product with acid stress. Degradation of IBP was not extensive, and few degradation products were present in samples with temperature and oxidation stresses. Base stress was not evaluated because of extensive precipitation in the samples.

Extensive degradation of IBP in both bulk-drug and tablet preparations was observed with light cabinet and sunlight stresses, resulting in the formation of as many as 10 degradation products. Degradation also was prominent in 36-month stability samples with as many as seven degradation products. Degradation products that formed under temperature and oxidation stresses also were found in light-stress and 36-month stability samples. Sunlight-exposed 36-month stability samples showed an additional three degradation products compared with nonstressed samples and also contained all major degradation products that were present in sunlight-stressed bulk-drug and tablet preparations. The degradation products that formed under any of the stresses that were studied showed no

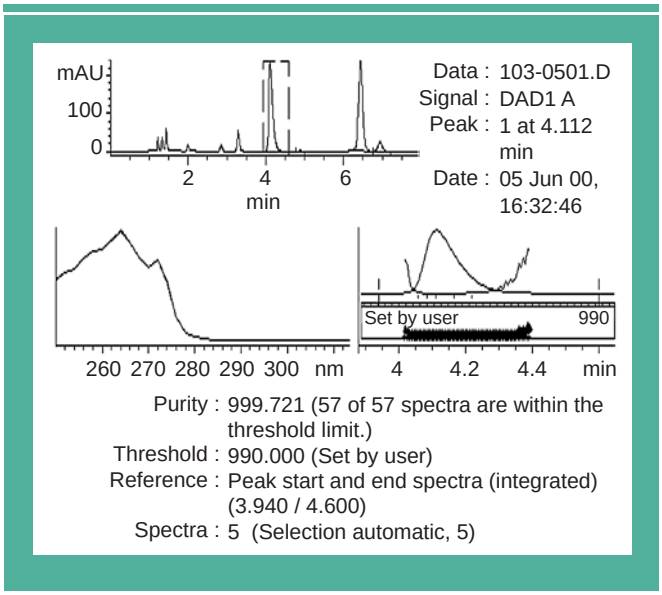

Figure 7: Photodiode array peak-purity profiles of 36-month stability samples exposed to light stress — IBP peak.

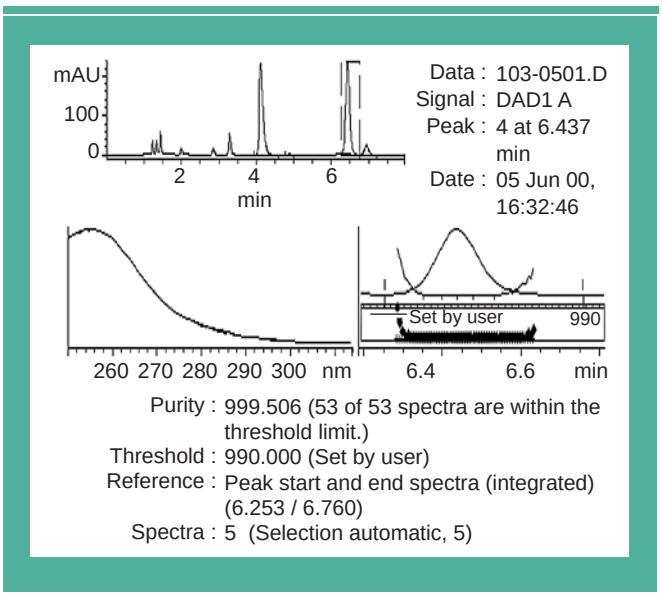

Figure 8: Photodiode array peak-purity profiles of 36-month stability samples exposed to light stress — 4-IBAP peak.

interference with the quantitation of IBP peaks as shown by peak-resolution and peak-purity data.

As recognized by the International Conference on Harmonization (ICH), decomposition products may be observed under forced-degradation conditions that are unlikely to be formed under accelerated or long-term stability testing (1). Furthermore, the ICH guidance states that although this information may be useful in developing and validating suitable analytical methods, examining specifically for all degradation products may not always be necessary if it has been demonstrated that these products are not formed in practice (1). The 36-month stability samples (stored at 27 °C) provided a worst-case example because they were tested 12 months past the 24-month expiration date for a marketed product. Exposure of these samples to sunlight stress further amplified degradation with the formation of two additional degradation products. In both nonstressed and sunlight-exposed 36-month samples, the peak-resolution and peak-purity data adequately demonstrated the specificity and selectivity of the method for the quantitation of IBP and the quantitation of 4-IBAP at its limit. The results presented here, therefore, demonstrate the stability-indicating nature of the IBP assay method and justify its use for quantitation of IBP content and limit of 4-IBAP in stability samples under both normal and accelerated storage conditions.

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