NADIA N. KONATÉ, MARKUS NAHRWOLD*
*Corresponding author
Minasolve Germany GmbH, Am Haupttor Bau 4208,
06237 Leuna, Germany

From pharma to skin care products Hexamidine diisethionate as preservative

For cosmetic products targeting sensitive skin

KEYWORDS: Hexamidine Diisethionate, preservatives, sensitive skin, safety, formulation.

Abstract The search for safe preservatives is facing several challenges today. Potent preservation systems which are yet gentle to the consumer's skin are highly demanded. Hexamidine Diisethionate (HD) is a preservative and antiseptic agent initially used in pharmaceutical over-the-counter (OTC) products. Its mildness and its efficacy at low use levels enable applications on sensitive skin, and even on mucous membranes. This article reviews the safety and performance profile of HD, and provides further data on its different skin care activities. Due to its cationic structure, HD may benefit from some preparation prior to formulation. The article therefore gives some guidelines on how to master formulation hurdles, and successfully utilize this interesting protection ingredient.

INTRODUCTION

Safe and efficient preservation have become key words in the cosmetic business, and this topic has never been discussed so intensively since the turn of the 21st century. Following these discussions, several highly efficient classical preservatives, used without issues over decades, became discredited and their usage further restricted. Ingredient suppliers are more and more striving to supply secure and efficient alternatives. Some suppliers also try to fulfill the strong demand for "green" preservatives. However, whether molecules stem from Mother Nature or are made by mankind, in both cases some are safe and others less. This article describes the safety and performance profile of a man-made substance. It acts as an efficient preservative and is safe and gentle to human skin.

A WELL KNOWN INGREDIENT ...

Hexamidine Diisethionate (HD) is a salt of the amidine base "Hexamidine" and two equivalents of the sulphonic acid "Isethionic Acid" (Figure 1). It has a long track record of use as anti-microbial agent since the 1950s, especially for products where mildness and safety are essential. Examples of applications are personal care products, over-the-counter (OTC) products for the local treatment of minor infections, e.g. eye drops and mouthwashes, as well as hygiene and antiseptic products (1). HD is listed as cosmetic ingredient, e.g. in the EU, US, China, Korea, Canada, Australia and New Zealand. In addition, Hexamidine and its salt "HD" are both listed as preservatives in Europe (2). According to Mintel Database, a total number of 191 personal care products containing HD have been launched worldwide from 2000 until 2015, 121 of which were skin care products and 45 were related to hygiene applications. The frequency of application of HD has steadily increased within this time frame (3).

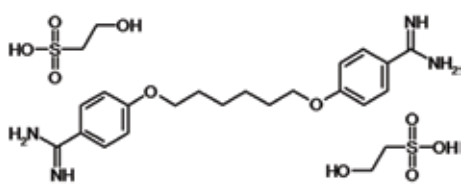


Figure 1. Structure of Hexamidine Diisethionate (HD).

... WITH PROVEN EFFICACY ...

HD shows a high antimicrobial activity against bacteria, fungi, yeasts, and amoebae (4). It even proved to be efficient against some multidrug resistant germs (5). The corresponding minimum inhibitory concentrations (MIC) are ranging from 1000 ppm for the gram negative bacterium *Pseudomonas aeruginosa*, down to 1 ppm for the mould *Aspergillus brasiliensis* (Figure 2). Common preservative boosting agents such as Pentylene Glycol further increase the antimicrobial efficacy of HD, resulting in even lower MIC values against bacteria. The MICs summarized in Figure 2 were determined in suspension tests.

Solutions of the tested substances in a 1:1-mixture of CASO bouillon and distilled water were incubated with either 5 x 10^8 cfu (bacteria) or 1 x 10^7 cfu (yeasts and moulds), and kept for 3 days at 37 °C (bacteria) or 4 days at 30 °C (yeasts and moulds). The lowest concentrations of HD where no turbidity was detected have been designated as the minimum inhibitory concentrations

Looking into cosmetic applications, the performance of HD in microbial challenge tests can be seen as the final proof of efficacy. In a sulfate-free shampoo at pH 5.5, HD at 0.1 % showed some difficulty in reducing the bacterial contamination (Figure 3A). Similar results were seen in a sulfate-based shampoo. Hence the failure of HD as an antibacterial agent could not be attributed to the presence of a natural gum, which makes the sulfate-free shampoo potentially more difficult to preserve. However, in the presence of an extra 1.9 % Pentylene Glycol (PG), the sulfate-free shampoo was fully preserved, reaching criteria A of the norm (Figure 3B). It was shown in internal studies that 3% PG was not sufficient to reach criteria A or B in this shampoo; hence it appears likely that synergistic protection is taking place between the 0.1% HD and 1.9% PG.

In most cases HD at 0.1% use-level is sufficient to preserve O/W emulsions (internal studies). In an O/W emulsion, designed for a sensitive and potentially irritated baby skin, a blend of even just 0.05% HD in Pentylene Glycol/water demonstrated unambiguous efficacy and achieved criteria A (Figure 4). In the two examples presented in Figures 3 and 4, the unpreserved shampoo or emulsion did not reach any of the criteria of the ISO norm.

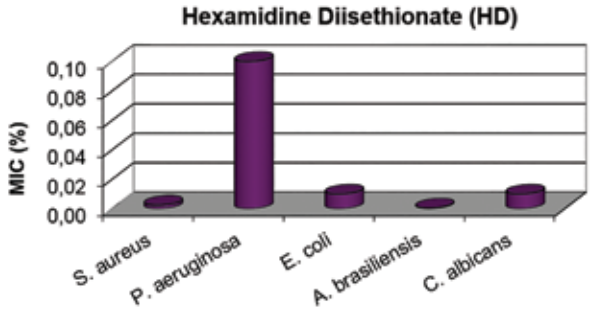
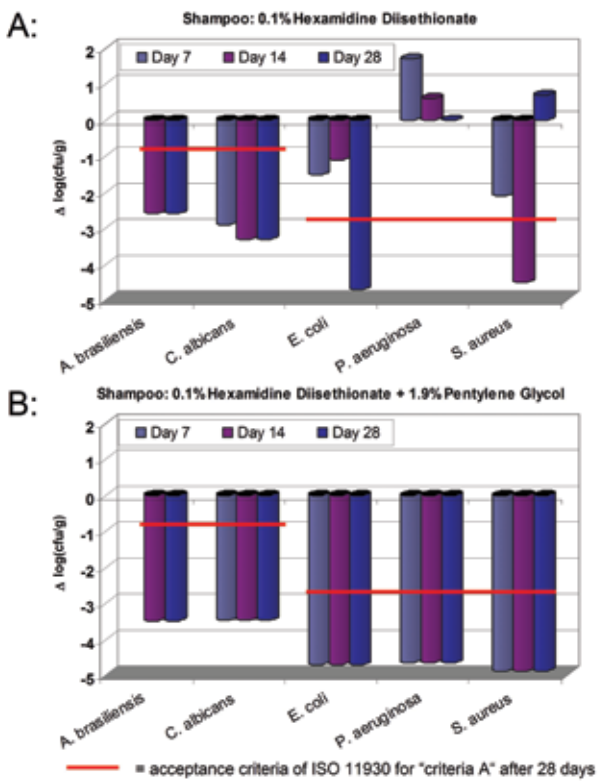


Figure 2. Minimum Inhibitory Concentrations (MIC) of HD.



C:

Phase	Ingredient	INCI	w/w %
A	Water	Aqua	74.4
	Xanthan Gum FNPC [1]	Xanthan Gum	0.6
	Plantacare 818 UP [2]	Coco-Glucoside	15.0
	Plantapon ACG HC [2]	Disodium Cocoyl Glutamate	5.0
	Tego Betain F 50 [3]	Cocamidopropyl Betain	5,0
B	*Preservative* [4]	*see headline of graphs*	*qs*
C	Citric acid solution	Aqua (and) Citric Acid	qs

Suppliers: 1) Jungbunzlauer, 2) BASF, 3) Evonik, 4) Minasolve

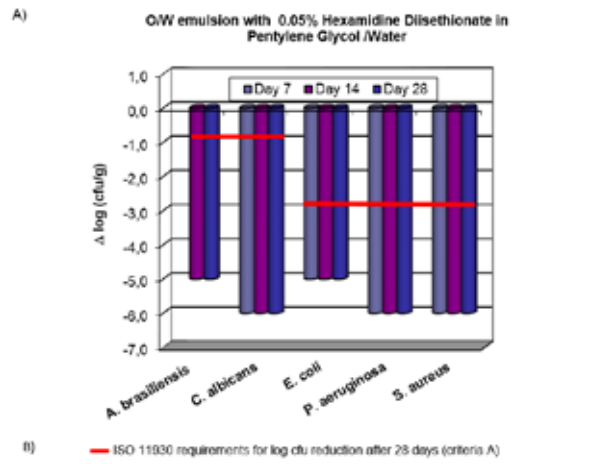
Figure 3. Challenge test results according to ISO 11930 for a sulfate-free shampoo (C), preserved with 0.1 % HD (A), and with 0.1 % HD + 1.9 % Pentylene Glycol (B).

Apart from its well known antimicrobial activity, HD is also an attractive skin care agent (1). As an example, Hexamidine was found to contribute to a strengthening of the stratum corneum, resulting in a lowering of the trans-epidermal water loss (6). Further skin conditioning effects can be achieved by combining HD with alkanediols. As well as providing an antimicrobial boosting effect, these diols also act as skin moisturizers and emollients. As an example, a blend of HD with Pentylene Glycol exhibits a long lasting moisturizing effect, similar to the standard moisturizer Glycerin. Both test products were applied as aqueous solutions on the forearms of 15 subjects of mixed genders, aged 18 – 65. The moisturizing impacts were determined by corneometry at 1 h, 2 h, 4 h, 8 h and 24 h after application (Figure 5).

… AND A REMARKABLE SAFETY PROFILE …

The Cosmetic Ingredient Review (CIR) Expert Panel and the European Union authorities both concluded that HD is safe for applications in leave-on and rinse-off products, at concentrations up to 0.1 % (2, 7). It is also suitable for oral and eye care products at a maximum use-level of 0.05 % (7).

The occurrence of allergic contact dermatitis with HD is very low, even for those possessing a very sensitive skin (8). In a recent study, children with a median age of 3.4 years ("Interquartile Range" IQR = 1.3–6.9 years) with atopic dermatitis ("neurodermatitis") were subjected to a patch test against different antiseptics. It was found that 3 out of the 641 tested children reacted positive towards HD, which was applied at a concentration of 1 % in a lotion (8b). In a human repeated insult patch test (HRIPT) carried out for Minasolve at PhD Trials/Lisbon, HD was tested on a panel of 101 subjects of mixed genders and aged 18-65; 33 % of the panelists had a sensitive skin. The test substance HD was prepared as a 5 % solution in Pentylene Glycol/water and applied ten times within 36 days under occlusive conditions. No irritating or allergic reactions were observed at any time, within 40 days after the first application. Based on these two studies, one can expect that the risk to develop an allergic reaction towards HD is quite low for "normal" users of cosmetics, and also for those with a sensitive skin.



	Ingredient	INCI	w/w %	Function
A	Water, demineralised	Aqua	86,5	Excipient
B	Cetyl Alcohol	Cetyl Alcohol	3,0	Thickener, co-emulsifier
	Stearyl Alcohol	Stearyl Alcohol	2,0	Thickener, co-emulsifier
	NatraGem E145NP [1]	Polyglycaryl-4 Laurate/Succinate (and) Aqua	3,0	Emulsifier
	Sweet Almond oil	Prunus Amygdalus Dulcis (Sweet Almond) Oil	2,0	Emollient
	Neossance Squalane [2]	Squalane	1,0	Emollient
C	Perfume Baby Muse [3]	Parfum	0,5	Perfume
D	MinaSolve Hexam+ [4]	Pentylene Glycol (and) Aqua (and) Hexamidine Diisethionate	1,0	Preservative
E	Sodium Hydroxide (2.5%)	Aqua (and) Sodium Hydroxide	to pH 5,5	pH-adjusting agent
	Buffer	Aqua (and) Citric Acid (and) Sodium Citrate	1,0	Buffering agent

Suppliers: 1) Croda, 2) Amyris/Safic-Alcan, 3) TechnicoFlor, 4) Minasolve

Figure 4. Challenge test results according to ISO 11930 (A) for an O/W baby cleansing milk (B), preserved with 0.05 % HD and 0.75 % Pentylene Glycol. The non-preserved emulsion showed no microbial count reduction at any time.

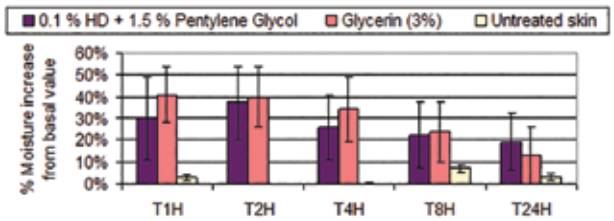


Figure 5. Moisturizing effect (corneometry) of a HD/Pentylene Glycol blend.

In terms of safety, it is also worth noting that Hexamidine and its salt Hexamidine Diisethionate (HD) do not contain any formaldehyde, and are not able to release this compound under normal conditions of use (9).

Depending on the manufacturing method, HD may contain trace amounts of toxic solvents such as chloroform, dioxane or toluene (7). Furthermore, in case of contact with lower alcohols during production, the isethionic acid may form potentially carcinogenic sulphonate esters. Nowadays, qualities of HD are available which are free of the toxic solvents and impurities mentioned above (e.g. "MinaSolve Hexam").
This is achieved through a novel manufacturing process, wherein the contact of HD with lower alcohols and halogenated solvents is systematically avoided. In this way the presence of harmful impurities is excluded.

… FOR COSMETIC APPLICATIONS

HD is soluble in water at up to 4 % at 20 °C, while Propylene Glycol dissolves more than 5 % of HD. Many other water soluble alkanediols are also efficient solvents for HD, as long as they are mixed with 10-20 % of water. Such blends can be easily added at any stage during product formulation, as opposed to the neat HD powder. Examples of suitable alkanediol solvents include 1,3-Propanediol, Butylene Glycol, Pentylene Glycol and Isopentyldiol.

The stability of HD in solution depends on the pH value. Figure 6 shows the evolution of the purity of hexamidine as a 5 wt.-% solution in a 1:1 mixture of pentylene glycol and water at 42 °C. The pH values of the solutions were adjusted with citric acid and sodium bicarbonate. The purity of hexamidine inside the solutions was measured by HPLC via UV-absorption at 263 nm. The solutions stayed stable over 10 weeks at pH 4-6.
Low pH-values ≤ 3 led to a slow degradation. High pH values of ≥ 6.5 resulted in a rapid hydrolysis of the amidine to the amide, with concurrent release of ammonia. This behaviour should be taken into account when formulating with HD; indeed, the pH should be kept within the range of 3.5-6 as soon as HD is present in the product under formulation. This implies that in surfactant based products, HD should be added as a solution (in water and/or in an alkanediol), after the alkaline surfactants have been added and the pH of the formulation has been lowered to 3.5-6.

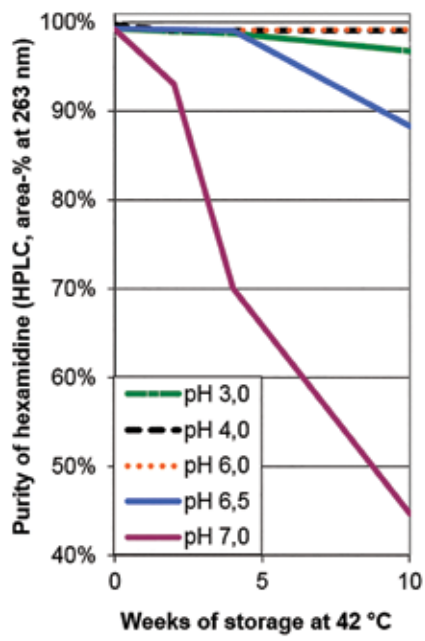


Figure 6. pH-dependent stability of Hexamidine in solution (solvent = Pentylene Glycol/water 1:1 w/w).

Being a cationic substance, HD can interact with anionic ingredients. It is mostly incompatible with polyacrylate based thickeners and its compatibility with Xanthan gum is often improved by the presence of surfactants in the formulation (e.g. glutamates or glucosides). Hence, in products where a polymeric thickening agent is required, HD is best formulated with non-ionic thickeners. Examples of suitable thickeners are celluloses and cellulose derivatives that are non glyoxal surface treated (to avoid discoloration), natural gums such as Guar, Arabic, or Konjac Mannan, and finally polyethylene oxide based thickeners like e.g. Poloxamers, and PEGs.

No macroscopic incompatibilities were noticed with simple mixtures of HD and anionic surfactants (e.g. Sodium Laureth Sulfate, Sodium Cocoamphoacetate or Sodium Cocoyl Glutamate).
Both sulfate-based and sulfate-free shampoos containing the aforementioned surfactants and HD remained clear and stable at ambient temperature and 42 °C, for 12 weeks.
For applications in color cosmetics, the compatibility of HD with charged pigments is to be checked individually. We have for example experienced a loss in color intensity in a blush containing carmine pigments.

From the above recommendations, one can draw the profile of the ideal cosmetic products when formulating with HD – either as a standalone preservative or as a liquid premix (e.g. in pentylene glycol/water). Suitable products should be generally acidic or slightly acidic. Preferred galenic forms are:

- O/W emulsions – thickened up with for example fats of high melting points and/or non-ionic polymers
- cleansing gels containing natural gums (e.g. shower gels, intimate gels).
- cleansing solutions (e.g. micellar waters, including solutions for wet wipes).

Further studies are planned to confirm the relevance of HD in W/O emulsions (macroscopic and microbial stability).

CONCLUSION

In view of the information presented in this article, Hexamidine Diisethionate (HD) can be seen as a valuable ingredient for the preservation of cosmetic products targeting sensitive skin. Thanks to its mildness and its proven safety profile, HD can be applied onto mucous membranes, and it can be considered as an interesting preservative system for baby products. The efficacy of HD is significantly improved by combination with short chain alkanediols, such as e.g. Pentylene Glycol. However, being a cationic substance, Hexamidine can interfere with several types of cosmetic ingredients, in particular with anionic polymeric thickeners. Generally it seems advisable to keep formulations with HD as simple as possible. This may also help to keep in control the irritation and sensitization potential of the cosmetic product as a whole.

REFERENCES AND NOTES

1. Parisi N., Matts P.J., Lever R., Hadgraft J., Lane M.E., *Int. J. Pharm.*, 493, 404-411 (2015).
2. *Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, Annex V; Off. J. Eur. Union*, L342, 198 (2009).
3. Mintel Database: http://www.gnpd.com (last checked on 13th July 2016).
4. Brasseur G., Favennec L., Perrine D., Chenu J.P., Brasseur P., *Cornea*, 13(5), 459-462 (1994).
5. Grare M. et al., *Clin. Microbiol. Infect.*, 16(5), 432-438 (2010).
6. a) Jarrold B.B., Kaczvinsky J., Matts P.J., Osborne R., Weitz S, *J. Am. Acad. Dermatol.*, 62/3 (Suppl. 1), AB62 (2010); b) Kaczvinsky J., Li J., Crowther J., Mirkovic S., Janson W., *J. Am. Acad. Dermatol.*, 62/3 (Suppl. 1), AB25 (2010).
7. Cosmetic Ingredient Review, *Int. J. Toxicol.*, 26 (Suppl. 3), 79-88 (2007).
8. a) Mullins R.J., *Med J. Aust.*, 185(3), 177 (2006); b) Mailhol C., Lauwers-Cances V., Ranc F., Paul C., Giordano-Labadie F. , *Allergy*, 64, 801-806 (2009).
9. de Groot A.C., Flyvholm M.-A., Lensen G., Menné T., Coenraads P-J., *Contact Dermatitis*, 61, 63–85 (2009).