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Effect of Formulation Matrix, Temperature, and Time on Formaldehyde Release from Formaldehyde-Releasing Preservatives

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Abstract

Formaldehyde is a chemical compound historically used for its antimicrobial and preservative properties. Due to its classification as a carcinogen and skin sensitizer, its use in cosmetics is restricted; however, formaldehyde-releasing preservatives are still permitted under specific conditions. The release of formaldehyde in cosmetic products may be influenced by factors such as temperature, storage time, and formulation matrix, raising potential safety and regulatory concerns. In this study, a full factorial design was applied to evaluate formaldehyde release in aqueous solutions at 40, 70, and 90 °C over 15, 30, and 60 min. In cosmetic matrices, temperatures of 40 and 70 °C were assessed at 0, 15, 30, and 60 min. Additionally, a three-month accelerated stability study was conducted to evaluate formaldehyde release over time in three different formulations. Formaldehyde release increased with both temperature and time in aqueous solutions, with diazolidinyl urea showing the highest levels, followed by DMDM hydantoin and imidazolidinyl urea. In cosmetic matrices, lower release levels were observed compared to aqueous systems; however, all formulations exceeded the 0.001% threshold established by European regulations. Under accelerated stability conditions, the emulsion exhibited the highest formaldehyde release, which may be associated with increased water availability promoting preservative hydrolysis. Overall, formaldehyde release was influenced by preservative structure, formulation matrix, temperature, and time. These findings highlight the importance of considering formulation composition and storage conditions in the evaluation of formaldehyde-releasing preservatives and may be relevant for safety assessment and regulatory compliance.

Keywords: formaldehyde release; cosmetic formulations; preservatives; stability; DMDM hydantoin; imidazolidinyl urea; diazolidinyl urea

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1. Introduction

Formaldehyde is a chemical compound that was widely used in the cosmetics industry for its antimicrobial properties and its strong preservative action. At room temperature, formaldehyde is a colorless gas with a pungent, suffocating odor [1–3]. At low levels, formaldehyde can cause eye and respiratory irritation. Low concentrations and prolonged

exposure are linked to the development of occupational asthma, while prolonged exposure to high concentrations can trigger bronchospasm attacks through an irritant mechanism in patients with bronchial hyperreactivity. Furthermore, aqueous formaldehyde solutions have been reported to have an irritant effect on the skin, which can lead to allergic contact dermatitis with prolonged exposure [4].

In the cosmetics industry, formaldehyde is not added directly to formulations because its use is restricted. This compound was classified as a carcinogen (category 1B) and a skin sensitizer (category 1) in Part 3 of Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) of the European Parliament. Furthermore, it is prohibited by the Cosmetics Regulation (EC) No 1223/2009 and is included in Annex II (List of Prohibited Substances in Cosmetic Products) [5]. Following this prohibition, the implementation of formaldehyde-releasing ingredients began. These preservatives, under certain conditions, decompose their chemical structures, releasing small amounts of formaldehyde [6,7]. Specifically, formaldehyde-releasing ingredients are defined as substances that release formaldehyde, either during their decomposition or synthesized from formaldehyde, and therefore may contain free formaldehyde residues [7]. Among the most used formaldehyde releasers are DMDM hydantoin, imidazolidinyl urea, diazolidinyl urea, and quaternium-15, among others [8,9].

Even though formaldehyde releasers are approved with permissible concentration limits as substances in cosmetic products, manufacturers must ensure that they are used within the established restrictions. On 8 July 2022, the European Commission published Regulation (EU) 2022/1181, which stipulates that whenever the total concentration of formaldehyde released in the final product exceeds 0.001% (10 ppm), regardless of whether the product contains one or more formaldehyde-releasing substances, the label must state "formaldehyde-releasing" [10]. In this respect, the use of these preservatives is essential to prevent the proliferation of microorganisms in cosmetic products; however, their use can present risks due to formaldehyde release, especially when products are subjected to temperature changes or prolonged storage [11].

The objective of this study was to evaluate formaldehyde release from three ingredients (DMDM hydantoin, imidazolidinyl urea, and diazolidinyl urea, Figure 1a, 1b and 1c, respectively), used as preservatives in cosmetics, as a function of the cosmetic matrix of the formulation, temperature, and time—variables that can influence the amount of formaldehyde released. To this end, the selected preservatives, prepared in aqueous solution and various cosmetic matrices, were subjected to different temperature and time conditions, which can occur during the manufacture of different cosmetic formulations, as well as during product storage throughout its shelf life or use. The quantification of released formaldehyde was performed using UV–Vis spectrophotometry, a sensitive analytical technique that allows for comparison of the results with the release limits permitted by current European Union regulations [12,13].

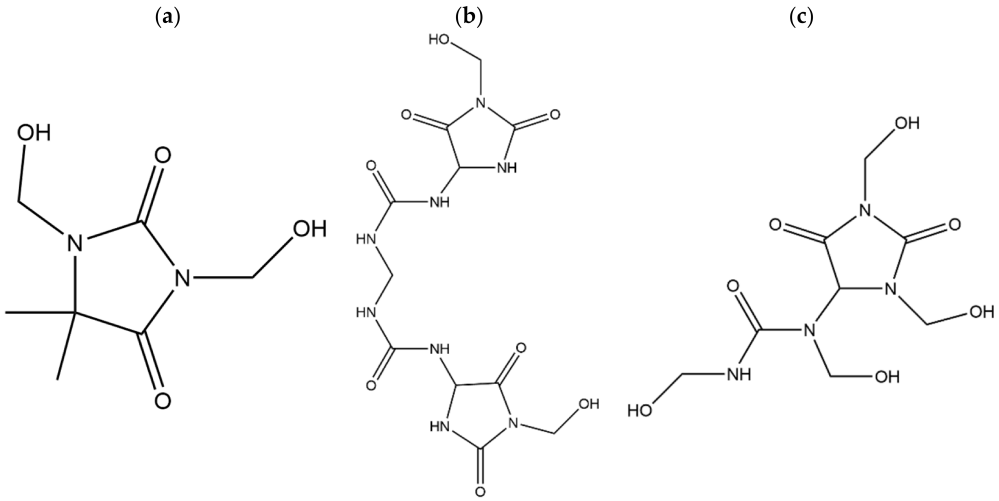


Figure 1. Structure of (**a**). DMDM Hydantoin (MW: 188.18 g/mol, LogP: −2.9, pKa (predicted): 13.41 ± 0.10), (**b**). Imidazolidinyl urea (MW: 388.29 g/mol, LogP = −3.4, pKa (predicted): 7.41 ± 0.10), (**c**). Diazolidinyl urea (MW: 278.22 g/mol, LogP: −2.5, pKa (predicted): 11.22 ± 0.46).

2. Materials and Methods

2.1. Reagents

Secondary standard grade certified reference material (CRM) formaldehyde was obtained from Sigma-Aldrich (St. Louis, MO, USA). Analytical grade acetic acid, sodium acetate and acetylacetone were obtained from Merck Chemical Supplies (Darmstadt, Germany). Raw material for cosmetic formulation DMDM hydantoin, imidazolidinyl urea, diazonidyl urea, lyophilized Aloe vera, and SepinovTM EM 10 (Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer), were donated by Prebel S.A. (Medellín, Colombia). Castor oil, polysorbate 80, sorbitol and propylene glycol were obtained from LyF chemicals (Medellín, Colombia).

2.2. Preparation of Nash Reagent (Acetylacetone Reagent)

In a 100 mL volumetric flask, 15 g of ammonium acetate were weighed, 0.3 mL of glacial acetic acid and 0.2 mL of acetylacetone were added, and the solution was brought to volume with deionized water [12,13].

2.3. Determination of Released Formaldehyde

Exactly 50 µL of 37% formaldehyde were transferred to a 100.0 mL volumetric flask, diluted to volume with deionized water, and homogenized. Then, from the calibration curve, aliquots of 0 µL, 25 µL, 100 µL, 200 µL, 300 µL, and 400 µL were taken from the stock solution and transferred to 25 mL volumetric flasks. A 5.0 mL volume of Nash reagent was added to each aliquot, the solution was homogenized, and the flasks were placed in a water bath for 10 min. After cooling for 5 min, the solution was diluted to volume with deionized water and homogenized. Each step was performed in triplicate [12,13].

2.4. Sample Treatment

To estimate the effect of temperature and time on each formaldehyde-releasing ingredient in aqueous solution, a full factorial design was used to evaluate three different temperatures (c.a 40, 70, and 90 °C), using an oil bath, at different sampling times of 15, 30, and 60 min.

For each of the three formaldehyde-releasing ingredients in solution, 100 mg of the ingredient was weighed and transferred to a 100 mL volumetric flask. Approximately 30 mL of water was added, and the mixture was shaken for one minute. For the solid

formaldehyde-releasing ingredients, 50 mL of deionized water was added, and the mixture was sonicated for 5 min before being diluted to volume. Then, a 500 µL aliquot was taken and transferred to a 25.0 mL volumetric flask. A 5.0 mL volume of Nash's reagent was added, the mixture was homogenized, and after 5 min, the flask was filled to the mark, and its absorbance was read at a wavelength of 412 nm. All measurements for each formaldehyde-releasing ingredient were performed in triplicate at time zero and at each time point described in Table 1.

Table 1. Full factorial design.

Preservative	Temperature °C	Time (min)
DMDM hydantoin	40 °C	15, 30, 60
	70 °C	15, 30, 60
	90 °C	15, 30, 60
Imidazolidinyl urea	40 °C	15, 30, 60
	70 °C	15, 30, 60
	90 °C	15, 30, 60
Diazonidyl urea	40 °C	15, 30, 60
	70 °C	15, 30, 60
	90 °C	15, 30, 60

2.5. Experimental Design

For the experimental design, each formaldehyde-releasing preservative (DMDM hydantoin, imidazolidinyl urea, diazonidyl urea) was evaluated at each temperature (40, 70, 90 °C) and each proposed time (15, 30, 60 min) (Table 1).

For the evaluation at 40 °C, 70 °C, and 90 °C, 50 mL of the solution containing each preservative was taken, placed in an airtight screw-cap bottle, and heated in an oil bath at the specified temperature. At each sampling time, the samples were cooled in an ice bath for 5 min to prevent formaldehyde loss through evaporation. A 500 µL aliquot was then transferred to a 25 mL volumetric flask, 5 mL of Nash reagent was added, the solution was diluted to the mark with water, heated to 40 °C, and allowed to react for 5 min, protected from light. The solution was then allowed to cool to room temperature, and its absorbance was recorded at a wavelength of 412 nm. This procedure was performed in triplicate for all three preservatives at each time and temperature. At the end of each measurement, the 500 µL aliquot initially taken was replaced with 500 µL of deionized water in each bottle used.

2.6. Design and Evaluation of Cosmetic Formulations

Three cosmetic formulations were prepared: a Niacinamide serum, an Aloe vera gel, and an O/W emulsion. Each formulation was replicated three times, using each formaldehyde-releasing preservative at the maximum concentration permitted by the European Union [10].

For the gel formulation, Aloe vera, Sepinov™ EM 10, sorbitol, propylene glycol, water, and the preservative (DMDM hydantoin, imidazolidinyl urea, diazonidyl urea) were used, as shown in Table 2. Sepinov EM10 was dispersed in the propylene glycol. Simultaneously, the Aloe vera, sorbitol, and preservative were dissolved in the total amount of water. The resulting solution was incorporated into the Sepinov dispersion, and finally, the mixture was blended in a rotor–stator homogenizer for 5 min.

For the formulation of the cold O/W emulsion, castor oil, polysorbate 80, Sepinov™ EM10, sorbitol, water, and the preservative (DMDM, imidazolidinyl urea, diazonidyl urea) were used, as detailed in Table 3. Each component of the formulation, except for the castor

oil, was pre-dissolved in a separate aliquot of the total water. These portions were then combined, and the remaining deionized water was added, mixing until all components were fully incorporated. Finally, the castor oil was slowly added to the mixture with constant stirring and blended in a rotor–stator homogenizer for 5 min.

Table 2. Gel formulations with each preservative.

Ingredient	DMDM Hydantoin	Imidazolidinyl Urea	Diazonidyl Urea
% Aloe vera	5.0	5.0	5.0
% Sepinov™ EM 10 [1]	3.0	3.0	3.0
% Sorbitol	3.0	3.0	3.0
% Propylene glycol	20.0	20.0	20.0
% Preservative	0.6	0.6	0.5
% water	68.4	68.4	68.5
Total	100.0	100.0	100.0

[1] INCI Name: Hydroxyethyl acrylate/Sodium acryloyldimethyl taurate copolymer.

Table 3. O/W emulsion formulations with each preservative.

Ingredient	DMDM Hydantoin	Imidazolidinyl Urea	Diazonidyl Urea
% Castor oil	31.0	31.0	31.0
% Polysorbate 80	1.5	1.5	1.5
% Sepinov™ EM 10 [1]	0.4	0.4	0.4
% Sorbitol	2.6	2.6	2.6
% Preservative	0.6	0.6	0.5
% BHT	0.4	0.4	0.4
% Water	63.5	63.5	63.6
Total	100.0	100.0	100.0

[1] INCI Name: Hydroxyethyl acrylate/Sodium acryloyldimethyl taurate copolymer.

For the formulation of the Niacinamide serum, Niacinamide, glycerin, SepinovTM EM 10, and the preservative (DMDM, imidazolidinyl urea, diazonidyl urea) were used, as detailed in Table 4. The niacinamide was solubilized with all the water, then the glycerin was added, and the Sepinov EM 10 was dispersed in this solution and mixed in a rotor–stator homogenizer for 5 min.

Table 4. Niacinamide serum formulations with each preservative.

Ingredient	DMDM Hydantoin	Imidazolidinyl Urea	Diazonidyl Urea
% Niacinamide	2.5	2.5	2.5
% Glycerin	20.0	20	20
% Sepinov™ EM 10 [1]	0.6	0.6	0.6
% Preservative	0.6	0.6	0.5
% Water	76.3	76.3	76.4
Total	100.0	100.0	100.0

[1] INCI Name: Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer.

2.7. Sample Treatment

To estimate the effect of temperature and time on formaldehyde release from each ingredient in the three cosmetic matrices, a full factorial design was implemented to evaluate two different temperatures (40 and 70 °C) using a temperature-controlled oil bath for 30 min.

To assess the formaldehyde released from each of the three cosmetic matrices containing the three formaldehyde-releasing ingredients at time zero, 3.2 g of product with DMDM

hydantoin, 3.2 g with imidazolidinyl urea, and 4.0 g with diazonidyl urea, respectively, were weighed out, each equivalent to approximately 20 mg of the preservative. These samples were then transferred to a 100.0 mL volumetric flask, approximately 30 mL of water were added, and the mixture was sonicated for 5 min. Subsequently, the volume was brought up to the mark, and a 2.5 mL aliquot was taken and transferred to a 25.0 mL volumetric flask. A 5.0 mL volume of Nash's reagent was added to this aliquot, the mixture was homogenized, and after 10 min, the volume was brought up to the mark. The absorbance was then measured at a wavelength of 412 nm. All measurements were performed in duplicate for each product (time zero).

For the evaluation at 40 °C and 70 °C, 10 g of each cosmetic matrix were placed in three separate flasks for each temperature. The flasks were then placed in an oil bath, and the temperature of the contents was monitored with a thermometer. At the end of the allotted time, the flasks were removed from the oil bath, and 3.2 g of product were weighed out containing DMDM hydantoin, 3.2 g containing imidazolidinyl urea, and 4.0 g containing diazolidinyl urea, respectively, equivalent to approximately 20 mg of the preservative. The process was then continued in the same manner as at time zero.

2.8. Accelerated Stability

An accelerated stability study was selected, in which the cosmetic matrices were subjected to stress conditions of temperature (40 °C ± 2 °C) and humidity (75% ± 5%) for 90 days (Climate chamber DiEs- C240V, Itagüí, Colombia) [14,15]. The objective was to detect changes in the concentrations of released formaldehyde every 30 days, as well as possible degradation or alterations in the physicochemical properties of the product.

All cosmetic formulations were stored at 40 °C ± 2 °C and 75% ± 5% relative humidity (Zone IVb) [14–16]. Analyses were conducted at 30, 60, and 90 days of stability, and the attributes of appearance, odor, and texture were evaluated by six individually selected sensory assessors. The samples were spread with the fingers onto flat spatulas and evaluated under white light. Descriptive and acceptance analyses of each of the evaluated attributes were performed following standard cosmetic acceptability criteria. For appearance and texture evaluation, mechanical, geometric, and surface attributes of the formulations perceptible through touch and vision were assessed [17–19].

Additionally, measurements of released formaldehyde corresponding to each cosmetic matrix were performed. To this end, samples of 1.6 g were collected for Imidazolidinyl Urea and DMDM Hydantoin, and an aliquot of 2 g for Diazolidinyl Urea. Each sample was transferred to a 100 mL flask, to which 30 mL of water were added, followed by 5 min of ultrasonication. The volume was then brought to the mark, and a 2.5 mL aliquot was transferred to a 25 mL flask, where 5 mL of Nash reagent was added. The mixture was left to stand for 10 min, brought to volume, and its absorbance was measured at a wavelength of 412 nm. All measurements were performed in duplicate for each cosmetic matrix.

2.9. Statistical Analysis

All results were expressed as the means of replicates, and the standard deviation and coefficients of variation were calculated. Data were analyzed using Design-Expert 13.0.5.0 software, which employed the Log Likelihood model for data analysis. To assess the significance of the three measured variables, an ANOVA was performed for each variable individually and in two- and three-way combinations. The combinations were: temperature–time; temperature–preservative; time–preservative; and temperature–time–preservative. Accelerated stability statistical analysis was performed using ANOVA in Design-Expert for each preservative and formulation.

3. Results

3.1. Concentrations of Formaldehyde Released from Three Preservatives in Aqueous Solution

A calibration curve was obtained (y = 0.2506x + 0.018, Figure 2), with a linear model that fits the collected data, with an R^2 of 0.9972, indicating good prediction for the data collected and those falling within the curve. The averages of three replicates ± the standard deviation of the amount of formaldehyde released according to temperature and time for each preservative are shown in Table 5.

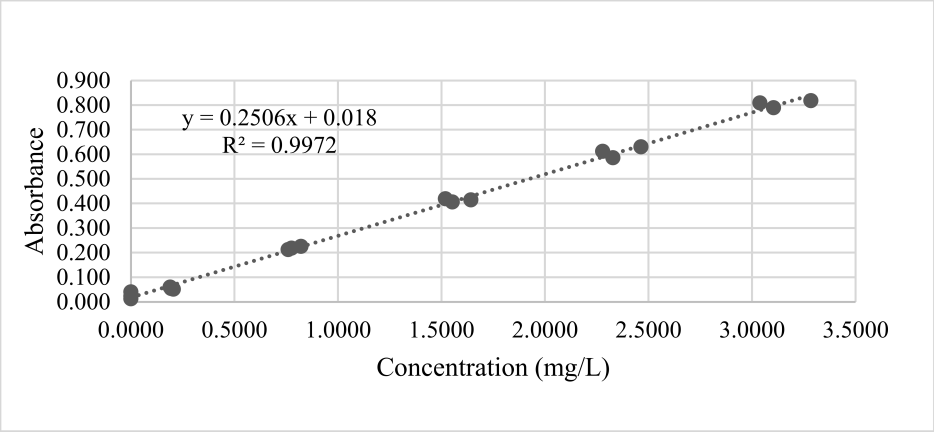


Figure 2. Calibration curve.

Table 5. Formaldehyde release from formaldehyde-releasing preservatives in aqueous solutions under different temperature and exposure-time conditions.

Preservative	Temperature (°C)	Time (min)	Formaldehyde Release (mg/kg Preservative)	Formaldehyde Release (% *w*/*w*)
DMDM Hydantoin	40	0	26,608.6 ± 1295.3	2.66
		15	27,232.0 ± 950.4	2.72
		30	28,311.3 ± 1022.8	2.83
		60	25,261.2 ± 899.9	2.53
	70	0	27,594.6 ± 1563.3	2.76
		15	31,548.9 ± 2295.6	3.15
		30	29,797.4 ± 1228.3	2.98
		60	36,412.8 ± 3271.4	3.64
	90	0	28,265.8 ± 1721.2	2.83
		15	91,096.7 ± 5312.5	9.11
		30	128,258.9 ± 2890.8	12.83
		60	148,248.7 ± 3247.7	14.82
Imidazolidinyl urea	40	0	19,553.1 ± 1766.6	1.96
		15	22,033.4 ± 603.5	2.20
		30	24,379.3 ± 296.7	2.44
		60	22,913.3 ± 1595.4	2.29
	70	0	22,684.5 ± 2352.0	2.27
		15	34,708.2 ± 333.1	3.47
		30	37,004.1 ± 1053.7	3.70
		60	117,723.7 ± 1115.8	11.77
	90	0	14,270.0 ± 2230.2	1.43
		15	125,461.2 ± 2804.0	12.55
		30	123,182.4 ± 935.5	12.32
		60	108,000.5 ± 6580.7	10.80

Table 5. *Cont.*

Preservative	Temperature (°C)	Time (min)	Formaldehyde Release (mg/kg Preservative)	Formaldehyde Release (% *w*/*w*)
Diazolidinyl Urea	40	0	28,991.5 ± 1410.7	2.90
		15	43,929.4 ± 4008.2	4.39
		30	40,010.2 ± 3259.7	4.00
		60	160,130.6 ± 7121.3	16.01
	70	0	29,725.7 ± 840.2	2.97
		15	61,228.8 ± 3228.9	6.12
		30	66,010.5 ± 3814.8	6.60
		60	173,160.1 ± 2667.3	17.32
	90	0	18,911.9 ± 2329.2	1.89
		15	160,431.4 ± 7544.5	16.04
		30	214,757.9 ± 7102.3	21.48
		60	211,934.7 ± 7655.1	21.19

Note: Formaldehyde release is expressed relative to the initial mass of preservative and does not represent the formaldehyde concentration in the final aqueous solution. Values reported as mg/kg correspond to milligrams of formaldehyde released per kilogram of preservative, while percentages represent grams of formaldehyde released per 100 g of preservative (% *w*/*w*).

3.2. Concentrations of Formaldehyde Released in Three Cosmetic Matrices

The concentrations of formaldehyde released by each preservative in each cosmetic matrix at time zero are presented in Table 6. Diazonidyl urea was found to have the highest concentrations in all matrices, followed by DMDM hydantoin and then imidazolidinyl urea in the serum and gel, while in the emulsion, imidazolidinyl urea showed higher concentrations than DMDM hydantoin. Furthermore, the emulsion exhibited the highest concentrations, followed by the serum and finally the gel.

Table 6. Formaldehyde released in each matrix at time zero.

Matrix	Preservative	Concentration (ppm)	Concentration (%)
Niacinamide Serum	DMDM hydantoin	2.0 ± 0.3	0.0002
	Imidazolidinyl urea	1.0 ± 0.2	0.0001
	Diazolidinyl urea	2.5 ± 0.4	0.0002
Aloe vera gel	DMDM hydantoin	1.3 ± 0.1	0.0001
	Imidazolidinyl urea	1.1 ± 0.1	0.0001
	Diazolidinyl urea	1.7 ± 0.0	0.0002
O/W emulsion	DMDM hydantoin	13.1 ± 0.5	0.0013
	Imidazolidinyl urea	15.3 ± 0.0	0.0015
	Diazolidinyl urea	11.8 ± 1.7	0.0012

Note: Formaldehyde concentration is expressed relative to the total mass of the cosmetic formulation (mg/kg formulation). The preservative concentrations incorporated into the formulations were 0.6% DMDM hydantoin, 0.6% imidazolidinyl urea, and 0.5% diazolidinyl urea.

The averages obtained from the data for formaldehyde released concentration, according to matrix, temperature, and preservative, are shown in Table 7. The data obtained were analyzed using Design Expert software. An analysis was performed for each preservative at two temperatures and in three cosmetic matrices. For imidazolidinyl urea, DMDM hydantoin, and diazolidinyl urea, adjusted coefficients of determination (r^2) of 0.9970, 0.9964, and 0.9997, respectively, were obtained, thus confirming that the predicted statistical model for each analysis fits the data and that the Log Likelihood model used is appropriate.

Table 7. Concentrations of formaldehyde release in relation to the cosmetic matrix, temperature and preservative.

Matrix	Preservative	Temperature (°C)	Concentration (ppm)	Concentration (%)
Niacinamide Serum	DMDM hydantoin	40	1710.4 ± 12.0	0.17
		70	2240.0 ± 144.8	0.22
	Imidazolidinyl urea	40	1271.5 ± 57.8	0.13
		70	1386.9 ± 65.5	0.14
	Diazolidinyl urea	40	2979.4 ± 13.1	0.30
		70	2699.71 ± 54.3	0.27
Aloe vera gel	DMDM hydantoin	40	166.5 ± 1.0	0.02
		70	165.9 ± 0.5	0.02
	Imidazolidinyl urea	40	139.5 ± 13.1	0.01
		70	198.3 ± 40.1	0.02
	Diazolidinyl urea	40	275.1 ± 12.1	0.03
		70	261.9 ± 23.3	0.03
O/W emulsion	DMDM hydantoin	40	1412.2 ± 147.3	0.14
		70	1172.8 ± 203.5	0.12
	Imidazolidinyl urea	40	931.3 ± 71.3	0.09
		70	1033.8 ± 203.6	0.10
	Diazolidinyl urea	40	1439.7 ± 63.1	0.14
		70	971.5 ± 218.2	0.10

Note: Formaldehyde concentration is expressed relative to the total mass of the cosmetic formulation (mg/kg formulation). The preservative concentrations incorporated into the formulations were 0.6% DMDM hydantoin, 0.6% imidazolidinyl urea, and 0.5% diazolidinyl urea.

3.3. Accelerated Stability

The concentrations of formaldehyde released from the gel, serum, and emulsion, containing DMDM hydantoin, imidazolidinyl urea, and diazonidyl urea, under temperature conditions of 40 °C ± 2 °C and humidity of 75% ± 5% suitable for an accelerated stability study of zone IVb, are shown in Table 8.

Using Design Expert software, an ANOVA was performed for each preservative (imidazolidinyl urea, DMDM hydantoin, and diazonidyl urea), considering the three matrices and the three sampling times. The software also yielded adjusted coefficients of determination (r^2) of 0.9915, 0.8939, and 0.9809, respectively, confirming that the statistical model for each analysis fits the data and that the previously mentioned log-likelihood model is significant and appropriate.

For the organoleptic analysis, specifications were defined based on the initial organoleptic analysis performed during the preparation of the formulations, and the following specifications were defined. Emulsion: Appearance: Homogeneous, without phase separation, uniform white color, and without visible particles. Odor: Characteristic, without rancid, acidic, or unpleasant notes. Texture: Creamy, uniform, and easy to apply, without lumps or a sticky feeling. Niacinamide Serum: Appearance: Transparent or slightly opalescent, without visible particles or turbidity. Odor: Characteristic, without rancid or unpleasant notes. Texture: Fluid, light, and rapidly absorbed, without a sticky feeling. Gel: Appearance: Translucent orange, without turbidity. Odor: Characteristic, without strange notes or rancidity. Texture: Smooth, homogeneous, without lumps or phase separation.

Table 8. Formaldehyde release concentrations in relation to the cosmetic matrix and time.

Matrix	Preservative	Time (Days)	Concentration (ppm)	Concentration (%)
Niacinamide Serum	DMDM hydantoin	30	130.8 ± 3.4	0.013
		60	334.7 ± 206.4	0.033
		90	201.7 ± 3.5	0.020
	Imidazolidinyl urea	30	61.8 ± 1.0	0.006
		60	234.6 ± 16.0	0.023
		90	109.4 ± 4.2	0.011
	Diazolidinyl urea	30	156.0 ± 5.5	0.016
		60	354.6 ± 187.5	0.035
		90	232.8 ± 6.1	0.023
Aloe vera gel	DMDM hydantoin	30	191.4 ± 10	0.019
		60	538.7 ± 55.7	0.054
		90	199.8 ± 10.7	0.020
	Imidazolidinyl urea	30	83.2 ± 50.4	0.008
		60	351.5 ± 3.1	0.035
		90	147.3 ± 5.7	0.015
	Diazolidinyl urea	30	300.4 ± 2.8	0.030
		60	716.7 ± 24.4	0.072
		90	325.2 ± 9.4	0.033
O/W emulsion	DMDM hydantoin	30	1358.3 ± 318.5	0.136
		60	1820.4 ± 85.6	0.182
		90	673.4 ± 429.4	0.067
	Imidazolidinyl urea	30	792.8 ± 14.8	0.079
		60	2646.2 ± 213.2	0.265
		90	660.4 ± 13.7	0.066
	Diazolidinyl urea	30	982.8 ± 27.8	0.098
		60	2322.4 ± 179.6	0.232
		90	1336.7 ± 115.2	0.134

Organoleptic parameters were measured in the cosmetic matrices at the three time points, and the results shown in Table 9 were obtained.

Table 9. Organoleptic parameters in accelerated stability.

		DMDM Hydantoin			Imidazolidinyl Urea			Diazolidinyl Urea		
Matrix	**Time (Days)**	**Appearance**	**Odor**	**Texture**	**Appearance**	**Odor**	**Texture**	**Appearance**	**Odor**	**Texture**
Serum	30	M	M	M	M	M	M	M	M	M
	60	NM [1,2]	M	M	NM [1,2]	M	M	NM [2]	M	M
	90	NM [1,2]	NM [3]	NM [4]	NM [1,2]	NM [3]	NM [4]	NM [1,2]	NM [3]	NM [4]
Emulsion	30	M			M	M	M		M	M
	60	NM [5]	M	NM [4]	M	M	M	M	M	M
	90	NM [5,6]	NM [7]	NM [4]	M	NM [7]	NM [4]	NM [5,6]	NM [7]	NM [4]
Gel	30	M	M	M	M	M	M	M	M	M
	60	M	M	M	M	M	M	M	M	M
	90	M	NM	NM [4]	M	NM	NM [4]	M	NM	NM [4]

M: It meets the specification. NM: It does not meet the specification. [1] Turbidity, [2] Yellowish color, [3] Strong smell of alcohol and plastic, [4] More fluid, [5] Phase separation, [6] Yellowish white, [7] Strong smell of grease.

4. Discussion

Formaldehyde-releasing preservatives contain hydroxymethyl (–CH_2OH) groups that can contribute to formaldehyde release through hydrolytic and/or decomposition processes under appropriate conditions, including those related to pH, temperature, and water availability [3,6,7,11,20,21]. The chemical structure of these preservatives may therefore influence their theoretical formaldehyde-releasing capacity. In the present study, imidazolidinyl urea and DMDM hydantoin contain two hydroxymethyl groups, whereas diazolidinyl urea contains four. Accordingly, diazolidinyl urea has a higher theoretical formaldehyde-releasing capacity, corresponding to a potential stoichiometric ratio of 1:4, compared with 1:2 for imidazolidinyl urea and DMDM hydantoin [9,22]. Consistent with this structural consideration, diazolidinyl urea showed a greater formaldehyde release than the other preservatives in both aqueous solutions and cosmetic matrices (Tables 5 and 6). However, the observed differences cannot be attributed solely to the number of hydroxymethyl groups, since formaldehyde release is also influenced by the chemical stability of each preservative and by the physicochemical characteristics of the formulation matrix. Thus, the results obtained in this study suggest that both the intrinsic chemical structure of the preservative and the formulation environment contribute to the magnitude and temporal profile of formaldehyde release.

The factorial design applied to evaluate formaldehyde release as a function of temperature, time, and preservative type showed statistically significant effects ($p < 0.0001$) for both main factors and their interactions (Table S1). These findings indicate that temperature and time influence each preservative differently. Additionally, the normal distribution of the data supports the suitability of ANOVA for this analysis based on the log-likelihood model.

At 40 °C, DMDM hydantoin and imidazolidinyl urea exhibited similar behavior, with no significant time-dependent variation (Figure S1), suggesting comparable release profiles under mild storage conditions. At higher temperatures (70 °C and 90 °C), DMDM hydantoin appeared to be primarily influenced by temperature rather than time (Figure S2), whereas imidazolidinyl urea was affected by both variables (Figure S3). In contrast, diazolidinyl urea was influenced by both temperature and time across all tested conditions (Figure S4), consistently showing higher levels of formaldehyde release.

In the cosmetic matrices, formaldehyde release varied according to both the preservative and the formulation type (Table 6), highlighting the influence of the formulation environment on formaldehyde release. Diazolidinyl urea exhibited the highest formaldehyde concentrations in the serum and gel matrices, whereas it showed the lowest concentrations in the emulsion. In contrast, imidazolidinyl urea and DMDM hydantoin showed different release profiles depending on the formulation matrix. These findings indicate that the higher theoretical formaldehyde-releasing capacity of diazolidinyl urea, associated with its greater number of hydroxymethyl groups, does not necessarily translate into higher formaldehyde concentrations in all cosmetic formulations. Compared with the corresponding aqueous systems (Table 5), the three preservatives generally showed lower formaldehyde concentrations when incorporated into the cosmetic matrices, suggesting that matrix composition can substantially modulate formaldehyde release. Despite the lower formaldehyde concentrations observed in some cosmetic matrices compared with the corresponding aqueous systems, the concentrations measured in the cosmetic formulations exceeded the regulatory labelling threshold established by the European Union. Commission Regulation (EU) 2022/1181, which amended the preamble of Annex V to Regulation (EC) No. 1223/2009, requires finished cosmetic products containing formaldehyde-releasing substances to bear the warning “releases formaldehyde” when the total concentration of formaldehyde released in the finished product exceeds 0.001% (10 ppm), irrespective of whether one or more formaldehyde-releasing substances are

present [10,22]. Therefore, the observed differences in formaldehyde release among preservatives and formulation matrices are relevant from both regulatory and product-safety perspectives. For imidazolidinyl urea, the cosmetic matrix was identified as a statistically significant factor ($p < 0.05$, Table S2), indicating that formulation type plays a key role in formaldehyde release. In particular, the serum matrix showed higher formaldehyde levels at both temperatures (Figure S5), while temperature itself did not appear to significantly affect release. This behavior highlights the importance of matrix composition in modulating preservative performance.

For DMDM hydantoin and diazolidinyl urea, both the cosmetic matrix and temperature, as well as their interaction, were statistically significant ($p < 0.05$; Tables S3 and S4), indicating a combined effect on formaldehyde release. Notably, similar behavior was observed in gel and emulsion matrices, where temperature effects were less pronounced (Figures S5–S7), whereas higher release levels were observed in the serum matrix. Diazolidinyl urea consistently exhibited the highest formaldehyde levels across all matrices, in agreement with the trends observed in aqueous systems.

Previous studies have reported that formaldehyde release is influenced by several factors, including pH, temperature, storage time, and interactions with other formulation components. Alkaline conditions tend to favor formaldehyde release, while increasing temperature enhances hydrolysis processes. Storage time is also relevant, as prolonged storage may lead to increased release. Furthermore, interactions with other ingredients may either promote or inhibit the decomposition of formaldehyde-releasing compounds [3,6,7,11,20,21]. From a mechanistic perspective, these findings highlight the critical role of water availability, rather than total water content, in governing hydrolysis-driven formaldehyde release.

In aqueous solution, DMDM hydantoin and imidazolidinyl urea exhibited similar behavior at room temperature, with relatively stable formaldehyde release over time, consistent with previous reports describing slow and progressive release mechanisms [6,21]. At elevated temperatures (70 °C and 90 °C), both preservatives showed increased release proportional to temperature, likely due to enhanced hydrolysis of CH_2OH groups (Figure 1a,b). Diazolidinyl urea showed the expected behavior based on its structure, as its four CH_2OH groups (Figure 1c) enable higher formaldehyde release under these conditions.

In cosmetic matrices, a similar trend was observed, with diazolidinyl urea showing the highest concentrations, followed by DMDM hydantoin and imidazolidinyl urea. However, overall formaldehyde levels were lower than in aqueous solution, likely due to reduced hydrolysis resulting from limited water availability. This observation supports the hypothesis that the extent of hydrolysis is controlled by the accessibility of water within the formulation [11,23].

In the accelerated stability study, nine formulations (three cosmetic matrices, each containing a different preservative) were evaluated under stress conditions (40 °C ± 2 °C and 75% ± 5% relative humidity, Zone IVb). ANOVA results indicated that the cosmetic matrix, time, and their interaction significantly influenced formaldehyde release ($p < 0.05$; Tables S5–S7). Under these conditions, the serum exhibited lower release levels, followed by the gel, while the emulsion showed the highest release (Figures S8–S10). This behavior differs from earlier observations and may be associated with longer sampling intervals and the inclusion of relative humidity, which likely increased water availability and promoted hydrolysis, particularly in the emulsion.

Although the oil-in-water emulsion contained less total water than the serum and gel, it may have exhibited greater water availability, as polymers present in gel and serum systems can bind water and reduce its reactivity. This increased availability of free water in the emulsion may have facilitated preservative hydrolysis and formaldehyde release. Additionally, emulsion systems are thermodynamically unstable and rely on emulsifiers

for stabilization. In this study, the emulsifying system (polysorbate 80 and hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer) may not have been sufficient under stress conditions. Thermal or chemical degradation, as well as possible structural instability, may have contributed to the observed behavior. Increased temperature enhances kinetic energy, which may promote droplet aggregation or coalescence, potentially affecting the release profile [24].

An atypical peak in formaldehyde release was observed at 60 days in all matrices (Figures S8–S10), deviating from the expected gradual release pattern. This behavior may be associated with progressive decomposition and release of formaldehyde from the donor preservatives evaluated in this study (diazolidinyl urea, imidazolidinyl urea, and DMDM hydantoin). Previous studies have demonstrated that formaldehyde release from these preservatives is influenced by storage time, temperature, pH, and the physicochemical characteristics of the cosmetic matrix [3,6,7,11,20,21]. In particular, diazolidinyl urea and imidazolidinyl urea can undergo decomposition processes that result in formaldehyde release [20,21], while DMDM hydantoin releases formaldehyde through decomposition and reaches a concentration-dependent equilibrium with free formaldehyde [25]. Thus, the increase in formaldehyde concentration observed up to 60 days may reflect progressive release from these preservatives during storage. At 90 days, the decrease in formaldehyde concentration may indicate a reduction in the amount of preservative available to generate additional formaldehyde and/or changes in the equilibrium between formaldehyde release and its removal from the formulation. Given the volatile nature of formaldehyde, partitioning between the formulation and the headspace may also contribute to the observed decrease. However, the degradation kinetics and residual concentrations of the individual preservatives, as well as formaldehyde partitioning into the headspace, were not directly investigated in the present study. Therefore, these proposed mechanisms require further investigation and should be experimentally verified in future studies.

All formulations evaluated in the accelerated stability study exceeded the 0.001% formaldehyde threshold established by European regulations (Table 8) [5]. These findings may be relevant for regulatory compliance and product safety considerations, particularly in cases where formaldehyde release is not strictly gradual.

Finally, organoleptic evaluation (Table 9) revealed changes in formulation stability during storage, including turbidity, phase separation, and the development of strong odors after 60 days, suggesting possible degradation processes. The serum and emulsion showed greater instability, particularly when formulated with imidazolidinyl urea and diazolidinyl urea, while the gel exhibited comparatively better stability, although textural changes were observed at 90 days. These results suggest that further optimization of formulation composition or preservative systems may be necessary. However, it should be noted that the primary objective of this study was to evaluate formaldehyde release under different conditions rather than to develop fully optimized formulations.

Study limitations. The relatively small number of replicates represents a significant limitation of this study. Three independent replicates were performed for the aqueous systems, while the cosmetic matrices were evaluated with two independent replicates. This limited sample size reduces the statistical power of the analysis and restricts the robustness with which interaction effects can be characterized, particularly for higher-order interactions. Furthermore, substantial variability was observed under some experimental conditions in the formulations evaluated. Therefore, the statistical results should be interpreted with caution, and the observed differences and interactions should be considered within the context of experimental variability. Further studies with larger sample sizes and additional independent replicates are needed to confirm these findings and provide more robust estimates of the effects of the preservative, the formulation matrix, and storage conditions.

5. Conclusions

Formaldehyde release from the evaluated cosmetic formulations varied according to storage time, temperature, preservative, and formulation matrix. Higher formaldehyde concentrations were generally observed under conditions of increased temperature and prolonged storage. The relative release profiles of diazolidinyl urea, imidazolidinyl urea, and DMDM hydantoin differed among the formulation matrices. Diazolidinyl urea exhibited the highest formaldehyde concentrations in the serum and gel matrices, whereas it showed the lowest concentrations in the emulsion, demonstrating that the formaldehyde-release pattern was matrix-dependent. Although formaldehyde concentrations in the cosmetic matrices were generally lower than those observed in the corresponding aqueous systems, the measured concentrations exceeded the 0.001% (10 ppm) labelling threshold established by European Union regulations for finished cosmetic products containing formaldehyde-releasing substances.

The increase in formaldehyde concentration observed up to 60 days followed by a decrease at 90 days represents an experimentally observed temporal pattern. Although changes in preservative availability, matrix characteristics, and formaldehyde partitioning may potentially contribute to this behavior, these mechanisms were not directly investigated in the present study and therefore cannot be confirmed from the available data. Overall, the results demonstrate that formaldehyde release varies according to the preservative system and formulation matrix under the evaluated storage conditions. These findings support the importance of formulation-specific evaluation of formaldehyde release during cosmetic product development and safety assessment. Further studies under real-use conditions and using complementary analytical approaches are warranted to better characterize formaldehyde release and potential consumer exposure.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cosmetics13050230/s1, Table S1: ANOVA table for the factorial model; Table S2: ANOVA table for Imidazolidinyl in three cosmetic matrices at 40 and 70 °C; Table S3: ANOVA table for DMDM hydantoin in three cosmetic matrices at 40 and 70 °C; Table S4: ANOVA table for diazolidinyl urea in three cosmetic matrices at 40 and 70 °C; Table S5: ANOVA for Imidazolidinyl urea in three cosmetic matrices at 30, 60 and 90 days; Table S6: ANOVA for DMDM hydantoin in three cosmetic matrices at 30, 60 and 90 days; Table S7: ANOVA for Diazonidyl urea in three cosmetic matrices at 30, 60 and 90 days; Figure S1: Change in concentration of formaldehyde released over time at 40 °C for each preservative; Figure S2: Concentration of formaldehyde released from DMDM hydantoin with respect to time and temperature; Figure S3: Concentration of formaldehyde released from imidazolidinyl urea with respect to time and temperature; Figure S4: Concentration of formaldehyde released from diazolidinyl urea with respect to time and temperature; Figure S5: Concentration of formaldehyde released from imidazolidinyl urea with respect to temperature and cosmetic matrix; Figure S6: Concentration of formaldehyde released from DMDM hydantoin with respect to temperature and cosmetic matrix; Figure S7: Concentration of formaldehyde released from Diazolidinyl urea with respect to temperature and cosmetic matrix; Figure S8: Concentration of formaldehyde released from imidazolidinyl urea with respect to the cosmetic matrix and time; Figure S9: Concentration of formaldehyde released from DMDM hydantoin relative to the cosmetic matrix and time, Figure S10. Concentration of formaldehyde released from Diazolidinyl urea with respect to the cosmetic matrix and time.

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