Original Research Article

Stability Evaluation of Acetylsalicylic Acid in Commercial Aspirin Tablets Under Different Storage Conditions

ABSTRACT

This study evaluated the stability of acetylsalicylic acid (ASA) in commercial Aspirin Protect 100 mg tablets under eight different storage conditions, including varying exposure to moisture, light, and temperature, with a focus on tablets stored in dosette boxes. Acid-base titration methods were used to assess ASA degradation and stability. Elevated moisture had the greatest impact on ASA stability, significantly reducing recovery factors to 85.38% and 81.10% under high humidity, while temperature influenced ASA stability, with notable deviations from control values at temperatures above 25°C (13.26% and 7.16% for two methods). Although storage at 18–25°C yielded acceptable results, reduced temperatures (<8°C) provided better stability. Direct sunlight exposure caused further degradation, reducing recovery values to as low as 82.5% and increasing deviations from control (-10.82% to -16.77%). Hydrolysis, exacerbated by environmental factors, was identified as the primary degradation pathway, leading to the formation of salicylic acid and acetic acid. Samples stored in under recommended conditions had the best stability, with recovery factors meeting pharmacopoeia standards (101.08% and 99.16% of labelled content). These findings underscore the importance of proper storage practices for ASA tablets to maintain their quality, safety, and therapeutic efficacy. While repackaging tablets into dosette boxes may improve compliance, it can compromise stability, highlighting the need for stricter storage guidelines to ensure optimal patient outcomes.

Keywords: acetylsalicylic acid, acid-base titration, dossete boxes, drugs' quality and stability, patient adherence and compliance

1. INTRODUCTION

Acetylsalicylic acid (ASA) is an active pharmaceutical ingredient (API) in Aspirin tablets, also known by its IUPAC name as 2-acetoxybenzoic acid. It is an organic molecule with carboxyl (-COOH) and acetyl ester (-OCOCH3) groups attached to the aromatic benzene ring. Organoleptic properties include its colour and appearance as white crystalline powder or crystals, with a sour taste and characteristic slightly vinegar-like odour. While remains stable in dry conditions, exposure to increased humidity rapidly induces hydrolysis, decomposing the molecule into two acids, salicylic and acetic (Fig. 1). The forced ASA degradation study performed by Kowalska et al. (2022) and Urich et al. (2023) confirmed that acetylsalicylic acid can be decomposed to salicylic acid when under the influence of high temperature, acidic, alkaline, oxidative, and hydrolytic conditions.

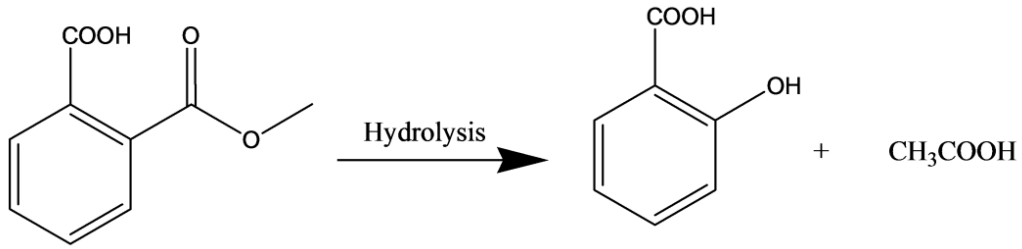

Fig. 1. The hydrolysis of ASA into salicylic acid and acetic acid

Synthesized in the late 19th century, this weak acid become widely used as a painkiller and, by the mid-20th century, became the most popular analgesic in the world, according to the Guinness World Records (Kosinski et al. 2018). Today, Aspirin is well-known not only for its analgesic, but also for its anti-inflammatory, antipyretic, and antiplatelet properties. In fact, by the end of 20th century, researchers discovered that low doses of this medication can reduce the risks of heart attacks and strokes. Inhibition of platelet cyclooxygenase (COX)-1 activity followed by inhibition of thromboxane (Tx) A2 generation and platelet aggregation is the basis of its antiplatelet effect (Gurbel et al. 2024). Additionally, recent studies have shown the wide range of possibilities ASA use in serious diseases prevention with significantly reduction in the incidence of various cancers, including colorectal, oesophagus, stomach, and breast cancers (Qiao et al. 2018; Bosetti et al. 2020; Schreinemachers et al. 1994; Thorat and Cuzick, 2013).

Due to its widespread use, maintaining the high quality, safety, and effectiveness of aspirin is crucial—from manufacturing though drug supply chain to consumption. Many patients store medications in dosette boxes (pill organizers), to keep track of their use. These organizers are convenient for medication adherence and are often kept in visible locations, such as shelves, tables, bags, bathroom cabinets, or refrigerators (Conn et al. 2015; Mylrea et al. 2012). However, storing medications as described may expose them to moisture, light, and temperature fluctuations, potentially compromising their quality and efficacy.

Storage conditions play a critical role in ensuring stability of pharmaceutical products. Improper storage can degrade the API, affecting the drug's efficacy, safety and therapeutic outcomes (Ansari, 2017).To preserve the integrity of pharmaceutical products, it is essential to perform qualitative/quantitative analyzes of APIs under various environmental conditions, ensuring that active compounds remain stable and effective until the product's expiration date.

A variety of analytical techniques are used to evaluate the impact of external conditions on drug quality. While modern analytical techniques with advanced instrumentation are indispensable for drug quality control, traditional methods retain their importance, particularly in resource-limited settings. Traditional techniques, such as acid-base titration, are cost-effective and require minimal resources compared to sophisticated instrumentation. Acid-base titration is widely employed for the precise quantitative analysis of ASA, verifying the aspirin content in pharmaceutical formulations and ensuring product quality and efficacy.

This study aimed to evaluate the effects of different storage conditions—including moisture, different temperatures, and light exposure—on the stability of acetylsalicylic acid tablets stored in dosette boxes. The study utilized simple acid-base titration methods to assess any degradation and quantify the stability of the tablets under varying conditions.

2. MATERIAL AND METHODS

2.1. Materials

Ethanol (C_2H_5OH) (Sigma Aldrich, USA), sodium hydroxide (NaOH) (Sigma Aldrich, USA), phenolphthalein indicator (Sigma Aldrich, USA), Aspirin Protect 100 mg tablets (Bayer, Germany), hydrochloric acid (HCl) (Sigma Aldrich, USA), chloroform (CH_3Cl) (Sigma Aldrich, USA), and distilled water were used in the study.

2.2. Instruments and Equipment

An analytical balance AX120 (Shimadzu), a magnetic stirrer, a Sonorex ultrasonic bath (Bandelin electronic Gmbh & Co. KG), standard laboratory titration equipment, and a distillation water still (GFL Gesellschaft Fuer Labortec) were employed.

2.3. Samples and storage conditions

A total of 320 Aspirin tablet samples were divided into four groups to monitor the impact of temperature, humidity, and light on drug quality (Table 1). The control sample (U8) was stored according to the manufacturer's recommendation (in the medication's external and internal packaging, protected from moisture and sunlight, at room temperature). All samples were exposed to different storage conditions for 30 days.

Table 1. Storage conditions of the Aspirin tablet samples

Parameter		Storage location	Sample ID
Temperature	>25°C	Kitchen (near oven)	U1

	18-25°C	Bedroom (nightstand)	U2
	<8°C	Kitchen (refrigerator)	U3
Humidity	increased	Bathroom (cabinet)	U4
	moderate	Bedroom (night stand)	U5
Light	direct sunlight	Living room	U6
	darkness	Bedroom (night stand)	U7
Under recommended storage conditions		Original pharmaceutical package	U8

2.4. Acid-Base Titrations

Acid-base titrations are used for the quantitative analysis of pharmacodynamically active substances that, due to their chemical nature, act as acids or bases. These titrations are performed by dissolving the analyte (acid or base) and the titrant (base or acid) in water or non-aqueous solvent. Slightly modified pharmacopeial procedures for the acid-base titration of acetylsalicylic acid (ASA), adapted to suit the specific needs of the study (USP, 2006; EDQM, 2024.). Two independent titration methods were applied, as described in the following sections.

Each titration method was repeated three times per sample, and the results are expressed as mean ± SD. The results obtained under various experimental storage conditions were compared to those from samples stored under the recommended conditions. The content of the API in the Aspirin tablets was calculated relative to the labelled content and expressed as a percentage, as shown in Equation (1).

$$\text{recovery factor}\ (\%) = \frac{\text{practical ASA content}}{\text{labeled ASA content}} \cdot 100\% \qquad (1)$$

To evaluate the impact of different storage conditions, the deviation in API content was calculated by comparing the tested samples to the control sample stored under recommended conditions, as shown in Equation (2).

$$\text{deviation}\ (\%) = \frac{\text{sample ASA content} - \text{control ASA content}}{\text{control ASA content}} \cdot 100\% \qquad (2)$$

2.4.1. Titration with 0.5 M HCl solution

- Ten Aspirin Protect 100 mg tablets were weighed and ground finely using a mortar.
- The mass of powder equivalent to 500 mg of acetylsalicylic acid was weighed and dissolved in 10 mL ethanol (96%) in an Erlenmeyer flask with a glass stopper.
- 50 ml of 0.5 M NaOH solution was added. After one hour, the solution was titrated with 0.5 M HCl using 0.2 ml of phenolphthalein solution as an indicator.
- Meanwhile, a blank sample was prepared and titrated.
- The consumption of 1 mL of 0.5 M HCl corresponds to 45.04 mg of acetylsalicylic acid.

2.4.2. Titration with 0.5 M NaOH solution

- Ten tablets of Aspirin Protect 100 mg were ground in a mortar.
- The amount of tablet mass containing 150 mg of acetylsalicylic acid was weighed.
- To the weighed amount of acetylsalicylic acid, 10 ml of chloroform was added.
- The mixture was mixed for 5 minutes in an ultrasonic bath and filtered through filter paper to remove any undissolved particles.

- After filtration, 5 mL of distilled water and 5 drops of phenolphthalein indicator solution were added to the filtrate.
- Titration was performed with 0.1 M NaOH until a persistent pink colour appeared.
- The amount of 0.1 M NaOH used corresponds to the acetylsalicylic acid content.
- 1 mL of 0.1 M NaOH corresponds to 0.02212 g of acetylsalicylic acid.

3. RESULTS AND DISCUSSION

3.1. Temperature impact

The data obtained from the acid-base titration assays presented in Table 2 highlight the impact of temperature on the quantitative API content in Aspirin Protect 100 mg tablets. As shown in the Table 2, the largest deviations from the control values were observed when the tablets were exposed to temperatures above 25°C, with a 13.26% deviation for method I and 7.16% for method II. The recovery factor, which accounts for the labelled API content, was 114.40% and 106.27%, respectively.

Table 2. Impact of temperature on the quantitative content of ASA in Aspirin tablets

Sample ID	Temperature (°C)	ASA (mg) content ± SD[a]		Recovery factor (%)		Deviation (%)	
		Method I	Method II	Method I	Method II	Method I	Method II
U1	>25	572.00±0.02	159.40±0.12	114.40	106.27	13.26	7.16
U2	15-25	463.90±0.01	137.10±0.02	92.80	71.40	-8.15	-7.83
U3	<8	477.40±0.03	143.78±0.02	95.40	85.80	-5.47	-3.33
U8	15-25[b]	505.04±0.13	148.74±0.03	101.08	99.16	n/a[c]	

[a] n=3, SD – standard deviation
[b] Control sample stored under recommended storage conditions.
[c] n/a – not applicable

While it was expected that the best match with the control values of API content in aspirin tablets would be achieved when stored at a temperature of 18-25°C, it is noteworthy that even better results were obtained for reduced temperatures <8°C. This is probably due to the slowing down the hydrolysis rate of ASA at lower temperatures, as demonstrated by studies using variable-temperature kinetics (Alibrandi et al. 1996).This is further confirmed by the recovery factor results, which showed improved values for both methods at lower temperatures. The obtained results can be attributed to the possible influence of other factors, as the tablet samples were not stored in the original medication packaging but rather placed in dosage boxes. Additionally, Mamede et al. (2006) reported that API in Aspirin tablets can interact with excipients when exposed to different temperatures. Thermal analysis revealed differences in decomposition temperatures compared to pure ASA, suggesting possible impacts on its pharmacological activity and physicochemical properties. Proper storage conditions, including not only the temperature range but also factors such as light, humidity, microbiological purity, pressure, and ventilation, are essential to maintain the quality of pharmaceutical products (Shafaat et al. 2013; Ali et al. 2022).

To ensure the quality of pharmaceutical products, controlled storage and transit conditions are necessary, especially when changes in quantitative content or loss of potency may affect the efficacy and safety of medications. Temperature changes during the storage of ASA can significantly impact on its stability. Some et al. (2001) reported that ASA undergoes temperature-dependent hydrolysis, affecting its pharmacokinetics, stability and pharmacodynamic properties.Additionally, increased pressure at room temperature is a crucial factor, especially since polymorphic transformation of ASA can occur, leading to structural and physicochemical changes in the molecule (Ali et al. 2022).

3.2. Humidity impact

High humidity in storage conditions can significantly impact the stability and degradation of Aspirin tablets. Studies by Yamazaki et al. (2010; 2011) have demonstrated that when humidity exceeds 55%, the decomposition rates of Aspirin tablets increase, leading to colour changes. This not only affects the drug's quality but also reduces patient compliance.

Further research by Veronica et al. (2020; 2022; 2024) revealed that the choice of excipients in Aspirin tablet formulations can play a crucial role in how the drug holds up in high-humidity environments. Among the excipients studied, crospovidones and cellulose were found to significantly accelerate the degradation of Aspirin (Ougi et al. 2020; Höckerfelt and Alderborn, 2014). These findings emphasize the importance of understanding how humidity affects the stability of medications, especially when formulating moisture-sensitive drugs like aspirin and storing them properly.

In the present study, the results from both acid-base titration methods show negative deviations when compared to the control sample stored under recommended conditions (Table 3). Both samples (U4 and U5) were stored in dosette boxes, outside of their original packaging. When comparing samples exposed to normal versus increased humidity, it is evident that elevated humidity accelerates the deterioration of Aspirin tablets quality. The significant decrease in recovery factors for sample U5 (85.38% and 81.10%) under increased humidity conditions underscores Aspirin's sensitivity to moisture. Even when stored in normal humidity, the samples stored in dosette boxes exhibited recovery factors below the acceptable range (94.50% and 89.90%), indicating that the lack of original packaging still allowed some degradation. The ester functional group in the structure of acetylsalicylic acid is a key factor contributing to its instability, as esters are highly susceptible to hydrolysis under a variety of conditions, both in vivo and in vitro. When exposed to moisture, hydrolysis occurs, resulting in the release of salicylic acid and acetic acid (Fig. 1).

Table 3. Impact of humidity on the quantitative content of ASA in Aspirin tablets

Sample ID	Humidity	ASA (mg) content ± SD[a]		Recovery factor (%)		Deviation (%)	
		Method I	Method II	Method I	Method II	Method I	Method II
U4	Normal	472.90±0.01	134.90±0.11	94.50	89.90	-6.36	-9.30
U5	Increased	426.90±0.07	121.60±0.14	85.38	81.10	-15.47	-18.25
U8	Normal[b]	505.04±0.13	148.74±0.03	101.08	99.16	n/a[c]	

[a] n=3, SD – standard deviation
[b] Control sample stored under recommended storage conditions.
[c] n/a – not applicable

These results are similar to those reported by Mylrea et al. (2012) which suggest that Aspirin underwent partial hydrolysis to salicylic acid, likely due to improper storage conditions, such as removing the tablets from their original packaging and storing them in dosette boxes. This contributed to the observed deterioration in quality and recovery factors. However, the degradation of ASA not only compromises the quality of the drug but also results in the formation of degradation products that can exert significant toxicological effects Salicylic acid, formed by hydrolysis of ASA in the gut, is a proven teratogen in animals. Further, exposure to salicylic acid after ingestion has been associated with reproductive and developmental toxicity (Andersen, 2003).

3.3. Sunlight impact

In their study, Al-Maydama et al. (2018) treated Aspirin with gamma rays, UV rays, and direct sunlight at a temperature of 40°C with varying exposure times. Their results showed that ASA samples treated at 40°C under UV exposure for 12 hours exhibited the lowest thermal stability and activation energy. Similarly, Daescu et al. (2021) demonstrated that UV light can cause photodegradation of ASA in aqueous solution. They compared the hydrolysis reaction of ASA with or without excipients in a 0.3 M phosphate buffer solution at different pH values. Their findings indicated that pure ASA exhibited a gradual increase in the intensity of photoluminescence excitation spectra and a decrease in photoluminescence emission. In contrast, ASA with excipients exposed to UV light underwent a phototautomerization process, yielding different outcomes attributed to the presence of salicylic acid.

The results from the present study indicate that direct sunlight exposure influenced the stability and integrity of Aspirin tablets (Table 4). The observed decrease in recovery values (90.00% and 82.5%) and the increased negative deviation from the control (-10.82% and -16.77%) suggest that sunlight accelerates the degradation of ASA in the commercial tablets. The quantitative analysis of ASA in sunlight-exposed samples revealed notable changes (450.40±0.03 mg versus 500.00 mg labelled, and 123.80±0.04 versus 150.00 mg labelled), highlighting the influence of environmental factors, such as UV radiation. As previously noted the hydrolysis of ASA, potentially exacerbated by the heat and sunlight, may lead to the conversion of API into salicylic acid and acetic acid, thereby reducing the tablets' potency.

Table 4. Impact of sunlight on the quantitative content of ASA in Aspirin tablets

Sample ID	Light	ASA (mg) content ± SD[a]		Recovery factor (%)		Deviation (%)	
		Method I	Method II	Method I	Method II	Method I	Method II
U6	Direct sunlight	450.40±0.03	123.80±0.04	90.00	82.50	-10.82	-16.77
U7	Dark	486.40±0.07	137.10±0.01	97.20	91.40	-3.69	-7.83
U8	Dark[b]	505.04±0.13	148.74±0.03	101.08	99.16	n/a[c]	

[a] n=3, SD – standard deviation
[b] Control sample stored under recommended storage conditions.
[c] n/a – not applicable

Samples stored in a dark place and protected from UV radiation yielded results, particularly those analyzed using Method I, which complied with the pharmacopoeia requirement that ASA content should fall within 95 to 105% of the labelled amount. A review of the literature reveals a notable lack of studies addressing the impact of sunlight exposure on stability of ASA in pharmaceutical products. These findings underscore the need for further research to provide recommendations and guidelines for the storage and handling of ASA tablets to prevent degradation and ensure optimal patient outcomes.

4. CONCLUSION

While repackaging Aspirin Protect 100 mg tablets into dossete boxes can enhance medication adherence and patient compliance, it may also significantly impact their stability. ASA, being a hydrolysable molecule, shows reduced stability when exposed to varying environmental conditions in dossete boxes.

The study findings revealed that elevated moisture levels had the most significant effect on the stability and quantitative content of ASA, followed by light and temperature. Notably, the best recovery results (101.08% and 99.16%) were observed in samples stored under the manufacturer's recommended conditions. These results underscore the critical importance of proper storage practices for ASA tablets to maintain their quality, safety, and therapeutic efficacy, which are easily compromised under suboptimal conditions.

COMPETING INTERESTS DISCLAIMER:
Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

CONSENT AND ETHICAL APPROVAL

This study did not require approval from an ethics committee, as it did not involve direct participation of patients or their inclusion as subjects of investigation. The research was exclusively focused on analytical aspects. Consequently, obtaining written informed consent from patients or volunteers was not applicable.

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