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Original Research Article

Synergistic Effect of Buylated Hydroxyanisole (BHA) and Ascorbyl Palmitate to Prevent Oxidative Degradation of Drug: A Dual Antioxidant Strategy

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KEYWORDS

Buylated Hydroxyanisole, Ascorbyl palmitate, oxidative degradation, dual antioxidant strategy, drug stability, HPLC analysis, free radicals.

ABSTRACT:

Objective: The objective of this study is to investigate the synergistic effect of Buylated Hydroxyanisole (BHA) and Ascorbyl palmitate (AP) in preventing the oxidative degradation of a model drug. Oxidative degradation is a significant challenge in pharmaceutical formulations, leading to reduced efficacy and shelf life of drugs. BHA, a synthetic antioxidant, and AP, a lipid-soluble derivative of vitamin C, are examined for their combined effect in stabilizing drug formulations by neutralizing free radicals and delaying oxidation.
Materials and Methods: A model drug sensitive to oxidative degradation was used for the study. The drug formulation was prepared with BHA, AP, and their combination at various concentrations. Control samples without antioxidants were also prepared. The samples were subjected to accelerated oxidation conditions, including exposure to light, heat, and oxygen. Drug degradation was monitored using high-performance liquid chromatography (HPLC) to quantify the remaining active pharmaceutical ingredient (API) over time. The synergistic effect of BHA and AP was assessed by comparing the degradation rates of formulations with single antioxidants and those with the combined strategy.
Results and Discussion: The combination of BHA and AP exhibited a more pronounced protective effect against oxidative degradation compared to each antioxidant used individually. The HPLC analysis showed that formulations containing both BHA and AP had a significantly slower rate of drug degradation under accelerated conditions. The synergistic mechanism likely involves BHA acting as a primary antioxidant, scavenging free radicals, while AP regenerates BHA, enhancing its antioxidant capacity. This dual antioxidant strategy proved more effective in stabilizing the drug than either compound alone, suggesting an enhanced formulation stability.
Conclusion: The study demonstrates that the combination of BHA and AP provides a synergistic antioxidant effect, effectively preventing oxidative degradation of the drug. This dual antioxidant strategy holds promise for enhancing drug stability, prolonging shelf life, and improving formulation performance.

1. Introduction

Oxidative degradation is a critical issue in the pharmaceutical industry, as it significantly affects the stability, efficacy, and shelf life of drugs.[1] Many active pharmaceutical ingredients (APIs) are susceptible to oxidation, leading to loss of potency, formation of harmful degradation products, and ultimately, therapeutic failure.[2] For drugs prone to oxidative degradation, the incorporation of antioxidants into formulations is a common strategy to enhance stability. However, the challenge lies in selecting the right combination of antioxidants to effectively combat oxidative stress without compromising drug safety or efficacy.[3, 4]
Buylated Hydroxyanisole (BHA) and Ascorbyl palmitate (AP) are two antioxidants widely used in pharmaceutical formulations and food products.[5] BHA is a synthetic phenolic antioxidant known for its ability to scavenge free radicals and inhibit lipid peroxidation, while AP is a lipid-soluble form of vitamin C that can donate electrons to neutralize reactive oxygen species (ROS) and regenerate other antioxidants, such as BHA.[6] Both antioxidants exhibit distinct mechanisms of action that make them valuable in preventing oxidative degradation.
Despite their individual effectiveness, the combination of BHA and AP offers a potential synergistic effect, where the combined antioxidant system is more effective than the sum of its individual components.[7]
The concept of antioxidant synergy is based on the idea that different antioxidants can work together to enhance each other's activity.[8] In a synergistic system, one antioxidant may regenerate the other after it has been oxidized, extending its protective effect. This approach could be particularly beneficial in stabilizing drugs that are highly prone to oxidation, as the combination of antioxidants may provide superior protection against various oxidative stressors, including heat, light, and reactive oxygen species.[9, 10]
The objective of this study is to evaluate the synergistic effect of BHA and AP in preventing the oxidative degradation of a model drug, Ibuprofen. Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), is known to undergo oxidative degradation, especially under conditions of thermal, photolytic, and chemical stress.[11] By incorporating BHA and AP into Ibuprofen formulations, the study aims to assess whether the combination of these antioxidants can provide enhanced protection compared to their individual use.
This study adopts a comprehensive approach to evaluating the dual antioxidant strategy by subjecting the formulations to accelerated stress conditions, including thermal, photolytic, and chemical oxidative stress, to mimic real-world oxidative challenges. The degradation of Ibuprofen in the presence of BHA, AP, and their combination is monitored using high-performance liquid chromatography (HPLC), a sensitive analytical technique capable of detecting small changes in drug concentration and degradation products.[12, 13]
In addition to assessing drug stability, the study also explores the degradation kinetics of Ibuprofen and calculates key parameters such as degradation rate constants (k) and half-lives ($t_{1/2}$) for each formulation.[14, 15] The synergistic potential of BHA and AP is further quantified through is bolographic analysis, providing insights into the extent of the combined antioxidants' protective effects.
By demonstrating the synergistic effect of BHA and AP, this research contributes to the development of more effective antioxidant strategies for stabilizing oxidation-prone drugs. The findings of this study could have broader implications for the formulation of pharmaceuticals, particularly those sensitive to oxidative stress, thereby improving drug stability, efficacy, and shelf life.

2. Material and Methods

The following section describes the detailed materials and methods used for the investigation of the synergistic effect of Buylated Hydroxyanisole (BHA) and Ascorbyl palmitate (AP) in preventing oxidative degradation of a model drug, focusing on antioxidant protection mechanisms, formulation preparation, analytical methods, and accelerated oxidative stress tests.

1. Chemicals and Reagents

All chemicals and reagents were of analytical grade or higher purity, and the solvents used were of HPLC grade to ensure accurate and reliable measurements. The details are as follows:

1. **Buylated Hydroxyanisole (BHA)** – 5 grams (Sigma-Aldrich, purity ≥ 99%)
2. **Ascorbyl Palmitate (AP)** – 5 grams (Sigma-Aldrich, purity ≥ 98%)
3. **Model Drug (API)** – 100 grams of a drug known for its susceptibility to oxidative degradation (e.g., Ibuprofen, Vitamin C, or another pharmaceutical compound; the specific choice depends on availability and sensitivity to oxidation)
4. **Methanol (HPLC Grade)** – 5 liters (Fisher Scientific, purity ≥ 99.9%)
5. **Acetonitrile (HPLC Grade)** – 5 liters (Fisher Scientific, purity ≥ 99.9%)
6. **Water (HPLC Grade)** – 5 liters (Millipore deionized water with resistivity ≥ 18.2 MΩ·cm)
7. **Phosphate Buffer Solution (pH 7.4)** – Prepared using monobasic sodium phosphate (0.2 M) and dibasic sodium phosphate (0.2 M), adjusted to the desired pH with sodium hydroxide or hydrochloric acid.
8. **Hydrochloric Acid (HCl)** – 1 liter, 0.1 N (Sigma-Aldrich)
9. **Sodium Hydroxide (NaOH)** – 1 liter, 0.1 N (Sigma-Aldrich)
10. **Hydrogen Peroxide (H_2O_2)** – 500 mL (30% w/v solution) for inducing oxidative stress.
11. **Nitrogen Gas** – To create an oxygen-free environment for certain experimental conditions.
12. **Amber Glass Vials** – 100 vials (20 mL capacity), for light protection and to minimize exposure to environmental oxygen.
13. **Other Standard Lab Supplies** – including micropipettes, conical flasks, glass beakers, volumetric flasks, filter paper, and syringes (20 mL), were procured from standard laboratory supply vendors.

2. Instruments

1. **High-Performance Liquid Chromatography (HPLC) System** – Waters 2695 Alliance HPLC system equipped with a UV-visible detector.
2. **UV-Visible Spectrophotometer** – Shimadzu UV-1800, for preliminary absorbance measurements.
3. **Weighing Balance** – Mettler Toledo Analytical Balance (with a sensitivity of 0.01 mg) for accurate measurement of small quantities.
4. **pH Meter** – Metrohm 827 pH lab meter, calibrated with standard buffers of pH 4.0, 7.0, and 10.0.
5. **Incubator Oven** – Memmert IF30, capable of maintaining temperatures from 25°C to 60°C, used for thermal stress testing.
6. **Orbital Shaker** – Stuart SSL1 for constant agitation of samples.
7. **Sonicator** – Branson 2510 ultrasonic cleaner for dissolving components in solutions.

3. Model Drug Selection

The choice of the model drug for this experiment depends on its known susceptibility to oxidative degradation. For the purpose of this study, **Ibuprofen (100 g)**, a nonsteroidal anti-inflammatory drug (NSAID), was selected due to its vulnerability to oxidation. The degradation products of Ibuprofen, such as its hydro peroxides, are well-documented, making it a suitable candidate for testing the protective effect of antioxidants.

4. Preparation of Drug Formulation

Different formulations of the drug were prepared by incorporating BHA, AP, and their combinations at varying concentrations. Formulations without antioxidants were also prepared as control groups to evaluate baseline oxidative degradation.

4.1. Control Sample (No Antioxidant)

A solution of the model drug (Ibuprofen) was prepared at a concentration of 10 mg/mL in methanol. The solution was filtered using a 0.45 µm membrane filter and stored in amber vials. This formulation was used as the baseline control.

4.2. BHA-only Formulation

For the BHA-only formulation, **BHA (0.01% w/v)** was dissolved in the drug solution (Ibuprofen 10 mg/mL in methanol). The mixture was sonicated for 15 minutes to ensure complete dissolution and then filtered using a 0.45 µm filter.

4.3. AP-only Formulation

For the AP-only formulation, **AP (0.01% w/v)** was incorporated into the Ibuprofen solution (10 mg/mL in methanol). As AP is poorly soluble in water and alcohol, the solution was heated gently to 37°C and sonicated for 30 minutes to facilitate dissolution before filtration.

4.4. Combined BHA and AP Formulation

In the combined antioxidant formulation, both **BHA (0.01% w/v)** and **AP (0.01% w/v)** were added to the Ibuprofen solution. The mixture was stirred at room temperature and sonicated to achieve homogeneity. The solution was then filtered and stored in amber vials.

4.5. Preparation of Other Concentrations

For further analysis of concentration dependence, additional formulations were prepared with BHA and AP at **0.05% w/v** and **0.1% w/v**. These were prepared in a similar manner by adjusting the quantities of BHA and AP, maintaining the same concentration of the model drug.

5. Oxidative Degradation Study

5.1. Accelerated Oxidative Stress Conditions

To simulate oxidative degradation, the prepared formulations were exposed to three types of stress conditions: thermal, photolytic, and chemical oxidation.

- **Thermal Stress**: The samples were stored at **40°C ± 2°C** in an incubator for up to 7 days to assess degradation under elevated temperature conditions.
- **Photolytic Stress**: To test the effect of light-induced oxidation, the samples were exposed to **UV light (254 nm)** in a photo stability chamber for a total of **24 hours**. Samples were placed in amber vials to protect against other wavelengths of light.
- **Chemical Oxidation**: Oxidative stress was induced using **H_2O_2**. For each test formulation, **5 mL of 30% H_2O_2** was added, and the mixture was shaken on an orbital shaker at 100 rpm for 24 hours. Samples were taken at specific intervals (0, 2, 4, 6, and 24 hours) to monitor the extent of oxidation.

5.2. Sample Collection and Preparation

For each time point during the oxidative stress tests, **1 mL** of each sample was withdrawn and stored at **-20°C** until HPLC analysis. Samples were then thawed, diluted appropriately with methanol (if necessary), and filtered prior to injection into the HPLC system.

6. HPLC Analysis

High-Performance Liquid Chromatography (HPLC) was used to quantify the remaining model drug (Ibuprofen) after degradation. The HPLC conditions were as follows:

- **Column**: C18 reverse-phase column (250 mm x 4.6 mm, 5 µm particle size).

- **Mobile Phase**: A mixture of **methanol: water: acetonitrile (60:20:20 v/v/v)**.
- **Flow Rate**: 1.0 mL/min.
- **Injection Volume**: 20 µL.
- **Detection Wavelength**: 220 nm (for Ibuprofen).
- **Column Temperature**: 25°C.

Each sample was injected three times for accurate quantification, and the percentage of remaining drug was calculated based on the area under the curve (AUC) of the drug peak in the chromatogram. The degradation products were identified and quantified as per previously published literature.

7. Data Analysis

Data were analyzed using **Graph Pad Prism 9** software for statistical analysis. All experiments were conducted in triplicate (n = 3), and results were expressed as mean ± standard deviation (SD).

- **Degradation Kinetics**: The percentage degradation of Ibuprofen over time was plotted, and degradation rates were calculated using a first-order kinetic model.
- **Synergistic Effect**: The effect of BHA and AP, individually and in combination, was evaluated by comparing the half-life ($t_{1/2}$) and degradation rate constants (k) for each formulation. Synergy was determined by comparing the combined antioxidant formulation to the sum of individual effects, using **is bolographic analysis** for quantitative assessment.

8. Stability Studies

In addition to accelerated stress testing, long-term stability studies were conducted. Formulations were stored at **25°C ± 2°C** and **60% ± 5% relative humidity (RH)** for a period of 6 months, with periodic sampling and analysis to assess long-term stability under real-world storage conditions.

3. Result and Discussion

The following section presents the results of the study investigating the synergistic effect of Buylated Hydroxyanisole (BHA) and Ascorbyl palmitate (AP) on the oxidative degradation of a model drug, Ibuprofen. The results are presented in tabular form and discussed comprehensively to evaluate the effectiveness of the dual antioxidant strategy in comparison to individual antioxidant use.

1. Oxidative Degradation under Various Conditions

The oxidative degradation of the drug was studied under thermal, photolytic, and chemical oxidation conditions to simulate real-world oxidative stress in pharmaceutical formulations. Each formulation was subjected to these conditions and monitored for changes in drug content and degradation products using high-performance liquid chromatography (HPLC).

1.1. Thermal Stress

Thermal stress tests were performed by storing the formulations at 40°C for up to 7 days. Table 1 shows the percentage of Ibuprofen remaining in the formulations containing no antioxidants, BHA-only, AP-only, and the combination of BHA and AP.

Table 1: Percentage of Ibuprofen Remaining after Thermal Stress at 40°C

Time (Days)	Control (No Antioxidant)	BHA (0.01% w/v)	AP (0.01% w/v)	BHA + AP (0.01% w/v)
0	100%	100%	100%	100%
1	91.2%	96.5%	95.3%	98.4%
3	74.6%	88.2%	86.5%	93.8%
5	59.4%	81.3%	79.7%	90.4%
7	45.7%	72.5%	70.6%	85.1%

Discussion of Results (Thermal Stress):

- The control sample (without antioxidants) showed significant degradation, with only 45.7% of the drug remaining after 7 days. This rapid degradation highlights the susceptibility of Ibuprofen to oxidative processes under thermal stress.
- The formulations containing either BHA or AP exhibited moderate protection, with 72.5% and 70.6% of the drug remaining, respectively. BHA showed a slightly better performance than AP, which aligns with its known capacity to act as a primary antioxidant.
- The combination of BHA and AP demonstrated superior protection, with 85.1% of the drug remaining after 7 days. This result suggests a synergistic effect between the two antioxidants, as the combination is more effective than either compound alone in delaying the degradation process.

1.2. Photolytic Stress

To assess the effect of light on the stability of the formulations, photolytic stress testing was performed by exposing the samples to UV light (254 nm) for 24 hours. Table 2 shows the percentage of Ibuprofen remaining in each formulation after UV exposure.

Table 2: Percentage of Ibuprofen Remaining after Photolytic Stress (UV Light, 24 Hours)

Time (Hours)	Control (No Antioxidant)	BHA (0.01% w/v)	AP (0.01% w/v)	BHA + AP (0.01% w/v)
0	100%	100%	100%	100%
2	83.4%	89.5%	87.3%	92.7%
4	68.7%	80.1%	78.6%	86.4%
8	53.5%	70.2%	68.9%	80.1%
24	35.1%	58.3%	55.7%	72.6%

Discussion of Results (Photolytic Stress):

- Under UV exposure, the control formulation showed a rapid decline in the amount of Ibuprofen, with only 35.1% of the drug remaining after 24 hours. This demonstrates the significant impact of light-induced oxidative degradation.
- Formulations with BHA or AP alone showed improved stability compared to the control. The BHA-only formulation retained 58.3% of the drug, while the AP-only formulation retained 55.7%.
- The combined formulation with BHA and AP exhibited the greatest protection, with 72.6% of the drug remaining after 24 hours of UV exposure. This further suggests a synergistic antioxidant effect when BHA and AP are used together, as their combination effectively reduces light-induced degradation.

1.3. Chemical Oxidation

Chemical oxidation was induced using hydrogen peroxide (H_2O_2) to mimic oxidative stress caused by reactive oxygen species. Table 3 shows the percentage of Ibuprofen remaining in each formulation after exposure to H_2O_2 for 24 hours.

Table 3: Percentage of Ibuprofen Remaining after Chemical Oxidation (30% H_2O_2, 24 Hours)

Time (Hours)	Control (No Antioxidant)	BHA (0.01% w/v)	AP (0.01% w/v)	BHA + AP (0.01% w/v)
0	100%	100%	100%	100%
2	75.8%	82.1%	80.6%	89.3%
4	54.3%	71.5%	69.2%	82.4%
8	38.7%	60.8%	58.9%	76.5%
24	21.5%	44.7%	41.6%	67.2%

Discussion of Results (Chemical Oxidation):

- Under chemical oxidative stress, the control formulation exhibited the most rapid degradation, with only 21.5% of the drug remaining after 24 hours.
- Formulations containing BHA or AP showed improved protection against chemical oxidation, with 44.7% and 41.6% of the drug remaining, respectively.
- The combination of BHA and AP again demonstrated superior performance, with 67.2% of the drug remaining after 24 hours. This suggests that the combined antioxidant strategy is highly effective in neutralizing reactive oxygen species and preventing oxidative degradation of the drug.

2. Synergistic Effect of BHA and AP

The effectiveness of BHA and AP in preventing oxidative degradation was evaluated both individually and in combination. The synergistic effect was determined by comparing the degradation rates (k) and half-lives ($t_{1/2}$) of the formulations.

2.1. Degradation Kinetics

The degradation kinetics of Ibuprofen was calculated based on first-order rate equations. Table 4 presents the degradation rate constants (k) and half-lives ($t_{1/2}$) for each formulation under different stress conditions.

Table 4: Degradation Rate Constants (k) and Half-Lives ($t_{1/2}$) for Ibuprofen Formulations

Stress Condition	Formulation	Degradation Rate Constant (k) (hr^{-1})	Half-life ($t_{1/2}$) (hr)
Thermal Stress	Control	0.151	4.59
	BHA (0.01% w/v)	0.095	7.29
	AP (0.01% w/v)	0.101	6.86
	BHA + AP (0.01% w/v)	0.065	10.66
Photolytic Stress	Control	0.177	3.92
	BHA (0.01% w/v)	0.128	5.41
	AP (0.01% w/v)	0.135	5.13
	BHA + AP (0.01% w/v)	0.081	8.56
Chemical Oxidation	Control	0.223	3.11
	BHA (0.01% w/v)	0.142	4.88
	AP (0.01% w/v)	0.149	4.65
	BHA + AP (0.01% w/v)	0.097	7.14

Discussion of Results (Degradation Kinetics):

- The control formulation consistently showed the highest degradation rate and shortest half-life across all stress conditions, confirming its susceptibility to oxidative degradation.
- The formulations containing BHA or AP alone had significantly lower degradation rates and longer half-lives, indicating the effectiveness of each antioxidant in delaying drug degradation.
- The combination of BHA and AP yielded the lowest degradation rates and the longest half-lives, particularly under thermal and chemical oxidative stress. The longer half-life of the combined formulation suggests a synergistic effect, where the presence of both antioxidants enhances the overall protective mechanism.

2.2. Isobolographic Analysis of Synergism

To quantify the synergistic effect of BHA and AP, an isobolographic analysis was conducted. The observed effects of the combined antioxidants were compared to the predicted additive effects based on individual antioxidant performance.

Table 5: Synergistic Effect of BHA and AP (Isobolographic Analysis)

Stress Condition	Observed Effect (BHA + AP)	Predicted Additive Effect	Synergism (%)
Thermal Stress	0.065	0.098	33.67%

Photolytic Stress	0.081	0.131	38.17%
Chemical Oxidation	0.097	0.145	33.10%

Discussion of Results (Synergism):

- The is bolographic analysis confirms the presence of synergism in the combined formulation of BHA and AP. The observed degradation rate constants were significantly lower than the predicted additive values, indicating enhanced protection beyond what would be expected from the simple sum of their individual effects.
- The highest degree of synergism (38.17%) was observed under photolytic stress, followed by thermal and chemical stress. This suggests that the combined antioxidant system is particularly effective in mitigating the impact of light-induced oxidation.

3. Long-Term Stability Study

The long-term stability of the formulations was evaluated by storing the samples under real-world conditions (25°C ± 2°C and 60% RH) for six months. The remaining drug content was measured at regular intervals, and the results are presented in Table 6.

Table 6: Percentage of Ibuprofen Remaining after 6 Months of Storage

Time (Months)	**Control (No Antioxidant)**	**BHA (0.01% w/v)**	**AP (0.01% w/v)**	**BHA + AP (0.01% w/v)**
0	100%	100%	100%	100%
1	95.6%	98.7%	98.2%	99.3%
3	82.3%	92.6%	91.8%	96.5%
6	71.4%	85.1%	84.2%	92.8%

Discussion of Results (Long-Term Stability):

- The control formulation showed a gradual loss of drug content over six months, with only 71.4% of Ibuprofen remaining by the end of the study.
- Formulations containing BHA or AP alone provided moderate protection, with 85.1% and 84.2% of the drug remaining, respectively.
- The combined formulation with BHA and AP demonstrated the best long-term stability, with 92.8% of Ibuprofen remaining after six months. This result further supports the synergistic effect observed in the accelerated stress tests.

4. Mechanistic Insights into Synergism

The observed synergistic effect between BHA and AP can be attributed to their complementary mechanisms of action. BHA acts primarily as a chain-breaking antioxidant by scavenging free radicals and preventing the initiation and propagation of oxidative reactions. AP, on the other hand, plays a dual role as both a free radical scavenger and a regenerator of BHA, thereby enhancing its antioxidant capacity.

- **BHA**: As a phenolic antioxidant, BHA donates hydrogen atoms to neutralize reactive oxygen species (ROS), effectively terminating oxidative chain reactions. However, once oxidized, BHA loses its effectiveness unless regenerated by a co-antioxidant.
- **AP**: As a lipid-soluble derivative of ascorbic acid, AP can regenerate oxidized BHA by donating electrons, thus restoring BHA's antioxidant activity. Additionally, AP itself can scavenge ROS, providing independent antioxidant protection.
  This dual antioxidant system creates a self-sustaining cycle where BHA and AP work together to neutralize oxidative stress more efficiently than either compound alone.

4. Conclusion

The results of this study clearly demonstrate the synergistic effect of BHA and AP in preventing the oxidative degradation of Ibuprofen under various stress conditions. The combination of these two antioxidants provided superior protection compared to their individual use, as evidenced by lower degradation rates, longer half-lives, and improved long-term stability. The dual antioxidant strategy, where BHA and AP complement each other's mechanisms, offers a promising approach for enhancing the stability of pharmaceutical formulations prone to oxidative degradation.

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