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POLYHEXAMETHYLENE BIGUANIDE HYDROCHLORIDE: FEATURES AND APPLICATIONS

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ABSTRACT: *Polyhexamethylene biguanide hydrochloride (PHMB) is a chemical biocide which is a polymer utilized in a wide variety of antimicrobial applications. This review provides a comprehensive literature of PHMB features from synthesis methods,mode of action, antimicrobial effects and safety considerations to both humans and environments. Effectiveness against cellular organisms is due to the basic biguanide group attached to a flexible spacer, a hexamethylene group. PHMB is a disinfectant with a broad spectrum of inducing cell death by disrupting cell membrane integrity. It is an environmentally friendly product noncorrosive and nontoxic to both humans and animals. It is used as a preservative in cosmetics, personal care products, fabric softeners, contact lens solutions, hand washes, and more. In cosmetics, the preservation of fruit and vegetables. It is also used to preserve wet wipes; to control odor in textiles; to prevent microbial contamination in wound irrigation and sterile dressings; to disinfect medical/dental utensil and trays, farm equipment, animal drinking water, and hard surfaces for food handling institutions and hospitals; and to deodorize vacuums and toilets. This agent can work at low concentrations with very fast action with a broad spectrum of action in addition of its wide acceptance and exploitation for potential multi-purpose functional use. It will be promising for advanced environmental treatments including food disinfection, water disinfection, surface disinfection, and meet the criteria for an ideal antimicrobial agent.*

KEYWORDS: Polyhexamethylene, Biguanide, PHMB, Disinfectant, Biocide, Environment

INTRODUCTION

Disinfecting agent is a substances used to control, prevent, or destroy harmful microorganisms (i.e., bacteria, viruses, or fungi) on inanimate objects and surfaces. It destroys or irreversibly inactivates most pathogenic microorganisms (Ewart,2001; EPA, 2004; Quinn and Markey, 2001; Kennedy et al., 2000). Chemical disinfectants were used scientifically around 150 years ago, but empiric practices can be found in ancient times . Since then several new biocides have been introduced and a significant amount of research on their activity against microorganisms has been performed. Biguanidines are an interesting class of compounds with many known or potential applications. It is bacteriostatic at lower concentrations, inhibiting membrane enzymes and promoting leakage of cellular constituents. Polyhexamethylene biguanide hydrochloride (Polyhexanide, PHMB) is a chemical biocide and a member of the polymeric guanidine family is used as a disinfectant and antiseptic and general disinfecting agents in the food industry and, very successfully, for the disinfection of swimming pools. This widely used biocide has been reviewed by US Environmental Protection Agency (EPA) and noted, with the exception of occupational users, as having very low aggregate risk of adverse health effects to the public or environment(EPA, 2005). PHMB binds to the negatively charged phosphate head groups of phospholipids at bacteria cell wall, causing increased rigidity, sinking nonpolar

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segments into hydrophobic domains, disrupting the membrane with subsequent cytoplas- mic shedding culminating in cell death (Kaehn, 2010). There have been no reported instances of bacteria acquiring resistance to PHMB. PHMB is well tolerated when used topically on skin, eyes, the ciliated epithelium of the nose, and wounds (Kaehn, 2010; Kramer et al., 2004; Dissemond et al., 2009; Kramer et al., 2008). The market for PHMB-containing products, which now includes liquids, gels and antimicrobial dressings, is expanding rapidly. This article outlines the evidence on the antimicrobial properties of PHMB.

Synthesis and Preparation

PHMB was firstly synthesized by Rose and Swain (1954). It is a cationic biguanide polymer which is utilized in a wide variety of antibacterial applications (O'Malley et al., 2007). Several methods have been devised in order to prepare PHMB. For instance, one of the current methods is to obtain PHMB by polycondensation of sodium dicyanamide and hexamethylenediamine in two steps (de Paula et al., 2011). Preparations of PHMB are polydisperse mixtures of polymeric biguanides, with a weighted average number (n) of 12 repeating hexamethylene biguanide units. The heterogeneity of the molecule is increased further by the presence of either amine, or cyanoguanidine or guanidine end-groups in any combination at the terminal positions of each chain. Equal amounts (in molar) of hexamethylenediamine and guanidine hydrochloride to be mixed in a round-bottomed three-necked flask, which is equipped with a mechanical stirrer and vacuum system. The mixture reacts at 100 °C for 60 min, and then at 170 °C for a certain time. During the reaction, by-product ammonia is neutralized by bubbling through aqueous HCl. At the end of reaction, the slightly yellow, viscous liquid solidifies upon cooling giving PHMG samples (Wei et al., 2009).

Physical and chemical properties

Polyhexamethylene biguanide hydrochloride is the chemical name with INCI Name: Polyaminopropyl Biguanide AND IUPAC Name: Homopolymer of N-(3-Aminopropyl)-Imidodicarbonimidic Diamide. PHMB is a polymer which in is neat form represents a solid/powder of > 94.2 % purity, colourless, odourless, non-corrosive and non-irritating antimicrobial biocide. It has a good water solubility of around 40 %. It is also soluble in alcohol and being used as common solvents for paints and lacquers (ECA, 2010). Average molecular weights in the range between 2670 and 4216 Da (SCCS, 2015). PHMB is a positively charged polymer having polymeric biguanide units in the backbone of its structure [−(CH2)6.NH.C(=NH). NH.C(=NH).NH-]n, (Figure1) where n ranges from 2 to 40 having an average value of 11 [Dugard and Mawdsley, 1982]. These properties make it as an interesting molecule to technological applications: It is as good a metal chelator as its parent molecule, biguanide (de Paula, 2011); the five conjugated amines when binding to neighboring molecules with multiple hydrogen bonds, will be attractive for supra molecular chemistry (Lebel et al., 2006). Films of PHMB are transparent and very adherent to metal, plastics and glass. It is a proton conductor, potentially applicable to proton exchange membrane fuel cells (Britz et al., 2010). Infrared absorption spectrum of PHMB showed that the most important are those located at 2,000–2,400 nm range, corresponding to nitrogen-related vibrations, including combination bands due to nitrogen-carbon bonds in the biguanide pseudo-aromatic ring. other bonds are due to methylene groups and residual hydration water (SCCS, 2015).

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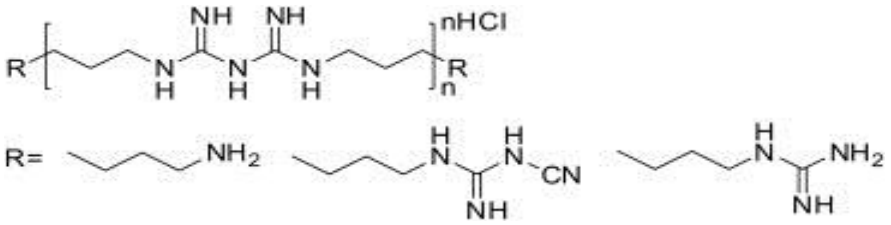

Figure. 1. Chemical structure of PHMB and its terminal groups.

Mode of Action

PHMB is a cationic biocide marketed worldwide, due to its excellent antimicrobial activity, chemical stability, low toxicity and reasonable cost (Vantocil, 2005; Roth and Brill, 2010). The mode of action of PHMB family, has been described by many researchers (Maris, 1995). When elucidated by transmission electron microscopy, the mode of action of PHMGH antimicrobial biocide demonstrated that the cell envelope was broken, resulting in cell content leakage into the medium (Oulé et al., 2008). The primary site of action is the cytoplasmic membrane, with resulting modification of membrane permeability. PHMB binds to the negatively charged phosphate head groups of phospholipids at bacteria cell wall, causing increased rigidity, sinking non-polar segments into hydrophobic domains, disrupting the membrane with subsequent cytoplasmic shedding culminating in cell death. This effect was observed to be due to electrostatic interaction of the PHMB with the acid phospholipids in the cytoplasmic membrane. Effectiveness against cellular organisms is due to the very basic biguanide group attached to a flexible spacer, a hexamethylene group. Maximal biocidal efficiency is obtained when six methylene groups are used as spacer between biguanide groups (Kaehn, 2010). Unlike certain antibiotics (penicillins, bacitracin and novobiocin), there is no accumulation of bacterial wall precursors; destruction is caused by rupture of the membrane and loss of permeability without lysis of the cell wall. Release of the cell constituents occurs at very low concentrations. PHMB has an effect on both planktonic bacteria and those in biofilms (Butcher, 2012). At the high concentrations used under antiseptic conditions, the bactericidal effect is very rapid, due to coagulation of the cytoplasm. Therefore, bacterial death is not due to leakage of the cell constituents at all concentrations of PHMB. (Maris, 1995). However, PHMB does not interfere with the proteins that make up animal cell membranes. It, therefore, has a specific antimicrobial action that does not affect animal cell integrity. Once inside the cell, there is evidence that PHMB binds to DNA and other nucleic acids, suggesting it may also damage or inactivate bacterial DNA (Allen et al, 2004). It was also showed that PHMG derivatives strongly affected bacterial enzymes activity in *S. aureus* than in *E. coli* (Walezak et al., 2014).

Safety

PHMB as a disinfectant, has been proved and tested to be a powerful bactericide. It has been reviewed by US Environmental Protection Agency (EPA) and noted as having very low aggregate risk of adverse health effects to the public or environment [EPA, 2005]. It has been proclaimed a safe product for the various application areas mainly human hygiene, public and private health areas, veterinary hygiene, food and feed areas, canned preservatives, film preservatives and drinking water. Koburger et al., (2010) concluded that PHMB was the most widely used antiseptic when prolonged use is needed and when prolonged contact is feasible. Its ability to give long-lasting protection puts it in the top position as a unique disinfectant in providing long-lasting, total bio safety to the user. PHMB is free of heavy metal and phenol compounds and also it is noncorrosive and nontoxic to both humans and animals because it is

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an environmentally friendly product (Vantocil 2005; Roth and Brill, 2010). Its performance and extremely low toxicity make it the best option in Bio Safety for slaughterhouses, livestock farming, chicken houses, feed stocks, food and feed storage facilities, transport vehicles, food processing units, kitchens and so on. In addition it can work at low concentrations very fast with a broad spectrum of action because of its relatively safe status, its wide acceptance and its exploitation for potential multi-purpose functional use (Krebs et al., 2005; Müller and Kramer, 2005; Oulé et al., 2008). PHMB is safe in clinical use and well tolerated when used topically on skin, eyes, the ciliated epithelium of the nose, and wounds (Kramer et al., 2004; Dissemond et al., 2009; Kramer et al., 2008; Schnuch et al (2000; 2007).

Applications

PHMG is a new generation of disinfectant with a wide scope of applications in agriculture and food processing plants, logistics, kitchens, transport vehicles. PHMB is a disinfectant with a broad spectrum of activity against bacteria, viruses and fungi, inducing cell death by disrupting cell membrane integrity (Ikeda et al, 1983; Ikeda et al, 1984; Moore and Gray, 2007;). and it is used as a preservative in cosmetics, personal care products, fabric softeners, contact lens solutions, hand washes, and more. In cosmetics, the preservation of fruit and vegetables (Koffi-Nevry et al., 2011; Kabara, 1984; Dugard and Mawdsley, 1982). PHMB is also used to preserve wet wipes; to control odor in textiles; to prevent microbial contamination in wound irrigation, sterile dressings; to deodorize vacuums and toilets (SCCS, 2005); to disinfect medical/dental utensil and trays, farm equipment, animal drinking water and hard surfaces for food handling institutions and hospitals. PHMB is used in antimicrobial hand washes and rubs and air filter treatments as an alternative to ozone. PHMB is also used as an active ingredient for recreational water treatment, as a chlorine free polymeric sanitizer, which is effective against a wide variety of microorganisms. It has been used in a wide range of applications from swimming pool sanitisers to preservatives in cosmetics and contact lens solutions (Bucher,2012). Clinical studies indicate it has a broad spectrum of activity, including against human immunodeficiency virus (HIV) (Wérthen et al, 2004; Krebs et al, 2005). PHMB appears to be available in presentations that provide clinicians with effective wound care modalities for most clinical scenarios and has also been used as a perioperative cleansing agent (Kramer, 1997), in mouth wash, (Rosin, 2002) in ophthalmology, (Kramer, 1997; Petrou-Binder, 2003). Petrou-Binder40 describes the germicidal effects of PHMB (Lavasept 0.02%) as eye drops prior to cataract surgery. PHMB can be found in swimming pool sanitizers, cosmetics, leather preservatives, contact lens disinfectants, cleanser in agriculture and food handling, in treatment of hatching eggs, fibers and textiles and technical fluids like cutting oils and glues (Kaehn, 2010).

Future prospects

PHMB is an excellent biocide that is an environmentally friendly product and expected to be used widely in future to provide valuable disinfection, cleaning and hygiene functions in a wide type of products such as cosmetics, deodorant, contact lenses solutions, fabric softeners, water treatments, wound care products and antimicrobial foam dressings. It is expected to be; a component of pool cleaners, skin disinfectants and urinary catheter flush solutions; sanitizers in different applications; disinfectant in hospitals and food and equipment in contact with food.

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CONCLUSION

An overview of some current features and applications of PHMB was given and discussed. PHMB is an environmentally friendly biocides. It is a new generation of disinfectant with a wide scope of applications in all aspects of life. PHMB is a disinfectant with a broad spectrum of activity against bacteria, viruses and fungi. This review provides a comprehensive literature of PHMB from synthesis methods, antimicrobial effects and safety considerations to both humans and environments. It is believed to continue to be used in wide ranging consumer and industrial products and by many market leading companies. PHMB as a disinfectant will be promising for advanced environmental treatments including food disinfection, water disinfection, surface disinfection, and meet the criteria for an ideal antimicrobial agent.

REFERENCES

Allen MJ, Morby AP, White GF (2004) Cooperativity in the binding of the cationic biocide polyhexamethylene biguanide to nucleic acids. Biochem Biophys Res Commun 318(2): 397–404

Britz, J.; Meyer, W.H.; Wegner, G (2010). Poly(alkylene biguanides) as proton conductors for high-temperature PEMFCs. Adv. Mater. 22:E72–E76.

Butcher M. (2012). PHMB: an effective antimicrobial in wound bioburden management. British Journal of Nursing, (21)12:s16-s21 de Paula, G F.; Netto, G I.; Mattoso, L H C (2011). Physical and Chemical Characterization of Poly(hexamethylene biguanide) Hydrochloride. Polymers. 3:928-941;

Dissemond, J., Gerber, V., Kramer, A. et al (2009). Practice-oriented expert recommendation for the treatment of critically colonised and local infected wounds using polihexanide. Zeitschrift für Wundheilung 14(1):20-26.

Dugard PH, Mawdsley SJ (1982) [14C]-Polyaminopropyl biguanide (PHMB): Absorption through human epidermis and rat skin in vitro, Imperical Chemical Industries, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No.: CTL/R/579, unpublished data, CBI, 15 October 1982.

ECA, (2010) European Chemicals Agency (2010). CLH report—Proposal for Harmonised Classification and Labeling; Substance Name: Polyhexamethylene biguanide or Poly (hexamethylene) biguanide hydrochloride or PHMB, France, Available online: http://echa.europa.eu/doc/consultations/ cl/clh_axrep_france_phmb.pdf (accessed on 20 February 2010).

EPA (2005), UnitedStatesEnvironmentalProtectionAgency,Washington, D.C. /http://www.epa.gov/oppsrrd1/REDs/phmb_red.pdfS, 2005 (accessed14.12.12).

EPA, (2004). UnitedStatesEnvironmental Protection Agency. Disinfectants for use on hard surfaces–Efficacy data requirements. Accessed at www.epa.gov/oppad001/dis_tss_docs/dis-01.htm on October 28, 2004.

Ewart SL (2001). Disinfectants and control of environmental contamination. In: Smith BL. editor. Large Animal Internal Medicine: diseases of horses cattle, sheep and goats. 3rd edition.. St. Louis: Mosby. pp. 1371- 1380.

Ikeda T, Ledwith A, Bamford CH, Hann RA (1984) Interaction of a polymeric biguanide biocide with phospholipid membranes. Biochim Biophys Acta 769(1): 57–66

Ikeda T, Tazuke S, Watanabe M (1983) Interaction of biologically active molecules with phospholipid membranes. I. Fluorescence depolarization studies on the effect of

ISSN 2055-0219(Print), ISSN 2055-0227(online)

polymeric biocide bearing biguanide groups in the main chain. Biochim Biophys Acta 735(3): 380–6

Kabara JJ (1984). Cosmetic and Drug Preservation: Orinciples and Practise (Cosmetic Science and Technology Series, Dekker M Inc., New York, NY USA (1984) pp 631.

Kaehn, K (2010). Polihexanide: A safe and highly effective biocide. Skin Pharmacol. Physiol. 23 1: 7–16.

Kennedy J, Bek J, Griffin D. Selection and use of disinfectants. University of Nebraska Cooperative Extension G00-1410-A. November 2000.

Koburger T Hübner N O, Braun M, Siebert J, Kramer A (2010). Standardized comparison of antiseptic efficacy of triclosan, PVP-iodine, octenidine dihydrochloride, polyhexanide and chlorhexidine digluconate. J. Antimicrob. Chemother. 65, 1712–1719.

Koffi-Nevry R, Manizan A L , Tano K , Clément Y B Y , Oulé M K, Koussémon M (2011). Assessment of the antifungal activities of polyhexamethylene-guanidine hydrochloride (PHMGH)- based disinfectant against fungi isolated from papaya (Carica papaya L.) fruit. Afr. J. Microbiol. Res.5(24);4162-4169.

Kramer A, Behrens-Baumann W(1997). Prophylactic use of topical anti-infectives in ophthalmology. Ophthalmologica. 211(Suppl 1):68-76.

Kramer, A., Daeschlein, G., Kammerlander, G. et al (2004). Consensus paper on wound antisepsis. Zentralbl für Wundheilung 9(3):110–120.

Kramer, A., Roth, B. Polihexanid (2008). In: Kramer, A., Assadian, O. (eds). Wallhنكers Praxis der Sterilisation. Stuttarg: Thieme, 2008: 789-93

Krebs FC, Miller SR, Ferguson ML, Labib M, Rando RF et al (2005) Polybiguanides, particularly polyethylene hexamethylene biguanide, have activity against human immunodeficiency virus type 1. Biomed Pharmacother 59(8): 438–445

Krebs FC, Miller SR, Ferguson ML, Labib M, Rando RF, Wigdahl B (2005). Polybiguanides, particularly amethylene biguanide, have activity against human immunodeficiency virus type 1. Biomed. Pharmacol.. 59: 438–445.

Lebel, O.; Maris, T.; Wuest, J.D (2006). Hydrogen-bonded networks in crystals built from bis(biguanides) and their salts. Can. J. Chem. 84:1426–1433.

Maris P (1995). Modes of action of disinfectants Rev. sci. tech. Off. int. Epiz., ,14 (1), 47-55.

Moore K, Gray D (2007) Using PHMB antimicrobial to prevent wound infection. Wounds UK 3(2): 96–102.

Müller G, Kramer A (2005). Effect of selected wound antiseptics on adult articular cartilage (bovine sesamoid bone) in the presence of Escherichia coli and Staphylococcus aureus. J. Orthopathol. Res., 23: 127-133.

O'Malley L.P., Shaw C.H., Collins A.N (2007). Microbial degradation of the biocide polyhexamethylene biguanide: isolation and characterization of enrichment consortia and determination of degradation by measurement of stable isotope incorporation into DNA. Journal of Applied Microbiology. 103 (2007): 1158–1169

Oulé MK, Richard A, Anne-Marie B, Tano K, Anne-Marie M, Stephanie M, Rose KN, Korami D, Lorraine F, Lamine D (2008). Polyhexamethylene guanidine hydrochloride-based disinfectant: a novel tool to fight meticillin-resistant Staphylococcus aureus and nosocomial infections. J. Med. Microbiol., 57: 1523-1528.

Petrou-Binder S (2003). PHMB-containing antiseptics 'may offer alternative' to iodine perioperative agents, say researchers. Available at: http://www.escrs.org/eurotimes/April2003/phmb.asp.

Quinn PJ, Markey BK (2001). Disinfection and disease prevention in veterinary medicine. In: Block SS, editor. Disinfection, sterilization and preservation. 5th edition. Philadelphia: Lippincott, Williams & Wilkins. pp1069-1103.

ISSN 2055-0219(Print), ISSN 2055-0227(online)

Rosin M, Welk A, Kocher T, Majic-Todt A, Kramer A, Pitten FA (2002). The effect of a polyhexamethylene biguanide mouthrinse compared to an essential oil rinse and a chlorhexidine rinse on bacterial counts and 4-day plaque regrowth. J Clin Periodontol. 29(5):392-399.

Roth, B.; Brill, F.H.H (2010). Polihexanide for wound treatment—how it began. Skin Pharmacol. Physiol. 23 (1): 4–6.

Scientific Committee on Consumer Safety (SCCS) (2015). Opinion of the scientific committee on consumer safety (SCCS) – 2nd Revision of the safety of the use of poly(hexamethylene) biguanide hydrochloride or polyaminopropyl biguanide (PHMB) in cosmetic products. Regulatory Toxicology and Pharmacology. 73(3): 885–886.

Schnuch A, Geier J, Brasch J, Fuchs T, Pirker C et al (2000) Polyhexamethylene biguanide: a relevant contact allergen? Contact Dermatitis 42(5): 302–303

Schnuch A, Geier J, Uter W, Basketter DA, Jowsey IR et al (2007). The biocide polyhexamethylene biguanide remains an uncommon contact allergen. Contact Dermatitis 56(4): 235–259

Vantocil (2005) IB Antimicrobial-Technical Information Bulletin; Arch Chemicals, Inc.: Cheschire, CT, USA, 2005

Walczak m., Richert A. & Burkowska‐But A. (2014): The effect of polyhexamethylene guanidine hydrochloride (PHMG) derivatives introduced into polylactide (PLA) on the activity of bacterial enzymes. J Ind Microbiol Biotechnol.; 41:1719–1724.

Wei, D; Ma, Q; Guan, Y; Hu, F; Zheng, A; Zhang, X; Teng, Z and Jiang, H. (2009). Structural characterization and antibacterial activity of oligoguanidine (polyhexamethylene guanidine hydrochloride). Materials Science and Engineering C 29 (2009) 1776–1780.

Werthén M, Davoudi M, Sonesson A, Nitsche DP, Mörgelin M et al (2004) Pseudomonas aeruginosa-induced infection and degradation of human wound fluid and skin proteins ex vivo are eradicated by a synthetic cationic polymer. J Antimicrob Chemother 54(4): 772–779.

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