

Photosensitivity of Internal Standard Valerophenone

Used in USP Ibuprofen Bulk Drug and Tablet Assay and Its Effect on the Quantitation of Ibuprofen and Its Impurities

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The results of forced degradation studies indicate the need for alternatives to the use of valerophenone as an internal standard calibration for quantifying ibuprofen in bulk drug and tablet assay samples.

In the ibuprofen (IBP) bulk drug (1) and tablet (2) assay methods (high-performance liquid chromatography [HPLC]) of the *United States Pharmacopeia* (USP), valerophenone (ISTD) is used in standard solutions for system-suitability determination and as an internal standard for the quantitation of ibuprofen in bulk drug and tablets. ISTD is prepared in a solution of 1% chloroacetic acid (pH 3.0 ± 0.05):acetonitrile (40:60). This ISTD solution is used as an extraction solvent for IBP tablets (tablet assay preparation) and for IBP bulk drug substances (bulk drug assay preparation) as well as for the preparation of system-suitability standard solutions. The HPLC mobile phase for this method is 1% chloroacetic acid (pH 3.0 ± 0.05):acetonitrile (40:60). The peak response ratios of IBP and 4-isobutylacetophenone (4-IBAP) to ISTD are factored in the quantitation of IBP and 4-IBAP in bulk drug and tablet assay samples. ISTD has been found to be sensitive to light during use in standard solutions and assay preparations in the laboratory (unprotected use), and has been shown to degrade extensively in samples exposed to light stress during the forced degradation studies (3). In this study, we examined the degradation of ISTD under different light sources in various solutions used in the ibuprofen assay methods (*i.e.*, system-suitability standard solution, extraction solution, and assay preparations of bulk drug and tablets) to assess the stability of ISTD and its potential effect on the quantitation of IBP and the limit of 4-IBAP in bulk drug and tablets.

Materials and methods

ISTD. ISTD is 1-phenyl-1-pentanone (CAS number 1009-14-9) with a molecular formula of $C_{11}H_{14}O$ ($C_6H_5CO(CH_2)_3CH_3$), and molecular weight of 162.231. It is a colorless to yellow liquid with a melting point ranging from 105 to 107 °C and a flash point of 103 °C.

Reference standards and drug source. The IBP active material was obtained from BASF (Bishop, TX). The 4-IBAP was obtained from TCI America (Portland, OR). ISTD was obtained from Sigma-Aldrich (Steinheim, Germany).

4-IBAP standard stock solution. The 4-IBAP standard stock solution was prepared in acetonitrile (ACN) at a concentration of 0.6 mg/mL and stored in the refrigerator.

ISTD/extraction solution. The ISTD/extraction solution was

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Table 1: Degradation of valerophenone (ISTD) in system-suitability standard solution under various sources of light.*

Time of exposure	ISTD	IBP	4-IBAP	Degradant		
				1 (2.0 min)	2 (2.2 min)	3 (3.3 min)
Light cabinet						
0 h	44.1	51.4	4.2	ND	ND	ND
2 h	43.3	51.8	4.1	ND	0.8	ND
4 h	42.4	51.8	4.2	ND	1.6	ND
10 h	39.3	51.9	4.2	0.3	4.3	ND
1 d	35.0	51.4	4.4	0.2	8.4	ND
2 d	26.8	52.8	4.7	0.4	15.2	ND
5 d	11.0	54.8	5.5	1.0	26.5	0.7
6 d	7.3	55.3	6.0	1.5	29.0	0.7
8 d	3.0	55.3	6.8	2.2	31.5	0.8
Sunlight						
0 h	44.5	51.4	4.1	ND	ND	ND
0.5 h	27.9	53.0	4.4	0.4	14.3	ND
1 h	14.9	55.0	4.6	0.5	24.3	ND
1.5 h	8.1	56.2	4.8	1.1	29.2	0.5
2 h	3.5	56.8	5.0	1.9	32.2	0.5
2.5 h	2.4	57.0	5.1	2.1	32.8	0.5
Laboratory light						
0 h	44.3	51.4	4.2	ND	ND	ND
1 week	44.2	51.4	4.2	ND	0.2	ND
2 weeks	44.1	51.4	4.2	ND	0.2	ND
3 weeks	44.0	51.5	4.2	ND	0.3	ND
4 weeks	44.0	51.4	4.2	ND	0.4	ND
Laboratory window light						
0 h	44.5	51.3	4.2	ND	ND	ND
1 d	41.9	51.4	4.3	ND	2.4	ND
2 d	40.2	51.4	4.3	ND	4.0	ND
5 d	35.1	52.0	4.7	ND	9.3	ND
6 d	33.2	52.2	4.7	ND	9.8	ND
8 d	28.1	52.3	5.1	0.2	13.8	0.4

* Components are expressed as a % of total peak area. ND indicates not detected.

prepared by adding 3.5 mL of ISTD (1.0 g/mL) to 4000 mL of ACN, mixing well, followed by the addition of 2000 mL of ACN and 4000 mL of 1% chloroacetic acid (pH 3.0 ± 0.05) and mixing well again (ACN:1% chloroacetic acid (60:40)). The ISTD/extraction solution was stored at room temperature.

System-suitability standard solution. Two mL of 4-IBAP standard stock solution was added to a 100-mL volumetric flask containing 1.2000 g of IBP active material qualified as a secondary standard (equivalency factor [Ke] of 1.005) by a USP IBP reference standard. The contents were diluted to a volume with extraction solution. The system-suitability determinations were made using this standard mixture (IBP, 4-IBAP, and ISTD), which was prepared fresh daily and in duplicate.

IBP tablet assay solutions. Expired lots of IBP 800 mg dosage strength were used to evaluate the effects of light on degradation of ISTD in tablet assay samples. An appropriate number of tablets were transferred to the extraction solvent containing

ISTD in a 1000-mL volumetric flask and diluted to a volume for a nominal concentration of ~12 mg of IBP/mL (2). Samples were extracted after 1 h using a wrist-action shaker (4).

IBP 800 mg with placebo in extraction solution. Excipients and IBP active material corresponding to an 800-mg tablet formulation were added to the extraction solution in amounts such that excipient and active concentrations in the extraction solution were similar to the concentrations in an 800-mg tablet assay preparation, as described above.

IBP active assay solutions. IBP active material was added to the extraction solution in an amount such that the concentration in the extraction solution was similar to the IBP concentration in the 800-mg tablet assay preparation described above.

Preparation of mobile phase. A 1% chloroacetic acid solution was prepared by dissolving 40 g of chloroacetic acid in 4000 mL of water. The pH was then adjusted with ammonium hydroxide to 3.0 ± 0.05 and filtered. The 1% chloroacetic acid solution and ACN were degassed in the HPLC system using an Agilent 1050 vacuum degasser (Agilent, Palo Alto, CA) and were mixed on line during HPLC analysis, in the ratio of 40:60, respectively.

HPLC equipment and conditions. An analysis of samples was performed by HPLC (Agilent) using a detector wavelength of 254 nm. The column, 4.6 mm × 25 cm, contained packing material L1. The column temperature was maintained at 40 °C. The flow rate was 2 mL/min. The Agilent “Chemstation” software was used to integrate and analyze HPLC peak responses for quantitation of the peaks by area percent as well as to evaluate system-suitability parameters.

Quantitation of ISTD and its degradates. Quantitation of ISTD and its degradates was performed by Agilent Chemstation software by integrating areas of each peak (peak response) and dividing the individual peak area in the chromatogram by the total peak area and expressing the amount of each peak as a percent of total peak area. Peaks greater than 0.1% were quantified and reported.

Conditions of light exposure and measured light intensities for each condition. Light intensities under various exposure conditions were measured twice, once at the beginning of the study

Table II: Degradation of valerophenone (ISTD) in extraction solution under various sources of light.*

Time of exposure	ISTD	Degradant		
		1 (2.0 min)	2 (2.2 min)	3 (3.3 min)
Light cabinet				
0 h	100.0	ND	ND	ND
2 h	98.6	ND	1.4	ND
4 h	97.0	ND	3.0	ND
10 h	92.1	0.6	7.3	ND
1 d	86.2	0.8	13.0	ND
2 d	69.7	0.9	29.9	ND
3 d	50.5	0.7	47.2	0.9
6 d	13.5	4.5	80.4	1.5
7 d	8.0	5.7	84.6	1.6
9 d	2.5	7.7	88.1	1.7
Sunlight				
0 h	100.0	ND	ND	ND
0.5 h	68.7	0.4	30.8	ND
1 h	44.5	0.9	53.5	0.8
1.5 h	27.3	2.2	69.1	1.1
2 h	12.2	4.3	82.3	1.3
2.5 h	6.1	5.7	86.8	1.4
3 h	3.3	6.6	88.7	1.5
Laboratory light				
0 h	100.0	ND	ND	ND
2 h	100.0	ND	ND	ND
4 h	100.0	ND	ND	ND
15 h	100.0	ND	ND	ND
48 h	100.0	ND	ND	ND
2 weeks	99.5	ND	0.5	ND
3 weeks	99.2	ND	0.8	ND
4 weeks	99.0	ND	1.0	ND
Laboratory window light				
0 h	100.0	ND	0	ND
1 d	94.0	ND	6.0	ND
2 d	89.7	ND	9.7	ND
5 d	80.1	ND	19.5	ND
6 d	77.0	ND	22.9	ND
8 d	66.4	ND	32.6	0.6

* Components are expressed as a % of total peak area. ND indicates not detected.

Table III: IBP active spiked into extraction solution containing ISTD, under various sources of light.*

Time of exposure	ISTD	IBP	Degradant		
			1 (2.0 min)	2 (2.2 min)	3 (3.3 min)
Light cabinet					
0 h	46.7	53.3	ND	ND	ND
3 d	16.9	56.2	0.6	24.6	0.6
Sunlight					
0 h	46.8	53.2	ND	ND	ND
2.5 h	ND	57.8	3.6	35.0	0.8
Laboratory light					
0 h	46.8	53.2	ND	ND	ND
4 weeks	46.5	53.1	ND	0.4	ND

* Components are expressed as a % of total peak area. ND indicates not detected.

Table IV: ISTD in tablet extracts, under various sources of light.*

Time of exposure	ISTD	IBP	Degradant		
			1 (2.0 min)	2 (2.2 min)	3 (3.3 min)
Light cabinet					
0 h	46.9	53.1	ND	ND	ND
9 d	18.4	56.2	0.6	23.5	0.5
Sunlight					
0 h	46.8	53.2	ND	ND	ND
3 h	4.3	58.9	1.9	33.8	0.6
Laboratory light					
0 h	46.9	53.1	ND	ND	ND
4 weeks	46.6	53.1	ND	0.3	ND
Laboratory window light					
0 h	46.8	53.2	ND	ND	ND
8 d	36.3	54.1	ND	9.4	ND

* Components are expressed as a % of total peak area. ND indicates not detected.

and again at the end of the study. A range was reported for each condition. The following equipment and conditions were used:

- Light cabinet containing fluorescent incandescent lighting in the range of 5705 to 6523 lux, with a temperature of ~30 °C (designated intensified light).
- Samples were placed in an open area outside the laboratory building. Sunlight varied considerably during the day depending on the position of the sun and the shading at certain times of the day because of shrubs nearby or clouds. Intensity, which was measured when the sunlight was bright on the samples, ranged from 80,729 to 95,799 lux. Temperature was not controlled.

- Samples were placed near glass windows inside the laboratory and the light intensity at this location ranged from 5382 to 5050 lux. Temperatures ranged from 23 to 26 °C.
- Light intensity in the laboratory (where all reagents and standard solutions were prepared and samples were extracted and analyzed by HPLC) ranged from 560 to 732 lux. Temperatures ranged from 23 to 25 °C.

System-suitability acceptance criteria. System-suitability tests were performed with each sample run sequence and the following acceptance criteria were established for the sample results in the run to be considered acceptable: The relative retention times should be ~0.75 for IBP, ~1.0 for ISTD, and ~1.2 for 4-IBAP. The tailing factor for an individual peak should not be >2.5. The resolution (R) among the IBP, ISTD, and 4-IBAP peaks is not <2.5. The relative standard deviation for 5 replicate standard injections should not be >2.0%.

Figure 1: Representative chromatograms of degradation of valerophenone (ISTD) in system-suitability solutions.

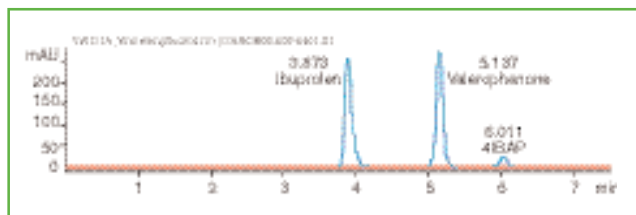


Figure 1a: Dark control sample showing IBP, ISTD, and 4-IBAP peaks in the chromatogram without any degradation for 4 weeks.

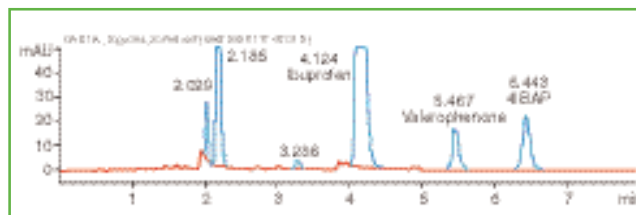


Figure 1b: Degradation in samples exposed to sunlight for 2.5 h.

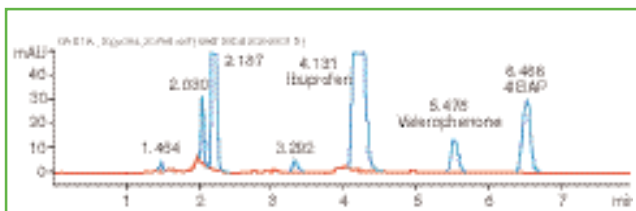


Figure 1c: Degradation in samples exposed to light in a light cabinet for 8 d.

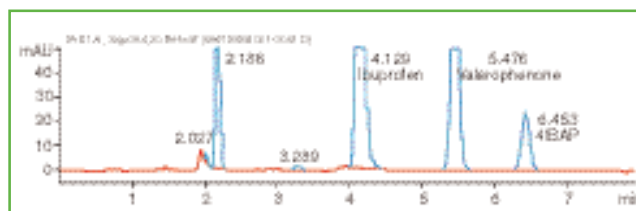


Figure 1d: Degradation in samples exposed to laboratory window light for 8 d.

Degradation of ISTD during storage in various types of solutions as applicable to the IBP bulk drug and tablet assay. The following solutions were examined after a specific time period for each type of light stress:

- ISTD in extraction solution (light cabinet, sunlight, laboratory light, and laboratory window light)
- ISTD in system-suitability standard solution (light cabinet, sunlight, laboratory light, and laboratory window light)
- ISTD with IBP bulk drug in extraction solution (light cabinet, sunlight, and laboratory light)
- ISTD in extraction solution with tablets (light cabinet, sunlight, laboratory light, and laboratory window light)
- ISTD in extraction solution with tablets in which IBP has degraded (light cabinet, sunlight, and laboratory light)
- ISTD in extraction solution with excipients (light cabinet, sunlight, and laboratory light)

Degradation products of ISTD from light stresses and their interference with IBP and 4-IBAP peaks. The retention times and the peak area percents of various components in the chromatogram were determined for each sample. On the basis of the retention times of known impurities of IBP, an assessment was made of the potential interference between ISTD and IBP degradation products.

Effect of degradation of ISTD on the quantitation of IBP and limit of 4-IBAP using the USP IBP assay method. The effect of degradation of ISTD on the quantitation of IBP and 4-IBAP was evaluated by estimating IBP and 4-IBAP amounts with and without ISTD degradation.

Evaluation of containers and closures for ISTD storage in the laboratory. System-suitability solutions with ISTD in both amber and clear glass bottles and screw caps were exposed to light in light cabinets for the evaluation of container closure effects. Peak area % of ISTD determined from the chromatograms of ISTD solutions in clear glass vials and amber vials were compared.

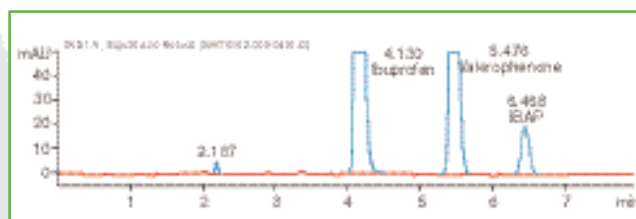


Figure 1e: Degradation in samples exposed to laboratory light for 4 weeks.

Results

System-suitability acceptance criteria were met for all run sequences, validating the results generated during the study. Results for degradation of ISTD in system-suitability standard solution are presented in Table I and Figures 1 and 2. In system-suitability solutions, ISTD degraded very rapidly under sunlight with ~95% of the ISTD degraded after 2.5 h of sunlight exposure. In a light cabinet, 11% ISTD degradation occurred after 10 h of exposure, while in laboratory window light, the degradation was ~37% after 8 days of exposure. Under laboratory light, an ~0.7% decrease in ISTD concentration was noted after 4 weeks. The dark control of system-suitability solution did not show any degradation after 4 weeks.

Results for the degradation of ISTD in extraction solution are presented in Table II and Figure 3. ISTD in extraction solution degraded very rapidly in sunlight with 97% degradation occurring after 3 h of sunlight exposure. In a light cabinet, ISTD degraded more slowly than in sunlight, with ~97% degradation after 9 days of exposure to this stress. Under laboratory window light conditions, ~34% of the ISTD degraded after 8 days, whereas under laboratory light conditions, ~1% of ISTD degraded after 4 weeks.

Results for degradation of ISTD with IBP bulk drug in extraction solution are presented in Table III. ISTD in extraction solution containing IBP degraded rapidly under sunlight, with

Figure 2: Representative chromatograms of degradation of ISTD in extract solution.

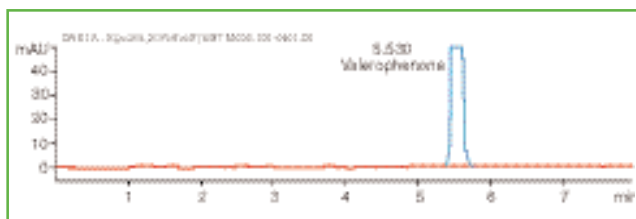


Figure 2a: Dark control sample showing ISTD in the chromatogram without any degradation for 4 weeks.

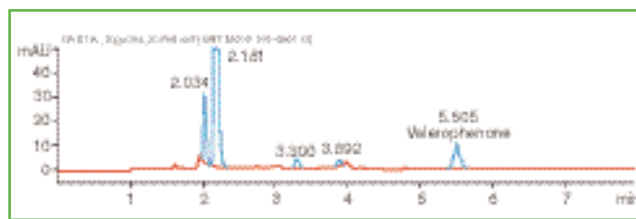


Figure 2b: Degradation in samples exposed to sunlight for 2 h.

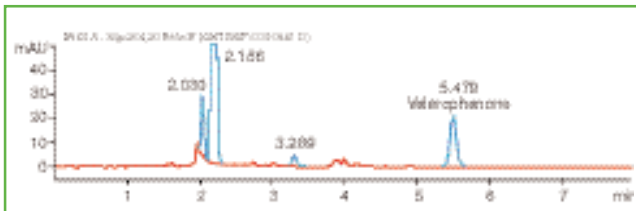


Figure 2c: Degradation in samples exposed to light in a light cabinet for 7 d.

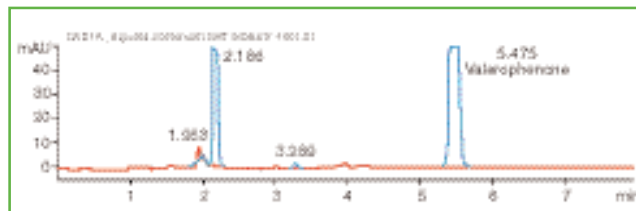


Figure 2d: Degradation in samples exposed to laboratory window light for 8 d.

no ISTD remaining after 2.5 h. Extensive degradation was also observed in a light cabinet with ISTD decreasing from 46.7% of peak area to 16.9% in 3 d. Degradation was ~0.6% under laboratory light conditions.

Results for degradation of ISTD in tablet assay preparation are presented in Table IV and Figure 3. ISTD in tablet extracts degraded in sunlight with 91% of the initial ISTD degraded after 3 h of sunlight exposure. In a light cabinet, ISTD degraded more slowly than in sunlight with ~61% of the initial ISTD degraded after 9 days of exposure to this stress and 4% after 10 h. Under laboratory window light conditions, ~22% of the ISTD degraded after 8 days, while under laboratory conditions ~0.6% of the ISTD degraded after 4 weeks.

For comparison, results of ISTD photodegradation in clear and amber glass vials are shown in Table V. In system-suitability solutions in which ISTD, IBP, and 4-IBAP were present, ~11% of the ISTD degraded when stored in clear glass vials and exposed to 10 h of light in a light cabinet. However, no degradation of ISTD was noted when amber vials were used, as shown in Table V. These results suggest that the amber vials offer ISTD suitable protection from light.

Discussion

ISTD degraded extensively under sunlight, and to a smaller degree under intensified light conditions and laboratory window light. Degradation of ISTD was noted in a system-suitability solution or IBP standard solution, in tablet preparations, and in IBP active solutions

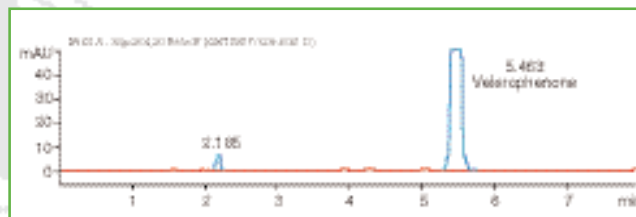


Figure 2e: Degradation in samples exposed to laboratory light for 4 weeks.

under intensified, sunlight, and laboratory window light conditions. The major degradation product of the ISTD was a peak at 2.2 min in all the test solutions and under all light sources (Tables I–IV), and this peak accounted for most of ISTD degradation. Other minor degradation peaks had retention times of

Table V: Stability of valerophenone (ISTD) in system suitability standard solution stored in clear glass vials versus amber vials, under various source of light.*

Time of exposure	ISTD	IBP	4-IBAP	Degradant		
				1 (2.0 min)	2 (2.2 min)	3 (3.3 min)
Light cabinet—clear glass vials						
0 h	44.1	51.4	4.2	ND	ND	ND
2 h	43.3	51.8	4.1	ND	0.8	ND
4 h	42.4	51.8	4.2	ND	1.6	ND
10 h	39.3	51.9	4.2	0.3	4.3	ND
Light cabinet—amber glass vials						
0 h	44.1	51.4	4.2	ND	ND	ND
2 h	44.1	51.7	4.2	ND	ND	ND
4 h	44.1	51.7	4.2	ND	ND	ND
10 h	44.1	51.7	4.2	ND	ND	ND

* Components are expressed as a % of total peak area. ND indicates not detected.

Figure 3: Representative chromatograms of degradation of valerophenone in tablet extract solutions.

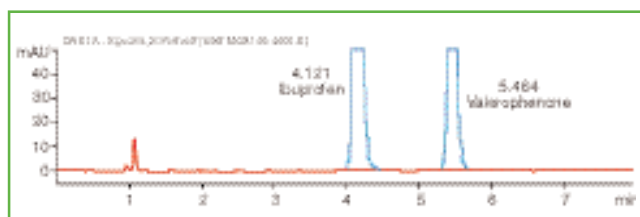


Figure 3a: Dark control sample showing IBP and peaks in the chromatogram without any degradation for 4 weeks.

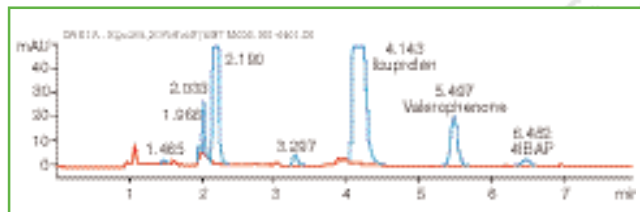


Figure 3b: Degradation in samples exposed to sunlight for 2 h.

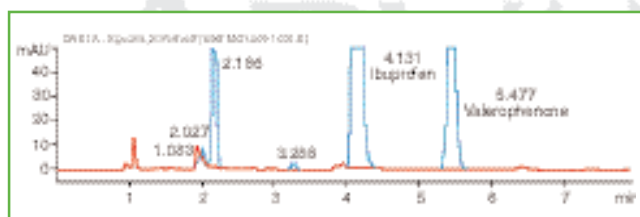


Figure 3c: Degradation in samples exposed to light in a light cabinet for 7 days.

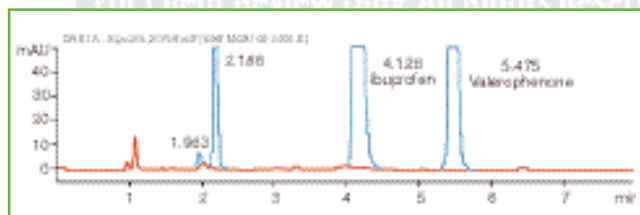


Figure 3d: Degradation in samples exposed to laboratory window light for 8 days.

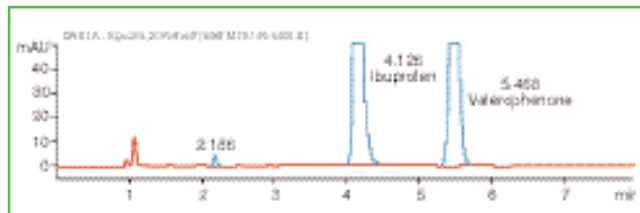


Figure 3e: Degradation in samples exposed to laboratory light for 4 weeks.

2.0 and 3.3 min. For example, in extraction solvent under sunlight where ~3% of ISTD was left after 3 h of exposure, ~89% of the degradation product was a peak at 2.2 min, ~6.6% was a peak at 2.0 min, and ~1.5% was a peak at 3.3 min (Table II). The degradation profile varied with light intensity. However, ISTD degradation in various light sources and solutions con-

sistently resulted in one or more of these degradation products (Tables I–IV).

The retention times of degradation products of ISTD formed under light stress matched closely with those of known IBP impurity/degradation product standards (3). For example, the ISTD degradation product peak with a retention time of 2.0 min matched that of an IBP impurity/degradant (retention time of ~2.0 min). Other impurities/degradation products of IBP, with retention times of ~2.1 and 3.3 min, are in close proximity to the other two degradation products of ISTD at ~2.3 and 3.3 min, respectively. These data suggest potential interference of ISTD degradation product peaks with major impurity/degradant peaks of IBP, resulting in overestimation of degradation products formed from IBP, even with a minimal amount of ISTD degradation. This finding raises questions about the suitability of using ISTD in USP IBP bulk drug and tablet assay methods.

Although very little degradation of ISTD was noticed under our laboratory light conditions, its degradation under laboratory window light raises questions about its use in current laboratory designs where daylight is used to complement laboratory electric lighting, and also raises questions about samples held for longer than 24 h in the laboratory. Retention of samples for out-of-specification investigations may also result in a compromised result. Ratios of the IBP and 4-IBAP peak areas with the ISTD peak area were taken into consideration for the quantitation of IBP in product release and stability samples. A decrease in the peak area of ISTD as a result of degradation because of its sensitivity to light will have an effect on the quantitation results for IBP and 4-IBAP in a proportional manner. Thus, a 5% degradation in the peak area of ISTD may reflect a 5% increase in IBP or 4-IBAP content in production or stability samples, thus raising questions about the integrity of the assay results. Similarly, other degradation products formed by ISTD may wrongly be assumed to be the degradation products of IBP.

Conclusions

Valerophenone (ISTD), used in system-suitability solutions and as the internal standard in USP ibuprofen (IBP) bulk drug and tablet assay methods, degraded under various light sources, with the degradation increasing with the intensity of light source. Degradation of ISTD under sunlight was extensive with approximately >90% degradation after ~3 h in all the solutions used in the USP IBP assay method, thus demonstrating the high susceptibility of ISTD to light exposure. Degradation of ISTD observed under laboratory window light and laboratory light conditions raises practical concerns regarding its use in the USP IBP bulk drug and tablet assays. The major degradation product of ISTD with a retention time of 2.2 min and two other minor degradation products (2.0 and 3.3 min) closely matched the retention times of known IBP impurities/degradation products. Because the ISTD peak response in standards and samples is used for the quantitation of IBP peak in the current USP IBP bulk drug and tablet assay methods, minor degradation of ISTD in system-suitability standard or assay solutions could have a significant effect on the IBP and 4-IBAP

quantitation results in release and stability samples. These results demonstrate light sensitivity of ISTD and the interference of its degradation products with IBP impurities/degradation products, which indicates that ISTD standard solutions, IBP assay preparations, and system-suitability solutions (where ISTD is present) should be protected from any light exposure. As shown above, sufficient precautions must be taken such as using amber glassware or other containers to protect ISTD. However, IBP tablet extraction procedures require 200- and 500-mL volumetric flasks. In a production quality control laboratory where a large number of samples are processed every day, the purchase of amber-colored volumetric flasks may be prohibitively expensive. An alternative is to consider eliminating the use of ISTD in the USP IBP assay method for bulk drug and tablets. Quantitation of IBP can be accomplished by comparing the peak area of the target peak in assay samples with that of its reference standard (an external standard method). The USP General Chapter, "Chromatography: High Pressure Liquid Chromatography," states "Reliable quantitative results are obtained by external calibration if automatic injectors or autosamplers are used" (5). An IBP assay method without ISTD has been developed and validated, an account of which was presented at the 2002 American Association of Pharmaceutical Scientists annual meeting (6).

References

1. "Ibuprofen," *USP 25-NF 20*, (US Pharmacopeial Convention, Rockville, MD, 2002), pp. 884–885.
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